London, 25 July 2013
EMA/CHMP/427081/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

ILARIS

International non-proprietary name: CANAKINUMAB

Procedure No. EMEA/H/C/001109/II/0026

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Table of contents

List of abbreviations

ACR	American College of Rheumatology
ACZ885	Canakinumab
AE	Adverse event
ANCOVA	Analysis of covariance
AUCxx	Area under the serum concentration-time curve at steady-state
AUCtau	Area under the serum concentration-time curve from time zero to the end of the dosing internal (tau) at steady state
CAPS	Cryopyrin-Associated Periodic Syndromes
CHAQ©	Child health assessment questionnaire
CHQ-PF50©	Child health questionnaire – parent form
CI	Confidence interval
CRP	C-reactive protein
Cmax	Maximum serum concentration
CV	Coefficient of variation
ECG	electrocardiogram
eCRF	Electronic case report/record form
ESR	Erythrocyte sedimentation rate
FDA	Food and Drug Administration
FAS	Full analysis set
IA	Interim analysis
IL-1β	Interleukin-1 beta
i.v.	Intravenous(ly)
ILAR	International league against rheumatism
JIA	Juvenile idiopathic arthritis
LS	Least squares
MAS	Macrophage activation syndrome
MTX	Methotrexate
NSAID	Non-steroidal anti-inflammatory drug
OR	Odds ratio
PK	Pharmacokinetics
PK-flare	Pharmacokinetics-flare
PRINTO	Pediatric rheumatology international trials organization
PRCSG	Pediatric rheumatology collaborative study group
q4w	Every 4 weeks
s.c.	Subcutaneous(ly)
sBLA	Biologics License Application submission
SAE	Serious adverse event
SCE	Summary of Clinical Efficacy
SD	Standard deviation
SJIA	Systemic juvenile idiopathic arthritis
VAS	Visual analog scale

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Novartis Europharm Ltd submitted to the European Medicines Agency on 7 November 2012 an application for a variation including an extension of indication.

This application concerns the following medicinal product:

Medicinal product:	**International non-proprietary name:**	**Presentations:**
Ilaris	canakinumab	See Annex A

The following variation was requested:

Variation(s) requested		**Type**
C.1.6 a)	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

The MAH proposed the update of sections 4.1, 4.2, 4.4, 4.8, 4.9, 5.1, 5.2 and 5.3 of the SmPC in order to extend the indication of canakinumab for the treatment of active Systemic Juvenile Idiopathic Arthritis (SJIA) in patients aged 2 years and older who have responded inadequately to previous therapy with non-steroidal anti-inflammatory drugs (NSAIDs) and systemic corticosteroids. Ilaris can be given as monotherapy or in combination with methotrexate. The Package Leaflet was proposed to be updated accordingly. In addition the MAH took the opportunity to align the PI with the latest QRD template.

The requested variation proposed amendments to the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0108/2012 on the agreement of a paediatric investigation plan (PIP) in children from 24 months to less than 18 years, and the granting of a (product-specific) waiver in children from birth to less than 24 months for the following condition:

Table 1. Treatment of juvenile idiopathic arthritis

At the time of submission of the application, the PIP was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice /Protocol assistance

The applicant received Protocol Assistance from the CHMP on 24 July 2008. The Protocol Assistance pertained to clinical aspects and in relation to paediatric development of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Jan Müller-Berghaus **Co-Rapporteur: Outi Mäki-Ikola**

Submission date:	7 November 2012
Start of procedure:	23 November 2012
Rapporteur's preliminary assessment report circulated on:	15 January 2013
Co-Rapporteur's preliminary assessment report circulated on:	16 January 2013
Joint Rapporteur's and Co-Rapporteur's assessment report circulated on:	12 February 2013
PRAC RMP advice and assessment overview adopted by PRAC:	02 February 2013
Request for supplementary information and extension of timetable adopted by the CHMP on:	25 February 2013
MAH's responses submitted to the CHMP on:	23 May 2013
Joint Rapporteur's preliminary assessment report on the MAH's responses circulated on:	24 June 2013
Updated Joint Rapporteur's and Co-Rapporteur's assessment report on the MAH's responses circulated on:	12 July 2013
PRAC RMP advice and assessment overview adopted by PRAC :	11 July 2013
CHMP opinion:	25 July 2013

2. Scientific discussion

2.1. Introduction

Canakinumab (Ilaris) is a recombinant human monoclonal anti-human antibody of the IgG1/kappa isotype subclass. It binds selectively and with high affinity, to interleukin-1β (IL-1β) with no cross-reactivity with IL-1α or the IL-1 receptor antagonist. The IL-1β-canakinumab complex cannot bind to the IL-1 receptor, rendering the bound IL-1β functionally ineffective.

Canakinumab is authorized for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS) and for the symptomatic treatment of adult patients with frequent gouty arthritis attacks (at least 3 attacks in the previous 12 months) in whom non-steroidal anti-inflammatory drugs (NSAIDs) and colchicine are contraindicated, are not tolerated, or do not provide an adequate response, and in whom repeated courses of corticosteroids are not appropriate.

SJIA (Systemic juvenile idiopathic arthritis) is a serious, rare condition responsible for high childhood mortality and severe morbidity, including arthritis, joint deformities and systemic manifestations which can lead to severe disabilities. SJIA presents as recurrent systemic symptoms, including spiking fevers, rash, lymphadenopathy, hepatosplenomegaly, serositis and arthritis. SJIA is associated with elevated erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) levels, and neutrophil and platelet counts, which reflect systemic inflammation. It is often accompanied by anemia and elevated transaminases (Ravelli and Martini 2007).

Joint damage is seen within 2 years, up to 50-70% have active arthritis as adults, 30-40% have long-term disabilities, and 25-50% need major surgery including joint replacement (Hashkes and Laxer 2005). Standard therapies such as NSAIDs (non-steroidal anti-inflammatory drugs), methotrexate (MTX) and corticosteroids are often insufficient to adequately control disease symptoms.

High doses of corticosteroids are often necessary to treat and avoid flares. Reduction of steroid use is a clinically meaningful objective as chronic use is associated with Cushing syndrome, obesity, hypertension, fractures, cataracts and growth retardation (Manson, et al 2009). Tocilizumab, an IL-6 receptor antagonist, was recently approved (RoActemra in European Union August 2011), as treatment for patients with poor response to NSAIDs and systemic corticosteroids.

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). Canakinumab was designed to specifically inhibit IL-1β and investigated to determine its impact on fever and other disease symptoms, as well as composite measures of clinical response and flares.

The current submission aims to extend the indication of Canakinumab to the treatment of active Systemic Juvenile Idiopathic Arthritis (SJIA) in patients aged 2 years and older who have responded inadequately to previous therapy with non-steroidal anti-inflammatory drugs (NSAIDs) and systemic corticosteroids. Ilaris can be given as monotherapy or in combination with methotrexate.

Protocol assistance was given from CHMP (EMA Scientific Advice Letter, 2008) on the primary efficacy variable of the paediatric adapted ACR30 at 15 days and was accepted as a valid marker of reduced disease burden.

