Australian Government
Department of Health
Therapeutic Goods Administration

# AusPAR Attachment 2

# Extract from the Clinical Evaluation Report for Canakinumab

Proprietary Product Name: Ilaris

Sponsor: Novartis Pharmaceuticals Australia Pty Ltd

**First round evaluation: 9 December 2013**

**Second round evaluation: 14 February 2014**

TGA Health Safety Regulation

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- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

# About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <http://www.tga.gov.au/product-information-pi>.

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# 1. List of abbreviations

| Abbreviation | Meaning |
|---|---|
| ACR | American College of Rheumatology |
| ACZ885 | canakinumab |
| 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 |
| CrCl | creatinine clearance |

| Abbreviation | Meaning |
|---|---|
| CRP | C-reactive protein |
| CTD | Common Technical Document |
| CV | coefficient of variation, or standard deviation as a percentage of the parameter value |
| DBP | diastolic blood pressure |
| DMARDS | Disease-Modifying Anti-rheumatic Drugs |
| EBV | Epstein Barr Virus |
| eCRF | electronic case report/record form |
| ECG | electrocardiogram |
| ELISA | enzyme-linked immunosorbent assay |
| ESR | erythrocyte sedimentation rate |
| EU | European Union |
| F | Bioavailability (refers to SC bioavailability for canakinumab) [%] |
| FAS | full analysis set |
| FCAS | Familial Cold Autoinflammatory Syndrome |
| FCU | Familial Cold Urticaria |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| Hb | haemoglobin |
| HERG | human Ether-à-go-go-Related Gene |
| HIV | human immunodeficiency virus |
| HR | hazard ratio |
| HRQoL | Health-Related Quality of Life |
| Ig | Immunoglobulin |
| ILAR | International League against Rheumatism |
| IL | interleukin |

| Abbreviation | Meaning |
|---|---|
| IL-1β | interleukin-1-beta |
| i.v. | intravenous |
| IVRS | Interactive Voice Response System |
| 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) |
| K-M | Kaplan Meier |
| LLN | lower limit of normal |
| LLOQ | lower limit of quantification |
| LS | least squares |
| mAb | monoclonal antibody |
| MAS | macrophage activation syndrome |
| MASAC | macrophage activation syndrome adjudication committee |
| MSD | Meso Scale Discovery |
| MTX | methotrexate |
| MWS | Muckle-Wells Syndrome |
| NOMID | Neonatal-Onset Multisystem Inflammatory Disease |
| NONMEM | Nonlinear Mixed Effects Modeling software |
| NSAIDs | Nonsteroidal Anti-Inflammatory Drugs |
| OR | odds ratio |
| pACR30 | paediatric ACR30: Improvement from baseline of at least 30% in at least 3 of response variables 1 to 6 and no intermittent fever, that is, body temperature ≤ 38°C, in the preceding week (variable 7), with no more than one variable 1-6 worsening by more than 30% |
| PD | pharmacodynamics |

| Abbreviation | Meaning |
|---|---|
| PI | Product Information |
| PK | pharmacokinetics |
| Pop PK | population pharmacokinetics |
| Pop PK/PD | population pharmacokinetics/pharmacodynamics |
| PRINTO | Paediatric Rheumatology International Trials Organisation group |
| PSUR | Periodic Safety Update Report |
| $PS_D$ | Permeability-surface area coefficient for exchange between plasma and tissue fluid for canakinumab (free and complex) [L/day] |
| $PS_L$ | Permeability-surface area coefficient of uncomplexed ligand, IL-1β [L/day] |
| PT | preferred term |
| q4w | every 4 weeks |
| QTc(F) | QT interval coreected 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 |
| SBP | systolic blood pressure |
| SC | Subcutaneous |
| SD | standard deviation |
| sJIA | Systemic Juvenile Idiopathic Arthritis |
| SMQ | standardised MedDRA query |
| SOC | system organ class |
| SS | safety set |
| $T_{1/2}$ | half-life |
| TB | tuberculosis |

| Abbreviation | Meaning |
|---|---|
| TGA | Therapeutic Goods Administration |
| Tmax | time to maximum serum concentration |
| TNF-α | Tumour Necrosis Factor alpha |
| ULN | upper limit of normal |
| VAS | visual analogue scale |
| $V_D$ | 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] |
| $V_{SS}$ | volume of distribution at steady-state |
| $V_Z/F$ | apparent volume of distribution |
| WBC | white blood cell |

# 2. 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 (Mellins et al 2011).*

*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 (Ravelli and Martini 2007; Woo et al 2006; Gurion, et al 2012). Joint symptoms usually arise later and the clinical course of the disease is highly variable.*

*SJIA is associated with a significant mortality (10-14%) (Batthish et al 2005), the highest of all forms of JIA. The main causes of death include infection and macrophage activation syndrome (MAS) (Woo et al 2006). 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 (Hashkes and Laxer 2005).*

*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 (Mellins et al 2011).*

*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.

# 3. Contents of the clinical dossier

## 3.1. Scope of the clinical dossier

The submission contained the following clinical information:

- Module 5
  - 3 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

## 3.2. Paediatric data

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

## 3.3. 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.

# 4. Pharmacokinetics

## 4.1. 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, 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 1, 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 Section 3.2.2. Therefore only summary results for the individual Phase III and extension studies have been presented.

**Table 1. 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.

### 4.1.1. Assays common to all PK/PD studies

The assay used to analyse canakinumab in human serum was a specific competitive enzyme-linked immunosorbent assay (ELISA) method with a lower limit of quantification (LLOQ) of 200 ng/mL. Total IL-1β was determined in human serum using a sandwich ELISA method based on a commercially available kit (Quantikine-HS kit from R&D Systems) with a lower limit of detection of 0.1 pg/mL.

The incidence of canakinumab antibodies was evaluated in all sJIA clinical studies and the impact of antibodies on safety, efficacy, and exposure was evaluated. Anti-canakinumab antibodies in serum were measured by surface plasmon resonance spectroscopy using the first established and formerly used Biacore® binding assay in Study A2203, and by a recently developed more sensitive homogeneous bridging Meso Scale Discovery (MSD) assay in studies G2305, G2301 and G2301E1.

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

## 4.2. Summary of pharmacokinetics

The information in the following summary is derived from conventional pharmacokinetic studies unless otherwise stated.

### 4.2.1. Pharmacokinetics in the target population

#### *4.2.1.1. Study A2203*

An overview of the study objectives and PK/PD sampling is presented in Table 1 above. In brief, this was a Phase II, multicentre, open label, repeat dose range finding study to assess the clinical safety, tolerability, immunogenicity, PK and efficacy of canakinumab in patients with active sJIA. The study consisted of 2 stages, a repeated single dose escalation in Stage I and a fixed dose re-dosing upon relapse in Stage II.

PK data was collected from all 26 sJIA patients (23 individual patients plus 3 re-enrolled patients) who received SC canakinumab in a dose ranging from 0.5 to 9 mg/kg. Single dose non-compartmental PK parameters were calculated from 21 patients aged 4 to 17 years of age (5 subjects lacked evaluable PK data).

Blood samples were collected in stage I at baseline (Day 1) and trough samples were taken pre-dose during treatment period on days 2, 3, 8, 15, 29, 43, 57, 71, 85, 99, 113, 127, 141 and 155. Sampling continued every two weeks until the last patient from the highest dose cohort had completed two cycles of remission. No samples were taken in stage II.

##### *4.2.1.1.1. Results*

As the majority of subjects received a second dose of canakinumab within 7 days of the first dose, $C_{max}$ per dose group could not be evaluated. In the 6 subjects with a single SC injection of canakinumab, peak serum levels were reached after a median of approximately 2 days (Table 2, below). Mean apparent half-life was 16.7 (SD = 5.45) days, apparent clearance (CL/F) was 0.256 (SD = 0.0993) L/d, and mean apparent volume of distribution (Vz/F) was 5.94 (SD = 2.54) L. Inter-subject variability was moderate with an observed coefficient of variation (CV) of approximately 39 % in CL/F. Mean exposure parameters increased with increasing canakinumab dose, but dose normalisation indicates approximate dose proportionality within the range of the dose groups studied.

**Table 2. Serum PK parameters after an initial SC dose of 0.5, 1.0, 1.5, 3.0, 4.5, or 9.0 mg/kg canakinumab in Paediatric patients**

| | Cmax/dose [ug/mL/mg] | Tmax↑ [day] | CL/F [mL/day] | Vz/F [mL] | T1/2 [day] |
|---|---|---|---|---|---|
| n | 6 | 6 | 21 | 21 | 21 |
| Mean | 0.1678 | 2.620 | 256.4 | 5941 | 16.65 |
| SD | 0.030560 | 2.0797 | 99.374 | 2541 | 5.4450 |
| Median | 0.1743 | 1.814 | 232.8 | 4950 | 15.66 |
| Min | 0.131 | 1.63 | 152 | 3230 | 8.55 |
| Max | 0.206 | 6.86 | 490 | 12400 | 29.2 |
| CV % | 18.21 | 79.37 | 38.75 | 42.78 | 32.70 |

↑reported for patients who receive a single dose in Period I

#### *4.2.1.2. Study G2305*

This study was a Phase III randomised, double-blind, placebo controlled, single dose study to assess the efficacy and safety of canakinumab in patients with sJIA and active systemic manifestations.

Blood samples for canakinumab and total IL-1β were collected from 41 of the 43 patients (2 did not have measured concentrations) on Days 1, 3, 15 and 29.

##### *4.2.1.2.1. Results*

PK data was not presented separately for this study, but pooled with data from other sJIA canakinumab studies in the PK model-based analysis (see Section 3.2.2).

#### *4.2.1.3. Study G2301*

This was a Phase III, multicentre, two-part study with an open-label, single-arm active treatment (Part I) followed by a randomised, double-blind, placebo-controlled, event-driven withdrawal design (Part II) of canakinumab in patients with SJIA and active systemic manifestations.

Blood samples were collected at Days 1, 3, 15, 29, 57, end of Part Ic (or start of Part Id) visit, every 6 months during Part II, end of Part II visit, and when flares occurred.

##### *4.2.1.3.1. Results*

The arithmetic mean trough concentrations (SD) of canakinumab on Day 29, Day 57, end of Part Ic (or Day 197) visit, and end of Part Id (or Day 225) visit were 11.29 (5.497), 17.03 (7.928), 20.82 (9.782) and 26.84 (9.893) µg/mL, respectively. The PK model-based analysis of these data was performed separately, after pooling with data from other canakinumab studies (see Section 3.2.2).

#### *4.2.1.4. Study G2301E1*

G2301E1 was a Phase III, open label extension to studies G2305 and G2301. The objective of the study was to assess the long-term safety, tolerability, and immunogenicity of canakinumab in patients with sJIA and active system manifestation.

Patients in G2301E1 had previously participated in Studies G2301 and G2305, and may have completed the previous study or discontinued prematurely due to disease flare, inability to taper steroid dose, or other reasons. They therefore had different levels of disease activity and histories of canakinumab response. Based on these factors it was decided to allocate patients into 1 of 4 analysis groups, according to their status at the end of their participation in the previous study. The 4 groups are as follows: Group 1 (G2301 Part II discontinuations), Group 2 (G2301 Part II completers), Group 3 (G2301 Part I steroid-tapering failures), and Group 4 (all others).

Blood samples were collected at Day 169, 337, 505, 673 and every 6 months for patients who continued beyond Day 673.

##### *4.2.1.4.1. Results*

Mean trough canakinumab concentrations (SD) at baseline were 16.10 (13.80), 34.39 (14.82), 12.67 (8.673) and 12.75 (7.552) µg/mL for Groups 1, 2, 3, and 4, respectively. At week 24, mean trough concentrations (SD) were 20.88 (10.05), 20.43 (9.042), 17.13 (11.50) and 19.32 (14.99) µg/mL for Groups 1, 2, 3, and 4, respectively. The PK model-based analysis of these data was performed separately, after pooling with data from other canakinumab studies (see Section 3.2.2).

### 4.2.2. Population pharmacokinetics in the target population

Three population pharmacokinetic/pharmacodynamic (Pop PK/PD) reports were included in the submission:

i. Characterising the pharmacokinetics and pharmacodynamics of canakinumab (an anti-interleukin-1β monoclonal antibody) in the prevention of flares for paediatric patients treated for systemic Juvenile Idiopathic Arthritis (sJIA) (ACZ885g-modelling report, based on studies A2203, G2305, G2301, and G2301E1)

ii. Modelling Report for I) A multi-centre, open-label, repeated dose range finding study to evaluate the safety, tolerability, immunogenicity, pharmacokinetics and efficacy of an anti-IL-1β monoclonal antibody (canakinumab) given subcutaneously in paediatric subjects with active systemic juvenile idiopathic arthritis (sJIA) II) Simulations to support dose regimen selection for Phase III trials (Study A2203)

iii. Exposure-response modelling of canakinumab or ACZ885 in the prevention of flares for paediatric patients treated for systemic Juvenile Idiopathic Arthritis (sJIA) Modelling Report (ACZ885g-hazard report, based on Study G2301)

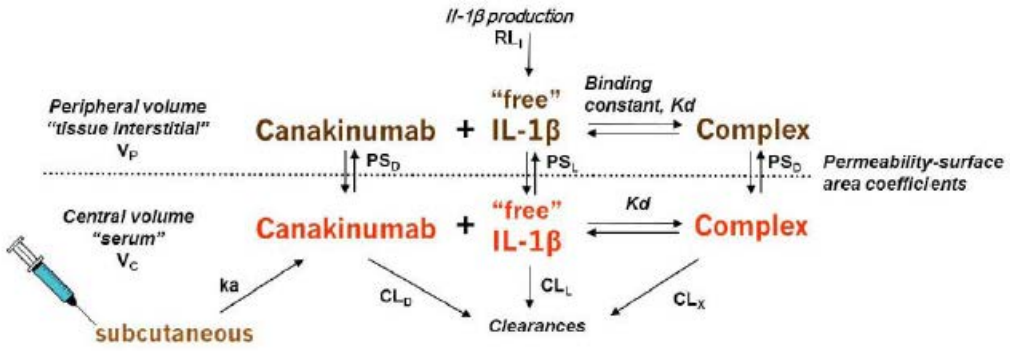
The PK analyses in the first and second modelling reports listed above were both based on the PK-Binding model that was submitted with the original canakinumab CAPS submission updated with data from additional canakinumab studies. The dataset used in the model to select the dose regimen in the Phase III trials included the original 7 canakinumab studies (with study populations including CAPS, asthma, rheumatoid arthritis, psoriasis and healthy volunteers) and Study A2203 in sJIA. The dataset used in the ACZ885g-modelling report additionally included the 3 Phase III sJIA studies (G2305, G2301 and G2301E1) and several further studies (including their extensions) across different disease populations (those previously mentioned, plus gouty arthritis). Because of the similar methodology used in the PK-binding models, only the ACZ885g modelling report methodology will be discussed in detail. There was a further reference to a Pop PK model in the G2305 clinical study report, which stated that concentrations of canakinumab from the 41 patients in the study were pooled with those from Study A2203 and fitted to a PopPK model. The model was not described in detail but again appears to be based on the model used in the CAPS submission. The results from this model are not further discussed here as the G2305 data were also incorporated into the ACZ885g-modelling report discussed below. The third report is an exposure-efficacy report (PK flare) and will be discussed in Section 4 (PK-flare was also analysed in both the ACZ885g-modelling report and the model from the dose-finding study – these results will also be discussed in Section 4). While canakinumab and IL-1β have a pharmacodynamic interaction, the results will be presented in Section 4 as it forms an integral part of the PK-Binding model.

#### *4.2.2.1. Characterising the PK and pharmacodynamics of canakinumab in the prevention of flares for paediatric patients treated for systemic Juvenile Idiopathic Arthritis (sJIA) (ACZ885g-modeling report)*

##### *4.2.2.1.1. Introduction*

A mechanistic target-mediated drug disposition model ('PK-Binding Model') was developed for the original canakinumab submission in CAPS. This was a two compartment PK model, with first order absorption from SC injection into a central compartment (serum), permeability surface area coefficients to describe the distribution of canakinumab and the canakinumab-IL-1β complex into the peripheral compartment, and first order elimination of canakinumab and the canakinumab-IL-1β complex. A schematic diagram of the dynamic relationship of canakinumab with IL-1β is depicted in Figure 1, below.

**Figure 1. PK-Binding Model for Canakinumab and IL-1β**




##### *4.2.2.1.2. Objectives and study design*

The objectives of this Pop PK/PD analysis were as follows:

- To update the population-based PK-Binding model previously developed and described in the canakinumab CAPS Modelling Report with data from sJIA patients pooled from studies A2203, G2305, G2301 and G2301E1
- To describe the PK of canakinumab and its pharmacodynamics of binding to IL-1β in sJIA patients
- To employ model-based simulation to estimate the steady-state exposures of canakinumab for sJIA paediatric patients stratified by age group (2-3, 4-5, 6-11, and 12-19 years) and bodyweight (≤ 40 kg, > 40 to ≤ 70 kg and > 70 kg)
- To determine whether canakinumab 4 mg/kg SC given every 4 weeks provides sufficient exposure to prevent flares in sJIA paediatric patients

There were 2 analysis populations in the dataset used in this model:

i. subjects from 28 clinical studies in different disease populations (CAPS, Rheumatoid Arthritis, sJIA, Gouty Arthritis, Japanese Healthy Volunteers, Non-Japanese Healthy Volunteers, and Psoriasis) who had received canakinumab and for whom the canakinumab and/or IL-1β plasma concentration were available. Pooling of different studies were required to provide PK and IL-1β information for the sparsely sampled sJIA studies to support estimation from the original PK-Binding model, and

ii. subjects from the pooled sJIA studies only. Within the sJIA pooled dataset, the records for flare and no flare were also collected for subsequent analyses.

In the pooled all-indication studies, there were 1,732 subjects overall, 39.7% were female, 16.4% were children, age ranged from 1 to 91 years (mean 43.6 years), weight ranged from 9.3 to 171 kg (mean 75.7 kg), and mean albumin was 42.2 g/L. In the pooled sJIA studies, there were 201 patients, 55.2% were female, age ranged from 1 to 19 years (mean 8.6 years), weight ranged from 9.3 to 102.6 kg (mean 32.8 kg), and mean albumin was 33.3 g/L (Table 3, below).

**Table 3. Demographic and laboratory data for sJIA studies (for covariates known to affect the PK properties of canakinumab)**

| Study | N | Demographic data for analysis population (mean ± SD & range) | | | | |
|---|---|---|---|---|---|---|
| | | Weight (kg) | Age (years) | Albumin (g/L) | M | F |
| A2203 | 23 | 33.7 ± 18.5 (13.6-90.6) | 9.5 ± 4.2 (4-19) | 36.0 ± 3.7 (29-46) | 12 | 11 |
| G2305 | 84 | 34.8 ± 22.3 (10.8-102.6) | 9.0 ± 4.7 (2-19) | 34.5 ± 5.5 (23-49) | 34 | 50 |
| G2301 | 177 | 33.1 ± 21.2 (9.3-102.6) | 8.6 ± 4.4 (1-19) | 34.5 ± 5.5 (21-49) | 79 | 98 |
| G2301E1 | 147 | 33.6 ± 21.8 (9.3-102.6) | 8.6 ± 4.4 (1-19) | 37.8 ± 4.8 (26-49) | 66 | 81 |
| SJIA POOL | 201 | 32.8 ± 21.0 (9.3-102.6) | 8.6 ± 4.5 (1-19) | 33.3 ± 4.7 (21-46) | 90 | 111 |

*Note the number of subjects for different studies may come from patients allowed to participate and/or rollover from one study to another, thus the total from the pooled sJIA studies does not equal the total from each of the individual sJIA studies

#### *4.2.2.1.3. Methodology*

The analysis was performed using the NONMEM software system, NONMEM VI version 2 extended/super extended (Icon Development Solutions, Ellicott City, MD, USA).

The PK/PD parameters included in the model were: clearance of drug ($CL_D$) and ligand ($CL_L$), central and peripheral volume for the drug ($V_D$, $V_P$); their interstitial flow rate ($PS_D$ and $PS_L$), ligand production rate ($R_{LI}$) and binding affinity ($K_D$). Minor modifications were made to 2 parameters ($K_A$ and F) to account for different canakinumab expression cell product and/or formulation.

The covariates tested included age, weight and albumin, which had previously been identified to affect the PK properties of canakinumab exposure. Also tested were height, gender, race, ethnicity, cell line, and disease indication.

*4.2.2.1.4. Data analysis and modelling methods*

Canakinumab and IL-1β concentration-time data were fitted to the established PK-Binding model. In the original CAPS model, parameters for which weight was a significant covariate ($CL_D$, $V_D$ and $V_P$) were centred on a 'typical' value of 70 kg. The 70 kg bodyweight was also used as the reference when running the PK-Binding model on the pooled all-indication dataset (mean weight 75.7 kg). However for the sJIA dataset, the mean weight was 32.8 kg, so the relevant model parameters were adjusted during post-processing using a 'typical' value of 33 kg.

The model estimated typical values of the parameters, inter-subject variability terms (CV) and the impact of patient and drug characteristics on the parameters. Covariate-parameter relationships were assessed visually, and examined for trends, with statistical significance assessed by backward elimination. The adequacy of the PK-Binding model in describing the concentration data was assessed using diagnostic plots and visual predictive check.

