NOVARTIS

Patient Safety & Pharmacovigilance

Canakinumab

ACZ885

EU Safety Risk Management Plan

Active substance(s) (INN or common name):	Canakinumab
Product(s) concerned (brand name(s)):	Ilaris
Document status:	Final
Version number:	14.0
Data lock point for this RMP	Safety: 30-Jun-2021 Clinical (last date of data collection): 30-Jun-2022
Date of final sign off	16-Apr-2024

Rationale for submitting an updated RMP:

The Risk Management Plan (RMP) version 14.0 is updated to reflect:

- Addition of 150 mg solution for injection in pre-filled pen (autoinjector) presentation
- Removal of Study ACZ885G2403 as an ongoing pharmacovigilance activity
- The RMP is also aligned with new RMP template version 6.4.

Summary of significant changes in this RMP:

Part	Major changes compared to RMP v 13.1
Part I	Pharmaceutical form is updated to include 150 mg solution for injection in pre-filled pen in alignment with the SmPC.
Part II	SI: No change SII: No change SIII: No change SIV: Study ACZ885G2403 is changed from on-going to completed, in reference to the SJIA Registry. SV: No change SVI: No change SVII: No change SVII: No change SVIII: No change
Part III	"Severe skin reactions" risk is re-named to "Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)", in reference to risks monitored by targeted follow-up checklists. Study ACZ885G2403: SJIA Registry, macrophage activation syndrome adjudication committee, and Study ACZ885H240 removed from additional pharmacovigilance activities.
Part IV	No change
Part V	Updated based on updated EU SmPC ("patient reminder card" is now referred to as "patient card"). Removal of Study ACZ885G2403: SJIA Registry from additional pharmacovigilance activities.
Part VI	150 mg solution for injection in pre-filled pen is added as a dosage form in alignment with the SmPC. Reference to the "patient reminder card" is updated to "patient card". Removal of Study ACZ885G2403: SJIA Registry from additional pharmacovigilance activities and other studies in the post-authorization development plan.
Part VII	Annex 4: Targeted follow-up checklist for macrophage activation syndrome and malignancy and neoplasm are updated. Annex 6: Reference to the "patient reminder card" is updated to "patient card".

Part	Major changes compared to RMP v 13.1

Other RMP versions under evaluation

None

Details of the currently approved RMP:

Version number: 13.1

Approved with procedure: EMEA/H/C/001109/IB/0079

Date of approval (opinion date): 20-Apr-2022

QPPV name: Dr Justin Daniels PhD

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorization holder´s QPPV. The electronic signature is available on file.

Table of contents

List of tables

List of abbreviations

ACR	American College of Rheumatology
ADA	Anti-Drug antibody
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine transaminase
AOSD	Adult-Onset Still's disease
AST	Aspartate transaminase
ATC	Anatomical therapeutic chemical
CAPS	Cryopyrin-Associated Periodic syndromes
CI	Confidence interval
CINCA	Chronic Infantile Neurologic Cutaneous Articular syndrome
COPD	Chronic Obstructive Pulmonary disease
CRP	C-reactive protein
CSR	Clinical study report
CT	Clinical trial
DILI	Drug induced liver injury
DRESS	Drug Reaction with Eosinophilia and Systemic Symptoms
ECOG	Eastern Cooperative Oncology Group
EEA	European Economic Area
EMA	European Medicines Agency
EULAR	The European League against Rheumatism
FCAS	Familial Cold Autoinflammatory syndrome
FCU	Familiar Cold Urticaria
FMF	familial Mediterranean fever
HCP	Health care professional
HLGT	High level group term
HPF	Hereditary Periodic Fevers
hs-CRP	High-Sensitivity C-Reactive Protein
IAC	Infection Adjudication Committee
IgG	Immunoglobulin
IL-1	Interleukin-1
IR	Incidence rate
MAH	Marketing Authorization Holder
MAS	Macrophage Activation Syndrome
MedDRA	Medical dictionary for regulatory activities
MKD	Mevalonate Kinase Deficiency
MTX	Methotrexate
MWS	Muckle Wells Syndrome
NOMID	Neonatal-Onset Multisystem Inflammatory Disease
PMS	Post-marketing study
PPD	Purified protein derivative
PRAC	Pharmacovigilance risk assessment committee
PSUR	Periodic Safety Update Report
PT	Preferred term
PTY	Patient-treatment-years
RA	Rheumatoid arthritis

RMP	Risk management plan
SAE	Serious adverse event
S.c.	Subcutaneous
SchS	Schnitzler syndrome
SCS	Summary of clinical safety
SJIA	Systemic Juvenile Idiopathic Arthritis
SMQ	Standard MedDRA query
SOC	System organ class
SmPC	Summary of Product Characteristics
SR	Survey response
TA	Triamcinolone acetate
T2DM	Type 2 Diabetes mellitus
TRAPS	TNF-α receptor Periodic Fever Syndrome
TNM	TNM Classification of Malignant Tumors
TNF	Tumor necrosis factor
USA	United States of America

1 Part I: Product(s) Overview

Table 1-1 Part I.1 – Product(s) Overview

Active substance(s) (INN or common name)	Canakinumab (Ilaris®)
Pharmacotherapeutic group(s) (ATC Code)	L04AC08
Marketing Authorization Holder	Novartis Europharm Limited
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Ilaris® in all countries (henceforth represented as Ilaris in the document)
Marketing authorization procedure	Centralized
Brief description of the product	**Chemical class:** Interleukin (IL) inhibitors. Canakinumab is a human monoclonal anti-human interleukin-1 beta (IL-1 beta) antibody of the IgG1/κ isotype.
	Summary of mode of action: Canakinumab binds with high affinity specifically to human IL-1 beta and neutralises the biological activity of human IL-1 beta by blocking its interaction with IL-1 receptors, thereby preventing IL-1 beta-induced gene activation and the production of inflammatory mediators.
	Important information about its composition: Canakinumab is produced in mouse myeloma Sp2/0 cells by recombinant DNA technology.
Hyperlink to the Product Information	[Proposed EU SmPC]

Indication(s) in the EEA	**Current:**
	Periodic fever syndromes:
	Ilaris is indicated for the treatment of the following auto-inflammatory periodic fever syndromes in adults, adolescents and children aged 2 years and older:
	• Cryopyrin-associated periodic syndromes (CAPS) including:
	  • Muckle-Wells syndrome (MWS),
	  • Neonatal-onset multisystem inflammatory disease (NOMID) / chronic infantile neurological, cutaneous, articular syndrome (CINCA),
	  • Severe forms of familial cold autoinflammatory syndrome (FCAS) / familial cold urticaria (FCU) presenting with signs and symptoms beyond cold-induced urticarial skin rash.
	• Tumour necrosis factor receptor associated periodic syndrome (TRAPS): Ilaris is indicated for the treatment of tumour necrosis factor (TNF) receptor associated periodic syndrome (TRAPS).
	• Hyperimmunoglobulin D syndrome (HIDS)/ mevalonate kinase deficiency (MKD): Ilaris is indicated for the treatment of hyperimmunoglobulin D syndrome (HIDS)/ mevalonate kinase deficiency (MKD).
	• Familial Mediterranean fever (FMF): Ilaris is indicated for the treatment of FMF. Canakinumab should be given in combination with colchicine, if appropriate.
	Gouty arthritis:
	Ilaris is indicated for the symptomatic treatment of adult patients with frequent gouty arthritis attacks (at least 3 attacks in the previous 12 months) in whom non-steroidal anti-inflammatory drugs (NSAIDs) and colchicine are

	contraindicated, are not tolerated, or do not provide an adequate response, and in whom repeated courses of corticosteroids are not appropriate. **Still's disease (including AOSD and SJIA):** Ilaris is indicated for the treatment of active Still's disease including adult-onset Still's disease (AOSD) and systemic juvenile idiopathic arthritis (SJIA) in patients aged 2 years and older who have responded inadequately to previous therapy with non-steroidal anti-inflammatory drugs (NSAIDs) and systemic corticosteroids. Canakinumab can be given as monotherapy or in combination with methotrexate.
	Proposed: Not applicable
Dosage in the EEA	**Current:** **Periodic fever syndrome:** • Cryopyrin-associated periodic syndromes (CAPS): Adults, adolescents and children aged 2 years and older. The recommended starting dose of canakinumab for adults, adolescents and children ≥ 4 years of age : • 150 mg for patients with body weight >40 kg • 2 mg/kg for patients with body weight ≥ 15 kg and ≤ 40 kg • 4 mg/kg for patients with body weight ≥ 7.5 kg and <15 kg The recommended dose of canakinumab for children 2 to < 4 years of age is: • 4 mg/kg for patients with body weight ≥ 7.5 kg This is administered every eight weeks as a single dose via subcutaneous injection. For patients with a starting dose of 150 mg or 2 mg/kg, if a satisfactory clinical response (resolution of rash and other generalized inflammatory symptoms) has not been achieved 7 days after treatment start, a second dose of canakinumab at 150 mg or 2 mg/kg can be considered. If a full treatment response is subsequently achieved, the intensified dosing regimen of 300 mg or 4 mg/kg every 8 weeks should be maintained. If a satisfactory clinical response has not been achieved 7 days after this increased dose, a third dose of canakinumab at 300 mg or 4 mg/kg can be considered. If a full treatment response is subsequently achieved, maintaining the intensified dosing regimen of 600 mg or 8 mg/kg every 8 weeks should be considered based on individual clinical judgement. For patients with a starting dose of 4 mg/kg, if a satisfactory clinical response has not been achieved 7 days after treatment start, a second dose of canakinumab 4 mg/kg can be considered. If a full treatment response is subsequently achieved, maintaining the intensified dosing regimen of 8 mg/kg every 8 weeks should be considered based on individual clinical judgement. Clinical experience with dosing at intervals of less than 4 weeks or at doses above 600 mg or 8 mg/kg is limited. • TRAPS, HIDS/MKD and FMF Adults, adolescents and children aged 2 years and older. The recommended starting dose of canakinumab in TRAPS, HIDS/MKD and FMF patients is: • 150 mg for patients with body weight >40 kg • 2 mg/kg for patients with body weight ≥ 7.5 kg and ≤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 treatment start, a second dose of canakinumab at 150 mg or 2 mg/kg can be considered. If a full treatment response is subsequently achieved, the

	intensified dosing regimen of 300 mg (or 4 mg/kg for patients weighing ≤40 kg) every 4 weeks should be maintained. Continued treatment with Ilaris in patients without clinical improvement should be reconsidered by the treating physician. **Gouty arthritis:** The recommended dose of canakinumab for adult patients with gouty arthritis is 150 mg, administered subcutaneously as a single dose during an attack. For maximum effect, canakinumab should be administered as soon as possible after the onset of a gouty arthritis attack. Patients who do not respond to initial treatment should not be re-treated with canakinumab. In patients who respond and require re-treatment, there should be an interval of at least 12 weeks before a new dose of canakinumab may be administered. **Still's Disease (AOSD and SJIA):** The recommended dose of canakinumab for patients with Still's disease (AOSD and SJIA) with body weight ≥ 7.5 kg is 4 mg/kg (up to a maximum of 300 mg) administered every four weeks via subcutaneous injection. Continued treatment with canakinumab in patients without clinical improvement should be reconsidered by the treating physician.
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	**Current:** • 150 mg powder for solution for injection • 150 mg/ml solution for injection
	Proposed: • 150 mg powder for solution for injection • 150 mg/ml solution for injection • 150 mg solution for injection in pre-filled pen
Is/will the product be subject to additional monitoring in the EU?	No

2 Part II Safety specification Module SI: Epidemiology of the indications and target population

2.1 Indication: Periodic fever syndromes

Canakinumab is indicated for the treatment of the following autoinflammatory periodic fever syndromes in adults, adolescents and children aged 2 years and older:

Cryopyrin-Associated Periodic Syndromes (CAPS): Canakinumab is indicated for the treatment of cryopyrin-associated periodic syndromes (CAPS) including:

- Muckle-Wells syndrome (MWS),
- Neonatal-onset multisystem inflammatory disease (NOMID) / chronic infantile neurological, cutaneous, articular syndrome (CINCA),
- Severe forms of familial cold autoinflammatory syndrome (FCAS) / familial cold urticaria (FCU) presenting with signs and symptoms beyond cold-induced urticarial skin rash.

Tumor necrosis factor receptor associated periodic syndrome (TRAPS): Canakinumab is indicated for the treatment of tumor necrosis factor (TNF) receptor associated periodic syndrome (TRAPS).

Hyperimmunoglobulin D syndrome (HIDS)/Mevalonate kinase deficiency (MKD): Canakinumab is indicated for the treatment of hyperimmunoglobulin D syndrome (HIDS)/mevalonate kinase deficiency (MKD).

Familial mediterranean fever (FMF): Canakinumab is indicated for the treatment of FMF. Canakinumab should be given in combination with colchicine, if appropriate.

Incidence:

The three rare diseases TRAPS, HIDS/MKD and FMF are a group of clinically distinct autoinflammatory conditions, which, together with CAPS, have been classified under a single term of periodic fever syndromes. The incidence of these conditions is not known, estimates available report very few cases diagnosed worldwide.

CAPS: In Germany, a pediatric, prospective, national epidemiological survey was established on periodic fever syndromes, with an active surveillance over three years (Jul-2003 to Jun-2006). Two to seven newly diagnosed CAPS patients aged 16 years or younger per year were identified, corresponding to an incidence of 3.43 per 10,000,000 person-years (95% CI 1.88, 5.77) (Lainka et al 2010).

TRAPS: The German prospective surveillance of children mentioned above identified pediatric (≤16 years) patients with TRAPS. The authors identified 23 new cases over the 3-year period, corresponding to a national annual incidence of 5.6 per 10,000,000 person-years (95% CI: 3.6, 8.5) (Lainka et al 2009).

HIDS: the above-reported study from Germany, also aimed at identifying pediatric (≤16 years) patients with HIDS. Sixteen cases of HIDS were identified, yielding an incidence of 3.9 (95% CI: 2.2, 6.4) per 10,000,000 person-years (Lainka et al 2012).

Prevalence:

As noted above, CAPS includes MWS, NOMID, CINCA, FCAS and FCU. The exact prevalence of CAPS is unknown. Based on data coming from highly specialized clinical centers in the EU and USA, the prevalence of CAPS is estimated to be in the range of 0.1 to 1/100,000 population (Giat and Lidar 2014). In France estimated CAPS prevalence at 1/360,000 has been reported recently (Baroja-Mazo et al 2014). However, many patients are diagnosed very late or not at all. Therefore, the real prevalence is likely to be higher. A paper, published in 2009, reported that in the USA approximately 250 adults and children had been diagnosed with FCAS and much fewer with MWS, while fewer patients with classic FCAS are reported in Europe where MWS is instead diagnosed more commonly (Hoffman 2009).

For MWS, prevalence estimation in the classical sense is not possible due to the extremely small number of cases and the non-systematic manner of case-finding and reporting. In the USA, an estimated 70 cases have recently been reported in 2006 (Brydges and Kastner 2006). The time period of ascertainment is not established, however. Thus, an estimate of incidence is not calculable. Five cases within Europe have been additionally reported, although it is unclear as

to how many of these overlap with reports in the literature (already enumerated) and reports from a coordinating center.

For NOMID, around 100 cases were reported worldwide (most of the cases are also from Europe or America; however, a few cases have been diagnosed in India and Thailand (Tunca and Ozdogan 2005).

FMF is the most frequent periodic febrile syndrome among the autoinflammatory syndromes. It is estimated that about 100,000 subjects worldwide are affected by FMF (Fonnesu et al 2009). FMF is prevalent mainly among eastern Mediterranean people: non-Ashkenazi Jews, Armenians, Turks, and Arabs, for whom the estimated prevalence is between 1/200-1/1000 (Fonnesu et al 2009). With a population of more than 67 million inhabitants, therefore, a large proportion of all the FMF cases in the world live in Turkey (Turkish FMF Study Group 2005).

Hyperimmunoglobulin D/Mevalonate kinase deficiency (HIDS/MKD) is also a rare autoinflammatory disease, the epidemiology of which is largely unknown. A prospective active surveillance study was recently conducted in Germany during a period of 3 years, by the German Paediatric Surveillance Unit for rare pediatric diseases, as discussed above yielding 16 cases from 10 families (Lainka et al 2012). Based on these patients, the prevalence of HIDS/MKD in children less than 16 years of age during the 3 years of observation was estimated at 6.2 (95% CI: 3.5, 10.2) per million in this age group (Lainka et al 2012). The international HIDS/MKD database collected data about patients with suspected and confirmed HIDS/MKD (van der Hilst et al 2008). Established in 1994 by Dutch researchers, this group had collected information by Jan 2007 (submitted online by the patients' physicians) on 244 patients out of whom a total of 126 patients with mutation-positive HIDS/MKD were identified (van der Hilst et al 2008).

Publications with available information on TRAPS epidemiology are extremely scarce. Clinical study groups, mostly from patients attending in- and out-patient rheumatology centers, are active at national and international level in Europe, and have published data to characterize the frequency, clinical signs, and genotypic features of the disease. A review paper reported a prevalence rate of 1 per million in the United Kingdom (Lachmann and Hawkins 2009).

In Germany, a pediatric, prospective, national epidemiological survey was established on periodic fever syndromes, with an active surveillance over three years (Jul-2003 to Jun-2006. The above mentioned study authors identified 23 new cases over a 3-year period, corresponding to a national annual incidence of 5.6 per 10,000,000 person-years (95% CI: 3.6, 8.5). By multiplying the incidence by the duration of the disease in these pediatric patients the authors estimated a prevalence rate of 8.96 (95% CI: 5.76, 13.60) per million children (Lainka et al 2009).

Demographics of the population in the authorized indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

CAPS

Disease symptoms of MWS, NOMID/CINCA, FCAS usually present in infancy and early childhood, and symptoms may be present at birth in the case of CINCA/NOMID (Church et al 2008). Owing to the severity of the disease, neonatal-onset multisystem inflammatory disease (NOMID)/chronic infantile neurologic, cutaneous and articular (CINCA)

syndrome is diagnosed quite early, while in FCAS, the mildest manifestation of CAPS, diagnosis is often delayed significantly (Kuemmerle-Deschner and Haug 2013). Males and females are equally affected. Most of the currently known CAPS patients are White, European and European descendants.

TRAPS, HIDS/MKD and FMF

TRAPS usually start in childhood and is diagnosed apparently more frequently in males. A survey in pediatric hospital wards in Germany identified 23 cases, with a median age of onset of 6 (range 1-16) years. An affected parent was present in 20% of patients (Lainka et al 2009).

More than 60% of the HIDS/MKD patients worldwide are of Dutch or French ancestry, although HIDS/MKD cases have been reported from around the world (Lainka et al 2012).

FMF is prevalent mainly among eastern Mediterranean people, where approximately 90% of patients develop FMF under 20 years of age. In Japan a nationwide survey of FMF was conducted between Jan-2009 and Dec-2009. The estimated total number of Japanese FMF patients was 292 (95% CI 187- 398). The male to female ratio was 1:1.3. The mean age at the time of diagnosis was 28.7 ± 18.5 years, and the mean age at onset of symptoms was 19.6 ±15.3 years (Migita et al 2012).

A recent publication reported data from an international, web-based registry on autoinflammatory diseases (the Eurofever project), which started enrollment in Nov-2009. Data available from 1880 patients with autoinflammatory diseases recruited during the first 21 months of life of the registry (Toplak et al 2012) identified 199 people with TRAPS. The majority of these patients (around 57%) were adults at the time of enrollment (Table 2-1).

Table 2-1 Demographic characteristics of patients enrolled in the Eurofever registry in the first 18 months

Disease	Patient number	M/F	Age at enrollment (years) Median (range)	Children*/ adults at enrollment	Western Europe	Eastern Europe	Eastern Southern Mediterranean	Others
TRAPS	199	101/98	23 (2–77)	85/114	192	4	2	1

* age <18 years.

Risk factors for the disease

CAPS

CAPS belongs to a group of rare hereditary autoinflammatory conditions. The correlations between genotype and phenotype and the potential influence of environmental factors remain poorly understood. CAPS is associated with mutations in the NLRP3 gene that result in over-activation of the inflammasome, increased secretion of IL-1beta and IL-18, and systemic inflammation (Giat and Lider 2014).

TRAPS, HIDS/MKD and FMF

Although the underlying genetic defects and molecular etiology differ across the periodic fever syndromes, the disease mechanism common across these autoinflammatory conditions involves

abnormal activation of the innate immune system, leading to dysregulation of cytokines and excessive inflammation (Ozen and Bilginer 2014).

The main existing treatment options:

CAPS

Many patients are prescribed corticosteroids, which can reduce symptoms when given in high doses, but cannot be used long-term because of side effects. Other treatment options include nonsteroidal anti-inflammatory drugs (NSAIDs) or antihistamines, but these are less adequate in relieving symptoms.

TRAPS, HIDS/MKD and FMF

There are currently no other approved treatments than Ilaris for HIDS/MKD and TRAPS. Treatment with NSAIDs or glucocorticoids can reduce the severity of symptoms but does not affect the frequency of febrile attacks (Hausmann and Dedeoglu 2013). Etanercept, a TNF-α inhibitor, has been shown in observational studies to reduce the frequency and intensity of febrile episodes in HIDS/MKD and TRAPS patients. However, data suggest that many patients fail to respond to etanercept and the level of response attained in some patients is inferior to that observed with IL-1 blockers (Caorsi et al 2012, ter Haar et al 2013, ter Haar and Frenkel 2014).

For patients with FMF, colchicine has shown to be effective in controlling febrile attacks and preventing secondary amyloidosis. However, colchicine is associated with the significant side effects of diarrhea and transient elevation of transaminases (ter Haar and Frenkel 2014) and the rare side effects of liver dysfunction, leukopenia, and neuromyopathy (Ozen and Bilginer 2014). Colchicine doses must be adjusted in patients with renal or liver failure, and other medications can affect the metabolism of colchicine (ter Haar and Frenkel 2014). Thus, approximately 5% of patients are intolerant to colchicine because of side effects. Additionally, 5-10% of FMF patients do not respond to colchicine treatment at all (Ben-Zvi and Livneh 2014). Patients who do not respond to or are intolerant to colchicine have very few, if any, treatment options.