2.2. Non-clinical aspects

2.2.1. Introduction

No new non-clinical studies were submitted in this application which was considered acceptable by the CHMP. Additional pharmacology information and an update of the pharmacokinetic data for the specific systemic juvenile idiopathic arthritis indication relevant for this application are reported below.

2.2.2. Pharmacology

The rationale for neutralizing IL-1β in sJIA is based on literature data. Animal models for sJIA are not available due to the very specific and not fully understood pathophysiology of sJIA. Evidence for a pivotal role of IL-1β in the pathophysiology of sJIA comes from clinical studies. Pascual et al (2005) demonstrated that sera from sJIA patients induced vast overexpression of IL-1β ex vivo when used to stimulate human peripheral blood mononuclear cells. Also, this study found IL-1β itself up-regulated in peripheral blood from sJIA patients leading to the hypothesis that blockade of IL-1 signalling in these patients may ameliorate disease. Treatment with anakinra, a recombinant human interleukin-1 receptor antagonist, indeed improved systemic symptoms, such as fever, and joint inflammation. This initial report was subsequently confirmed in a number of open label and controlled studies using anakinra (Zeft et al 2009; Quartier et al 2011).

The pharmacology data as provided with the marketing authorisation application is also applicable for the present application and no new data is considered necessary by the CHMP.

2.2.3. Pharmacokinetics

A detailed comparison of pharmacokinetics of canakinumab in NHP vs. human adults and sJIA patients (see table below) and an up-date of the safety margin using systemic concentration values from subjects which are representative of the sJIA population (in the table below) is provided.

Table 1. Comparative pharmakinetics (Mean (SD)) of ACZ885

Parameters	Rhesus Monkey[e]	Marmoset Monkey[a,b]		Humans	
				Healthy Adults[c]	sJIA Patients[d]
Dose	2 mg/kg i.v.	5 mg/kg i.v. [a]	5 mg/kg s.c. [b]	10 mg/kg i.v.	4 mg/kg s.c.
CL(L/day)	0.012 (0.00168)	0.004 (0.0008)	0.007 (0.002)	0.137 (0.0351)	0.106 (0.00689)
Cl (L/day/kg)[g]	0.004	0.0114	0.02	0.00196	0.003
Vz (L)	0.3 (0.12)	n.a	n.a	5.07 (0.99)	n.a
Vss (L)	0.26 (0.07)	0.02 (0.004)	n.a	n.a	3.21[h]
$T1/2_{,terminal}$ (day)	17.4 (5.2)	4.33 (0.548)	7.07 (1.83)	26.4 (5.70)	21[h]
F % (s.c bioavailability)	n.a	n.a	60	n.a	68.9[f]

a Parameters presented are based on results obtained from [Study DMPK (US) R01-957] and adjusted for a marmoset weighing 0.350 kg
b Parameters presented are based on results obtained from [Study DMPK R0600200] for NSO-derived ACZ885 and adjusted for a marmoset weighing 0.350 kg
c Results from [Study CACZ885B2101]
d Parameters presented based on the population PK-binding model for a typical sJIA patient: BW= 33 kg, Age=9yrs [ACZ885 sJIA Modeling Report].
e Parameters presented are based on results obtained from [Study R01-1005] and adjusted for rhesus monkey weighing 3 kg.
f The s.c. bioavailability (F) was estimated based on the PK-binding model for the product type intended for market.
g parameters presented are based on marmoset weighing 0.350 kg, rhesus monkey 3 kg, and Human: 33 kg (median patient body weight in sJIA studies) for sJIA patients and 70 kg for Healthy Adults.

h Vss = Vd+Vp and was derived from the population estimates of Vd and Vp for a typical sJIA patient: BW= 33 kg, Age=9yrs. Similarly, T1/2 was derived from formula T1/2=0.693*Vss/CL, where CL and Vss are population estimates from a typical adult sJIA patient [ACZ885 sJIA Modeling Report].
n.a. not available or not applicable

Human PK and total IL-1β data were described by a population based PK-binding model. This model was updated from the original model included in the CAPS submission with data from sJIA clinical trials, as well as data from gouty arthritis patients and additional new data from RA and CAPS patients. The kinetics of canakinumab and its binding to IL-1β is presented fully across the age group of sJIA population.

Using the population PK parameter values from the PK-binding model, canakinumab concentration-time profiles were simulated for a typical sJIA patient weighing 33 kg, based on a dosing regimen of 4 mg/kg every 4 weeks for six months, to ensure that steady state is achieved. The AUC and Cmax from the last dosing interval were estimated for each subject in sJIA trials, and summary statistics were calculated for these two exposure metrics. The AUC from 0-tau at steady state was calculated, and divided by tau (dose interval) to obtain the average steady-state (Cavg,ss) concentration.

The simulated exposure data and exposure multiples were compared to data from the marmoset GLP toxicology study (see table below).

Comparison based on observed canakinumab concentrations in marmosets and predicted steady state concentrations in sJIA patients show that plasma concentrations that are well tolerated in animals exceed 62-fold (C_{max}) and 104-fold (C_{avg}) the plasma concentrations in paediatric SJIA patients, treated with up to 4 mg/kg via the subcutaneous route every 4 weeks.

Table 2. Comparative systemic exposure in marmosets and sJIA patients

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

a AUCss and Cmax,ss values obtained from simulations with the population PK binding model [ACZ885 sJIA Modeling Report]
b Parameters in sJIA patients were compared with highest mean (male and female) AUC0-24h,ss/24h and Cmax,ss, respectively, observed at 150 mg/kg s.c. in 13 week study in marmosets [Study 0470033] to calculate the exposure multiple; AUC0-24h was normalized to 24h in marmosets administered ACZ885 twice weekly to get an approximate of Cavg; in sJIA patients, average steady-state canakinumab concentration (Cavg,ss) was derived as AUCss/tau, where tau depicts 4 week (28 days) dosing frequency.
c Parameters in sJIA patients were compared with highest mean (male and female) AUC0-96h,ss/96h, observed at 100 mg/kg i.v. in 26 week study in marmosets [Study 0380070] to calculate the exposure multiple; tau or dosing interval is approximately 96h in marmosets administered ACZ885 twice weekly; in sJIA patients, average steady-state canakinumab concentration (Cavg) was derived as AUCss/tau, where tau depicts 4 week (28 days) dosing frequency.

2.2.4. Toxicology

No new additional toxicological investigations were performed and therefore no new data are provided in this submission.

2.2.5. Ecotoxicity / environmental risk assessment

According to Directive 2001/83/EC and Guideline EMEA/CHMP/SWP/4447/00, medicinal products consisting of substances occurring naturally in the environment, such as electrolytes, vitamins, proteins etc. do not need to be accompanied by an environmental risk assessment because they are unlikely to result in significant risk to the environment.

2.2.6. Discussion on non-clinical aspects

No new non-clinical studies were performed to support this variation application as the non-clinical data reviewed in the context of the canakinumab initial MAA are applicable for the present application. This was considered acceptable by the CHMP.