***4.2.2.1.5. Results***

*4.2.2.1.6. Canakinumab PK*

The PK-Binding model adequately described the canakinumab and IL-1β concentration-time data, with relatively low residual within-patient error (25.7% and 37% CV, respectively), implying reasonably high predictability of the model to describe both canakinumab and total IL-1β data.

The population mean clearance of canakinumab ($CL_D$) for a sJIA patient with body weight of 70 kg and serum albumin of 43 mg/mL was 0.196 ± 0.01 L/day which was comparable to that seen in other canakinumab study populations (Table 4, below). The volumes of distribution of the central ($V_D$) and peripheral compartment ($V_P$) were 3.63 ± 0.19 L and 2.64 ± 0.15 L, respectively. For a bodyweight of 33 kg and serum albumin of 43 g/L, the estimated $CL_D$ was 0.106 L/day, $V_D$ was1.55 L, $V_P$ was 1.66 L, and the terminal half-life was 22 days. The time to steady state was approximately 110 days (5 half-lives) with an accumulation ratio (steady-state AUC/single-dose AUC) of 1.6 fold. The degree of unexplained inter-subject variation in the primary PK parameters was approximately 30 to 45% for $CL_D$, $V_D$, and $V_P$. Significant covariates for the PK parameters were the same as identified in the previous model (weight, albumin, and age). In particular, there was increased clearance as weight increased, and a reduction in absorption with increasing age. There was no trend in weight normalised clearance versus age or weight.

**Table 4. Final Parameter Estimates for Each Study Population**

| | $CL_D$ (L/day for 70 kg at 43 g/L albumin) | $CL_L$ (L/day) | $R_{LI}$ (ng/day) | $K_d$ (nM) |
|---|---|---|---|---|
| sJIA | 0.196 ± 0.0148 | 6.22 ± 0.907 | 8.05 ± 0.913 | 1.50 ± 0.264 |
| CAPS | 0.176 ± 0.0156 | 10.92 ± 1.143 | 9.853 ± 1.049 | 1.616 ± 0.318 |
| Healthy Volunteers, Japanese | 0.179 ± 0.0157 | 20.59 ± 1.650 | 4.822 ± 0.970 | 0.591 ± 0.289 |
| Healthy Volunteers, Non-Japanese | 0.150 ± 0.0157 | 16.11 ± 1.571 | 5.007 ± 0.979 | 1.002 ± 0.316 |
| Asthma | 0.176 ± 0.0159 | 25.00 ± 1.795 | 6.118 ± 0.995 | 0.603 ± 0.294 |

| | $CL_D$ (L/day for 70 kg at 43 g/L albumin) | $CL_L$ (L/day) | $R_{LI}$ (ng/day) | $K_d$ (nM) |
|---|---|---|---|---|
| Rheumatoid Arthritis | 0.216 ± 0.0160 | 17.23 ± 1.263 | 10.46 ± 1.035 | 0.480 ± 0.282 |
| Psoriasis | 0.196 ± 0.0161 | 17.23 ± 1.577 | 7.060 ± 1.041 | 0.431 ± 0.288 |
| Gouty Arthritis | 0.191 ± 0.0158 | 11.44 ± 1.153 | 8.009 ± 1.011 | 1.064 ± 0.299 |

*4.2.2.1.7. Dynamics of IL-1β*

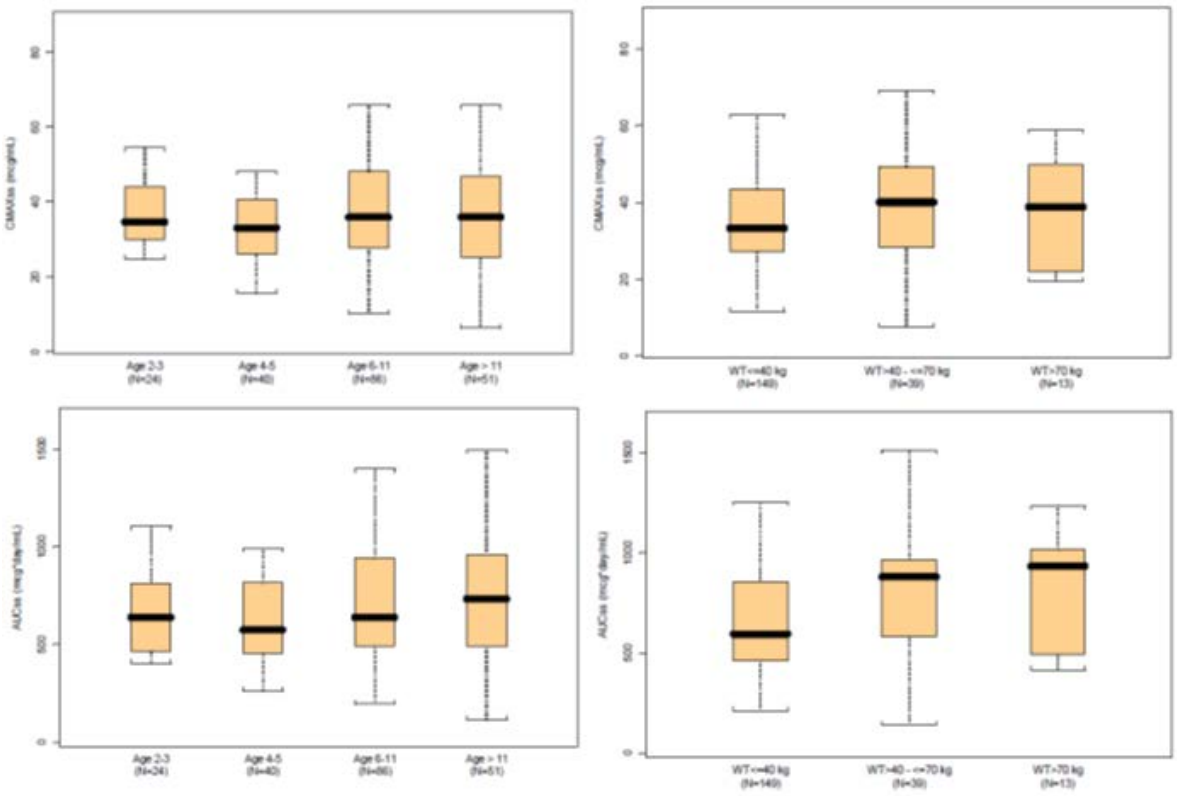
The estimated IL-1β clearance was 6.22 L/day (CV 79%), with a terminal half-life of 4.2 days. The IL-1β production rate was 8.05 ng/day (CV 72%), with a dissociation constant ($K_D$) of 1.5 nM (CV 52%) (Table 4). The IL-1β clearance was lower, and IL-1β production rate and the dissociation constant were generally higher in sJIA than in the other indications. In particular, the IL-1β clearance was 75.5% higher and the production rate only 22% higher in CAPS than that in sJIA. The sponsor considered that these differences between CAPS and sJIA support the higher canakinumab dose requirements in sJIA. A weak trend was noted between IL-1β clearance and IL-1β production rate versus age (higher in younger patients), but this was less pronounced than the trend seen in CAPS. No trend was observed between age and $K_D$.

*4.2.2.1.8. Model simulations*

Model-based simulations were used to obtain estimates of steady-state canakinumab exposures in sJIA patients using the PK and PD parameter estimates determined by the PK Binding model for a bodyweight-tiered dose of 4 mg/kg stratified by specific age (2-3, 4-5, 6-11, 12-20 years) and bodyweight (≤40 kg, >40 to ≤70 kg and >70 kg).

The model simulations demonstrated comparable exposures in the different age groups (overall average ± SD: $C_{MINss}$ 14.68 ± 8.80 µg/mL, $C_{MAXss}$ 36.50 ± 14.92 µg/mL and $AUC_{ss}$ 696.09 ± 326.55). These simulations predicted that more than 95% of subjects administered 4 mg/kg SC dose of canakinumab achieved steady-state trough levels above the previously estimated critical flare concentration (*Ki*) of 2 µg/mL. While exposure based on $AUC_{ss}$ or $C_{MINss}$ was approximately 20% higher in sJIA patients with a weight >40 kg than in those ≤40 kg, the exposure distributions did overlap (Figure 2., below).

**Figure 2. Simulated steady-state exposure ($C_{maxss}$, $AUC_{ss}$) of Canakinumab for sJIA patients stratified by age group (left panel) and bodyweight (right panel) (Total = 201)**




Note: The lower and upper end of ends of boxes represent the 25th and 75th percentiles of distribution, the bold line in the box represents the median, and the whiskers 5th and 95th percentiles of the data. N represents the number of subjects.

#### *4.2.2.2. Simulations to support dose and regimen selection for Phase III trials (ACZ885a-modeling report, Study A2203)*

##### *4.2.2.2.1. Results*

*4.2.2.2.2. Canakinumab PK*

The PK-Binding model adequately described the canakinumab and IL-1β concentration-time data, with low residual within-patient error (7.5% and 10.1% CV, respectively), implying high predictability of the model to describe both canakinumab and total IL-1β data. The means of the post hoc estimates from the PK-binding model specifically for the 23 sJIA patients in Study A2203 are listed in Table 5, below. The estimated clearance of canakinumab was 0.184 (± 0.0745) L/d with a low total volume of distribution (i.e. $V_D$+$V_P$) of 3.35 L. When normalised for a bodyweight of 70 kg, clearance of canakinumab increased to an estimated 0.208 L/d. The absolute SC bioavailability of canakinumab (F) was estimated to be 61.7%.

**Table 5. Mean PK and PD parameters of canakinumab (compartmental, obtained from the post hoc step of NONMEM) in sJIA patients receiving at least one dose of canakinumab (n=23) in Study A2203**

| | CLD (L/day) | VD (L) | CLL (L/day) | RLI (ng/day) | VP (L) | PSD (L/day) | PSL (L/day) | KD (nM) | KA (1/day) | F1 |
|---|---|---|---|---|---|---|---|---|---|---|
| Mean | 0.184 | 2.00 | 26.8 | 23.3 | 1.35 | 0.309 | 0.322 | 0.708 | 0.419 | 0.617 |
| %CV | 41% | 41% | 51% | 70% | 51% | 31% | 45% | 126% | 37% | na |

*4.2.2.2.3. Dynamics of IL-1β*

Total IL-1β concentrations increased after canakinumab dosing, which is indicative of capture or binding of IL-1β by canakinumab. The estimated IL-1β clearance was 26.8 L/day, the production rate was 23.3 ng/day, with a dissociation constant ($K_D$) of 0.708 nM.

### 4.3. Evaluator's overall 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)
- $T_{max}$ occurred after a median of approximately 2 days (mean 2.6, range 1.6 - 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 $CL_D$, $V_D$, and $V_P$, 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

# 5. Pharmacodynamics

### 5.1. Studies providing pharmacodynamic data

PK data collected in the Phase II/III studies as described in Section 3, 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).

## 5.2. Summary of pharmacodynamics

### 5.2.1. Simulations to support dose and regimen selection for Phase III trials (ACZ885a-modeling report, Study A2203)

#### *5.2.1.1. Objectives and study design*

The objectives of this integrated PK/PD model simulation were to use mathematical modelling to predict the kinetics and response of:

- Canakinumab monoclonal antibody in plasma
- Clinical symptoms of inflammatory relapse (flare) due to over expression of IL-1β, to enable the setting of a posology for patients and the design for Phase III clinical studies through simulating canakinumab concentrations and clinical symptoms of relapse

The analysis population for this report were the 23 sJIA patients who participated in Study A2203 (see Section 6.1.2.1). An additional 233 patients from studies in CAPS and other indications from the original PK binding model were included in order to provide supportive PK and IL-1β information for the sparsely sampled Study A2203.

With respect to baseline demographics and disease history of the sJIA patients, in brief, 52% were male; age ranged from 4 to 19 years (mean 10 years); and mean dose of prednisolone equivalent corticosteroid was 0.32 mg/kg/day. Patients from the other indications were slightly more likely to be male (57%), with an age range of 4 to 74 years.

#### *5.2.1.2. Data analysis and modelling methods*

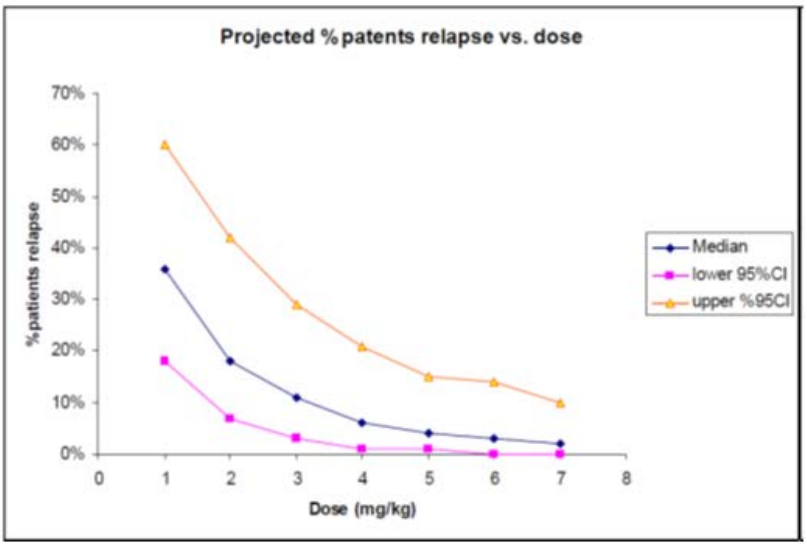
The PK binding model was the same as was previously used in the CAPS submission (excluding the covariate for disease type). The sJIA PK parameter estimates were extracted and used to build a non-linear mixed effect PK-flare model. The PK-flare model was then used to perform simulations for the probability of relapse for sJIA patients given at the simulated doses from 1-7 mg/kg administered SC.

##### *5.2.1.2.1. Results*

The PK-flare model successfully fitted relapse data with a critical flare concentration of canakinumab which ranged from 0.01 - 20 µg/mL. The canakinumab concentration at which there is a 50% probability of clinical flare was estimated at 2 µg/mL (74% CV). Steroid usage and baseline CRP were found to be significant covariates in explaining some of the variability in *Ki* (a higher baseline CRP was associated with a higher canakinumab concentration at the point of flare, and a decrease in steroid usage during the study was associated with a lower canakinumab concentration at the point of flare).

Based on the PK-flare model simulations, the projected percentage of patients who would relapse at the end of 4 weeks following a single dose of canakinumab between 1 and 7 mg/kg ranged from a high of 36% on 1 mg/kg down to 2% on 7 mg/kg. At a dose of 4 mg/kg it was estimated that 6% (95% prediction interval 1 - 21%) would relapse. While higher doses may give greater responses, the 4 mg/kg dose is approaching saturation of the response (Figure 3.).

**Figure 3. Simulated dose response after 4 weeks**




| Dose | Median | 95% CI |
|---|---|---|
| 1 mg/kg | 36% | 16% - 60% |
| 2 mg/kg | 18% | 7% - 42% |
| 3 mg/kg | 11% | 3% - 29% |
| 4 mg/kg | 6% | 1% - 21% |
| 5 mg/kg | 4% | 1% - 15% |
| 6 mg/kg | 3% | 0% - 14% |
| 7 mg/kg | 2% | 0% - 10% |

#### *5.2.1.3. Characterising the PK and pharmacodynamics of canakinumab in the prevention of flares for paediatric patients treated for systemic Juvenile Idiopathic Arthritis (sJIA) (ACZ885g-modeling report)*

##### *5.2.1.3.1. Objectives and study design*

The PD objectives of this Pop PK/PD analysis were as follows:

- To determine whether canakinumab 4 mg/kg SC given every 4 weeks provides sufficient exposure to prevent flares in sJIA paediatric patients

The sJIA PK parameter estimates from the PK binding model were extracted and used to build a non-linear mixed effect PK-flare model. Flare records were collected as per the study-specific criteria.

Model-based simulations were carried out to determine the concentration of canakinumab (including IL-1β) at the visit time for flare assessment. The median and/or average values were also compared with the previous *Ki* value (2 µg/mL, model estimated concentration at 50% probability of flare) determined from the PK-Flare model derived from the Phase II dose-ranging Study A2203.

##### *5.2.1.3.2. Results*

Simulated concentrations of canakinumab at flare varied widely both within and between the sJIA studies, ranging from 0 - 41 µg/mL, with the median predicted concentration centred at 5.8 µg/mL. The mean predicted concentration at flare in the studies was as follows: A2203 (4.77 ± 7.5 µg/mL), G2305 (0.5 ± 1.8 µg/mL), G2301 (11.6 ± 9.3 µg/mL) and G2301E1 (12.9 ± 8.8 µg/ml). The concentration at flare generally increased with increasing canakinumab dose (Study A2203), and was higher in the canakinumab group compared with the placebo group. The 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; $p < 0.0001$). The predicted canakinumab flare concentration was comparable among groups stratified by age or bodyweight, ranging from 7 to 13 µg/mL.

#### *5.2.1.4. Exposure-response modelling of canakinumab in the prevention of flares for paediatric patients treated for systemic Juvenile Idiopathic Arthritis (sJIA) (ACZ885g-hazard report)*

##### *5.2.1.4.1. Objectives and study design*

The objectives of this integrated PK/PD model simulation were as follows:

- To explore the canakinumab exposure-flare reduction relationship with a discrete hazard model using average weekly plasma concentration data imputed from the canakinumab population PK-binding model
- To explore the impact of patient baseline characteristics such as age, gender, body weight, baseline steroid use, baseline steroid strata, and baseline paediatric ACR30 strata on the hazard of flare
- To draw inferences concerning dose-flare reduction at different doses by simulating probabilities of flare in patients on placebo and bodyweight-tiered dosage regimens of 1 - 6 mg/kg of canakinumab SC every 4 weeks

The analysis population for this report were the 100 patients who participated in Part II of Study G2301 (see Section 6.1.1.2). Only the data in the double-blind phase in Part II and the first time-to-flare data were used to build the exposure-flare hazard model.

Patients' baseline demographics and disease history are reported in Section 6.1.1.2.11. In brief, 55% were female; age ranged from 2 to 19 years old (mean 9.1 years); and baseline prednisolone equivalent corticosteroid doses ranged from 0.02 to 1.0 mg/kg/day (mean dose 0.32 mg/kg/day).

##### *5.2.1.4.2. Data analysis and modelling methods*

Canakinumab plasma concentrations were collected from every patient throughout Study G2301. Pop PK modelling methods were used to explore the relationship between the hazard of flare presentation and canakinumab plasma concentration over time, and to see if a model could reproduce the observed Kaplan-Meier (K-M) curves of flaring. Each trial simulation included between subject variations (PK parameters, dosing history, corticosteroid dose, and entry time of each subject into Part II). For model validation, in each simulated trial, 100 patients were randomised in a 1:1 ratio to placebo or 4 mg/kg canakinumab dose arm. Five-hundred clinical trial simulations were run mimicking the study design of G2301. For each simulated clinical trial, K-M curves of flaring were obtained for placebo and canakinumab arms. Goodness-of-fit was assessed by plotting the median simulated K-M curve of each arm with the observed K-M curve of the corresponding treatment arm in Study G2301.

Clinical simulations were also performed to determine whether 4 mg/kg was an appropriate dose in preventing flare events in patients who had tapered steroids and in who the disease was under control. In each of 1,000 simulated trials, 700 patients per study were equally randomised to 1 of 7 treatment arms including placebo, 1 mg/kg, 2 mg/kg, 3 mg/kg, 4 mg/kg, 5 mg/kg, and 6 mg/kg of canakinumab. These simulations represent the flare outcome of patients entering from Part I of Study G2301 at 4 mg/kg and being switched to alternative doses.

##### *5.2.1.4.3. Final model*

The observed flare pattern for canakinumab treated patients in Study G2301 was biphasic, with an initial higher hazard in the first approximately 140 days, with a lower, stable risk thereafter (Figure 4, below). The sponsor proposed 2 possible explanations for this:

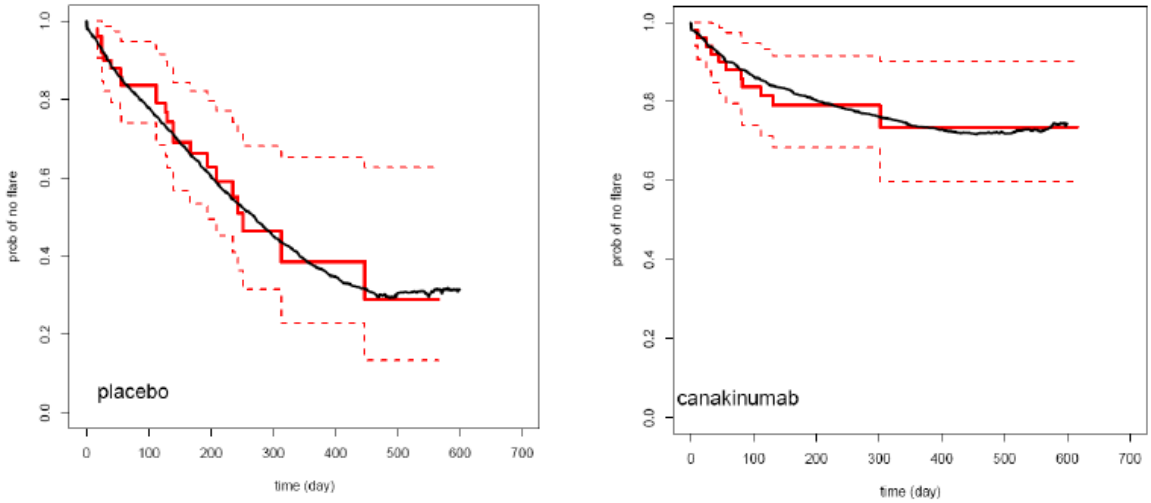
- a study population with varying degrees of disease severity and hence a different background flare risk (heterogeneous background hazard model), or

- a study population with varying degrees of responsiveness/sensitivity to canakinumab therapy (heterogeneous canakinumab responsiveness model).