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

CAPS

All the disorders that are recognized under CAPS, i.e. FCAS, MWS, and NOMID can impair daily activities in affected patients, although they vary in severity. Patients with NOMID have a more chronic and severe pattern of symptoms, but patients with FCAS and MWS also experience frequent, intermittent episodes of incapacitation, due to symptoms such as fever, rash, arthralgia, fatigue that can vary in intensity from day to day. Patients try to limit exposure to factors such as cool temperature that can trigger attacks. Patients with CAPS generally have chronically elevated levels of acute-phase proteins, like serum amyloid A, associated with reactive amyloidosis and renal failure, a serious complication of CAPS.

The severity of NOMID is variable, and death may occur in young adulthood in 20% of the patients because of infection, secondary amyloidosis, or cachexia (Dollfus et al 2000).

TRAPS, HIDS/MKD and FMF

Although the inflammatory attacks cause much morbidity and significantly decrease the quality of life (QoL) of patients, the major cause of mortality and most serious complication in patients with TRAPS, HIDS/MKD or FMF is represented by progressive secondary amyloidosis that may develop over several years and can progress to chronic kidney disease with subsequent renal failure. Renal amyloidosis is observed in up to 25-40% of TRAPS patients, 3% of HIDS/MKD patients and up to 60% of untreated FMF patients (van der Hilst et al 2005).

MKD encompasses a continuous spectrum of disease phenotypes with varying levels of severity, from HIDS/MKD (with its phenotype of fever episodes) to a severe disorder known as mevalonic aciduria, which includes severe fever episodes and other complications such as cerebellar ataxia, mental retardation, failure to thrive and frequently early death (Mulders-Manders and Simon 2015).

Important co-morbidities:

Details of co-morbidities and disease complications relevant to CAPS, TRAPS, HIDS/MKD and FMF are presented in Table 2-2.

Table 2-2 Important co-morbidities found in the target population

	Incidence	Prevalence	Mortality	Main co-prescribed medications
Amyloidosis	26% in patients with MWS (Lachmann et al 2006)	In a European cohort, 25% of patients with MWS presented amyloidosis (Glaser and Goldbach-Mansky 2008). A renal amyloidosis was reported in one study in patients with FMF 54 (8.2%) (Balci-Peynircioğlu et al 2015) Systemic amyloidosis is a complication, and amyloid nephropathy is a frequent cause of death in patients with FCU (Shinawi 2013).	Up to 20% of NOMID/CINCA patients died from various complications such as infections, vasculitis, and amyloidosis before reaching childhood (Hashkes and Lovell 1997).	Mainly symptomatic to treat cardiac or renal involvement
Infections	No data available	No data available	No data available	Antimicrobial drugs according to microbe`s vulnerability.
Ophthalmic changes	No data available	83% (in n=26 patients), including optic disc edema and optic atrophy in patients with NOMID (Dollfus et al 2000). Elevated intracranial pressure (NOMID/CINCA) \ nongranulomatous uveitis is seen in 50% of NOMID/CINCA patients. In more than 80% of NOMID/CINCA patients the optic nerve head is affected (Dolfus et al 2000). Retinitis pigmentosa reported in one study in MKD patients (Siemiatkowska et al 2013).	No data available	According to underlying disorder.
Hearing loss	No data available	Progressive sensorineural hearing loss leading to deafness in 22% of patients with NOMID (Dollfus et al 2000) and in patients with MWS (Ahmadi et al 2011).	Not applicable	According to underlying disorder
Renal disease	No data available	Renal disease from AA amyloidosis occurs in 2% of patients with FCAS (Hoffman 2003). Renal amyloidosis is observed in up to 60% of untreated FMF patients, in 25-40% of TRAPS and in	No data available	Mainly symptomatic, dialysis/replacement therapy in end-stage-renal disease.

	Incidence	Prevalence	Mortality	Main co-prescribed medications
		up to 3% of HIDS/MKD patients (van der Hilst et al 2005). 22% of FMF patients reported additional kidney problems: haematuria and/or proteinuria, recurring acute pyelonephritis, tubulointerstitial nephritis and glomerulonephritis (Salehzadeh 2015).		
Cardiopulmonary disease	No data available	20% and 80 % of patients with FMF have pleuritis, 45% of the patients experienced pleural attacks (Salehzadeh 2015). In up to 20-50% of patients with TRAPS recurrent pericarditis observed (Cantarini et al 2009).	No data available	According to underlying disorder
Gastro-intestinal disorder	No data available	Abdominal pain reported (72%), associated with diarrhea (82%) in patients with HIDS (Bader-Meunier et al 2011). Appendectomy 30 (4.6%), cholecystectomy 20 (3.1%) reported in one study in patients with FMF (Balci-Peynircioglu et al 2015).	No data available	Mainly symptomatic, According to underlying
Muscular and skeletal involvement	No data available	Approximately 30% -50% of FMF patients complain of arthritides (Salehzadeh 2015).	No data available	According to underlying disorder
Macrophage activation syndrome (MAS)	No data available	No data available	In French Survey 3 out of 50 HIDS patients, deceased due to MAS secondary to staphylococcal sepsis (Bader-Meunier et al 2011)	According to underlying disorder
Increased IgA	No data available	80% of patients with HIDS present with concomitant increased IgA (Bader-Meunier et al 2011)	No data available	According to underlying disorder

2.2 Indication: Gouty arthritis

Indicated for the symptomatic treatment of adult patients with frequent gouty arthritis attacks (at least three attacks in the previous 12 months) in whom non-steroidal anti-inflammatory drugs (NSAIDs) and colchicine are contraindicated, not tolerated, or do not provide an adequate response and in whom repeated courses of corticosteroids are not appropriate.

Incidence:

The crude incidence of gout in a large UK electronic health records database (The Health Improvement Network [THIN]) was estimated at 268 per 100,000 person-years (95% CI 265-272) among individuals aged 20 years or older. 72.8% of the subjects were male. The incidence of first flare starting one month after the initial diagnosis of gout was 13700 (95% CI 13400-14000) per 100,000 person-years (Rothenbacher et al 2010).

Prevalence:

Gout is the most common cause of inflammatory arthritis in men, with a prevalence of at least 1% of subjects in Western countries (Mikuls et al 2005). Limited data is available for refractory gouty arthritis.

Demographics of the population in the authorized indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

Gout is very uncommon in premenopausal females and males below 30 years of age. In ages younger than 65, men had 4 times higher prevalence than women (4:1), but in the older age groups (> 65), the gender gap narrowed to 1 woman to every 3 men with gout and/or hyperuricemia (3:1 ratio) (Wallace et al 2004).

Various risk factors which predispose to gout are obesity, alcohol intake, hypertension, renal insufficiency, diuretic use, family history of gout and environmental or occupational exposure to lead (Aggarwal et al 2001). The fact that some of these underlying conditions that could impact on treatment are also independent risk factors for flares further contributes to the complexity of prevention and treatment of gout flares.

The main existing treatment options:

In the last two decades, there have been four major international gout guidelines: European League against Rheumatism (EULAR) in 2006, American College of Rheumatology (ACR) in 2012 and 3e Initiative - Multinational Evidence, Exchange and Expertise group in 2014, plus the 2014 British Society of Rheumatology (BSR) guidelines (Khanna and Fitzgerald 2015).

For treatment of acute gout, three guidelines, ACR, BSR and 3e initiative recommend NSAIDs, corticosteroids or oral colchicine to be similarly effective. However, EULAR (Zhang et al 2006) recommended oral colchicine and/or NSAID as first-line agents over corticosteroids for the treatment of acute attacks. When selecting colchicine, all guidelines recommend using low-dose colchicine. A large claims database study identified NSAIDs as the most commonly prescribed drugs (Primatesta et al 2011) in a population of gout patients.

Regarding urate-lowering treatment, since the introduction of febuxostat, with the exception of the ACR, all guidelines recommended allopurinol as first line with febuxostat and/or uricosuric as second line (Khanna and Fitzgerald 2015).

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

The mortality is mainly driven by the close link with underlying comorbid cardiometabolic disorders. Chronic gout may lead to disabling arthritis and is also a risk factor for adverse cardiometabolic disorders such as ischemic heart disease or myocardial infarction (Richette and Bardin 2010).

Important co-morbidities:

Table 2-3 Important co-morbidities found in the target population

Comorbidities	Incidence	Prevalence	Mortality	Main co-prescribed medications
Metabolic syndrome	No data available	More than 50% of patients with gout have cardiometabolic disorders (Rothenbacher et al 2010).	No data available	Treatment of underlying cardiometabolic disorders according to guidelines (Zhang et al 2006).

2.3 Indication: Still's disease (including Adult-Onset Still's disease [AOSD] and Systemic Juvenile Idiopathic Arthritis [SJIA])

Canakinumab is indicated for the treatment of active Still's Disease including AOSD and SJIA in patients aged 2 years and older who have responded inadequately to previous therapy with non-steroidal anti-inflammatory drugs (NSAIDs) and systemic corticosteroids. Canakinumab can be given as monotherapy or in combination with methotrexate.

Incidence:

SJIA is a heterogeneous form of arthritis in childhood which represents 10% to 20% of all juvenile idiopathic arthritis (JIA) in the Caucasian populations of Northern America and Europe (Woo 2006, Weiss and Ilowite 2007). The incidence of JIA varies across countries: it is reported between 1 and 22 per 100,000 person-years (Weiss and Ilowite 2007). The variations can partly be explained by different study designs as well as case definitions used by various studies. Also a north–south gradient seems to exist in disease incidence in Europe (Modesto et al 2010). Information available on SJIA is relatively limited.

Table 2-4 Incidence of juvenile idiopathic arthritis

Country, Author (year)	Study population and study design	Incidence per 100,000 person-years (95% CIs)	Comments
Spain; (Modesto et al 2010)	Children <16years. Multicenter, prospective-retrospective population-based study	JIA: 6.9 (5.8-8.1) SJIA: 0.5 (0.2-0.8)	Incidence higher in females
Norway; (Riise et al 2008)	Children <16 years. Multicenter, population based study	14(10-19)	Incidence higher in females than in males (17 vs. 11)

Country, Author (year)	Study population and study design	Incidence per 100,000 person-years (95% CIs)	Comments
Estonia; (Pruunsild el al 2007a)	Children <16 years. Population based cross-sectional study	Mean annual incidence 21.7 (15.4-26.7)	Incidence higher in females (22.9 vs. 19.3) than in males
France; (Danner et al 2006)	Children <16 years. Retrospective study	3.2 (1.62-5.80)	-
Czech republic; (Hanova et al 2006)	Children <16 years. Population based survey	13 (1-20)	-
EU Nordic countries; (Berntson et al 2003)	Children <16 years. Longitudinal, prospective, population based study	15 (13-17)	-

Estimates of incidence of AOSD ranged between 0.16 and 2.0 per 100,000, with a female predominance reported in most studies (Table 2-5).

Table 2-5 Incidence of adult-onset Still disease

Country; Author (Year)	Study population and Study Design	Incidence rate per 100,000 (95% CI)	Comments
Turkey; (Balci et al 2015)	Patients diagnosed at the Department of Rheumatology of Trakya University Medical Faculty Patients older than 16 years Retrospective, hospital patient records review	Annual incidence Overall: 0.62 Females: 0.95 Males:0.25	Median age: 44.5 (18-74) Females: 76.2% Males: 23.8%
Greece; (Baxevanos et al 2012)	Patients diagnosed at the Internal Medicine Department of the Hatzikosta General Hospital of Ioannina Patients who were 16 years or above Retrospective, hospital based patient records review	Annual incidence: 2.0	Males: 68% Females: 32% Mean age at diagnosis: 33.8 years
Norway; (Evensen and Nossent 2006)	-Patients diagnosed at the University Hospital of Northern Norway - Age – 15 years or more Retrospective hospital based patient records review.	Annual incidence: 0.4 (0.11–0.97).	Mean age at diagnosis: 33.8 (15-77) Males: 80%
Japan; (Wakai et al 1997)	-Patients diagnosed at Internal Medicine departments of general and university hospitals in Japan -Patients aged 16 years or older Retrospective, hospital based patient records review	Annual incidence: Females: 0.34 Males: 0.22	Female: male ratio: 2.1
France; (Magadur-Joly et al 1995)	Patients diagnosed by Internal medicine and Rheumatology practitioners -Patients aged 15 years and 3 months or older -Brittany and Loire regions Retrospective, patient records review	Average Annual Incidence: 0.16	Mean age: 36 years

Prevalence:

The prevalence of JIA varies between 8 to 150 per 100000 children (Weiss and Ilowite 2007), and it was found to be lower in countries like France compared to Spain and Estonia. The national arthritis data workgroup in USA reviewed available national surveys to provide

estimates of arthritis in USA: it estimated that 294,000 children (95% CI 188,000- 400,000) were affected by juvenile arthritis (Helmick et al 2008). Prevalence of SJIA varies from 6% to 20% of all JIA across studies (Danner et al 2006, Woo 2006, Weiss and Ilowite 2007).

Table 2-6 Prevalence of juvenile idiopathic arthritis

Country; (Author year)	Study population and study design	Prevalence per 100,000 (95% CIs)	Comments
Spain; (Modesto et al 2010)	Children <16years. Multicenter, prospective-retrospective population-based study	JIA: 39.7 (36.1-43.7) SJIA: 3.5 (2.5-4.8)	Prevalence higher in girls
France; (Solau-Gervais et al 2010)	Children <16 years. Survey among pediatricians and rheumatologists	15.7	-
Estonia; (Pruunsild et al 2007b)	Children <16 years. Population based cross-sectional study	83.7 (72.4-95.8)	Prevalence higher in girls
France; (Danner et al 2006)	Children <16 years. Retrospective study	19.8 (19.3-20.3). Of the cases, 8.9% had systemic arthritis	-
Czech republic; (Hanova et al 2006)	Children <16 years. Population based survey	140 (117-280)	-

Estimates of prevalence of AOSD ranged between 3.4 per and 6.9 per 100,000, with a substantial female predominance (Table 2-7).

Table 2-7 Prevalence of adult-onset Still's Disease

Country; Author (Year)	Study population and study design	Prevalence per 100,000 (95% CI)	Comments
Turkey; (Balci et al 2015)	- Patients diagnosed at the Department of Rheumatology of Trakya University Medical Faculty - Patients older than 16 years Retrospective, Hospital based patient record review	Overall: 6.77 Females: 10.8 (7.1-13.9) Males: 3.2 (1.2- 5.2)	-Median age: 44.5 (18-74) years -Females-32 (76.2%) Males- 10 (23.8%) -Female to male ratio: 3.2
Japan; (Asanuma et al 2015)	-Patients who were admitted to the hospital - Department of Internal medicine or Rheumatology -Patients aged 16 years or older Retrospective, Hospital based patient records review	Overall prevalence: 3.9	Mean age at onset: 46±19 years Male:female ratio: 1:2.57
Norway; (Evensen and Nossent 2006)	-Patients diagnosed at the University Hospital of Northern Norway -Patients aged above 15 years Retrospective study, hospital based patient record review	Point prevalence In 1990: 3.4 (0.8–9.4) In 2000 : 6.9 (2.7–14.2)	Mean age at diagnosis: 33.8 (15-77) years Males: 80% Females: 20%
Japan; (Wakai et al 1997)	- Patients diagnosed at Internal Medicine departments of general and university hospitals in Japan - Patients aged 16 years or older Retrospective, Hospital based patient records review	Crude prevalence: Males: 0.73 Females:1.47	Age – 16 years or older 16-19: 7 (5.7%) 20-24: 20 Sex ratio (female to male) - 2.1

Demographics of the population in the authorized indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

SJIA has been found to be more frequent among females than in male patients. SJIA is also known as Still's Disease, and when symptoms begin in adulthood, the condition is known as adult onset still's disease.

The actual risk factors for JIA remain poorly understood. JIA is an autoinflammatory disease, in which the immune system attacks and destroys cells and tissues (particularly in the joints) for no apparent reason. The immune system may get provoked by changes in the environment or by errors in the gene, resulting in activation of the innate immune response and with subsequent release of inflammatory cytokines, including increased levels of IL-1 which plays a central role in the diseases.

The main existing treatment options:

NSAIDs and corticosteroids were considered first line treatments for SJIA and disease modifying anti-rheumatic drugs (DMARDs), of which methotrexate is the most common, as second line. However, approved targeted biologic agents which demonstrated robust efficacy and acceptable safety profiles have become recommended first line therapies in appropriate patients. The most recent ACR treatment guidelines recommend anti-IL-1 and anti-IL-6 therapies as first line therapies in SJIA patients with moderate to severe disease activity and active systemic features (Ringold et al 2013). In 2018, anakinra, a biologic agent targeting IL-1, was approved by the EMA as first line therapy for Stills disease including SJIA and AOSD.

Treatment for AOSD is similar, but corticosteroids are preferred as first line treatment in adults. In children, corticosteroid avoidance is preferred because of the risk of corticosteroid-related side effects.

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

The reported mortality rate of patients with JIA diagnosed between 1992 and 2001 followed for up to 9 years was 0.6% in North America (Hashkes et al 2010). Most deaths in JIA are among patients with SJIA. Most deaths in SJIA patients are secondary to Macrophage Activation Syndrome (MAS), infection resulting from immunosuppression, or cardiac complications (Wallace and Levinson 1991, Weiss and Ilowite 2007). MAS is overtly present in around 10% of children with SJIA and some evidence suggests a prevalence of subclinical MAS in another 30-40% of patients (Minoia et al 2015).

AOSD patients can also suffer from MAS and other rare, multisystemic complications (Jamilloux et al 2015, Kadavath and Efthimiou 2015).

Table 2-8 Mortality among JIA patients

Country; Author (year)	Study population and study design	Mortality rate; SMR (95% CIs)	Comments
Indianapolis, USA (Hashkes et al 2010)	Children < 16 years; pediatric rheumatology disease registry	For patients with SJIA the mortality rate over a 7.9 years mean period was 0.6%, with a standardized mortality ratio	-

Country; Author (year)	Study population and study design	Mortality rate; SMR (95% CIs)	Comments
		(SMR) of 1.8 (0.66-3.92) in those followed up for >= 9 years	
Scotland, UK; (Thomas et al 2003)	Children <16 years. Population based cohort	SMR for juvenile chronic arthritis: males 3.39 (1.97-5.46); females 5.09 (3.19-7.75) (average 7 years follow-up)	-

The severity of the disease course is heterogeneous, with 23-30% of patients reported to still have active disease after 10 years; morbidity is high within this group (Woo 2006). Predictors of poor outcome include the presence of systemic features 6 months after onset, thrombocytosis, and the presence of polyarthritis with hip involvement.

Secondary complications (e.g. growth failure, osteoporosis, deformities and loss of function) and amyloidosis are the medical complications of untreated disease, which also entail possible serious developmental consequences and social isolation (Packham and Hall 2002).

The clinical course of AOSD typically follows one of 3 patterns, which affect treatment choices (Kadaveth and Efthimiou 2015). These are:

- a self-limiting or monocyclic course, of mainly systemic symptoms with spontaneous resolution
- an intermittent or polycyclic systemic course, which needs repeated therapy and may have an arthritic component
- a chronic articular course, which is hard to treat, even with combined therapy and can lead to destructive arthritis.

Important co-morbidities:

Table 2-9 Co-morbidity of target population

Comorbidities	Incidence	Prevalence	Mortality	Main co-prescribed medications
Amyloidosis	No data available	In Sweden, 9% had renal amyloidosis among 33 patients with SJIA who were followed for a median duration of 10 years (Svantesson et al 1983). In a study in UK amyloidosis was found among 8.9% of 231 patients with JIA. Among those with SJIA 19.2% had amyloidosis (Packham and Hall 2002).	In a study in Finland, among 24 patients with JIA which included 11 with SJIA, 9 patients died due to JIA after a mean follow up of 15.4 years. Of them 5 died due to amyloidosis (Immonen et al 2008)	Mainly symptomatic to treat cardiac or renal involvement
Ophthalmic changes	In studies across USA, Asia and Scandinavia, incidence of uveitis varied from 0 to 2.9%	In a study in Canada uveitis was found among 13.1% of patients diagnosed with JIA. Only 1% of patients with SJIA had uveitis (Saurenmann et al 2007). In a retrospective study in Sweden 15.7% of patients with JIA had	No data available	According to underlying disorder.

Comorbidities	Incidence	Prevalence	Mortality	Main co-prescribed medications
	(Carvounis et al 2006)	uveitis while 33% of those with SJIA (1/3) had uveitis (Skarin et al 2009).		
Renal disease	No data available	In a study in Finland among 24 patients with JIA which included 11 with SJIA, none had renal insufficiency although 67% were proteinuric (Immonen et al 2008).	No data available	According to underlying disorder.

3 Part II Safety specification Module SII: Non-clinical part of the safety specification

Canakinumab has undergone comprehensive pre-clinical safety testing [CTD 2.4, Non-clinical Overview]. The safety profile of canakinumab (150 mg powder for solution for injection, as a lyophilizate form (LYO) reconstituted with water for injections) has been adequately demonstrated and the pre-clinical data package of canakinumab supports its clinical use. Animals in toxicity studies have shown exposures at least 93-fold (Cavg) in excess of the plasma concentrations achieved in patients, treated with the highest recommended clinical dose of 4 mg/kg (or up to 300 mg) every 4 weeks and 8 mg/kg (or up to 600 mg) every 8 weeks of canakinumab subcutaneously and the results have not shown adverse effects of canakinumab or any specific safety concern for its use in the clinics.

In order to have a more patient friendly presentation, canakinumab 150 mg/1 mL has been developed as a solution ready to use in vial, prefilled syringe and prefilled pen (autoinjector). The excipients used in the canakinumab 150 mg/mL solution for injection in vial, in a prefilled syringe and prefilled pen (autoinjector) are pharmacopoeia compendial excipients commonly and safely used in parenteral products.

