Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Canakinumab

Proprietary Product Name: Ilaris

Sponsor: Novartis Pharmaceuticals Australia Pty Ltd

November 2014

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of the commonly used abbreviations

Abbreviation	Meaning
ACR	American College of Rheumatology
ADA	anti-drug antibody
ADR	adverse drug reaction
ALT/AST	alanine aminotransferase/aspartate aminotransferase
AE	adverse event
APTT	activated partial thromboplastin time
AUC	Area under the serum concentration-time curve
AUCss	Area under the serum concentration-time curve at steady-state
BP	blood pressure
BMI	body mass index
CAPS	Cryopyrin-Associated Periodic Syndromes
CDS	Company core data sheet
CHAQ	Childhood Health Assessment questionnaire
CHQ-PF50	Child Health Questionnaire – parent form
CI	confidence interval
CINCA	Chronic Infantile Neurological, Cutaneous, Articular Syndrome
CL_D	Clearance from serum of canakinumab (same as CL defined under noncompartmental analysis) [L/day)]
CL/F	apparent clearance
CL_L	Clearance of uncomplexed ligand, IL-1β [L/day]
Cmax	maximum serum concentration
Cmin	minimum serum concentration
CMH	Cochran-Mantel Haenszel
CRP	C-reactive protein
CTD	Common Technical Document

Abbreviation	Meaning
CV	coefficient of variation, or standard deviation as a percentage of the parameter value
ECG	electrocardiogram
ELISA	enzyme-linked immunosorbent assay
ESR	erythrocyte sedimentation rate
EU	European Union
FAS	full analysis set
FCAS	Familial Cold Autoinflammatory Syndrome
FCU	Familial Cold Urticaria
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HR	hazard ratio
HRQoL	Health-Related Quality of Life
Ig	Immunoglobulin
ILAR	International League against Rheumatism
IL	interleukin
IL-1β	interleukin-1-beta
IV	intravenous
JIA	juvenile idiopathic arthritis
K_A	Absorption rate constant for SC administration [1/day]
K_D	equilibrium dissociation constant for binding of canakinumab to IL-1β [nM]
Ki	critical flare concentration at which there is a 50% probability of clinical relapse (flare)
LLN	lower limit of normal
mAb	monoclonal antibody
MAS	macrophage activation syndrome

Abbreviation	Meaning
MASAC	macrophage activation syndrome adjudication committee
MSD	Meso Scale Discovery
MTX	methotrexate
NOMID	Neonatal-Onset Multisystem Inflammatory Disease
NSAIDs	Non-steroidal Anti-Inflammatory Drugs
OR	odds ratio
PD	pharmacodynamics
PI	Product Information
PK	pharmacokinetics
Pop PK	population pharmacokinetics
Pop PK/PD	population pharmacokinetics/pharmacodynamics
PSUR	Periodic Safety Update Report
PT	preferred term
QTc(F)	QT interval corrected using Fridericia's formula
RA	Rheumatoid Arthritis
R_{LI}	production or release rate of uncomplexed ligand, IL-1β [ng/day]
RMP	Risk Management Plan
SAE	serious adverse event
SC	Subcutaneous
SD	standard deviation
sJIA	Systemic Juvenile Idiopathic Arthritis
SOC	system organ class
SS	safety set
$T_{1/2}$	half-life
Tmax	time to maximum serum concentration
TNF-α	Tumour Necrosis Factor alpha

Abbreviation	Meaning
ULN	upper limit of normal
V_D	volume of distribution of the central, systemic, serum compartment of canakinumab or IL-1β [L]
V_P	volume of distribution of the peripheral, tissue fluid compartment of canakinumab or IL-1β [L]
V_Z/F	apparent volume of distribution

I. Introduction to product submission

Submission details

Type of submission:	Extension of Indications
Decision:	Approved
Date of decision:	7 August 2014
Active ingredient:	Canakinumab
Product name:	Ilaris
Sponsor's name and address:	Novartis Pharmaceuticals Australia Pty Ltd
Dose forms:	Powder for injection ± water for injection
Strength:	150 mg
Container:	Vials
Pack sizes:	1 or 4
Approved therapeutic use:	*Ilaris is indicated for the treatment of active Systemic Juvenile Idiopathic Arthritis (SIIA) in patients aged 2 years or older.*
Route of administration:	Subcutaneous (SC) injection
Dosage:	Treatment should be initiated and supervised by a specialist physician experienced in the diagnosis and treatment of sJIA. The recommended dose of Ilaris for sJIA patients with body weight ≥7.5 kg is 4 mg/kg (up to maximum of 300 mg) administered every four weeks via subcutaneous injection. The treating physician should consider whether patients without clinical improvement should continue treatment with Ilaris. See Product Information (PI) (Attachment 1) for details.
ARTG numbers:	159573 and 187078

Product background

Ilaris (canakinumab 150 mg powder for injection) is currently registered in Australia by Novartis Pharmaceuticals Australia Pty Ltd for

the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS), in adults and children aged 2 years and older including:

- *Familial Cold Autoinflammatory Syndrome (FCAS) /Familial Cold Urticaria (FCU)*
- *Muckle-Wells Syndrome (MWS)*
- *Neonatal-Onset Multisystem Inflammatory Disease (NOMID)/Chronic Infantile Neurological, Cutaneous, Articular Syndrome (CINCA).*

This AusPAR describes the application by the sponsor to extend the indications for Ilaris to include:-

'treatment of active Systemic Juvenile Idiopathic Arthritis (sJIA) in patients 2 years and older'.

Canakinumab is a fully human monoclonal anti-human interleukin-1beta (IL-1beta) antibody of the IgG/kappa isotype. It binds with high affinity to human IL-1beta and neutralises the biological activity of human IL-1beta by blocking its interaction with IL-1 receptors, thereby preventing IL-1beta-induced gene activation and the production of inflammatory mediators such as interleukin-6 or cyclooxygenase-2. Canakinumab is therefore suited to treat diseases and pathologies characterised by local or systemic overproduction of IL-1beta.

Systemic onset Juvenile Idiopathic Arthritis (sJIA) (WHO ICD-10 code[1]: M08.2[2]) is a subset of Juvenile Idiopathic Arthritis (JIA/JA/JRA/JCA[3]: WHO ICD-10 Code: M08). The latter, Juvenile Idiopathic Arthritis, is a general term used to describe inflammatory arthritis diagnosed in children 16 years of age or younger. Systemic onset Juvenile Idiopathic Arthritis or sJIA accounts for approximately 6 to 11% of the cases of Juvenile Idiopathic Arthritis and is characterised by fever, rash, swollen lymph glands and/or other systemic symptoms.

The peak onset of sJIA is between the ages of 18 months and 2 years but may develop at any age. Patients are classified as having:

- a monocyclic course, with remission within 2 to 4 years (about 42% of patients),
- persistent disease with arthritis becoming more prominent on remission of the systemic features and lasting no more than 5 years (about 51%), or
- a relapsing course characterised by flares of systemic features and mild arthritis (about 7%).

Up to 30% of patients still have the active disease after 10 years. There are 368 new cases of JIA estimated to occur each year in Australia, with (as noted previously) 6 to 11% of these being systemic onset, that is, sJIA.

The proposed dose of Ilaris for sJIA patients with body weight ≥ 7.5 kg is 4 mg/kg (up to a maximum of 300 mg) administered every four weeks by subcutaneous (SC) injection.

The currently approved dose/dosage regimen for CAPS is as follows:

Treatment should be initiated and supervised by a specialist physician experienced in the diagnosis and treatment of CAPS. The recommended starting dose of Ilaris for CAPS patients is:

Adults and children ≥4 years of age:

- 150mg with body weight >40 kg
- 2 mg/kg with body weight ≥15 kg and ≤40 kg
- 4 mg/kg with body weight ≥7.5 kg and <15 kg

Children 2 to <4 years of age:

- 4 mg/kg for patients with body weight ≥7.5 kg

[1] ICD-10 is the tenth revision of the International Statistical Classification of Diseases and Related Health Problems (ICD), a medical classification list by the World Health Organization (WHO).
[2] Juvenile arthritis with systemic onset
[3] JIA= Juvenile idiopathic arthritis; JA=juvenile arthritis; JRA= juvenile rheumatoid arthritis ; JCA= juvenile chronic arthritis.

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

Regulatory status

Canakinumab was designated as an orphan drug on 11 April 2013 for the treatment of active systemic Juvenile Idiopathic Arthritis (sJIA) in patients aged 2 years and older.

Canakinumab (Ilaris) was initially approved by the TGA in April 2010 for the indication of *Cryopyrin-Associated Periodic Syndromes (CAPS) in adults and children aged 4 years and older*. In February of 2014 the patient group covered by the indication was extended to include children between the ages of 2 and 4. Canakinumab is presently approved for the indication of CAPS, in adults and children aged 2 years and older as follows;

For the treatment of CAPS, in adults and children aged 4 years and older including:

- *Familial Cold Autoinflammatory Syndrome (FCAS) /Familial Cold Urticaria (FCU);*
- *Muckle-Wells Syndrome (MWS);*
- *Neonatal-Onset Multisystem Inflammatory Disease (NOMID)/Chronic Infantile Neurological, Cutaneous, Articular Syndrome (CINCA).*

Applications for the same indication have been approved by the US FDA (9 May 2013), EU (26 August 2013) and Canada (12 December 2013) (See Table 1 below) as well as Singapore (1 April 2014) and Switzerland (15 May 2014).

Table 1. Indications approved overseas

Country	Tradename	Indication
US	ILARIS	ILARIS is an interleukin-1β blocker indicated for the treatment of: • Cryopyrin-Associated Periodic Syndromes (CAPS), in adults and children 4 years of age and older including: Familial Cold Autoinflammatory Syndrome (FCAS), Muckle-Wells Syndrome (MWS) • Active Systemic Juvenile Idiopathic Arthritis (SJIA) in patients aged 2 years and older
EU	ILARIS	*(in addition to approved indication for CAPS treatment)* Ilaris is indicated for the treatment of active 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. Ilaris can be given as monotherapy or in combination with methotrexate.
Canada	ILARIS	*(in addition to approved indication for CAPS treatment)* Ilaris is indicated for the treatment of active Systemic Juvenile Idiopathic Arthritis (SJIA) in patients aged 2 years and older.

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent Product Information please refer to the TGA website at <http://www.tga.gov.au/product-information-pi>.

II. Quality findings

There was no requirement for a quality evaluation in a submission of this type.

III. Nonclinical findings

Introduction

No new nonclinical data were submitted. An Addendum to the sponsor's Nonclinical Overview plus 18 cited references were submitted to discuss the specific systemic juvenile idiopathic arthritis indication.

Pharmacokinetics

Comparative systemic exposure

The comparative systemic exposure data from previously submitted nonclinical studies needs to be updated for the clinical data for the new indication. The sponsor submitted human pharmacokinetic (PK) and total IL-1β data described by a population based PK-binding model [ACZ885 sJIA Modeling Report]. This model was updated from the original model included in the CAPS submission [ACZ885 CAPS Modelling Report] with data from sJIA clinical trials, as well as data from gouty arthritis patients and additional new data from RA and CAPS patients. The kinetics of canakinumab and its binding to IL-1β is presented fully across the age group of sJIA population. Using the population PK parameter values from the PK binding model, canakinumab concentration-time profiles were simulated for a typical sJIA patient weighing 33 kg, based on a dosing regimen of 4 mg/kg every 4 weeks for six months, to ensure that steady state is achieved. The area under the serum concentration versus time curve (AUC) and peak serum concentration (C_{max}) from the last dosing interval were estimated for each subject in sJIA trials, and summary statistics were calculated for these two exposure metrics. The $AUC_{0-\tau}$ at steady state was calculated, and divided by τ (dose interval) to obtain the average steady-state (Cavg,ss) concentration. The simulated exposure data and exposure multiples were compared to data from the marmoset Good Laboratory Practice (GLP) toxicology study (Table 2).

Table 2. Comparative systemic exposure in marmosets and sJIA patients

Typical sJIA Patients			Exposure Multiple		
Dose	[a]AUCss/28d (Cavg,ss) µg /mL	[a]Cmax,ss µg/mL	[b]Based on AUC0-24h,ss/24h of 2023 µg/mL at 150 mg/kg s.c.	[b]Based on Cmax,ss of 2273 µg/mL at 150 mg/kg s.c.	[c]Based on AUC0-96h,ss/96h (Cavg) of 2579 µg/mL at 100 mg/kg i.v.
4 mg/kg s.c. q4 weeks	24.9	36.5	81.4	62.3	104

[a] AUCss and Cmax,ss values obtained from simulations with the population PK-binding model [ACZ885 sJIA Modeling Report]
[b]Parameters in sJIA patients were compared with highest mean (male and female) AUC0-24h,ss/24h and Cmax,ss, respectively, observed at 150 mg/kg s.c. in 13 week study in marmosets [Study no. 0470033] to calculate the exposure multiple; AUC0-24h was normalized to 24h in marmosets administered ACZ885 twice weekly to get an approximate of Cavg; in sJIA patients, average steady-state canakinumab concentration (Cavg,ss) was derived as AUCss/tau, where tau depicts 4 week (28 days) dosing frequency.
[c] Parameters in sJIA patients were compared with highest mean (male and female) AUC0-96h,ss/96h, observed at 100 mg/kg i.v. in 26 week study in marmosets [Study no. 0380070] to calculate the exposure multiple; tau or dosing interval is approximately 96h in marmosets administered ACZ885 twice weekly; in sJIA patients, average steady-state canakinumab concentration (Cavg) was derived as AUCss/tau, where tau depicts 4 week (28 days) dosing frequency.

Nonclinical summary

- No new nonclinical data were submitted. This is acceptable as the efficacy of canakinumab in sJIA was appropriately derived from clinical studies and a thorough nonclinical hazard assessment was previously performed for the CAPS indication and its subsequent variation to extend the patient group to children 2 to 4 years old.

- The sponsor submitted an Addendum to the Nonclinical Overview (plus 18 cited references) which discussed the specific systemic juvenile idiopathic arthritis indication and also updated the nonclinical exposure margins.
- Simulated exposure data from a population-based PK model (typical sJIA patient; 33 kg, dosing regimen of 4 mg/kg every 4 weeks for six months, steady state) were compared to exposure data obtained from the previously submitted marmoset 13 week SC and 26 week intravenous (IV) toxicology studies. The relative exposure ratios at the No observable Adverse Effect Levels (NOAELs) from the pivotal marmoset toxicology studies were approximately 80 to 100. Therefore, the new indication and its associated dosage regimen do not significantly affect the risk assessment of canakinumab toxicity as the relative exposure ratios are very high.

Nonclinical conclusions and recommendation

- There are no nonclinical objections to the registration of canakinumab for the treatment of active Systemic Juvenile Idiopathic Arthritis (sJIA) in patients aged 2 years and older.
- No changes to the Product Information are recommended.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Clinical rationale

The sponsor has explained the rationale for this indication as follows:

> *SJIA is a unique type of childhood arthritis that is rare and meets the definition of an orphan disease. It is classed as a subtype of juvenile idiopathic arthritis (JIA), and accounts for about 10% of JIA cases in Europe and North America, and about 30% in India and 50% in Japan.*[4]
>
> *SJIA presents as recurrent systemic symptoms, including spiking fevers, rash, lymphadenopathy, hepatosplenomegaly and serositis. It is also associated with elevated erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), neutrophil and platelet counts from systemic inflammation, anemia, and elevated transaminases.*[5,6,7] *Joint symptoms usually arise later and the clinical course of the disease is highly variable.*

[4] Mellins ED, Macaubas C, Grom AA (2011). Pathogenesis of systemic juvenile idiopathic arthritis: some answers, more questions. Nat Rev Rheumatol; 7:416-26.
[5] Ravelli A, Martini A (2007). Juvenile idiopathic arthritis. Lancet; 369:767-78.
[6] Woo P, Southwood TR, Prieur AM et al (2000). Randomised, placebo-controlled, crossover trial of low-dose oral methotrexate in children with extended oligoarticular or systemic arthritis. Arthritis Rheum; 43(8):1849-57
[7] Gurion R, Lehman TJA, Moorthy LN (2012). Systemic arthritis in children. A review of clinical presentation and treatment. Int J Inflammation: article 271569; 2012:1-16.

SJIA is associated with a significant mortality (10-14%)[8], the highest of all forms of JIA. The main causes of death include infection and macrophage activation syndrome (MAS)[6]. Morbidity is high as most never achieve long-term remission. Joint damage is seen within 2 years, up to 50% have active arthritis as adults, up to 30% have long-term disabilities, and over 25% need major surgery including joint replacement.[9]

Unfortunately, there is no cure yet for sJIA. The goal of treatment is clinical remission of systemic features and joint inflammation, improved quality of life and reduced need of corticosteroids. Other medicines used for other JA subtypes are also currently used for sJIA – starting with NSAIDs, followed by corticosteroids, DMARDs and/or biologicals such as TNF-α or interleukin inhibitors. NSAIDs may provide symptomatic relief but have no significant influence on long-term outcomes. Corticosteroids are potent anti-inflammatory agents but do not prevent long-term joint destruction and may result in significant adverse effects, particularly in children, when used systemically over a long period of time. DMARDs and anti-TNFα may not always be effective in sJIA, may lose efficacy over time or discontinued due to adverse effects.

Although the underlying cause of sJIA is not yet clear, sJIA, like CAPS, is widely seen as an auto-inflammatory condition driven by innate pro-inflammatory cytokines, including the interleukins 1 and 6 (IL-1 and IL-6). IL-1 is a protein with pleiotropic effects, which up-regulates its own transcription and that of IL-6, and other cytokines. Beyond driving systemic inflammation, IL-1 can lead to the destruction of cartilage and bone.[4]

IL-1β is considered to be a major cytokine effector of inflammasome-driven inflammation in sJIA. Canakinumab was designed to specifically inhibit IL-1β without interfering with other pathways of IL-1 signalling, such as IL-1α. Thus, canakinumab represents a targeted therapy against the inflammatory process in sJIA. It was therefore investigated to determine its impact on fever and other disease symptoms, as well as composite measures of clinical response and flares.

Evaluator's comment: This rationale is valid and acceptable

Guidance

The general paediatric guidelines include:

- CPMP/ICH/2711/99 Note for Guidance on Clinical Investigation of Medicinal Products in the Paediatric Population. Effective: 19 April 2001
- EMEA/CHMP/PEG/194810/2005 Reflection Paper: Formulations of Choice for the Paediatric Population. Effective: 29 June 2009
- CHMP/EWP/147013/2004 Guideline on the role of Pharmacokinetics in the Development of Medicinal Products in the Paediatric Population (corrigendum). Effective: 24 August 2009

In addition, there is one TGA adopted European guideline for juvenile idiopathic arthritis that is related to the submission:

- CPMP/EWP/422/04 Guideline on Clinical Investigation of Medicinal Products for the Treatment of Juvenile Idiopathic Arthritis. Effective: 26 June 2009

[8] Batthish M, Schneider R, Ramanan AV, et al (2005). What does "active disease" mean? Patient and parent perceptions of disease activity in the systemic arthritis form of juvenile idiopathic arthritis (SO-JIA). Rheumatology; 44:796-9.
[9] Hashkes PJ, Laxer RM (2005). Medical treatment of juvenile idiopathic arthritis. JAMA; (294): 1671-84.

Contents of the clinical dossier

The submission contained the following clinical information:

- 2 population pharmacokinetic and/or pharmacodynamic (Pop PK/PD) analyses.
- 2 pivotal Phase III efficacy/safety studies (G2301 and G2305)
- 1 Phase II repeated dose finding study (Study A2203)
- 1 uncontrolled extension study (G2301E1)
- 1 integrated immunogenicity report of patients treated with canakinumab in sJIA.
- 1 amendment to integrated immunogenicity report of patients treated with canakinumab (this was a simple correction to a typographical error in the percentage of treatment-related immunogenicity positive rate for gouty arthritis [from 1.7 to 2.1%] and no evaluation was required).
- 13 bioanalytic reports from studies in sJIA patients, 2 bioanalytic reports from studies in CAPS patients.
- 1 integrated Summary of Efficacy, 1 integrated Summary of Safety

Paediatric data

The submission included paediatric pharmacokinetic, pharmacodynamic, efficacy and safety data.

Good clinical practice

The sponsor has stated that the submitted Studies A2203, G2301, G2301E1 and G2305 were conducted in compliance with Good Clinical Practice (GCP), and in accordance with the ethical principles of the Declaration of Helsinki. The study protocols and all amendments were reviewed by the Independent Ethics Committee or Institutional Review Board for each participating centre, and informed consent was obtained from each patient in writing before randomisation.

Pharmacokinetics

Studies providing pharmacokinetic data

Clinical pharmacokinetic (PK) data in the sJIA population were collected in the Phase II dose-finding study (A2203), the pivotal Phase III studies (G2301 and G2305), and the extension study (G2301E1) based on a sparse sampling approach. Study A2203 also collected single dose PK data. An overview of these studies is presented in Table 3 below. It was planned for the PK data from these studies to be pooled with other canakinumab studies to ensure a broader demographic range for the population and to support estimation from the original PK-Binding model in CAPS. This model has been updated with sJIA study data and is presented in *Population Pharmacokinetics in the target population* (Attachment 2). Therefore only summary results for the individual Phase III and extension studies have been presented.

Table 3. Tabular overview of clinical studies providing PK/PD data

Study	Phase	Study objectives	Study Design		Subjects treated with Canakinumab
			Dosing	PK/PD Sampling	
A2203	II	Repeat dose range, efficacy, safety, tolerability, immunogenicity, PK/PD	Stage I: Cohorts I, II or III- 0.5, 1.5, or 4.5 mg/kg s.c. SD, re-dosed at day 3 or 8 if no improvement. For improved patients re-dose upon each relapse. In Stage II: 4 mg/kg (max 300 mg/day)	PK (ACZ885) and PD (IL-β1): Baseline (pre-dose), Days 2, 3, 8, 15, 29, 43, 57, 71, 85, 99, 113, 127, 141, 155 and every 2 weeks until last patient from highest dose completes two cycles of remission. No samples in Stage II	23
G2305	III	Efficacy, Safety, Tolerability, PK/PD, Immunogenicity	Placebo or 4 mg/kg s.c. SD (max 300 mg/day)	PK (ACZ885) and PD (IL-β1): Baseline (pre-dose), Days 3, 15 and 29 (or PPW),	43
G2301	III	Efficacy, ability to taper use of steroids, safety, tolerability, immunogenicity and PK/PD	Part I: 4 mg/kg s.c. (max 300 mg/day) every 4 weeks (max 32 weeks); Part II: Placebo or 4 mg/kg s.c. q 4 wk (max 300 mg/day)	PK (ACZ885) and PD (IL-β1): Baseline (pre-dose), Day 3, 15, 29 (pre-dose), 57 (pre-dose), 197 (pre-dose), 225 (pre-dose), every 6 months (pre-dose) during part II and end of study (or PPW)	Part I: 177; Part II: 50
G2301E1	III	Open label extension to G2305 and G2301. Long term safety, efficacy, tolerability and immunogenicity	2 or 4 mg/kg s.c. every 4 weeks for up to 2 years	Days 2, 169, 337, 505, 673 (or PPW), every 6 months, and in case of flare or anaphylactic reaction (8 weeks post anaphylactic reaction)	147

PC=placebo controlled; SD=single dose; PPW= premature patient withdrawal

The sponsor also submitted 15 bioanalytical reports: 13 from studies in sJIA patients and 2 from studies in CAPS patients.