The heterogeneous canakinumab responsiveness model was abandoned when it was unable to estimate the increased concentration of canakinumab at which 50% of flare hazard is suppressed for less responsive patients.

The heterogeneous background hazard model investigated 19 scenarios, with the fraction of patients who tended to flare early in part II ranging from 0% to 18% (the maximum percentage that enabled the model to converge). Thirteen of these scenarios (flare early fractions of 6% to 18%) were considered equally plausible. After accounting for the baseline corticosteroid dose, no other covariates were statistically significant.

**Figure 4. Observed K-M and point-wise median of 500 simulated K-M of flaring for placebo (left) and canakinumab (right) from the final model**




Red solid lines are observed K-M curves; red dashed lines are their 95% CIs; black solid lines are point-wise median of simulated K-M curves.

#### *5.2.1.4.4. Results*

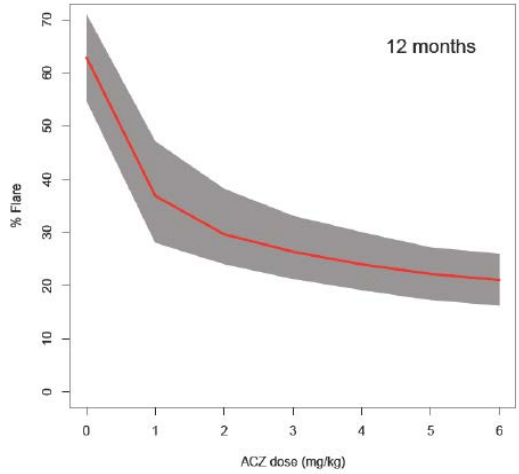
##### *5.2.1.4.5. Canakinumab exposure-flare reduction relationship in sJIA*

Using individual PK profiles from the PK-binding model, simulations based on the heterogeneous background hazard model determined the median probability of flare over 12 months for the placebo arm as 63% (90% CI: 55% to 71%). For the same time period, 4-weekly treatment with SC canakinumab resulted in median probabilities of flare ranging from 21% (6 mg/kg), to 37% (1 mg/kg). Treatment with canakinumab 4 mg/kg reduced the placebo flare rate by 39% (90% CI: 28% to 49%) (Table 6Table  and Figure 5, below).

**Table 6. Model predicted flare rate by canakinumab dose in 12 months**

| | canakinumab dose (mg/kg) | | | | | | |
|---|---|---|---|---|---|---|---|
| | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| Median rate | 63% | 37% | 30% | 26% | 24% | 22% | 21% |
| 90% CI | (55,71)% | (28,47)% | (24,38)% | (21,33)% | (19,30)% | (17,27)% | (16,26)% |
| % improvement over 4mg/kg | -162% | -54% | -24% | -10% | 0% | 7% | 12% |
| odds ratio over 4mg/kg | 5.374 | 1.851 | 1.336 | 1.135 | 1.000 | 0.904 | 0.846 |

**Figure 5. Model predicted flare rate by canakinumab dose in 12 months**




## 5.3. Evaluator's overall conclusions on pharmacodynamics

- Predicted concentrations of canakinumab at flare varied widely both within and between the sJIA studies, ranging from 0 - 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 $\mu$ g/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% 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 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

# 6. 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 which was discussed in Section 4.2.1.1. 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. The efficacy and safety findings from this study will be discussed in Sections 6 and 7.

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.

# 7. Clinical efficacy

## 7.1. Systemic juvenile idiopathic arthritis

### 7.1.1. Pivotal efficacy studies

#### *7.1.1.1. Study G2305*

##### *7.1.1.1.1. Study design, objectives, locations and dates*

This 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. It was conducted in 40 centres in 18 countries, commencing on 22-Jul-2009 with a completion date of 02-Dec-2010. The primary objective of the study was to demonstrate that the proportion of patients who met the adapted American College of Rheumatology paediatric 30 (ACR30) criteria at Day 15 is higher with canakinumab compared to placebo.

The secondary objectives of the study were to evaluate the following:

- Effect of treatment with canakinumab as compared to placebo with respect to the adapted ACR30/ACR50/ACR70/ACR90/ACR100 criteria at Day 29
- Efficacy (% of patients who meet the adapted ACR50 criteria) of canakinumab as compared to placebo at Day 15
- Effect of treatment with canakinumab as compared to placebo with respect to the adapted ACR70/ACR90/ACR100 criteria at Day 15
- Efficacy of canakinumab as compared to placebo with respect to overall pain over the last week assessed on a 0-100 mm visual analogue scale (VAS) in the Childhood Health Assessment Questionnaire (CHAQ) by Day 15 and Day 29
- Efficacy of canakinumab as compared to placebo to show clinical signs of response (% of patients who have body temperature ≤ 38°C) at Day 3
- Change in Health-Related Quality of Life over time by use of the cross culturally adapted and validated version Child Health Questionnaire (CHQ)

- Change in disability over time by use of the cross culturally adapted and validated version of the CHAQ
- Safety, tolerability and immunogenicity of canakinumab

*7.1.1.1.2. Inclusion and exclusion criteria*

The main eligibility criteria included:

- Male or female patients aged ≥2 to <20 years with a confirmed diagnosis of sJIA as per ILAR definition at least 2 months prior to enrolment and onset of disease <16 years of age.
- Patients must have had active disease defined as:
  - at least 2 joints with active arthritis
  - documented spiking, intermittent fever (body temperature >38° C) for at least 1 day during the screening period within 1 week before first canakinumab/placebo dose
  - C-reactive protein (CRP) >30 mg/L (normal range < 10 mg/L)
- No concomitant use of second line agents such as disease-modifying and/ or immunosuppressive drugs with the exception of:
  - Stable dose of methotrexate (maximum of 20 mg/m$^2$/week) for at least 8 weeks prior to the screening visit, and folic/folinic acid supplementation (according to standard medical practice of the centre)
  - Stable dose of no more than one non-steroidal anti-inflammatory drug for at least 2 weeks prior to the screening visit
  - Stable dose of steroid treatment ≤ 1.0 mg/kg/day (maximum 60 mg/day for children over 60 kg) in 1-2 doses per day of oral prednisone (or equivalent) for at least 3 days prior to randomisation

The following criteria were grounds for exclusion:

- History of hypersensitivity to study drug or to biologics
- Diagnosis of active macrophage activation syndrome (MAS) within the last 6 months
- Active or recurrent bacterial, fungal or viral infection, including patients with evidence of human immunodeficiency virus (HIV) infection, hepatitis B or hepatitis C infection
- Any of the risk factors for tuberculosis (TB)
- Underlying metabolic, renal, hepatic, infectious or gastrointestinal conditions
- History of malignancy of any organ system (other than localised basal cell carcinoma of the skin), treated or untreated, within the past 5 years, regardless of whether there was evidence of local recurrence or metastases
- Clinical evidence of liver disease or liver injury
- Presence of moderate to severe impaired renal function or evidence of urinary obstruction or difficulty in voiding
- Recent use of corticosteroids >1.0 mg/kg/day, intra-articular, peri-articular or intramuscular corticosteroid injections, other biologics and investigational drugs prior to the Baseline visit

*7.1.1.1.3. Study treatments*

Patients were randomised to canakinumab or placebo in a 1:1 ratio, and received a SC injection of canakinumab (4 mg/kg) or placebo on Day 1. The maximum total single dose of canakinumab

allowed was 300 mg. Any patient who required a dose greater than 150 mg (patients > 37.5 kg) received two SC injections.

*7.1.1.1.4. Efficacy variables and outcomes*

The main efficacy variables consisted of the adapted ACR Paediatric response (components shown below), parent's or patient's assessment of pain based on the 0-100 mm VAS in the Child Health Assessment Questionnaire (CHAQ), and the Child Health Questionnaire (CHQ)-PF50.

The adapted ACR Paediatric response variables are the following:

1. Physician's global assessment of disease activity on a 0-100 mm VAS
2. Parent's or patient's (if appropriate in age) global assessment of patient's overall wellbeing based upon the 0-100 mm VAS in the CHAQ
3. Functional ability: CHAQ
4. Number of joints with active arthritis
5. Number of joints with limitation of motion
6. Laboratory measure of inflammation: CRP (mg/L) (standardised to a normal range of 0-10 mg/L)
7. Absence of intermittent fever due to sJIA during the preceding week

Using the adapted ACR Paediatric response variables, the adapted ACR Paediatric 30/50/70/90/100 criteria are defined as meeting all of the following:

- improvement from baseline of ≥ 30%, ≥ 50%, ≥ 70%, ≥ 90%, or 100%, respectively, in at least 3 of the first 6 response variables
- no intermittent fever (that is, oral or rectal body temperature ≤ 38°C) in the preceding week (response variable 7)
- no more than one of the first 6 response variables worsening by more than 30%

*7.1.1.1.5. Flare*

The occurrence of flare was an assessment during the course of the study, but it was not an endpoint of the study. It was collected because some G2305 patients were expected to roll over in to other studies (G2301 and G2301E1) where flare will be evaluated. Flare was defined as at least 1 of the following:

1. Reappearance of fever (>38°C, lasting for at least 2 consecutive days) not due to infections
2. Flare according to the JIA paediatric criteria for flare (all criteria must have been met):
   - ≥ 30% worsening in at least 3 of the first 6 response variables
   - ≥ 30% improvement in not more than 1 of the first 6 response variables

Note:

- If the physician or parent global assessment was one of the 3 response variables used to define flare, worsening of ≥ 20 mm must have been present.
- If the number of active joints or joints with limitation of motion was one of the 3 response variables used to define flare, worsening in ≥ 2 joints must have been present.
- If CRP was used to define flare, CRP must have been > 30 mg/L.

*7.1.1.1.6. Inactive disease*

Although not an endpoint of the study, inactive disease was assessed for the same reasons outlined for flare, above. Inactive disease was defined as meeting all of the following:

- No joints with active arthritis
- No fever (body temperature ≤ 38°C)
- No rheumatoid rash, serositis, splenomegaly, hepatomegaly or generalised lymphadenopathy attributable to JIA
- Normal ESR or CRP
- Physician's global assessment of disease activity indicating no disease activity (that is, best possible score ≤ 10 mm)

Other efficacy variables included:

- X-ray of both hands and wrists
- Monitoring of sexual maturation (Tanner stages)

The primary efficacy outcome was the difference in the proportion of patients who met the adapted ACR Pediatric 30 criteria at Day 15 with canakinumab compared to placebo.

Secondary efficacy outcomes included the effect of treatment with canakinumab as compared to placebo with respect to:

- the adapted ACR Pediatric 30/50/70/90/100 criteria at Day 29
- the adapted ACR Pediatric 50/70/90/100 criteria at Day 15
- patient's pain intensity (0 – 100 mm VAS) at Day 15 and Day 29
- body temperature ≤ 38°C at Day 3
- CHQ-PF50 physical score for 5–18 years old over time
- CHQ-PF50 psychosocial score for 5–18 years old over time
- CHAQ disability score over time

Evaluator's comment: The outcome variables are well established for JIA studies, widely used, and are consistent with the TGA adopted guideline (CPMP/EWP/422/04 Guideline on Clinical Investigation of Medicinal Products for the Treatment of Juvenile Idiopathic Arthritis. Effective: 26 June 2009).

*7.1.1.1.7. Randomisation and blinding methods*

Randomisation was via an Interactive Voice Response System (IVRS), stratified by number of affected joints (≤ 26, >26), non-responder to anakinra (yes or no), and level of current corticosteroid use (≤ 0.4 mg/kg or > 0.4 mg/kg oral prednisone [or equivalent]).

*7.1.1.1.8. Blinding methods included:*

1. Randomisation data were kept strictly confidential until the time of unblinding. Data was accessible only by an independent, unblinded qualified study person at the investigator's site who prepared the study medication.
2. The canakinumab/placebo treatments were supplied in the form of syringes filled with solutions that were identical in appearance.

Evaluator's comment: The success of randomisation appears adequate based on the comparability of the baseline demographic and disease characteristics of the canakinumab and placebo groups. Although there was some mismatch in the age group distribution and baseline disease characteristics, this is not unexpected when dealing with small patient numbers (see Table 8). Success of blinding was not formally assessed; because the efficacy outcomes were conducted by the investigator, subjective, and certain AEs were characteristic of canakinumab, there was some potential for unblinding.

*7.1.1.1.9. Analysis populations*

The Full Analysis Set (FAS) consisted of all randomised patients who received at least one dose of study drug. Following the intent-to-treat principle, patients were analysed according to the treatment they were assigned to at randomisation.

The Safety Set consisted of all patients who received at least one dose of study drug and had at least one post-baseline safety assessment (which included a statement that a patient had no adverse events). Patients were analysed according to treatment received. There was no Per-Protocol Analysis Set.

Evaluator's comment: The analysis populations were appropriate.

*7.1.1.1.10. Sample size*

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 give 90% power to detect a significant treatment difference using a one-sided significance test with $\alpha$=0.025 based on Fishers' exact test. Following the introduction of an interim analysis (Protocol Amendment 4), the power of the study was 89%.

Evaluator's comment: Protocol Amendment 4 was written because of slower than anticipated recruitment to the study and the publication of an abstract (DeBenedetti et al 2010) in a similar sJIA patient population that reported a lower response in patients on placebo (24%) compared with the original assumption of 30% for the sample size calculation. The interim analysis was conducted with 84 patients randomised. An independent Data Monitoring Committee (DMC) reviewed the results of the interim analysis which were positive, and recommended that the study be stopped early.

*7.1.1.1.11. Statistical methods*

The two treatment groups were compared using the Cochran-Mantel-Haenszel (CMH) test adjusting for the stratification factors as defined by the electronic case report form (eCRF).

In addition to the one-sided p-value, the common odds ratio (OR) was estimated together with the 95% two-sided confidence interval (CI) for the common OR. Breslow & Day's test was used to assess the homogeneity of the ORs of responding between canakinumab and placebo treated patients across the strata.

An unstratified Fisher's exact test was used as a supportive analysis. The overall difference in proportions between treatment groups was estimated together with the 95% two-sided CI.

If the primary objective was achieved, secondary endpoints were assessed in a closed testing procedure in order to control the overall Type I error rate (one-sided tests) in the evaluation of these secondary efficacy variables.

In Protocol amendment 4, an interim analysis was implemented. The spending function approximating O'Brien-Fleming boundaries were used to determine criteria for the interim and final analyses to protect the overall false positive rate of the trial at 0.025. For the anticipated sample size of 84 patients at the interim analysis and 122 patients at final analysis the alpha levels of 0.00697 and 0.02287 were calculated respectively.

Evaluator's comment: The statistical analyses were appropriate.

*7.1.1.1.12. Participant flow*

A total of 84 patients were randomised, 43 to canakinumab and 41 to placebo (Table 7, below). The only reported reason patients discontinued from the study was unsatisfactory therapeutic effect (including failure to meet the adapted ACR Paediatric 30 criteria at Day 15, that is, the

primary efficacy endpoint). In the placebo group 90.2% of patients discontinued from the study for this reason compared with only 14.0% of patients in the canakinumab group.

**Table 7. Patient disposition (Randomised Set, G2305)**

| | ACZ885 N=43 n (%) | Placebo N=41 n (%) | All patients N=84 n (%) |
|---|---|---|---|
| Completed | 37 (86.0) | 4 (9.8) | 41 (48.8) |
| Discontinued | 6 (14.0) | 37 (90.2) | 43 (51.2) |
| **Reason for discontinuation** | | | |
| Unsatisfactory therapeutic effect | 6 (14.0) | 37 (90.2) | 43 (51.2) |

Evaluator's comment: Because of the large proportion of discontinuations due to lack of efficacy in the placebo group, there are limited placebo data for safety comparisons.

*7.1.1.1.13. Major protocol violations/deviations*

There were a large number of patients with mostly minor protocol violations (34 [79%] on canakinumab and 22 [53.7%] on placebo). Six patients (3 in each treatment group) had a pre-defined deviation (patient was not discontinued despite not meeting the adapted ACR 30 Paediatric criteria at Day 15) that would have excluded them from a per protocol analysis (although a per protocol analysis was not planned nor performed). Two additional protocol deviations included one patient on placebo who did not have a CRP level >30 mg/L at baseline, and one patient on canakinumab who had urine protein ≥ 2+ (considered moderately to severely impaired) at study entry).

Evaluator's comment: The protocol deviations are not considered likely to have had a material impact on the study conclusions.

There were five protocol amendments, as summarised below:

- Protocol Amendment 1: changed the criteria for which a patient would discontinue between Days 15-29 due to declining efficacy after first demonstrating a clinical response (a minimum adapted ACR Pediatric 30 response) at Day 15
- Protocol Amendment 2: ensured that joint counts were performed by a trained joint assessor, however, the amendment was retracted on 28-Oct-2009 following feedback from the health authorities
- Protocol Amendment 3: was written based on feedback from health authorities to: 1) clarify absence of fever in the secondary objectives, 2) ensure that patients were on a stable dose of corticosteroids at least 3 days prior to baseline, and 3) clarify the transition of G2305 placebo or canakinumab patients to Study G2301 or G2301E1, respectively, if they did not maintain a minimum adapted ACR Pediatric 30 response after Day 15
- Protocol Amendment 4: implemented an interim analysis
- Protocol Amendment 5: described the implementation of an adjudication committee for MAS and the follow-up to be conducted on MAS cases that are identified in the study

*7.1.1.1.14. Baseline data*

Baseline demographics of patients are shown in Table 8, below. 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 6-11 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).

**Table 8. Baseline Demographics (Study G2305)**

| | ACZ885 N=43 | Placebo N=41 | All patients N=84 |
|---|---|---|---|
| **Sex – n (%)** | | | |
| Male | 16 (37.2) | 18 (43.9) | 34 (40.5) |
| Female | 27 (62.8) | 23 (56.1) | 50 (59.5) |
| **Age (years)** | | | |
| n | 43 | 41 | 84 |
| Mean | 8.3 | 9.7 | 9.0 |
| SD | 5.08 | 4.32 | 4.75 |
| Median | 8.0 | 9.0 | 8.0 |
| Min-Max | 2 – 18 | 4 – 19 | 2 – 19 |
| **Age groups – n (%)** | | | |
| 2- < 4 years | 9 (20.9) | 0 (0.0) | 9 (10.7) |
| 4 - < 6 years | 8 (18.6) | 7 (17.1) | 15 (17.9) |
| 6 - < 12 years | 14 (32.6) | 22 (53.7) | 36 (42.9) |
| 12 - < 20 years | 12 (27.9) | 12 (29.3) | 24 (28.6) |
| **Race – n (%)** | | | |
| Caucasian | 40 (93.0) | 37 (90.2) | 77 (91.7) |
| Black | 2 (4.7) | 0 (0.0) | 2 (2.4) |
| Asian | 0 (0.0) | 1 (2.4) | 1 (1.2) |
| Native American | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Pacific Islander | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Other | 1 (2.3) | 3 (7.3) | 4 (4.8) |
| **BMI ($kg/m^2$)** | | | |
| n | 43 | 40 | 83 |
| Mean | 18.957 | 19.120 | 19.035 |
| SD | 4.2702 | 4.8990 | 4.5565 |
| Median | 17.440 | 17.405 | 17.440 |
| Min-Max | 13.22 – 29.89 | 13.44 – 32.55 | 13.22 – 32.55 |

Baseline CRP levels, number of active joints, number of joints with limited range of motion, pain intensity using a 0-100 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. The median time from sJIA diagnosis to study entry was longer in patients on canakinumab (approximately 2.3 years) versus placebo (approximately 2.0 years). Most of the patients reported systemic signs of disease after the first 6 months of diagnosis (79.8%). Overall, 36.9% had a prior use of anakinra, 33.3% etanercept, 3.6% tocilizumab, and 8.3% adalimumab, with no relevant differences between the two treatment groups.

Prior to commencing the study, the majority of patients had taken (and discontinued) medications (79.1% canakinumab versus 75.6% placebo). The most common of these medications were anakinra (32.6% versus 31.7%), etanercept (23.3% versus 17.1%), prednisone (23.3% versus 7.3%), prednisolone (16.3% versus 22.0%), methylprednisolone (14.0% versus 12.2%), methotrexate (16.3% versus 12.2%), and ibuprofen (4.7% versus 17.1%). During the study, 95.3% of the canakinumab and 97.6% of the placebo patients were taking a concomitant medication. The most commonly used medications were steroids (79.1% versus 75.6%), methotrexate (67.4% versus 58.5%), NSAIDs (65.1% versus 73.2%; ibuprofen, naproxen or indomethacin), and paracetamol (23.3% versus 24.4%).