The 150 mg powder for solution for injection and the 150 mg/1 mL solution for injection (in a vial) are the pharmaceutical forms currently approved for Ilaris. These market presentations allow weight-base dosing in patients with low body weight. The solutions for injection in pre-filled syringe and in auto-injector are used in clinical trials where fixed dosing regimens are required for exploratory indications.

Table 3-1 Key Safety findings (from non-clinical studies)

Findings in pre-clinical safety studies	Relevance to human usage
Repeat dose toxicity	
Histopathology examination in a 13-week tolerability study of ACZ885 in marmosets (Study No 0470033) revealed a dose-related minimal lymphoid hyperplasia in male animals.	This finding is not considered to be biologically or toxicologically relevant. In a single study in marmosets (13-week subcutaneous toxicity study, Study no. 0470033), histopathology examination revealed a dose-related minimal lymphoid hyperplasia in male animals only which was considered unlikely to be of toxicological or biological significance for the following reasons: there were no changes in immunophenotyping when lymphocyte populations (CD3, CD4, CD8, CD14, CD16, CD20, CD 56) were assessed by flow cytometry (splenic suspensions and blood), the observation was not present in females in that study, and the observation was not present in either male or female animals in any other study. In the 12-week human rheumatoid arthritis (RA) study A2201, 10% of actual enrolled patients were enrolled into a splenic ultrasound sub-study. Sequential scans yielded no abnormal findings. The topic of “Lymphoid organ toxicity” has been deleted from the list of ‘important potential risks' in this RMP.
In the immunotoxicity mouse study with the 01BSUR mouse surrogate, at high doses (50 and 150 mg/kg/ week), thymus weight was increased at the end of the	There were no concurrent macroscopic, microscopic, or functional consequences associated with the increase in thymus weight. The change was reversible

Findings in pre-clinical safety studies	Relevance to human usage
4-week dosing period of the study (Study No. 0670570)	after 4 weeks. The increase in thymus weight was therefore not considered to be toxicologically relevant.
Developmental toxicity	
An embryo-fetal development study of ACZ885 in marmosets (Study No. 0480152) noted slightly lower number of fetuses per litter at 150 mg/kg.	The number of fetuses per litter (and consequently total litter weight) was slightly lower in females given 150 mg/kg of ACZ885 (mean number of pups per litter: Control – 2.5; 15 mg/kg – 2.1; 50 mg/kg – 2.3; 150 mg/kg – 1.9) and appeared to be due to an increased tendency for singlet and twin pregnancies in the 150 mg/kg dose group at the expense of triplet pregnancies Marmosets have greater variation in litter size than other primates and the distribution of litter size observed in this study may simply reflect normal variation in this species (Tardif et al 2003, Windle et al 1999).
In the mouse embryo-fetal development study (Study 0680148), 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 an increased incidence of fetuses with incomplete ossification of frontal bones at the 150 mg/kg/dose.	These findings were considered indicative of a transient delay in ossification. Because delayed ossifications are a common occurrence in rodents (Carney and Kimmel 2007) and because of the absence of any other skeletal changes, these findings were not considered to show teratogenicity.
Carcinogenicity	
In line with ICH S6 no carcinogenicity study was performed. There is also extensive preclinical data to support the role of IL-1β in several distinct steps in carcinogenesis: • Tumor initiation is the first step in carcinogenesis and involves the acquisition of mutations in normal cells that allow a selective growth advantage (Grivennikov et al 2010). Il-1βis thought to create a microenvironment that promotes tumor initiation, as demonstrated by attenuation of chemically induced tumor formation in a mouse strain deficient in IL-1β (Dinarello 2006, Krelin et al 2007). • Tumor promotion is the second step in carcinogenesis and is characterized by the growth of a primary tumor from a transformed cell. This step is mediated in part by tumor associated macrophages (TAM) and cytokines that these TAMs produce, including IL-1β (Lin et al 2007, Grivennikov et al 2010). • The third step in carcinogenesis is angiogenesis, in which blood vessel formation is induced to generate a vascular network for the primary tumor. In this process, IL-1β is thought to play a critical role, as tumors in mice deficient in IL-1β failed to induce vascular endothelial growth factor (VEGF) expression and subsequent tumor angiogenesis (Voronov et al 2003). • The final step in carcinogenesis is metastasis. IL-1β is thought to play an important role in this step as well via the induction of genes critical for invasion and cell adhesion (Elaraj et al 2006). Using a mouse model of lung cancer metastasis, Yano and colleagues demonstrated that tumors genetically	Clinical data from over 10,000 patients in CANTOS conducted over 6 years (with a median treatment duration of 3.47 years, over 68% of patients were treated for ≥ 3 years, and 21,745 years of canakinumab treatment exposure), shows that there is no evidence of an increased risk of malignancy with canakinumab and indicates a positive effect with respect to reduction of lung cancer: • The incidence of malignancy in patients is comparable in patients treated with all 3 doses of canakinumab versus placebo. • There were fewer deaths due to malignancy. • There was a significant reduction in lung cancer incidence and fatal lung cancer incidence at the 300 mg dose with evidence of dose dependency. Overall, CANTOS confirms that there is no evidence of an increased risk for malignancy with canakinumab.

Findings in pre-clinical safety studies	Relevance to human usage
programed to express high levels of IL-1β developed lung metastasis more rapidly than controls, with treatment with an anti-IL-1β antibody inhibited formation of lung metastasis (Yano et al 2003). • Taken together, these results suggest an important role for IL-1β in multiple steps of carcinogenesis and targeting IL-1β may hold promise as an anti-tumor strategy. Based upon the weight of evidence described above and because canakinumab has been on the market since 2009 without any emerging evidence of carcinogenicity, Novartis does not believe that further work with canakinumab (non-human primate specific) or the surrogate antibody (01BSUR) is required to contribute to our understanding of the potential carcinogenic risk to patients treated with canakinumab.	

Conclusions: Safety concerns from non-clinical data

Safety concerns
Important identified risks (confirmed by clinical data)
Infections
Important potential risks (not refuted by clinical data or which are of unknown significance)
Malignancy

4 Part II Safety specification Module SIII Clinical trial exposure

4.1 Part II Module SIII Clinical trial exposure

Overall, 11,320 patients (including M2301/CANTOS and D2310/CAN-COVID patients) were exposed to canakinumab in completed clinical trials including investigator initiated trials. Cumulative patient exposure in completed clinical trials, excluding IITs except for CACZ885P2201T and CACZ885GDE01T, which are integrated IITs, till data lock point (DLP) of the RMP (30-Jun-2021) is 29,204.4 patient-treatment-years (PTYs) (Ilaris-PSUR-01Jul2018to30Jun2021).

Table 4-1 Completed Novartis sponsored global and local studies, and Investigator initiated trials, across all indications

Indication	Study Number (ACZ885 studies)
Healthy Volunteers	A1101/A2106/A2104/A2108/M2101
SJIA	A2203/G2305/G2301/G2301E1/G2306/G1301
CAPS	A2102/D2304/D2306/D2201/D2308/D2307/D2307E1/DCA01$^{\$}$/D2401/DBE02
Gouty Arthritis	A2212/H2251/H2251E1/H2255/H2356/H2356E1/H2356E2/H2357/H2357E1/ H2357E2/H2357E3/H2361/H2361E1/H2358
RA	A2201/A2101/A2204/A2206/A2207/A2211/A2201E1/A2201E2
T2DM	A2213/I2202/I2207
Cardiovascular	I2206/M2301
Other auto-inflammatory diseases	DTR01*/D2204*/ D2203/D2402*
Psoriasis	A2202
COPD	B2204
Wet AMD	F2201
Mild Asthma	B2101
Osteoarthritis	C2201
Dry Eye Syndrome	PJMR0092202
Abdominal aortic aneurysm	X2201
Hereditary Periodic Fevers	N2301/N2301E2
Peripheral artery disease	M2201
Polymyalgia Rheumatica	PJMR0012201
AOSD	GDE01T
COVID19	D2310
Pulmonary sarcoidosis	X2205
Sickle Cell Disease	X2206
Oncology and Hematology studies	CACZ885T2301, CACZ885U2301, CACZ885V2301, CACZ885V2201C, CACZ885V2101, CPDR001C2101, CPDR001X2103, CPDR001J2201, CPDR001X2X01B, CADPT01A12101C, CACZ885TUS03R, CACZ885NTR01, CACZ885NIL01T

*Local Investigational study, $Local CPO study
Data are from completed studies as of cut-off date 30-Jun-2021.

In the tables below, cumulative patient exposure based upon actual exposure data from completed clinical trials for healthy volunteers and the approved indications (periodic fever syndromes, gouty arthritis, and Still's disease) are presented by dose level, duration, age group

and gender and racial group. The exposure tables for the CAPS indication only present exposure for the canakinumab treatment groups as no comparators were included in the CAPS studies.

4.1.1 Healthy volunteers

Table 4-2 Estimated cumulative subject exposure from completed investigational clinical trials by dose level (Healthy volunteers)

Dose level	Completed Studies	
	Subjects	Subject-Time (Years)
Canakinumab	556	95.9
150 mg AI	40	13.2
150 mg SS	40	11.8
<150 mg or 2 mg/kg	21	6.7
150 mg or 2 mg/kg	145	44.2
>150 mg or 2 mg/kg	80	20.0
200 mg of pre-filled syringe in needle safety device or autoinjector compared to two injections (150 and 50 mg)	230 (V2101 Oncology BE HV)	Not applicable as blinded study.
Comparator	63	14.2
Aggripal + Menjugate	26	4.1
Placebo	37	10.1

- Include healthy volunteers as of cut-off date 30-Jun-2021.
- Source: Ilaris PSUR 01Jul2018to30Jun2021-Table 5-3

Table 4-3 Cumulative subject exposure from completed investigational clinical trials by duration (Healthy volunteers)

	≥1 day		≥12 weeks		≥24 weeks		≥36 weeks		≥48 weeks		≥96 weeks		≥144 weeks		≥192 weeks	
Treatment	**n**	**PTY**	**n**	**PTY**	**n**	**PTY**	**n**	**PTY**	**n**	**PTY**	**n**	**PTY**	**n**	**PTY**	**n**	**PTY**
	%	**%**	**%**	**%**	**%**	**%**	**%**	**%**	**%**	**%**	**%**	**%**	**%**	**%**	**%**	**%**
Canakinumab	326	95.9	273	88.9	0	0	0	0	0	0	0	0	0	0	0	0
	100	100	83.7	92.7	0	0	0	0	0	0	0	0	0	0	0	0
Aggripal + Menjugate	26	4.1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	100	100	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Placebo only	37	10.1	27	8.5	0	0	0	0	0	0	0	0	0	0	0	0
	100	100	73.0	84.1	0	0	0	0	0	0	0	0	0	0	0	0

- n=number of subjects in each duration subgroup.
- The denominators used for % calculation are from the ≥1 day column.
- Data is from completed studies as of cut-off date of 30 Jun 2018
- Source: Annex 7 (Ilaris PSUR 01Jul2017to30Jun2018-Appendix 8.1-Table 6).

Table 4-4 Cumulative adult and geriatric subject exposure from completed investigational clinical trials, age group and gender (Healthy volunteers)

		Adult				Elderly				Total	
		18-<65 years		65-<75 years		75-<85 years		≥85 years			
Treatment	Gender	n %	PTY %	n %	PTY %	n %	PTY %	n %	PTY %	n %	PTY %
Canakinumab	Female	145	41.1	0	0	0	0	0	0	145	41.1
		100	100	0	0.0	0	0	0	0	100	100
	Male	181	54.8	0	0	0	0	0	0	181	54.8
		100	100	0	0	0	0	0	0	100	100
	Total	326	95.9	0	0	0	0	0	0	326	95.9
		100	100	0	0	0	0	0	0	100	100
Aggripal + Menjugate	Female	15	2.4	0	0	0	0	0	0	15	2.4
		100	100	0	0	0	0	0	0	100	100
	Male	11	1.7	0	0	0	0	0	0	11	1.7
		100	100	0	0	0	0	0	0	100	100
	Total	26	4.1	0	0	0	0	0	0	26	4.1
		100	100	0	0	0	0	0	0	100	100
Placebo only	Female	10	2.9	0	0	0	0	0	0	10	2.9
		100	100	0	0	0	0	0	0	100	100
	Male	27	7.2	0	0	0	0	0	0	27	7.2
		100	100	0	0	0	0	0	0	100	100
	Total	37	10.1	0	0	0	0	0	0	37	10.1
		100	100	0	0	0	0	0	0	100	100

- n=number of subjects in each age subgroup.
- The denominators used for % calculation are from the Total column.
- Data are from completed studies as of cut-off date 30 Jun 2018.
- Source: Annex 7 (Ilaris PSUR 01Jul2017to30Jun2018-Appendix 8.1-Table 4).

Table 4-5 Cumulative subject exposure from completed investigational clinical trials by racial group (Healthy volunteers)

	Asian		Black		Caucasian		Native American		Pacific islander		Other	
Treatment	n %	PTY %	n %	PTY %	n %	PTY %	n %	PTY %	n %	PTY %	n %	PTY %
Canakinumab	65	20.3	46	12.5	206	60.2	2	0.65	0	0	7	2.1
	19.9	21.2	14.1	13.1	63.2	62.8	0.6	0.7	0	0	2.1	2.2
Aggripal + Menjugate	0	0	0	0	26	4.1	0	0	0	0	0	0
	0	0	0	0	100	100	0	0	0	0	0	0
Placebo only	21	6.5	0	0	15	3.2	0	0	0	0	1	0.33
	56.8	64.5	0	0	40.5	32.2	0	0	0	0	2.7	3.3

- n=number of subjects in each duration subgroup.
- The denominators used for % calculation are from the Total column.
- Data are from completed studies as of cut-off date 30 Jun 2018.
- Source: Annex 7 (Ilaris PSUR 01Jul2017to30Jun2018-Appendix 8.1-Table 5).

4.1.2 Periodic fever syndromes

4.1.2.1 CAPS

Table 4-6 Estimated cumulative subject exposure from completed investigational clinical trials by dose level (CAPS)

Treatment dose level	Completed Studies	
	Subjects	Subject-Time (Years)
Canakinumab	458	1309.3
150 mg or 2 mg/kg	251	693.8
300 mg or 4 mg/kg	110	368.2
450 mg or 6 mg/kg	20	54.1
600 mg or 8 mg/kg	51	139.2
750 mg or 10 mg/kg	4	9.6
Missing	22	44.4

- Data are from completed studies as of cut-off date 30 Jun 2018.
- Source: Annex 7 (Ilaris PSUR 01Jul2017to30Jun2018-Appendix 8.1-Table 2).

Table 4-7 Cumulative subject exposure from completed investigational clinical trials by duration (CAPS)

Treatment	≥1 day		≥12 weeks		≥24 weeks		≥36 weeks		≥48 weeks		≥96 weeks		≥144 weeks		≥192 weeks	
	n %	PTY %	n %	PTY %	n %	PTY %	n %	PTY %	n %	PTY %	n %	PTY %	n %	PTY %	n %	PTY %
Canakinumab	450	1309.3	441	1308.2	426	1302.3	385	1281.3	370	1269.0	294	1169.3	201	958.1	172	866.6
	100	100	98.0	99.9	94.7	99.5	85.6	97.9	82.2	96.9	65.3	89.3	44.7	73.2	38.2	66.2

- n=number of subjects in each duration subgroup.
- The denominators used for % calculations are from the "≥1 day" column.
- Data are from completed studies as of cut-off date 30 Jun 2018.
- Source: Annex 7 (Ilaris PSUR 01Jul2017to30Jun2018-Appendix 8.1-Table 6).

Table 4-8 Cumulative pediatric (0-<12 years of age) and adolescent (12-<18 years of age) subject exposure from completed investigational clinical trials by indication, age group and gender (CAPS)

		<2 years		2-<4 years		4-<6 years		6-<12 years		12-<18 years		Total	
Treatment	Gender	n %	PTY %	n %	PTY %	n %	PTY %	n %	PTY %	n %	PTY %	n %	PTY %
Canakinumab	Female	2	5.9	12	17.1	13	31.9	29	72.7	34	90.1	90	217.7
		2.2	2.7	13.3	7.9	14.4	14.7	32.2	33.4	37.8	41.4	100	100
	Male	5	12.4	10	30.3	6	19.4	27	77.5	35	109.9	83	249.5
		6.0	5.0	12.0	12.1	7.2	7.8	32.5	31.1	42.2	44.1	100	100
	Total	7	18.2	22	47.4	19	51.3	56	150.2	69	200.0	173	467.1
		4.0	3.9	12.7	10.1	11.0	11.0	32.4	32.1	39.9	42.8	100	100

- n=number of subjects in each age subgroup.
- The denominators used for % calculations are from the Total column.
- Data are from completed studies as of cut-off date 30 Jun 2018.
- Source: Annex 7 (Ilaris PSUR 01Jul2017to30Jun2018-Appendix 8.1-Table 3).

Table 4-9 Cumulative adult and geriatric subject exposure from completed investigational clinical trials, age group and gender (CAPS)

		Adult				Elderly				Total	
		18-<65 years		65-<75 years		75-<85 years		≥85 years			
Treatment	Gender	n %	PTY %	n %	PTY %	n %	PTY %	n %	PTY %	n %	PTY %
Canakinumab	Female	145	435.9	8	18.6	2	4.9	0	0	155	459.4
		93.5	94.9	5.2	4.0	1.3	1.1	0	0	100	100
	Male	120	366.3	8	15.1	1	0.5	1	0.92	130	382.8
		92.3	95.7	6.2	3.9	0.8	0.1	0.8	0.2	100	100
	Total	265	802.2	16	33.7	3	5.4	1	0.92	285	842.2
		93.0	95.3	5.6	4.0	1.1	0.6	0.4	0.1	100	100

		Adult				Elderly				Total	
		18-<65 years		65-<75 years		75-<85 years		≥85 years			
Treatment	Gender	n %	PTY %	n %	PTY %	n %	PTY %	n %	PTY %	n %	PTY %

- n=number of subjects in each age subgroup.
- The denominators used for % calculations are from the Total column.
- Data are from completed studies as of cut-off date 30 Jun 2018.
- Source: Annex 7 (Ilaris PSUR 01Jul2017to30Jun2018-Appendix 8.1-Table 4).

Table 4-10 Cumulative subject exposure from completed investigational clinical trials by racial group (CAPS)

Treatment	Asian		Black		Caucasian		Native American		Pacific islander		Other	
	n %	PTY %	n %	PTY %	n %	PTY %	n %	PTY %	n %	PTY %	n %	PTY %
Canakinumab	29	71.1	2	4.8	371	1006.3	1	2.2	0	0	5	14.4
	6.3	5.4	0.4	0.4	81.0	76.9	0.2	0.2	0	0	1.1	1.1

n=number of subjects in each racial subgroup.
The denominators used for % calculations are from the Total column.
Data are from completed studies as of cut-off date 30 Jun 2018.
Source: Annex 7 (Ilaris PSUR 01Jul2017to30Jun2018-Appendix 8.1-Table 5).

4.1.2.1 TRAPS, HIDS/MKD and FMF

Table 4-11 Patient exposure by cohort, Study N2301 Epoch 4

Duration of exposure	TRAPS ACZ885 N=53	HIDS ACZ885 N=66	crFMF ACZ885 N=60
≤ 4 weeks	0 (0.0)	0 (0.0)	1 (1.7)
4≤8 weeks	0 (0.0)	0 (0.0)	0 (0.0)
8≤12 weeks	-	-	1 (1.7)
24≤28 weeks	0 (0.0)	0 (0.0)	0 (0.0)
28≤32 weeks	0 (0.0)	0 (0.0)	0 (0.0)
32≤36 weeks	0 (0.0)	0 (0.0)	0 (0.0)
36≤40 weeks	1 (1.9)	0 (0.0)	0 (0.0)
40≤44 weeks	0 (0.0)	0 (0.0)	0 (0.0)
44≤48 weeks	0 (0.0)	0 (0.0)	0 (0.0)
48≤52 weeks	0 (0.0)	0 (0.0)	0 (0.0)
52≤56 weeks	0 (0.0)	0 (0.0)	0 (0.0)
56≤60 weeks	0 (0.0)	0 (0.0)	0 (0.0)
60≤64 weeks	1 (1.9)	1 (1.5)	0 (0.0)
64≤68 weeks	1 (1.9)	0 (0.0)	2 (3.3)
68≤72 weeks	18 (34.0)	14 (21.2)	9 (15.0)
>72 weeks	32 (60.4)	51 (77.3)	47 (78.3)
Duration of exposure (days)			
n	53	66	60
Mean	504.8	511.1	499.1
SD	39.28	19.75	90.51
Minimum	279.0	436.0	1.0
Median	505.0	507.0	511.5
Maximum	602.0	596.0	575.0

- Percentage (%) is calculated using total count in respective treatment group as the denominator.
- Source: [Study N2301 Table 14.3-1.1c].

4.1.3 Gouty Arthritis

Table 4-12 Estimated cumulative subject exposure from completed investigational clinical trials by dose level (Gouty arthritis)

Treatment dose level	Completed Studies	
	Subjects	Subject-Time (Years)
Canakinumab	**1179**	**987.5**
≤100 mg LYO	234	107.5
Split 150 mg LYO	46	39.7
150 mg LYO	550	345.8
150 mg Pre-filled syringe	415	405.6
≥200 mg LYO	110	89.0
Comparator	**599**	**283.8**
Colchicine	108	47.0
Dexamethasone	3	1.1
Triamcinolone acetonide	488	235.7

- Data are from completed studies as of cut-off date 30 Jun 2018.
- Source: Annex 7 (Ilaris PSUR 01Jul2017to30Jun2018-Appendix 8.1-Table 2].