None of the pharmacokinetic studies had deficiencies that excluded their results from consideration.

Evaluator's conclusions on pharmacokinetics

- Sparse PK data were collected as part of the 4 Phase II/III clinical studies in sJIA (A2203, G2305, G2301 and G2301E1).
- Time to peak plasma concentration (T_{max}) occurred after a median of approximately 2 days (mean 2.6, range 1.6 to 6.9 days) in sJIA patients. This compares with a reported T_{max} of approximately 7 days in the current approved PI for CAPS patients.
- Based on AUC, dose-proportionality between 0.5 and 9.0 mg/kg was demonstrated.
- Data from the sJIA studies were incorporated into a previously developed population-based PK-Binding model, which adequately described the canakinumab and IL-1β concentration-time data.
- Previously identified covariate-parameter relationships (weight on clearance from serum of canakinumab (CL_D), volume of distribution of the central, systemic, serum compartment of canakinumab (V_D) and volume of distribution of the peripheral, tissue fluid compartment of canakinumab (V_P), serum albumin on CL_D, and age on the subcutaneous drug absorption rate) were confirmed to be statistically significant (p-value < 0.0001), with weight and age being the most clinically relevant. Clearance increased as weight increased, and there was a reduction in absorption with increasing age. No other significant covariates were identified.
- Based on a typical weight of 33 kg and serum albumin of 43 g/L, the estimated clearance of canakinumab in sJIA patients was 0.106 L/day, and the volume of distribution was 3.21 L.
- The accumulation ratio of canakinumab 4 mg/kg SC every 4 weeks in sJIA patients was 1.6 fold.
- Canakinumab clearance was comparable to that seen in patients with other diseases, including CAPS, asthma, rheumatoid arthritis, psoriasis and gout.
- Increased canakinumab clearance at higher body weights is not entirely compensated by dosing by weight, therefore increased exposure was observed in sJIA patients >40 kg (although exposure distributions overlapped).

- Canakinumab absorption is inversely related to age (faster in younger patients) but this is not reflected in steady state exposure which was comparable across the different age groups (2-3, 4-5, 6-11, and >11 years). This may explain the shorter T_{max} in sJIA compared with CAPS.
- The IL-1β clearance was lower and IL-1β production rate and the dissociation constant were generally higher in sJIA than in the other indications. The resulting higher levels of IL-1β in sJIA patients may explain the need for a higher canakinumab dose.
- Turnover of IL-1β was modestly higher in younger children.

Pharmacodynamics

Studies providing pharmacodynamic data

PK data collected in the Phase II/III studies were used in the development of PK-flare models to explore the canakinumab exposure-efficacy relationship. The PK-flare model enabled the estimation of the critical flare concentration, *Ki*, at which there is a 50% probability of clinical relapse (flare).

Evaluator's conclusions on pharmacodynamics

- Predicted concentrations of canakinumab at flare varied widely both within and between the sJIA studies, ranging from 0 to 41 µg/mL.
- Predicted mean concentration at flare was statistically different from the predicted mean concentration at no flare (8.1 ± 9.1 µg/mL versus 14.5 ± 10.4 µg/mL; $p < 0.0001$). This predicted concentration at flare is lower than the PK-binding model simulations of C_{MINss} (14.68 ± 8.80 µg/mL) suggesting that the proposed 4 mg/kg dose of canakinumab is appropriate.
- More than 95% of subjects administered 4 mg/kg SC dose of canakinumab had their steady-state trough levels above the *Ki* estimated in study A2203 (2 µg/mL).
- The PK-flare model based on Study A2203 data predicted a 6% median probability of flare with 4 weekly canakinumab 4 mg/kg SC treatment. While higher doses further reduced the probability of flare (down to 2% with 7 mg/kg), the 4 mg/kg dose is approaching saturation of the response.
- The exposure-hazard model based on G2301 Part II data predicted that 4 mg/kg of canakinumab SC every 4 weeks reduced the flare rate over placebo by approximately 39% (90% confidence interval (CI): 28% to 49%) over 12 months. Doses greater than 4 mg/kg were predicted to provide only marginal gain in flare reduction whereas doses less than 4 mg/kg would significantly increase risk of flare over 6 and 12 months.
- An exposure-hazard model demonstrates that canakinumab decreases significantly ($p<0.001$) the likelihood of flare with potentially full flare suppression in a concentration dependent manner.
- After accounting for the baseline steroid use, no other covariates (age, gender, body weight, daily steroid usage, and baseline American College of Rheumatology (ACR) strata) offered further improvement to the hazard model.
- The exposure-flare reduction model is based on the Part II of the G2301 study. All patients have successfully completed Part I of the study as responders to canakinumab therapy at 4 mg/kg canakinumab SC every 4 weeks. The predicted flare rates of

different canakinumab doses are therefore valid for patients who have successfully tapered steroid while receiving 4 mg/kg canakinumab every 4 weeks.

Dosage selection for the pivotal studies

The dose used in the Phase III studies was based on the PK/PD model analysis performed in Study A2203. Study A2203 was a Phase II, multi-centre, open-label, repeated dose range finding study that evaluated the safety, tolerability, immunogenicity, PK, PK/PD relationships and efficacy of canakinumab SC in paediatric patients with active sJIA.

Data on the relapse history was combined with the sampled concentrations of canakinumab in order to construct a PK/PD model describing disease relapse in the responding patients. Based on the model analysis, it was estimated that 94% of sJIA patients would not flare at a dose of 4 mg/kg over a 4 week period. While there was an incremental efficacy gain at doses above 4 mg/kg, it was not considered large enough to justify higher monthly dosing. Therefore a dose of 4 mg/kg every 4 weeks was chosen to ensure that the majority of patients would benefit from the treatment.

Evaluator's comment: The justification for selecting the 4 mg/kg dose of canakinumab for the Phase III studies in sJIA is acceptable.

Efficacy

Studies providing efficacy data

The sponsor submitted 2 pivotal Phase III efficacy/safety studies (G2301 and G2305) in patients with sJIA.

Evaluator's conclusions on efficacy

Study G2305 was a randomised, double-blind, placebo-controlled, single-dose, 4 week study assessing the short term efficacy of canakinumab 4 mg/kg in 84 patients (43 on canakinumab, 41 on placebo) aged 2 to 19 years with active sJIA. Study G2301 consisted of a 32 week open-label, single-arm active treatment period (+ steroid tapering) in 177 patients, followed by a randomised, double-blind, placebo controlled, and event-driven withdrawal study of flare prevention in 100 patients. Supportive evidence was provided by a Phase II dose finding study (23 patients), and a long-term extension study (147 patients). Overall, 201 patients aged 2 to 19 years (24 aged 2 - <4, 40 aged ≥4 - <6, 86 aged ≥6 - <12, and 51 aged ≥12 - <20 years) were followed for 301.2 patient-years. Collectively, the studies observed an adequate number of patients for an acceptable duration of time to assess efficacy and safety of canakinumab 4 mg/kg SC in the sJIA indication. Study designs and conduct, choice of efficacy endpoints, and statistical analyses were appropriate, and consistent with the relevant EU guidelines.

There are no established national data about the incidence of juvenile arthritis in Australia but global incidence has been reported in the range of 7 to 23 per 100,000 person years in the USA and northern Europe.[10] In addition, due to the low occurrence, diverse nature and use of overlapping definitions, characterising the epidemiology of juvenile arthritis is difficult. However, it is not unreasonable to assume that the baseline demographic and

[10] Australian Institute of Health and Welfare (AIHW) 2008.
Australia's health 2008 is the 11th biennial health report of the Australian Institute of Health and Welfare. It's the nation's premier source of statistics and informed commentary on: - patterns and determinants of health and illness- health across the life stages- the supply and use of health services- expenditure and workforce- and health sector performance.

disease characteristics of the study participants reflect the sJIA population in Australia. Therefore, the study results should be generalisable to potential sJIA recipients in Australian clinical practice. The majority of patients were female (55%), Caucasian (86%), with a mean age at study baseline of 8.6 years (range 1 to 19 years).

Study G2305 demonstrated that canakinumab was more effective than placebo in achieving an ACR30 response[11] at Day 15. Overall, 83.7% on canakinumab and 9.8% on placebo achieved this outcome. The odds ratio (OR) for this comparison was statistically significant and represents a clinically meaningful outcome (OR 62.29; 95% CI: 12.68, 306.07; $p < 0.0001$). The proportion of patients achieving an ACR30 at Day 29 (81.4% versus 9.8%), and achieving higher levels of ACR response at Day 15 and Day 29 were also higher with canakinumab than placebo. The superiority of canakinumab compared with placebo was also observed with other secondary efficacy measures including the individual components of the ACR criteria, fever at Day 3 (0% versus 13.2%), pain intensity, quality of life (Child Health Questionnaire – parent form (CHQ-PF50)), number of flares (3 versus 31) and percentage who achieved inactive disease at Day 15 (32.6% versus 0%). Subgroup analysis by age, gender, and the stratification factors (anakinra responder status, level of baseline corticosteroids, and number of active joints), generally showed no effect on the response to canakinumab.

The active treatment phase of Study G2301 achieved the primary objective, with 44.5% (90% CI: 37.1, 52.2; $p<0.0001$) of patients able to taper their steroids. In Part II, patients on canakinumab had a statistically significant reduction in flare compared with placebo (Hazard ratio (HR) 0.36; 95% CI: 0.17, 0.75; $p=0.0032$). A clinically relevant reduction in flare remained if patients who discontinued the study were censored rather than counted as flared but the result lost its statistical significance (HR 0.51; 95% CI: 0.23, 1.12; $p=0.0445$). Median time to flare was 236 days in patients on placebo and could not be estimated in the canakinumab group as less than 50% flared during the study. The proportion of patients who achieved an ACR30 by Day 15 and 29 in Part I was 81.3% and 88.8%; similar to that seen in Study G2305. ACR responses were largely maintained or improved throughout the 32 weeks of Part I of the study. Clinically relevant reductions in steroid dose were achieved, with reductions from a mean of 0.34 mg/kg to 0.05 mg/kg in those patients who were successful steroid taperers. In Part II only the first of the secondary endpoints achieved a statistically significant result, with a lower probability of experiencing a worsening in ACR level in the canakinumab group compared with the placebo group (HR 0.49; 95% CI: 0.27, 0.90; $p=0.0131$). No significant improvement in disability (Childhood Health Assessment questionnaire (CHAQ)) or quality of life (CHQ-PF50) was noted, and the difference to placebo was smaller than seen with these outcomes in Study G2305. This may reflect the fact that patients in G2305 were canakinumab naïve or that patients in G2301 had already responded to canakinumab in Part I of the study. The proportion of patients with inactive disease (an exploratory outcome) was higher in the canakinumab treatment group (62%) than in the placebo group (34%).

The dose-finding study (patients on doses of 0.5 to 9 mg/kg) was supportive of the pivotal studies, with 59% patients achieving an ACR30, 18% with inactive disease and 42% of steroid users able to reduce or discontinue steroid use. Study G2301E1 followed a diverse group of sJIA patients from previous canakinumab studies (responders and non-responders). The results demonstrated that 25/40 (62.5%) who were non-responders at entry became a responder by Month 3, and 23/40 (57.5%) were responders at the time of the interim analysis. Among the responders, 103/107 (96%) remained responders at Month 3 and 101/107 (94%) were responders at the time of the interim analysis. Higher

[11] ACR30 response is defined as an improvement of at least 30% from the baseline assessments in any three of six core outcome variables, with no more than one of the remaining variables deteriorating by more than 30% and resolution of fever.

ACR responses were also largely maintained. Of interest, 26 patients who had achieved steroid tapering or who were steroid free received at least 3 consecutive doses of canakinumab 2 mg/kg for a median duration of 224 days (range 59 to 511 days). All 26 patients (17 patients previously treated with canakinumab and 9 patients previously treated with placebo) maintained an ACR100[12] during the time they received the reduced dose and none discontinued the study due to lack of efficacy. Therefore there is a possibility that some sJIA patients may be able to be controlled on a canakinumab dose lower than is currently proposed. This possibility needs further investigation and the sponsor has committed within the Risk Management Plan (RMP) to a new Phase IV study to evaluate the efficacy and safety of canakinumab dose reduction or dose interval prolongation in canakinumab treatment-naïve patients who are both responders and who satisfy pre-defined criteria.

It is important to note that in Study G2305 14% of participants receiving canakinumab discontinued the study due to unsatisfactory therapeutic response. In Part I of study G2301 this percentage was 41%, including 15% who did not achieve an initial response by Day 15, 8% who lost their initial response after Day 15, and 15% who failed steroid-tapering. While Study G2301E1 did show that some non-responders can subsequently achieve a response, it is important to consider how long a patient should receive the drug if no response is seen.

In the pooled analysis some differences in efficacy were noted in some subgroups (for example, ACR responses tended to be lower in the two younger age-groups compared with the two older age-groups, in females compared with males, and in those ≤40 kg compared with those >40 kg). However, the CIs overlapped suggesting that efficacy in the subgroups was consistent with overall efficacy. The pooled analysis also suggests a reduced response in patients with a more severe disease state, however overall the data support the efficacy of canakinumab in the treatment of active sJIA in patients aged 2 to 19 years.

Safety

Studies providing safety data

Safety data from the sJIA studies were pooled to increase the sample size to detect rarer events, and are presented here (where relevant) in addition to study-specific safety results. In the pooled analyses, all events that occurred in the placebo arm of Part II of Study G2301 were assigned to the canakinumab arm because of the long half-life of canakinumab and because all patients had received at least one dose of canakinumab prior to being randomised to placebo.

Studies providing evaluable safety data

The following studies provided evaluable safety data:

- In the pivotal efficacy studies, safety assessments included the collection of all adverse events (AEs), serious adverse events (SAEs), pregnancies, the regular monitoring of haematology, blood chemistry and urine performed at a central laboratory, and regular assessments of vital signs, physical condition and body weight.
- The dose-response and non-pivotal efficacy studies provided safety data, as follows:
  - Study A2203 provided data on AEs, SAEs and pregnancies. Safety assessments included the regular monitoring of haematology, blood chemistry and urine and regular assessments of vital signs, physical condition and body weight. CRP and

[12] Defined as remission.

ESR were monitored more frequently than the standard laboratory tests and both were used as part of the clinical response. In addition infection occurrence was monitored during the study. Local tolerability at the site of the subcutaneous injection was measured at 48 hours after the first and second doses of canakinumab.

– Study G2301E1 provided the same safety data as the pivotal efficacy studies.

Patient exposure

Patient exposure to canakinumab in Phase III studies in sJIA is summarised in Table 4, below.

Table 4. Exposure to Canakinumab and comparators in Phase III sJIA clinical studies (patient years).

Study type/Indication	Controlled studies		
	Canakinumab	Placebo	Total Canakinumab
G2305	3.25	1.20	3.25
G2301 Part I	58.05	-	58.05
G2301 Part II	31.84	24.78	31.84
G2301E1	155.94	-	155.94
TOTAL	249.08	25.98	249.08

In the combined Phase II and III sJIA studies, 201 patients were exposed to canakinumab for a total of 301.2 patient years (Table 5, below).

Evaluator's comment: The limited placebo exposure somewhat compromises a comparison of safety issues with canakinumab in the sJIA population.

Table 5. Duration of exposure to canakinumab in pooled sJIA studies. Safety Population.

Exposure	SJIA pediatric Canakinumab N=201
Duration by time interval – n (%)	
≥ 1 day	201 (100.0)
≥ 12 weeks	165 (82.1)
≥ 24 weeks	144 (71.6)
≥ 36 weeks	136 (67.7)
≥ 48 weeks	130 (64.7)
≥ 96 weeks	78 (38.8)
≥ 144 weeks	19 (9.5)
≥ 192 weeks	5 (2.5)
Summary statistics (days)	
Mean duration (days)	547.3
Median duration (days)	617.0
Min (days)	4
Max (days)	1829
Patient-years	301.2

Study A2203

All patients received at least one dose study drug (0.5 mg/kg, 1.5 mg/kg and/or 4.5 mg/kg). Total patient years of exposure were not presented but one patient (4%) had 2 to <4 months exposure, 9 (36%) had 4 - <6 months, 1 (4%) had 10 - <12 months, 5 (22%) had 12 - <24 months, and 7 (30%) had 24 months or more exposure.

Study G2305

All randomised patients received one dose of canakinumab or placebo on Day 1 only. The mean duration in the study was higher in the canakinumab group (27.6 days) compared to the placebo group (10.7 days) as more patients in the placebo group discontinued early from the study due to unsatisfactory therapeutic effect. Total patient years of exposure were 3.25 for the canakinumab group, and 1.20 for the placebo group.

Study G2301

In Part I, patients received a single dose of canakinumab 4 mg/kg SC, with a maximum total single dose of 300 mg every 4 weeks. The median duration of exposure in Part I was 113 days (this includes an additional 28 days of exposure to canakinumab for the 32 patients who had received canakinumab in Study G2305 and completed the study before entering Part Ib of the present study). Most patients (80.2%) received between 2 and 8 doses of canakinumab. Overall, the mean/median number of doses in Part I was 4.25/4.0. The total patient years of exposure were 58.05 in Part I.

In Part II, patients were randomised to canakinumab or placebo in a 1:1 ratio, and received a single dose of canakinumab 4 mg/kg or placebo SC every 4 weeks. The median duration of exposure in Part II was higher in the canakinumab group than in the placebo group (221.5 versus 163.5 days, and a higher percentage of patients in the canakinumab group received more than 8 doses of study drug compared with those in the placebo group (46.0% versus 28.0%). This was the result of the earlier and higher rate of discontinuation in placebo patients. The total patient years of exposure were 31.84 for the canakinumab group, and 24.78 for the placebo group in Part II.

Study G2301E1

All patients received at least one dose of canakinumab 4 mg/kg SC, with a maximum total single dose of 300 mg every 4 weeks. A total of 31 patients received at least one reduced dose of canakinumab (2 mg/kg) SC every 4 weeks, with 26 patients receiving at least three consecutive doses. The median duration of study participation was 49.0 weeks (range 3 to 144 weeks) with a mean duration of 55.3 weeks. The total patient years of exposure were 155.94.

Safety issues with the potential for major regulatory impact

Unwanted immunological events

Immunogenicity

Development of anti-canakinumab antibodies was assessed in the individual studies and in a separate analysis for data from all studies.

Study G2305

No anti-canakinumab antibodies were detected. One patient, in the placebo group, showed a positive immune response at both Screening and end of study that was not considered to be treatment related. Immunogenicity was not assessable for 7 patients in the canakinumab group due to drug concentration above the acceptable level. However, as they did not exhibit an unexpected PK/PD profile and no immunogenicity-related AEs were reported, it was felt unlikely that these patients produced antibody. One patient reported a mild allergic (skin) reaction of one day's duration on Day 2 that was not

considered by the investigator to be related to study medication and with further follow-up was believed to be due to a food allergy.

Study G2301

Anti-canakinumab antibodies were detected in 12 patients. For 8 patients, the antibodies detected were not considered to be treatment related because they were detected before the start of canakinumab treatment. For the 4 remaining patients, no immunogenicity associated AEs were reported and there were no observed effects on the PK/PD profile.

Study A2203

No anti-canakinumab antibodies were detected.

Study G2301E1

Anti-canakinumab antibodies were detected in 5 patients. Of these 5 patients, 3 patients (with previous canakinumab therapy) had antibodies detected at baseline (study entry) and 2 patients at post-baseline. None of these patients had immunogenicity-associated AEs (hypersensitivity or allergy related) reported and there were no observed effects on the PK/PD behaviour and no changes to these patients' ACR response level.

Integrated Immunogenicity Report of Patients Treated with Canakinumab in sJIA

Background/Methodology

An overview of the immunogenicity of canakinumab in the sJIA studies was submitted by the sponsor (date of report: 28 September 2012). Anti-canakinumab antibodies were analysed in serum of patients from studies A2203, G2301, G2305 and G2301E1 at specific time points during the treatment phase depending on the study design but always included a baseline pre-dose measurement, a sample taken approximately 4 weeks post dose and an end of study sample. Additional samples were collected if anaphylaxis or anaphylactoid reactions occurred after injection, with additional characterisation to detect IgE raised to canakinumab. Canakinumab concentration was measured at the same time to permit interpretation of the immunogenicity data (that is, to consider the possibility of false negatives due to high canakinumab concentrations referred to as drug tolerance of the immunogenicity assay).

The assay used in study A2203 was based on a Biocore assay, which was replaced in 2010 with a bridging meso scale discovery (MSD) assay with increased sensitivity. Both assays have been validated. All samples were subjected to routine screening for anti-drug antibodies (ADAs); those that tested positive were subjected to the confirmation assay, and then titrated to determine the intensity of response. A positive result on both screening and confirmatory assays triggered further analysis of the samples, which involved a neutralisation enzyme-linked immunosorbent (ELISA) assay to evaluate the potential of ADAs to block binding of canakinumab to soluble IL-1β.

The sponsor also established an event-driven approach, searching the clinical trial database for any AE that could potentially be related to immunogenicity, including administration site reactions, hypersensitivity reactions, autoimmune disorders and immune disorders. When an immune-related AE occurred, samples were collected and tested using the MSD assay. If the event could not be explained by the presence of ADAs using the MSD assay, further testing with a neutralising antibody assay was considered. Patients who discontinued due to loss an initial response to treatment (≥ACR30 at Day 15) were also assessed for ADAs and indirect evidence of antibody production post-treatment.

Posttreatment ADAs were classified in three categories: transient, persistent or other:

- Transient: single IG positive time point(s) followed by IG negative time point(s)
- Persistent: two or more consecutive IG positive time points for an interval that spans >16weeks

- Other:
  - Patients with only one sample collected;
  - Patients with at least 2 samples collected at an interval <16weeks due to study design; and
  - Other patients that do not fit into the definitions above of transient and persistent.

Results

Of the 201 sJIA patients in the studies, 196 patients had immunogenicity testing and 14 patients had ADAs detected. Of these 14 patients, 8 patients had ADA detected at baseline only and thus are not considered as treatment-induced, while 6 had posttreatment ADAs with no baseline ADA detected, representing an incidence of 3.1% (6/196). Of the posttreatment ADA patients, 2 were classified as being transient, 1 persistent and 3 other. No neutralising antibodies were detected in any of the sJIA patients. No events of anaphylaxis or anaphylactoid reactions were reported; therefore IgE testing was not performed in any of the sJIA studies.

None of the 6 patients with posttreatment ADAs had any apparent efficacy consequences, and only 1 patient had a potential allergy/hypersensitivity AE (eyelid oedema and mild coughing, both resolved without action being taken). Comparison of the trough canakinumab and total IL-1β concentrations at the times when antibodies were detected with concentrations at other times did not reveal any differences.

Eighteen patients met the definition of loss of efficacy because they

1. showed initial response (≥ adapted Paediatric ACR30) on Day 15 in the study where they received their first dose of canakinumab; and

2. subsequently discontinued the program due to unsatisfactory therapeutic effect secondary to becoming a non-responder.