Most patients had medical histories consistent with the diagnosis of sJIA, including infections and infestations (37.2% versus 29.3%), gastrointestinal disorders (20.9% versus 26.8%),

musculoskeletal and connective tissue disorders (18.6% versus 17.1%), skin and subcutaneous tissue disorders (20.9% versus 12.2%), and blood and lymphatic system disorders (9.3% versus 17.1%), for canakinumab versus placebo groups, respectively. The most common histories by preferred term were varicella (11.6% versus 2.4%) and anaemia (4.7% versus 14.6%).

*7.1.1.1.15. Results for the primary efficacy outcome*

There was a higher proportion of patients with an ACR30 at Day 15 in the canakinumab group (83.7%) compared with the placebo group (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).

The supportive analysis (unstratified Fisher's exact test) revealed similar findings: OR 47.57; difference in proportions -73.96%; 95% CI: -88.26, -59.67; p<0.001.

**Table 9. Responders to treatment according to the adapted ACR Paediatric 30 criteria at Day 15: Comparison between treatment groups (Full Analysis Set, Study G2305)**

| Treatment | N | Responders n (%) | Estimated odds ratio to placebo | 95%CI of odds ratio | p-value |
|---|---|---|---|---|---|
| ACZ885 | 43 | 36 (83.7) | 62.29 | (12.68, 306.07) | <0.0001 * |
| Placebo | 41 | 4 (9.8) | | | |

Comparison of treatment groups using CMH test adjusting for stratification factors. An odds ratio >1 indicates that ACZ-treated patients are more likely to respond than placebo patients. (1) p-value from CMH test.

Evaluator's comment: The wide CI reflects the small sample size.

In general, the results were consistent for all ACR responders at Day 15 regardless of stratification factor, gender and age. 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). Baseline corticosteroid usage did not affect response to canakinumab: the proportion of responders was 84.8% (28/33 patients) in the lower steroid use category and 80% (8/10 patients) in the higher steroid use category. The response was lower in patients with >26 joints affected (6/9, 67%) than in those in the ≤26 joints category (30/34, 88%), but this may be the result of small patient numbers.

*7.1.1.1.16. Results for other efficacy outcomes*

Each of the steps in the closed testing procedure for the secondary efficacy outcomes was satisfied (all were statistically significant).

The percentage of responders to treatment according to the adapted ACR paediatric criteria is shown in Figure 6 and Table 10, below. The proportion of responders at each ACR level at Day 15 or 29 was significantly higher in the canakinumab group compared to the placebo group (all p<0.0001), and the proportion of responders on canakinumab was generally higher on Day 29 compared with Day 15. By Day 15, 60.7% of patients on canakinumab had achieved a minimum ACR70 (67.4% at Day 29), compared with only 2.4% of patients on placebo (also 2.4% at Day 29). In general, the results were consistent regardless of stratification factor, gender and age.

**Figure 6. Percentage of responders to treatment according to the adapted ACR Paediatric criteria, by visit, criteria and treatment (Full Analysis Set)**

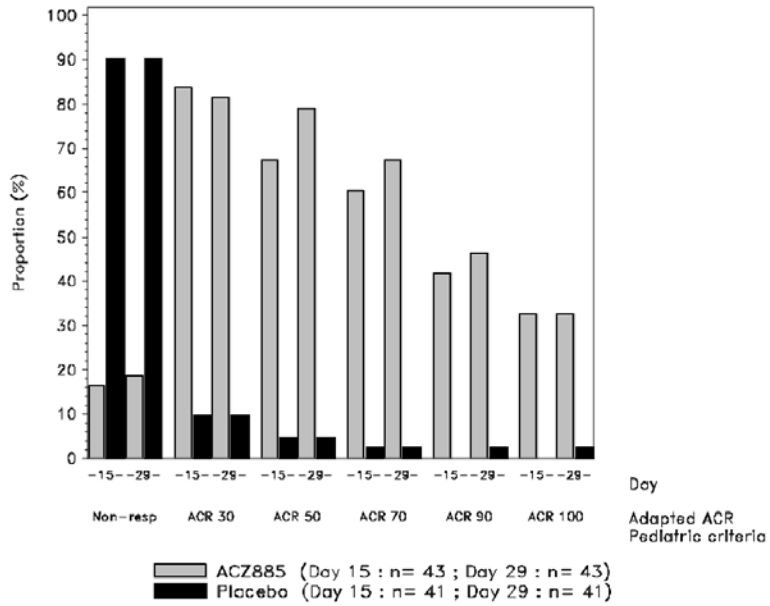



**Table 10. Responders to treatment according to the adapted ACR Pediatric criteria: Comparison between treatment groups, by visit (Full Analysis Set, G2305)**

| Criteria / time point | Treatment | n | Responders n (%) | Estimated odds ratio | 95% CI of odds ratio | p-value (1) |
|---|---|---|---|---|---|---|
| **ACR 30 - Day 29** | ACZ885 | 43 | 35 (81.4) | 62.29 | (12.68, 306.07) | <0.0001 * |
| | Placebo | 41 | 4 (9.8) | | | |
| **ACR 50 - Day 15** | ACZ885 | 43 | 29 (67.4) | 58.00 | (10.13,332.13) | <0.0001 * |
| | Placebo | 41 | 2 (4.9) | | | |
| **ACR 50 - Day 29** | ACZ885 | 43 | 34 (79.1) | 106.76 | 16.26, 701.10 | <0.0001 * |
| | Placebo | 41 | 2 (4.9) | | | |
| **ACR 70 - Day 15** | ACZ885 | 43 | 26 (60.5) | 86.81 | (10.23,736.72) | <0.0001 * |
| | Placebo | 41 | 1 (2.4) | | | |
| **ACR 70 - Day 29** | ACZ885 | 43 | 29 (67.4) | 105.27 | 12.01, 922.79 | <0.0001 * |
| | Placebo | 41 | 1 (2.4) | | | |
| **ACR 90 - Day 15** | ACZ885 | 43 | 18 (41.9) | NotEst | NotEst | <0.0001 * |
| | Placebo | 41 | 0 | | | |
| **ACR 90 - Day 29** | ACZ885 | 43 | 20 (46.5) | 40.64 | ( 5.24,315.19) | <0.0001 * |
| | Placebo | 41 | 1 (2.4) | | | |
| **ACR 100 - Day 15** | ACZ885 | 43 | 14 (32.6) | NotEst | NotEst | <0.0001 * |
| | Placebo | 41 | 0 | | | |
| **ACR 100 - Day 29** | ACZ885 | 43 | 14 (32.6) | 22.67 | ( 2.80,183.21) | 0.0001 * |
| | Placebo | 41 | 1 (2.4) | | | |

All of the component response variables in the adapted ACR paediatric criteria also demonstrated a higher response in the canakinumab group compared with the placebo group. For example, the median changes from baseline at Day 15 were:

- Physician's global assessment of disease activity: -40 mm (-50%) versus -2.0 mm (-3%)
- Patient's/parent's) global assessment of the patient's overall wellbeing: -36.0 mm (-73%) versus 2.0 mm (1%)
- CHAQ disability score (LS mean difference): -0.69 (p = 0.0002)
- number (%) of active joints: -6 (-67%) versus 0 (0%)
- number (%) of joints with a limited range of motion: -5 (-73%) versus 0 (0%)

- CRP: -100.0 mg/L (-55%) versus 5.7 mg/L (4%)

Patients on canakinumab also did better than those on placebo with respect to:

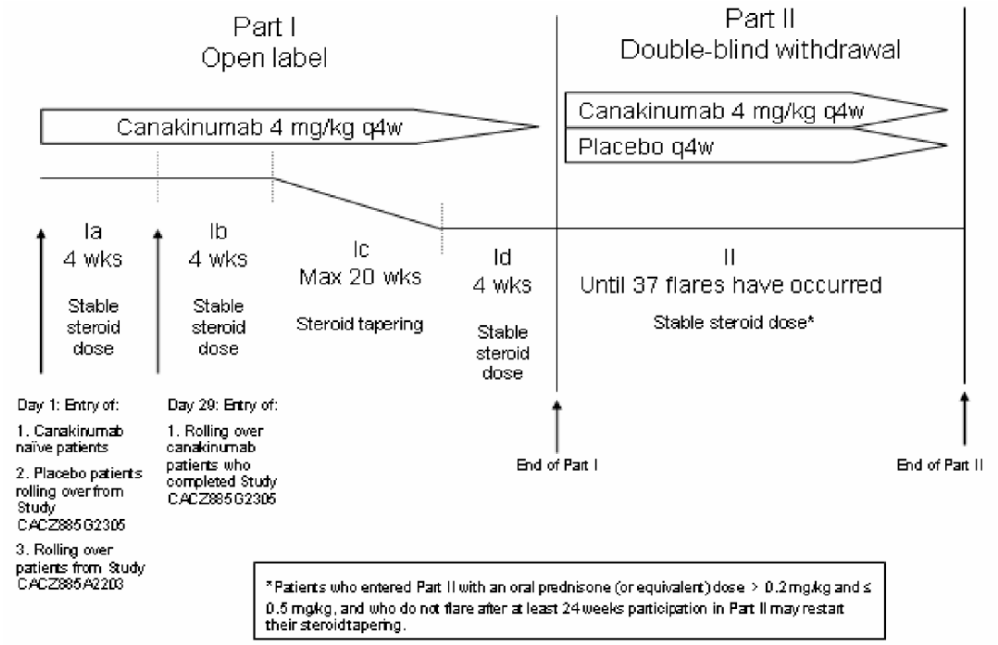
- % Fever at day 3: 0% versus 13.2%, respectively (p=0.0098)
- Pain intensity [0-100 mm VAS] (LS mean difference at Day 15/Day 29): -46.42/-41.86 (both p<0.0001)
- CHQ-PF50 (LS mean difference physical score/psychosocial score): 12.07/7.28 (both, p<0.005)
- Flare (number): 3 versus 31 (no p-value calculated as not a study endpoint, see Section 6.1.1.1.4)
- Inactive disease (% at Day 15): 32.6% versus 0% (no p-value calculated as not a study endpoint, see Section 6.1.1.1.4)

#### *7.1.1.2. Study G2301*

##### *7.1.1.2.1. Study design, objectives, locations and dates*

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. It was conducted in 63 centres in 21 countries, commencing on 6 July 2009 with a completion date of 12 September 2011. 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 (Figure 7., below). 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.

**Figure 7. Study design (G2301)**




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.

Secondary objectives for Part I of the study were to evaluate:

- the number of patients who reached a steroid dose ≤ 0.2 mg/kg at end of Part Ic
- the level of steroid tapering achieved at the end of Part Ic
- the efficacy (percentage of patients who met the adapted ACR Paediatric 30/ 50/ 70/90/ 100 criteria) of canakinumab in Part I
- the efficacy of canakinumab based on the percentage of patients who had a body temperature ≤ 38°C at Day 3 in Part Ia
- the time to adapted ACR Paediatric 50 criteria and normal C-reactive protein (CRP <10mg/L) during Part I
- the time to adapted ACR Paediatric 70 criteria and normal CRP (<10 mg/L) during Part I

The secondary objective for Part II of the study was to evaluate:

- the maintenance of efficacy of canakinumab as compared to placebo (length of time patients continuously maintained or improved their adapted ACR Paediatric 30/ 50/ 70/ 90/ 100 criteria at entry into Part II)

Secondary objectives for both Parts I and II of the study were to evaluate:

- the change in disability over time by use of the cross culturally adapted and validated version of the Child Health Assessment Questionnaire (CHAQ©)
- the change in Health-Related Quality of Life (HRQoL) over time by use of the cross culturally adapted and validated version Child Health Questionnaire (CHQ)
- the safety, tolerability and immunogenicity of canakinumab
- the pharmacokinetics (PK)/pharmacodynamic (PD) of canakinumab

Exploratory objectives for both Parts I and II of the study were to explore:

- the change in HRQoL over time by use of EuroQoL Five Dimension questionnaire (EQ-5D) (for patients ≥ 12 years of age) or EQ-5D proxy (for patients 8 – 11 years of age)
- the impact of treatment with canakinumab on sleepiness in children over time by use of the Pediatric Daytime Sleepiness Scale (PDSS)
- the impact of treatment with canakinumab on growth velocity
- the impact of treatment with canakinumab on physical development in children and adolescents from ages 6 ‑ 20 by use of the Tanner stages scale
- protein, mRNA and DNA biomarkers (for example, HLA-DQA1) in order to identify retrospectively responder/non-responder patients

For only Part II of the study, the exploratory objectives were to explore:

- the time to inactive disease
- the percentage of patients who would meet the definition of inactive disease on medication as defined by Wallace, Ruperto, and Giannini (2004)
- the progression of joint erosions in the affected hand and/or wrist by x-ray in a subset of volunteer patients

Evaluator's comment: this study design minimised the time a patient might be exposed to placebo which is consistent with the TGA adopted EU guideline (CPMP/EWP/422/04 Guideline on Clinical Investigation of Medicinal Products for the Treatment of Juvenile Idiopathic Arthritis. Effective: 26 June 2009).

*7.1.1.2.2. Inclusion and exclusion criteria*

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

*7.1.1.2.3. Study treatments*

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, see Section 6.1.2.2).

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. Randomisation was stratified by oral prednisone (or equivalent) dose at the end of Part I (two strata: ≤ 0.4 mg/kg, > 0.4 mg/kg) and degree of adapted ACR Paediatric response reached at the end of Part Id (two strata: > adapted ACR Paediatric 50 criteria met [for example, ACR70, 90 or 100], ≤ adapted ACR Paediatric 50 criteria met [for example, ACR 30 or 50]). Steroid doses were to remain stable for the first 24 weeks of treatment in Part II, but could be tapered thereafter if the oral prednisone (or equivalent) dose was >0.2 mg/kg.

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.

Concomitant use of second line agents such as disease-modifying and/or immunosuppressive drugs was not allowed with the exception of the following:

- Steroid treatment ≤ 1.0 mg/kg/day (maximum 60 mg/day for children over 60 kg) in 1-2 doses of oral prednisone (or equivalent)
- Stable dose of methotrexate (maximum of 20 mg/ m2/ week) and folic/folinic acid supplementation (according to standard medical practice of the centre)
- Stable dose of no more than one NSAID

Where possible, patients remained on their current medication for the duration of the study.

*7.1.1.2.4. Efficacy variables and outcomes*

The main efficacy variables were the adapted ACR Paediatric response variables as defined for Study G2305.

*7.1.1.2.5. Steroid tapering assessments*

To be considered a successful steroid taperer, patients must have maintained a minimum adapted ACR30 Paediatric response and met one of the following criteria:

- Patients with a steroid dose > 0.8 mg/kg oral prednisone (or equivalent) at the start of Part Ic who were able to reduce their steroid dose to ≤ 0.5 mg/kg oral prednisone (or equivalent)
- Patients with a steroid dose ≥ 0.5 mg/kg and ≤ 0.8 mg/kg oral prednisone (or equivalent) at the start of Part Ic who were able to reduce their steroid dose by at least 0.3 mg/kg/day oral prednisone (or equivalent) from baseline
- Patients who were able to achieve an oral prednisone (or equivalent) dose ≤ 0.2 mg/kg/day at the end of Part Ic

Flare was defined as per Study G2305. For Part I of the study, the flare assessment was based on comparison with the previous visit, while for Part II the assessment was compared with the visit at the start of Part II.

Inactive disease (an exploratory outcome) was defined as per Study G2305.

Other efficacy variables included:

- X-ray of both hands and wrists
- monitoring of sexual maturation (Tanner stages)
- change in disability over time by use of the cross culturally adapted and validated version of the CHAQ
- change in Health-Related Quality of Life (HRQoL) over time by use of the cross culturally adapted and validated version CHQ
- parent's or patient's assessment of pain based on the 0-100 mm VAS in the CHAQ, and the CHQ-PF50

The primary efficacy outcome for Part I was to assess if canakinumab allowed tapering of steroids (as defined above) in at least 25% of the patients who were on oral steroids at entry into Part I by the end of Part Ic.

The primary efficacy outcome for Part II was the difference between canakinumab and placebo in the time to a flare event.

The secondary and exploratory outcomes for Parts I and II have previously been described in Section 6.1.1.2.1 in the discussion of objectives.

Evaluator's comment: The outcome variables are well established for JIA studies, widely used, and are consistent with the TGA adopted guideline (CPMP/EWP/422/04 Guideline on Clinical Investigation of Medicinal Products for the Treatment of Juvenile Idiopathic Arthritis. Effective: 26 June 2009).

*7.1.1.2.6. Randomisation and blinding methods*

Randomisation and blinding was not required for Part I (open-label, active treatment period).

Randomisation into Part II was via an IVRS, 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).

During Part II, patients, investigator staff, persons performing the assessments, and data analysts were to remain blind to the identity of the treatment from the time of randomisation until study completion and unblinding of the data. The blinding methods included:

- Randomisation data were kept strictly confidential until the time of unblinding. Data was accessible only by an independent, unblinded pharmacist/nurse/physician or authorised personnel at the investigator's site to enable preparation of the study medication for patients
- The canakinumab/placebo treatments were supplied in the form of syringes filled with solutions that were identical in appearance

Evaluator's comment: The success of randomisation appears adequate based on the comparability of the baseline demographic and disease characteristics of the canakinumab and placebo groups, although there was some mismatch in the age group distribution and baseline disease characteristics (see Tables 11 and 12). Success of blinding was not formally assessed; because the efficacy outcomes were conducted by the investigator, potentially subjective and certain AEs were characteristic of canakinumab, there was some potential for unblinding.

*7.1.1.2.7. Analysis populations*

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).

The SS for Part I (SS I) and Part II (SS II) consisted of all patients who received at least one dose of study drug and had at least one safety assessment in Part I or Part II, respectively. The statement that a patient had no adverse events (AEs) was considered to constitute a safety assessment. Patients were analysed according to treatment received.

There was no Per-Protocol Analysis Set.

Evaluator's comment: The analysis populations were appropriate.

*7.1.1.2.8. Sample size*

The sample size for Part II 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. 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.

Assuming an exponential distribution of flares (events) in the canakinumab group (as shown in the exposure-response modelling [Figure 4.3]), the constant weekly hazard rate estimated from the overall event rate (0.25) at week 24 was $\lambda 1$=0.01199. A Weibull distribution of flare events was assumed in the placebo group up to week 24 (estimated time of wash-out of canakinumab from Part I) and thereafter according to an exponential distribution with a constant weekly hazard rate $\lambda 2$=0.0502 as estimated from the overall event rate (0.7) at week 24. Based on these assumptions, the number of events needed 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 and 24 in the placebo group).

Evaluator's comment: There was no clinical justification for the choice of percentage of patients who flare in the 1st 24 weeks of treatment. The sponsor will be asked to provide the basis for their choice of percentage flare.

*7.1.1.2.9. Statistical methods*

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.

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.

Evaluator's comment: The statistical analyses were appropriate.

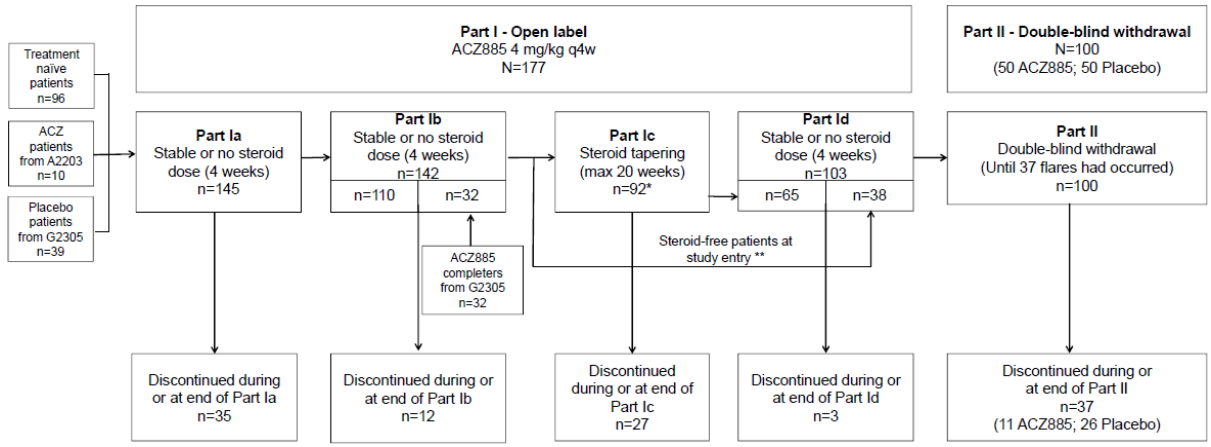
*7.1.1.2.10. Participant flow*

In total, 206 patients were screened; 29 were not enrolled because of: unacceptable laboratory value(s) (n=12), did not meet diagnostic/severity criteria (n=11), and other (n=7). Of the 177 patients who entered Part I of the study (135 treatment naïve entered at Part 1a, 32 who had previously received canakinumab in Study G2305 entered at Part 1b), 100 were randomised into Part II (50 each to canakinumab and placebo). Thirty-seven patients (11 on canakinumab, 26 on placebo) discontinued during or at the end of Part II (Figure 8, below).

The primary reason for the discontinuation of 72 (40.7%) patients from Part I of the study was unsatisfactory therapeutic effect. All 72 patients were withdrawn by the investigator for protocol-driven, efficacy-related reasons (that is, no initial response at Day 15 [n=27], loss of response after Day 15 [n=15], or steroid tapering failure [n=26]). In addition there was one death, and 4 withdrawals due to adverse events (AEs).