Table 4-13 Cumulative subject exposure from completed investigational clinical trials by duration (Gouty arthritis)

Treatment	≥1 day		≥12 weeks		≥24 weeks		≥36 weeks		≥48 weeks		≥96 weeks		≥144 weeks		≥192 weeks	
	n %	PTY %	n %	PTY %	n %	PTY %	n %	PTY %	n %	PTY %	n %	PTY %	n %	PTY %	n %	PTY %
Canakinumab (LYO)	940	581.9	750	552.9	552	498.1	420	429.5	314	341.8	17	42.8	8	23.6	0	0
	100	100	79.8	95.0	58.7	85.6	44.7	73.8	33.4	58.7	1.8	7.3	0.9	4.1	0	0
Canakinumab (Pre-filled syringe)	415	405.6	370	399.1	298	378.4	229	338.4	187	304.5	86	188.1	0	0	0	0
	100	100	89.2	98.4	71.8	93.3	55.2	83.5	45.1	75.1	20.7	46.4	0	0	0	0
Colchicine	108	47.0	100	46.1	82	38.7	0	0	0	0	0	0	0	0	0	0
	100	100	92.6	98.2	75.9	82.4	0	0	0	0	0	0	0	0	0	0

Treatment	≥1 day		≥12 weeks		≥24 weeks		≥36 weeks		≥48 weeks		≥96 weeks		≥144 weeks		≥192 weeks	
	n %	PTY %	n %	PTY %	n %	PTY %	n %	PTY %	n %	PTY %	n %	PTY %	n %	PTY %	n %	PTY %
Dexamethasone	3	1.1	3	1.1	0	0	0	0	0	0	0	0	0	0	0	0
	100	100	100	100	0	0	0	0	0	0	0	0	0	0	0	0
Triamcinolone acetonide	488	235.7	372	219.4	191	169.5	118	129.9	84	103.0	0	0	0	0	0	0
	100	100	76.2	93.1	39.1	71.9	24.2	55.1	17.2	43.7	0	0	0	0	0	0

- n=number of subjects in each duration subgroup.
- The denominators used for % calculations are from the "≥1 day" column.
- Data are from completed studies as of cut-off date 30 Jun 2018.
- Source: Annex 7 (Ilaris PSUR 01Jul2017to30Jun2018-Appendix 8.1-Table 6).

Table 4-14 Cumulative adult and geriatric subject exposure from completed investigational clinical trials, age group and gender (Gouty arthritis)

		Adult				Elderly				Total	
		18-<65 years		65-<75 years		75-<85 years		≥85 years			
Treatment	Gender	n %	PTY %	n %	PTY %	n %	PTY %	n %	PTY %	n %	PTY %
Canakinumab (LYO)	Female	42	27.7	18	14.0	6	4.3	0	0	66	46.0
		63.6	60.2	27.3	30.5	9.1	9.3	0	0	100	100
	Male	745	445.7	108	74.2	21	16.1	0	0	874	536.0
		85.2	83.2	12.4	13.8	2.4	3.0	0	0	100	100
	Total	787	473.4	126	88.2	27	20.3	0	0	940	581.9
		83.7	81.3	13.4	15.2	2.9	3.5	0	0	100	100
Canakinumab (Pre-filled syringe)	Female	23	20.4	8	11.1	5	2.4	0	0	36	34.0
		63.9	60.1	22.2	32.8	13.9	7.1	0	0	100	100
	Male	319	311.6	52	52.0	7	7.4	1	0.64	379	371.6
		84.2	83.9	13.7	14.0	1.8	2.0	0.3	0.2	100	100
	Total	342	332.0	60	63.1	12	9.8	1	0.64	415	405.6
		82.4	81.9	14.5	15.6	2.9	2.4	0.2	0.2	100	100
Colchicine	Female	6	2.8	1	0.46	0	0	0	0	7	3.3

Treatment	Gender	Adult				Elderly				Total	
		18-<65 years		65-<75 years		75-<85 years		≥85 years			
		n %	PTY %	n %	PTY %	n %	PTY %	n %	PTY %	n %	PTY %
		85.7	85.9	14.3	14.1	0	0	0	0	100	100
	Male	87	38.1	12	4.9	2	0.69	0	0	101	43.7
		86.1	87.2	11.9	11.2	2.0	1.6	0	0	100	100
	Total	93	40.9	13	5.4	2	0.69	0	0	108	47.0
		86.1	87.1	12.0	11.4	1.9	1.5	0	0	100	100
Dexamethasone	Female	1	0.41	0	0	0	0	0	0	1	0.41
		100	100	0	0	0	0	0	0	100	100
	Male	2	0.67	0	0	0	0	0	0	2	0.67
		100	100	0	0	0	0	0	0	100	100
	Total	3	1.1	0	0	0	0	0	0	3	1.1
		100	100	0.0	0	0	0	0	0	100	100
Triamcinolone acetonide	Female	21	12.5	6	4.2	4	1.6	0	0	31	18.2
		67.7	68.3	19.4	22.8	12.9	8.9	0	0	100	100
	Male	386	177.0	62	34.7	7	4.1	2	1.7	457	217.5
		84.5	81.4	13.6	15.9	1.5	1.9	0.4	0.8	100	100
	Total	407	189.5	68	38.8	11	5.8	2	1.7	488	235.7
		83.4	80.4	13.9	16.5	2.3	2.4	0.4	0.7	100	100

n=number of subjects in each age subgroup.
The denominators used for % calculations are from the Total column.
Data are from completed studies as of cut-off date 30 Jun 2018.
- Source: Annex 7 (Ilaris PSUR 01Jul2017to30Jun2018-Appendix 8.1-Table 4).

Table 4-15 Cumulative subject exposure from completed investigational clinical trials by racial group (Gouty arthritis)

Treatment	Asian		Black		Caucasian		Native American		Pacific islander		Other	
	n %	PTY %	n %	PTY %	n %	PTY %	n %	PTY %	n %	PTY %	n %	PTY %
Canakinumab (LYO)	114	56.2	80	38.0	671	438.4	6	4.0	1	0.46	68	44.9

Treatment	Asian		Black		Caucasian		Native American		Pacific islander		Other	
	n %	PTY %	n %	PTY %	n %	PTY %	n %	PTY %	n %	PTY %	n %	PTY %
	12.1	9.7	8.5	6.5	71.4	75.3	0.6	0.7	0.1	0.1	7.2	7.7
Canakinumab (Pre-filled syringe)	16	12.4	82	62.6	312	328.0	0	0	0	0	5	2.5
	3.9	3.0	19.8	15.4	75.2	80.9	0	0	0	0	1.2	0.6
Colchicine	5	2.2	4	1.6	87	37.6	1	0.47	2	0.93	9	4.2
	4.6	4.7	3.7	3.4	80.6	80.0	0.9	1.0	1.9	2.0	8.3	9.0
Dexamethasone	1	0.41	0	0	2	0.67	0	0	0	0	0	0
	33.3	38.1	0	0	66.7	61.9	0	0	0	0	0	0
Triamcinolone acetonide	77	26.1	56	27.3	336	174.6	1	0.25	0	0	18	7.5
	15.8	11.1	11.5	11.6	68.9	74.1	0.2	0.1	0	0	3.7	3.2

- n=number of subjects in each racial subgroup.
- The denominators used for % calculations are from the Total column.
- Data are from completed studies as of cut-off date 30 Jun 2018.
- Source: Annex 7 (Ilaris PSUR 01Jul2017to30Jun2018-Appendix 8.1-Table 5).

Table 4-16 Number of doses per patient and duration in study by treatment (Safety set) (Gouty arthritis)

Duration in study	ACZ885 150 mg s.c. N=67 n (%)	Triam 40 mg i.m. N=69 n (%)	All Patients N=136 n (%)
1-28 days	1 (1.5)	4 (5.8)	5 (3.7)
29-56 days	2 (3.0)	2 (2.9)	4 (2.9)
57-84 days	18 (26.9)	20 (29.0)	38 (27.9)
≥85 days	46 (68.7)	43 (62.3)	89 (65.4)

- A patient is counted in only one duration range per treatment.
- Source: Study H2358 (Table 14.3-1.1a and Table 14.3-1.2a).

4.1.4 Still's disease (AOSD and SJIA)

Table 4-17 Estimated cumulative subject exposure from completed investigational clinical trials by dose level (SJIA)

Treatment dose level	Completed Studies	
	Subjects	Subject-Time (Years)
Canakinumab	445	1079.5
150 mg or 2 mg/kg q4w	8	38.7
4 mg/kg sc q4w up to a maximum of 300 mg each dose	412	967.5
300 mg or 4 mg/kg	6	33.1
Comparator	41	1.2
Placebo only	41	1.2

Source: Ilaris PSUR 01Jul2018to30Jun2021-Appendix 8.1-Table 2

Table 4-18 Cumulative subject exposure from completed investigational clinical trials by duration (SJIA)

Treatment	≥1 day		≥12 weeks		≥24 weeks		≥36 weeks		≥48 weeks		≥96 weeks		≥144 weeks		≥192 weeks	
	n %	PTY %	n %	PTY %	n %	PTY %	n %	PTY %	n %	PTY %	n %	PTY %	n %	PTY %	n %	PTY %
Canakinumab	445	1079.5	383	1074.4	349	1062.8	332	1053.3	318	1042.4	253	948.5	147	711.3	120	620.3
	100	100	86.1	99.5	78.4	98.4	74.6	97.6	71.5	96.6	56.9	87.9	33.0	65.9	27.0	57.5
Placebo only	41	1.2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	100	100	0	0	0	0	0	0	0	0	0	0	0	0	0	0

- n=number of subjects in each duration subgroup.
- The denominators used for % calculations are from the "≥1 day" column.
- Data are from completed studies as of cut-off date 30 Jun 2021.
- Source: Ilaris PSUR 01Jul2018to30Jun2021-Appendix 8.1-Table 6

Table 4-19 Cumulative pediatric (0-<12 years of age) and adolescent (12-<18 years of age) subject exposure from completed investigational clinical trials, age group and gender (SJIA)

		<2 years		2-<4 years		4-<6 years		6-<12 years		12-<18 years		Total	
Treatment	Gender	n %	PTY %	n %	PTY %	n %	PTY %	n %	PTY %	n %	PTY %	n %	PTY %
Canakinumab	Female	0	0	28	38.8	36	62.5	110	266.7	75	186.8	249	554.8
		0	0	11.2	7.0	14.5	11.3	44.2	48.1	30.1	33.7	100	100
	Male	0	0	20	32.0	32	53.8	75	207.2	50	149.7	177	442.7
		0	0	11.3	7.2	18.1	12.2	42.4	46.8	28.2	33.8	100	100
	Total	0	0	48	70.8	68	116.3	185	473.9	125	336.5	426	997.4
		0	0	11.3	7.1	16.0	11.7	43.4	47.5	29.3	33.7	100	100
Placebo only	Female	0	0	0	0	5	0.1	13	0.5	5	0.1	23	0.7
		0	0	0	0	21.7	15.2	56.5	73.0	21.7	11.9	100	100
	Male	0	0	0	0	2	0.1	9	0.3	5	0.1	16	0.4
		0	0	0.0	0.0	12.5	18.7	56.3	66.0	31.3	15.3	100	100
	Total	0	0	0	0	7	0.2	22	0.8	10	0.2	39	1.1
		0	0	0.0	0.0	17.9	16.4	56.4	70.5	25.6	13.1	100	100

- n=number of subjects in each age subgroup.
- The denominators used for % calculations are from the Total column.
- Data are from completed studies as of cut-off date 30 Jun 2021.
- Source: Ilaris PSUR 01Jul2018to30Jun2021-Appendix 8.1-Table 3

Table 4-20 Cumulative adult and geriatric subject exposure from completed investigational clinical trials, age group and gender (SJIA)

Treatment	Gender	Adult				Elderly				Total	
		18-<65 years		65-<75 years		75-<85 years		≥85 years			
		n %	PTY %	n %	PTY %	n %	PTY %	n %	PTY %	n %	PTY %
Canakinumab	Female	9	33.9	0	0	0	0	0	0	9	33.9
		100	100	0	0	0	0	0	0	100	100
	Male	10	48.1	0	0	0	0	0	0	10	48.1
		100	100	0	0	0	0	0	0	100	100
	Total	19	82.1	0	0	0	0	0	0	19	82.1
		100	100	0	0	0	0	0	0	100	100
Placebo only	Female	0	0	0	0	0	0	0	0	0	0
		0	0	0	0	0	0	0	0	0	0
	Male	2	0.05	0	0	0	0	0	0	2	0.05
		100	100	0	0	0	0	0	0	100	100
	Total	2	0.05	0	0	0	0	0	0	2	0.05
		100	100	0	0	0	0	0	0	100	100

- n=number of subjects in each age subgroup.
- The denominators used for % calculations are from the Total column.
- Data are from completed studies as of cut-off date 30 Jun 2021.
- Source: Ilaris PSUR 01Jul2018to30Jun2021-Appendix 8.1-Table 4

Table 4-21 Cumulative subject exposure from completed investigational clinical trials by racial group (SJIA)

Treatment	Asian		Black		Caucasian		Native American		Pacific islander		Other	
	n %	PTY %	n %	PTY %	n %	PTY %	n %	PTY %	n %	PTY %	n %	PTY %
Canakinumab	27	60.8	12	20.1	374	935.7	1	0.3	0	0	30	60.8
	6.1	5.6	2.7	1.9	84.0	86.7	0.2	0	0	0	6.7	5.6
Placebo only	1	0.01	0	0	37	1.0	0	0	0	0	3	0.17
	2.4	0.7	0	0	90.2	85.4	0	0	0	0	7.3	13.9

Treatment	Asian		Black		Caucasian		Native American		Pacific islander		Other	
	n %	PTY %	n %	PTY %	n %	PTY %	n %	PTY %	n %	PTY %	n %	PTY %

- n=number of subjects in each racial subgroup.
- The denominators used for % calculations are from the Total column.
- Data are from completed studies as of cut-off date 30 Jun 2021.
- Source: Ilaris PSUR 01Jul2018to30Jun2021-Appendix 8.1-Table 5.

5 Part II Safety specification Module SIV: Populations not studied in clinical trials

5.1 Part II SIV.1 Exclusion criteria in pivotal clinical studies within the development program

The exclusion criteria in the pivotal clinical studies represent patient populations who would not routinely initiate an immunomodulatory biologic agent (Table 5-1). These are patients who have an acute active infection, a known chronic infection, high risk to be immunocompromised or with a known hypersensitivity to canakinumab or any of the excipients.

Table 5-1 Important exclusion criteria in pivotal studies in the development program

Criteria	Reason for exclusion	Missing information?	Rationale for not including as missing information
Pregnant or nursing women	Due to potential safety concerns in pregnant/lactating women, enrollment in clinical studies is not generally permitted.	No	The MAH has provided an interval and cumulative review of the available information on pregnant and lactating women. The amount of information gathered over the years suggests that the population may no longer be considered missing information.
Prior malignancy other than basal cell skin carcinoma	Exclusion of patients with a history of malignancy is standard. Inclusion of these patients could make it difficult to ascertain whether malignancy events reported were related to canakinumab.	No	There is no clinical evidence that inhibiting IL-1β with canakinumab increases the risk of malignancy. Canakinumab is currently under evaluation as a therapeutic option in oncology.
Impaired renal function	Inclusion of this condition would interfere with an appropriate assessment of safety.	No	Since canakinumab is a human IgG immunoglobulin with large molecular size (~150 kDa), little intact immunoglobulin can be filtered by the kidney, hence little antibody is expected to be excreted in the urine (Wang et al 2008; Chakraborty et al 2012). However, the topic of long term effect on renal function was monitored closely and based on the adequate data from long term completed studies and post-marketing data, the safety concern is no longer considered as missing information.
Hypersensitivity to the active substance or to any of the excipients	This avoids the risk of potential anaphylactic reaction in patients with known hypersensitivity to study drug/excipients	No	Consistent with standard of care

Criteria	Reason for exclusion	Missing information?	Rationale for not including as missing information
Active, severe infections	This is a precautionary measure to reduce risk of worsening an active infection	No	Consistent with routine clinical practice for immunomodulatory biologic therapies
Known hepatic disorder (e.g. cirrhosis, hepatitis B and hepatitis C or ALT/AST levels >3x ULN or total bilirubin >2x ULN).	These are precautionary measures to prevent a possible exacerbation of known hepatitis infection. Inclusion of this condition would interfere with an appropriate assessment of safety.	No	Main elimination route for canakinumab is intracellular catabolism and no hepatic metabolism of canakinumab is anticipated. The pharmacokinetic properties of canakinumab are not expected to be affected by hepatic impairment.
History of tuberculosis (e.g. positive purified protein derivative skin test without negative chest x-ray)	This was a precautionary measure to prevent a possible exacerbation of tuberculosis infection	No	Consistent with routine clinical practice for immunomodulatory biologic therapies
History of being immunocompromised (e.g., positive Human Immunodeficiency Virus at screening)	This was a precautionary measure to prevent a possible infection, including an opportunistic infection in immunocompromised patient (Smolen et al 2010).	No	Consistent with routine clinical practice for immunomodulatory biologic therapies
Recent live vaccinations, or plans for live vaccination during the trial	This was a precautionary measure to prevent potential secondary transmission of an infection by live vaccines (van Assen et al 2011)	No	Consistent with routine clinical practice for immunomodulatory biologic therapies
Ongoing treatment with immunosuppressive agents, radiation therapy, or chemotherapy	This was a precautionary measure to prevent a synergistic effect on immunosuppression resulting in increased incidence of infections that was observed with co-administration of TNF-inhibitors and IL-1 blocking agents (Smolen et al 2010)	No	Consistent with routine clinical practice for immunomodulatory biologic therapies

5.2 Part II Module SIV.2. Limitations to detect adverse reactions in clinical trial development programs

Table 5-2 Limitations of ADR detection common to clinical trial development programs

Ability to detect adverse reactions	Limitation of trial program	Discussion of implications for target population
Which are rare	Approximately, 4152 subjects have received canakinumab treatment in completed Novartis-sponsored investigational clinical trials in approved indications cumulatively.	As per the “rule of threes” if no events of a particular type are observed in a study of X individuals, then one can be 95% certain that the event occurs no more often than 3/X. According to this guide, any event which is not observed in this

Ability to detect adverse reactions	Limitation of trial program	Discussion of implications for target population
		population occurs, with 95% certainty, less often than 1 in 1384 exposed individuals, or has an incidence of 0.07%.
Due to prolonged exposure	The duration of key pivotal studies in the approved indications was generally less than 2 years in gouty arthritis, less than 3 years in CAPS whilst a quarter of patients were treated for at least 192 weeks (nearly 4 years) in SJIA. However, the scope to assess the impact on patient safety to prolonged canakinumab exposure beyond 2 years in a clinical trial setting is inherently limited. There is no evidence of bone marrow, renal, neoplastic, pulmonary or hepatic organ system impact due to prolonged exposure in the clinical trial program.	Data collected to date do not suggest an adverse effect of long-term exposure. This includes information from the completed extension studies H2356E2 and H2357E3 in gouty arthritis and the completed study G2301E1 in SJIA, the CAPS Registry (D2401), and in the recently completed study G2403*.
Due to cumulative effects	The duration of key pivotal studies in the approved indications was generally less than 2 years in gouty arthritis, less than 3 years in CAPS whilst a quarter of patients were treated for at least 192 weeks (nearly 4 years) in SJIA. In CAPS patients, the expected accumulation ratio was 1.3-fold following 6 months of subcutaneous administration of 150 mg canakinumab every 8 weeks. After repeated administration of 4 mg/kg every 4 weeks the accumulation ratio of canakinumab was 1.6 fold in SJIA patients. Steady state was reached after 110 days. In the gouty arthritis population, the expected accumulation ratio was 1.1-fold following subcutaneous administration of 150 mg canakinumab every 12 weeks.	Data collected to date do not suggest an adverse effect due to cumulative effects.
Which have a long latency	Due to the well-known inherent limitations of clinical trial development programs, adverse drug reactions with a long latency period are unlikely to be detected.	Long latency adverse drug reactions are defined as ADRs which occur six months or more after initial exposure (Fletcher and Griffin 1991). Based on the review of the safety profile for patients with more than six months of exposure there is no evidence for canakinumab induced long latency adverse drug reactions.

*Since submission of RMP version 9.0, it has been agreed that the SJIA Registry will change from being based on the EU Pharmachild registry (Study ACZ885G2401 [G2401]) to being based on the US and Canada CARRA registry (Study ACZ885G2403 [G2403]).

5.3 Part II Module SIV.3. Limitations in respect to populations typically underrepresented in clinical trial development programs

Table 5-3 Exposure of special populations included or not in clinical trial development programs

Special population	Exposure
Children	There has been extensive paediatric experience with canakinumab. Canakinumab is indicated for the treatment of CAPS, TRAPS, HIDS/MKD and FMF in adults and children aged 2 years and older. The safety and efficacy of canakinumab in CAPS, TRAPS, HIDS/MKD and FMF patients under 2 years of age have not been established. Limited data on CAPS and HIDS/MKD patients under 2 years are available. Gouty arthritis is not prevalent in children and canakinumab is indicated only in adults. Canakinumab is indicated for the treatment of active Still's disease in patients aged 2 years and older.
Elderly	In CAPS trials, only 8 elderly (aged ≥ 65 years) patients were treated with canakinumab. There was only 1 TRAPS patient aged ≥65 years, and none elderly patient with FMF and HIDS/MKD was treated with canakinumab. In gouty arthritis trials, 217 elderly (aged ≥ 65 years) patients were treated with canakinumab (lyophilized powder + pre-filled syringes). Still's disease: In SJIA trials, there were no patients in the age group of ≥ 65 years; some young adults (aged up to 20 years at study entry) were included. There have been no Novartis-sponsored clinical trials in AOSD.
Pregnant and nursing women	Of the 135 pregnancies reported cumulatively (maternal and paternal exposure), the pregnancy outcome was reported in 75 cases and was unknown in 60 cases; 47 cases reported normal healthy newborn and in the review of the remaining 28 cases with either abortion or adverse event in the newborn did not show any evidence of causal association with canakinumab. There were no safety concerns identified from any of the pregnancies reported cumulatively (Ilaris PSUR 01Jul2018to30Jun2021). During the reporting interval, a conference abstract discussing concentrations of canakinumab in breastmilk and sera of infant (1 patient) was identified during routine literature screening. While concentrations of canakinumab were identified in the milk, there was no detectable canakinumab in the serum of the infant. Breast feeding was not recommended during ILARIS therapy. No special actions have been taken or are being proposed. All pregnancies will be followed up for complete information using standard Novartis procedures. This will continue to be monitored as part of the pharmacovigilance plan.
Patients with relevant comorbidities	
Patients with hepatic impairment	No studies in hepatic-impaired patients have been conducted with canakinumab as it is known that the majority of IgG elimination occurs via intracellular catabolism, following fluid-phase or receptor-mediated endocytosis (Wang et al 2008). Any future safety data on the use of canakinumab in patients with hepatic insufficiency will continue to be collected during routine pharmacovigilance activities.
Patients with renal impairment	Four patients with moderate to end-stage renal insufficiency were administered canakinumab in study (ACZ885A2102). The apparent clearance values (CL/F) in these patients ranged from 0.196 to 0.246 L/day after a 150 mg s.c. dose. These values were similar to the mean adult CL/F value of 0.228 L/day, suggesting lack of any significant effect of renal impairment on canakinumab PK. Since canakinumab is a human IgG immunoglobulin with large molecular size (~150 kDa), little intact immunoglobulin can be filtered by the kidney, hence little antibody is expected to be excreted in the urine (Wang et al 2008; Chakraborty et al 2012).