Exposure multiples were newly calculated based on up-dated human pharmacokinetic data in children with sJIA. The available studies in marmosets provide a sufficiently high exposure multiple to establish an adequate safety margin of the proposed s.c. dose of 4 mg/kg canakinumab.

2.2.7. Conclusion on the non-clinical aspects

The non-clinical pharmacology, pharmacokinetic and toxicity data which were evaluated during the initial marketing authorization of canakinumab are considered appropriate to support the proposed use of canakinumab in patients with sJIA.

2.3. Clinical aspects

2.3.1. Introduction

The clinical program to demonstrate efficacy and safety in the target indication and population includes 2 pivotal, blinded, placebo-controlled phase III studies (Studies G2305 and G2301), 1 phase II dose-ranging study (Study A2203), and 1 uncontrolled extension study (Study G2301E1).

Canakinumab is approved in the EU to treat CAPS at the dose of 2 mg/kg for patients with a body weight below 40 kg and 150 mg for patients with a bodyweight above 40 kg administered subcutaneously (s.c.) every 8 weeks. This registration dossier aims to obtain marketing authorization of canakinumab for the treatment of active SJIA in patients aged 2 years and above, at a recommended dose of 4 mg/kg (maximum total single dose of 300 mg) administered subcutaneously every 4 weeks.

The open-label repeated dose range finding study A2203 was used to define the dose used in the phase III trials (4 mg/kg). The efficacy of 4 mg/kg every 4 weeks was investigated in two randomized, double-blind, placebo-controlled pivotal trials G2305 and G2301. Study G2305 was planned to demonstrate the superiority of a single dose of canakinumab 4 mg/kg versus placebo in patients with active SJIA. Study G2301 was a 2-part study. Part I (consisting of 4 subparts, Ia-Id) was designed to confirm the efficacy of canakinumab 4 mg/kg every 4 weeks seen in G2305 but in an open-label study design (Part Ia), and to assess whether canakinumab allows for successful tapering of steroid therapy (Part Ic). Part II was designed to demonstrate the efficacy of canakinumab versus placebo in delaying the onset of a new flare event in a treatment withdrawal study design.

Study G2301E1, an open-label extension study to G2305 and G2301, was planned to support long-term efficacy.

The combined efficacy data analysis is used to evaluate the 12-week efficacy of canakinumab 4 mg/kg given every 4 weeks in canakinumab treatment-naïve patients in various subgroups.

Furthermore, data from CAPS studies were presented to support safety of canakinumab in a population with another auto-inflammatory condition.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Table 3. Tabular overview of clinical studies

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
Source: [A2203], [G2305], [G2301] and [G2301E1]

2.3.2. Pharmacokinetics

The pharmacokinetics (PK) of canakinumab and total IL-1β kinetics (free and antibody bound) have been characterized in healthy subjects as well as in various patient populations (including CAPS, asthma, psoriasis and RA patients) in the original CAPS submission, and subsequently in gouty arthritis patients. In this submission, the PK of canakinumab and total IL-1β kinetics pertinent to the SJIA patients are presented.

Phase II and III studies conducted primarily to determine the appropriate canakinumab dose and to establish the efficacy and safety of canakinumab in SJIA patients also included evaluation of canakinumab serum concentrations (studies [A2203], [G2305], [G2301], and [G2301E]).

The corresponding PK/PD parameters derived from the non-compartmental or compartmental analysis are summarized in the table below.

Table 4. Mean (SD) Pharmacokinetic parameters in SJIA studies

Study	Age (years)	Dose (mg/kg)	N	CL (L/d)	Vc (L)	Vp (L)	CLd (L/d)
A2203*	4 to 17	0.5 to 9.0	21	0.256 (0.0993)	5.94 (2.54)	NA	NA
G2305	2 to <4	4	8	0.0528 (0.0189)	0.539 (0.218)	0.624 (0.0711)	0.146 (0.0827)
	4 to <6	4	7	0.0731 (0.0173)	0.848 (0.305)	0.743 (0.142)	0.0805 (0.0317)
	6 to <12	4	14	0.110 (0.0359)	1.51 (0.561)	0.858 (0.145)	0.0986 (0.0532)
	12 to <20	4	12	0.219 (0.111)	4.64 (2.83)	1.34 (0.281)	0.0747 (0.0464)

CL=, Clearance from serum, Vc= Volume of distribution of central compartment, Vp= Volume of distribution of peripheral compartment, and CLd= Distribution clearance between serum and tissue

* Parameters reported are apparent clearance (CL/F) and apparent volume of distribution (Vz/F) calculated by noncompartmental analysis

† Data from [A2203], [G2305], [G2301] and [G2301E1] was pooled and analyzed using PK-binding model (presented in Table 3-3).

Source: [A2203] and [G2305]

Methods – analysis of data submitted

The collection of serum samples for canakinumab and IL-1β PK/PD analyses in studies A2203, G2305, G2301and G2301E1 was based on sparse sampling approach. The population based PK-binding model included in the original CAPS submission was previously derived to describe the PK of canakinumab and total IL-1β properties. The model was updated to include data from SJIA clinical trials, as well as data from other disease population.

Canakinumab was analyzed in human serum using a specific competitive ELISA method with an 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.

The PK- efficacy response relationship of canakinumab in SJIA patients was first investigated for Study A2203 and was subsequently analysed with data from Phase 3 SJIA studies. PK-safety relationship of canakinumab was explored using the data from Phase III studies G2305 and G2301.

PK Results

Study A2203

This study was a Phase II, multi-center, open label, repeat dose range finding study to assess the clinical safety, tolerability, immunogenicity, pharmacokinetics and efficacy of canakinumab in patients with active systemic juvenile idiopathic arthritis (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.

In Stage I, a total of 23 unique patients with three patients being enrolled twice in different cohorts were randomized to one of 3 starting doses of canakinumab 0.5, 1.5 or 4.5 mg/kg, corresponding to cohorts I, II or III, respectively. If patients treated with first dose did not show measureable improvement, a second injection of the same dose of canakinumab was administered between Day 3 to Day 9. Patients who experience a measurable improvement were re-dosed upon each relapse until they entered Stage II of the study. In Stage II, all responding patients received a fixed dose of 4 mg/kg canakinumab. During this period corticosteroid tapering was allowed at the discretion of the investigator and according to local medical practice. In Stage I, serum canakinumab (PK) and IL-1β (PD) samples were collected 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 completed two cycles of remission. No PK or PD samples were taken in Stage II.

The enrolled patients had an average age of 10 years (range: 4 to 19 years). 26 (23 unique subjects, plus 3 re-enrolled) pharmacokinetic profiles were obtained. 5 data sets had missing data at the terminal phase, therefore non-compartmental PK parameters were calculated from 21 data sets from subjects receiving canakinumab dose ranging from 0.5 to 9 mg/kg (see table below). Peak serum concentration of canakinumab (Cmax) per dose group could not be evaluated in most subjects, since the majority of them received a second dose within 7 days of the first dose. In the six subjects for who only had a single s.c. injection of canakinumab, peak serum levels were reached in approximately 2 days. Apparent half-life following the single s.c. dose administration was 16.7 (SD=5.45) days. Average apparent clearance (CL/F) of 0.256 (SD= 0.0993) L/d and average apparent volume of distribution (Vz/F) of 5.94 (SD=2.54) L was reported for these pediatric patients. Moderate inter-subject variability with a coefficient of variation of approximately 39 % was observed in CL/F.