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]). The primary reason for discontinuation in Part II for both treatment groups was unsatisfactory therapeutic effect (22% canakinumab; 40% placebo). All discontinuations due to AEs (n=4, 8%) were in the placebo arm.

**Figure 8. Patient disposition (Safety Set I and Safety Set II)**




Evaluator's comment: The large number of discontinuations from Part I of the study was primarily due to an unsatisfactory therapeutic effect. Therefore efficacy during the withdrawal phase is being conducted in responders.

*7.1.1.2.11. Major protocol violations/deviations*

A total of 8 (4.5%) patients had pre-defined, per protocol deviations in Part I of the study: 4 patients who were not discontinued despite loss in ACR response (after an initial response), 2 patients for whom steroid tapering was not initiated (based on investigator's judgement) despite being eligible, 1 patient for whom steroid tapering was initiated although the patient was not eligible, and 1 patient who did not meet ACR30 at Day 15 and was not discontinued. One patient (on placebo) was discontinued from Part II of the study due to a protocol deviation (unblinding following a serious adverse event of gastrointestinal viral infection).

Evaluator's comment: The protocol deviations are not considered likely to have had a material impact on the study conclusions.

There were seven protocol amendments, as summarised below:

- Protocol Amendment 1: changed the criteria for which a patient would discontinue due to flare in Part I, to that of not having achieved ACR30 response or not maintaining a minimum ACR30 response. Also the stable steroid dose level that allowed a patient to taper off

steroids after 24 weeks in Part II was lowered to a threshold of > 0.2 mg/kg/day. Lastly, the entry criteria for rollover patients from the G2305 and A2203 studies was changed so that the requirement of intermittent fever and CRP > 30 mg/L would not be applicable

- Protocol Amendment 2: ensured patients from Study A2203 could continue to receive continuous treatment in subsequent Phase III studies provided that the patient did not meet the discontinuation criteria of A2203 or the safety discontinuation criteria of G2301
- Protocol Amendment 3: ensured that the joint counts were performed by a trained joint assessor, who should not be involved in any other aspects of the patient's care, and the same evaluator was performing these assessments at all visits. Amendment 3 was retracted on 28-Oct-2009 based on feedback from the health authorities
- Protocol Amendment 4: was written based on feedback from the EMEA to update the following: to replace 'absence of fever' in the secondary objectives with 'body temperature ≤ 38°C'; to ensure that patients were on a stable dose of corticosteroids for at least 3 days prior to baseline; to clarify the transition of G2305 placebo patients to the G2301 study if they did not maintain a minimum ACR30 response between Days 15 and 29; and to clarify the handling of A2203 rollover patients when there was a gap of at least 6 months between the patient's last dose in A2203 and entry into G2301. Early in the study, the criteria for eligibility to taper oral steroids included having a CRP level <10 mg/L
- Protocol Amendment 5: released approximately 1 year after the original protocol, eliminated this criterion so that patients who were doing well clinically were not unnecessarily exposed to higher steroid doses than required. Some patients who enrolled in the study prior to this amendment may have not have the chance to initiate steroid tapering (in Part Ic or Part II) or the chance to taper their steroids successfully in Part Ic. As such, however, the primary objective of Part I of the study, to assess if canakinumab allowed tapering of steroids as per protocol in at least 25% of the patients, was still met. This amendment also clarified the visits to be completed in Part I by steroid-free patients at study start
- Protocol Amendment 6: implemented an adjudication committee for macrophage activation syndrome (MAS) and follow-up to be conducted on MAS cases identified during the study. This amendment also provided information on ending the study in the event that there are patients still active in Part I at the time the 37th flare was reached in Part II
- Protocol Amendment 7: introduced the possibility performing an interim analysis, (which was not performed), and adjusted the statistical hypothesis in the statistical methods section for Part I to be fully aligned with the objective

Evaluator's comment: These amendments were not considered to have affected the interpretation of study results as they were minor and occurred prior to study unblinding.

The following changes were made to the planned analysis:

- A supportive analysis for Part I was added to repeat the primary analysis for patients with steroid level >0.2 mg/kg/day at study entry. The proportion of patients who successfully tapered steroid according to the protocol was tested one-sided against 25%
- The exploratory assessments of PDSS and EQ-5D state of health and utility scores (EQ- 5D for patients ≥ 12 years of age or EQ-5D proxy for patients 8 – 11 years of age) for Part II were conducted by means of an analysis of covariance of the change in score from end to start of Part II, adjusted for baseline (date of randomisation) measurement. This approach was chosen instead of a repeated measures model adjusted for visit, because of the low number of visits with PDSS and EQ-5D measurements (two visits only) during Part II

- Similarly, the analysis of covariance model with repeated measures approach to evaluate between-treatment differences in joint erosions was not conducted due to the low number of visits with x-ray measurements of hands and wrists
- The same notable abnormality for calcium was selected for the <16 years old as for the ≥16 years old.
- An analysis of an improved disability score (decrease ≥0.19) from baseline or worsening (increase ≥0.13) from baseline, or neither a decrease nor an increase has been added
- A post hoc sensitivity analysis was performed comparing the steroid calculations performed by Novartis versus that of the investigator-calculated prednisone equivalent dose in the clinical database

Evaluator's comment: These changes were not considered to have affected the interpretation of study results.

*7.1.1.2.12. Baseline data*

Baseline demographics of patients entering Part I and Part II are shown in Table 11 below. 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 6-11 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 4-5 years in the placebo group (22%) compared with the canakinumab group (10%), and the converse in patients aged 6-11 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.

**Table 11. Baseline demographics (Study G2301)**

| | Part I (FAS I) | Part II (FAS II) | | |
|---|---|---|---|---|
| | **Canakinumab (n=177)** | **Canakinumab (n=50)** | **Placebo (n=50)** | **Total (n=100)** |
| **Sex – n (%)** | | | | |
| Male | 79 (44.6) | 22 (44.0) | 23 (46.0) | 45 (45.0) |
| Female | 98 (55.4) | 28 (56.0) | 27 (54.0) | 55 (55.0) |
| **Age (years)** | | | | |
| n | 177 | 50 | 50 | 100 |
| Mean (S.D.) | 8.7 (4.46) | 9.1 (4.18) | 9.0 (4.76) | 9.1 (4.45) |
| Median (Min–Max) | 8.0 (1, 19) | 8.0 (2, 18) | 8.0 (3, 19) | 8.0 (2, 19) |
| **Age groups - n (%)** | | | | |
| 2 - <4 years | 21 (11.9) | 5 (10.0) | 5 (10.0) | 10 (10.0) |
| 4 - <6 years | 32 (18.1) | 5 (10.0) | 11 (22.0) | 16 (16.0) |
| 6 - <12 years | 76 (42.9) | 24 (48.0) | 18 (36.0) | 42 (42.0) |

| | Part I (FAS I) | Part II (FAS II) | | |
|---|---|---|---|---|
| 12 - <20 years | 48 (27.1) | 16 (32.0) | 16 (32.0) | 32 (32.0) |
| >= 20 years | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| **Predominant Race - n (%)** | | | | |
| Caucasian | 151 (85.3) | 41 (82.0) | 42 (84.0) | 83 (83.0) |
| Black | 7 (4.0) | 2 (4.0) | 1 (2.0) | 3 (3.0) |
| Asian | 6 (3.4) | 3 (6.0) | 2 (4.0) | 5 (5.0) |
| Other | 13 (7.4) | 4 (8.0) | 5 (10.0) | 9 (9.0) |
| **BMI ($kg/m^2$)** | | | | |
| n | 167 | 47 | 48 | 95 |
| Mean (S.D.) | 18.98 (4.878) | 19.91 (5.955) | 18.73 (4.499) | 19.31 (5.275) |
| Median (Min-Max) | 17.35 (13.1, 41.3) | 18.11 (13.8, 41.3) | 17.32 (13.1, 34.2) | 17.47 (13.1, 41.3) |

Key baseline disease characteristics of patients entering Part I and Part II are shown in Table 12, below. Most patients had a polyarthritic pattern of disease, with a median time from sJIA diagnosis to study entry of slightly more than 2 years (757 days). 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, and the mean (±SD) oral prednisone equivalent dose was 0.37 (±0.275) mg/kg/day. At baseline, 53% of patients were receiving methotrexate treatment and 66% were receiving NSAIDs. Disease history was broadly similar between the two treatment groups with the exceptions of a longer median time from sJIA diagnosis to study entry in patients on canakinumab (approximately 2.7 years) versus placebo (approximately 1.8 years); a higher percentage of patients in the canakinumab treatment arm had 2 or more flares in the 12 months prior to study entry compared with placebo (58% versus 40%, respectively); and a higher percentage of patients in the canakinumab treatment arm had systemic signs after the first 6 months of disease compared with placebo (90% versus 72%, respectively).

**Table 12. Baseline Disease Characteristics (Study G2301)**

| | Part I (FAS I) | Part II (FAS II) | | |
|---|---|---|---|---|
| | **Canakinumab (n=177)** | **Canakinumab (n=50)** | **Placebo (n=50)** | **Total (n=100)** |
| **Pattern of onset of arthritis in the first 6 months of disease** | | | | |
| Polyarthritis | 133 (75.1%) | 36 (72.0) | 36 (72.0) | 72 (72.0) |
| Oligoarthritis | 35 (19.8%) | 11 (22.0) | 12 (24.0) | 23 (23.0) |
| Monoarthritis | 3 (1.7%) | 2 (4.0) | 0 (0.0) | 2 (2.0) |
| No arthritis | 6 (3.4%) | 1 (2.0) | 2 (4.0) | 3 (3.0) |

| | Part I (FAS I) | Part II (FAS II) | | |
|---|---|---|---|---|
| **Presence of systemic signs after the first 6 months of disease - n (%)** | | | | |
| No | 23 (13.0) | 4 (8.0) | 11 (22.0) | 15 (15.0) |
| Yes | 148 (83.6) | 45 (90.0) | 36 (72.0) | 81 (81.0) |
| Missing | 6 (3.4) | 1 (2.0) | 3 (6.0) | 4 (4.0) |
| **Time from sJIA diagnosis to study entry (days)** | | | | |
| n | 124 | 36 | 39 | 75 |
| Mean | 1123.8 | 1349.8 | 973.2 | 1154.0 |
| S.D. | 1098.91 | 1102.57 | 1110.01 | 1115.15 |
| Median | 757.0 | 1000.0 | 658.0 | 806.0 |
| Min–Max | 56, 5367 | 136, 4517 | 56, 5367 | 56, 5367 |
| **CRP at baseline (standardised in mg/L)** | | | | |
| n | 177 | 50 | 50 | 100 |
| Mean | 198.43 | 182.79 | 182.19 | 182.49 |
| S.D. | 146.629 | 164.772 | 141.225 | 152.675 |
| Median | 160.0 | 120.65 | 148.60 | 137.90 |
| Min–Max | 3.3, 742.0 | 6.0, 651.2 | 5.6, 742.0 | 5.6, 742.0 |
| **Number of flares in the past 12 months** | | | | |
| 0 | 13 (7.3) | 4 (8.0) | 6 (12.0) | 10 (10.0) |
| 1 | 56 (31.6) | 14 (28.0) | 23 (46.0) | 37 (37.0) |
| 2 | 35 (19.8) | 9 (18.0) | 6 (12.0) | 15 (15.0) |
| 3 to 5 | 40 (22.6) | 11 (22.0) | 7 (14.0) | 18 (18.0) |
| 6 to 10 | 14 (7.9) | 5 (10.0) | 6 (12.0) | 11 (11.0) |
| 11 to 15 | 7 (4.0) | 2 (4.0) | 1 (2.0) | 3 (3.0) |
| Continuous flare (>15 or indefinable) | 7 (4.0) | 2 (4.0) | 0 (0.0) | 2 (2.0) |
| Missing | 5 (2.8) | 3 (6.0) | 1 (2.0) | 4 (4.0) |

The majority of patients (84.2%) were taking a medication prior to study start, including: anakinra (35.6%), prednisone (20.3%), etanercept (17.5%), prednisolone (16.9%) and methotrexate (16.9%). During Part I nearly all patients (98.9%) took a concomitant medication: steroids were used by 74.0% of patients [prednisone (36.2%) and prednisolone (28.8%)], methotrexate was used by 54.2% of patients, and NSAIDs were used by 72.9% of patients (mostly ibuprofen, indomethacin and naproxen). In Part II, 94.0% canakinumab and 92.0% placebo patients took concomitant medications: steroids (16% versus 30.0%), methotrexate (58% versus 52%), and NSAIDs,(58% versus 70%, mainly ibuprofen, indomethacin and naproxen).

Evaluator's comment: The study participants are considered to be representative of patients with sJIA as per the requested indication.

*7.1.1.2.13. Results for the primary efficacy outcome*

**Part I**

In Part I, 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 (Table 13, below). The rate of flare was similar in both treatment groups for the 1st 4 months, continued at a similar rate thereafter in the placebo group, with few flares after 4 months in the canakinumab group. 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]).

**Table 13. Survival analysis of time to flare in 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. | 0.36 ( 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 estimable. * Statistically significant on one-sided significance level 0.025.

Evaluator's comment: In Table 10-2 on page 108 of 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 bias 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. The sponsor will be asked to comment on this.

*7.1.1.2.14. Results for other efficacy outcomes*

**Part I**

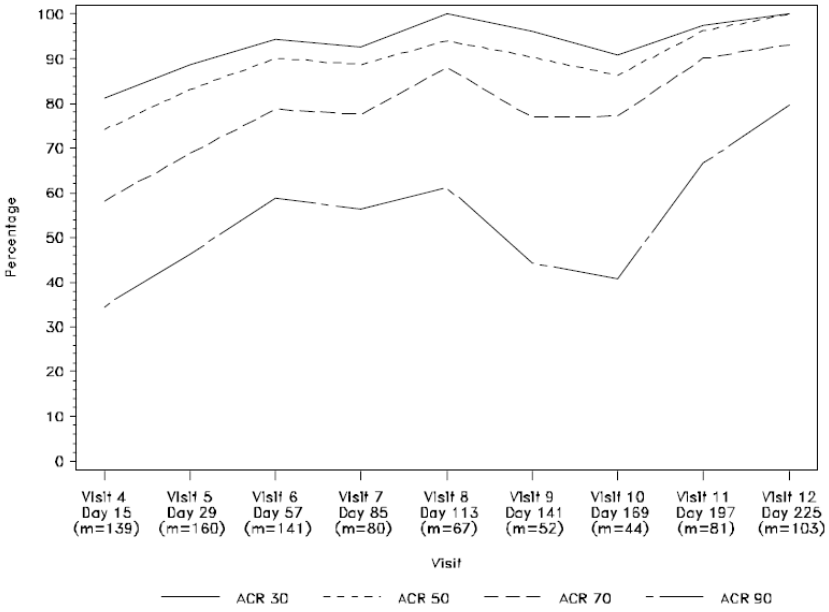
Of the 128 patients who were taking steroids at entry into Part I, 66 (51.6%) were on an oral steroid dose ≤ 0.2 mg/kg at the end of Part Ic, including 42 (32.8%) who were steroid free. Among the 57 patients classified as successful steroid taperers, the median baseline dose was 0.27 mg/kg/day, and the median change from baseline was -0.26 mg/kg/day (Table 14, below).

**Table 14. Oral steroid dose at end of Part Ic (Full Analysis Set I, Study G2301)**

| | Patients taking oral steroids at entry of study Part | ACZ885 N=177 Oral steroid dose (mg/kg/day) at end of Part Ic (1) | | |
|---|---|---|---|---|
| Study Part | m (%) | | n (n/m %) | 95% exact CI |
| Part I | 128 (72.3) | steroid free | 42 (32.8) | (24.8, 41.7) |
| | | > 0 mg/kg and ≤ 0.2 mg/kg | 24 (18.8) | (12.4, 26.6) |
| | | > 0.2 mg/kg | 26 (20.3) | (13.7, 28.3) |
| Part Ic | 92 (52.0) | steroid free | 42 (45.7) | (35.2, 56.4) |
| | | > 0 mg/kg and ≤ 0.2 mg/kg | 24 (26.1) | (17.5, 36.3) |
| | | > 0.2 mg/kg | 26 (28.3) | (19.4, 38.6) |

By Day 15, 81.3% of patients had an ACR 30 response, and 18.0% had an ACR 100 response. The percentage of responders at each ACR level varied throughout the study, but in general increased with time (Figure 9, below). At the end of Part I (last assessment available), 77.1% of patients had an ACR 30 response, and 34.3% had an ACR 100 response. Improvement in each of the ACR core component variables was also observed during Part I. Of the patients achieving a minimum ACR50 or ACR70, 30 to 50% had an elevated CRP.

**Figure 9. Minimum ACR pediatric response level achieved in part I, by visit (full analysis Set I, Study G2301)**




m=number of patients with an assessment in the given visit.

All of the component response variables in the adapted ACR paediatric criteria also improved during Part I. For example, the mean/median changes from baseline at the end of Part I were:

- physician's global assessment of disease activity: -48.2 mm (-73.5%)

- patient's/parent's) global assessment of the patient's overall wellbeing: -39.8 mm (-60.8%)
- CHAQ disability score: -0.88 (-79.4%)
- number (%) of active joints: -7 (-88.1%)
- number (%) of joints with a limited range of motion: -5 (-83.3%)
- CRP: -114.8 mg/L (-87.4%)

The majority of patients (139/141, 98.6%) with body temperature measurements had no fever (≤38º C) at Day 3 in Part Ia.

**Part II**

In order to control the overall Type I error rate (α = 0.025, one sided tests), secondary endpoints were assessed in a closed testing procedure to evaluate superiority of canakinumab over placebo. 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)

Only the first step in the closed testing procedure was satisfied.

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) (table 15, below). 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. Maintenance of ACR response was similar in both treatment groups for the first 2 months, before diverging.

**Table 15. Survival analysis of time to worsening in ACR level 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 | 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.

No statistically significant difference in the CHAQ disability score, the CHQ-PF50 physical health and psychosocial health scores, or adapted ACR paediatric criteria response variables were observed between the placebo and canakinumab treated groups (Tables 16 and 17 below).

**Table 16. Change in CHAQ disability and CHQ-PF50 scores in Part II: repeated measures ANCOVA, by treatment (FAS II, Study G2301)**

| Parameter | | n | LS Mean | Standard Error | Difference to Placebo | 95% CI | One-sided p-value |
|---|---|---|---|---|---|---|---|
| Change in CHAQ | ACZ885 | 50 | 0.1184 | 0.17592 | -0.0073 | (-0.1407, 0.1260) | 0.4571 |

| Parameter | | n | LS Mean | Standard Error | Difference to Placebo | 95% CI | One-sided p-value |
|---|---|---|---|---|---|---|---|
| | Placebo | 50 | 0.1258 | 0.18241 | | | |
| CHQ-PF50 physical health score | ACZ885 | 39 | 3.9 | 2.54 | 4.2 | (-0.1, 8.4) | 0.0280 |
| | Placebo | 37 | -0.3 | 2.53 | | | |
| CHQ-PF50 psychosocial health score | ACZ885 | 39 | 2.5 | 1.88 | 3.0 | (-0.2, 6.1) | 0.0328 |
| | Placebo | 37 | -0.5 | 1.86 | | | |

**Table 17. Adapted ACR paediatric criteria response variables in Part II: Summary statistics, by treatment (FAS II, Study G2301)**

| | | N | Median value (start of Part II) | Median change (to last assessment available) |
|---|---|---|---|---|
| Physician's global assessment of disease activity (mm) | ACZ885 | 50 | 0 | 0 |
| | Placebo | 50 | 0 | 0.5 |
| Parent's or patient's global assessment of patient's overall well-being (mm) | ACZ885 | 50 | 0 | 0 |
| | Placebo | 50 | 0 | 1.0 |
| Number of active joints/number of joints with limited range of motion | ACZ885 | 50 | 0/0 | 0/0 |
| | Placebo | 50 | 0/0 | 0/0 |
| CRP (mg/L) | ACZ885 | 50 | 5.0 | 0 |
| | Placebo | 50 | 7.9 | 2.1 |

Inactive disease was an exploratory efficacy outcome. While a higher proportion of patients on canakinumab had inactive disease than those on placebo by the end of Part II (62% versus 34%; OR 3.4; 95% CI 1.5, 8.0), median time to inactive disease from the start of Part II was similar (30.0 versus 33.0 days for canakinumab and placebo, respectively).

Canakinumab appeared to have no negative effect on growth parameters (height, weight and BMI).

Results for Study G2301 were not presented by subgroup (age, gender, etc), but this has been performed in the pooled analysis in Section 6.1.3.

### 7.1.2. Other efficacy studies

#### *7.1.2.1. Study A2203*

Study A2203 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. The study consisted of a 15-day screening period, a maximum run-in period of 72 hours (only for patients who discontinued

anakinra therapy), and a 2-stage treatment period (a repeated single dose escalation in Stage I and a fixed dose re-dosing upon relapse in Stage II). Patients were randomised into one of 3 cohorts in Stage I based on the starting dose of canakinumab: 0.5 mg/kg (Cohort I), 1.5 mg/kg (Cohort II), and 4.5 mg/kg (Cohort III). Patients who experienced a measurable improvement in fever and CRP in a particular cohort received the same dose again upon relapse (fever, CRP, or flare) until they were able to enter Stage II. Patients who did not experience a measurable improvement within 1 week received a 2nd injection of the same dose of canakinumab (that is, in total they received 1, 3 or 9 mg/kg); if there was still no improvement they were considered non-responders and were followed only for safety, immunogenicity and PK. The dose administered in Stage II (4 mg/kg) was based on an analysis of the available efficacy and safety data performed at the end of Stage I. Steroid tapering was allowed in Stage II at the discretion of the investigator. Treatment duration/follow-up was variable, with 9 (39%) patients having an exposure duration of 4 to <6 months, 5 (22%) 12 to <24 months, and 7 (30%) 24 months or more.