	As renal impairment is a common co-morbidity in gouty arthritis patients, creatinine clearance was explored as a potential factor influencing canakinumab PK. The differences in clearance values in mildly or moderately renal-impaired patients and patients with normal renal function were well within the estimated inter-subject variability in clearance across the entire population of subjects in which canakinumab was investigated. Therefore, the difference was considered not clinically relevant and no dose adjustment is necessary for patients with renal impairment. Any future safety data on the use of canakinumab in patients with renal impairment will continue to be collected during routine pharmacovigilance activities.
Patients with other relevant co-morbidity	Patients with other specific co-morbidity were not studied in dedicated trials in the approved indications.
Patients with a disease severity different from the inclusion criteria in the clinical trial population	The current approved indications for CAPS and SJIA reflect the populations studied in the clinical trials. For AOSD, Novartis has not conducted any clinical trials, and approval of the indication is based on literature review and similar efficacy across all SJIA age subgroups. For gouty arthritis, the approved indication is for patients with severe disease and there is no data supporting use in patients with less severe disease. In the SJIA studies, patients were required to have fever as part of the active-disease definition. Data on patients with less severe disease even without fever being a prominent symptom was collected.
Population with relevant different ethnic origin	The majority of the patients treated within the CAPS and SJIA trials were Caucasian. There were a substantial number of Asian patients (n=13, 25%) with NOMID in the CAPS population, which can be attributed to study D2308, conducted in Japan. The majority of the patients treated within the TRAPS, HIDS/MKD and FMF trial (N2301) were Caucasian (TRAPS 90.9%, HIDS/MKD 91.9%, and FMF 87.1%). A Study G1301 (interim analysis) in Japanese SJIA patients (N=19) showed similar efficacy and safety as in the overall population included in pivotal studies. A study (A1101) in Japanese healthy volunteers (HV) employed 6-cohort, single ascending dose design. A total of 48 Japanese healthy male subjects were enrolled in the study. In each cohort, eight subjects were randomly assigned to the active drug (six subjects) or placebo (two subjects). In the pooled gouty arthritis dataset, each treatment group, consisted mainly of Caucasians (66.7 – 80.6%). Races other than Caucasians were represented unevenly across the treatment groups (e.g. Blacks 3.7 – 19.8%, other races 0-33.3%).
Subpopulations carrying relevant genetic polymorphisms	Genetic polymorphisms have not been assessed in clinical trials in CAPS, gouty arthritis or SJIA patients.

6 Part II Safety specification Module SV: Post-authorization experience

6.1 Part II Module SV.1. Post-authorization exposure

6.1.1 Part II Module SV.1.1 Method used to calculate exposure

The estimate of patient exposure is calculated based on worldwide sales volume in number of vials sold during each PSUR reporting interval and the average dose administered per patient each year. Data by indication are not available in the post-marketing setting.

The recommended starting dose of canakinumab for CAPS patients is 150 mg or 2 mg/kg administered every 8 weeks. Up titration to higher doses can be used. Although the dose varies with body weight, usually a single 150 mg vial is used on each occasion. Therefore, it was estimated that a patient would use 6.5 vials in a year, whatever their body weight. In TRAPS, HIDS/MKD and FMF, 150 mg or 2 mg/kg body weight dose is given every four weeks. If a satisfactory clinical response has not been achieved 7 days after treatment start, a second dose of Ilaris at 150 mg or 2 mg/kg can be considered. If a full treatment response is subsequently achieved, the intensified dosing regimen of 300 mg (or 4 mg/kg for patients weighing ≤ 40 kg) every 4 weeks should be maintained. In SJIA, the dose is higher and is given every 4 weeks, such that SJIA patients will use 13-26 vials per year. In gouty arthritis, one vial is used per attack, no more frequently than every 12 weeks, i.e. a maximum of 4 vials per year.

The estimated exposure is based on 6.5 vials per patient per year and is likely to over or under estimate actual exposure.

6.1.2 Part II Module SV.1.2. Exposure

The cumulative patient exposure since the IBD of the product is estimated to be approximately 59707 PTY (Ilaris-PSUR-01Jul2018to30Jun2021).

The estimated cumulative exposure from marketing experience by region is Table 6-1. Exposure data by indication, age, gender and dose is not available. Canakinumab is always administered subcutaneously, so exposure by route of administration is not presented.

The estimated cumulative exposure numbers from marketing experience by regions are presented in the table below.

Table 6-1 Exposure by region

Region	Exposure (PTY)
EU including EEA	19667
CCI	CCI
CCI	CCI
ROW	16085
Total	59707
CCI	

Source: Ilaris PSUR 01Jul2018to30Jun2021-Table 5-4.

7 Part II Safety specification Module SVI: Additional EU requirements for the safety specification

7.1 Potential for misuse for illegal purposes

There is no reason to suspect any pharmacological action that could result in drug abuse. Furthermore, no such reports were received during clinical trials and therefore no risk minimization activities are proposed.

8 Part II Safety specification Module SVII: Identified and potential risks

8.1 Part II Module SVII.1. Identification of safety concerns in the initial RMP submission

This section is not applicable as this RMP is not an initial submission. The current version is RMP version 14.0.

8.2 Part II Module SVII.2: New safety concerns and reclassification with a submission of an updated RMP

Infections and Opportunistic infections important identified risks are merged into "Infections (including opportunistic infections)" risk for better clarity in presenting analyses of this risk.

Canakinumab – immunosuppressants combination therapy toxicity risk is upgraded from important potential risk to important identified risk (applicable to all indications) as cases of infections reported with concomitant immunosuppressive medication were proportionally more likely to be serious, including opportunistic, life-threatening or fatal.

Pharmacodynamic interactions is removed as an important potential risk as no cases have been received reporting suspected pharmacodynamic interaction with other immunosuppressive therapies leading to infections. The nature of this risk is also reflected in the Important potential risk of Canakinumab – immunosuppressants combination therapy toxicity, which is more objectively evaluated using ATC code search of concomitant medication rather than a MedDRA search of interactions reported as AEs.

Interactions with drugs eliminated by CYP450 enzymes is removed as an important potential risk as there were 4 cases reported cumulatively, and of these 2 are CYP450 enzyme substrates, and none are considered to have a narrow therapeutic index.

Pregnancy and nursing women is removed as missing information as the MAH has provided an interval and cumulative review of the available information on pregnant and lactating women. The amount of information gathered over the years suggests that the population may no longer be considered missing information.

During the current reporting interval, two signals were ongoing (DRESS and Pulmonary complications) and two were closed (Anaphylactic reaction and Suicidal ideation). A review of data concerning DRESS indicated a potential association between this reaction and the use of IL-1 inhibitors as a class effect. DRESS was added as an important potential risk in the RMP and PSUR and the SmpC and PL have been updated accordingly.

Above updates are endorsed by PRAC (EMEA/H/C/PSUSA/00000526/202106, 10-Feb-2022).

DRESS

DRESS is added as a new important potential risk endorsed by PRAC (EMEA/H/C/PSUSA/00000526/202106, 10-Feb-2022) based on the available evidence from Eudravigilance, literature and cumulative review of cases indicating a potential association between the use of IL-1 inhibitors (class effect) and DRESS, as well as the uncertainties, rarity

and severity of DRESS including potentially fatal outcomes, predominantly in the pediatric population with SJIA.

8.3 Part II Module SVII.3: Details of important identified risks, important potential risks and missing information

An evaluation of information relevant to important identified and important potential risks, and missing information (Table 8-1) was based on the pooled analysis of studies in respective indications. In addition, results from completed studies (D2401, N2301, H2358 and G2306) that were not part of the pool are presented separately for each risks for an indication. A brief overview of these studies are presented below.

Study ACZ885D2401 (D2401, in CAPS): β-Confident - Clinical Outcomes and Safety: A registry Study of Ilaris® (canakinumab) Patients: An open-label, long-term, prospective, observational study to monitor the safety and effectiveness of Ilaris® in CAPS patients. A total of 288 patients from 12 countries in Europe and the US were enrolled. The study was completed on 03-Jun-2016 and was published on 17-Jun-2016.

Study ACZ885N2301 (N2301, in TRAPS, HIDS, or FMF): A randomized, double-blind, placebo controlled study of canakinumab in patients with Hereditary Periodic Fevers (TRAPS, HIDS, or crFMF), with subsequent randomized withdrawal/dosing frequency reduction and open-label long-term (112 week) treatment epochs. The study was completed on 04-Jul-2017 and the CSR was published on 15-Nov-2017. Number of patients: 193.

- The first treatment epoch, Epoch 2, was a 16-week randomized, double-blind, placebo controlled, epoch to assess the efficacy and safety of canakinumab at a starting dose of 150 mg q4w (or 2 mg/kg for patients weighing ≤ 40 kg), with up-titration to 300 mg q4w (or 4 mg/kg for patients weighing ≤ 40 kg) in 150 mg q4w non-responders.
- Epoch 3 was a 24-week randomized withdrawal epoch that assessed whether canakinumab responder from Epoch 2 could maintain clinical efficacy on extended dosing intervals of 150 mg or 300 mg q8w; patients who did not maintain a clinical response on a q8w regimen were permitted to up-titrate to 150 mg or 300 mg q4w regimens, respectively.
- Finally, Epoch 4 was a 72-week, open-label epoch, assessing the long-term maintenance of efficacy and long-term safety in patients at dose regimens of 150 mg q8w, 300 mg q8w, 150 mg q4w, or 300 mg q4w.

Study ACZ885H2358 (H2358, in gouty arthritis): A randomized, double-blind, double-dummy, active controlled study of canakinumab vs. triamcinolone on the treatment and prevention of gout flares in patients with frequent flares, for whom NSAIDs and/or colchicine are contraindicated, not tolerated or ineffective. The study was completed on 19-May-2015 and the CSR was published on 13-Oct-2016. A total of 136 patients were randomized to treatment, 67 to canakinumab 150 mg s.c. and 69 to triamcinolone acetonide 40 mg i.m.

Study ACZ885G2306 (G2306, in SJIA patients): Pediatric efficacy and safety with first-line use of canakinumab; an open-label canakinumab dose reduction or dose interval prolongation efficacy and safety study in patients with SJIA. The study was completed on 25-Sep-2017 and the CSR was published on 11-Jun-2018. A total of 182 patients (Cohort 1: 84 and Cohort 2: 98) entered the study.

Table 8-1 Summary of safety concerns addressed in this section

Important identified risks	Infections (including opportunistic infections)
	Drug induced liver injury (DILI, hepatic transaminase and bilirubin elevations) (for Still's disease)
	Canakinumab – immunosuppressants combination therapy toxicity
Important potential risks	Malignancy
	Drug induced liver injury (DILI, hepatic transaminase and bilirubin elevations) (for periodic fever syndromes and gouty arthritis)
	Macrophage activation syndrome (for Still's disease)
	Interactions with vaccines
	Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
Missing information	Effects on growth (for periodic fever syndromes and Still's disease)

8.3.1 Part II Module SVII.3.1. Presentation of important identified risks and important potential risks

8.3.1.1 Important identified risk: Infections (including opportunistic infections)

8.3.1.1.1 Periodic fever syndromes

CAPS

Infections

In the CAPS pooled dataset, the most frequently reported AEs in CAPS patients were in the SOC of "Infections and Infestations", in particular the PT Nasopharyngitis. "Infections and infestations" were the SOC with the most frequently reported suspected events, 19% of CAPS population [Meta-analysis CSR Table 14.3.1-1.7].

The final analysis results from Study D2307 which was completed subsequent to the pooled analysis were consistent with the CAPS pooled data set for the risk of infections and did not alter the safety profile of canakinumab with longer exposure.

In Study D2401, there were 52 serious infections in 38 (13.3%) patients in the Registry population (IR: 5.17 events per 100-PTY, 95% CI: 3.86-6.55) [Study D2401 Table 10-10]. Thirty-two (13.2%) CAPS patients reported 43 serious infections (IR: 4.85 events per 100-PTY, 95% CI 3.51-6.54) [Study D2401-Table 10-9]. The most common serious infections in CAPS patients were pneumonia (5 events), urinary tract infection (4 events), bronchitis (3 events), and tonsillitis (3 events). All other serious infections occurred only once or twice.

Opportunistic infections

In the pooled CAPS population and from Studies D2307 and D2401, a review of the AEs identified as potential opportunistic infections by the broad search used did not confirm that any of these events were true opportunistic infections.

TRAPS, HIDS/MKD and FMF

Infections

In Study N2301, infections were the most commonly reported type of AE for each of the three disease cohorts over the 112-week treatment period (Epochs 2-4) (85.2% in crFMF, 91.5% in HIDS/MKD and 88.5% in TRAPS patients, respectively). The majority of the infection AEs were non-serious and of mild to moderate severity. Most represented an infection of the respiratory tract (21.3% in crFMF cohort (0.06 /100 patient-days), 31% in HIDS cohort (0.06 /100 patient-days) and 26.2% in TRAPS cohort (0.11/100 patient-days)). Additionally, no evidence for a dose effect and incidence for infection AEs during the trial was apparent. The incidence of infection SAEs was similar for crFMF (13.1%), and HIDS/MKD (19.7%) cohorts which were both higher relative to the TRAPS (3.3%) cohort (Ilaris PSUR 01Jul2017to30Jun2018).

Overall, the infection profile observed in the study N2301 was consistent with that of the CAPS pooled dataset.

Opportunistic infections

One HIDS/MKD patient receiving canakinumab 300 mg q4w with a SAE of herpes virus infection was adjudicated by the Infections Adjudication Committee (IAC) as an opportunistic infection. The SAE was reported as mild severity by the investigator who considered the infection to be related to study treatment. The patient continued in the trial with no change to the canakinumab dose and completely recovered from the infection (Ilaris PSUR 01Jul2017to30Jun2018).

8.3.1.1.2 Gouty arthritis

Infections

In the gouty arthritis pooled dataset, "Infections and infestations" was the most frequently affected SOC in the canakinumab groups (19.9%) with no observed dose-effect. The most common infections reported across the canakinumab groups were nasopharyngitis, upper respiratory tract infections, urinary tract infections and bronchitis. Most of the infection AEs were mild to moderate in severity in all treatment groups.

The final analysis results from Studies H2357E3 and H2361E1 which were completed subsequent to the pooled analysis were consistent with the gouty arthritis pooled data set for the risk of infections and did not alter the safety profile of canakinumab with longer exposure.

Similarly, in Study H2358, the infections events were consistent with the pooled dataset and did not alter the safety profile of canakinumab.

Opportunistic infections

Review of the AEs identified as potential opportunistic infections using a broad search did not confirm that any of these events were true opportunistic infections. The final analysis results from Studies H2357E3 and H2361E1 which were completed subsequent to the pooled analysis were consistent with the gouty arthritis pooled data set for the risk of potential opportunistic infections and did not alter the safety profile of canakinumab with longer exposure.

Similarly, in Study H2358, there were no incidence of true opportunistic infections reported by the investigator and therefore the safety profile of canakinumab remains unaltered.

8.3.1.1.3 Still's disease (AOSD and SJIA)

Infections

In the SJIA pooled population, the SOC most commonly affected by AEs was "Infections and infestations" (75% patients). Infection SAEs affected 51 patients (15.7%) in total. Infection AEs were predominantly mild or moderate; severe infection AEs were reported for 22 patients (6.8%). The most common infections were nasopharyngitis, upper respiratory tract infection, rhinitis, gastroenteritis and pharyngitis. In Study G2306 Part I, frequently reported PTs under the identified risks, 'infections and infestations' were: nasopharyngitis, upper respiratory tract infection, rhinitis and pharyngitis. The incidence of infections was 70.6% in Cohort 1 and 75.5% in Cohort 2. SAEs reported were: pneumonia and viral infection AEs (2 events each in Cohort 2); gastroenteritis (1 event each in Cohort 1 and Cohort 2); appendicitis, atypical pneumonia and respiratory tract infection (1 event each in Cohort 1); bronchitis, infectious mononucleosis, otitis media and otitis media acute (1 event each in Cohort 2) (ACZ885G EU label update SCS Table 2-7). However, none of these SAEs led to study drug discontinuation and all events resolved with or without concomitant treatment [Study G2306-Listing 16.2.7-1.1]. In Part II, an overall incidence of 86.8% in the dose reduction group and 78.4% in the dose interval prolongation group for 'infections and infestations' was noted.

The incidence of SAEs was low and only 2 SAEs (influenza and otitis media were reported in the dose reduction group (2 mg/kg q4w) [Study G2306-Table 12-13]. Study treatment was interrupted in the patient with influenza and the event resolved without concomitant treatment [ACZ885G EU label update SCS Appendix 1-Table ADAR002-1.2]. The patient with otitis media was treated with concomitant medications and resolved with sequela.

The overall infection profile observed in G2306 study, is consistent with that observed in the approved indications without any impact on the benefit risk profile of canakinumab.

Opportunistic infections

Review of the AEs identified as potential opportunistic infections using a broad search in the SJIA pooled population did not confirm that any of these events were true opportunistic infections.

In Study G2306, there were no infections AEs that were adjudicated as opportunistic infections by the infection adjudication committee in Part I or Part II of the study.

Following receipt of a single well-documented case report of atypical mycobacterial infection and subsequent death due to sepsis in Study DDE03T, the review presented in PSUR 9 (01-Jul-2013–31-Dec-2013) concluded that an increased risk of opportunistic infections such as serious /systemic fungal infection, herpes zoster or atypical mycobacterial infection could not be excluded. The EU SmPC was amended, and opportunistic infections was changed to be an important identified risk in the RMP. It is not considered to be an indication-specific risk.

Table 8-2 Important identified risk: Infection (including opportunistic infections): Other details

Infection	Details
Potential mechanisms	IL-1 is a pro-inflammatory cytokine secreted by macrophages and dendritic cells. It enhances the immune response (activation and proliferation of T and B cells upon antigen stimulation), the inflammatory process and haematopoiesis. Inhibiting IL-1

Infection	Details
	could therefore have an effect on the immune response against bacteria and other infectious agents. However, IL-1β does not play a central role in host protection against acute Mycobacterium infections and in containing latent infections, unlike other pro-inflammatory cytokines such as TNF-α. Therefore, IL-1β blockade is not expected to increase the risk of TB infections. In prior studies, patients treated with IL-1 inhibitors or IL-1 receptor antagonists have not shown an increased risk of developing TB or other opportunistic infections.
Evidence sources and strength of evidence	Given the biologic plausibility and the well-characterized risk of infections in the marketed indications, infections are not unexpected. In CANTOS, the large double-blind phase III study in the prevention of recurrent cardiovascular events, serious infections were reported slightly more frequently in canakinumab treated patients compared to placebo. The rate of confirmed opportunistic infections in CANTOS, including TB, was very low and comparable across the treatment groups, including placebo. Most of the cases of non-tuberculous opportunistic infection were confounded and all cases of confirmed TB occurred in patients in TB-endemic areas. There were no cases of reactivation of TB.
Characterization of the risk	For CAPS: Of the 146 (75.3%) patients reporting infections in the CAPS pooled dataset, 13 (6.7%) were considered to be serious. In the pooled CAPS population, review of the AEs identified as potential opportunistic infections using broad search criteria did not confirm that any of these events were true opportunistic infections. For TRAPS, HIDS/MKD and FMF: Overall, the infection profile observed in the N2301 study was consistent with that of the CAPS pooled dataset. One HIDS/MKD patient receiving canakinumab 300 mg q4w with a SAE of herpes virus infection was adjudicated by the IAC as an opportunistic infection. The SAE was reported as mild severity by the investigator who considered the infection to be related to study treatment. For Gouty Arthritis: In the gouty arthritis pooled dataset, 193 patients (18.6%) in the canakinumab treatment groups reported infection AEs; 16 patients (1.5%) reported infection SAEs. Review of the AEs identified as potential opportunistic infections using a broad search did not confirm that any of these events were true opportunistic infections. For Still's disease: In the SJIA pooled population, the SOC most commonly affected by AEs was "Infections and infestations" (71.1% of patients). Infection SAEs affected 30 patients (14.9%) in total, but no specific infection SAE affected more than 2% of patients. Review of the AEs identified as potential opportunistic infections using a broad search did not confirm that any of these events were true opportunistic infections.
Risk factors and risk groups	In CANTOS, the pattern of Infection AEs and SAEs in the different subgroups based on age, sex, race, ethnicity, region, time since index MI, BMI, medical history of gout, co-existing T2DM and baseline hsCRP level was generally consistent with that observed for the overall population. Subgroups generally considered at higher risk for infections (the elderly and diabetic patients) had an increased incidence of infections in CANTOS compared with patients in subgroups considered to be at lower risk but with a pattern of between-treatment differences that was comparable to that observed in the overall population. There was no evidence of increased incidence of infection with canakinumab in the elderly. However, cellulitis and infectious pneumonia were more frequent in patients with diabetes and asthma/COPD, respectively, than in patients without these conditions. Immunocompromised patients are at risk of developing opportunistic infections. Therefore, patients taking immunosuppressant medication are at risk and patients in geographic areas with high endemic tuberculosis are at increased risk of TB.
Preventability	Caution should be exercised when administering canakinumab to patients with infections, a history of recurring infections or underlying conditions which may predispose them to infections. Patients with an active infection should not be started on canakinumab. If a patient develops a serious infection, the patient should be

Infection	Details
	monitored and canakinumab should not be re-administered until the infection resolves. Vigilance towards reactivation of tuberculosis is warranted as IL-1β plays a protective role in the defense. As there is some evidence of false positive PPD testing for tuberculosis in patients receiving canakinumab, 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. Since CANTOS excluded patients with latent or active TB unless anti-TB therapy had been initiated or completed at the time of randomization, patients at high risk (e.g. from geographic areas with high endemic tuberculosis) should be screened for active or latent tuberculosis infection prior to receiving treatment with canakinumab. A contraindication (for active, severe infections) is included in the EU SmPC section 4.3 (Contraindications) and a warning is included in the EU SmPC section 4.4 (Special warnings and precautions for use). The package leaflet (PL) also includes appropriate wording to alert the patient.
Impact on the benefit-risk balance of the product	Although treatment with canakinumab did not have a large effect on the reporting rate of infections overall, the increased risk of infections is consistent with the mechanism of action and imbalances were seen for serious and fatal infections (with a difference of approximately 1 death per 1,000 patient years for 150 mg compared to placebo). The incidence of opportunistic infections in the CANTOS study was very low, with most patients who developed these infections having risk factors such as diabetes or being in a geographic area with high endemic tuberculosis, with no marked imbalance for the treatment arms. This risk can be well managed through appropriate product labelling. The benefits of sustained efficacy (compared to placebo) outweigh the well characterized and manageable risk of Infections.
Public health impact	The majority of the reported infections were not severe and neutrophils remained within the normal range. As such, the impact on public health is considered to be low as the characteristics of these infections seem to be comparable to infections in non-treated patients. Although the majority of the reported infections were not severe, in rare cases they could have an impact on public health if not managed as per the label, given that some infections could be potentially fatal.