None of these patients had a posttreatment positive ADA detected, although 2 did have a positive ADA at baseline. Indirect evidence of ADA effects on efficacy was also investigated using the observed canakinumab and total IL-1β levels and those generated on the population-based PK-binding model for each patient. The levels were highly variable between patients, and there was no obvious trend of a reduction in either canakinumab or IL-1β binding ability in these patients.

In total, 89 patients were identified with 182 AEs potentially related to immunogenicity. No anaphylaxis or anaphylactoid reaction AEs were reported. SAEs were experienced by 5 of the 89 patients, yet none of these qualified as immunogenicity-related and all had more plausible alternative explanations. Eighteen patients experienced 22 AEs that qualified as immunogenicity-related (6 x cough, 5 x erythema/erythematous rash, 3 x oedema) none of which were serious or resulted in study discontinuation. Eleven of the events required no action, with the remaining 11 events required concomitant medications (antihistamines, morphine, antibiotics, expectorant, or antiseptic).

See also Attachment 2.

Postmarketing data

The sponsor submitted Periodic Safety Update Report 07 (PSUR 07) covering the period 1 July 2012 to 31 December 2012. Safety changes made to the Core Data Sheet during the period covered by PSUR 07 included:

- Warning and Precautions: Macrophage Activation Syndrome added.
- Adverse Drug Reactions: updated with the type of infections most frequently reported.

The only action taken for safety reasons was the imposition of a temporary clinical hold in two clinical studies (CACZ885H2358 and CACZ885I2206) due to the detection of a quality defect (shrunken lyophilized cake) in placebo vials being utilized in those studies.

No new safety findings were observed in Novartis sponsored clinical trials, non-interventional studies, investigator initiated trials, or individual case safety reports (ICRS) (although event rate was slightly increased compared with PSUR 06).

Ilaris RMP version 5 (30 September 2011) lists three important identified risks (infections, neutropenia and thrombocytopenia) and 12 important potential risks (opportunistic infections, immunogenicity/allergenicity, lymphoid organ toxicity, autoimmunity reactions, severe injection site reactions, malignancy, disorders of lipoprotein metabolism, drug induced liver injury (Drug-induced liver injury (DILI), hepatic transaminase and bilirubin elevations), vertigo, canakinumab / immunosuppressant combination therapy toxicity (for CAPS), benzyl alcohol toxicity (for CAPS) and increased uric acid (for gouty arthritis)). After evaluation of reports in the Novartis Safety database, review of relevant publications, clinical and preclinical trial databases and epidemiological data, the sponsor did not consider that there was any new relevant data on any of these issues.

The sponsor concluded that: 'The risks as described in RMP version 5.0 and the currently valid SmPC correctly reflect the knowledge of the product. The risks will continue to be monitored in accordance with current regulatory pharmacovigilance practices and the outlined risk management.'

Evaluator's conclusions on safety

Using the pooled sJIA dataset for safety (Studies A2203, G2305 and G2301, and an interim report from the ongoing extension Study G2301E1), there were 201 patients aged 2 to 19 years who received canakinumab 4 mg/kg every 4 weeks for a total of 301.2 patient years, including 130 patients treated for at least 48 weeks. There were 24 patients aged 2 to < 4 years, 40 aged 4 to < 6 years, 86 aged 6 to- ≤ 12 years, and 51 aged 12 to < 20 years. This represents adequate exposure to detect common AEs but may not be sufficient to detect rarer events.

While adverse events were observed in 85.1% of patients, the majority were mild to moderate in intensity, with only 16.9% being considered severe. The AEs seen were consistent with the known safety profile of canakinumab and/or the diagnosis of sJIA. The most common AEs included: nasopharyngitis (29.4%), pyrexia (25.9%), cough (25.9%), vomiting (22.9%), diarrhoea (22.4%), upper respiratory tract infection (22.4%), and headache (20.9%). Serious AEs were reported in 31% of patients, with almost half being infections. Infections are a known risk with canakinumab but only gastroenteritis and varicella affected more than 2 patients (4 patients each) and the rate of infections was similar between canakinumab and placebo where these results were available. Four deaths occurred in sJIA patients but 3 occurred long after canakinumab was ceased (4 months to 2 years), and none were considered related to the study drug.

Elevations in liver transaminases (> 3x upper limit of normal (ULN)) were noted with canakinumab treatment (19 patients, 9.5%), however the majority resolved within 1 month and all but 1 had resolved within 3 months. In 5 patients the abnormalities were temporally associated with macrophage activation syndrome (MAS). While the proportion of sJIA patients with elevated transaminases is higher than reported in CAPS patients (rare according to the current approved PI), they were mostly mild and transient and were consistent with the abnormal liver function tests (LFTs) that are often seen in patients with active sJIA and reflect the underlying inflammatory process.

Neutropenia and thrombocytopenia are also known risks with canakinumab, and were reported in sJIA patients. However they were generally not associated with any clinical

sequelae. Many other laboratory parameters normalised with canakinumab treatment through a reduction in inflammation.

MAS was an event of particular interest because it is a known, life-threatening disorder that can occur in sJIA patients and is thought to reflect insufficient disease control rather than a treatment specific effect. Twelve cases were diagnosed during the canakinumab sJIA studies, with 9 adjudicated as probable MAS: 7 on canakinumab (2.5 per 100 patient-years) and 2 on placebo (7.7 per 100 patient-years). The overall incidence was comparable to the background rate reported in the literature, which suggests that canakinumab is not causally involved in its development. However as there is a large degree of uncertainty in the estimated background rate of MAS and the rate in the placebo group is based on limited placebo exposure (and one of the two placebo cases had previously received canakinumab), the relationship remains uncertain and requires ongoing investigation.

A small percentage (3.1%) of sJIA patients developed anti- canakinumab antibodies; however no neutralising antibodies were detected. There were no apparent efficacy consequences, and only 1 patient had a potential allergy/hypersensitivity AE.

In summary, the data demonstrates that canakinumab was generally well-tolerated and has an acceptable safety profile in patients with sJIA. The AE profile is similar to that seen in CAPS patients with the exception of MAS. While there was a higher incidence of some AEs in sJIA compared with CAPS, this is not unexpected in view of the higher dose used in sJIA and factoring in those AEs that are consistent with the diagnosis of sJIA rather than the treatment.

First round benefit-risk assessment

First round assessment of benefits

The benefits of canakinumab in the proposed usage are:

- 83.7% of patients on canakinumab achieved an ACR30 response at Day 15, compared with 9.8% on placebo in the pivotal Study G2305. This comparison was statistically significant and clinically meaningful (OR 62.29; 95% CI: 12.68, 306.07; p<0.0001).
- Response was generally similar regardless of gender or age-group (2 to <4 years 77.8%, 4 to <6 years 87.5%, 6 to <12 years 85.7%, and 12 to <20 years 83.3%; male 87.5%, female 81.5%).
- Higher levels of ACR response were also significantly higher in the canakinumab group compared with the placebo group on Days 15 and 30.
- Improvements were also seen in the ACR core component variables, pain and quality of life measures.
- A large proportion of patients (44.5%) were able to reduce their steroid usage, including 32.8% who became steroid free.
- Canakinumab treatment reduced the relative risk of flare by 64% compared with placebo (HR 0.36; 95% CI: 0.17, 0.75; p=0.0032) in the pivotal study G2301. Median time to flare was 236 days for placebo but could not be determined for the canakinumab group as less than 50% flared.
- Patients on canakinumab were less likely to experience a worsening in ACR level than those on placebo (HR 0.49; 95% CI: 0.27, 0.90; p=0.0131). Median time to worsening in ACR level was 141 days for placebo but could not be determined for the canakinumab group as less than 50% flared.

- Efficacy was maintained or improved for a median of 49 weeks of follow-up.

First round assessment of risks

The risks of canakinumab in the proposed usage are:

- The probability of experiencing a flare event in Part II of Study G2301was lower for patients receiving canakinumab treatment compared with placebo treatment. However, this result was potentially not statistically significant if patients who discontinued the study for any reason (with the exception of flare) were censored at the time of study discontinuation rather than counted as flared (relative risk reduction in flare of 49% with canakinumab treatment relative to placebo; HR 0.51; 95% CI: 0.23 to 1.12; p=0.0445).
- While significant improvements in disability (CHAQ) and quality of life (CHQ-PF50) were found in Study G2305, this was not replicated in Study G2301. In addition, the mean differences between the canakinumab group and the placebo group were smaller than seen with these outcomes in Study G2305. This may reflect the fact that patients in G2305 were canakinumab naïve or that patients in Part II of G2301 had already responded to canakinumab in Part I of the study.
- There were a large number of discontinuations (due to lack of efficacy) from the placebo arm of Study G2305 and to a lesser degree from Part II of Study G2301 which limited the safety comparisons.
- There is a known risk of infection, including serious infection with canakinumab. In the limited placebo-controlled data available in sJIA patients, more patients on canakinumab reported infections and serious infections than patients on placebo but after adjusting for exposure there was little difference in infectious AE incidence.
- Macrophage activation syndrome is a life-threatening disorder that can occur in sJIA. More 'probable' cases were reported in patients on canakinumab (7) than on placebo (2) but after adjusting for exposure the incidence was higher in the placebo group (2.5 versus 7.7 probable MAS/100 patient-years). MAS epidemiology data are not robust, and the placebo data was limited therefore this event needs ongoing assessment.
- Neutropenia and thrombocytopenia were reported but were generally not associated with clinical sequelae.

Anti-canakinumab antibodies developed in 6 patients (3.1%) but no neutralising antibodies were detected.

First round assessment of benefit-risk balance

The benefit-risk balance of canakinumab, given the proposed usage, is favourable.

First round recommendation regarding authorisation

It is recommended that the canakinumab indications are extended to include

> '*treatment of active Systemic Juvenile Idiopathic Arthritis (sJIA) in patients aged 2 years and older*'

subject to satisfactory responses being received in relation to the questions posed under *Clinical questions* below. The wording of the sJIA indication proposed by the sponsor is identical to that in the US label. However, in the EU Summary of Product Characteristics the indication is restricted to sJIA patients:

'who have responded inadequately to previous therapy with non-steroidal anti-inflammatory drugs (NSAIDs) and systemic corticosteroids. Ilaris can be given as monotherapy or in combination with methotrexate.'

While the EU indication is probably a more realistic reflection of the patients who will be prescribed canakinumab in clinical practice, the only other biological medicine currently registered in Australia for sJIA (Actemra) is not 'restricted' based on response to previous therapies. Therefore the proposed indication is considered acceptable.

The proposed changes to the PI are recommended for approval, subject to additional recommendations of modifications of the PI (the details of these are beyond the scope of this AusPAR).

In the pooled sJIA studies 8 patients had a QTc(F)[13] > 500 msec. Although there was no effect on corrected QT interval[14] in nonclinical studies, it is recommended that the sponsor be asked to confirm whether there has been a Thorough QT study in the past, and if so what was the result of the study.

Clinical questions

Efficacy

1. The adapted American College of Rheumatology (ACR) Paediatric response variables included C-reactive protein (CRP) as the laboratory measure of inflammation whereas erythrocyte sedimentation rate (ESR) is specified in the EU guideline. Please justify the use of CRP.

2. The sample size for Part II of Study G2301 was determined on the basis of a difference between the active and placebo groups in the percentage of patients who flare in the first 24 weeks of Part II of 25% versus 70%, respectively. Please provide the clinical justification for the percentages chosen.

3. The probability of experiencing a flare event in Part II of Study G2301was lower for patients receiving canakinumab treatment compared with placebo treatment. If patients who discontinued the study for any reason (with the exception of flare) were censored at the time of study discontinuation (rather than counted as flared), the results showed a non-significant relative risk reduction in flare of 49% with canakinumab treatment relative to placebo (HR 0.51; 95% CI: 0.23 to 1.12; p=0.0445).

4. The G2301 Clinical Study Report it states that 37 patients discontinued Part II, 26 (52%) from the placebo arm and 11 (22%) from the canakinumab arm. The primary reason for discontinuation in Part II for both treatment groups was unsatisfactory therapeutic effect (22% canakinumab; 40% placebo). A further 6 patients discontinued from the placebo arm, 4 due to adverse events, 1 due to protocol deviation (unblinding due to SAE) and 1 due to withdrawal of consent. Given the higher percentage of discontinuations in the placebo arm and that these were considered 'flares' in the primary analysis, this may have biased the efficacy results in favour of canakinumab. Therefore the analysis that censored patients may be a better reflection of the comparative efficacy of canakinumab and placebo. Please comment on the decision to classify discontinuations as 'flares', the impact of the uneven

[13] QT interval corrected using Fridericia's formula

[14] In cardiology, the QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. The QT interval represents electrical depolarization and repolarization of the ventricles. A lengthened QT interval is a marker for the potential of ventricular tachyarrhythmias like torsades de pointes and a risk factor for sudden death.

distribution of discontinuations in the placebo and canakinumab arms and how this has influenced the reported efficacy of canakinumab.

Second round evaluation of clinical data submitted in response to questions

Response to efficacy question 1. Choice of ESR versus CRP

The sponsor explained that both the ESR and CRP are commonly used acute phase reactants, that there is a high correlation between the two measures, and that they can be used interchangeably for the purposes of calculating ACRs and for tracking subclinical and overt inflammation/disease activity. CRP was chosen by the sponsor because of its more rapid response to inflammation allowing for potentially earlier detection of treatment effect or disease relapse.

Evaluator's comment: This response is acceptable.

Response to efficacy question 2. Choice of placebo and canakinumab flare rates for sample size calculation.

The sponsor indicated that at the time when Study G2301 was planned there was limited data available to use for endpoint assumptions. The flare rate for the canakinumab group was based on existing Phase I/II data where 4/15 patients (approximately 25%) flared in < 4 weeks. The choice of 70% for the placebo group was based on consultation with external sJIA clinical experts.

Evaluator's comment: This response is acceptable.

Response to efficacy question 3. Classification of discontinuations as 'flares'.

The sponsor conducted an additional post hoc sensitivity analysis which defined flares as per the protocol definition or discontinuations from Part II due to unsatisfactory therapeutic effect. Using this modified flare definition, 5 of the 6 placebo patients discontinued for reasons other than an unsatisfactory response and were censored, and only 1 patient (who had met the definition for flare prior to being discontinued for an AE [reported as a protocol violation]) was counted as flared. The modified flare definition did not change the number of flares in the canakinumab group (n=11) but reduced the number of flare events by 5 in the placebo group (from 26 to 21). The results of this post hoc sensitivity analysis showed a significant relative risk reduction in flares in the canakinumab group of 57% (HR 0.43; 95% CI: 0.20 to 0.92; p=0.0127 [one-sided significance level 0.025]) (Table 6).

Table 6. Survival analysis of time to modified flare during Part II (FAS II, (Study G2301)

			Kaplan-Meier estimate	Stratified log-rank test	
Treatment	n	Number of events	Median in days (95%-CI)	Hazard ratio to Placebo (95%-CI)	One-sided p-value
ACZ885	50	11	Not est.	0.43 (0.20, 0.92)	0.0127*
Placebo	50	21	253.0 (196.0 , Not est.)		

Evaluator's comment: This revised definition of flare (excluding [censoring] patients who discontinued for reasons other than lack of efficacy) for the sensitivity analysis is more appropriate for the evaluation of efficacy, and the results are supportive of the primary analysis. The response is acceptable.

Second round benefit-risk assessment

Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of canakinumab in the proposed usage are unchanged from those identified in the First round assessment.

Second round assessment of risks

After consideration of the responses to clinical questions, the risks of canakinumab in the proposed usage are:

- The probability of experiencing a flare event in Part II of Study G2301was lower for patients receiving canakinumab treatment compared with placebo treatment. This result was not statistically significant in a sensitivity analysis when patients who discontinued the study for any reason (with the exception of flare) were censored at the time of study discontinuation. In an additional post hoc sensitivity analysis which included discontinuations from Part II due to unsatisfactory therapeutic effect as flares and censored discontinuations for other reasons, canakinumab treatment reduced the relative risk of flare by 57% compared with placebo (HR 0.43; 95% CI: 0.20 to 0.92; p=0.0127).

The other risks of canakinumab in the proposed usage are unchanged from the First round assessment.

Second round assessment of benefit-risk balance

The benefit-risk balance of canakinumab, given the proposed usage, is favourable.

Second round recommendation regarding authorisation

Satisfactory responses have been received in relation to the questions posed by this evaluator. The recommendation regarding authorisation is otherwise unchanged from the First round recommendation.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan Core RMP Version 7.1 dated 18 May 2013 (data lock 31 December 2012 for postmarketing data) with Australian Specific Annex (ASA) Version 3.1 dated 26 June 2013 which was reviewed by the TGA's Office of Product Review (OPR).

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 7.

Table 7. Sponsor's summary of the Ongoing Safety Concerns

Important identified risks	Infections Neutropenia Thrombocytopenia
Important potential risks	Opportunistic infections Immunogenicity/allergenicity Lymphoid organ toxicity Autoimmunity reactions Severe injection site reaction Malignancy Disorders of lipoprotein metabolism DILI (Hepatic transaminase and bilirubin elevations) Vertigo Canakinumab – immunosupressants combination therapy toxicity (for CAPS) Increased uric acid levels (for gouty arthritis) Macrophage activation syndrome (MAS) (for SJIA) Potential interactions with vaccines Potential pharmacodynamics interactions Potential interactions with drugs eliminated by CYP450 enzymes
Important missing information	Pregnancy Long term effect on kidney function Effects on growth (for CAPS and SJIA) Long term safety data Long term efficacy (for CAPS and SJIA)

Pharmacovigilance plan and risk minimisation activities

The major changes to the Core-RMP Version 7.1, dated 18 May 2013 compared to the previously evaluated Core-RMP Version 6, dated 31 December 2011 has been summarised by the sponsor in the following statement '*All information from the previous RMP version 6.1 was transferred to the new core template and appropriate sections were updated to comply with new template requirements. As a part of the RMP strategy, missing information on safety data was extended to all indications and long term efficacy for CAPS and SJIA was added as missing information*.' The sponsor does refer to a 'list' in the Core-RMP V7.1 that summarises these changes. However, there is no list present.

In summary, routine and additional pharmacovigilance activities are proposed by the sponsor to monitor and further elucidate the 3 important identified risks, 15 important potential risks and 5 important areas of missing information.

- routine pharmacovigilance activities for important identified, potential risks and missing information. This includes 6 targeted questionaries (classified by the sponsor as additional pharmacovigilance) for Infections, Opportunistic infections, Immunogenicity/Allergenicity (hypersensitivity including anaphylaxis), Malignancy, Vertigo and MAS (for sJIA).
- additional activities are proposed for some of the risks including three ongoing studies (including Ilaris Registry CACZ885D2401 which included Australian patients and CACZ885H2401in which the inclusion of Australian patients is to be confirmed by the sponsor) and a planned sJIA Pharmachild registry.
- The sponsor proposes routine (PI; for the 3 important identified risks and 11 out of the 14 important potential risks) and additional risk minimisation activities.

Currently, no additional risk minimisation activities will occur in Australia until after patients have commenced treatment with Ilaris. The sponsor makes the following statement regarding additional risk minimisation activities in Australia (ASA version 3.1 Section 6.2):

'At the time of writing this document, no patients in Australia, outside of clinical trials, have been supplied Ilaris. Novartis will develop Australian specific-material for both prescribers and patients for the CAPS and SJIA indications based on the Novartis globally developed educational material templates presented in Section 10 of RMP v7.1. Materials for physicians will refer to and align with Australia approved Product Information for full prescribing information. The development will occur once suitable patients have been identified and will be treated with Ilaris'.

The canakinumab educational materials have been previously evaluated and approved by the TGA. The sponsor has provided the following summary of updates to these materials:

'This annex contains details of the proposed updates to the educational materials for physicians and patients for Ilaris (canakinumab).

Detailed information is shown about:

- the current Ilaris **Physician Information Guide** for the Cryopyrin-Associated Periodic Syndromes (CAPS) and the Gouty Arthritis (GA) indications
- the new Ilaris **Physician Information Guide** for the Systemic Juvenile Idiopathic Arthritis (SJIA) indication
- the current Ilaris **Injection Administration Guide** for the Cryopyrin-Associated Periodic Syndromes (CAPS) and the Gouty Arthritis (GA) indications
- the new Ilaris **Injection Administration Guide** for the Systemic Juvenile Idiopathic Arthritis (SJIA) indication
- the current Ilaris **Injection Administration Guide for the injection kit** for the Cryopyrin-Associated Periodic Syndromes (CAPS) and the Gouty Arthritis (GA) indications
- the new Ilaris **Injection Administration Guide for the injection kit** for Systemic Juvenile Idiopathic Arthritis (SJIA) indication
- the current Ilaris **Patient Alert Card** for the Cryopyrin-Associated Periodic Syndromes (CAPS) and the Gouty Arthritis (GA) indications
- the proposed new Ilaris **Patient Alert Card** for the Systemic Juvenile Idiopathic Arthritis (SJIA) indication.

The proposed updates of this educational material will be made available to all countries where applicable after it is approved by the relevant authorities. These materials have been approved by the CHMP as part of the CAPS extension indication application (EMEA/H/C/1109/II/21) and gouty arthritis new indication (EMEA/H/C/1109/II/10).'

Reconciliation of issues outlined in the RMP report

Table 8 summarises the OPR's first round evaluation of the RMP, the sponsor's responses to issues raised by the OPR and the OPR's evaluation of the sponsor's responses.'

The sponsor should be aware that safety considerations may be raised by the nonclinical and clinical evaluators. It is important to ensure that the information provided in response to these includes consideration of the relevance for the Risk Management Plan, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.

Table 8a. Reconciliation of issues outlined in the RMP report

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
The sponsor has not adequately declared all changes to this updated core-RMP version 7.1 compared to the previously submitted core RMP version 6. This has negatively affected the quality of the submitted materials and complicated the evaluation process.	*Novartis acknowledges the evaluator's comments on the summary of major changes to the core RMP from version 6 to 6.1, 7 and 7.1. In order to address the evaluator's comments, Novartis provides a detailed account of all [RMP changes] in this response. The [EU RMP v7.1], a copy of which is provided in this response, is the most current version submitted to and approved by the EMA on 26 August 2013. The format of this EU RMP aligns with EMA guideline 'Guideline on good pharmacovigilance practices:* *Module V-Risk management systems (EMA/838713/2011, June 2012)'. Part IV of the EU RMP includes an efficacy study (CACZ885D2401 (CAPS Registry)) which is a specific obligation and/or condition of Market Authorisation in the EU. This registry protocol has previously been provided to the TGA.* *In response to the TGA's observation in the submission notification letter (milestone 2) dated 29 July 2013, a summary of differences between the submitted core RMP v7.1 and the EU*	This is acceptable.
The Delegate may wish to note that the proposed indication in Australia is broader than that proposed in Europe and the United States: i) The approved indication in the EU restricts canakinumab use to patients 'who have responded inadequately to previous therapy with non-steroidal anti-inflammatory drugs (NSAIDs) and systemic corticosteroids'. ii) The indication should include the recommended weight of 'children >7.5kg'.	*Novartis acknowledges the evaluator's observation on the indication that is approved in the EU, but believes that the evolving clinical treatment guidelines and data from studies support a broader use. The US approved indication states that 'Ilaris is indicated for the treatment of active Systemic Juvenile Idiopathic Arthritis (SJIA) in patients aged 2 years and older.' This is in line with the current treatment paradigms which are rapidly changing with the advent of new more targeted highly efficacious biologic therapies. In 2011, the American College of Rheumatology*	Deferred to Delegate.