A total of 23 patients were enrolled in the study (with 3 patients enrolled twice[1]) with a ratio of 5:10:11 for the three starting doses of 0.5, 1.5 and 4.5 mg/kg respectively. The data from all patients was included in the efficacy and safety analysis but PK parameters could only be calculated for 21 patients. The mean age of the patients was 10 years (range 4 – 19 years), 52% were male, 96% were Caucasian, and the mean weight was 33.7 kg (range 13.6 – 90.6 kg). Mean duration of arthritis was 56.9 months (range 7 – 204 months), 19 patients (83%) were using steroids at baseline (mean dose 0.32 mg/kg), and 16 (70%) had previously received anakinra treatment.

There were no defined primary or secondary efficacy outcomes, but responders (ACR30 and above) were defined according to the adapted ACR Paediatric response variables, as used in the pivotal studies. Overall there were 13/22 (59%) responders (2 in Cohort I [40%], 8 in Cohort II [80%], and 5 [46%] in Cohort III), with 4 patients (18%) considered to have inactive disease. 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. Confidence intervals were wide and overlapped each dose group. Of the 19 patients using corticosteroids on study entry, 11 were able to reduce their steroid dose, including 5 who were able to discontinue steroid use.

Evaluator's comment: While the 3 mg/kg and 4 mg/kg doses were equivalent for median time to relapse in this study, as discussed in Section 4.2.1.1 and Section 5 the 4 mg/kg dose was chosen for the pivotal studies based on the PK/PD model analysis.

#### *7.1.2.2. Study G2301E1*

Study G2301E1 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. It was conducted in 61 centres in 20 countries, commencing on 7 September 2009 with an interim data lock date of 10 August 2012. The objective of the study was to assess long-term safety, tolerability and immunogenicity of canakinumab, and to assess efficacy at an exploratory level by investigating disease control defined by maintenance of at least an adapted ACR30 criteria.

The following patients were eligible to participate in the open-label extension study:

- Patients from Study G2305 (randomised to canakinumab) or G2301 who achieved an adapted ACR30 response 15 days after their initial dose of canakinumab but clinically

[1] patients [information redacted] (cohort I) were enrolled again as patients [information redacted] respectively in cohort III, patient [information redacted] (cohort II) was enrolled again as patient [information redacted] in cohort III.

deteriorated as defined by a minimum adapted ACR30 response not being maintained after Day 15 and intervention that was deemed necessary by the investigator

- Patients in Study G2301 who were not eligible to enter Part II (withdrawal part) because they were not able to meet the corticosteroid entry criteria of 0.5 mg/kg oral prednisone (or equivalent) or were not able to taper their steroids by at least 0.3 mg/kg
- Responder patients in Part I or Part II who were maintaining their minimum ACR30 response or had not flared when G2301 was stopped
- Study G2301 patients who were responders in Part I (achieved and maintained a minimum adapted ACR30) but experienced a flare in Part II

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 are included in the efficacy and safety analysis populations for this interim analysis. The median duration of study participation at the time of data lock was 49 weeks (range 3 to 144 weeks). Nearly all patients (97.3%) were taking at least one concomitant medication during the study, including steroid medications (57.1%); methotrexate medications (56.5%), and NSAIDs (66.7%).

Patients were analysed according to their status at the end of their participation in the previous study, for this interim efficacy analysis. The 4 groups are as follows:

- Group 1 (G2301 Part II discontinuations due to flares, non-response or any other discontinuation): 33 patients (23 placebo, 10 canakinumab) who discontinued prematurely from Part II of Study G2301 due to a flare event (17 were non-responders and 16 responders)
- Group 2 (G2301 Part II completers): 63 patients (24 placebo, 39 canakinumab) who were minimum ACR30 responders when they completed Study G2301 Part II (all responders)
- Group 3 (G2301 Part I steroid-tapering failures): 40 patients who discontinued Part I of Study G2301 because they were not able to successfully taper their steroid dose as required by the G2301 protocol (17 were non-responders and 23 responders)
- Group 4 (all others): 11 patients; a mixed group who did not fulfil the criteria for Group 1, 2, or 3 above, including 8 patients from Study G2301, plus 3 patients from Study G2305 (all had previously received canakinumab treatment) (6 were non-responders and 5 responders)

Efficacy was evaluated with respect to:

- percentage of patients who met the adapted pediatric ACR 30/50/70/90/100
- number of patients who were able to taper oral steroids
- number of patients who reached oral steroid-free regimen
- number of oral steroid-free patients who were able to reduce the canakinumab dose to 2 mg/kg every 4 week
- percentage of patients who met the definition of inactive disease on medication and possible clinical remission on medication
- change in disability over time by use of the cross culturally adapted and validated version of the CHAQ

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.

The detailed results for each individual group are summarised below:

- Group 1: Even though patients flared in Part II, patients receiving canakinumab in the extension were able to regain their response. For the 17 patients in this group who entered the extension as a non-responder, the majority (12 patients, 70.6%) achieved a minimum ACR30 response by Month 3, and 10 patients (58.8%) had a minimum ACR70 response at Month 3. At the time of the interim lock, 10 of 17 patients (58.8%) had a minimum ACR70 response
- Group 2: At Month 3 (62/63; 98.4%) achieved a minimum ACR30 response or higher. All patients (63/63, 100.0%) maintained their baseline ACR30 response throughout the study until time of database lock. Sixty patients (60/63, 95.2%) maintained an ACR90 response or better throughout the study until the last assessment before database lock
- Group 3: Although efficacy was not as high in this group of patients compared to the other groups, many showed improvement. At Month 3, 9/16 patients (56.3%) who were non-responders at baseline achieved a minimum ACR30 response or higher. At Month 6, 8/9 patients (88.9%) had a minimum ACR30 response or higher
- Group 4: At Month 3, 4/6 patients (66.7%) who were non-responders at baseline achieved a minimum ACR30 response or higher. A similar pattern of the results was observed for patients who had a minimum ACR70, 90, and 100

In total, 69 patients entered the extension study on steroids of whom 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.

Evaluator's comment: While the 2 mg/kg dose appeared to be effective in a number of patients in the extension study who had achieved steroid tapering or who were steroid free, in the PK/PD model based on Study A2203 an estimated 18% of patients would relapse after 4 weeks on the 2 mg/kg dose compared with 6% on 4 mg/kg (Figure 3.). It is possible that the patients remaining in the extension trial are a 'select' group that respond to a lower dose. It is not known if these patients are identifiable in any way, and/or whether they would have responded to a lower dose from the outset. The potential for canakinumab dose reduction, and under what circumstances, needs to be explored.

Throughout the study, 44/147 patients (30%) experienced a flare and 95/146 (65%) reached inactive disease status on at least one visit. The highest percentage of flares occurred in Group 4 (54.5%), followed by Group 3 (52.5%), Group 1 (33.3%), with the lowest percentage in Group 2 (9.5%). Inactive disease status was highest in Group 2 (96.8%), followed by Group 1 (51.5%), Group 4 (40.0%), and Group 3 (32.5%).

## 7.2. Analyses performed across trials (pooled analyses and meta-analyses)

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. Subgroup analysis of the efficacy variables were performed according to demographic and background factors (age, gender, race, and body weight), baseline disease characteristics (disease duration, active disease joint count, baseline oral steroid level), prior reported treatment (anakinra, steroids, methotrexate or NSAIDs), or concomitant therapy (steroids and/or methotrexate). Efficacy results were presented in frequency tables using the Full Analysis Set (FAS). Missing values in the different subgroup analyses were not replaced.

The majority of patients (79.8%) achieved at least an ACR30 at Day 15, which was largely maintained through to Day 85 (70.2%). Although a smaller proportion of patients achieved an ACR90 (36.5%) or ACR100 (21.3%) at Day 15, these proportions improved with time such that by Day 85, 48.9% and 30.3% of patients had achieved an ACR90 or ACR 100, respectively (Table 18, below). Of those patients who achieved an ACR30 response at Day 15, 15.4% had lost that response by Day 71. Median improvements in the ACR criteria response components were also observed at Days 15, 29, 57 and 85. Improvements were also seen in CHAQ disability score, CRP, and parent's or patient's assessment of pain (VAS).

**Table 18. Adapted ACR Paediatric response and inactive disease status achieved at Day 15, 29, 57, and 85 in the 12-week efficacy pooled group (FAS)**

| | ACZ885 (N=178) Responders n (% ) | | | |
|---|---|---|---|---|
| **ACR criteria** | **Visit: Day 15** | **Visit: Day 29** | **Visit: Day 57** | **Visit: Day 85** |
| ACR30 | 142 (79.8) | 138 (77.5) | 135 (75.8) | 125 (70.2) |
| ACR50 | 125 (70.2) | 129 (72.5) | 127 (71.3) | 122 (68.5) |
| ACR70 | 102 (57.3) | 108 (60.7) | 110 (61.8) | 108 (60.7) |
| ACR90 | 65 (36.5) | 75 (42.1) | 81 (45.5) | 87 (48.9) |
| ACR100 | 38 (21.3) | 49 (27.5) | 53 (29.8) | 54 (30.3) |
| Inactive disease | 36 (20.2) | 46 (25.8) | 54 (30.3) | 50 (28.1) |

In the subgroup analyses some differences in efficacy were noted (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. For the baseline disease factor subgroups, efficacy was again generally consistent with overall efficacy although there were some exceptions including:

- Number of joints with active arthritis - the response rates for patients with a lower joint count were generally higher compared to those with a higher joint count
- Baseline oral steroid level - ACR response rates tended to be higher for steroid-free patients compared with those using oral steroids at baseline, and those on lower steroid doses (≤0.4 mg/kg/day) compared with those in the higher oral steroid dose level category (>0.4 mg/kg/day). This trend was more apparent at higher ACR response levels
- Anakinra exposure – ACR responses were generally lower in patients who had discontinued anakinra due to lack of efficacy compared with anakinra naive patients or those who had discontinued for other reasons
- CRP at Day 15 –ACR response rates tended to be higher in patients with a CRP that was normal on Day 15 compared with those with an elevated CRP. This trend was more apparent at higher ACR response levels

Evaluator's comment: The ACR response data in the pooled studies was generally consistent with that reported in the individual studies. While it is of interest to note that there may be some variability in ACR response in some of the subgroups (lower response in those with potentially more severe disease), the studies contributing to this pooled analysis were not powered to look at subgroup analyses, and some of the subgroups had very small patient numbers.

## 7.3. Evaluator's conclusions on clinical efficacy

The sponsor has provided data from 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. 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 (AIHW 2008). 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 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 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; $p < 0.0001$). 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 (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 (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 (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 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 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 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.

# 8. Clinical safety

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.

## 8.1. Studies providing evaluable safety data

The following studies provided evaluable safety data:

#### 8.1.1. Pivotal efficacy studies

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.

Other safety assessments included:

- Standard 12-lead ECG
- Baseline estradiol and testosterone levels in female and male patients, respectively, who had reached Tanner stage 2 or above
- Clinical assessment of serositis, splenomegaly, hepatomegaly, and generalised lymphadenopathy attributable to sJIA
- Sonography of spleen and liver
- Local tolerability at the site of SC injection

Occurrence of biologic features of MAS such as haemorrhages, central nervous system dysfunction, hepatomegaly, serum fibrinogen level < 2.5 g/L, cytopenia, hypertriglyceridaemia, decreased platelet count, increased aspartate transaminase, and hyperferritinemia were carefully monitored by the investigator, and significant findings were recorded.

#### 8.1.2. Pivotal studies that assessed safety as a primary outcome

Not applicable.

#### 8.1.3. Dose-response and non-pivotal efficacy studies

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 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 1st and 2nd doses of canakinumab
- Study G2301E1 provided the same safety data as the pivotal efficacy studies

### 8.2. Other studies evaluable for safety only

Not applicable.

### 8.3. Pivotal studies that assessed safety as a primary outcome

Not applicable.

### 8.4. Patient exposure

Patient exposure to canakinumab in Phase III studies in sJIA is summarised in Table 19, below.

**Table 19. Exposure to Canakinumab and comparators in Phase III sJIA clinical studies (patient years).**

| Study type/Indication | Controlled studies | | Total Canakinumab |
|---|---|---|---|
| | Canakinumab | Placebo | |
| 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 20, below).

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

**Table 20. 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 |

### 8.4.1. 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 - <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.

### 8.4.2. 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.

#### 8.4.3. 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.

#### 8.4.4. 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.

### 8.5. Adverse events

#### 8.5.1. All adverse events (irrespective of relationship to study treatment)

##### *8.5.1.1. Pivotal studies*

*8.5.1.1.1. Study G2305*

In total, 55.8% of patients on canakinumab and 39.0% of patients on placebo experienced an AE. All AEs were either mild (canakinumab 44.2% and placebo 36.6%) or moderate (canakinumab 11.6% and placebo 2.4%) in severity; no severe AEs were reported. The system organ classes (SOCs) most commonly affected were infections and infestations, gastrointestinal disorders, skin and subcutaneous tissue disorders, and nervous system disorders (see Table 21, below). The most frequent AEs by preferred term (PT) for canakinumab versus placebo patients were: diarrhoea (7% versus 2%), nasopharyngitis (7% versus 2%), URTI (7% versus 0%), abdominal pain, bronchitis, pyrexia and rash maculo-papular (4.7% versus 0% each), and headache (4.7% versus 2%). Macrophage activation syndrome or MAS (PT: haematophagic histiocytosis) was reported in 2 patients (1 on canakinumab, 1 on placebo).

**Table 21. AEs by primary system organ class (≥3.0%) (Safety set, Study G2305)**

| | ACZ885 N=43 n (%) | Placebo N=41 n (%) |
|---|---|---|
| No. of patients with AE(s) | 24 (55.8) | 16 (39.0) |
| **Primary system organ class** | | |
| Infections and infestations | 13 (30.2) | 5 (12.2) |
| Gastrointestinal disorders | 7 (16.3) | 2 (4.9) |
| Skin and subcutaneous tissue disorders | 6 (14.0) | 1 (2.4) |
| Nervous system disorders | 4 (9.3) | 1 (2.4) |
| Respiratory, thoracic and mediastinal disorders | 3 (7.0) | 1 (2.4) |
| General disorders and administration site conditions | 2 (4.7) | 1 (2.4) |
| Musculoskeletal and connective tissue disorders | 2 (4.7) | 2 (4.9) |
| Investigations | 1 (2.3) | 2 (4.9) |

A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.

AEs were generally comparable across the age groups (bearing in mind the small numbers and shorter time spent on placebo) and the two genders (Table 22). Females tended to have an excess of gastrointestinal and skin AEs, while males had an excess of neurological AEs.

**Table 22. AEs by age group and gender (Safety set, Study G2305)**

| | Canakinumab | | Placebo | |
|---|---|---|---|---|
| | N | N (%) | N | N (%) |
| Age Group | | | | |
| 2 - <4 years | 9 | 4 (44) | 0 | 0 (0) |
| 4 - <6 years | 8 | 5 (62.5) | 7 | 3 (42.9) |
| 6 - <12 years | 14 | 8 (57.1) | 22 | 11 (50.0) |
| >12 years | 12 | 7 (58.3) | 12 | 2 (16.7) |
| **Gender** | | | | |
| Male | 16 | 9 (56.3) | 18 | 6 (33.3) |
| Female | 27 | 15 (55.6) | 23 | 10 (43.5) |

To account for the discrepancy in time spent on canakinumab versus time spent on placebo, exposure-adjusted incidence of AEs was calculated (Table 23, below). Infections and infestations and gastrointestinal disorders remained the most commonly affected SOCs. The higher percentage of AEs in the canakinumab patients compared with the placebo patients was no longer (or less) apparent when comparing the exposure-adjusted incidence rates of AEs.

**Table 23. Exposure-adjusted AEs by Primary SOC (Safety set, Study G2305)**

| | Canakinumab N = 43 | | Placebo N = 41 | |
|---|---|---|---|---|
| | n | Rate per 100 pt days | n | Rate per 100 pt days |
| Number of events | 49 | 4.12 | 27 | 6.15 |
| Primary System Organ Class | | | | |
| Infections and infestations<br>Nasopharyngitis<br>Upper respiratory tract infection<br>Bronchitis<br>Gastroenteritis | 15<br>3<br>3<br>2<br>1 | 1.26<br>0.25<br>0.25<br>0.17<br>0.08 | 6<br>1<br>0<br>0<br>2 | 1.37<br>0.23<br>0.00<br>0.00<br>0.46 |
| Musculoskeletal and connective tissue disorders | 2 | 0.17 | 2 | 0.46 |
| Gastrointestinal disorders<br>Diarrhoea<br>Abdominal pain | 9<br>3<br>2 | 0.76<br>0.25<br>0.17 | 4<br>1<br>0 | 0.91<br>0.23<br>0.00 |
| Skin and subcutaneous disorders | 6 | 0.51 | 2 | 0.46 |
| Respiratory, thoracic, and mediastinal disorders | 3 | 0.25 | 1 | 0.23 |
| General disorders and administration site disorders | 2 | 0.17 | 2 | 0.46 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 1 | 0.08 | 1 | 0.23 |
| Investigations | 1 | 0.08 | 2 | 0.46 |
| Nervous system disorders | 4 | 0.34 | 1 | 0.23 |
| Blood and lymphatic system disorders | 2 | 0.17 | 1 | 0.23 |

N denotes the total number of patients and n denotes the total number of events experienced (a single patient may experience an event multiple times).

#### *8.5.1.1.2. Study G2301*

During Part I, 78.0% of patients experienced an AE. The SOCs most commonly affected were infections and infestations (54.8%; primarily nasopharyngitis, upper respiratory tract infection and rhinitis), gastrointestinal disorders (29.4%; primarily vomiting, abdominal pain and diarrhoea), and respiratory, thoracic and mediastinal disorders (20.9%; primarily cough). The most frequent AEs by PT were nasopharyngitis (15.3%), headache (13.0%) and cough (11.3%). MAS was reported in 4 (2.3%) patients. The majority of AEs occurring during Part I were either mild (51.4%) or moderate (21.5%) in severity. Nine (5.1%) patients had a severe AE. Most severe AEs were also reported as SAEs, with the exception of 3 events (increased serum ferritin, anxiety, and pyrexia).

During Part II, AEs were reported by 80.0% of patients in the canakinumab group and 70.0% in the placebo group. For both treatment groups, infections and infestations were the most commonly affected SOC (54.0% canakinumab and 38.0% placebo). The most frequently reported AEs were arthralgia (24.0% versus 10%), cough (16.0% versus 12%), nasopharyngitis (14% each), pyrexia (14.0% versus 10%), rhinitis (10% versus 14.0%), upper respiratory tract infection (12% versus 10.0%), abdominal pain and pain in the extremity (12% versus 8%, each) in the canakinumab and placebo groups, respectively. MAS was reported in 1 (2.0%) patient in the placebo group. In both treatment groups, the majority of AEs occurring in Part II were mild (36.0% canakinumab versus 34.0% placebo) or moderate (34.0% versus 28.0%, respectively) in severity. Severe AEs were reported in 5 (10.0%) patients on canakinumab and 3 (6.0%) patients on placebo. Most severe AEs were also reported as SAEs, with the exception of 4 events [rash papular and arthralgia (both patients randomised to canakinumab), and coagulopathy and pruritus (both patients randomised to placebo).

Evaluator's comment: Because patients on canakinumab spent more time in Part II of the study than those on placebo, and because the patients on placebo had been on canakinumab in Part I of the study, it is difficult to directly compare the AEs in each group. In an attempt to account for this, exposure-adjusted incidence of AEs was also presented (see below).

After adjusting for exposure, the overall incidence of AEs per 100 patient-days was comparable between the canakinumab and placebo groups (2.34 versus 2.53, respectively) (Table 24, below). AEs with a higher exposure-adjusted incidence in the canakinumab group than the placebo group included:

- musculoskeletal and connective tissue disorders (0.42 versus 0.19, respectively), particularly arthralgia (0.15 versus 0.06) and back pain (0.09 versus 0.00); and gastrointestinal disorders (0.36 versus 0.25) such as abdominal pain (0.12 versus 0.06).

AEs that were more frequent in the placebo group compared with the canakinumab group included:

- infections and infestations (0.63 versus 0.59, respectively), such as nasopharyngitis (0.15 versus 0.09) and rhinitis (0.17 versus 0.05); nervous system disorders (0.27 versus 0.08), primarily headache (0.24 versus 0.04); investigations (0.14 versus 0.09); respiratory, thoracic and mediastinal disorders (0.25 versus 0.18); and skin and subcutaneous tissue disorders (0.27 versus 0.19).