8.3.1.2 Important identified risk: Drug induced liver injury (DILI, hepatic transaminases and bilirubin elevations) (for Still's disease)

8.3.1.2.1 Still's disease (SJIA and AOSD)

In the SJIA pooled population, the most frequent liver function laboratory abnormalities were elevations of serum transaminases above the upper limit of normal (ULN); such elevations occurred in 38% of patients for ALT and 34% of patients for AST. For most SJIA patients the elevations remained ≤3x ULN. For ALT, values >3x ULN were reported in 9.0% of patients, with higher values in fewer patients; a similar pattern was observed for AST. The majority of these abnormalities were mild and transient, and there were no cases that were indicative of drug-induced liver toxicity or Hy's law cases. The rate of transaminase elevations did not increase with exposure to canakinumab. In some cases the elevated values occurred close to or in association with infections, SJIA flares or MAS [ACZ885G SCS Appendix 1-Listing 2.24], and AST and ALT abnormalities were more common in patients with oral steroid use at baseline than in those without steroid use [ACZ885G SCS Appendix 1-Table 3.3-2a11].In the SJIA population the most common hepatic AEs were ALT increased (5.9%), AST increased (3.7%) and hepatic enzyme increased (3.7%). The single patient with an AE preferred term of 'hepatic failure' (the event did not meet the criteria for an SAE) had transaminase elevations (ALT 107 U/L, AST 131 U/L) 3 days after an AE of mild gastroenteritis [ACZ885G SCS Appendix 1-

Listing 2.24]. The total bilirubin level was within the normal range at the time of the AE and at all subsequent visits. Isolated transaminase elevations were reported for this patient subsequently in the study, but values were within the normal range at the last visit and the patient continued into the extension.

In Study G2306 Part I, the incidence of potential drug-induced liver injury events in Cohort 1 and Cohort 2 was 16.2% and 11.2%, respectively, with elevated liver enzymes being the most commonly reported event and most of the AEs were of mild and moderate severity. MTX-induced hepatotoxicity (drug-induced liver injury (PT)) was reported in 2 patients as a non-serious AE and no action was taken with the study drug; both events resolved [Study G2306-Listing 16.2.7-1.1]. None of the liver enzyme elevations met the criteria for Hy's Law nor were reported as SAEs [Study G2306-Listing 16.2.7-1.1] and [Study G2306-Section 12.4.3].

In Part II, the incidence of potential drug-induced liver injury events in the dose reduction and dose prolongation arms was 5.3% and 2.7%, respectively. Liver enzyme elevation, hepatomegaly and hypofibrinogenaemia were reported as 1 event each in 3 patients and none of these events were considered to be related to the study drug.

Overall, there were no new safety concerns identified and therefore the benefit risk profile remains unaltered.

Table 8-3 Important identified risk: Drug induced liver injury (DILI, hepatic transaminases and bilirubin elevations) (for Still's disease): Other details

Drug induced liver injury (DILI, hepatic transaminases and bilirubin elevations)	Details
Potential mechanisms	Unknown. For bilirubin elevations: Displacement from carrier proteins (reduced with anti-inflammatory effect)
Evidence source and strength of evidence	Current evidence is based on a clinical data, literature, and post marketing experience.
Characterization of the risk:	Cumulatively, 151 cases (22 CT, 75 PMS, 49 SR and 5 Lit; 139 HCP and 12 non-HCP) of DILI (Ilaris PSUR 01Jul2018to30Jun2021). In Study G2306 in SJIA, none of the liver enzyme elevations met the criteria for Hy's law nor were reported as SAEs (Ilaris PSUR 01Jul2017to30Jun2018).
Risk factors and risk groups	Unknown.
Preventability	Unknown
Impact on the benefit-risk balance of the product	The new information received in the review period of (Ilaris PSUR 01Jul2018to30Jun2021) does not change the benefit-risk profile of canakinumab.
Public health impact	Low

8.3.1.3 Important identified risk: Canakinumab – immunosuppressants combination therapy toxicity

The identified risk is of increased infections if patients are treated simultaneously with one or more immunosuppressant. The EU SmPC includes a Warning about concomitant use of IL-1 blockers with TNF inhibitors. There were no reports of combination therapy toxicity in patients

with periodic fever syndromes (CAPS, TRAPS, HIDS/MKD and FMF) and Still's disease in clinical trials.

Table 8-4 Important identified risk: Canakinumab – immunosuppressants combination therapy toxicity: Other details

Canakinumab – immunosuppressants combination therapy toxicity	Details
Potential mechanisms	Canakinumab binds to and neutralizes the activity of human IL-1β, a pro-inflammatory cytokine. Hence, any other biologic drugs targeting the immune system (pertaining to immunosuppressant's ATC code L04) may lead to a synergistic immune suppression.
Evidence source(s) and strength of evidence	Current evidence is based on literature, clinical trial and post marketing experience.
Characterization of the risk:	Cumulatively to 30-Jun-2021, in comparison to all infection cases and to all infection cases which do not contain a concomitant immunosuppressant retrieved by the search, once filtered for the same indications of PFS and Still's disease (and including cases with unreported/unknown indication), the infections that were reported in patients taking concomitant immunosuppressive medication were proportionally more likely to be serious (176/288; 61.1%) including opportunistic (23/288; 8.0%), life-threatening (12/288; 4.2%) or fatal (10/288; 3.5%) than in the population not on concomitant immunosuppressants (920/2460; 37.4%), (50/2460; 2.0%), (29/2460; 1.2%) and (34/2460; 1.4%) respectively. In addition, although the cases containing ATC codes L04AA, AB, and AX accounted for approximately one tenth of all cases cumulatively, these cases accounted for a third of all SAEs of opportunistic and life-threatening infections, and a quarter of all fatal infections.
Risk factors and risk groups	Concomitant treatment with one or more biologics or immunosuppressant drugs along with canakinumab increases the risk to infection.
Preventability	The prescribing information alert physicians to exercise caution when administering Ilaris to patients with underlying conditions which may predispose them to infections and warns of the concomitant administration of other anti IL-1 therapies and antiTNF agents.
Impact on the benefit-risk balance of the product	The new information received in the review period of Ilaris PSUR 01Jul2018to30Jun2021 does not change the benefit-risk profile of canakinumab.
Public health impact	Low

Note: ATC code L04AA: selective immunosuppressants, AB: TNF-α inhibitors; AX: other immunosuppressants

8.3.1.4 Important potential risk: Malignancy

8.3.1.4.1 Periodic fever syndromes

CAPS

There have been no reports of malignancy in the CAPS pooled dataset clinical trial patients.

The final analysis result from Study D2307 which was completed subsequent to the pooled analysis did not show any incidence of malignancies and therefore the safety profile of canakinumab with longer exposure remains unaltered.

In Study D2401, there were 14 events of malignant and benign neoplasms among 11 CAPS patients (4.5%), 8 events of which were considered serious by the Investigator. Non-benign neoplasms were reported for 5 CAPS patients, all of which were adults and/or elderly. In 4 of these patients, the malignancy was reported as an SAE: 3 events of rectal cancer were reported in one 76 year old MWS patient who had a fatal outcome, one event of adenocarcinoma of the left axillary lymph node was reported in a 44 year old FCAS patient, one event of gastrointestinal neoplasm was reported in a 45 year old MWS patient and one event of prostate cancer was reported in a 72 year old MWS patient [D2401 SCS-Section 2.1.5.2]. Narratives are provided for these patients in [Study D2401-Section 14.3.3]. One patient had basal cell carcinoma that was not reported as an SAE [Study D2401-Listing 16.2.7-1.1].

TRAPS, HIDS/MKD and FMF

No malignancy cases were reported in any of the 3 disease cohorts (crFMF, HIDS/MKD and TRAPS) in Study N2301.

8.3.1.4.2 Gouty arthritis

In the gouty arthritis pooled dataset, malignancy AEs explored using the ‘Malignant or unspecified tumours (SMQ) identified 3 malignancies (0.3%) across the canakinumab treatment groups; the events were Adenocarcinoma of colon (1), Prostate cancer (1), and Squamous cell carcinoma (1). All reported malignancies across the canakinumab treatment groups were serious.

The final analysis results from Studies H2357E3 and H2361E1 which were completed subsequent to the pooled analysis showed 3 malignancy cases in each studies. None of these malignancies were suspected to be related to study drug by the investigators and all were adjudicated as malignancies usually seen in this population by the independent Malignancy Adjudication Committee. Therefore, the overall safety profile of canakinumab with longer exposure remained unaltered.

In Study H2358, there no reports of malignancy and the safety profile of canakinumab remained unaltered.

8.3.1.4.3 Still’s disease (AOSD and SJIA)

Adverse events from Malignant or unspecified tumours (SMQ) were reported for 2 (0.6%) patients and including SAEs of anaplastic large cell lymphoma T- and null-cell types (PT) and

splenic neoplasm malignancy unspecified (PT). There were no cases of malignancy reported in Study G2306.

Table 8-5 Important potential risk: Malignancy: Other details

Malignancy	Details
Potential mechanisms	Immunosuppression could potentially lead to an increase in the risk for malignancies. However, canakinumab is not a broad-spectrum immunosuppressant that severely impairs tumor surveillance or anti-tumor immune mechanisms.
Evidence source(s) and strength of evidence	A hypothetical risk which is based on potential mechanistic plausibility, although the growing body of evidence suggests that IL-1β has a more likely role in tumor promotion rather than in antitumor immunity. No evidence supporting this risk was observed in CANTOS but rather a lower incidence of reported overall malignancy events and lung cancer events in particular were observed in this large double-blind phase 3 study.
Characterization of the risk:	Cumulatively, 710 cases (651 CT, 34 PMS, 24 SR and 1 Lit; 698 HCP and 12 non-HCP) of malignancy. Of these 710 cases, 103 cases were retrieved during the current reporting interval. No changes to the safety profile concerning the risk of malignancy were identified (Ilaris PSUR 01Jul2018to30Jun2021).
Risk factors and risk groups	In a JIA cohort in PD malignancies were identified. The incidence was found to be 0.46 cases per 1000 person years. Patients with SJIA were at increased risk of lymphoproliferative malignancies and overall cancers as well.
Preventability	Unknown
Impact on the benefit-risk balance of the product	None.
Public health impact	No impact on public health as untreated individuals are not affected.

8.3.1.5 Important potential risk: Drug induced liver injury (DILI, hepatic transaminases and bilirubin elevations) (for periodic fever syndromes and gouty arthritis)

This risk is assessed using both laboratory data and AE reports.

8.3.1.5.1 Periodic fever syndromes

CAPS

In the CAPS pooled dataset, no patient had concomitantly raised bilirubin and ALT or AST levels (no Hy's law cases)., but two patients (both in the MWS group) had ALT levels greater than 10xULN. The first patient PD experienced the elevations for a single visit only (Day 457,) and at the subsequent visit values were within normal ranges [Meta-analysis CSR-Listing 14.3.4-1.1]. The second patient PD concomitantly had an AST level 8 times the ULN. This patient had elevated ALT (greater than 5x ULN) and AST (greater than 3x ULN) levels at baseline. Values gradually decreased from Day 78 to Day 298, and for the last 795 days of assessments, the patient's ALT and AST levels were within normal ranges.

Hepatic transaminase elevation AEs were reported for 8 patients (4.1%) in the CAPS population, with no elevations in the FCAS phenotype group. Liver function test abnormal and transaminases increased were reported by 3 and 2 patients, respectively. No patients experienced bilirubin elevation AEs. Hepatic transaminases elevation AEs were of mild to

moderate severity. One patient in the 600 mg or 8 mg/kg dose group had a liver enzyme elevation AE (elevated alkaline phosphatase level which was asymptomatic and not suspected of being study drug related). There were no liver enzyme elevation AEs in patients aged 2-3 years [Meta-analysis CSR-Listing 14.3.2-2.5].

The final analysis result from Study D2307 which was completed subsequent to the pooled analysis was consistent with results of the CAPS pooled data set for the risk of DILI and did not alter the safety profile of canakinumab with longer exposure.

In Study D2401, there were 5 patients with elevated liver enzymes reported among all registry patients, 4 of which were CAPS patients. Elevated liver enzymes and/or bilirubin were likely due to underlying hepatobiliary conditions such as cholestasis (n=1 patient), cholelithiasis (n=3 patients) and hepatic steatosis (n=1 patient). None of the events were suspected to be related to Ilaris by the Investigator [Study D2401-Section 10.5.6].

TRAPS, HIDS/MKD and FMF

In Study N2301, 6.2% of the patients reported hepatic AEs. Most of the AEs were mild to moderate intensity and 2 patients (1%) had SAEs.

Drug-induced liver injury (DILI) was assessed by adverse events reported during the treatment periods (epochs 2-4) in all 3 disease cohorts of crFMF, HIDS/MKD and TRAPS. Additionally, none of the liver enzyme elevations met the criteria for Hy's Law nor were reported as SAEs for any disease cohort during the trial. Overall, there were no new safety concerns regarding DILI identified.

8.3.1.5.2 Gouty arthritis

In the gouty arthritis pooled dataset, hepatic transaminases elevations were higher in the canakinumab treatment groups compared to triamcinolone and colchicine (Table 8-6). In the canakinumab ≤100 mg group in patient PD ALT and AST ≥10x ULN abnormalities were noted on Day 178, 25 weeks after the patient received canakinumab; bilirubin and ALP were normal and GGT was >4x ULN at this time. In another patient [H2251-PD in the canakinumab ≤100 mg group, bilirubin ≥2x ULN and AST >3x ULN abnormalities were noted on Day 176, 25 weeks after the patient received canakinumab; ALT and ALP were >ULN and GGT was >4x ULN at this time. Similar abnormalities were also found at screening in this patient. This patient's LFTs on Day 176 met the laboratory criteria for Hy's law (i.e. ALT or AST >3x ULN and total bilirubin >2x ULN and ALP <2x ULN). However, this patient presented with similar laboratory abnormalities at screening [Study H2251-Listing 16.2.8-1.2]. There were no other cases of transaminases of > 3x ULN combined with bilirubin of >2x ULN (Hy's Law).

The frequency of hepatic transaminase elevations reported as AEs in the canakinumab groups are shown in Table 8-6. The majority of the AEs were mild in severity.

Table 8-6 Important potential risk: Drug induced liver injury (DILI, hepatic transaminases and bilirubin elevations) (Clinical trial data: Gouty arthritis pooled dataset)

	ACZ885 ≤100 mg N=278 n (%)	ACZ885 Split 150 mg N=53 n (%)	ACZ885 150 mg (LYO) N=407 n (%)	ACZ885 150 mg (Pre-filled syringe) N=301 n (%)	ACZ885 ≥200 mg N=107 n (%)	All ACZ885 N=1037	Triam N=419 n (%)	Colch N=108 n (%)
ALP Total	273	53	401	299	106	1024	413	108
>1.5x ULN	0	0	0	0	0	0	4 (1.0)	1 (0.9)
ALT Total	273	53	401	299	106	1024	413	108
≥ 3 x ULN	7 (2.6)	1 (1.9)	6 (1.5)	7 (2.3)	5 (4.7)	26 (2.6)	9 (2.2)	2 (1.9)
≥ 5 x ULN	3 (1.1)	0	0	2 (0.7)	1 (0.9)	6 (0.6)	1 (0.2)	0
≥ 10 x ULN	1 (0.4)	0	0	0	0	1 (0.1)	0	0
≥ 20 x ULN	0	0	0	0	0	0	0	0
AST Total	273	53	401	299	106	1024	413	108
≥ 3 x ULN	5 (1.8)	1 (1.9)	3 (0.7)	4 (1.3)	2 (1.9)	14 (1.4)	7 (1.7)	1 (0.9)
≥ 5 x ULN	1 (0.4)	1 (1.9)	0	1 (0.3)	0	3 (0.3)	2 (0.5)	0
≥ 10 x ULN	1 (0.4)	0	0	1 (0.3)	0	2 (0.2)	1 (0.2)	0
≥ 20 x ULN	0	0	0	0	0	0	0	0
Total Bilirubin (Total)	273	53	401	299	106	1024	413	108
> ULN	22 (8.1)	4 (7.5)	31 (7.7)	20 (6.7)	3 (2.8)	73 (7.2)	32 (7.7)	6 (5.6)
≥ 1.5 x ULN	4 (1.5)	0	4 (1.0)	6 (2.0)	0	13 (1.3)	3 (0.7)	0
≥ 2 x ULN	1 (0.4)	0	2 (0.5)	1 (0.3)	1 (0.9)	4 (0.4)	0	0
≥1.5 x ULN and ALT and/or AST ≥3 x UL	1 (0.4)	0	1 (0.2)	0	0	2 (0.2)	0	0
≥2 x ULN and ALT and/or AST ≥3 x ULN	1 (0.4)	0	0	0	0	1 (0.1)	0	0
Hepatic transaminase elevation AEs (Total)	12 (4.3)	1 (1.9)	23 (5.7)	12 (4.0)	5 (4.7)	45 (4.3)	19 (4.5)	3 (2.8)
Cholestasis and jaundice of hepatic origin (SMQ)	0	0	1 (0.2)	0	0	1 (0.1)	0	0

	ACZ885 ≤100 mg N=278 n (%)	**ACZ885 Split 150 mg N=53 n (%)**	**ACZ885 150 mg (LYO) N=407 n (%)**	**ACZ885 150 mg (Pre-filled syringe) N=301 n (%)**	**ACZ885 ≥200 mg N=107 n (%)**	**All ACZ885 N=1037**	**Triam N=419 n (%)**	**Colch N=108 n (%)**
Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (SMQ)	1 (0.4)	0	2 (0.5)	1 (0.3)	0	4 (0.4)	3 (0.7)	0
Hepatitis, non-infectious (SMQ)	1 (0.4)	0	1 (0.2)	0	0	2 (0.2)	0	0
Liver related investigations, signs and symptoms (SMQ)	11 (4.0)	1 (1.9)	20 (4.9)	10 (3.3)	5 (4.7)	39 (3.8)	14 (3.3)	3 (2.8)
Liver related coagulation and bleeding disturbances (SMQ)	0	0	0	1 (0.3)	0	1 (0.1)	1 (0.2)	0
Maximum severity								
Mild	8 (2.9)	1 (1.9)	18 (4.4)	10 (3.3)	4 (3.7)	35 (3.4)	12 (2.9)	0
Moderate	3 (1.1)	0	5 (1.2)	2 (0.7)	0	8 (0.8)	6 (1.4)	2 (1.9)
Severe	0	0	0	0	0	0	1 (0.2)	0
Asymptomatic	1 (0.4)	0	0	0	1 (0.9)	2 (0.2)	0	1 (0.9)
Serious	0	0	0	0	0	0	0	0

- N=Total number of patients in a treatment group, n = Number of patients meeting the criterion (i.e. who are abnormal)/who experienced an AE, Total = number of patients with evaluable data and the denominator for the percentage calculation.
- A patient with multiple occurrences of AE severity under one treatment is counted only once.
- Pooled data are based on studies H2251, H2255, H2356, H2357, H2356E1, H2357E1, H2356E2, H2357E2 and H2361.
- Source: Annex 7 (RMP Table 5.2, Table 5.3).

The final analysis results from Studies H2357E3 and H2361E1 which were completed subsequent to the pooled analysis were consistent with the gouty arthritis pooled data set for the risk of DILI and did not alter the safety profile of canakinumab with longer exposure.

Similarly, in Study H2358, overall the incidence of the liver function abnormalities were consistent with the pooled dataset and did not alter the safety profile of canakinumab.