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
	issued treatment guidelines which recommend anti-IL1 therapy be used as first line therapy in SJIA patients with active systemic features with or without arthritis and irrespective of current therapy (Beukelman et al 2011). In the phase III Ilaris SJIA clinical program, patients were allowed to use Ilaris as monotherapy or in combination with a NSAID and/or MTX and/or a corticosteroid. The response rates were similar for all groups, although the Ilaris monotherapy subgroup in the pooled 12-week efficacy analysis, demonstrated slightly higher ACR30 response rates [SCE section 3.3.5]. Novartis believes that physicians should be able to have the flexibility to prescribe Ilaris in accordance to the treatment guidelines and reflective of how it was studied in the phase III program. *Novartis does not agree that this important information be communicated in the indication, but instead believes it is more appropriate communicated to prescribers in the Dose and Administration section of the label.*	
The following should be added to the list of ongoing safety concerns, unless the sponsor can provide compelling justification for their exclusion: Lactation should be added as missing information for completeness Decreased creatinine clearance Urinary proteinuria Drug-induced liver injury (DILI) should be re-classified from a potential to an identified risk Leukopenia should be considered as an identified risk in addition to the already listed neutropenia Pulmonary complications in SJIA Musculoskeletal pain and arthralgia Eosinophilia	*Lactation* *The important missing information 'Pregnancy' also refers to breastfeeding and lactation. Novartis will clarify this at the time of the next routine update. In addition, the Australian-Specific Annex will be revised to reflect that the missing safety information for Pregnancy also includes Lactation.* *Other ongoing safety concerns* *As stated in PSUR 8 (data lock point of 30 Jun 2013), the in-depth review of the available information reveal no safety signals. In contrary to EMA, Novartis concluded that the Core RMP version 7.1 and CDS accurately reflect the safety profile of Ilaris. However, the 7 safety topics have been accepted by Novartis for the [EU RMP v7.1] following the request by* *the CHMP and are considered to be adopted also in Australia as local*	The recommendation remains. The TGA will not accept the core RMP Version 7.1 due to the unacceptable differences in the core RMP Version 7.1 and EU-RMP Version 7.1.

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
	deviations. Novartis Confidential Page 11 Response to TGA Ilaris (ACZ885 canakinumab) Novartis provides detailed justification for exclusion of the following safety topics as ongoing safety concerns from the company's Core RMP v7.1 below (See Sponsor's response).	
It is noted that the following risk has been removed from the list of ongoing safety concerns. Benzyl alcohol toxicity (for CAPS) This risk, however, related to the CAPS indications for canakinumab. It is recommended that the sponsor justify this exclusion in the next update of the RMP.	*A discussion on the trace levels of benzyl alcohol to justify the removal of benzyl alcohol toxicity (for CAPS) as potential risk is included in the Periodic Safety Update Report 6 covering the period 01 January to 30 June 2012 (PSUR 6) submitted to the TGA on 27 August 2012.* *A toxicological assessment report of Novartis on the reduced benzyl alcohol limit of 0.5 µg/mL in the drug substance concluded that benzyl alcohol at such level does not represent a toxicological risk for adults or term-born infants.* *Benzyl alcohol is not added as an excipient ingredient in Ilaris drug product, nor used as a starting material or solvent in the current manufacturing process for canakinumab drug substance. However, its presence cannot be completely excluded as benzyl alcohol may leach out from the membranes of drug substance storage bags. Testing of drug substance batches stored at -60ºC at the end of 36-months shelf-life shows concentrations below 0.5 µg benzyl alcohol per mL of drug substance.* *The level of benzyl alcohol is further reduced during Ilaris drug product manufacture by dilution with excipients. When treated with canakinumab, an infant of 2.5 kg (treated at the maximum dose of 8 mg/kg) would receive a dose of 20 mg canakinumab, resulting in 0.067 µg benzyl alcohol subcutaneously. In summary, adults and children treated with the maximum dose of Ilaris would be exposed to benzyl alcohol levels several orders of magnitude below those reported to lead to toxic signs after intravenous administration. A cumulative search*	This is acceptable.

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
	of the Novartis safety database for spontaneous and solicited reports revealed no case reports associated with benzyl alcohol toxicity. The removal of the benzyl alcohol toxicity as a potential risk has been documented in the updated Australian-Specific Annex to the RMP [ASA v4] provided in this response.	
The proposed pharmacovigilance plan contains a number of internal inconsistencies that require clarification:	*Sponsor provided a response to the inconsistencies identified by the evaluator.*	This is acceptable
The ASA v3.1 does not list two planned studies regarding sJIA identified by the core RMP version 7.1. The sponsor should amend the ASA accordingly. These studies are: Phase IV study (under development) SJIA Pharmachild registry	*The Australian-Specific Annex [ASA v4] has been updated to add the two planned SJIA related studies (ACZ885G2306: Phase IV study on dose reduction or dose interval prolongation; ACZ885G2401: SJIA Pharmachild registry) in the pharmacovigilance plan. Copies of the latest study protocols for [ACZ885G2306] and [ACZ885G2401] are provided in Module 1.13.1.*	This is acceptable.
As a condition of marketing approval for canakinumab in the treatment of sJIA in the United States, the following study has been requested: 'a long-term safety study in 100 paediatric patients 2 to 17 years of age with systemic JIA (sJIA) treated with canakinumab to evaluate for the risks of serious infections, neutropenia, thrombocytopenia, severe injection site reactions, and MAS. The study should include a control group of sJIA patients not receiving canakinumab. Patients should be followed for 5 years'. The sponsor should include this study in the pharmacovigilance plan.	*Novartis accepts the request and has updated the Australian-Specific Annex [ASA v4] to add the proposed long-term safety study for sJIA requested by the US FDA in the pharmacovigilance plan. A copy of the study protocol for [ACZ885G2403] has been provided to the TGA.*	This is acceptable.
Unfortunately, the protocols for the two planned studies involving patients with sJIA have not been submitted with this application. Therefore, they cannot be evaluated at this stage. It is recommended that the sponsor submit these protocols to the TGA.	*Copies of the latest protocols for [ACZ885G2306] and [ACZ885G2401] studies are provided.*	The protocols have now been provided by the sponsor, however in light of this additional information it is now reasonable to suggest that the sponsor implement a registry of Australian patients taking

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
		canakinumab. This was strongly advised by ACSOM (see ACSOM meeting notes attached below).
The sponsor has not adequately addressed a number of issues regarding the potential for medication error etc within the core RMP version 7.1. As a result, this section cannot be evaluated at this time. It is recommended that the sponsor address these issues, including up to date information regarding the post-marketing experience of medication error and off-label usage.	*In order to address the potential issues on medication errors, overdose, transmission of infectious agents, misuse for illegal purposes, and off-label use for paediatric use that are not discussed by the core RMP, Novartis hereby provides the [EU RMP v7.1] which we propose to apply in Australia. These issues are discussed in Section 7 (Part II Safety Specification Module SVI). The major differences are summarised as part of the response to recommendation 1 above in order to facilitate review of the replacement document.*	This is acceptable.
Table 10-3 in core RMP version 7.1 is inconsistent with the list of ongoing safety concerns presented in table 8-1. This should be amended.	*Novartis wishes to clarify that only the safety concerns that have additional risk minimisation activities (beyond routine) are discussed in section 10.1: Risk Miminisation Measures by Safety Concern (Tables 10-1 to 10-10) in line with the summary table (Table 10-11). Nonetheless, Novartis will make the necessary changes to also include important and potential risks that have routine but no additional risk minimisation activities at the time of the next update. In the [EU RMP v7.1] provided with this response, the list of safety concerns is shown in Table 9-1 with the additional concerns for sJIA of DILI, leukopenia, decreased estimated creatinine clearance and proteinuria, musculoskeletal pain and arthralgia, pulmonary complications: pulmonary hypertension and interstitial lung disease, eosinophilia. The risk mimimisation measures for all 29 safety concerns are now described in section 12.1.*	This is acceptable.
(a) The updated Australian-specific material should be submitted to the TGA for review, prior to supply of canakinumab.	*Novartis agrees that Australian-specific educational material for physicians, patients and carers of paediatric patients will be developed*	The sponsor should advise the TGA of the planned dates for supply and submit

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
(b) The educational materials should be made available to physicians and patients at the time of supply (this is also a condition of market approval in the EU). (c) The patient alert card for sJIA should include a paediatric alert card for carers of paediatric patients. The sponsor has agreed to a similar recommendation for the CAPS indication. (d) It is recommended that the sponsor provide feedback on the effectiveness and/or usefulness of the educational materials for sJIA patients.	*and submitted for approval by the Office of Product Review prior to supply of Ilaris in Australia. These educational materials will be made available to physicians, patients and their carers at the time of supply. Effectiveness and/or usefulness of the education materials for sJIA will be evaluated through planned assessment of Periodic Safety Update Reports (PSURs), where changes in the pattern of the RMP risks and all safety topics are closely monitored.*	these materials as soon as possible to the TGA for review
In regard to the proposed routine risk minimisation activities, the Delegate may wish to revise the draft Product Information document as follows: (a) Under 'Precautions' an additional warning regarding the risks of leukopenia should be added. This is also in line with the conditions of approval in the EU. (b) Under 'Paediatric patients' an additional statement should be added clarifying that Ilaris is not indicated in children below 2 years or <7.5kg. (c) Under 'Paediatric population' the Delegate may wish to consider the wording regarding potential for increased risk of infection in paediatric patients, especially those aged under 11 years: In light of the CAPS study results which showed a significant difference in the rates of infection in the younger paediatric population compared to older paediatric patients. Table 7-1 in the core RMP version 7.1 shows that 100% of the paediatric CAPS patients aged from 2 to 3 years developed infections. Of the group aged 4 to 11 years, 82.1% developed infections. This was reduced to 73.5% in the older paediatric age group from 12 to 17 years, a similar result to the adult population of 75.3%. This revised statement should also	*a) Novartis does not agree to add a warning statement on leukopenia in order to align with the conditions of approval in the EU. Novartis is of the opinion that the proposed statement on observed 'decreased white blood cells' available in the Precaution Laboratory Parameters – Haematology section of the Australian PI, as well as the Adverse Effects section with information from sJIA clinical trials on decreased white blood cell counts, appropriately inform the treating physicians and patients on the risk of a decrease in white blood cell counts.* *b) Novartis accepts that the statement 'The safety and efficacy of Ilaris in CAPS and sJIA patients under 2 years of age have not been established' that was originally proposed with this application to replace the currently approved paediatric dosage statement is no longer appropriate, following our response to RMP recommendation 12(d) for the CAPS patient group and dosage regimen application. Thus, the [draft PI] has been amended so that the Dosage and Administration statement for paediatric patients is 'Ilaris is not indicated for use in children below 2 years or with body weight below 7.5 kg due to a lack of clinical data.'* *c) Novartis acknowledges the evaluator's comments on infection*	Deferred to Delegate

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
include information regarding the importance of close medical supervision and follow-up of any infections, particularly in patients aged under 4 years.	*risk in CAPS patients, where the relevant statements in the PI are still being negotiated with the TGA. However, Novartis does not agree to include a statement on the potential for increased risk of infection in paediatric patients with sJIA below 11 years of age. The sponsor also does not agree to include a statement to recommend close medical supervision and follow-up of any infections for sJIA, particularly in patients aged under 4 years in the 'Paediatric population' section of the PI's Dosage and Administration. The observed incidence rates of infection were comparable across age groups in the pooled sJIA patient population without indicating an increased risk of infection for any of the subgroups. Please note that in accordance with previous instructions by the TGA for the sJIA application, the attached draft PI does not include the proposed changes for the CAPS application that are still under evaluation by the TGA except when relevant to this response.*	
In regard to the proposed routine risk minimisation activities, the Delegate may wish to revise the draft Consumer Medicine Information document as follows: (a) Under the section 'When you must not take it', a statement should be added regarding infections, to the effect of 'If you have any current infection, you should not take Ilaris'. (b) Under 'Side effects', a statement should be added regarding the increased risk of infection in young children and the importance of immediate medical follow up. This statement should focus on the difficulties in identifying infections in young children. For example, 'If your child is taking Ilaris and shows any signs that they may be unwell, such as increased irritability, see your doctor immediately'.	*In response to similar recommendations for the application to revise the CAPS indication, Novartis accepts the requests and had amended the draft CMI accordingly and will include in the revised document provided with this response.*	Deferred to Delegate

Table 8b. Additional recommendations

Additional recommendations		
The ACSOM committee noted the initial data which suggests there will be widespread uptake of canakinumab in Australia. Furthermore, the committee noted that canakinumab is a high yield, but high risk drug used in the treatment of a highly debilitating condition. Although canakinumab appears to have substantial efficacy, there are also a number of serious adverse event associated with its use. ACSOM advised that the proposed pharmacovigilance studies were useful, however noted that the absolute number of patients was quite small, especially given the frequency of potentially serious adverse events in trials and the number of patients who were likely to be prescribed canakinumab in Australia. In this context ACSOM considered that a registry of Australian patients taking canakinumab would be a useful pharmacovigilance activity and would help to detect rare but potentially life threatening adverse events. Members discussed the planned Phase IV study which aims to explore the efficacy and safety.	The sponsor has stated that Australian patients can be included in the CACZ885D2401 Ilaris Registry. The following statement can be found within the ASA: *Proposed and ongoing studies are applicable to Australia. That is, the design of these studies applies to Australian patients who may be treated with Ilaris for approved or proposed indications.*	Currently, the method by which Australian patients will be included in this study remains unclear. The sponsor is requested to confirm that a statement will be included in the canakinumab educational materials regarding how Australian patients can join this study.

Summary of recommendations

It is considered that the sponsor's response to the TGA request for further information has adequately addressed all of the issues identified in the RMP evaluation report, aside from final changes to the product information document (see *Outstanding issues* below).

Outstanding issues

Issues in relation to the RMP

In regards to routine risk minimisation, final changes to the Australian product information and proposed indication are deferred to the Delegate.

In regards to the proposed dosing regimen, Advisory Committee on the Safety of Medicines (ACSOM) commented that the above dosing instructions for the CAPS indication are difficult to interpret and noted the large discontinuities in the dosing regimen, for example, patients weighing 16 kg receive a dose of 32 mg, while patients weighing 14 kg receive a dose of 56 mg. The committee was unsure of the rationale for this regimen.

The sponsor must provide a copy of the updated Australian educational materials as soon as possible to the TGA for review. The sponsor is requested to confirm that a statement will be included in the canakinumab educational materials regarding how Australian patients can join the Ilaris Registry Study CACZ885D2401.

The updated ASA contains the following statement in regards to the development of Australian educational materials: '*The development will occur once suitable patients have been identified and will be treated with Ilaris.'* The sponsor should amend this statement to clarify that these materials will be developed and reviewed by the TGA *prior to supply* of canakinumab in Australia. It is requested that this statement be included as a condition of registration for canakinumab in SJIA.

The sponsor has provided an updated EU-RMP. However, the data lock point for this RMP is 31 December 2012 for postmarketing data. This is more than 12 months out of date and the sponsor is requested to submit a more current EU-RMP to the TGA for review prior to approval.

Otherwise, the sponsor has addressed all issues in relation to the RMP.

Advice from the Advisory Committee on the Safety of Medicines (ACSOM)

A summary of the advice is provided below; the full ACSOM report is attached at the end of this document.

- The committee noted that while the summary of ongoing safety concerns proposed by the sponsor is extensive, as this is a drug which has the potential to cause a number of serious adverse events, ACSOM advised that the ongoing safety concerns should be updated in accordance with the recommendations outlined in the Office of Product Review (OPR) Risk Management Plan (RMP) evaluation report.
- Members noted the likely risk of vaccine interactions, given current Australian National Immunisation Program (NIP) guidelines and the age group which would be using canakinumab. ACSOM noted the recommendation in the product information (PI) that '*No data are available on either the effects of live vaccination or the secondary transmission of infection by live vaccines in patients receiving Ilaris. Therefore, live vaccines should not be given concurrently with Ilaris. It is recommended that, if possible, paediatric and adult patients should complete all immunisations in accordance with current immunisation guidelines prior to initiating Ilaris therapy'.*
- Members were concerned that the risk of pulmonary toxicity had not been adequately addressed. The committee commented that risks of pulmonary toxicity had increased exponentially with the advent of biological and monoclonal antibody therapy.
- The committee was also concerned that elevations in serum transaminases (alanine transaminase (ALT) and/or aspartate transaminase (AST)) occurred in approximately 41% of patients and that 1.5% of patients had elevated bilirubin levels. Most notably, ALT/AST values which were three times the upper limit of normal were reported in 2 (4.1%) patients receiving canakinumab and 1 (2.0%) patient on placebo. ACSOM noted that the observed increases in transaminases could be due to the assay used in the tests. Pyridoxal phosphate increases in blood during inflammation and it is also a co-factor used to measure liver transaminase activity (ALT and AST). Pyridoxal phosphate is not added to most assays. In assays of transaminases where pyridoxal phosphate is not added, ALT and AST can be decreased by inflammation, and therefore

might appear to become elevated when inflammation subsides as a result of a treatment. The committee advised that it would appropriate to ask the sponsor whether the assays used to measure liver function had added pyridoxal phosphate. The results maybe confounded by changes in inflammatory response if pyridoxal phosphate was not added.

- ACSOM supported the idea of ensuring that patients and carers as well as health professionals were aware of the potential for infection, noting that by canakinumab binding selectively to Interleukin-1 beta (IL-1β), infection could manifest without the usual clinical signs, that normally manifest as a result of the IL-1β-dependant inflammatory response, such as fever. The committee supported the sponsor's proposed use of a patient alert card or bracelet to raise awareness of this. The committee added that, in particular, it is important for health professionals and patients to be aware of the risk of urinary tract infections, upper respiratory tract infections and injection site reactions.
- The committee noted the initial data which suggests there will be widespread uptake of canakinumab in Australia. Furthermore, the committee noted that canakinumab is a high yield, but high risk drug used in the treatment of a highly debilitating condition. Although canakinumab appears to have substantial efficacy, there are also a number of serious adverse event associated with its use. ACSOM advised that the proposed pharmacovigilance studies were useful, however noted that the absolute number of patients was quite small, especially given the frequency of potentially serious adverse events in trials and the number of patients who were likely to be prescribed canakinumab in Australia. In this context ACSOM considered that a registry of Australian patients taking canakinumab would be a useful pharmacovigilance activity and would help to detect rare but potentially life threatening adverse events.
- Members discussed the planned Phase IV study which aims to explore the efficacy and safety of dose reduction or dose interval prolongation in canakinumab treatment-naive patients who are both responders and who satisfy pre-defined criteria for inclusion. The committee advised that the results from this study would be quite important as the dose-response data are not very clear and it would appear that lower doses would also be effective. The committee also noted that patients' responses to canakinumab persisted long after the dosing had ceased. In this context, members indicated that the results from the Phase IV study may provide greater insight in this regard. ACSOM advised that the results from this study should be used to inform prescribers of the most appropriate maintenance dosing schedule. Until such time as the results from this study are available, the committee advised that practical guidance should be provided to prescribers on how dosing can be reduced over time, how to monitor for development of anti-drug antibodies and clarity around appropriate dosing in non-responders.
- The committee noted that in Europe the recently approved dosage regimen for patients aged 4 years and older is:
  - 150 mg with body weight > 40 kg
  - 2 mg/kg with body weight ≥ 15 kg and ≤ 40 kg
  - 4 mg/kg for patients with body weight ≥ 7.5 kg and < 15 kg
- and for patients aged two to four years dosing is:
  - 4 mg/kg for patients with body weight ≥ 7.5 kg
- ACSOM commented that the above dosing instructions for the CAPS indication are difficult to interpret and noted the large discontinuities in the dosing regimen, for example, patients weighing 16 kg receive a dose of 32 mg, while patients weighing 14

kg receive a dose of 56 mg. The committee was unsure of the rationale for this regimen.

- The committee was concerned about the risks associated with the use of canakinumab during pregnancy. ACSOM advised that the animal studies used to determine the suitability of canakinumab for use in pregnancy were insufficient as the pharmacological response in animals does not sufficiently predict a human response, as human viruses which animals are not exposed to cannot be taken into consideration. The committee further advised that the information in the PI regarding this should be clarified and use during pregnancy should be restricted until human data is available. The committee advised that until such data is available, canakinumab should be in Pregnancy Category D[15] or X[16], not B3[17].

Key changes to the updated RMP

In their response to the TGA request for further information the sponsor provided an updated EU-RMP Version 7.1 dated 13 August 2013 with Australian Specific Annex dated 31 January 2014. Key changes from the version evaluated in the first round evaluation are summarised below (Table 9).

Table 9. Key changes to the RMP

	Key change
Safety specification	Additional Identified risks for SJIA: - Drug Induced Liver Injury (DILI, Hepatic transaminases and Bilirubin elevations) - Leukopenia - Decreased estimated creatinine clearance and proteinuria - Musculoskeletal pain and arthralgia Additional Important Potential risks for SJIA: - Eosinophilia - Pulmonary complications: pulmonary hypertension and interstitial lung disease Removal of important potential risk: benzyl alcohol toxicity (for CAPS)
Pharmacovigilance activities	Updated study status and milestones. Additional information in the ASA relating to the inclusion of Australian patients into CACZ885D2401.
Risk minimisation activities	Details of the proposed updates to the educational materials

The evaluator has no objection to the above changes and recommends to the Delegate that the updated version is implemented (see below).

[15] Category D: Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.
[16] Category X: Drugs which have such a high risk of causing permanent damage to the fetus that they should not be used in pregnancy or when there is a possibility of pregnancy.
[17] Category B3: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.
Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

Suggested wording for conditions of registration

RMP

The European Risk Management Plan (Version 7.1 dated 13 August 2013, data lock point 31 December 2011 for clinical trial data and 31 December 2012 for post marketing data), and the Australian Specific Annex (Version 4 dated 31 January 2014), both must be revised and updated to the satisfaction of the TGA prior to the approval of this application.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

The drug's formulation is that of a lyophilised powder that is reconstituted with water for injections and administered as a subcutaneous injection. No new relative bioavailability studies or biocomparability studies were conducted specific to the sJIA clinical program as the drug product used in the Phase III trials is the same as the current marketed product.

Nonclinical

No new nonclinical data were submitted. The nonclinical evaluator was of the opinion that this strategy was acceptable as the efficacy of canakinumab in sJIA was appropriately derived from clinical studies and a thorough nonclinical hazard assessment was previously performed for the CAPS indication and its subsequent variation to extend the CAPS patient group to include also children aged 2 to 4 years.

The sponsor submitted an Addendum to the Nonclinical Overview (plus 18 cited references) which discussed the specific systemic juvenile idiopathic arthritis indication and also updated the non-clinical exposure margins.