Table 5. Serum PK parameters after an initial s.c dose of 0.5, 1.0, 1.5, 3.0, 4.5 or 9.0 mg/kg canakinumab in pediatric 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

Source: [Study A2203 PT-Table 14.2-9.2] and [Study A2203 PT-Table 14.2-9.3]
†: reported for patients who received a single dose in Period 1.

The summary of mean exposure parameters per dose regimen is shown in the table below. These data indicate that there is approximate dose proportionality of Cmax and AUC in this patient population.

The IL-1β data collected in this study were pooled with data from other canakinumab studies.

Table 2-3 Summary of mean (SD) of exposure parameters (AUCs, Cmax) per dose regimen [A2203]

Dose (mg/kg)	N	AUClast (day*ug/mL)	AUCinf (day*ug/mL)	Cmax (ug/mL)
0.5	1	50.34 ()	52.56 ()	2.550 ()
1.0	4	151.9 (37.350)	156.4 (37.619)	
1.5	2	212.6 (72.795)	221.4 (78.870)	6.800 (2.6163)
3.0	7	465.0 (325.11)	488.3 (337.94)	
4.5	3	574.8 (189.76)	583.7 (183.99)	24.90 (2.0075)
9.0	4	1000 (278.74)	1009 (277.04)	

Study G2305

This study was a Phase III randomized, double-blind, placebo controlled, single dose study to assess the efficacy and safety of canakinumab in patients with SJIA and active system manifestation. The primary objective of the study was to demonstrate that the proportion of patients who met the adapted ACR Pediatric 30 criteria on Day 15 was higher with canakinumab compared to placebo.

A total of 84 patients, in 40 centers in 18 countries, with an average age of 9 years (range: 2 to 19 years) were randomized to treatment (43 to canakinumab and 41 to placebo). Patients were followed for 4 weeks, with the primary efficacy endpoint (Adapted ACR pediatric 30 on Day 15), secondary efficacy endpoints and safety analysis up to Day 29.

Patients received a s.c. injection of canakinumab (4 mg/kg) or placebo on Day 1. The maximal total single dose of canakinumab allowed was 300 mg. Serum canakinumab and IL-1 β samples were collected at baseline (Day 1), Days 3, 15 and 29 (or Premature Patient Withdrawal (PPW)). PK samples

were also collected in case of flare and in case of an anaphylactic reaction (a sample at the time of the event and also 8 weeks later).

A population pharmacokinetic model with two-compartment disposition and first-order absorption was developed to characterize the PK properties of canakinumab obtained from only this study [G2305] population. The IL-1β data collected in this study was pooled with data from other canakinumab studies. Since there was only s.c. dosing in this study, the values for Ka and F were fixed to known values for the product types from a previous model with extensive data from all product types. The mean (SD) values of individual PK parameter estimated for patients in various age groups (2 to <4, 4 to <6, 6 to <12, and 12 to <20 years) are shown in the table below.

The mean total distribution volume (Vss) [Volume of distribution of the serum compartment (Vc) + Volume of distribution of the tissue compartment (Vp)] in the oldest age group patients (i.e. 12 to <20 years) was approximately 5.98 L and the mean total serum clearance (CL) was estimated to be 0.219 L/day. The CL and Vss of canakinumab were progressively lower as the age in the patient population decreased, as a result that clearance and volume of distribution of canakinumab were a function of body weight. These results suggested the appropriateness of body weight–based dosing for patients in various age groups (2 to < 20).

Table 6. Summary of mean (SD) of PK parameters by age group [G2305]

PK	Age group (number of subjects)			
Parameter	2 to <4 (n=8)	4 to <6 (n=7)	6 to <12 (n=14)	12 to <20 (n=12)
CL (L/d)	0.0528 (0.0189)	0.0731 (0.0173)	0.110 (0.0359)	0.219 (0.111)
Vc (L)	0.539 (0.218)	0.848 (0.305)	1.51 (0.561)	4.64 (2.83)
Vp (L)	0.624 (0.0711)	0.743 (0.142)	0.858 (0.145)	1.34 (0.281)
CLd (L/d)	0.146 (0.0827)	0.0805 (0.0317)	0.0986 (0.0532)	0.0747 (0.0464)

CL=, Clearance from serum, Vc= Volume of distribution of central compartment, Vp= Volume of distribution of peripheral compartment, and CLd= Distribution clearance between serum and tissue

Source: [G2305- Listing 16.2.5-3.2]

Study G2301

G2301 was a Phase III, multicenter, two-part study with an open-label, single-arm active treatment (Part I) followed by a randomized, double-blind, placebo-controlled, event-driven withdrawal design (Part II) of canakinumab in patients with SJIA and active system manifestation.

The primary objective of the study in Part I was to assess if monthly canakinumab 4 mg/kg allowed tapering of steroids in at least 25% of patients. The main objective in part II was to demonstrate that the time to flare was longer with canakinumab than with placebo.

In Part I, patients received a single dose of canakinumab (4 mg/kg) subcutaneously (s.c.) every 4 weeks. Part I had four subparts. Parts Ia and Ib aimed to induce and maintain at least an ACR30 response without tapering of steroids and to ensure patients had 8 weeks canakinumab treatment before Part Ic, which aimed to reduce steroid dose prior to entering Part II. Part Id was designed to stabilize patients on an achieved steroid dose for 4 weeks before entering Part II. 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). In Part II (double-blind withdrawal period), patients were randomized to canakinumab or placebo in a 1:1 ratio, and received a s.c. injection of canakinumab (4 mg/kg) or placebo every 4 weeks. The study was stopped when the required number of 37 flare events had occurred in Part II.

A total of 177 patients, from 63 centers in 21 countries, entered Part I with an average age of 8.7 years (range: 1 to 19 years). In Part II, 100 patients (50 patients in canakinumab and 50 patients in placebo) with an average age 9.1 years (range: 2 to 19 years) entered the study. Serum canakinumab (PK) and IL-1β (PD) samples were collected at baseline (Day 1), Days 3, 15, 29, 57, end of Part Ic (or

Day 197) visit, and end of Part Id (or Day 225) visit, in part I, every 6 months (pre-dose) during part II and end of study (or PPW). PK samples were also planned in case of flare and in case of an anaphylactic reaction (a sample at the time of the event and also 8 weeks later).

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 MAH analyzed common subjects that had concentration data on Day 197 and 225. The mean±SD canakinumab concentrations for 43 common subjects at Day 197 and 225 were similar; 23.4±8.98 µg/ml (at day 197) vs. 23.6±7.33 µg/ml (at day 225). These concentrations show that the steady state is maintained at Day 197 and 225. The PK model-based analysis of these data was performed separately, after pooling with data from other canakinumab studies.

Study G2301E1

G2301E1 was a Phase III, and open label extension to 2 pivotal trials 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.