Table 8-7 Important potential risk: Drug induced liver injury (DILI, hepatic transaminases and bilirubin elevations) (for periodic fever syndromes and gouty arthritis): Other details

Drug induced liver injury (DILI, hepatic transaminases and bilirubin elevations	Details
Potential mechanisms	Unknown For bilirubin elevations: Displacement from carrier proteins (reduced with anti-inflammatory effect)
Evidence source and strength of evidence	Current evidence is based on a clinical data, literature and post marketing experience.
Characterization of the risk:	Cumulatively, 212 cases (68 CT, 101 PMS, 39 SR and 4 Lit; 192 HCP and 20 non-HCP) of DILI (Ilaris PSUR 01Jul2018to30Jun2021). In a 112 week Study N2301 in periodic fever syndromes, none of the liver enzyme elevations met the criteria for Hy's law nor were reported as SAEs.
Risk factors and risk groups	Unknown.
Preventability	Unknown.
Impact on the benefit-risk balance of the product	The new information received in the review period of Ilaris PSUR 01Jul2018to30Jun2021 does not change the benefit-risk profile of canakinumab.
Public health impact	Low

8.3.1.6 Important potential risk: Macrophage activation syndrome (for Still's disease)

8.3.1.6.1 Still's disease (SJIA and AOSD)

MAS is a well-known serious complication observed in patients with SJIA and AOSD. Although the epidemiology of MAS in Still's disease is not well studied, approximately 7-17% of patients develop full blown MAS, while mild 'subclinical' MAS may be seen in as many as one third of patients with active systemic disease. MAS is a life-threatening condition and the reported mortality rate can be as high as 20-30 % (Sawhney et al 2001; Stephan et al 2001; Arlet et al 2006). Multiple triggers have been identified, namely flares of Still's disease itself and infections. Accordingly, MAS episodes may not be an adverse effect of drug treatment and treatments to control the underlying Still's disease may need to be increased in the setting of an MAS event. The EU SmPC includes a suitable Warning about MAS.

Overall, in the SJIA pooled population, MAS events were reported by 26 patients (8%,) and AEs reported as histiocytosis haematophagic (PT) in 23 patients (7.1%), including two (1 canakinumab and 1 placebo patient) with a fatal outcome. Of the remaining patients, 13 discontinued treatment, 9 had fully recovered and 1 was reported as improving at the time of study discontinuation [ACZ885G SCS-Table 2-22].

Table 8-8 Important potential risk: Macrophage activation syndrome (for Still's disease) (Clinical trial data: SJIA pooled population)

	Any ACZ885 N=324 n (%)
Macrophage activation syndrome	26 (8.0)
Histiocytosis haematophagic (PT)	23 (7.1)
Maximum severity	
Mild	0
Moderate	6 (1.9)
Severe	20 (6.2)
Asymptomatic	0
Serious	25 (7.7)

- N=Total number of patients in a treatment group, n = Number of patients who experienced an AE.
- A patient with multiple occurrences of AE severity under one treatment is counted only once.
- SJIA Studies A2203, G2305, G2301, G2301E1.
- Source: Annex 7 (RMP Table 3.2, Table 3.3).

Additionally, MAS events have been reported outside the clinical development program and are reviewed in each PSUR.

In Study G2306 Part I, macrophage activation syndrome was reported only in Cohort 2 (3 patients, 3.1%) as SAEs and 1 event led to study discontinuation. All SAEs were resolved by the end of the study [ACZ885G EU label update SCS Section 2.1.5.2.3].

In Part I, a total of 20 potential MAS cases (AEs and/or qualifying non-MAS AEs/lab abnormalities) were identified for adjudication by the MAS adjudication committee, 4 in Cohort 1 and 16 in Cohort 2 [Study G2306-Table 14.3.1-2.1a]. One patient presented with 2 potential MAS cases approximately 9 months apart. The first case was based on laboratory changes adjudicated as 'unlikely MAS.' The patient later presented with an AE of histiocytosis hematophagic that was adjudicated as 'possible MAS'. Three additional patients had cases that were re-adjudicated during the study following the collection of additional information (2 of these cases were upgraded from 'possible MAS' or 'unlikely MAS' to 'probable MAS', whereas the laboratory changes in the third patient were downgraded from an initial assessment of 'possible MAS' to 'unlikely MAS' [Study G2306-Listing 16.2.7-1-3].

In Part II, a total of 4 events were identified for adjudication, 2 cases each in the dose reduction and dose interval prolongation arm [Study G2306-Table 14.3.1-2.1b]. Of these, 2 events were reported as SAEs, one each in the dose reduction and dose interval prolongation arms [Study G2306-Table 12-13], [Study G2306-Table 14.3.1-1.6b]. The case in the dose reduction arm was adjudicated as 'unlikely MAS' with SJIA disease activity as an alternative explanation. The case in the dose interval prolongation arm was adjudicated as 'probable MAS', but without histologic confirmation or meeting current formal hemophagocytic lymphohistiocytosis criteria [Study G2306-Listing 16.2.7-1-3].

A review of the cumulative data from the aforementioned clinical trials did not reveal any new or changing safety information and continues to suggest that canakinumab does not increase the risk of MAS in patients with SJIA.

Table 8-9 Important potential risk: Macrophage activation syndrome: Other details

Macrophage activation syndrome	Details
Potential mechanisms	Unknown
Evidence source(s) and strength of evidence	Unknown
Characterization of the risk:	One hundred and twenty two serious cases from ILARIS approved indications from the reporting interval of Ilaris PSUR 01Jul2018to30Jun2021, were reviewed for eligibility for MAS adjudication. Of the 108 cases which fulfilled the criteria for MAS adjudication,13 cases were adjudicated as 'probable' MAS, 8 cases were adjudicated as 'possible' MAS and 10 cases adjudicated as 'unlikely' MAS. The remaining 76 cases did not have enough information for the committee to properly adjudicate. Fatal outcome was reported in 44/108 cases. No noteworthy case was identified (Ilaris PSUR 01Jul2018to30Jun2021).
Risk factors and risk groups	Patients with Still's disease, systemic lupus erythematosus and Kawasaki disease are at highest risk, although MAS has been reported in patients with any rheumatic condition.
Preventability	Early diagnosis to allow for aggressive treatment, close monitoring of known triggers such as infection and worsening Still's disease flares. The EU SmPC includes a suitable warning.
Impact on the benefit-risk balance of the product	Considering the significant clinical benefit that patients can obtain from this treatment, preventability and the low impact on the patient safety with this risk, the benefit is considered as outweighing the risk.
Public health impact	MAS is a well-known serious complication observed in patients with SJIA and AOSD. Although the epidemiology of MAS in Still's disease is not well studied, approximately 7-17% of patients with Still's disease develop full blown MAS, while mild 'subclinical' MAS may be seen in as many as one third of patients with active systemic disease. MAS is a life-threatening condition and the reported mortality rate can be as high as 20-30% (9-11). Multiple triggers have been identified, namely Still's disease flares and infections.

8.3.1.7 Important potential risk: Interactions with vaccines

There is potential for an interaction with vaccines since canakinumab may interfere with normal immune response to new antigens. Therefore, potentially, vaccinations may not be effective in patients receiving canakinumab. Cumulatively, 22 cases (one CT, 17 PMS and four SR) were received for interactions between canakinumab and vaccines, including four cases reported in current reporting interval. No significant follow-up reports were received for these cases during the current reporting interval. The cumulative analysis of the data received for interactions with vaccines does not reveal any new relevant or changing safety information.

The presence of protective antibody levels following immunization with inactivated vaccines was assessed in Studies D2307 and D2307E1 [SCS-Section 2.1.5.11]. In Study D2307, 7/17 patients received 31 vaccinations (10 different types,) and in Study D2307E1, 4 patients (23.5%) received 20 vaccinations (8 different types). Protective antibody titer levels were observed following all but 1 of the 51 total vaccinations. Overall, canakinumab had no negative impact

on post-vaccination antibody production or on the maintenance of antibody levels following vaccination.

In the CAPS Registry population of Study D2401 (N=285), 87 (30.5%) patients received at least 1 of any type of non-live vaccine, 44 (15.4%) patients had missing or unknown information regarding vaccination and the remainder received no vaccines during the study period [SCS-Section 2.1.5.11]. Of the 87 patients who received at least 1 non-live vaccine, 74 were CAPS patients. Nineteen (21.8%) patients from the Registry population, including 18 (24.3%) CAPS patients, had at least 1 reaction associated with vaccination. Note that 1 additional CAPS patient received a Pneumovax vaccination that was not captured in the Study D2401 listings because no vaccination date was entered by the site. This patient reported an SAE (erysipelas) related to vaccination. Taking this additional case into account, there were 88 patients, including 75 CAPS patients, who received at least 1 vaccine and 20 patients, including 19 CAPS patients, had at least 1 reaction associated with vaccination.

No drug-drug and drug-disease interactions were studied in the N2301 study in patients with TRAPS, HIDS/MKD and FMF.

Interaction studies were not performed in Study H2358 in Gouty arthritis patients.

In Study G2306, there was 1 patient in Part I reporting vaccination site erythema, pruritus and swelling and 1 patient in Part II reporting vaccination site reaction which resolved completely; no action was taken with the study drug. These reactions were expected with vaccination and were not suspected to be related to the study drug (Annex 7 RMP Table 2-1, Table 2-2) and [Study G2306-Listing 16.2.7-1.1].

Table 8-10 Important potential risk: interactions with vaccines: Other details

Interactions with vaccines	Details
Potential mechanisms	Since the drug may interfere with normal immune response to new antigens, vaccinations may not be effective in patients receiving canakinumab.
Evidence source and strength of evidence	Current evidence is based on a clinical data, literature and post marketing experience.
Characterization of the risk:	Cumulatively, 40 cases (1 CT, 31 PMS, and 8 SR; 27 HCP and 13 Non-HCP) were received for interactions between canakinumab and vaccines, including 13 cases reported in reporting interval of Ilaris PSUR 01Jul2018to30Jun2021. The cumulative analysis of the data received for interactions with vaccines does not reveal any new relevant or changing safety information.
Risk factors and risk groups	Since this is a potential risk, no attributable risk increase due to canakinumab has been established. Therefore, by definition, no risk groups or risk factors can be identified.
Preventability	The EU SmPC Section 4.4 (Special warnings and precautions for use) recommends that adult and pediatric patients receive all vaccinations, as appropriate prior to initiation of Ilaris therapy. 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 unless the benefits clearly outweigh the risks. Should vaccination with live vaccines be indicated after initiation of Ilaris treatment, the recommendation is to wait for at least 3 months after the last Ilaris injection and before the next one.
Impact on the benefit-risk balance of the product	This is a potential risk that is manageable, so has no impact on benefit risk balance.

Interactions with vaccines	Details
Public health impact	Low.

8.3.1.8 Important potential risk: Drug reaction with eosinophilia and systemic symptoms (DRESS)

Table 8-11 Important potential risk: Drug reaction with eosinophilia and systemic symptoms (DRESS)

Drug reaction with eosinophilia and systemic symptoms (DRESS)	Details
Potential mechanisms	Not known
Evidence source and strength of evidence	Current evidence is based on literature, and post marketing experience, for this class effect risk.
Characterization of the risk	Cumulatively up to 30-Jun-2021, 105 cases (10 CT, 63 PMS, and 23 SR; 91 HCP and 14 Non-HCP) were reported. Thirteen cases were identified as possible, probable or definite cases of DRESS occurring in Ilaris treated patients, based on Regiscar diagnostic criteria, with evidence of a causal relationship with Ilaris is still lacking (Ilaris PSUR 01Jul2018to30Jun2021). The causality assessment using the WHO-UMC causality categories were "Unlikely" in nine cases and "Unassessable/Unclassifiable" in the remaining four cases. In particular PD confounding factors were present and, in one case the opinion of consulting dermatologist and pathologist evaluation of the skin biopsy did not support a diagnosis of DRESS.
Risk factors and risk groups	All 13 cases retrieved by the search were reported in pediatric patients, twelve of whom had underlying SJIA and one with autoinflammatory disease not further specified.
Preventability	Unknown
Impact on the benefit-risk balance of the product	The incidence of DRESS was very low, with no evidence of causal association. Therefore, the risk of DRESS is considered to be low and to have a low impact on the benefit-risk balance.
Public health impact	Low

8.3.2 Part II Module SVII.3.2. Presentation of the missing information

Table 8-12 Missing information: Effects on growth (for periodic fever syndromes and Still's disease)

Effects on growth	Details
Evidence source	Canakinumab was studied in periodic fever syndrome (CAPS, TRAPS, HIDS/MKD, FMF and Still's disease with majority of subjects in clinical trials being children and there was no evidence to suggest any impact on growth due to ILARIS therapy.
Anticipated risk/ consequence of the missing information:	The number of subjects studied and the duration of therapy was considered small to confirm any 'effect on growth" in children due to canakinumab treatment. Therefore, this topic was considered as missing information and included in ILARIS RMP version 2.0 dated 03 Sep 2009 for close monitoring and discussion in each PSUR. There were no new safety findings revealed from the ongoing clinical trials or literature and the cumulative analysis of

Effects on growth	Details
	cases from the safety database did not reveal any change in the known safety profile of canakinumab with respect to ‘effects on growth (for periodic fever syndromes and Still’s disease)’.

9 Part II Safety specification Module SVIII: Summary of the safety concerns

Table 9-1 Table Part II SVIII.1: Summary of safety concerns

Important identified risks	Infections (including opportunistic infections) Drug induced liver injury (DILI, hepatic transaminase and bilirubin elevations) (for Still's disease) Canakinumab – immunosuppressants combination therapy toxicity
Important potential risks	Malignancy Drug induced liver injury (DILI, hepatic transaminase and bilirubin elevations) (for periodic fever syndromes and gouty arthritis) Macrophage activation syndrome (for Still's disease) Interactions with vaccines Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
Missing information	Effects on growth (for periodic fever syndromes and Still's disease)

10 Part III: Pharmacovigilance plan (including post-authorization safety studies)

Details of pharmacovigilance activities intended to identify and/or further characterize safety concerns are provided in below subsections.

10.1 Part III.1. Routine pharmacovigilance activities

Adverse event reporting and signal detection.

10.1.1 Routine pharmacovigilance activities beyond ADRs reporting and signal detection

10.1.1.1 Specific adverse reaction follow-up questionnaires:

Specific adverse event targeted follow-up checklists will be used to collect additional data to help further characterize and/or closely monitor each of the safety concerns of Ilaris (canakinumab) specified below:

- Infections (including opportunistic infections)
- Malignancy
- Macrophage activation syndrome
- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Other forms of routine pharmacovigilance activities:

None.

10.2 Part III.2. Additional pharmacovigilance activities

None.

10.3 Part III.3 Summary of additional pharmacovigilance activities

Table 10-1 Part III.1: Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
None.				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are specific obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None.				
Category 3 - Required additional pharmacovigilance activities				
None.				

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates

11 Part IV: Plans for post-authorization efficacy studies

Not applicable.

12 Part V: Risk minimization measures (including evaluation of the effectiveness of risk minimization activities)

12.1 Part V.1. Routine risk minimization measures

Table 12-1 Table Part V.1: Routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Important identified risks	
Infections (including opportunistic infections)	Addressed in EU SmPC in: Section 4.3 (Contraindication), Section 4.4 (Special warnings and precautions for use) Section 4.5 (Interaction with other medicinal products and other forms of interaction) and Section 4.8 (Undesirable effects-summary of the safety profile)
Drug induced liver injury (DILI, hepatic transaminase and bilirubin elevations) (for Still's disease)	Addressed in EU SmPC in: Section 4.4 (Special warnings and precautions for use), and Section 4.8 (Undesirable effects).
Canakinumab – immunosuppressants combination therapy toxicity	Addressed in EU SmPC in: Section 4.4 (Special warning and precautions for use) and Section 4.5 (Interaction with other medicinal products and other forms of interaction)
Important potential risks	
Malignancy	Addressed in EU SmPC in: Section 4.4 (Special warnings and precautions for use)
Drug induced liver injury (DILI, hepatic transaminase and bilirubin elevations) (for periodic fever syndromes and gouty arthritis)	Addressed in EU SmPC in: Section 4.4 (Special warnings and precautions for use), and Section 4.8 (Undesirable effects).
Macrophage activation syndrome (for Still's disease)	Addressed in EU SmPC in: Section 4.4 (Special warnings and precautions for use)
Interactions with vaccines	Addressed in EU SmPC in: Section 4.4 (Special warnings and precautions for use) and Section 4.5 (interaction with other medicinal products and other forms of interaction)
Drug reaction with eosinophilia and systemic symptoms (DRESS)	Addressed in EU SmPC in: Section 4.4 (Special warnings and precautions for use)
Missing information	
Effects on growth (for periodic fever syndrome and Still's disease)	No risk minimization measure is considered necessary at this time.

12.2 Part V.2. Additional risk minimization measures

Patient cards

Objectives and rationale: Patient cards are provided with an objective to minimize risks of infections (including opportunistic infections) and MAS, and administration of live vaccines to new born following in-utero exposure to canakinumab. These patient cards should be provided by the physician to all patients receiving canakinumab indicating afore mentioned risks with canakinumab use. Patient cards are provided in Annex 6.

Target audience and planned distribution path:

The treating physician should provide any patient who will receive Ilaris with the patient card relevant to his/her disease. Distribution includes but it is not limited to: field based representative direct customer delivery or drop off, mail/post, electronic mail, websites download, smartphone application downloads, use of the supply chain, (e.g. inclusion with the package itself). The methods for distribution and the target audience in each country are determined at national level by the local Health Authority, where applicable.

Plans to evaluate the effectiveness of the interventions and criteria for success:

The effectiveness of the patient cards will be assessed by evaluating the change in reporting frequency of infections (including opportunistic infections), MAS and pregnancy cases over time.

12.3 Part V.3 Summary of risk minimization measures

Table 12-2 Summary of pharmacovigilance and risk minimization activities by safety concerns

Safety concern	Risk minimization measures	Pharmacovigilance activities
Important identified risks		
Infections (including opportunistic infections)	Addressed in EU SmPC in: Section 4.3 (Contraindication), Section 4.4 (Special warnings and precautions for use) Section 4.5 (Interaction with other medicinal products and other forms of interaction) and Section 4.8 (Undesirable effects-summary of the safety profile) Additional risk minimization activities: Patient card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for adverse reaction. Additional pharmacovigilance activities: None
Drug induced liver injury (DILI, hepatic transaminase and bilirubin elevations) (for Still's disease)	Addressed in EU SmPC in: Section 4.4 (Special warnings and precautions for use), and Section 4.8 (Undesirable effects).	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Safety concern	Risk minimization measures	Pharmacovigilance activities
Canakinumab – immunosuppressants combination therapy toxicity	Addressed in EU SmPC in: Section 4.4 (Special warning and precautions for use) and Section 4.5 (Interaction with other medicinal products and other forms of interaction)	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Important potential risks		
Malignancy	Addressed in EU SmPC in: Section 4.4 (Special warnings and precautions for use)	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for adverse reaction Additional pharmacovigilance activities: None
Drug induced liver injury (DILI, hepatic transaminase and bilirubin elevations) (for periodic fever syndromes and gouty arthritis)	Addressed in EU SmPC in: Section 4.4 (Special warnings and precautions for use), and Section 4.8 (Undesirable effects).	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Macrophage activation syndrome (for Still's disease)	Addressed in EU SmPC in: Section 4.4 (Special warnings and precautions for use) Additional risk minimization activities: Patient card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for adverse reaction Additional pharmacovigilance activities: None
Interactions with vaccines	Addressed in EU SmPC in: Section 4.4 (Special warnings and precautions for use) and Section 4.5 (interaction with other medicinal products and other forms of interaction) Additional risk minimization activities: Patient card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
Drug reaction with eosinophilia and systemic symptoms (DRESS)	Addressed in EU SmPC in: Section 4.4 (Special warnings and precautions for use)	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for adverse reaction
Missing information		
Effects on growth (for periodic fever syndrome and Still's disease)	No risk minimization measure is considered necessary at this time	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None

Safety concern	Risk minimization measures	Pharmacovigilance activities
		Additional pharmacovigilance activities: None

13 Part VI: Summary of the risk management plan for canakinumab (Ilaris)

This is a summary of the risk management plan for canakinumab (Ilaris). The RMP details important risks of canakinumab (Ilaris), how these risks can be minimized, and how more information will be obtained about canakinumab's (Ilaris) risks and uncertainties (missing information).

Canakinumab (Ilaris) EU summary of product characteristics (EU SmPC) and its package leaflet provide essential information to healthcare professionals and patients on how canakinumab (Ilaris) should be used.

This summary of the RMP for canakinumab (Ilaris) should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of the canakinumab (Ilaris) RMP.

13.1 Part VI: I. The medicine and what it is used for

Canakinumab (Ilaris) is authorized for periodic fever syndromes, gouty arthritis, and Still's disease in the EEA (see EU SmPC for the full indications). It contains canakinumab as the active substance and it is given in the form of 150 mg powder for solution for injection, 150 mg/ml solution for injection, and 150 mg solution for injection in pre-filled pen.

Further information about the evaluation of canakinumab's (Ilaris) benefits can be found in canakinumab's (Ilaris) EPAR, including in its plain-language summary, available on the EMA website (https://www.ema.europa.eu/en/medicines).

13.2 Part VI: II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of canakinumab (Ilaris), together with measures to minimize such risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and EU SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status - the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In the case of canakinumab (Ilaris), these measures are supplemented with additional risk minimization measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of canakinumab's (Ilaris) is not yet available, it is listed under 'missing information' below.

13.2.1 Part VI – II.A: List of important risks and missing information

Important risks of canakinumab (Ilaris) are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered or taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of canakinumab (Ilaris). Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected.