**Table 24. Exposure-adjusted incidence of adverse events in Part II (≥0.10) by primary system organ class (Safety Set II, Study G2301)**

| | ACZ885 N=50 | | Placebo N=50 | |
|---|---|---|---|---|
| | n | Rate per 100 pt days | n | Rate per 100 pt days |
| Number of events | 272 | 2.34 | 229 | 2.53 |
| **Primary system organ class** | | | | |
| Infections and infestations | 69 | 0.59 | 57 | 0.63 |
| Musculoskeletal and connective tissue disorders | 49 | 0.42 | 17 | 0.19 |
| Gastrointestinal disorders | 42 | 0.36 | 23 | 0.25 |
| Skin and subcutaneous tissue disorders | 22 | 0.19 | 24 | 0.27 |
| Respiratory, thoracic and mediastinal disorders | 21 | 0.18 | 23 | 0.25 |
| General disorders and administration site conditions | 13 | 0.11 | 9 | 0.10 |
| Injury, poisoning and procedural complications | 12 | 0.10 | 8 | 0.09 |
| Investigations | 10 | 0.09 | 13 | 0.14 |
| Nervous system disorders | 9 | 0.08 | 24 | 0.27 |

Sensitivity analyses were performed to assess the residual effects of canakinumab in patients subsequently randomised to placebo. 'Placebo' defined as including only those patients who had ceased canakinumab >3 months (3 half-lives) or >6 months had little effect on the results, although AE rates in the placebo group tended to decrease while those in the canakinumab group increased somewhat.

#### *8.5.1.2. Other studies*

##### *8.5.1.2.1. Study A2203*

In Stage I, 22/23 (96%) of patients experienced at least one AE. The most commonly affected primary SOCs were gastrointestinal disorders (83%), infections & infestations (65%) and general disorders (57%). The most common AEs were: abdominal pain and vomiting (35% each), pyrexia (30%), and cough, headache, and rhinitis (26% each). Small patient numbers limits interpretation of distribution of AEs by dose.

In Stage II, all 11 patients experienced at least one AE. The most commonly affected primary SOCs were infections & infestations (73%) and gastrointestinal disorders (64%), The most common AEs were: cough (36%), diarrhoea and gastroenteritis (27% each), and abdominal pain, abdominal pain upper, arthritis, influenza, pyrexia, rectal haemorrhage, tenosynovitis and vomiting (18% each).

The majority of AEs were considered mild or moderate in severity.

##### *8.5.1.2.2. Study G2301E1*

A total of 128 patients (87.1%) experienced at least one AE during the study. The most commonly affected (≥15%) primary SOCs were infections and infestations (66.0%), gastrointestinal disorders (44.2%), musculoskeletal and connective tissue disorders (38.8%), general disorders and administration site conditions (32.0%), respiratory, thoracic, and mediastinal disorders (27.2%), skin and subcutaneous disorders (24.5%), injury, poisoning and procedural complications (23.8%), nervous system disorders (19.7%), and investigations (16.3%). The most frequently reported AEs (≥10%) were nasopharyngitis (22.4%), pyrexia (18.4%), vomiting (18.4%), cough (16.3%), diarrhoea (16.3%), upper respiratory tract infection (15.6%), headache (15.0%), rhinitis (14.3%), arthralgia (13.6%), gastroenteritis (12.9%), juvenile arthritis (12.2%), oropharyngeal pain (12.2%), and abdominal pain (10.9%). MAS was reported in 4 (2.7 %) patients. The majority (72.8%) of AEs were considered mild or moderate in severity. Twenty-one patients (14.3%) experienced AE(s) that were considered severe. The only severe events that were experienced by more than 1 patient were pyrexia, gastroenteritis, varicella, MAS (2 patients each, 1.4%); and juvenile arthritis (7 patients, 4.8%).

#### *8.5.1.3. Pooled sJIA studies*

Overall, 85.1% of patients experienced at least one AE during the study. The most commonly affected primary 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.

### 8.5.2. Treatment-related adverse events (adverse drug reactions)

#### *8.5.2.1. Pivotal studies*

##### *8.5.2.1.1. Study G2305*

AEs suspected by the investigator to be related to study medication were reported in 5 (11.6%) patients in the canakinumab group and 1 (2.4%) patient in the placebo group. The adverse drug reactions (ADRs) in the canakinumab group were bronchopneumonia, rash maculo-papular, MAS, hepatitis (moderate in severity), neutropaenia, and leukopaenia (1 patient), allergic oedema (1 patient), headache and varicella (1 patient), dizziness (1 patient), and pruritus (1 patient). In the placebo group, the ADRs were fatigue and thirst (1 patient).

A comprehensive search for drug-related hepatic disorders in Part II was performed using Standardised MedDRA Query (SMQ). The two treatment groups had similar incidences and types of SMQs reported, with the exception of gastrointestinal nonspecific inflammation and dysfunctional conditions which were more common in the canakinumab group than in the placebo group (16.3% versus 4.9%). There was one case of drug-related hepatic disorder in each treatment group (moderate hepatitis on canakinumab, mild hepatomegaly on placebo).

##### *8.5.2.1.2. Study G2301*

AEs suspected by the investigator to be related to study medication during Part I were reported in 30 (16.9%) patients. The SOCs reporting the most ADRs were infections and infestations (8 patients, 4.5%) and gastrointestinal disorders (6 patients, 3.4%). Most ADRs by PT occurred in 1 or 2 patients, except for MAS (4 patients), and headache (3 patients).

A comprehensive search for drug-related hepatic disorders in Part I was performed using SMQ. The most frequently reported SMQ categories were gastrointestinal non-specific inflammation and dysfunctional conditions (25.4%), and oropharyngeal disorders (12.4%). 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).

During Part II ADRs were reported in 13 (26.0%) patients in the canakinumab group and 6 (12.0%) in the placebo group. The most common ADRs in the canakinumab group were related to infections and infestations (7 patients, 14.0%), followed by skin and subcutaneous tissue disorders (3 patients, 6.0%) and investigations (2 patients, 4.0%). In the placebo group, the most common ADRs were related to investigations (3 patients, 6.0%), followed by gastrointestinal disorders, infections and infestations, and respiratory, thoracic and mediastinal disorders (each occurring in 2 patients, 4.0%).

A comprehensive search for drug-related hepatic disorders in Part II was performed using SMQ. The two treatment groups had similar incidences and types of SMQs reported, with the exception of oropharyngeal disorders which were more common in the canakinumab group than in the placebo group (24.0% versus 12.0%), particularly with respect to oropharyngeal infections (16.0% versus 6.0%). 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) (see also Section 7.5.1.1.1).

#### *8.5.2.2. Other studies*

##### *8.5.2.2.1. Study A2203*

The sponsor stated that the majority of AEs were not suspected to be related to study drug. No summary table of total number of ADRs was provided, but from the individual patient listings, 27 events had a suspected relationship to study drug. The most common ADRs were related to infections and infestations (6 events), followed by gastrointestinal disorders (5 events), and general disorders and administration site conditions (4 events).

*8.5.2.2.2. Study G2301E1*

AEs that were suspected to be related to study drug were experienced by 34 patients (23.1%). Suspected events that were experienced by more than 1 patient were upper respiratory tract infection (5 patients, 3.4%); MAS and juvenile arthritis (4 patients each, 2.7%); cough and nasopharyngitis (3 patients in each, 2.0%); neutropaenia, leukopaenia, influenza-like illness, pyrexia, oral candidiasis, skin papilloma, abdominal pain, conjunctivitis, oral herpes, and injection site erythema (2 patients in each, 1.4%).

***8.5.2.3. Pooled sJIA studies***

The SOCs reporting the most 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 PT occurred in ≤3 patients, except for MAS (10 patients, 5%), URTI (7 patients, 3.5%), headache (6 patients, 3%), abdominal pain, neutropenia, and pyrexia (5 patients each, 2.5%), ALT increased, oral candiasis, juvenile arthritis and cough (4 patients each, 2.5%).

### 8.5.3. Deaths and other serious adverse events

***8.5.3.1. Pivotal studies***

*8.5.3.1.1. Study G2305*

There were no deaths reported during the study. Four patients had SAEs, 2 in each treatment group. There were 2 cases of MAS (one in each treatment group), 2 cases of serious infection on canakinumab (bronchopneumonia and varicella), and 1 serious infection (gastroenteritis) on placebo.

*8.5.3.1.2. Study G2301*

One patient died during Part I, and no deaths were reported in Part II, although 1 patient died 1 month after receiving the sixth dose of placebo in Part II. The patient who died in Part I was a 13 year old male who had received 3 doses of canakinumab (Days 1, 31 and 59), and experienced SAEs on Day 40 (severe adenovirus gastroenteritis), and Day 62 (pulmonary hypertension, pyrexia, increased serum ferritin and interstitial lung disease). He was diagnosed with MAS on day 64, and died on day 81 due to pulmonary hypertension which occurred in association with MAS. The patient who died after Part II was a 15 year old female who had received 8 doses of canakinumab in Part I and 6 doses of placebo in Part II. She experienced SAEs of renal colic, cardiac arrest, sepsis (uro-sepsis), septic shock and MAS.

SAEs were reported in 15 (8.5%) patients in Part I (one of whom was the patient who died), and 12 (12%) patients in Part II (6 each on placebo and canakinumab) (Table 25, below). Serious infections were the most commonly reported class of SAEs in Part I (7 patients, 4.0%) and Part II (2 patients, 4.0%, each) and consisted of single events with no predominance of organ class or pathogen. Four (2.3%) patients in Part I and 1 patient in the placebo group in Part II had MAS (PT: hematophagic histiocytosis) (discussed further in Section 7.8). Three patients had hepatic events reported as part of an SAE: (i) hepatitis, severe. This patient also had a clinically notably high ALT and AST (both > 10x ULN) which were associated with concomitant MAS and normalised with resolution of the MAS; (ii) ALT and AST increased in association with possible intercurrent viral illness. Both resolved within 30 days; (iii) Elevated ALT and AST which resolved within 30 days.

**Table 25. Infectious SAEs by preferred term (Safety Set II, G2301)**

| | ACZ885 N=50 n (%) | Placebo N=50 n (%) |
|---|---|---|
| Patients with SAE(s) | 6 (12.0) | 6 (12.0) |
| **Infections and infestations** | 2 ( 4.0) | 2 ( 4.0) |
| Otitis media | 1 ( 2.0) | 0 ( 0.0) |
| Respiratory tract infection | 1 ( 2.0) | 0 ( 0.0) |
| Measles | 0 ( 0.0) | 1 ( 2.0) |
| Pneumonia | 0 ( 0.0) | 1 ( 2.0) |
| Sepsis | 0 ( 0.0) | 1 ( 2.0) |
| Septic shock | 0 ( 0.0) | 1 ( 2.0) |

### *8.5.3.2. Other studies*

#### *8.5.3.2.1. Study A2203*

No deaths occurred either during the study or the follow-up period. One death was reported to the sponsor approximately 7 weeks after study completion and about 27 months following the last dose of study medication. The patient was a 22 year old female who had received 2 doses of 1.5 mg/kg canakinumab. Cause of death was pneumococcal sepsis (encephalitis).

SAEs were reported in 8 patients in the 1.5 mg/kg treatment group and 4 patients in the 4.5 mg/kg treatment group in Stage I and by 3 patients in Stage II. All SAEs improved or were resolved and all patients continued in the study. In Stage I infections were the most commonly reported SAE (5, 21.7%), followed by gastrointestinal disorders and general disorders and administration site conditions (3, 13.0%, each). In Stage II, the most commonly reported SAE was musculoskeletal and connective tissue disorders (2, 18.2%). Two patients had SAEs that were suspected to be related study drug, 1 case of EBV infection, and 1 case hematoma, prolonged APTT, gastroenteritis and syncope. None of the observed SAEs were considered to be definitely related to treatment by the investigators.

#### *8.5.3.2.2. Study G2301E1*

No patients died during the study. However, one patient discontinued from the study due to unsatisfactory treatment effect and died approximately 3 months afterwards due to disease progression. This death was not considered likely to be related to treatment with canakinumab.

SAEs were reported in 30 (20.4%) patients. The most commonly reported SAEs were sJIA-related musculoskeletal and connective tissue disorders (10.2%) and infections and infestations (10.2%). All but one (pneumonia, ongoing at time of report) of the serious infections resolved with standard treatment. The only serious infections occurring more than once were varicella (3 cases) and gastroenteritis (2 cases) (Table 26, below). Three patients (2.0%) experienced MAS that was adjudicated as 'probable MAS' (see Section 7.8). One additional patient had the SAEs of cytomegalovirus infection and MAS reported after the cut-off date to undergo adjudication.

**Table 26. Infectious and Musculoskeletal SAEs by preferred term (Safety Set, G2301E1)**

| | ACZ885 N=147 n (%) |
|---|---|
| **Patients with SAE(s)[1]** | **30 (20.4)** |
| **Infections and infestations** | **15 (10.2)** |
| Varicella | 3 ( 2.0) |
| Gastroenteritis | 2 ( 1.4) |
| Cytomegalovirus infection | 1 ( 0.7) |
| Device related sepsis | 1 ( 0.7) |
| Febrile infection | 1 ( 0.7) |
| Gastrointestinal infection | 1 ( 0.7) |
| Impetigo | 1 ( 0.7) |
| Parvovirus infection | 1 ( 0.7) |
| Peritonitis | 1 ( 0.7) |
| Pharyngitis streptococcal | 1 ( 0.7) |
| Pneumonia | 1 ( 0.7) |
| Pseudocroup | 1 ( 0.7) |
| Scarlet fever | 1 ( 0.7) |
| Septic shock | 1 ( 0.7) |
| Tonsillitis streptococcal | 1 ( 0.7) |
| Toxoplasmosis | 1 ( 0.7) |
| Wound infection | 1 ( 0.7) |
| Yersinia infection | 1 ( 0.7) |
| **Musculoskeletal and connective tissue disorders** | **15 (10.2)** |
| Juvenile arthritis | 13 ( 8.8) |
| Arthralgia | 2 ( 1.4) |
| Musculoskeletal chest pain | 2 ( 1.4) |
| Arthritis | 1 ( 0.7) |
| Osteoarthritis | 1 ( 0.7) |

#### *8.5.3.3. Pooled sJIA studies*

Four deaths occurred during the sJIA studies. 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, MAS, pyrexia, abdominal pain, gastroenteritis, varicella, arthralgia, and arthritis (Table 27, below).

**Table 27. Most frequent SAEs (>1%) in pooled sJIA studies (Safety Population)**

| | SJIA pediatric Canakinumab N=201 n (%) |
|---|---|
| **Any preferred term** | **62 (30.8)** |
| Juvenile arthritis | 18 (9.0) |
| Histiocytosis haematophagic | 10 (5.0) |
| Pyrexia | 9 (4.5) |
| Abdominal pain | 4 (2.0) |
| Gastroenteritis | 4 (2.0) |
| Varicella | 4 (2.0) |
| Arthralgia | 3 (1.5) |
| Arthritis | 3 (1.5) |

### 8.5.4. Discontinuation due to adverse events

#### *8.5.4.1. Pivotal studies*

##### *8.5.4.1.1. Study G2305*

No patient discontinued from the study due to an AE or SAE.

*8.5.4.1.2. Study G2301*

Five patients discontinued due to an AE in Part I, all due to SAEs (including the patient who died, 2 patients with MAS, 1 patient with increased CRP, ALP, platelet and WBC count, and 1 patient with sJIA exacerbation). Six patients (all in the placebo group) discontinued due to an AE in Part II, 3 due to SAEs (2 with multiple AEs, 1 with sJIA exacerbation/flare) and 3 due to non-serious AEs (sJIA exacerbation/flare, vomiting, uveitis).

#### *8.5.4.2. Other studies*

*8.5.4.2.1. Study A2203*

No patients discontinued from the study due to an AE or SAE.

*8.5.4.2.2. Study G2301E1*

Eight patients (5.4%) discontinued the study prematurely due to SAEs and one patient discontinued due to an AE. The events that led to discontinuation in more than 1 patient were juvenile arthritis (6 patients; 4.1%) and MAS (2 patients, 1.4%).

#### *8.5.4.3. Pooled sJIA studies*

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

### 8.5.5. Laboratory tests

Haematology, renal function, and liver function results are presented for the individual studies, and for the pooled sJIA studies. All other safety parameters are presented based on the pooled sJIA studies only.

As described in the *Clinical rationale*, sJIA is widely believed to be an auto-inflammatory condition, and is associated with elevated ESR, CRP levels, neutrophil and platelet counts, and transaminases. Anaemia is also common at presentation. Baseline values of these haematology and biochemistry parameters were consistent with the underlying pathophysiology of sJIA, and improvements (normalisation) in these results were consistent with an anti-inflammatory response to treatment with canakinumab (Table 28, below). Notable abnormalities in laboratory tests will be presented in the sections below.

**Table 28. Haematology/Biochemistry– Change from baseline to end of period in sJIA pooled group (Safety population)**

| | n | Baseline | Last assessment |
|---|---|---|---|
| Haemoglobin (g/L) | 197 | 104.1 | 116.5 |
| WBC ($10^9$/L) | 197 | 14.12 | 7.97 |
| Absolute Neutrophils ($10^9$/L) | 197 | 10.78 | 4.96 |
| Platelets ($10^9$/L) | 190 | 524.7 | 403.5 |
| ALT (U/L) | 201 | 14.9 | 25.4 |
| AST (U/L) | 201 | 22.4 | 29.3 |
| Bilirubin (µmol/L) | 201 | 3.9 | 5.2 |
| CrCl (mL/min/$m^2$) | 199 | 128.17 | 121.51 |
| Total Cholesterol | 201 | 3.89 | 4.09 |

| | n | Baseline | Last assessment |
|---|---|---|---|
| Triglycerides | 201 | 1.12 | 1.15 |

### 8.5.6. Liver function

#### *8.5.6.1. Pivotal studies*

##### *8.5.6.1.1. Study G2305*

Newly occurring notable increases in ALT and AST were reported in one patient in the canakinumab group, and no patients in the placebo group. This patient had both an ALT and AST >10xULN at Day 28. These values were associated with concomitant MAS and normalised with resolution of the MAS.

##### *8.5.6.1.2. Study G2301*

The majority of patients had normal baseline ALT, AST and alkaline phosphatase, which remained normal throughout Part I. Four (2.3%) patients had notably high ALT and/or AST values, 3 of who subsequently had normal values. The remaining patient's abnormal values were noted after a diagnosis of MAS, and no subsequent values were available. Two (1.1%) patients had notably high alkaline phosphatase. No patient had combined abnormalities involving ALT/AST with total bilirubin (Hy's Law) in Part I.

Similarly at baseline and the start of Part II, most patients in both treatment groups had normal ALT, AST, and alkaline phosphatase which remained normal throughout Part II of the study. Notably high ALT and/or AST were reported for 2 (4.1%) patients in the canakinumab group and 1 (2.0%) in the placebo group, all had normal values at the next visit. Notably high alkaline phosphatase was reported in 1 (2.0%) patient on canakinumab and 3 (6.0%) patients on placebo. No patient had combined abnormalities involving ALT/AST with total bilirubin (Hy's Law) in Part II.

#### *8.5.6.2. Other studies*

##### *8.5.6.2.1. Study A2203*

No notable abnormalities were reported.

##### *8.5.6.2.2. Study G2301E1*

Five patients (3.4%) had a newly occurring notable abnormal AST and 10 patients (6.9%) a notable abnormal ALT. Eleven patients had both newly occurring notable abnormal AST and ALT. None met the criteria of Hy's law.

#### *8.5.6.3. Pooled sJIA studies*

There were 19 (9.5%) sJIA patients with ALT and/or AST values > 3 x ULN (Table 29, below). 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.

**Table 29. Incidence of clinically notable liver enzyme abnormalities (pooled sJIA studies (Safety population)**

| Parameter<br>Notable criterion | SJIA pediatric<br>N=201<br>n/Total (%) |
|---|---|
| **Alanine transaminase (ALT)(SGPT)** | |
| > ULN | 76/201 (37.8) |
| > 3 x ULN | 18/201 ( 9.0) |
| > 5 x ULN | 11/201 ( 5.5) |
| > 8 x ULN | 6/201 ( 3.0) |
| > 10 x ULN | 4/201 ( 2.0) |
| **Aspartate transaminase (AST)(SGOT)** | |
| > ULN | 69/201 (34.3) |
| > 3 x ULN | 12/201 ( 6.0) |
| > 5 x ULN | 5/201 ( 2.5) |
| > 8 x ULN | 2/201 ( 1.0) |
| > 10 x ULN | 1/201 ( 0.5) |
| **Alkaline phosphatase** | |
| ≥ ULN | 20/201 (10.0) |
| ≥ 1.5 x ULN | 7/201 ( 3.5) |
| ≥ 2 x ULN | 2/201 ( 1.0) |
| > 3 x ULN | 1/201 ( 0.5) |
| ≥ 5 x ULN | 0/201 ( 0.0) |
| > 3 x ULN and total bilirubin > 2 x ULN | 0/201 ( 0.0) |
| < 2 x ULN and total bilirubin > 2 x ULN and ALT or AST > 3 x ULN | 0/201 ( 0.0) |
| **Total Bilirubin** | |
| > ULN | 3/201 (1.5) |
| > 1.5 x ULN | 2/201 ( 1.0) |
| > 2 x ULN | 2/201 ( 1.0) |
| > 2 x ULN and ALT or AST > 3 x ULN | 0/201 ( 0.0) |
| > 2 x ULN and ALT or AST > 5 x ULN | 0/201 ( 0.0) |
| > 2 x ULN and ALT or AST > 10 x ULN | 0/201 ( 0.0) |

## 8.5.7. Kidney function

### *8.5.7.1. Pivotal studies*

#### *8.5.7.1.1. Study G2305*

Two patients in the canakinumab group (and no patients in the placebo group) had newly occurring notable decreases in creatinine clearance (CrCl). In both cases the CrCl improved by the next visit.