Simulated exposure data from a population-based PK model were compared to exposure data obtained from the previously submitted marmoset 13 week SC and 26 week IV toxicology studies. The typical sJIA patient in the population-based PK model weighed 33 kg and was subjected to a dosing regimen of 4 mg/kg every 4 weeks for six months steady state. When the model and the marmoset data were compared, the relative exposure ratios at the NOAELs in the pivotal marmoset toxicology studies were approximately 80 to 100. Therefore the nonclinical evaluator was of the opinion that the new indication and its associated dosage regimen do not significantly affect the risk assessment of canakinumab toxicity as these relative exposure ratios are very high. The clinical Delegate concurs.

There were no nonclinical objections to the registration of canakinumab for the treatment of active sJIA in patients aged 2 years and older.

No changes to the Product Information were recommended on the basis of the nonclinical findings.

Clinical

Pharmacokinetics

Clinical pharmacokinetic (PK) data in the sJIA population and based on a sparse sampling approach were collected in the Phase II dose-finding study (A2203), the pivotal Phase III

studies (G2301 and G2305) and the extension study (G2301E1). Study A2203 also collected single dose PK data.

The findings are summarised in *Evaluator's overall conclusions on pharmacokinetics above.*

Pharmacodynamics

PK data collected in the Phase II/III studies were used in the development of PK-flare models to explore the relationship between canakinumab exposure and efficacy. The PK-flare model enabled the estimation of the critical flare concentration, *Ki*, the latter being the concentration at which there is a 50% probability of clinical relapse (flare).

The findings are summarised under *Evaluator's overall conclusion on pharmacodynamics above.*

Dosage selection for the pivotal studies

The dose used in the Phase III studies was based on the PK/PD model analysis performed in Study A2203. From this analysis it was estimated that 94% of sJIA patients would not flare at a dose of 4 mg/kg over a 4 week period. As noted by the clinical evaluator, while there was some gain in efficacy at doses above this level, the level of the gain was not considered large enough to justify higher monthly dosing. The Delegate would agree with the clinical evaluator that the justification for selecting the 4 mg/kg dose of canakinumab for the Phase III studies in sJIA is acceptable.

Efficacy

There were two pivotal Phase III efficacy and safety studies (G2301 and G2305), one Phase II repeated dose-finding study (A2203) and one uncontrolled extension study (G2301E1).

Pivotal efficacy studies

Study G2305 was a randomised, double-blind, placebo-controlled, single-dose, 4 week study assessing the short term efficacy of canakinumab 4 mg/kg in patients aged 2 to 19 years with active sJIA. The primary objective of the study was to demonstrate that the proportion of patients meeting the adapted paediatric ACR30 criteria[18] at Day 15 was higher with canakinumab compared with placebo. There were a number of secondary objectives. Patients were randomised to canakinumab or placebo in a 1:1 ratio and received either canakinumab 4 mg/kg SC or placebo on Day 1.

Statistical considerations, sample size calculation etc.

The Full Analysis Set (FAS) consisted of all randomised patients who received at least one dose of study drug. The sample size was determined on the basis of detecting a treatment difference of 30% between the active and placebo groups in the proportion of patients who responded (60% versus 30% respectively). The sample size was calculated to be 61 patients per group in order to yield 90% power to detect a significant treatment difference using a one-sided significance test with $\alpha = 0.025$ based on Fisher's exact test. If the primary objective was achieved, secondary endpoints were assessed in a closed testing procedure in order to control the overall Type 1 error rate (one-sided tests).

[18] Adapted American College of Rheumatology paediatric 30 criteria – improvement from baseline of at least 30%, in at least 3 of the first 6 response variables [Physician's global assessment, parent's or patient's (as appropriate) global assessment, functional ability (CHAQ), number of joints with active arthritis, number of joints with limitation of motion and CRP].

Participant flow

A total of 84 patients were randomised, 43 to canakinumab and 41 to placebo. This fell well short of the projected enrolment based on the sample size calculation of 61 in each treatment group, that is, a total enrolment of 122 patients. The only reported reason patients discontinued from the study was unsatisfactory therapeutic effect with 90.2% of patients in the placebo group continuing for this reason compared with 14.0% of patients in the canakinumab group. In its pre Advisory Committee on prescription medicines (ACPM) response the sponsor is requested to explain how the projected short fall in enrolment may have affected the power calculations of the study.

Baseline data

The majority of patients (92%) were Caucasian, 41% were male, and the mean age was 9.0 years with the largest proportion of patients being aged 6 to 11 years (43%). Canakinumab and placebo groups were generally comparable with the exception of the number of patients aged 2 to <4 years (all on canakinumab), and a lower proportion of patients aged 6 to <12 years on canakinumab than on placebo (32.6% versus 53.7%, respectively).

Baseline CRP levels, number of active joints, number of joints with limited range of motion, pain intensity using a 0 to 100 mm VAS, and CHAQ scores are consistent with a population of sJIA patients with moderately severe active disease. Baseline disease appeared to be slightly more severe in patients in the canakinumab group compared to patients in the placebo group, based on patient's global assessment of overall wellbeing (62.9 versus 55.6), pain (69.7 versus 60.9), number of active joints (15.8 versus 12.4), and number of joints with limited range of motion (14.3 versus 12.4), although all of these variables varied widely.

Results for the primary efficacy outcome

There was a higher proportion of patients with an ACR30 at Day 15 in the canakinumab group (36/43 or 83.7%) compared with the placebo group (4/41 or 9.8%). Patients in the canakinumab group were more likely to respond to treatment compared with patients in the placebo group (OR 62.29; 95% CI [12.68, 306.07]; p<0.0001). As noted by the clinical evaluator, the wide CI reflects the small sample size.

The results were consistent for all ACR responders at Day 15 regardless of gender, age or baseline corticosteroid usage. For example, in patients aged 2 to <4 years of age, an ACR30 was seen in 7/9 (77.8%) patients (there were no placebo patients in this age category).

Results for other efficacy outcomes

Each of the steps in the closed testing procedure for the secondary efficacy outcomes was satisfied. In other words, each of those outcomes was statistically significant.

Study G2301

This was a 2 part Phase III study to evaluate the efficacy and safety of canakinumab 4 mg/kg every 4 weeks (q4w) in patients with sJIA and active systemic manifestations. Part I consisted of a 32 week open-label, single-arm active treatment, and Part II was a randomised, double-blind, placebo controlled, event-driven withdrawal study of flare prevention. Part I had four sub-parts. The aims of Parts Ia and Ib were to induce and maintain at least an ACR30 response without steroid tapering. Part Ic aimed to reduce steroid dose prior to the potentially long duration of Part II and to evaluate steroid tapering in responders. Part Id was designed to stabilise patients on an achieved steroid dose before entering Part II. The study design is shown in Figure 7 of the CER.

The primary objective of Part I was to assess if canakinumab allowed tapering of steroids as per protocol in at least 25% of the patients, while for Part II, the primary objective was

to demonstrate that the time to flare was longer with canakinumab than with placebo. There were a number of secondary and exploratory objectives.

The inclusion and exclusion criteria were the same as those for Study G2305, with the exception that patients did not have to be canakinumab naive.

In Part I, patients received a single dose of canakinumab (4 mg/kg to a maximum of 300 mg) SC every 4 weeks. Patients on steroids were not permitted to taper the dose in Parts Ia or Ib, but could do so in Part Ic if the ACR30 response was maintained. This reduced steroid dose was to be maintained in Part Id. Patients who were unable to maintain a minimum ACR30 response in Parts Ia, Ib, or Ic were discontinued from the study but were eligible to enter the extension study, G2301E1.

Patients who maintained a minimum ACR30 response throughout Part I were randomised to either canakinumab (4 mg/kg to a maximum of 300 mg) or matching placebo SC every 4 weeks in Part II. Therefore, patients in the placebo group had received at least one dose of canakinumab in Part I of the study.

The planned duration of Part I was a maximum of 32 weeks (Part Ia: 4 weeks; Part Ib: 4 weeks; Part Ic: up to 20 weeks; Part Id: 4 weeks). The average planned duration of Part II was estimated to be 75 weeks. The study was stopped when the required number of 37 flare events had occurred in Part II and all eligible patients had completed Parts Ic and/or Id.

Statistical considerations, sample size calculation etc.

Randomisation and blinding was not required for Part I (open-label, active treatment period). Randomisation into Part II was stratified by oral prednisone (or equivalent) dose at baseline (two strata: ≤ 0.4 mg/kg, > 0.4 mg/kg) and degree of adapted ACR Paediatric response reached at end of Part Id (two strata: > ACR50, ≤ ACR50).

Part I and Part II of the trial each had a Full Analysis Set (FAS) and a Safety Set (SS). The FAS for Part I (FAS I) and Part II (FAS II) consisted of all patients who received at least one dose of study drug in Part I or Part II, respectively. Patients were analysed according to the treatment they were assigned at randomisation in Part II (intention-to-treat principle). There was no Per-Protocol Analysis Set.

The sample size for Part II was determined on the basis of the difference between the active and placebo groups in the percentage of patients who flared in the first 24 weeks of Part II, the percentages of patients to flare estimated to be 25% of those in the active group versus 70% in the placebo group. The sample size was calculated to be 29 patients per group (Part II) in order to give 90% power to detect a significant treatment difference using a one-sided significance test with $\alpha=0.025$ based on Fishers' exact test. The clinical evaluator requested that the sponsor provide the clinical justification for these percentage estimates. The sponsor's response was dealt with in the second round of evaluation.

Analysis of the primary outcome for Part I of the study was descriptive only, comprising the frequency and percentage of patients who were able to taper oral steroids together with a two-sided 90% exact confidence interval (CI).

The primary outcome for Part II of the study (time to flare events in Part II with canakinumab versus placebo) was analysed using a one-sided stratified log-rank test at the 2.5% significance level with the stratification factors entered as explanatory variables. The hazard ratio (HR) and its associated 95% two-sided CIs were estimated. Kaplan-Meier (K-M) estimates and the 95% CIs of the probability of experiencing a flare event were calculated from the beginning of Part II. The cumulative event of the probability to stay flare free (1-the probability of experiencing a flare) were plotted against time.

As noted by the clinical evaluator, sustained efficacy was important, therefore patients who discontinued the study while in Part II were counted as flares unless they discontinued because of inactive disease for at least 24 weeks in Part II.

Participant flow

Of the 177 patients who entered Part I of the study, 100 were randomised into Part II (50 each to canakinumab and placebo). There were 72 (72/177 or 40.7%) patients from Part I of the study who discontinued and the primary reason motivating discontinuation was unsatisfactory therapeutic effect. These 72 were made up as follows: 27 who withdrew with no initial response at Day 15, 15 who withdrew because of loss of response after day 15, 26 because of steroid tapering failure, 2 with CRP ≥ 10 and 2 with flare. In addition, there were 4 who withdrew because of adverse events and one person who died.

In Part II, 63 patients completed the study (either achieved 24 consecutive weeks of inactive disease or were still active in Part II at the time of study closure [that is, after the 37 flare events were achieved]). There were 11 discontinuations in the canakinumab group (11/50 or 22%) and 26 discontinuations in the placebo group (26/50 or 52%). The primary reason for discontinuation in Part II for both treatment groups was unsatisfactory therapeutic effect (11/50 or 22% canakinumab; 20/50 or 40% placebo). All discontinuations due to AEs (n=4, 8%) were in the placebo arm. As well in the placebo group, there was one subject who withdrew consent and one protocol deviation.

Baseline data

In Part I, the majority of patients (85%) were Caucasian, 45% were male, and the mean age was 8.7 years with the largest proportion of patients being aged 6 to 11 years (43%). There were 21 patients (12%) aged 2 - ≤4 years. This distribution was similar in Part II in both the placebo and canakinumab groups, with the exception of a larger proportion of patients aged 4 to 5 years in the placebo group (22%) compared with the canakinumab group (10%), and the converse in patients aged 6 to 11 years (36% in the placebo group, 48% in the canakinumab group). There were 10 patients (5 each in the placebo and canakinumab groups, 10%) aged 2 - ≤4 years.

Most patients had a polyarthritic pattern of disease. The majority of patients reported the presence of systemic signs after the first 6 months of disease (83.6%) and the median number of active joints was 10.0. Approximately 72% of patients were taking a steroid at baseline. Disease history was broadly similar between the two treatment groups. The majority of patients (84.2%) were taking a medication prior to study start. The Delegate agrees with the clinical evaluator that the study participants were representative of patients with active sJIA.

Results for the primary efficacy outcome

Part I

The primary objective of Part I of the study was to assess whether canakinumab allowed tapering of steroids as per protocol in at least 25% of the patients who entered the study taking a steroid. This objective was achieved as 57 (44.5%) of the 128 patients who were taking steroids at entry into Part I achieved successful steroid tapering at the end of Part Ic ($p<0.0001$; 90% CI: 37.1, 52.2).

Part II

The probability of experiencing a flare event in Part II was lower for patients receiving canakinumab treatment compared with placebo treatment. There was a statistically significant 64% relative risk reduction of experiencing a flare in patients on canakinumab compared with placebo (hazard ratio [HR] 0.36; 95% CI: 0.17 to 0.75; p=0.0032). The median time to flare in the placebo group was 236 days and could not be estimated in the

canakinumab group as less than 50% of patients flared during the study. Please see Table 10 below which is copied from the CER (Attachment 2).

Table 10. Survival analysis of time to flare in Part II, FAS, Study G2301

Treatment	n	Number of events	Kaplan-Meier estimate Median in days (95%-CI)	Stratified log-rank test Hazard ratio to Placebo (95%-CI)	One-sided p-value
ACZ885	50	11	Not est.	0.36 (0.17, 0.75)	0.0032 *
Placebo	50	26	236.0 (141.0 , 449.0)		

Log-rank test adjusted for stratification factors prednisone (or equivalent) dose and ACR 70 Paediatric response reached at the end of Part Id. Patients who discontinued the study while in Part II were counted as flared unless they discontinued because of inactive disease for at least 24 weeks in Part II. Not est. = Not

The rate of flare was similar in both treatment groups for the first 4 months, continued at a similar rate thereafter in the placebo group, with few flares after 4 months in the canakinumab group. In the study there was a higher rate of discontinuations in the placebo arm and these discontinuations were considered 'flares' in the primary analysis. If patients who discontinued the study for any reason (with the exception of flare) were censored at the time of study discontinuation (rather than counted as flared), the results showed a non-significant relative risk reduction to flare of 49% with canakinumab treatment relative to placebo (HR 0.51; 95% CI: 0.23 to 1.12; p=0.0445 [one-sided significance level 0.025]). As noted in a comment by the evaluator, the counting of these discontinuations as 'flares' may have biased the efficacy results in favour of canakinumab and so the analysis that censored such patients may be a better reflection of the comparative efficacy of canakinumab and placebo. The sponsor was asked to comment on this at the time clinical questions were sent to the sponsor at the end of the first round of evaluation. The sponsor's response will be examined later in this overview. The ACPM will be asked to comment on this issue. The Delegate would like the sponsor to clarify the exact number of flares in each group in the above analysis which showed a non-significant relative risk reduction to flare of 49%. Was the above analysis using censored results pre-specified in any way? The Delegate would like to foreshadow that the sponsor will be requested to provide a detailed summary of all these various analyses, the primary, the first re-analysis using censored data (that is, the one above with the non-significant result) and the second re-analysis which the sponsor submitted in answer to the clinical questions.

Results for other efficacy outcomes

Part I

Steroid reduction

Of the 128 patients who were taking steroids at entry into Part I, 66 (51.6%) were on an oral steroid dose ≤ 0.2 mg/kg at the end of Part Ic, including 42 (32.8%) who were steroid free.

Response according to adapted ACR paediatric criteria

The minimum and maximum ACR responses achieved in Part I of the study are shown in Table 11. The minimum ACR paediatric response levels achieved in Part I are shown graphically in Figure 9 in the CER. From both Table 11 and Figure 9, one can observe a pronounced dip in the response levels between Visits 8 and 10 before the levels rise again. The sponsor is requested to comment on the possible reasons for this dip. Otherwise the Delegate would agree with the clinical evaluator that the percentage of responders did, in general, increase with time.

Table 11. ACR paediatric response achieved in Part I, summary statistics by visit and overall [FAS I]

		ACZ885 N=177	
Time point	Response criterion	Minimum response n (n/m %) (1)	Maximum response n (n/m %) (1)
Visit 4 Part Ia (Day 15)	m	139	139
	Non-Responders	26 (18.7)	26 (18.7)
	ACR 30	113 (81.3)	10 (7.2)
	ACR 50	103 (74.1)	22 (15.8)
	ACR 70	81 (58.3)	33 (23.7)
	ACR 90	48 (34.5)	23 (16.5)
	ACR 100	25 (18.0)	25 (18.0)
Visit 5 Part Ia/b (Day 29)	m	160	160
	Non-Responders	18 (11.3)	18 (11.3)
	ACR 30	142 (88.8)	9 (5.6)
	ACR 50	133 (83.1)	23 (14.4)
	ACR 70	110 (68.8)	36 (22.5)
	ACR 90	74 (46.3)	25 (15.6)
	ACR 100	49 (30.6)	49 (30.6)
Visit 6 Part Ib/c (Day 57)	m	141	141
	Non-Responders	8 (5.7)	8 (5.7)
	ACR 30	133 (94.3)	6 (4.3)
	ACR 50	127 (90.1)	16 (11.3)
	ACR 70	111 (78.7)	28 (19.9)
	ACR 90	83 (58.9)	29 (20.6)
	ACR 100	54 (38.3)	54 (38.3)
Visit 7 Part Ic (Day 85)	m	80	80
	Non-Responders	6 (7.5)	6 (7.5)
	ACR 30	74 (92.5)	3 (3.8)
	ACR 50	71 (88.8)	9 (11.3)
	ACR 70	62 (77.5)	17 (21.3)
	ACR 90	45 (56.3)	22 (27.5)
	ACR 100	23 (28.8)	23 (28.8)
Visit 8 Part Ic (Day 113)	m	67	67
	Non-Responders	0 (0.0)	0 (0.0)
	ACR 30	67 (100.0)	4 (6.0)
	ACR 50	63 (94.0)	4 (6.0)
	ACR 70	59 (88.1)	18 (26.9)
	ACR 90	41 (61.2)	19 (28.4)
	ACR 100	22 (32.8)	22 (32.8)
Visit 9 Part Ic (Day 141)	m	52	52
	Non-Responders	2 (3.8)	2 (3.8)
	ACR 30	50 (96.2)	3 (5.8)
	ACR 50	47 (90.4)	7 (13.5)
	ACR 70	40 (76.9)	17 (32.7)
	ACR 90	23 (44.2)	10 (19.2)
	ACR 100	13 (25.0)	13 (25.0)
Visit 10 Part Ic (Day 169)	m	44	44
	Non-Responders	4 (9.1)	4 (9.1)
	ACR 30	40 (90.9)	2 (4.5)
	ACR 50	38 (86.4)	4 (9.1)
	ACR 70	34 (77.3)	16 (36.4)
	ACR 90	18 (40.9)	11 (25.0)
	ACR 100	7 (15.9)	7 (15.9)
Visit 11 Part Ic/d (Day 197)	m	81	81
	Non-Responders	2 (2.5)	2 (2.5)
	ACR 30	79 (97.5)	1 (1.2)
	ACR 50	78 (96.3)	5 (6.2)
	ACR 70	73 (90.1)	19 (23.5)
	ACR 90	54 (66.7)	24 (29.6)
	ACR 100	30 (37.0)	30 (37.0)
Visit 12 Part Id (Day 225)	m	103	103
	Non-Responders	0 (0.0)	0 (0.0)
	ACR 30	103 (100.0)	0 (0.0)
	ACR 50	103 (100.0)	7 (6.8)
	ACR 70	96 (93.2)	14 (13.6)
	ACR 90	82 (79.6)	25 (24.3)
	ACR 100	57 (55.3)	57 (55.3)
End of Part I	m	175	175
	Non-Responders	40 (22.9)	40 (22.9)
	ACR 30	135 (77.1)	7 (4.0)
	ACR 50	128 (73.1)	15 (8.6)
	ACR 70	113 (64.6)	23 (13.1)
	ACR 90	90 (51.4)	30 (17.1)
	ACR 100	60 (34.3)	60 (34.3)

(1) n= number of patients who satisfy the criteria, m=number of patients with an assessment in the given visit. Patients included only once, in category corresponding to the highest ACR response achieved.
Overall during Part I summarizes the maximal treatment response achieved at any visit during Part I.

At the end of Part I, 22.9% of patients (40/175) were non-responders while 77.1% (135/175) achieved a minimum ACR 30 response. Only 4.0% (7/175) of patients achieved a maximum ACR 30 response. Interestingly, while the percentages of those achieving a minimum ACR response steadily decreased as the ACR target increased, the converse was true for the maximum ACR response. That is to say that the percentages of those achieving a maximum ACR response steadily increased as the ACR target increased. This meant that,

at the end of Part I, there were 34.3% (60/175) of patients who achieved both a minimum and a maximum ACR 100 result. Thus it would appear that if one responded very well to the drug, one responded very well indeed. Also of interest was that, at all time points, all those patients who achieved a minimum ACR 100 response also achieved a maximum ACR 100 response. Of course this may be reflective of the way the minimum and maximum criteria are defined at each level, in that the window of separation between minimum and maximum becomes relatively smaller as one increases from ACR 30 to ACR 100. The sponsor is asked to comment on this finding.

All of the component response variables[19] in the adapted ACR paediatric criteria also improved during Part I.

Summary statistics for the parent's or patient's assessment of pain using a 0 to 100 mm VAS as part of the CHAQ were also provided by the sponsor. At baseline the mean value was 66.7 mm (n = 176). From the beginning of Part Ia to the start of Part Ic, the mean change from baseline was -42.0 mm (absolute change) with -59.0% relative change at Day 15 (n = 139) and -53.5 mm (absolute change) with -80.5% relative change at Day 57 (n = 140). During Part Ic, the decreased level of pain was still evident despite steroid tapering with mean changes from baseline (absolute and relative changes, respectively) as follows: -53.4 mm [-79.4%] at Day 85 (n = 79), 53.8 mm [-81.9%] at Day 113 (n = 66), 53.2 mm [-82.8%] at Day 141 (n = 51) and -50.9 mm [-77.0%] at Day 169 (n = 43). At the end of Part I, the mean change from baseline was -46.4 mm (absolute change) [-67.9% (relative change)] (n = 174). Overall during Part I, 87.4% of patients (152/174) showed at least a 20 mm decrease in pain on the VAS.

Part II

Once the primary objective for Part II had been achieved, secondary endpoints were assessed in a closed testing procedure to evaluate superiority of canakinumab over placebo. This was done in order to control the overall Type I error rate ($\alpha = 0.025$, one-sided tests) in the evaluation of the secondary efficacy variables.