Table 13-1 List of important risks and missing information

Important identified risks	Infections (including opportunistic infections) Drug induced liver injury (DILI, hepatic transaminase and bilirubin elevations) (for Still's disease) Canakinumab – immunosuppressants combination therapy toxicity
Important potential risks	Malignancy Drug induced liver injury (DILI, hepatic transaminase and bilirubin elevations) (for periodic fever syndromes and gouty arthritis) Macrophage activation syndrome (for Still's disease) Interactions with vaccines Drug Reaction with Eosinophilia and Systemic Symptoms(DRESS)
Missing information	Effects on growth (for periodic fever syndromes and Still's disease)

13.2.2 Part VI - II B: Summary of important risks

Table 13-2 Important identified risk: Infections (including opportunistic infections)

Evidence for linking the risk to the medicine	IL-1 is a pro-inflammatory cytokine secreted by macrophages and dendritic cells. It enhances the immune response (activation and proliferation of T and B cells upon antigen stimulation), the inflammatory process and haematopoiesis. Inhibiting IL-1 could therefore have an effect on the immune response against bacteria and other infectious agents. Given the biologic plausibility and the well-characterized risk of infections in the marketed indications (CAPS, TRAPS, HIDS/MKD, FMF, Still's disease, Gouty arthritis), infections are not unexpected. In CANTOS, the large double-blind phase 3 study in prevention of the occurrence of cardiovascular events, serious infections were reported slightly more frequently in canakinumab treated patients compared to placebo. Opportunistic infections have occasionally been reported in patients treated with canakinumab in the marketed indications and, theoretically, inhibition of IL-1 may increase the risk of opportunistic infection. However, in CANTOS, a large double-blind phase 3 study, the rate of confirmed opportunistic infections, including TB, was very low and comparable across the treatment groups, including placebo. Most of the cases of non-tuberculous opportunistic

	infection were confounded and all cases of confirmed TB occurred in patients in TB-endemic areas. There were no cases of reactivation of TB.
Risk factors and risk groups	In CANTOS, the pattern of Infection AEs and SAEs in the different subgroups based on age, sex, race, ethnicity, region, time since index MI, BMI, medical history of gout, co-existing T2DM and baseline hsCRP level was generally consistent with that observed for the overall population. Subgroups generally considered at higher risk for infections (the elderly and diabetic patients) had an increased incidence of infections in CANTOS compared with patients in subgroups considered to be at lower risk but with a pattern of between-treatment differences that was comparable to that observed in the overall population. There was no evidence of increased incidence of infection with canakinumab in the elderly. However, cellulitis and infectious pneumonia were more frequent in patients with diabetes and asthma/COPD, respectively, than in patients without these conditions.
Risk minimization measures	Addressed in EU SmPC in: Section 4.3 (Contraindication), Section 4.4 (Special warnings and precautions for use) Section 4.5 (Interaction with other medicinal products and other forms of interaction) and Section 4.8 (Undesirable effects-summary of the safety profile) Additional risk minimization activities: Patient card
Additional pharmacovigilance activities	None

Table 13-3 Important identified risk: Drug induced liver injury (DILI, hepatic transaminase and bilirubin elevations) (for Still's disease)

Evidence for linking the risk to the medicine	Mechanism of action is not known. For bilirubin elevations: Displacement from carrier proteins (reduced with anti-inflammatory effect). Current evidence is based on a clinical data, literature, and post marketing experience.
Risk factors and risk groups	Unknown.
Risk minimization measures	Addressed in EU SmPC in: Section 4.4 (Special warnings and precautions for use), and Section 4.8 (Undesirable effects).
Additional pharmacovigilance activities	None

Table 13-4 Important identified risk: Canakinumab – immunosuppressants combination therapy toxicity

Evidence for linking the risk to the medicine	Canakinumab binds to and neutralizes the activity of human IL-1β, a pro-inflammatory cytokine. Hence, any other drugs targeting the immune system may lead to a synergistic immune suppression. Current evidence is based on literature, clinical trial, and post marketing experience.
Risk factors and risk groups	Concomitant treatment with one or more biologics or immunosuppressant drugs along with canakinumab increases the risk to infection.
Risk minimization measures	Addressed in EU SmPC in: Section 4.4 (Special warning and precautions for use) and Section 4.5 (Interaction with other medicinal products and other forms of interaction)

Additional pharmacovigilance activities	None

Table 13-5 Important potential risk: Malignancy

Evidence for linking the risk to the medicine	Immunosuppression could potentially lead to an increase in the risk for malignancies. However, canakinumab is not a broad-spectrum immunosuppressant that severely impairs tumor surveillance or anti-tumor immune mechanisms. A hypothetical risk which is based on potential mechanistic plausibility, although the growing body of evidence suggests that IL-1β has a more likely role in tumor promotion rather than in antitumor immunity. No evidence supporting this risk was observed in CANTOS but rather a lower incidence of reported overall malignancy events and lung cancer events in particular were observed in this large double-blind phase 3 study.
Risk factors and risk groups	In a JIA cohort in Sweden malignancies were identified. The incidence was found to be 0.46 cases per 1000 person years. Patients with SJIA were at increased risk of lymphoproliferative malignancies and overall cancers as well.
Risk minimization measures	Addressed in EU SmPC in: Section 4.4 (Special warnings and precautions for use)
Additional pharmacovigilance activities	None

Table 13-6 Important potential risk: Drug induced liver injury (DILI, hepatic transaminase and bilirubin elevations) (for periodic fever syndromes and gouty arthritis)

Evidence for linking the risk to the medicine	Mechanism of action is not known. For bilirubin elevations: Displacement from carrier proteins (reduced with anti-inflammatory effect). Current evidence is based on a clinical data, literature, and post marketing experience.
Risk factors and risk groups	Unknown.
Risk minimization measures	Addressed in EU SmPC in: Section 4.4 (Special warnings and precautions for use), and Section 4.8 (Undesirable effects).
Additional pharmacovigilance activities	None

Table 13-7 Important potential risk: Macrophage activation syndrome (for Still's disease)

Evidence for linking the risk to the medicine	Unknown
Risk factors and risk groups	Patients with Still's disease, systemic lupus erythematosus and Kawasaki disease are at highest risk, although MAS has been reported in patients with any rheumatic condition.
Risk minimization measures	Addressed in EU SmPC in: Section 4.4 (Special warnings and precautions for use) Additional risk minimization activities: Patient card
Additional pharmacovigilance activities	None

Table 13-8 Important potential risk: Interactions with vaccines

Evidence for linking the risk to the medicine	Interactions with vaccines: Since the drug may interfere with normal immune response to new antigens, vaccinations may not be effective in patients receiving canakinumab. Current evidence is based on a clinical data, literature, and post marketing experience.
Risk factors and risk groups	Since this is a potential risk, no attributable risk increase due to canakinumab has been established. Therefore, by definition, no risk groups or risk factors can be identified.
Risk minimization measures	Addressed in EU SmPC in: Section 4.4 (Special warnings and precautions for use) and Section 4.5 (interaction with other medicinal products and other forms of interaction) Additional risk minimization activities: Patient card

Table 13-9 Important potential risk: Drug reaction with eosinophilia and systemic symptoms (DRESS)

Evidence for linking the risk to the medicine	Current evidence is based on literature, and post marketing experience for this class effect risk.
Risk factors and risk groups	All 13 cases of DRESS occurring in Ilaris-treated patients were reported in pediatric patients, twelve of whom had underlying SJIA and one with autoinflammatory disease not further specified.
Risk minimization measures	Addressed in EU SmPC in: Section 4.4 (Special warnings and precautions for use)

Table 13-10 Important missing information: Effects on growth (for periodic fever syndromes and Still's disease)

Risk minimization measures	None

13.2.3 Part VI – II C: Post-authorization development plan

13.2.3.1 II.C.1 Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization of canakinumab (Ilaris) and all specific obligations have been fulfilled.

13.2.3.2 II.C.2. Other studies in post-authorization development plan

There are no studies required for Ilaris.

14 Part VII: Annexes

Annex 4 - Specific adverse drug reaction follow-up forms

Ilaris (canakinumab)

Infections

In addition to collecting routine information for this adverse event, please ensure the following additional information is provided and/or confirmed.

Event Description: Summary of clinical course

- Diagnosis *(Please include corresponding event onset dates)*
  - Is the event a newly identified/ new onset infection Yes ☐ No ☐ Unknown ☐
  - Is the infection recurrent Yes ☐ No ☐ Unknown ☐
  - Is the infection an exacerbation of previous infection Yes ☐ No ☐ Unknown ☐
  - Is the infection chronic Yes ☐ No ☐ Unknown ☐
  - Is the infection considered to be "opportunistic"Yes ☐ No ☐ Unknown ☐
- Agent/ microorganism
  - Is the infection caused by a Gram-positive bacterium Yes ☐ No ☐ Unknown ☐
  - Is the infection caused by a Gram-negative bacterium Yes ☐ No ☐ Unknown ☐
  - Is the infectiona Mycobacterial infectionYes ☐ No ☐ Unknown ☐

a systemic Herpes infection Yes ☐ No ☐ Unknown ☐

a Polyomavirus infectionYes ☐ No ☐ Unknown ☐

a Cytomegalovirus infectionYes ☐ No ☐ Unknown ☐

a systemic fungal infection

(e.g. Cryptococcal, Aspergillus or Pneumocystis infection) *(Please specify)*

Yes ☐ No ☐ Unknown ☐

a Toxoplasma infection Yes ☐ No ☐ Unknown ☐

☐ None of the above *(Please specify)*

- Treatment *(Please specify the treatment received)*
  - Did the patient receive intravenous treatment for infection Yes ☐ No ☐ Unknown ☐
  - Did the clinical course of infection require change of drug Yes ☐ No ☐ Unknown ☐
  - Did the treatment require strength and/or frequency changeYes ☐ No ☐ Unknown ☐
- Outcome
  - Did the anti-infective treatment result in improvement of infection
    Yes ☐ No ☐ Unknown ☐
  - Did the infection result in a complicated clinical course Yes ☐ No ☐ Not applicable ☐
  - Did the patient undergo a procedure due to infection

(i.e. surgery, abscess incision drainage, chest tube)Yes ☐ No ☐ Not applicable ☐

- Diagnostic tests ***(****Please check all that apply and specify reference range if applicable)*

Test	Baseline levels (at ILARIS start)				Current levels (at onset of infection)			
	Date	Result	Unit		Date	Result	Unit	
Absolute neutrophil count				☐ Unknown				☐ Unknown
Absolute lymphocyte count				☐ Unknown				☐ Unknown

Absolute white blood cell count				☐ Unknown				☐ Unknown

Were any of the following diagnostic tests performed? *(Please check all that apply and describe)*

- ☐ Culture of blood, urine, cerebrospinal, peritoneal or pleural fluids
- ☐ Imaging studies (e.g. MRI, CAT or CT)
- ☐ Bone marrow examination
- ☐ Specialized serologic tests
- ☐ None of the above

Patient History:Does the patient have a history of any of the following prior to the start of Ilaris? *(Please check all that apply and describe)*

- ☐ Recurrent infections or chronic infections
- ☐ Chronic disease (e.g. diabetes, cancer, Kaposi's sarcoma)
- ☐ Poor nutritional status (e.g. BMI < 21)
- ☐ Poor social status
- ☐ Corticosteroid use
- ☐ Traveling or contact with contagious agent
- ☐ Long-term use of antibiotics
- ☐ Invasive device (e.g. dialysis, catheter, feeding tube)
- ☐ Any biologics used
- ☐ Surgical procedure (e.g. cerebrospinal fluid shunt)
- ☐ Other relevant history *(please specify)*
- ☐ Trauma with open wound or burns
- ☐ Any chemotherapy or radiation therapy
- ☐ Weakened immune system (e.g. HIV/AIDS)
- ☐ Peripheral vascular disease
- ☐ None of the above

Did the patient receive any immunosuppressant concomitantly with Ilaris? Yes ☐ No ☐ Unknown ☐

If yes, please specify:

- ☐ Methotrexate
- ☐ Corticosteroids
- ☐ Anti- IL inhibitors
- ☐ Other biologics: _____
- ☐ TNF inhibitors
- ☐ Anti-CD20 agents
- ☐ Others: _____

Macrophage Activation Syndrome

Targeted Follow-up Checklist
Ilaris Macrophage Activation Syndrome

In addition to collecting routine information for this adverse event, please ensure the following additional information is provided.

Event Description:

1) Did the patient present with any of the following signs or symptoms? **Check all that apply and provide photocopies of relevant results, if available.**

☐ Concurrent or recent infection Date of onset of event: (____ / ____ / ____) dd mm yyyy

If microorganism was identified, please, specify:
_____

☐ Sepsis Date of onset of event: (____ / ____ / ____) dd mm yyyy

If microorganism was identified, please, specify:
_____

☐ Non-remitting high fever of unknown etiology Date of onset of event: (____ / ____ / ____) dd mm yyyy

☐ Liver/spleen enlargement Date of onset of event: (____ / ____ / ____) dd mm yyyy

☐ Enlargement of the lymph nodes Date of onset of event: (____ / ____ / ____) dd mm yyyy

☐ Hemorrhagic manifestations Date of onset of event: (____ / ____ / ____) dd mm yyyy

☐ CNS dysfunction Date of onset of event: (____ / ____ / ____) dd mm yyyy

☐ Other organ involvement (i.e., renal, cardiac) Date of onset of event: (____ / ____ / ____) dd mm yyyy

Please specify:
_____

2) Were any of the following diagnostic tests performed? **Check all that apply and provide photocopies of lab results or specify if not provided)**.

☐ ESR
☐ Leukocyte count, differential
☐ Hemoglobin
☐ Ferritin
☐ Platelet count
☐ Liver function tests (Bilirubin, AST, ALT, AP, LDH, etc.)
☐ Coagulation factors (i.e., fibrinogen, etc.)
☐ CRP
☐ Triglycerides
☐ Electrolytes
☐ T-cell function test
☐ MAS-associated tests (i.e., sCD-163, sIL2 receptor, etc)
☐ Evidence of hemophagocytosis in the bone marrow or bronchoalveolar lavage or other organ (i.e. liver)
☐ Viral titer/PRC results (if available) for Herpes, EBV, CMV, Parvovirus, others
☐ Other significant diagnostic test or procedure (please specify) _____

Relevant medical history (concurrent and pre-existing conditions)

(Please specify medical condition and date of onset)

3) Does the patient have a history of any of the following? **Check all that apply.**

☐ Autoinflammatory/autoimmune conditions. If yes, please specify _____
☐ Flaring of the autoinflammatory/autoimmune condition during the current event
☐ Previous macrophage activation syndrome / hemophagocytic lymphohistiocytosis
☐ Other medically significant chronic condition(s). If yes, please specify
_____

4) Did the patient receive any of the following drugs or therapy at the time of the event? **Check all that apply.**

☐ Corticosteroids
☐ Chemotherapy (i.e. Methotrexate, etc)
☐ Plasmapheresis
☐ Intravenous IgG
☐ Anti-TNF inhibitor
☐ Sulfasalazine
☐ Antibiotics
☐ NSAIDs
☐ Other immunomodulation therapy. If yes, please specify and provide dates of onset and discontinuation
_____
__

5) Did the patient receive treatment of the event with any of the following therapies? **Check all that apply.**

☐ Immunomodulation therapy (i.e., cyclosporine, etc), If yes, please specify_____

☐ Antibiotics. If yes, please specify
_____

☐ Other. If yes, please specify
_____

Targeted Follow-up Checklist
Malignancy and Neoplasm

In addition to collecting routine information for this adverse event, please ensure the following additional information is provided.

Description of the event (malignancy / neoplasm):

- Diagnosis/date of diagnosis
- Location
    - Is the cancer localized? If not, please provide details on further locations (metastases):
    -
- Location of biopsy site(s) and result **(for lymphomas, please provide lymph node biopsy as well as gene rearrangement studies if performed):**
- Histological typing of cancer including immunophenotyping and molecular profile **(please provide a copy of report or an English summary):**
- Staging of the neoplasm (TNM):
- ECOG status /Current treatment plan:

Were any of the following diagnostic tests performed? Check all that apply and specify which test(s), dates and results

- ☐ Biopsies
- ☐ Bone marrow aspiration
- ☐ Blood test, urine test, biomarkers
- ☐ Imaging tests (e.g. x-ray, CT scan, MRI scan, PET scan, mammogram, PSA screening)
- ☐ Exploratory surgery (planned or completed)
- ☐ EBV serology test
- ☐ Other viral serology tests (e.g. HIV, HCV)
- ☐ None of the above

Relevant medical history (concurrent and pre-existing conditions)

(Please specify medical condition and date of onset)

Check all that apply and provide details as applicable:

- ☐ Infection
- ☐ Smoking
- ☐ Personal history of malignancy
- ☐ Immunosuppression condition (e.g. HIV, transplantation)
- ☐ Autoimmune disease (e.g. psoriasis, Sjogren Syndrome, rheumatoid arthritis)
- ☐ Exposure to carcinogens (environmental, occupational)
- ☐ UV exposure, PUVA/UVB
- ☐ Alcohol abuse
- ☐ Family history of malignancy
- ☐ Immunosuppression therapy
- ☐ None of the above

Targeted Follow-up Checklist
Severe Skin Reactions

In addition to collecting routine information for this adverse event, please ensure the following additional information is provided.

Event Description:

Did the patient present with any of the following signs or symptoms? **Check all that apply**

- ☐ Infiltration
- ☐ Blistering of rash
- ☐ Desquamation (skin loss)/skin peeling *(please specify %)*
- ☐ Nikolsky's symptom
- ☐ Involvement of mucous membrane
- ☐ Rash
- ☐ Itching
- ☐ Joint aches
- ☐ Visual symptoms
- ☐ General ill feeling
- ☐ Fever
- ☐ Chills
- ☐ Headache
- ☐ Body aches
- ☐ Electrolyte imbalances
- ☐ Eating/Swallowing difficulties
- ☐ Genital lesions
- ☐ Necrosis
- ☐ Cough
- ☐ None of the above
- ☐ Other *(please specify)*

Was the rash associated with any other systemic symptoms or abnormalities?
☐ Yes (*please describe)* ☐ No ☐ Unknown

Time to onset of general symptoms after starting suspected medication?

Time to onset of cutaneous symptoms after starting suspected medication?

Description of lesion(s) on the skin: (type [erythematic, papules, plaques, eczema, blisters, etc. with estimated % of body surface], topography [sun exposed areas only, trunk and upper extremities, face, etc.], start and stop date(s) of skin lesion(s))

Was there a final diagnosis?
☐ **Yes** *(please describe and whether it was confirmed by a dermatologist* ☐ **No** ☐ **Unknown**

Were any of the following diagnostic tests performed? **Check all that apply and please specify which test(s), dates and results**

- ☐ Skin lesion biopsy
- ☐ Immunofluorescence testing
- ☐ Microscopic examination of skin
- ☐ Genetic test
  - ►Was genotyping of HLA (Human Leukocyte Antigen) done? ☐ Yes ☐ No ☐ Unknown
  - ►Was HLA-B*1502 allele positive? ☐ Yes ☐ No ☐ Unknown
  - ►Was HLA-A*3101 allele positive? ☐ Yes ☐ No ☐ Unknown
- ☐ None of the above

Relevant medical history (concurrent and pre-existing conditions)
(Please specify medical condition and date of onset)

Does the patient have a history of any of the following prior to the start of the suspect drug? **Check all that apply**

- ☐ Herpes simplex
- ☐ Streptococcal infection
- ☐ Immunization *(please specify)*
- ☐ Drug allergy *(please specify)*
- ☐ Staphylococcal infection
- ☐ Mycoplasma pneumonia
- ☐ Bone marrow or organ transplant
- ☐ Non-drug allergy *(please specify)*

- ☐ HIV
- ☐ Influenza
- ☐ Typhoid
- ☐ Excessive UV light exposure
- ☐ Carrying HLA-B12 gene
- ☐ Graft-versus-host disease
- ☐ Hepatitis
- ☐ Diphtheria
- ☐ Radiation therapy
- ☐ Systemic lupus erythematosus
- ☐ None of the above
- ☐ Other relevant history *(please specify)*

Was the patient taking any of the following drugs? **Check all that apply**

- ☐ Anticonvulsants (e.g. phenytoin)
- ☐ Sulfonamide antibiotics
- ☐ Non-sulfonamide antibiotics
- ☐ Barbiturates
- ☐ NSAIDS
- ☐ Allopurinol
- ☐ Acetaminophen/Paracetamol
- ☐ Corticosteroids
- ☐ None of the above

Please indicate the treatment (if any) provided to the patient for this event.
Please specify treatment (corticosteroids, cyclophosphamide, other)

Drug	Dose	Dates (Start-Stop)

Outcome of event (include date if appropriate):

Action taken with suspect drug with regard to event (include date if appropriate):

Annex 6 - Details of proposed additional risk minimization activities

Key messages of the additional risk minimization measure:

Patients will be provided with patient card alerting them about risks associated with use of canakinumab such as risk of infections.

Patients' educational materials

In order to increase understanding of the safe and effective use of Ilaris, physicians should provide patients or their caregiver with a patient card highlighting the following aspects:

Content: Patient card

Infection

- The increased risk of infections, including serious infections, associated with treatment with canakinumab.
- The need to inform the health care provider and to seek immediate medical attention if patient experiences fever lasting longer than 3 days or other symptoms that might be due to an infection such as: (A) prolonged fever, cough or headache; (B) localized redness, warmth or swelling of the skin; or (C) persistent cough, weight loss and low-grade fever
- For periodic fever syndromes and Still's disease: it is not recommended to treat with canakinumab if the patient has an active infection requiring medical intervention.
- For gouty arthritis: it is not recommended to treat with canakinumab if the patient has an active infection.

Vaccinations

- The need for patients to talk to their doctor about any vaccinations they may need before starting treatment with canakinumab.

Pregnancy

- If you received canakinumab while you were pregnant, it is important that you inform the baby's doctor 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 canakinumab before giving birth.

Macrophage activation syndrome (Still's disease only)

- Patients with Still's disease may develop a condition called macrophage (a type of white blood cell) activation syndrome (MAS), which can be life-threatening. Patients are monitored for known triggers of MAS that include infections and worsening of Still's disease.

In addition, space for healthcare professional to enter details of patients and canakinumab treatment (dose, date of first dose of canakinumab administered etc) and space for prescriber's details are also provided.