#### *8.5.7.1.2. Study G2301*

Newly occurring, notable CrCl decreases of ≥ 25% from baseline (as derived with the Schwartz formula used for children and adolescents[2]) were reported for 28 (16.0%) of patients in Part I. Of these, 8 patients had notable decreases of ≥ 25% from average baseline at 2 or more consecutive visits at least 14 days apart during Part I. The abnormal values resolved at the next visit for 5 patients, but continued to the end of study for the remaining 3 patients. For all 8 patients, the notable decreases lasting 2 or more consecutive visits showed no worsening over time. The majority of these patients with any CrCl decrease of ≥ 25% from baseline had negative or trace urine protein.

Newly occurring, notable CrCl decreases were reported for 9 (18.8%) of patients in the canakinumab group and 11 (22.0%) patients in the placebo group in Part II. Of these, 5 patients (2 canakinumab patients and 3 placebo patients) had decreases of ≥ 25% from average baseline at 2 or more consecutive visits at least 14 days apart during Part II. The abnormal values resolved at the next visit for 2 patients (one in each treatment group), but continued to the end

[2] $CrCl=(k*Ht)/Cr_{serum}$ where K=0.55 for children and adolescent girls, and 0.70 for adolescent boys

of study for the other 3 patients. For all 5 patients, the notable decreases lasting 2 or more consecutive visits showed no worsening over time. The majority of the patients with any CrCl decrease of ≥ 25% from baseline had negative or trace urine protein.

#### *8.5.7.2. Other studies*

##### *8.5.7.2.1. Study A2203*

No notable abnormalities were reported.

##### *8.5.7.2.2. Study G2301E1*

CrCl (as derived with the Schwartz formula) was decreased ≥25% from baseline in 25 (18.1%) patients. The decrease was transient for 16 patients and resolved at the next visit. The remaining 9 patients had abnormal results (≥25% decrease for 2 consecutive visits which were at least 14 days apart).

#### *8.5.7.3. Pooled sJIA studies*

Twenty-nine patients (14.6%) had a notable reduction in 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.

### 8.5.8. Haematology

#### *8.5.8.1. Pivotal studies*

##### *8.5.8.1.1. Study G2305*

Three patients in each treatment group had newly occurring notably low Hb, 2 patients in the canakinumab group had notably low absolute neutrophils, and 2 patients in the canakinumab group and one patient in the placebo group had notably low platelets.

##### *8.5.8.1.2. Study G2301*

**Part I**

Six (3.4%) patients had a newly occurring notably low Hb value. Hb returned to normal values for 3 patients. No subsequent value was available for the remaining 3 patients who discontinued the study due to unsatisfactory therapeutic effect. Newly occurring, notably low WBC count was reported for 17 (9.7%) patients. The subsequent value(s) returned to normal range for a majority of patients (13/17), while for the remaining 4 patients the last value available was notably low. Ten (5.7%) patients had a newly occurring notably low neutrophil value. For 7 patients, the subsequent value(s), including those in Part II, were normal, whereas no subsequent values were available for the other 3 patients. Newly occurring notably low platelet count was reported for 11 (6.3%) patients. For all but 2 patients, the subsequent platelet count(s) available, including those recorded during Part II, were within normal range. No bleeding disorders were reported for any of the 11 patients with notably low counts.

**Part II**

One patient had a newly occurring notably low Hb. No subsequent Hb value is available and no AEs in Part II were reported for this patient. One patient had a newly occurring decrease of ≥ 20 g/L from baseline in Hb (following post-operative bleeding). Later values were all within normal range. Newly occurring notably low WBC count (≤0.8×LLN) was reported for 5 (10.4%) patients in the canakinumab group and 2 (4.0%) in the placebo group. The subsequent value(s) returned to normal for 2 patients, but remained notable low for the remaining 3 patients. For both patients in the placebo group the WBC count was normal at the next assessment. Six (12.5%) patients in the canakinumab group and 1 (2.0%) patient in the placebo group had a newly occurring notably low neutrophil value. For all but one patient in the canakinumab group, the subsequent neutrophil value(s) available returned to normal range. Three (6.3%) patients

in the canakinumab group and 1 (2.0%) in the placebo group had a newly occurring notably low platelet count. All patients had normal platelet counts at subsequent assessments.

Evaluator's comment: The abnormal baseline haematological values (anaemia, leucocytosis, and thrombocytosis) are typical of active sJIA.

#### *8.5.8.2. Other studies*

##### *8.5.8.2.1. Study G2203*

No notable abnormalities were reported.

##### *8.5.8.2.2. Study A2203*

Nine (6.4%) patients had a newly occurring decrease of ≥ 20 g/L from baseline in Hb; 5 of these were transient and returned to their previous levels and 4 remained decreased at their last study visit. Newly occurring, notably low WBC count was reported for 18 patients (12.3%). The subsequent WBC value(s) returned to normal range for 14 of these patients and decreased at the last study visit for 4 patients. Newly occurring notably low platelet count was reported for 10 (6.2%) patients. With the exception of one patient, the low platelet counts were transient and subsequent platelet counts were within normal range. None of these patients had AEs related to bleeding.

#### *8.5.8.3. Pooled sJIA studies*

Table 30 summarises the newly occurring clinically notable abnormalities of haematology in 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 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.

**Table 30. Haematology: Incidence of clinically notable abnormalities, newly occurring, post-baseline in SJIA pooled groups (Safety population)**

| Parameter<br>Notable criterion | SJIA pediatric<br>N=201<br>n/Total (%) |
|---|---|
| **Absolute Eosinophils** | |
| ≥1.1 x ULN | 75/200 (37.5) |
| **Absolute Lymphocytes** | |
| < LLN | 46/200 (23.0) |
| **Absolute Neutrophils** | |
| ≤ 0.9 x LLN | 27/200 (13.5) |
| < $1x10^9$/L | 12/200 ( 6.0) |
| **Hemoglobin** | |
| ≥ 20 g/L decrease from baseline | 17/197 (8.6) |
| < 100 g/L (if ≥16 years) or<br>< 85 g/L (if <16 years) | 17/200 (8.5) |
| **Platelets** | |
| < LLN | 19/200 (9.5) |
| < $100x10^9$/L | 8/200 (4.0) |
| **WBC (Total)** | |
| ≤ 0.8 x LLN | 33/200 (16.5) |
| ≥ 1.2 x ULN | 23/200 (11.5) |
| **Absolute Neutrophils** | |
| G1:<LLN – 1.5 x $10^9$/L | 11/200 ( 5.5) |
| G2:<1.5 – 1.0 x $10^9$/L | 38/200 (19.0) |
| G3:<1.0 – 0.5 x $10^9$/L | 11/200 ( 5.5) |
| G4:<0.5 x $10^9$/L | 1/200 ( 0.5) |
| **Hemoglobin** | |
| G1:< LLN – 100 g/L | 35/200 (17.5) |
| G2:< 100 – 80 g/L | 26/200 (13.0) |
| G3:< 80 – 65 g/L | 11/200 (5.5) |
| G4:< 65 g/L | 2/200 (1.0) |
| **Platelets** | |
| G1:<LLN – 75.0 x $10^9$/L | 18/200 ( 9.0) |
| G2:<75.0 – 50.0 x $10^9$/L | 1/200 ( 0.5) |
| G3:<50.0 – 25.0 x $10^9$/L | 0/200 ( 0.0) |
| G4:<25.0 x $10^9$/L | 1/200 ( 0.5) |
| **WBC (Total)** | |
| G1:<LLN – 3.0 x$10^9$/L | 69/200 (34.5) |
| G2:<3.0 – 2.0 x$10^9$/L | 12/200 ( 6.0) |
| G3:<2.0 – 1.0 x$10^9$/L | 3/200 ( 1.5) |
| G4:<1.0 x$10^9$/L | 0/200 ( 0.0) |

### 8.5.9. Electrocardiograph

#### *8.5.9.1. 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.

Evaluator's comment: The sponsor stated in the clinical safety summary that in preclinical toxicology studies of canakinumab 'heart function was monitored and there was no effect on corrected QT interval (using Fridericia's formula; QTcF) [Study 0280160], [Study 0380070]. In addition, there was no off target binding in the heart tissue in tissue cross-reactivity studies [Study 0680267] . Canakinumab is a large molecule and therefore should not bind to nor influence HERG channels.'

### 8.5.10. Vital signs

#### *8.5.10.1. Pooled sJIA studies*

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 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.

#### *8.5.10.2. Canakinumab concentration – safety endpoint report*

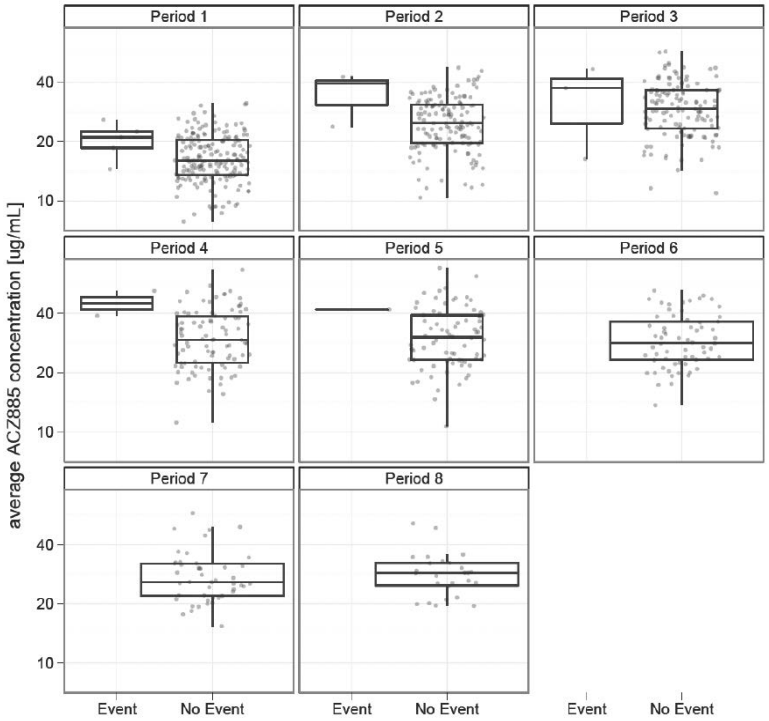
The sponsor explored the relationship between canakinumab concentration and the incidence of specific safety endpoints (AEs), as observed in sJIA patients enrolled in studies G2305 and G2301 (Part I only). The clinical AEs selected were: abdominal pain, cough, headache, infection, MAS, pyrexia, SAE infection, and vomiting; and laboratory abnormality events (WBC ≤ 0.8X LLN, AST >3X ULN, ALT >3X ULN, haemoglobin >20g/L decrease from baseline, platelet count < LLN, absolute Neutrophil count <0.9X LLN, estimated creatinine clearance≥ 25% decrease from baseline and total cholesterol >1.5 ULN).

Average canakinumab concentrations were predicted for each patient using the PK binding model. This was done for each dose of canakinumab 4 mg/kg for up to 8 doses, resulting in 8 treatment periods. These concentrations were then graphically compared in subjects with and without the events of interest in that treatment period. Canakinumab predicted concentration data were available for 188 patients after the 1st canakinumab dose, but declined rapidly to 26 patients after the 8th canakinumab dose.

In all of the 8 periods, the distribution of the individual average canakinumab concentration in patients with each of the clinical AEs was similar to that in patients without the AEs. The time-course of canakinumab concentration in the subjects with versus those without the clinical AE did not show a particular trend. Indeed, the AEs were evenly distributed across the dosing intervals rather than occurring at peak exposure.

With the laboratory AEs, again the canakinumab concentration appeared to be similar in patients with and without the AEs. The exception was abnormal (low) neutrophil count, where the canakinumab concentration was generally higher in patients with the abnormal count compared with patients without the abnormal count (Table 31, below).

**Table 31. Distribution of the individual average canakinumab concentrations for patients with and without abnormal neutrophils event by period**




## 8.6. Postmarketing experience

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).

The current ILARIS RMP (version 5, 30 Sep 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 (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.'*

## 8.7. Safety issues with the potential for major regulatory impact

### 8.7.1. Liver toxicity

Discussed in Section 7.5.1.

### 8.7.2. Haematological toxicity

Discussed in Section 7.5.3.

### 8.7.3. Serious skin reactions

Not applicable. In particular, there were no reported cases of Stevens-Johnson syndrome or toxic epidermal necrolysis.

### 8.7.4. Cardiovascular safety

Discussed in Section 7.5.4.

## 8.8. Unwanted immunological events

### 8.8.1. Immunogenicity

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

#### *8.8.1.1. 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.

#### *8.8.1.2. 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.

#### *8.8.1.3. Study A2203*

No anti-canakinumab antibodies were detected.

#### *8.8.1.4. 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.

#### *8.8.1.5. Integrated immunogenicity report of patients treated with Canakinumab in sJIA*

##### *8.8.1.5.1. 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 (i.e. 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 adverse event (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 couldn't 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.

Post-treatment 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.

##### *8.8.1.5.2. 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 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). 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 post-treatment 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).

## 8.9. Other safety issues

### 8.9.1. Macrophage activation syndrome (MAS)

*Macrophage activation syndrome (MAS) is a well-known, serious and potentially fatal complication of SJIA (Stephan et al 2001, Grom 2004, Arlet et al 2006). Approximately 7-17% of SJIA patients experience full-blown MAS during the course of their illness (Sawhney et al 2001, Moradinejad and Ziaee 2011), and mild MAS may be seen in as many as half of patients with active systemic disease (Bleesing et al 2007; Behrens et al 2007). The pathophysiology of MAS is not fully understood, but is defined by an inappropriate uncontrolled proliferation of T cells leading to expansion of tissue macrophages (histiocytes) that exhibit hemophagocytic activity. This leads to cytopenia, multiple organ dysfunction, fever, rash and potentially death. Common triggers include infections, most often viral infections such as Epstein-Barr virus (EBV) and cytomegalovirus, as well as medications, stress and SJIA flares.*

*MAS has been reported in patients receiving the anti-IL1 blocking agent anakinra and in those receiving tocilizumab, which is an approved therapy for SJIA (Ravelli et al 2012), as well as in patients treated with canakinumab. In order to provide a complete evaluation of MAS for SJIA patients using canakinumab, an external independent MAS adjudication committee (MASAC) was formed.* (Source: sponsor's Summary of Clinical Safety)

MASAC reviewed all potential cases of MAS in the sJIA studies. Cases were identified through a programmed search of the safety database for pre-specified AE preferred terms and/or laboratory abnormalities. The adjudication codes along with the MASAC's assessment of the probability of MAS are summarised below:

- Adjudication code 1 (probable MAS): Clinically consistent with MAS with either histologic confirmation or meets current formal HLH guideline criteria
- Adjudication code 2 (probable MAS): Clinical and laboratory features consistent with MAS but without histologic confirmation or meeting current formal HLH criteria

- Adjudication code 3 (possible MAS): Laboratory features consistent with MAS but without clinical features, histologic confirmation, or meeting current formal HLH criteria
- Adjudication code 4 (unlikely MAS): Some clinical and/or laboratory features of MAS, but with possible alternative explanation
- Adjudication code 5 (insufficient info): Insufficient information for adjudication

#### *8.9.1.1. Study G2305*

Two cases of MAS were reported as SAEs, and a further 4 events (one in the canakinumab group and three in the placebo group) were identified for adjudication by a search of the clinical database. Both MAS SAEs were adjudicated as clinical and laboratory features consistent with MAS (code 2, probable MAS), the remaining 4 cases were adjudicated as some clinical features of MAS but with a possible alternative explanation (code 4, unlikely MAS).

#### *8.9.1.2. Study G2301*

Five cases of MAS were reported as SAEs. Four occurred during Part I, 2 of which were adjudicated as clinically consistent with MAS (code 1, probable MAS), and two were adjudicated as having some clinical features of MAS, but with possible alternative explanation (code 4, unlikely MAS). The one case in Part II was adjudicated as clinically consistent with MAS (code 1, probable MAS).

An additional 20 cases were identified for adjudication by a search of the clinical database. Of these, 14 cases occurred in Part I and 6 in Part II (4 canakinumab and 2 placebo). Two cases were adjudicated as laboratory features consistent with MAS (code 3, possible MAS). The remaining 18 cases were adjudicated as some clinical features of MAS but with a possible alternative explanation (code 4, unlikely MAS).

#### *8.9.1.3. Study A2203*

One case of MAS was reported as an AE.

#### *8.9.1.4. Study G2301E1*

Eleven potential cases of MAS were reported for adjudication. The 3 cases that were reported as SAEs were adjudicated as probable MAS, there were 3 cases of possible MAS, and the remaining 5 cases were adjudicated as unlikely MAS.

#### *8.9.1.5. Expert paper*

The sponsor provided an expert paper on MAS (undated), which described the MAS experience within the canakinumab sJIA clinical program. It states that 'at the time of the interim database lock' (presumably of Study G2301E1) there were 12 AEs reported as MAS, including 2 (1 canakinumab and 1 placebo patient) with a fatal outcome. Of these 12 events, 1 occurred in Study A2203; 2 in Study G2305; 5 in Study G2301; and 4 in Study G2301E1. In Study 2305, 1 case had received canakinumab and 1 placebo. In Study 2301, 4 patients developed MAS in the open-label Part I, and 1 developed MAS 6 months after being randomized to placebo in Part 2. The time adjusted rate of reported MAS is presented in Table 32, below.

**Table 32. Time adjusted rate of Reported MAS in the Canakinumab sJIA Clinical Program**

| | SJIA Clinical Program | | |
|---|---|---|---|
| | On canakinumab | On placebo | Difference canakinumab–placebo (95% CI) |
| Patient-years exposure (yrs)[1] | 276 | 26 | |
| Number of reported MAS AEs[2] | 10 | 2 | |
| **Rate of MAS AEs/100 pt-yrs** | **3.6** | **7.7** | **- 4.1 (-15.0, 6.8)** |
| Patient-years exposure (yrs) | 276 | 26 | |
| Number of MAS AEs Adjudicated as Probable MAS[3] | 7 | 2 | |
| **Rate of MAS AEs adjudicated as Probable MAS/100 pt-yrs** | **2.5** | **7.7** | **-5.2 (-16.0, 5.7)** |
| Number of Adjudicated cases as Probable or Possible MAS[4] | 12 | 2 | |
| **Rate of MAS AEs adjudicated as Probable or Possible MAS/100 pt-yrs** | **4.3** | **7.7** | **-3.4 (-14.3, 7.6)** |

1Exposure up to G2301E1 interim analysis database lock date of Aug 10, 2012; [2]Excludes patient G2301E1-0200-00203 who was initially reported with a diagnosis of MAS (vs Parvovirus) and subsequently updated with a final diagnosis of parvovirus after adjudication by MASAC. Includes patient G2301E1-0080-00201 who was not adjudicated because event reported after adjudication cut-off date. [3]No MAS reported AEs were adjudicated as Possible MAS; [4]Includes all reported MAS AEs and cases identified through clinical study program AE and lab databases search. Includes patient G2301E1-0200-00203 who was adjudicated before diagnosis was changed by investigator. Patient G2301-0011-00101 who received canakinumab followed by placebo is counted in the placebo group; AE= adverse event

Evaluator's comment: There is a discrepancy between the number of MAS cases reported in the G2301E1 CSR and in the Expert Report which appears to be because one patient had the MAS SAE reported after the cut-off date for adjudication. This would not change the interpretation of these results.

## 8.10. Evaluator's overall conclusions on clinical 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 – 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 - < 4 years, 40 aged 4 - < 6 years, 86 aged 6 - ≤ 12 years, and 51 aged 12 - < 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 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 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 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.

Macrophage activation syndrome 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.

# 9. First round benefit-risk assessment

## 9.1. 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 - <4 years 77.8%, 4 - <6 years 87.5%, 6 - <12 years 85.7%, and 12 - <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

## 9.2. 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.

## 9.3. First round assessment of benefit-risk balance

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

## 9.4. 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 in Section 9. 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 modification of the PI as recommended.

In the pooled sJIA studies 8 patients had a QTc(F) > 500 msec. Although there was no effect on corrected QT interval in preclinical 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.

# 10. Clinical questions

## 10.1. Pharmacokinetics

No questions.

## 10.2. Pharmacodynamics

No questions.

## 10.3. Efficacy

1. The adapted ACR Paediatric response variables included CRP as the laboratory measure of inflammation whereas 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).

In Table 10-2 on page 108 of 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 distribution of

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

# 11. Second round evaluation of clinical data submitted in response to questions

## 11.1. 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.

## 11.2. 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.

## 11.3. 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 33).

**Table 33. 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.

### 11.4. Second round benefit-risk assessment

#### 11.4.1. 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 Section 8.1.

### 11.5. 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 form Section 8.2.

### 11.6. Second round assessment of benefit-risk balance

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

# 12. Second round recommendation regarding authorisation

Satisfactory responses have been received in relation to the questions posed in Section 9. The recommendation regarding authorisation is otherwise unchanged from the first round recommendation made in Section 8.

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