Testing for statistical significance was performed for the following secondary variables:

1. Maintenance of adapted ACR Paediatric 30/50/70/90/100 criteria during Part II
2. Change in disability over time by CHAQ
3. Change in HRQoL over time by CHQ-PF50 (physical and psychosocial summary scores)

Maintenance of efficacy

A survival analysis of the time to worsening in ACR level in Part II is shown in the table below (Table 12; also in Attachment 2). The probability of experiencing a worsening in ACR level in Part II was lower for the canakinumab group compared with the placebo group. This corresponds to a statistically significant relative risk reduction of 51% for worsening in ACR level (hazard ratio of 0.49; 95% CI: 0.27 to 0.90; p=0.0131). The median time to worsening in ACR level was 141 days for the placebo group, but could not be observed for the canakinumab group as less than 50% of patients experienced a worsening in ACR level in Part II.

[19] Physician's global assessment, parent's or patient's (as appropriate) global assessment, functional ability (CHAQ), number of joints with active arthritis, number of joints with limitation of motion and CRP

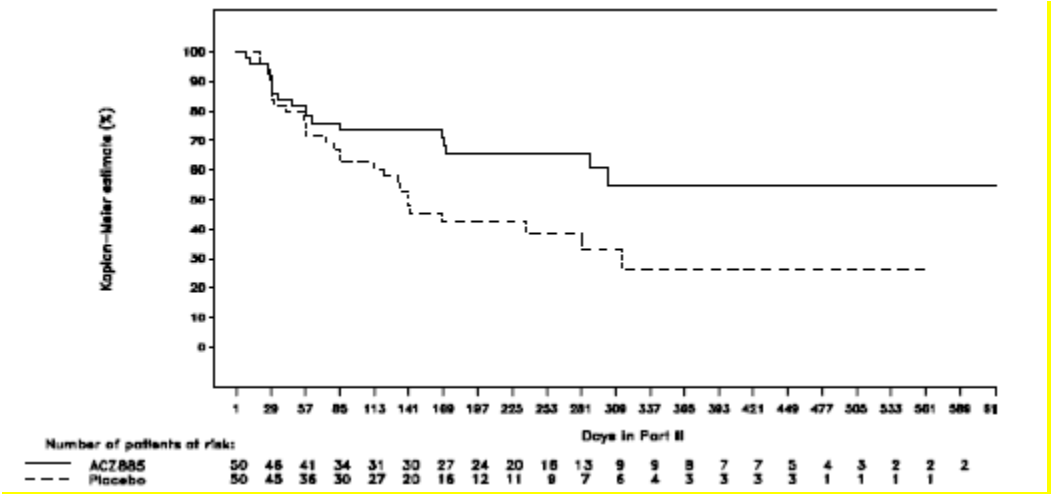
Table 12. Survival analysis of time to worsening in ACR level during Part II, Study G2301 [FAS II]

			Kaplan-Meier estimate	Stratified log-rank test	
Treatment	n	Number of events	Median in days (95% CI)	Hazard ratio to Placebo (95% CI)	One-sided p-value
ACZ885	50	18	Not est. (171.0, Not est.)	0.49 (0.27, 0.90)	0.0131*
Placebo	50	29	141.0 (85.0, 281,0)		

Log-rank test adjusted for stratification factors prednisone (or equivalent) dose and adapted ACR 70 Paediatric response reached at the end of Part Id as covariates. Not est.= Not estimable. *Statistically significant on one-sided significance level 0.025.

Figure 1, shows that in the first 2 months in Part II the probability of not worsening, that is, of maintaining one's ACR response was similar for both treatment groups. However, beyond 2 months, the probability that the ACR response was maintained was greater in the canakinumab group than in the placebo group.

Figure 1. Kaplan-Meier estimate of the probability of not worsening in ACR response during Part II, by treatment group [FASII]



CHAQ disability score

The CHAQ functional ability score is the third response variable in the adapted ACR paediatric criteria. At the beginning of Part II, the median value at baseline in the CHAQ score was 0 for the canakinumab group and 0.1 for the placebo group. At the end of Part II the median change from the start of Part II was 0 for both groups. Thus there was no difference between the two groups in the least squares (LS) mean change over the duration of Part II of the study in the CHAQ disability score (p = 0.4571). Thus the requirements for the success of the second secondary endpoint were not met and so the closed testing procedure for the secondary endpoints had to stop here.

With regard to the CHAQ there was little difference between treatment groups as far as a minimal clinically important difference of improvement was concerned. However, as pointed out by the sponsor, there were more patients with a minimal clinically important difference of worsening in the placebo group when compared with the canakinumab group. Thus at the end of Part II, 14.0% (7/50) of patients in the canakinumab group and 12.0% (6/50) of patients in the placebo group showed a minimal clinically important difference of improvement while 18.0% (9/50) patients in the canakinumab group showed a minimal clinically important difference of worsening compared to 32.0% (16/50) of patients in the placebo group.

Growth velocity (an exploratory endpoint)

Canakinumab appeared to have no negative affect on height as reflected by a small but positive increase in the median change from baseline in height percentile of +2.09 at the end of the study (compared with a change of -0.50 in the placebo group). For the canakinumab group, the largest changes in height percentiles occurred in the two lowest categories. The percentage of patients in the canakinumab group who entered the study in the lowest height percentile category (20th percentile) was 51%. At the end of the study this percentage had decreased to 39%. The percentage of patients in the canakinumab group in the 20th -40th percentile category increased from 22% at baseline to 31% at the end of Part II. The percentages of subjects in all groups of the other higher height percentile categories increased slightly by a few points. For those in the placebo group there was essentially no change between baseline and the end of the study in the composition of the height percentile categories. The changes in weight and body mass index (BMI) percentiles were similar to those for height.

Physical development based on Tanner scale

A shift table of physical development in Part II using the Tanner stages scale was provided by the sponsor and it was stratified by sex and age category. No unexpected effects on physical development were seen.

Other efficacy studies

Study A2203: This was a multi-centre, open label, repeated dose range finding study to evaluate the safety, tolerability, immunogenicity, pharmacokinetics and efficacy of canakinumab given subcutaneously in paediatric subjects with active sJIA. A total of 23 patients were enrolled in the study. Overall there were 13/22 (59%) responders. Median time to relapse ranged from 56 days in patients receiving <3 mg/kg to 100 days in patients receiving 3 mg/kg. Patients on 4 mg/ kg or >4 mg/kg relapsed at a median of 90 or 72 days, respectively. While the 3 mg/kg and 4 mg/kg doses appear to be equivalent in this small study, the 4 mg/kg was the one chosen for use in the pivotal studies and, as noted by the clinical evaluator, this decision was made after analysis of the PK/PD model.

Study G2301E1: This is an ongoing open-label extension study of canakinumab 4 mg/kg every 4 weeks in patients with sJIA and active systemic manifestations who participated in Studies G2301 and G2305. Dose reduction to 2 mg/kg SC every 4 weeks was permitted in individual patients depending on patient's clinical response to the 4 mg/kg dose.

A total of 147 patients were enrolled in the study (40 who were non-responders and 100 who were responders at entry into the extension study). All were included in the efficacy and safety analysis populations for this interim analysis.

Among the 40 patients entering the extension study as a non-responder, 25 (62.5%) became a responder by Month 3, with 18 (72%) achieving a minimum ACR70, 12 (48%) an ACR90 and 7 (28%) an ACR100 response. At the time of the interim analysis, 23/40 (57.5%) patients were responders, and 17 (74%) had a minimum ACR70 response.

Overall, the majority of patients (103/107, 96%) entering the study as a responder remained as a responder at Month 3, with 98% achieving a minimum ACR50, 95% an ACR70, 81% an ACR90, and 65% an ACR100 response. At the time of the interim analysis, 6 of 107 (6%) patients had lost their responder status, 94% had an ACR30, and 95% had a minimum ACR70 response.

In total, 69 patients entered the extension study on steroids and of these, 13 were able to reduce their steroid dose and 20 to discontinue steroids. Even among those patients who had failed steroid tapering in Part I of Study G2301, 17 (43%) patients were able to successfully taper their steroids, including 10 (25%) who became steroid free.

Overall, 31 patients received at least one dose of 2 mg/kg, and 26 patients received at least 3 consecutive reduced doses for a median duration of 224 days (range 59 to 511 days). All 26 patients (17 patients previously treated with canakinumab and 9 patients previously treated with placebo) maintained an ACR100 during the time they received the reduced dose, and none discontinued the study due to lack of efficacy.

Data from the phase III trials G2305, G2301 and G2301E1 were pooled to evaluate the 12 week efficacy in canakinumab treatment naïve patients who had received at least one dose of canakinumab. The ACR response data in the pooled studies was generally consistent with that reported in the individual studies.

Summary of efficacy

There were 2 pivotal Phase III studies in patients with sJIA.

Study G2305 was a randomised, double-blind, placebo-controlled, single-dose, 4 week study assessing the short term efficacy of canakinumab 4 mg/kg in 84 patients (43 on canakinumab, 41 on placebo) aged 2 to 19 years with active sJIA. Because this was only a single-dose study, it is more akin to a proof-of-concept study, albeit on a larger scale. The study demonstrated that canakinumab was more effective than placebo in achieving an ACR30 response at Day 15. Overall, 83.7% on canakinumab and 9.8% on placebo achieved this outcome. The OR for this comparison was statistically significant and represents a clinically meaningful outcome (OR 62.29; 95% CI: 12.68, 306.07; $p < 0.0001$). Secondary efficacy outcomes were supportive and sub-group analyses by age, gender and disease-related factors showed no marked effects on the treatment response.

The pivotal study which must be considered the principal pivotal study is the Study G2301 which consisted of a 32 week open-label, single-arm active treatment period (+ steroid tapering) in 177 patients, followed by a randomised, double-blind, placebo controlled, and event-driven withdrawal study of flare prevention in 100 patients. The active treatment phase of Study G2301 achieved the primary objective, with 44.5% (90% CI: 37.1, 52.2; $p<0.0001$) of patients able to taper their steroids. In Part II, patients on canakinumab had a statistically significant reduction in flare compared with placebo (HR 0.36; 95% CI: 0.17, 0.75; p=0.0032). A clinically relevant reduction in flare remained if patients who discontinued the study were censored rather than counted as flared, but the result lost its statistical significance (HR 0.51; 95% CI: 0.23, 1.12; p=0.0445). In answer to one of the clinical questions asked at the end of the First round evaluation, the sponsor provided yet another analysis, a post hoc sensitivity analysis which defined 'flares' as per the protocol definition or discontinuations from Part II due to unsatisfactory therapeutic effect. The results of this post-hoc sensitivity analysis showed a significant relative risk reduction in flares in the canakinumab group of 57% (HR 0.43; 95% CI: 0.20 to 0.92; p=0.0127 [one-sided significance level 0.025]). There will be more discussion of these re-analyses later in this overview. The Delegate will be requesting further information from the sponsor in relation to this issue.

There was an extension Study G2301E1 which followed a diverse group of sJIA patients from previous canakinumab studies (responders and non-responders). The results demonstrated that 25/40 (62.5%) who were non-responders at entry became a responder by Month 3, and 23/40 (57.5%) were responders at the time of the interim analysis. Among the responders, 103/107 (96%) remained responders at Month 3, and 101/107 (94%) were responders at the time of the interim analysis. The clinical evaluator noted that in this study there were 26 patients who, having achieved steroid tapering or freedom from steroids, received at least 3 consecutive doses of canakinumab 2 mg/kg for a median duration of 224 days (range 59 to 511 days) and that all these 26 patients maintained an ACR100 during the time they received the reduced dose and none of the 26 discontinued the study due to lack of efficacy. This would appear to suggest that some sJIA patients may

be able to be controlled on a canakinumab dose lower than is currently proposed. The sponsor is requested to comment on this issue.

On the downside it is important to note, as did the clinical evaluator, that in Study G2305 14% of participants receiving canakinumab discontinued the study due to unsatisfactory therapeutic response. In Part I of study G2301 this percentage was 41%, including 15% who did not achieve an initial response by Day 15, 8% who lost their initial response after Day 15, and 15% who failed steroid-tapering. This information must be communicated clearly in the proposed PI. Such results raise the issue of how long one should persist with treatment when no response is seen. The sponsor is requested to comment on this issue in its pre-ACPM response and on how it intends to address this issue in the PI.

Safety

Patient exposure

In the combined Phase II and III sJIA studies, 201 patients were exposed to canakinumab for a total of 301.2 patient years. The 201 patients were made up as follows: 24 patients aged 2 to 4 years, 40 aged 4 to 6 years, 86 aged 6 to 12 years and 51 aged 12 to 20 years. There were 130 patients treated for at least 48 weeks.

The Delegate will focus on the safety reporting from the pooled sJIA studies.

All AEs (irrespective of relationship to study treatment)

Overall, 85.1% of patients experienced at least one AE during the study. The most commonly affected primary System organ Classes (SOCs) (by both percentage and exposure-adjusted AE rates) were: infections and infestations (71.1%, 264.9 per 100 patient years), gastrointestinal disorders (52.7%, 152.4), and musculoskeletal and connective tissue disorders (41.8%, 95.0). The most frequently reported AEs were: nasopharyngitis (29.4%), pyrexia (25.9%), cough (25.9%), vomiting (22.9%), diarrhoea (22.4%), upper respiratory tract infection (22.4%), headache (20.9%), rhinitis (19.9%), abdominal pain (19.9%), gastroenteritis (18.4%), and arthralgia (17.9%). Headache was the most common AE based on exposure-adjusted incidence. The highest incidence of AEs occurred in the first 4 weeks of treatment, then generally declined or showed no specific pattern of change. The only exception to this was AEs in the Musculoskeletal and connective tissue disorders SOC, which increased after 24 weeks. The majority of AEs were mild or moderate in intensity, with 16.9% having a severe AE. Individual severe AEs generally occurred in only 1 patient with the following exceptions: pneumonia and MAS (3 patients each), gastroenteritis, septic shock, and varicella (2 patients each).

Subgroup analyses of the incidence of AEs by age group were conducted but were limited due to the small sample sizes in each subgroup and the small number of events. While there were some differences noted, there was no clear relationship with age. For example, anaemia and lymphadenopathy tended to be more common in older patients, while AEs in the SOC 'Injury, poisoning and procedural complications' were more common in younger patients. No trend was seen for infections, but MAS was more commonly reported in patients aged 12 to <20 years.

Treatment-related AEs (adverse drug reactions)

The SOCs reporting the most adverse drug reactions (ADRs) were infections and infestations (14.9%), general disorders and administration site conditions (7.5%), gastrointestinal disorders (6.5%), and investigations (6.5%). Most ADRs by Preferred term (PT) occurred in ≤3 patients, except for MAS (10 patients, 5%), upper respiratory tract infection (URTI) (7 patients, 3.5%), headache (6 patients, 3%), abdominal pain, neutropenia, and pyrexia (5 patients each, 2.5%), alanine aminotransferase (ALT) increased, oral candiasis, juvenile arthritis and cough (4 patients each, 2.5%).

Deaths and other serious adverse events

Four deaths occurred during the sJIA studies. serious AEs (SAEs) were reported in 62 (30.8%) patients. The most commonly reported SAEs were infections and infestations (14.9%), and sJIA-related musculoskeletal and connective tissue disorders (11.9%). The most frequent SAEs (occurring in >1% of patients) were: juvenile arthritis (18/62 or 9.0%), MAS (10/62 or 5.0%), pyrexia (9/62 or 4.5%), abdominal pain (4/62 or 2.0%), gastroenteritis (4/62 or 2.0%), varicella (4/62 or 2.0%), arthralgia (3/62 or 1.5%), and arthritis (3/62 or 1.5%).

Discontinuation due to AEs

Overall, 19 patients (9.5%) discontinued due to AEs, mostly due to SAEs (15 patients).

Liver function

In each of the pivotal studies there was a comprehensive search for drug-related hepatic disorders using Standardised Medical Dictionary for Regulatory Activities (MedDRA) Query (SMQ)[20]. In Study G2305 there was one case of drug-related hepatic disorder in each treatment group (moderate hepatitis on canakinumab, mild hepatomegaly on placebo). In Part I of Study G2301, drug-related hepatic disorder was reported in 9 (5.1%) patients, consisting mainly of investigations for liver-related signs and symptoms (7 patients, 4.0%). Only 3 of these events were considered severe (2 cases of non-infectious hepatitis, and 1 case of hepatic failure which resolved). In Part II of Study G2305, Hepatic disorders consisted entirely of liver-related investigations, and were reported with comparable frequency between the treatment groups (8.0% canakinumab versus 10.0% placebo).

In the pooled sJIA studies, There were 19 (9.5%) sJIA patients with ALT and/or aspartate aminotransferase (AST) values > 3 x upper limit of normal (ULN). For 12 of these patients, the abnormality occurred only once and resolved within 1 month. Six of the remaining 7 patients had more than a single elevation, and/or the abnormality lasted up to 3 months. The remaining patient had a persistent elevation that lasted from Day 215 to Day 866. All these patients also had elevations of < 3 x ULN at other time points. In 5 of the patients with ALT and/or AST values > 3 x ULN, there was a temporal association with MAS. AEs of hepatic failure and autoimmune hepatitis were each reported at the same time as ALT and/or AST values > 3 x ULN for 1 patient each, as were hepatitis and hepatomegaly for 2 patients each. One patient with a transaminase elevation > 3 x ULN was discontinued due to an AE of hepatic enzymes increased. Only 1.5% of patients had bilirubin levels > ULN. There were no patients with abnormalities of liver function parameters corresponding to Hy's Law.

The sponsor, in its pre-ACPM response, is requested to provide a summary of the background to the comprehensive search for drug-related hepatic disorders undertaken in the pivotal studies. What was the particular motivation behind this search? The sponsor is requested to give an up-to-date summary of the incidence of the incidence/frequency of disturbances of liver function and of liver-related adverse events in the sJIA database, in the CAPS database and in the entire canakinumab safety database.

Kidney function

In the pooled sJIA studies, Twenty-nine patients (14.6%) had a notable reduction in creatinine clearance (CrCl) (generally from a high baseline), but the CrCl remained within the normal range in 25 of these patients. In the remaining 4 cases the CrCl was <1.2 x ULN.

[20] Standardised MedDRA Queries (SMQs) are tools developed to facilitate retrieval of MedDRA-coded data as a first step in investigating drug safety issues in pharmacovigilance and clinical development. SMQs are validated, pre-determined sets of MedDRA terms grouped together after extensive review, testing, analysis, and expert discussion.

The sponsor is asked to clarify whether there were any patients who developed renal failure at any time while on canakinumab.

Haematology

The clinically notable haematological abnormalities were summarised for the pooled sJIA studies. While notable abnormalities were common for several of the parameters, mostly they were isolated and were generally associated with either no or mild clinical sequelae. Patients with absolute neutrophil counts of < $1x10^9$/L or Common Terminology Criteria (CTC) Grades 2, 3 and 4 were reviewed for AEs of infection that occurred at a time close to the abnormal value, including those infections that occurred prior to the neutrophil count abnormal values. Most patients did not have infection AEs within 42 days of the neutrophil abnormalities, and of those with infections, the majority were mild or moderate in severity. Only 1 severe infection AE was reported (pseudocroup) and this resolved within 2 days of hospitalisation. The patient continued on study treatment. Low platelet counts were reported in 19 patients, mostly isolated values, and with no AEs related to bleeding reported at or near the time of the abnormal platelet count. Notably high eosinophilia was reported in 75 patients; in 11 patients there were temporally associated AEs related to atopy or allergy, in a further 10 there were AEs related to atopy or allergy but not within 42 days of the abnormal eosinophil count, and in the remaining 54 patients there were no such AEs. There was no increase in hypersensitivity reactions in these patients.

ECG

In the pooled sJIA studies clinically significant abnormal ECG results were observed in 7 patients. Subsequent evaluations reported abnormalities in 3 of these patients. The ECG abnormalities were consistent with the existing medical histories in 2 patients, and no further assessment was performed on the remaining patient following discontinuation from the study due to unsatisfactory therapeutic effect. Twenty-three patients had a QTc(F) > 450 msec, 18 > 480 msec and 8 > 500 msec. In those patients with a QTc(F) > 500 msec, 3 had the value at baseline (2 had subsequent assessments < 500 msec and it was the final assessment for the remaining patient who discontinued due to unsatisfactory therapeutic effect), 1 had subsequent assessments which were < 500 msec, and for 4 the value was the final available assessment. None of the patients with QTc(F) greater than 500 msec had cardiovascular AEs.

Vital signs

Clinically notable increases and decreases in systolic blood pressure (BP) were observed in 22.6% and 27.1%, respectively, of sJIA patients. Generally these abnormalities were isolated, with normal values recorded at subsequent visits. Increases and decreases in diastolic blood pressure (BP) were also recorded (14.1% versus 19.1%, respectively), but again were generally not persistent. None of these patients had AEs of hypertension reported.

Postmarketing experience

No new safety findings were observed in Novartis sponsored clinical trials, non-interventional studies, investigator initiated trials or individual case safety reports.

Unwanted immunological effects

See Attachment 2 for details.

Development of anti-canakinumab antibodies was assessed in the individual studies and in a separate analysis for data from all studies.

Of the 201 sJIA patients in the studies, 196 patients had immunogenicity testing and 14 patients had ADAs detected. Of these 14 patients, 8 patients had ADA detected at baseline only and thus are not considered as treatment-induced, while 6 had post-treatment ADAs with no baseline ADA detected, representing an incidence of 3.1% (6/196). Of the post-

treatment ADA patients, 2 were classified as being transient, 1 persistent and 3 other. No neutralising antibodies were detected in any of the sJIA patients. No events of anaphylaxis or anaphylactoid reactions were reported; therefore IgE testing was not performed in any of the sJIA studies.

None of the 6 patients with post-treatment ADAs had any apparent efficacy consequences, and only 1 patient had a potential allergy/hypersensitivity AE (eyelid oedema and mild coughing, both resolved without action being taken).

Eighteen patients met the definition of loss of efficacy because they 1) showed initial response (≥ adapted Paediatric ACR30) on Day 15 in the study where they received their first dose of canakinumab; and 2) subsequently discontinued the program due to unsatisfactory therapeutic effect secondary to becoming a non-responder. None of these patients had a post-treatment positive ADA detected, although 2 did have a positive ADA at baseline.

In total, 89 patients were identified with 182 AEs potentially related to immunogenicity. No anaphylaxis or anaphylactoid reaction types of AEs were reported. SAEs were experienced by 5 of the 89 patients, yet none of these qualified as immunogenicity-related, and all had more plausible alternative explanations. Eighteen patients experienced 22 AEs that qualified as immunogenicity-related (6 x cough, 5 x erythema/erythematous rash, 3 x oedema) none of which were serious or resulted in study discontinuation. Eleven of the events required no action, with the remaining 11 events required concomitant medications (antihistamines, morphine, antibiotics, expectorant, or antiseptic).