Eligible patients aged 2 to < 20 years with a confirmed diagnosis of SJIA and who had responded to canakinumab treatment in studies G2305 and G2301 were enrolled in this extension study to receive canakinumab 4 mg/kg every 4 weeks s.c. for up to 2 years.

An option to receive a dose of 2 mg/kg every 4 weeks s.c. was available for individual patients who had achieved steroid tapering or who were steroid free.

A total of 147 patients from 61 centers in 20 countries with an average age of 9.5 years (range: 2 to 20 years) were enrolled in the study. Serum canakinumab (PK) and IL-1β (PD) samples were collected at baseline (Day 1), Days 169, 337, 505, 673 (or PPW), every 6 months (predose) for patients who continued beyond Day 673. PK samples were also planned in case of flare and in case of an anaphylactic reaction (a sample at the time of the event and also 8 weeks later). Efficacy was assessed every 12 weeks, except for CRP which was measured every 4 weeks.

The population of patients entering G2301E1 was diverse, due to patients' prior study participation status. To obtain a better understanding the following subgroups were defined for analysis: Group 1 (G2301 Part II discontinuations), Group 2 (G2301 Part II responders), Group 3 (G2301 Part I steroid tapering failures) and Group 4 (all others).

Mean trough concentration (SD) at baseline was 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 week 24 values in all groups did not indicate further increase from the values observed on Day 197 and 225, reflecting that the steady state is maintained.

The PK model-based analysis of these data was performed separately, after pooling with data from other canakinumab studies.

Population PK analysis

The definitive assessment of canakinumab pharmacokinetics and IL-1β kinetics was based on the PK-binding model that included all subjects in SJIA Phase II/III program.

Objectives

- To update the established population-based PK-Binding model previously developed with additional data from SJIA patients pooled from studies A2203, G2305, G2301 and G2301E1

- To describe the pharmacokinetics of canakinumab and its pharmacodynamics of bindings to IL-1β in SJIA patients

- To employ model-based simulation to estimate the steady-state exposures of canakinumab for SJIA pediatric patients stratified by age group (2-3, 4-5, 6-11, 12-19) and bodyweight (≤ 40 kg, > 40 to ≤ 70 kg and > 70 kg)

- To determine whether canakinumab given 4 mg/kg s.c every 4 weeks provides sufficient exposure to prevent flares in SJIA pediatric patients

Data source

The NONMEM dataset used for the PK-Binding model were derived previously in the original analysis but updated with the additional SJIA studies including other disease populations (eg, CAPS, Gouty Arthritis, Rheumatoid Arthritis, Japanese Healthy Volunteer, Non-Japanese Healthy Volunteer, and Psoriasis) totaling 28 clinical studies including their extensions. Pooling of different studies were required to provide PK and IL-1β information for the sparsely sampled SJIA studies to support estimation from the PK-Binding model.

A separate dataset containing only SJIA pooled studies was created . It contained additional variables including the records for observed flares for which the posthoc estimates from the PK-Binding model will be merged to create a new dataset for simulating steady-state kinetics.

Covariates: Summary of Demographic data

A summary of the demographic variables for each SJIA studies are listed in the table below pertaining to specific covariates previously identified to affect the PK properties of canakinumab exposure [ACZ885 CAPS Modeling Report].

Table 7. Demographic data for SJIA studies

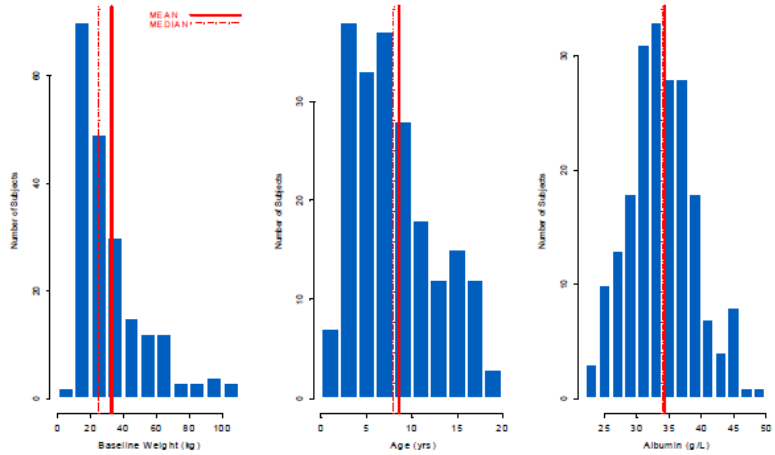
Study	N	Demographic data for analysis population (mean ± SD & range)				
		Weight (kg)	Age (years)	Albumin (g/L)	M	F
A2203	23	33.7 ± 18.5 (13.6-90.6)	9.5 ± 4.2 (4-19)	36.0 ± 3.7 (29-46)	12	11
G2305	84	34.8 ± 22.3 (10.8-102.6)	9.0 ± 4.7 (2-19)	34.5 ± 5.5 (23-49)	34	50
G2301	177	33.1 ± 21.2 (9.3-102.6)	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 will not sum up with the total from each of the individual SJIA studies

The SJIA PK population in the analysis included all 201 unique SJIA patients with ages ranging from 2 to < 20 years and body weight ranging from 9.3 to 102.6 kg.

Graphical distribution of demographic covariates is shown in the figure below.

Figure 1. Histogram of the Covariate Distribution for Bodyweight, Age and Albumin



Covariate factors assessed included age, gender, race/ethnicity, weight, and albumin, as well as immunogenicity status.

Raw data plots

The figure below shows the canakinumab concentration time profile relative to previous dose on a log-scale with a rich PK profile collected for A2203 and sparse samples for Phase 3 studies. The figure below shows the respective profiles for IL-1ß by all four studies.

Figure 2. Concentration-Time Profile of Canakinumab by SJIA studies

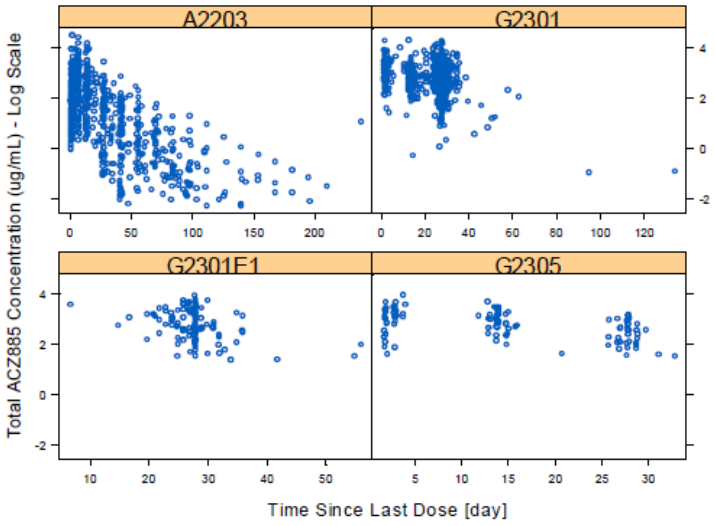
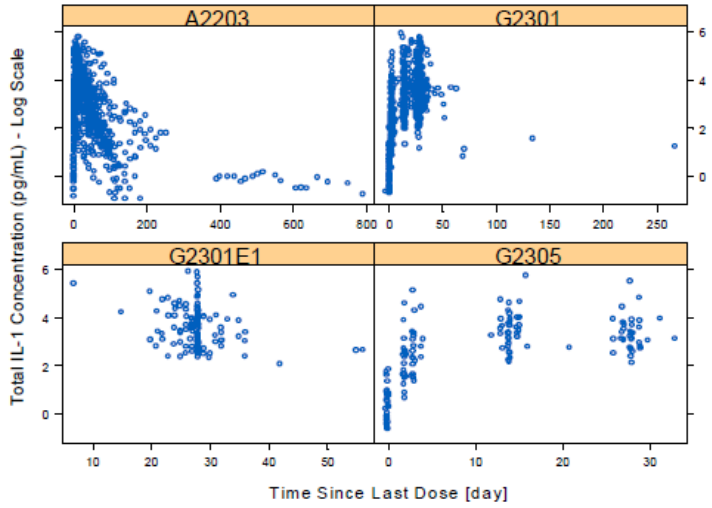


Figure 3. Concentration-Time Profile of IL-1β by SJIA studies



Methods

The analysis was performed using the NONMEM software system, NONMEM VI version 2 extended/super extended (Icon Development Solutions, Ellicott City, MD, USA), the NMTRAB subroutines version III level 1.1, and the PREDPP model library version V level 1.0 utilizing the MODESIM high performance computing environment accessed from GPSII. Data preparation and presentation were performed using SAS® software version 8.2 (SAS Institute Inc) and S-Plus Version 8.01 (Insightful Corporation).

A summary of the parameters in the model is listed in the table below:

Table 8. Parameters in the Population Model

CL_D	Clearance from serum of canakinumab [L/day]
V_D	Volume of distribution of the central, 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]
PS_D	Permeability-surface area coefficient for exchange between plasma and peripheral compartment for canakinumab (free and complex) [L/day]
k_a	Absorption rate constant for s.c. administration [1/day]
F	Bioavailability (refers to s.c. bioavailability for canakinumab) [%]
CL_L	Clearance of uncomplexed ligand, IL-1β [L/day]
R_{LI}	Production or release rate of uncomplexed ligand, IL-1β [ng/day]
PS_L	Permeability-surface area coefficient of uncomplexed ligand, IL-1β [L/day]
K_D	Equilibrium dissociation constant for binding of ACZ885 to IL-1β [nM]

Results:

Canakinumab and total IL-1β plasma concentration-time data were adequately described by the population-based PK-Binding model. The PK-Binding model parameter estimates are presented in the table below.

Table 9. Final Estimates of Model Parameters for SJIA Patients

Parameter [units]	Population mean θ ± SE (%RSE) [95% Confidence Interval]	Inter-individual variance ω^2 ± SE (%RSE) [95% Confidence Interval]	Coefficient of Variation (CV)	Shrinkage
Canakinumab parameters				
ACZ Clearance – 70 kg (CLD, L/day at 43 g/L albumin)	0.196 ± 0.0148 (7.55%) [0.167 – 0.225]	0.131 ± 0.00934 (7.13%) [0.113 – 0.149]	36.2%	9.30%
ACZ Clearance – 33 kg (CLD, L/day at 43 g/L albumin)	0.106 ± 0.00689 (6.5%) [0.092 – 0.120]			
Central distribution volume – 70 kg (V_D, L)	3.63 ± 0.194 (5.34%) [3.25 – 4.01]	0.204 ± 0.0269 (13.2%) [0.151 – 0.257]	45.2%	21.2%
Central distribution volume – 33 kg (V_D, L)	1.55 ± 0.091 (5.87%) [1.37 – 1.73]			
Peripheral distribution volume – 70 kg (V_P, L)	2.64 ± 0.15 (5.68%) [2.35 – 2.93]	0.0734 ± 0.0146 (19.9%) [0.0448 – 0.102]	27.1%	42.2%
Peripheral distribution volume – 33 kg (V_P, L)	1.66 ± 0.0946 (5.70%) [1.47 – 1.85]			
Intercompartmental permeability flow (PS_D, L/d)	0.463 ± 0.0698 (15.1%) [0.326 – 0.6]	0.272 ± 0.108 (39.7%) [0.0603 – 0.484]	52.2%	43.9%
Absorption rate constant (k_a, 1/d)	Table 9-2	0.195 ± 0.0421 (21.6%) [0.112 – 0.278]	44.2%	38.9%
Logit bioavailability	Table 9-2			
IL-1β parameters				
Clearance for ligand (CL_L, L/d)	6.22 ± 0.907 (14.6%) [4.44 – 8]	0.623 ± 0.0715 (11.5%) [0.483 – 0.763]	78.9%	26.4%
Production rate of ligand (R_{LI}, ng/d)	8.05 ± 0.913 (11.3%) [6.26 – 9.84]	0.523 ± 0.0388 (7.42%) [0.447 – 0.599]	72.3%	13.8%
Intercompartmental permeability flow (PS_L, L/d)	0.478 ± 0.09 (19.2%) [0.292 – 0.644]	0.544 ± 0.135 (24.8%) [0.279 – 0.809]	73.8%	32.4%
Binding constant (K_d, nM)	1.5 ± 0.264 (17.6%) [0.983 – 2.02]	0.27 ± 0.044 (16.3%) [0.184 – 0.356]	52%	33.2%
Covariates				
Weight on CL_D	0.823 ± 0.0367 (4.46%) [0.751 – 0.895]			
Albumin on CL_D	-0.986 ± 0.0904 (9.68%) [-1.17 - -0.799]			
Weight on V_D	1.13 ± 0.0499 (4.42%) [1.03 – 1.23]			
Weight on V_P	0.616 ± 0.0525 (8.52%) [0.513 – 0.719]			
Age on k_A	-0.292 ± 0.0593 (20.3%) [-0.408 - -0.176]			
Covariances in OMEGA matrix				
CL_D:V_D		0.126 ± 0.0144 (11.43%) [0.10 – 0.15]		
V_P:PS_D		0.0551 ± 0.0298 (54.1%) [0.00 – 0.11]		
V_P :PS_L		0.005 ± 0.0298 (596%) [-0.05 – 0.06]		
PS_D:PS_L		0.139 ± 0.111 (79.86%) [-0.08 – 0.36]		
CL_L:R_{LI}		0.426 ± 0.0418 (9.81%) [0.34 – 0.51]		
Residual variances				
Canakinumab (µg/mL)		0.0662 ± 0.0046 (6.95%) [0.0572 – 0.0752]	25.7%	
IL-1β (pg/mL)		0.137 ± 0.01 (7.3%) [0.117 – 0.157]	37.0%	
Objective function	-25206.13			

* Logit transformation: F = exp(X)/(1+exp(X))