Macrophage activation syndrome

In order to provide a complete evaluation of MAS for sJIA patients using canakinumab, an external independent MAS adjudication committee (MASAC) was formed. The committee reviewed all potential cases of MAS in the sJIA studies. In the CER, there is a table showing the time adjusted rate of reported Macrophage Activation Syndrome (MAS) in the canakinumab sJIA clinical program. The numbers of adjudicated cases of probable or possible MAS were 12 on canakinumab and 2 on placebo giving rates of probable or possible MAS per 100 patient-years of 4.3 on canakinumab versus 7.7 on placebo. This overall incidence is comparable to the background rate reported in the literature. As noted by the clinical evaluator, given that there is a large degree of uncertainty in the estimated background rate of MAS and that the rate in the placebo group was based on limited placebo exposure and also that one of the two placebo cases had previously received canakinumab, the relationship remains uncertain and does require ongoing monitoring and investigation. If one removes the case from the placebo arm, that is, the case involving previous use of canakinumab, the time-adjusted placebo rate is immediately halved and the rate on canakinumab exceeds that on placebo. The sponsor is requested to provide all possible details about the case of the patient in the placebo arm with previous exposure to canakinumab. How long before this patient developed MAS, was he/she exposed to canakinumab and for how long? How long was this patient in the placebo arm before developing MAS? The sponsor is also requested to provide the most up-to-date summary of the incidence/frequency of cases of MAS in the sJIA safety database, in the CAPS database and in the entire canakinumab safety database (that is, covering all uses of the drug). What assurances can the sponsor provide that canakinumab is not causally related to the development of MAS?

Overall assessment of safety

The Delegate would agree with the clinical evaluator that canakinumab was generally well tolerated in the sJIA clinical development program. As noted by the evaluator, the AE profile, apart from macrophage activation syndrome, is similar to that observed in CAPS patients. The sponsor has already been asked to provide an up-to-date summary of the incidence of cases of macrophage activation syndrome in its global safety database. As also

noted by the clinical evaluator, while there was a higher incidence of some AEs in sJIA compared with that in CAPS, this is not unexpected in view of the higher dose used in the treatment of sJIA and after taking into account those AEs which are consistent with a diagnosis of sJIA rather than with the treatment.

Questions asked of the sponsor by the clinical evaluator at the end of the first round of evaluation

There were 3 questions asked of the sponsor related to efficacy. The first concerned the choice of ESR versus CRP and the sponsor explained that the latter was chosen because of its more rapid response to inflammation. The second question concerned the choice of placebo and canakinumab flare rates for sample size calculation. The choice of the flare rate for the canakinumab group was based on existing Phase I/II data where 4 out of 15 patients, that is, approximately 25%, flared in the first 4 weeks. The choice of 70% for the placebo group was based on consultation with external sJIA clinical experts. The Delegate agrees with the evaluator that these responses are acceptable. The ACPM is asked to comment on the choice of 25% and 70% as target flare rates for the canakinumab and placebo groups, respectively.

The third question concerned the issue of classifying discontinuations as 'flares'. The sponsor conducted an additional post hoc sensitivity analysis which defined flares as per the protocol definition or discontinuations from Part II due to unsatisfactory therapeutic effect. Using this modified flare definition, 5 of the 6 placebo patients discontinued for reasons other than an unsatisfactory response and were censored and only 1 patient (who had met the definition for flare prior to being discontinued for an AE [reported as a protocol violation]) was counted as flared. The modified flare definition did not change the number of flares in the canakinumab group (n=11), but reduced the number of flare events by 5 in the placebo group (from 26 to 21). The results of this post hoc sensitivity analysis showed a significant relative risk reduction in flares in the canakinumab group of 57% (HR 0.43; 95% CI: 0.20 to 0.92; p=0.0127 [one-sided significance level 0.025]). The clinical evaluator was of the opinion that the revised definition of flare (censoring patients who discontinued for reasons other than lack of efficacy) for the sensitivity analysis is more appropriate for the evaluation of efficacy. Furthermore the results of this re-analysis were supportive of the primary analysis.

The Delegate however, has concerns. In such a small study, it was obviously of the utmost importance that the definition of flare should have been as precise as possible. This was all the more so given that the double-blind withdrawal phase of the study, namely Part II, was to continue until a total of 37 flare events had occurred. The very power of the study was predicated upon this outcome in that the number of events required to achieve a power of at least 90% with a log-rank test of canakinumab versus placebo was calculated to be 37 events (13 in the canakinumab group and 24 in the placebo group). What implications for the power of the study are there, if 5 or 6 of the events, that is, 13.5% to 16% of the required total, were not in fact genuine 'flares'.

The Delegate requests that the sponsor, in their pre-ACPM, give a full and detailed accounting of every single 'flare' event, of each of the 37 events, considered in the primary analysis. This should be done in a table with 2 columns, one for the canakinumab group and one for the placebo group. Please provide, in at most a couple of lines for each event, the salient features of that event including the time from the beginning of Part II to the 'flare', whether or not the 'flare' met the protocol definition of 'flare' and if not give an explanation of how the definition was not met and why the event was included as a 'flare' and finally the age of the child at the time of the 'flare'. Then the sponsor is requested to explain, in full, each of the re-workings of the primary analysis which involved the censoring of patients. The first re-working is that analysis the results of which showed a non-significant relative risk reduction to flare of 49% with canakinumab treatment

relative to placebo (HR 0.51; 95% CI: 0.23 to 1.12; p=0.0445 [one-sided significance level 0.025]), that is, the analysis discussed in the CER. Please indicate which of the 37 patients included in the primary analysis were censored for this re-analysis and explain why they were censored. The sponsor was requested to explain why this re-analysis was done at the time it was done. Was it the result of a protocol amendment? Was this first re-analysis in any way pre-specified in the protocol?

The second re-working was that submitted by the sponsor in response to Efficacy Question 3 and was the analysis which showed a significant relative risk reduction in flares in the canakinumab group of 57% (HR 0.43; 95% CI: 0.20 to 0.92; p=0.0127 [one-sided significance level 0.025]). Once again please indicate which of the 37 patients included in the primary analysis were censored for this re-analysis and explain why they were censored.

Clinical evaluator's recommendation (if applicable)

The clinical evaluator recommended that the canakinumab indications be extended to include

> '*treatment of active Systemic Juvenile Idiopathic Arthritis (sJIA) in patients aged 2 years and older*'

Risk management plan

The RMP evaluator noted that the sponsor had provided an updated EU-RMP to the TGA. However, as noted by the RMP evaluator, the data lock point for this RMP was 31 December 2012 for postmarketing data which is more than 12 months out of date. The sponsor was therefore requested to submit a more current EU-RMP to the TGA for review prior to approval.

The RMP evaluator has proposed a condition of registration which mentions the following EU-RMP:

> '*The European Risk Management Plan (Version 7.1 dated 13th August 2013, data lock point 31st December 2011 for clinical trial data and 31st December 2012 for post marketing data), and the Australian Specific Annex (Version 4 dated 31st January 2014)*'.

The Delegate requested the sponsor to clarify how the above EU-RMP and ASA need to be revised and updated. The Delegate is aware of the need to have a more up-to-date data lock point for postmarketing data. The Delegate is also aware of a request by the RMP evaluator to amend the proposed statement in the ASA relating to the development of Australian educational materials. The latter issue is discussed in some more detail below. Is the sponsor aware of any further revisions and/or amendments which are required?

The Delegate indicated that a suitably worded condition of registration in relation to the RMP will constructed when all outstanding issues concerning the RMP are resolved.

When advice was sought from the ACSOM, this committee commented that the dosing instructions for the CAPS indication are difficult to interpret and noted the large discontinuities in the dosing regimen, for example, patients weighing 16 kg receive a dose of 32 mg, while patients weighing 14 kg receive a dose of 56 mg. The committee was unsure of the rationale for this regimen. The Delegate notes that this comment is in relation to the CAPS indication and so it is not strictly relevant to this submission which concerns sJIA. If the sponsor wishes to make a brief comment on this issue then it is invited to do so. The sponsor should note that the Delegate intends to impose a condition of registration attached to the approval of this submission, a condition that the sponsor must commence discussions about the CAPS dosing instructions with the relevant clinical

unit within 3 months of the approval of this submission. The Advisory Committee on Prescription Medicines (ACPM) is invited to make a comment if it so wishes.

The RMP evaluator was also of the opinion that the sponsor must provide a copy of the updated Australian educational materials as soon as possible to the TGA for review. The sponsor is requested to confirm that a statement will be included in the canakinumab educational materials regarding how Australian patients can join the Ilaris Registry Study CACZ885D2401. In its pre-ACPM response, the sponsor is requested to address these two issues specifically and outline its proposed course of action in relation to each of those issues.

The final outstanding issue identified by the RMP evaluator was as follows: 'The updated ASA contains the following statement in regards to the development of Australian educational materials: '*The development will occur once suitable patients have been identified and will be treated with Ilaris.'* The sponsor should amend this statement to clarify that these materials will be developed in a timely fashion so that they may be reviewed by the TGA prior to canakinumab being supplied in Australia. It is requested that this statement be included as a condition of registration for canakinumab in SJIA'. The sponsor will be requested to respond to this comment by the RMP evaluator and to outline its proposed course of action in relation to the timing of the development of Australian educational materials.

Risk-benefit analysis

Delegate's considerations

In the single dose study, G2305, 83.7% of patients on canakinumab achieved an ACR30 response at Day 15, compared with 9.8% on placebo. This comparison was statistically significant and clinically meaningful. The treatment response was not affected by gender or age.

In the principal pivotal study, G2301, the primary efficacy criterion of Part I was achieved, in that 57 (44.5%) of the 128 patients who were taking steroids at entry achieved successful tapering of their steroid dose at the end of Part Ic.

In Part II of the principal pivotal study, canakinumab treatment reduced the relative risk of flare by 64% compared with placebo (HR 0.36, 95% CI[0.17, 0.75], p = 0.0032]. Median time to flare was 236 days for placebo but could not be determined for the canakinumab group as the proportion of patients who flared in that group was less than 50%. As has been seen there has been considerable debate about the precise definition of 'flare' used in the study. The primary result was not statistically significant if patients who discontinued the study for any reason (with the exception of flare) were censored at the time of study discontinuation rather than counted as flared. The results of this first sensitivity analysis were submitted with the dossier. In response to a question from the clinical evaluator about this issue of censoring, an additional post hoc sensitivity analysis was submitted by the sponsor. This second re-working of the primary analysis included discontinuations from Part II due to unsatisfactory therapeutic effect as flares and censored discontinuations for other reasons. The Delegate has expressed concerns already. G2301 was a study in a relatively small number of patients and the duration of Part II of this study was in fact driven by the number of flare events. The number chosen was 37, also a small number. Upon this number were based the power calculations for the study. There appear to be 5-6 flare events in doubt, all in the placebo group and these 5-6 comprise a not insignificant proportion of the total number, 37, of flares. What are the implications for those power calculations? The Delegate has asked the sponsor to provide, in its pre-ACPM response, a tabular summary of these flare events and to answer a number of questions about the definitions of flare used and the two post-hoc sensitivity analyses.

In the principal pivotal study, G2301, there were a number of secondary efficacy variables, the first of which was the only one which was statistically significant. The probability of experiencing a worsening in ACR level in Part II was statistically significantly lower for the canakinumab group compared with the placebo group. The remainder of the secondary endpoints showed supportive trends.

In the principal pivotal study, G2301, 40.7% of patients withdrew from Part I because of unsatisfactory therapeutic effect. The primary reason for discontinuation in Part II for both treatment groups was unsatisfactory therapeutic effect (22% canakinumab versus 40% placebo). This raises questions about how long should a prescriber persist with canakinumab in the face of continuing nil or poor response. The sponsor has been asked to respond to this issue in its pre-ACPM response. It is most important that information about discontinuations due to unsatisfactory therapeutic effect be communicated in a transparent and accurate fashion. The sponsor will also be asked to address this issue in its pre-ACPM response.

On the other hand there appeared to be at least 26 patients who were able to maintain effective responses on a lower dose, namely 2 mg/kg. The Delegate understands that the possibility of lower dosing is to be tested in a future study. The sponsor will be asked to provide the details of this projected study in its pre-ACPM response.

There is a known risk of infection, including serious infection, with canakinumab. After adjustments for exposure, there was little difference in infectious AE incidence between canakinumab and placebo. The sponsor will be asked to confirm that there were no marked differences between the various paediatric age groups, for example between younger and older children.

Macrophage activation syndrome (MAS) is a rare, life-threatening disorder that can occur in sJIA. After adjustment for exposure, the incidence was higher in the placebo group. However, one of the two patients on placebo who developed MAS had had previous exposure to canakinumab. This would appear to throw into doubt the findings of the time-adjusted rates of MAS. The sponsor has been requested to provide a detailed comment on this issue.

Neutropaenia and thrombocytopaenia, though reported, did not appear to be associated with serious clinical sequelae. Anti-canakinumab antibodies developed in a small proportion (3.1%) of patients. No neutralising antibodies were detected and the development of antibodies did not appear to be associated with particular safety outcomes or with reduced efficacy. However, one must remember that one is dealing with very small numbers.

Overall, the Delegate would agree with the clinical evaluator that the balance of benefit versus risk appears to be in favour of benefit. However, the most important issue to be resolved concerns the question around the integrity of the primary analysis for the principal pivotal study, G2301. It is an issue which the Delegate has requested the sponsor to address in its pre-ACPM response. That is why the Delegate is not in a position to say, at this time, that the application for Ilaris should be approved for registration. The Delegate would like the ACPM to provide some comment on this issue, particularly once the members of the committee have been able to read what the sponsor has to say in its pre-ACPM response.

With regard to the wording of the indication and whether it should be made more restrictive in line with the indication approved in the EU, the Delegate is of the view that the indication should be worded as simply as possible, provided that there are no safety ramifications. The Delegate prefers the simple wording sought by the sponsor, wording which has been approved in both the USA and Canada. The children who require treatment for sJIA in Australia would be most likely seen by specialists in tertiary referral centres. In most cases the options of non-steroidal anti-inflammatory drugs (NSAIDs) and

corticosteroids would have been explored in the patient's work up. There may be rare cases where urgent treatment with a biological is considered in the particular patient's best interests and the Delegate is of the view that this decision is best left to the clinician. The Delegate would be most interested to hear the view of the ACPM in this regard.

Conditions of registration

1. There will be a condition of registration regarding the implementation of the relevant EU RMP together with the Australian Specific Annex. The sponsor is to confirm both the exact versions of the latter and the nature of any revisions required to these documents before implementation.
2. There will be a condition relating to the submission of any final or updated reports of any ongoing or extension clinical studies and of any interim or final reports of any projected studies. The particular wording of this condition will be drafted once the sponsor confirms the identity of these outstanding studies/reports.
3. There may be a need for a condition specifying the timing of the development of Australian educational materials. Whether or not this is the case is dependent upon the sponsor's response to this issue raised by the RMP evaluator.

Delegate's summary of issues

The main issue concerns the precise definition of 'flare' and whether patients should or should not have been censored for not meeting this definition. The sponsor has been asked to provide a detailed summary of this issue in the pre-ACPM response.

Delegate's proposed action

The Delegate not being in a position to say, at this time, that the application for Ilaris should be approved for registration sought the advice of ACPM.

Delegate's request for ACPM advice

The committee is requested to provide advice on the following specific issues:

1. The validity of the result of the primary analysis for the principal pivotal study G2301, particularly as it concerns the precise definition of 'flare' used in Part II of that study and whether or not a number of patients' results should have been excluded from consideration.
2. The proposed wording of the indication, that is '*for the treatment of active Systemic Juvenile Idiopathic Arthritis (sJIA) in patients aged 2 years and older*' and whether it needs to be made more restrictive.
3. The committee is requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Delegate's questions for the sponsor

1. The sponsor is requested to explain how the shortfall in enrolment in the study G2305 may have affected the power calculations of the study.
2. The sponsor has been asked for a detailed commentary on the issue of the precise definition of 'flare' in the principal pivotal study G2301, on whether or not certain patients' results should have been excluded from the primary analysis because of failure to meet the definition of flare and on the degree to which such exclusions would have affected the power assumptions and calculations of the study.

3. From both Table 11 and in Figure 9 of the CER, one can observe a pronounced dip in the response levels between Visits 8 and 10 before the levels rise again. The sponsor is requested to comment on the possible reasons for this dip.
4. The sponsor is requested to clarify the way in which the minimum and maximum ACR criteria are defined at each level. Is it true to say that the window of separation between the minimum and the maximum becomes relatively smaller as one moves from ACR 30 to ACR 100? This was prompted by the observation that, at the end of Part I, there were 34.3% (60/175) of patients who achieved both a minimum and a maximum ACR 100 result at the end of Part I of G2301.
5. There is a suggestion from the extension Study G2301E1 that some sJIA patients may be able to be controlled on a canakinumab dose lower than is currently proposed, namely 2 mg/kg. The sponsor is requested to comment on this issue and to comment on the fact there is a study which is planned to examine the efficacy of this lower dose.
6. The sponsor is requested to comment on the relatively high percentages of patients who discontinued from both pivotal studies because of unsatisfactory therapeutic response. Such results raise the issue of how long one should persist with treatment when no response is seen. The sponsor is requested to comment on this issue and on how it intends to address the matter in the PI.
7. The sponsor is requested to provide a summary of the background to the comprehensive search for drug-related hepatic disorders undertaken in the pivotal studies. What was the particular motivation behind this search? The sponsor is requested to give an up-to-date summary of the incidence of the incidence/frequency of disturbances of liver function and of liver-related adverse events in the sJIA database, in the CAPS database and in the entire canakinumab safety database.
8. The sponsor is asked to clarify whether there were any patients who developed renal failure at any time while on canakinumab.
9. The sponsor is asked to confirm that there were no marked differences in the rates of infection, particularly serious infection, between the various paediatric age groups, for example between younger and older children.
10. The sponsor is requested to provide all possible details about the patient in the placebo arm who developed macrophage activation syndrome and who had a history of exposure to canakinumab. How long before this patient developed MAS was he/she exposed to canakinumab and for how long? How long was this patient in the placebo arm before developing MAS? The sponsor is also requested to provide the most up-to-date summary of the incidence/frequency of cases of MAS in the sJIA safety database, in the CAPS database and in the entire canakinumab safety database (that is, covering all uses of the drug). What assurances can the sponsor provide that canakinumab is not causally related to the development of MAS?
11. The sponsor is requested to clarify to what degree the data evaluated for the indication of sJIA accords with the principle that the total clinical experience must generally include data on a large and representative group of patients (for example 100) exposed to the substance for at least 12 months.
12. The sponsor is requested to identify the precise versions of the EU-RMP and ASA to be included in the relevant condition of registration. The RMP evaluator has indicated that the EU-RMP and the ASA both need to be revised and updated and the Delegate seeks clarification from the sponsor as to the precise amendments required.
13. If the sponsor wishes to make a comment about ACSOM's concern about the dosing instructions for the CAPS indication, then the sponsor may do so. However, the Delegate sees it as more appropriate for the sponsor to commence discussions with

the relevant TGA clinical unit and so the Delegate will devise an appropriately worded condition of registration.

14. The sponsor is requested to respond to the concerns of the RMP evaluator about firstly the provision of a copy of the updated Australian educational materials to the TGA and secondly about the inclusion of a statement in those educational materials as to how Australian patients may join the Ilaris registry study. The RMP evaluator also expressed concern that the Australian educational materials should be available for review by the TGA prior to the supply of canakinumab in Australia. The sponsor is to be requested to explain whether this is feasible and if not, why not?
15. The sponsor is to be requested to supply the details of all outstanding clinical studies and/or reports, including projected clinical studies. See the proposed condition of registration number 2.

Response from sponsor

Novartis Pharmaceuticals Australia Pty Limited acknowledges receipt of the Delegate's Overview for the above mentioned application to extend the indications for Ilaris canakinumab 150mg powder for injection as follows (new text is underlined below):

> *Ilaris is indicated for the treatment of Cryopyrin-Associated Periodic Syndromes*
>
> *(CAPS), in adults and children 2 years and older including:*
>
> - Familial Cold Autoinflammatory Syndrome (FCAS)/Familial Cold Urticaria (FCU)
> - Muckle-Wells Syndrome (MWS)
> - Neonatal-Onset Multisystem Inflammatory Disease (NOMID)/Chronic Infantile
> - Neurological, Cutaneous, Articular Syndrome (CINCA)
>
> ***Ilaris is indicated for the treatment of active Systemic Juvenile Idiopathic Arthritis***
>
> ***(sJIA) in patients aged 2 years and older.***

The sponsor notes that the Delegate agrees with the clinical evaluator that the benefit/risk balance of treating sJIA with Ilaris favours the benefits. Overall, the Delegate agrees with the clinical evaluator that balance of benefit appear to outweigh the risks.

However, the Delegate has expressed certain concerns, particularly around the integrity of the primary analysis for the principal pivotal study, G2301. The Delegate has sought the advice of the ACPM on this matter, as well as the proposed wording of the indications. In addition, the Delegate has asked the sponsor a series of specific questions, which are responded to in the second part of this section. Finally, the sponsor has briefly commented on the proposed conditions of registration and the RMP.

Validity of the results of the primary analysis

Although its underlying cause is unclear, sJIA is widely seen as an auto-inflammatory condition driven by innate pro-inflammatory cytokines, including interleukins 1 and 6 (IL-1 and IL-6). The IL-1 protein drives systemic inflammation and can lead to destruction of cartilage and bone, therefore an IL-1β inhibitor such as canakinumab represents targeted therapy against the inflammatory processes in sJIA.

Novartis' pivotal studies for sJIA consist of: G2305 (blinded) where the efficacy of a single dose of 4 mg/kg canakinumab was compared to placebo in helping patients improve ACR response, systemic and other health assessments; G2301 Part I (open-label) to assess if

canakinumab use allows tapering of steroids while retaining at least ACR30 response; G2301 Part II (blinded) to demonstrate that canakinumab can prolong the time between occurrence of flares. An extension study, G2301E1, assesses the long-term safety and efficacy of canakinumab in sJIA disease control via maintenance of at least ACR30 response.

The Delegate's concerns on the effect of enrolment shortfalls on G2305 study power, the precise definition of flares and impact of discontinuations due to flares in G2301 Part II, and the total clinical experience from a limited number of patients over a limited period are addressed in greater detail in the second part of this response. In summary:

- The Data Monitoring Committee concluded that the primary endpoint had been reached in Study G2305 with high statistical significance, advised that enrolling more patients would not substantially increase the statistical power of the efficacy analysis and felt that it would be improper to expose additional patients to placebo.
- A 'flare event' in Study G2301 Part II was either due to a disease flare or a discontinuation for any reason other than inactive disease. A new sensitivity analysis to count patients with unsatisfactory therapeutic response as flares while censoring patients who discontinued for any other reason shows no significant change in conclusions for the primary endpoint analysis.
- Considering that the indications under investigation are for orphan diseases, the long term exposure to canakinumab still meets the TGA's guidelines. In sJIA, 130 paediatric patients have been exposed to canakinumab for at least 48 weeks and 78 for at least 96 weeks. When CAPS patients are also included, 257 patients have used canakinumab for >48 weeks and 135 for >96 weeks. Novartis will continue to expand its safety database on Ilaris as more patients are exposed to canakinumab.

Despite clinical study limitations inherent to orphan diseases, the overall analysis supports the use of Ilaris in children to achieve disease remission, relief of symptoms, reduced reliance on steroids and reduction of time to relapse.

Proposed wording of the indications

Novartis has noted the comments of the Delegate with regard to the wording of the indication.

The sponsor agrees that it would be appropriate in this instance that the indication should be worded as simply as possible, rather than opt for more explicit wording approved in EU, for the same reasons cited by the Delegate.