The table above shows that relatively precise estimate were obtained for PK Binding model fixed effect (structural PK) parameters. The covariate effect parameters were less precisely estimated which is

understandable given the relatively small size (sparse samples) of the analysis dataset for SJIA and is reflected with zero being included in the 95% confidence interval. Residual within-patient error was relatively low for both total canakinumab and total IL-1β (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 (CLD) for a SJIA patient with body weight of 70 kg (reference value) and serum albumin of 43 mg/mL (reference value) was 0.196±0.01 L/day which is consistent with the previously reported values across other indications. The volumes of distribution of the central (VD) and peripheral compartment (VP) were 3.63±0.19 L and 2.64±0.15 L, respectively. The central volume would equate well with that of plasma and the ratio of the central and peripheral volumes suggest that approximately 42% of the drug distributed from the central compartment into the peripheral space. The typical values for CLD, VD and VP when adjusted to a bodyweight reference of 33 kg was 0.106±0.007 L/day, 1.55±0.091 L and 1.66±0.095 L, respectively. The estimated terminal half-life was 22 days. The time to steady state was approximately 110 days (5 half-lives). The degree of unexplained intersubject variation in the primary PK parameters was approximately 30 to 45% for clearance and the two volumes (Table 9-1).

Covariates for the pharmacokinetic parameters were the same as in the previous model: bodyweight on clearance and the two volumes of distribution, allometrically scaled with weight, plus serum albumin on clearance and age on the subcutaneous drug absorption rate, both with a negative exponent.

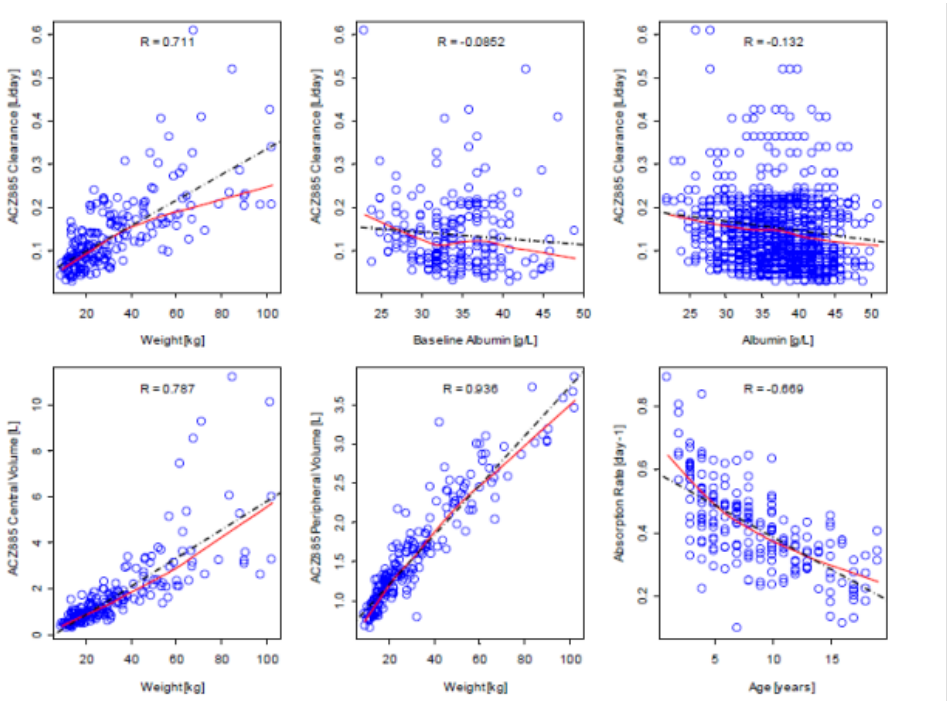
In the backward deletion of covariates for albumin and weight on CLD, weight on VD and VP and age on KA the significance of the covariates identified in the population-based PK-Binding model was confirmed. All covariate-parameter relationships were statistically significant (p-value < 0.0001), confirming the importance of these covariates in the population-based PK-Binding model.

The final model fitted well both the total canakinumab and the total IL-1β data, indicating that the model assumptions of pseudo-equilibrium, shared volumes of distribution, and complex clearance equivalent to drug clearance were reasonable. The plots of the weighted residuals versus time and versus predicted values were well centered with few outliers. The plots of observed versus population average predicted concentrations and versus individual predicted concentrations showed the predicted concentrations were uniformly distributed along the line of identity.

Shrinkage (Table 9-1) was low for the clearance of canakinumab (9.3%) and the rate of IL-1β production (13.8%), reasonable for IL-1β clearance (26.4%) and the volume of distribution (21.2%). It was more than 30% for the binding constant, rate of absorption, the peripheral volume, the intercompartmental permeability flow (PSD and PSL) for canakinumab and IL-1β, respectively.

Further graphical assessments by comparing the relationship between the individual parameters (eg CLD, VD, VP, KA) and covariates in the PK-Binding model showed a general trend confirming age, bodyweight and albumin are influencing covariates on the PK of canakinumab as shown in the figure below.

Figure 4. Covariates Relationship of Bodyweight and Albumin on Clearance and Volumes and Age on Absorption rate for SJIA patient (n = 201)



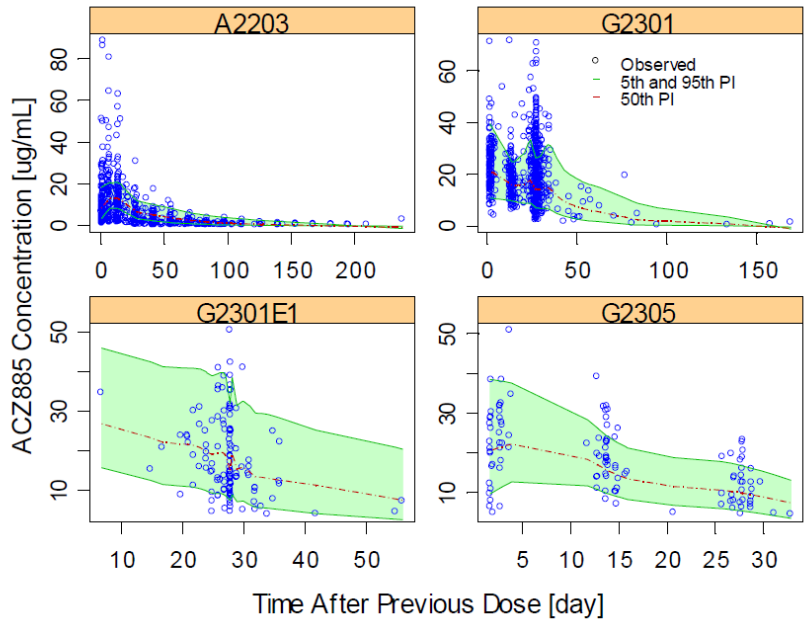
The solid line through the points in each plot is a local regression (loess in SPLUS) with a span of 2/3 and dashed line is the linear least-square fitting.

Plots of the normalized random effects of those parameters versus the included explored covariates for the final model were well centered with no obvious trends confirming that the relationships were described properly. Potential relationships between PK parameters and continuous covariates (e.g. age, weight, height, scr) and categorical covariates (gender, Race, Ethnicity) were graphically assessed (scatterplots). No apparent relationship was evident for the PK parameters and the other tested covariates.