This is consistent with recommendations of the Australian clinical guideline for the diagnosis and management of juvenile idiopathic arthritis[1]. It is important that children presenting with sJIA are diagnosed early and referred promptly to a paediatric rheumatologist so that aggressive intervention with appropriate therapy can reduce long-term join damage and disability. However, the differential diagnosis of sJIA in general practice can be difficult and the time it takes for children with the condition to be seen by a specialist may vary.

NSAIDs would generally be initiated in general practice once a diagnosis is made. However, NSAIDs may provide temporary, symptomatic relief; while corticosteroids may reduce inflammation but does not prevent long-term joint destruction and are not recommended for long-term use, particularly in children, due to its significant adverse effects. Methotrexate and new biologicals such as anti-TNF-alpha, IL-1-beta or IL-6 inhibitors may not always be as effective in sJIA compared to other forms of JIA, may

become less effective or lose effectiveness[21]over time or may have adverse effects that result in discontinuation. According to the Australian guidelines, the use of these agents is typically seen as the role of the specialist paediatric rheumatologist. Canakinumab would represent an important new treatment option for the management of sJIA. The sponsor believes it is important that the decision to treat with canakinumab should be left to the treating physician.

It is important that the Indications accurately reflect the intended benefit of the drug, and avoid use of less effective treatments if the disease is correctly diagnosed earlier.

Response to the delegate's questions and request for further information

Furthermore, Novartis is pleased to clarify the following matters which have been summarised by the Delegate.

1. *Study G2305 - explain effect of shortfall in enrolment on power of the study*

An interim analysis for Study G2305 was performed due to the slower than anticipated recruitment in the study. A recently published double-blind placebo-controlled tocilizumab sJIA study[22] was the first to report a placebo response rate in sJIA. The approximate 25% rate observed in that study was lower than the placebo response rate of 30% used to calculate the sample size for the Study G2305 with canakinumab. The independent Data Monitoring Committee (DMC) for G2305 met in a closed session to review the unblinded data from the interim analysis and concluded that the primary endpoint had been reached with high statistical significance and determined that enrolling more patients would not substantially increase the statistical power of the efficacy analysis.

Additionally, DMC felt that it would be improper to expose additional patients to placebo and therefore recommended that enrolment be stopped. This is the basis for completion of Study G2305 with less than the originally planned number of patients. There was therefore no impact on the power of the primary variable which showed a highly significant between-treatment difference in favour of canakinumab.

2. *Study G2301 Part II – detailed comment on precise definition of 'flares', on whether or not patients' results should have been excluded from primary analysis because of the failure to meet the definition, and on the degree such exclusions affect the power assumptions and calculations of the study*

The primary efficacy variable for Part II of the study was the time to a 'flare event', which was prospectively defined as (a) disease flares and (b) discontinuations in that Part II of the study for any reason other than inactive disease. To evaluate the efficacy-based reasons for discontinuation, a new sensitivity analysis was performed where patients who discontinued Part II due to 'unsatisfactory therapeutic effect' are counted as flared while patients who discontinued Part II for any other reason are censored at the time of study discontinuation. One patient randomised to placebo who discontinued due to an adverse event had first met the flare definition 7 days prior to discontinuation and is included in the sensitivity analysis as a flare event.

This sensitivity analysis showed no change in the number of flare events (n=11; 10 with flare and 1 who became a non-responder) in the canakinumab group and a decrease of 5 flare events for a total of 21 flare events in the placebo group (see Table 13). This corresponds to a 57% statistically significant reduction in the risk of flares for

[21] NHMRC-approved Clinical Guideline for the Diagnosis and Management of Juvenile Idiopathic Arthritis,RACGP 2009, p12

[22] DeBenedetti F, Brunner H, Ruperto N, et al [2010] Efficacy and safety to tocilizumab in patients with systemic juvenile idiopathic arthritis [SJIA]: 12-week data from the Phase 3 TENDER trial, Ann Rheum Dis; 69[Suppl 3]:146

canakinumab treatment compared with placebo treatment (hazard ratio of 0.43; 95% CI:0.20 to 0.92; p=0.0127).

Table 13. Survival analysis of time to modified flare in Part II - sensitivity analysis (full analysis Set II)

			Kaplan-Meier estimate	Stratified log-rank test	
Treatment	n	Number of events	Median in days (95%-CI)	Hazard ratio to Placebo (95%-CI)	One-sided p-value
ACZ885	50	11	Not est.	0.43 (0.20, 0.92)	0.0127*
Placebo	50	21	253.0 (196.0, Not est.)		

Source: Tables 14.2-1.8 and Table 14.2-1.9

Log-rank test adjusted for stratification factors prednisone (or equivalent) dose and adapted ACR 70 Pediatric response reached at the end of Part Id as covariates. Patients who discontinued the study while in Part II were counted as censored unless they discontinued due to unsatisfactory therapeutic response or experienced a flare as per definition.

Not est. = Not estimable. * Statistically significant on one-sided significance level 0.025.

3. *Study G2301 Part I – explain decrease in ACR response between Visits 8 and 10 (Day 113 and 169)*

For those patients using a concomitant corticosteroid, the steroid dose was reduced to the lowest level possible over a maximum 20-week period from Day 57 (Visit 6) until Day 197 (Visit 11). The time spent in this phase of the study varied depending on the success of oral steroid tapering. If successful, a patient would advance to the Day 197 visit at their next regularly scheduled visit to receive their last canakinumab dose before randomisation in Part II of the study at the Day 225 visit. Patients who were unsuccessful at reducing their steroid dose at the end of the maximum 20-week period were not randomized in Part II but were allowed to rollover into the extension trial. As expected, the number of patients at Visits 9 (Day 141) and 10 (Day 169) were comparatively low and increasingly represented patients who experienced increased disease activity with steroid dose reduction which explains the decrease in the percent of patients at the highest ACR response levels observed in Visits 9 and 10.

4. *Study G2301 Part I ACR minimum and maximum criteria at each level – clarify the width/window of range from ACR30 to ACR100, since there are many patients (34.3%) who achieved both minimum and maximum result at ACR100.*

Minimum' ACR response data represents the cumulative number and percent of the evaluable patients at that visit who achieved at least (≥) that level of ACR response, whereas 'maximum' ACR response represents the patients whose reported score exactly equalled (=) that level of ACR response only. For complete transparency, the maximum ACR response was added to the relevant table in Study G2301 CSR so the reader will be able to see clearly the exact number and percent of patients who achieved that exact ACR level.

An example is presented in Table 14 below on the Day 57 visit for 141 patients with evaluable ACR data, including 8 (5.7%) non-responders. The remaining 133 (94.3%) had a minimum (≥) ACR30 response. Included in this group were 6 (4.3%) patients whose response exactly equalled an ACR30 score. These 6 patients were therefore not counted amongst those with minimum ACR response at the next levels, that is, for the ACR50 level, only 127 patients are counted (133 minus 6) as having a minimum score of ACR50. The 16 (11.3%) patients whose response was exactly ACR50 were excluded from the next level and so on. The difference between minimum and maximum, described as 'window of separation' by the Delegate, narrows at higher ACR levels such that at the ACR100 level, the minimum and maximum ACR represent the same exact patients.

Table 14. ACR pediatric response achieved in Part I: Summary statistics at Day 57 (full analysis set I)

Time point	Response criterion	Minimum response n (n/m %) (1)	Maximum response n (n/m %) (1)
Visit 6 Part Ib/c	m	141	141
(day 57)	Non-Responders	8 (5.7)	8 (5.7)
	ACR 30	133 (94.3)	6 (4.3)
	ACR 50	127 (90.1)	16 (11.3)
	ACR 70	111 (78.7)	28 (19.9)
	ACR 90	83 (58.9)	29 (20.6)
	ACR 100	54 (38.3)	54 (38.3)

5. *Study G2301E1 patients dose at 2 mg/kg – comment on possibility of controlling sJIA at this lower dose, and whether a study is planned to examine its efficacy*

To address investigator requests for a lower maintenance dose for patients who had demonstrated a sustained long-term strong response, a dose reduction to 2 mg/kg SC every 4 weeks was allowed for a select group of patients in the G2301E1 extension trial. It is important to note that the majority of patients in this study were treated effectively at the 4 mg/kg dose since the PK/PD modelling based on Study A2203 indicates that higher relapse rates could occur at the lower dose, as noted by the (TGA) clinical evaluator.

Only patients who were not using a corticosteroid and who had demonstrated a strong clinical response to the 4 mg/kg dose were considered for dose reduction and only initiated at the request of the investigator and agreed to by Novartis. Based on the positive experience observed in these patients, Novartis plans to initiate a study to evaluate patients randomised to one of two different canakinumab taper regimens (reduced dose or increased dose interval). These patients will be those with inactive disease for at least 24 continuous weeks on canakinumab treatment without concomitant corticosteroid or methotrexate. Novartis is currently finalising the study protocol and anticipates clinical start by fourth quarter of 2014.

6. *Study G2301 & G2305 – comment on discontinuations due to unsatisfactory response, how long treatment should persist, and how it will be addressed in the PI*

The reasons for early discontinuation in both studies varied and included unsatisfactory therapeutic response, adverse events, withdrawn consent and death. The stated reason 'unsatisfactory therapeutic response' included patients who were required to leave the primary study (mostly G2301) because of study design (that is, not reducing concurrent corticosteroid to low enough level; having non-responder status because of developing a fever which the investigator could not exclude sJIA as the cause despite an otherwise strong response). These patients were allowed to roll over into the G2301E1 extension trial to continue canakinumab and most did.

Novartis is of the opinion that treating physicians should use their clinical judgment to determine whether or not their patient should continue or discontinue canakinumab treatment. The sponsor therefore proposes to include a statement in the Dosage section [of the PI] for sJIA that *'Continued treatment with Ilaris in patients without clinical improvement should be reconsidered by the treating physician'* which is also in the approved EU SmPC.

7. *Comprehensive search conducted by Novartis on drug-related hepatic disorders – summarise background, motivation, and incidence found.*

Drug-induced liver injury (DILI, hepatic transaminases and bilirubin elevations) was a potential risk that may develop during canakinumab treatment when investigating other indications such as CAPS, rheumatoid arthritis and gouty arthritis. Thus, a comprehensive search for drug-related hepatic disorders in each of the pivotal studies for sJIA was conducted to further develop the safety specification of Ilaris.

Novartis included a review, including clinical chemistry criteria employed, findings and conclusions with their response. In summary, Novartis concluded that there is no new or changing signal in relation to the risk of drug-induced liver injury.

8. Renal failure – clarify incidence during canakinumab treatment.

There was no case of renal failure in the sJIA pooled population.

9. Rates of infection across the various paediatric age groups – confirm that no marked differences observed.

The observed incidence rates of infection were comparable across age groups in the pooled sJIA patient population without indicating an increased risk of infection for any of the subgroups (Table 15).

Table 15. Infections adverse events in the pooled sJIA and CAPS patient populations by age groups

Age groups (years)	sJIA n/N(%)	CAPS n/N(%)
≥2-<11	103/141 (73.0%)	28/33 (84.8%)
≥2-<4	18/24 (75%)	7/7 (100%)
≥4-<6	26/40 (65%)	5/5 (100%)
≥6-<12	66/86 (76.7%)	18/23 (78.3%)
≥12-<20	33/51 (64.7%)	32 /42 (76.2%)
≥20	0/0	84/117 (71.8)

N=number of patients, n= number of patients with at least one event

10. MAS - provide details for patient in placebo arm, and previous exposure history to canakinumab; provide summary of MAS cases and assurance against causal link

One of the two placebo patients who was reported with a Macrophage Activation Syndrome (MAS) adverse event had first received canakinumab prior to developing MAS. This patient had received 8 doses of canakinumab before being randomised to receive placebo. The patient had received 6 consecutive placebo doses, representing more than 5 half-lives of canakinumab elapsed, before developing MAS. The case was reviewed by the MAS adjudication committee (MASAC) and adjudicated as 'probable MAS'. Details of the patient's serious adverse events, including the MAS event were provided to the TGA.

A summary of the conclusions from an independent external expert report on MAS was also included since it is a known, life-threatening disorder that may develop in patients with rheumatic conditions, particularly sJIA; a review of MAS adverse event reports and the MASAC activities; and a comparison of MAS incidence rates in patients who were randomised to placebo whether canakinumab-naïve or not.

In conclusion, there has been no change in the incidence rate of MAS since submission and canakinumab treatment does not appear to affect the risk of developing MAS in sJIA patients. Novartis will continue to monitor the risk of MAS as part of pharmacovigilance activities and will advise health authorities if there is a change in this risk.

11. Long-term exposure to canakinumab by reasonable number of patients (~100) –clarify data available in accordance with investigational guidelines

At the time of original submission, 64.7% (130/201 patients) were exposed to canakinumab for at least 48 weeks and 78/201 (38.8%) had at least 96 weeks of exposure (Table 16 below). This exceeds the TGA guidelines of at least 100 patients with one year (12 doses-48 weeks) exposure. The total patient year exposure was 300 patient years.

The dataset represents one of the largest created for this orphan indication.

Table 16. Duration of exposure to study drug in sJIA and CAPS pooled groups (Safety population)

Exposure	sJIA pediatric canakinumab N=201	CAPS pediatric canakinumab N=77	sJIA + CAPS pediatric canakinumab N=278	All sJIA + CAPS (peds+adults) canakinumab N=395
Duration by time interval – n (%)				
≥ 1 day	201 (100.0)	77 (100.0)	278 (100.0)	395 (100.0)
≥ 12 weeks	165 (82.1)	76 (98.7)	241 (86.7)	354 (89.6)
≥ 24 weeks	144 (71.6)	69 (89.6)	213 (76.6)	321 (81.3)
≥ 36 weeks	136 (67.7)	55 (71.4)	191 (68.7)	278 (70.4)
≥ 48 weeks	130 (64.7)	48 (62.3)	178 (64.0)	257 (65.1)
≥ 96 weeks	78 (38.8)	16 (20.8)	94 (33.8)	135 (34.2)
≥ 144 weeks	19 (9.5)	2 (2.6)	21 (7.6)	27 (6.8)
≥ 192 weeks	5 (2.5)	0 (0.0)	5 (1:8)	11 (2.8)
Summary statistics (days)				
Mean duration (days)	547.3	443.6	518.6	527.7
Median duration (days)	617.0	379.0	552.0	505.0
Min (days)	4	29	4	4
Max (days)	1829	1093	1829	1884
Patient-years	301.2	93.5	394.7	570.6

sJIA studies A2203, G2305, G2301, G2301E1 (up to G2301E1 interim analysis database lock date)
CAPS studies A2102, D2304, D2306, D2201, D2308 (48 week data)
Exposure was calculated without adjusting for possible gaps between enrolment of patients in different studies.

12. EU RMP and ASA versions – to be updated as condition of registration to address concerns by RMP evaluator.

Novartis acknowledges the RMP evaluator's concerns that the EU RMP v7.1 provided with the response to TGA's questions had a post-marketing data lock point which is more than 12 months out of date.

Novartis has amended the EU RMP to version 8.0 with a data lock point of 31 December 2013 consistent with the latest available PSUR. Aside from the updated data lock point and exposure data, the EU RMP has also moved opportunistic infections from a potential risk to an identified risk; updated the missing information on 'Pregnancy' as 'Pregnancy and lactation'; and proposed the temporary suspension of the gouty arthritis registry (H2401) due to limited utilisation in this indication.

The updated EU RMP will be provided to the TGA when approved by EMA, together with an updated ASA. The ASA will include information that educational materials will be developed and submitted to the TGA for review and approval prior to supply of Ilaris in Australia and instructions on how Australian patients will be able to join relevant disease registries.

13. Dosing instructions for CAPS indication – comment on ACSOM's concern.

Novartis had already discussed the dosage instructions for the CAPS indication with the TGA's Delegate when finalising the PI for a separate application to extend the patient population and dosing regimen for CAPS, which was approved on 13 February 2014.

14. Australian education materials – response on availability and content.

In Novartis' response to the RMP evaluator's recommendation (Item #12.a-d), Novartis agreed that Australian specific educational material for physicians, patients and carers of paediatric patients will be developed and submitted for approval by the TGA's Office of Product Review prior to supply of Ilaris in Australia. Novartis will advise the TGA of the planned date for supply of Ilaris in Australia.

These educational materials will be made available to physicians, patients and the carers of the patients at the time of supply. Effectiveness and/or usefulness of the education materials for sJIA will be evaluated through planned assessment of PSURs, where changes in the pattern of the RMP risks and all safety topics are closely monitored.

15. Provision of outstanding clinical study protocols/synopses and reports to TGA

Novartis generally submits new clinical study reports as part of Category 1 applications or safety-related requests (with data) to include new information in the PI or extend the approved use of the medicine. Novartis would be willing to provide copies of these reports once available and upon request by the TGA.

Risk management plan

The safety profile of canakinumab is established in clinical studies and postmarketing reviews for various indications, and will be managed through RMP activities.

Novartis recognises that like most monoclonal antibodies, Ilaris has known and potential risks, including increased incidence of serious and opportunistic infections. Relevant warnings and precautions have been included in the Australian PI to ensure that the safety of patients is taken into account, when treatment is initiated and maintained for the approved Indications.

Novartis acknowledges that the orphan Indications for Ilaris means limited exposure to Ilaris but will continue to update its safety database and risk management as additional patients use the drug during clinical studies and the postmarketing period.

Safe and effective use of Ilaris by patients with sJIA and CAPS will be promoted through educational materials for physicians, patients and their carers.

Conclusion

Novartis believes that the overall clinical data available represents a positive benefit/risk ratio for Ilaris in the treatment of sJIA, as requested by our application to extend its Indications. Furthermore, Novartis is of the opinion that:

- The issue on definition of flares and resulting analysis does not diminish the findings from the pivotal studies that canakinumab provides sustained benefit to patients;
- The responses to the Delegate's specific questions addresses any lingering concerns and reaffirms the Delegate's view of canakinumab having an overall positive benefit/risk profile in sJIA;
- The Indications should be suitably worded to allow effective management in clinical practice.

Novartis accepts the Delegate's comments to clarify the wording of the patient population in the Indications section, and proposes the amended Indications as:

> *Ilaris is indicated for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS), in adults and children 2 years or older including:*
>
> - Familial Cold Autoinflammatory Syndrome (FCAS)/Familial Cold Urticaria (FCU)
> - Muckle-Wells Syndrome (MWS)
> - Neonatal-Onset Multisystem Inflammatory Disease (NOMID)/Chronic Infantile
> - Neurological, Cutaneous, Articular Syndrome (CINCA)
>
> *Ilaris is indicated for the treatment of active Systemic Juvenile Idiopathic Arthritis (sJIA) in patients aged 2 years or older.*

The sponsor provides an assurance to work with the TGA in considering further amendments to the PI and any specific conditions of registration during the post-ACPM stage.

Advisory committee considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The submission seeks to register an extension of indications for a currently registered product.

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the delegate and considered Ilaris powder for injection containing 150 mg of Canakinumab to have an overall positive benefit–risk profile for the Delegate's amended indication;

> *Ilaris is indicated for the treatment of active Systemic Juvenile Idiopathic Arthritis (sJIA) in patients aged 2 years and older.*

Proposed conditions of registration:

The ACPM agreed with the Delegate on the proposed conditions of registration and specifically advised;

- On the need for the submission of the dose reduction study among any other trials to be completed.
- The ACPM was strongly supportive that the TGA should see the proposed educational materials before supply of the product.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments:

The ACPM agreed with the Delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI) and specifically advised on the inclusion of the following:

1. A statement of the incidence of Macrophage Activation Syndrome (MAS) should be reported in the clinical trials section.
2. A statement in the Precautions and Adverse events sections in the PI and relevant sections of the CMI should make clear that MAS appears to be a continuing risk during canakinumab therapy. The statement suggested in the clinical evaluation report canakinumab does not prevent MAS, even in patients whose underlying sJIA is well controlled with this treatment is recommended for the PI.
3. Pending the planned study of dose reduction, the sponsor should provide more detail about experience to date with attempts at dose reduction and provide guidance for clinicians when patients have responded well to treatment.
4. The PI should include the maximum time until benefit is seen and provide guidance on when to cease canakinumab if no clinical benefit is seen. It is recommended that the sponsor include details from the clinical trial data of the longest latent period observed before which a benefit was perceived. A definition of 'benefit' should also be included, such as a sustained benefit which would satisfy the primary endpoint of the study.
5. The statement in the PI that concomitant treatment with TNF inhibitors is not recommended as it may increase the risk of serious infection should be expanded to contraindicate canakinumab in combination with tocilizumab, which is also indicated for sJIA. Despite the apparent lack of data, that combination would not be recommended for similar reasons.

6. The statement proposed for the Dosage and Administration section *Continued treatment with Ilaris in patients without clinical improvement should be considered by the treating physician*, was redundant and instead there should be guidance on when treatment should be discontinued when no clinical benefit is being seen.

Specific advice

The ACPM advised the following in response to the specific Delegate's questions on this submission:

1. The validity of the result of the primary analysis for the principal pivotal study G2301, particularly as it concerns the precise definition of 'flare' used in Part II of that study and whether or not a number of patients' results should have been excluded from consideration.

In regards to the reanalysis of Study G20301, the ACPM accepted the view of the evaluator that the subsequent sensitivity analysis was valid and was a more appropriate evaluation of efficacy than the original analysis, which included discontinuations for reasons other than flare.

The ACPM agreed that the original Intent-to-Treat (ITT) analysis and the sensitivity analysis both provided evidence for the efficacy of canakinumab in sJIA.

2. The proposed wording of the indication, that is, 'for the treatment of active Systemic Juvenile Idiopathic Arthritis (sJIA) in patients aged 2 years and older' and whether it needs to be made more restrictive.

The ACPM agreed with the indication proposed by the Ddelegate and was of the view that treatment with canakinumab should not be limited to those patients who have had difficulties with corticosteroids.

The ACPM was of the view that as sJIA is potentially fatal it should be left to the experienced and specialist physicians likely to be treating these patients to decide if canakinumab use is appropriate.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Ilaris (canakinumab 150 mg powder for injection) for the new indication:

> *Ilaris is indicated for the treatment of active Systemic Juvenile Idiopathic Arthritis (sJIA) in patients aged 2 years or older.*

Specific conditions of registration applying to these goods

1. The Ilaris (canakinumab) EU-Risk Management Plan (RMP), version 7.1, dated 13 August 2013 and the Australian Specific Annex, AsA v4 (dated 311anuary 2014), included with submission PM-2013-01501-1-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.
2. The ponsor must submit to the TGA, for review and approval by the Office of Product Review, the EU-RMP v8.0 and the appropriateIy updated Australian Specific Annex, AsA vs, as soon as possible after implementation of the EU-RMP v8.0 in the EU.
3. The sponsor must submit to the TGA for evaluation, either as a Category I application or, if appropriate, a safety-related request with data), the final clinical study report for

each of the following ongoing studies in sJIA: firstly, Study G2301El and secondly Study G2306. These reports must be submitted as soon as possible after finalisation. If, for whatever reason, there are interim clinical study reports released prior to the release of the final clinical study report, then any such interim reports must also be submitted, either as a Category I application or, if appropriate, a safety-related request (with data).

Attachment 1. Product Information

The Product Information approved for main Ilaris at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <http://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

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