Plots of the random effect of the parameters in the final model versus body weight, age, serum albumin, SJIA studies, cell line, race , ethnicity, gender and disease indications showed no trends and therefore these covariates were not explored further in the PK-Binding model.

The result of the performance check demonstrates that the model is generally consistent with the observed values for SJIA with respect to time. Figure 10-25 represents the 90% prediction interval and observed concentration and shows that there was reasonable overall agreement between the nominal and expected percentage of observed values outside the 90% prediction interval. Overall, 26% of the observed concentrations were outside the 90% prediction interval, with 19% falling below and 7% falling above the interval with a slight over-prediction.

Figure 5. Visual Predictive Check of Observed and Predicted Canakinumab Concentrations versus Time in SJIA patients by Studies



A summary of pharmacokinetic parameters in a typical SJIA patients (typical value at 33 kg and 43 g/L albumin) is presented in Table 3-3. In SJIA patients, for a model typical body weight of 33 kg and serum albumin of 43 g/L, the estimated serum clearance of canakinumab was 0.106 ± 0.00689 L/day. The corresponding volume of distribution at steady state was 3.21 L. The estimated half-life (T1/2) of canakinumab was 22 days. Serum clearance of canakinumab and its volumes of distribution were dependent on body weight in an allometric relationship. The exponent was approximately 0.823 ± 0.0367 for clearance with a formula CLD = 0.106× (BW/33 kg)0.823 (see table below).

Table 10. PK parameter estimates of canakinumab for SJIA patients

Parameter [units]	Typical value ± SEM (%RSE)
Drug Clearance (CL or CLD, L)	0.106 ± 0.00689 (6.5%)
(at bodyweight of 70 kg)	0.196± 0.0148 (7.6%)
Bodyweight effect on CL	$CL_D = 0.106\times (BW/33\ kg)^{0.823}$
Central volume of distribution (V_D, L)	1.55 ± 0.091 (5.87%)
Peripheral volume of distribution (V_P, L)	1.66 ± 0.0946 (5.70%)
Inter-compartmental permeability flow (PS_D, L/d)	0.463 ± 0.0698 (15.1%)
Absorption rate constant for Product Type D (k_a, d^{-1})	0.295 ± 0.015
SC Bioavailability of Product Type D (%)	68.9 ± 3.65

Source: [ACZ885 SJIA PPK Modeling Report-Table 9-1 and Table 9-2]

The individual ("posthoc") parameter estimates for canakinumab that were not shrunk to the mean were summarized for SJIA patients. The summary of individual parameters stratified by age and bodyweight were presented in the two tables below.

Table 11. Summary of Individual Parameters Across Stratified Age Group for SJIA Patients

Table 9-8 Summary of Individual Parameters Across Stratified Age Group for SJIA Patients

GROUP	Age 2-3	Age 4-5	Age 6-11	Age 12-19	ALL
N	24	40	86	51	201
PARM	CLD [L/day/kg]				
MEAN	0.005	0.005	0.004	0.004	0.005
STD	0.002	0.002	0.002	0.002	0.002
%CV	34.35	44.09	40.94	42.59	42.29
MEDIAN	0.004	0.005	0.004	0.004	0.004
MIN	0.002	0.002	0.002	0.002	0.002
MAX	0.007	0.012	0.010	0.009	0.012
2.5P	0.002	0.003	0.002	0.002	0.002
97.5P	0.007	0.010	0.009	0.008	0.009
PARM	VD [L/kg]				
MEAN	0.038	0.045	0.045	0.058	0.047
STD	0.011	0.017	0.015	0.026	0.019
%CV	27.59	36.77	33.30	45.10	40.68
MEDIAN	0.039	0.043	0.041	0.052	0.043
MIN	0.020	0.026	0.019	0.025	0.019
MAX	0.064	0.108	0.090	0.131	0.131
2.5P	0.021	0.027	0.024	0.027	0.024
97.5P	0.056	0.076	0.077	0.128	0.099
PARM	CLL [L/day/kg]				
MEAN	0.461	0.531	0.325	0.186	0.347
STD	0.340	0.386	0.232	0.138	0.292

GROUP	Age 2-3	Age 4-5	Age 6-11	Age 12-19	ALL
N	24	40	86	51	201
%CV	73.72	72.75	71.49	74.26	84.13
MEDIAN	0.382	0.435	0.266	0.130	0.269
MIN	0.143	0.070	0.014	0.024	0.014
MAX	1.509	1.927	1.046	0.741	1.927
2.5P	0.176	0.131	0.040	0.053	0.054
97.5P	1.397	1.248	0.933	0.424	1.156
PARM	RLI [ng/day/kg]				
MEAN	0.591	0.711	0.458	0.237	0.468
STD	0.623	0.661	0.470	0.194	0.510
%CV	105.43	92.99	102.65	81.87	109.04
MEDIAN	0.398	0.412	0.298	0.168	0.307
MIN	0.101	0.108	0.042	0.023	0.023
MAX	3.173	2.866	2.410	0.980	3.173
2.5P	0.148	0.124	0.073	0.060	0.064
97.5P	2.236	2.729	1.913	0.748	2.006
PARM	KD [nM]				
MEAN	1.575	1.563	1.593	1.505	1.563
STD	0.552	0.575	0.610	0.435	0.554
%CV	35.08	36.81	38.30	28.89	35.42
MEDIAN	1.502	1.490	1.525	1.507	1.502
MIN	0.647	0.463	0.178	0.486	0.178
MAX	3.010	3.003	3.752	3.164	3.752
2.5P	0.648	0.646	0.454	0.693	0.488
97.5P	2.901	2.921	3.131	2.419	3.007

Due to high shrinkage, other parameters are not presented.

Table 12. Summary of Individual Parameters Across Stratified Bodyweight for SJIA Patients

GROUP	WGT ≤ 40 kg	WGT > 40 and ≤ 70 kg	WGT > 70 kg	ALL
N	149	39	13	201
PARM	CLD [L/day/kg]			
MEAN	0.005	0.004	0.003	0.005

GROUP	WGT ≤ 40 kg	WGT > 40 and ≤ 70 kg	WGT > 70 kg	ALL
N	149	39	13	201
STD	0.002	0.002	0.001	0.002
%CV	40.64	39.92	42.77	42.29
MEDIAN	0.005	0.003	0.003	0.004
MIN	0.002	0.002	0.002	0.002
MAX	0.012	0.009	0.006	0.012
2.5P	0.002	0.002	0.002	0.002
97.5P	0.010	0.008	0.006	0.009
PARM	VD [L/kg]			
MEAN	0.045	0.054	0.061	0.047
STD	0.015	0.022	0.037	0.019
%CV	34.22	41.47	60.36	40.68
MEDIAN	0.042	0.046	0.040	0.043
MIN	0.019	0.025	0.026	0.019
MAX	0.108	0.125	0.131	0.131
2.5P	0.023	0.028	0.028	0.024
97.5P	0.078	0.120	0.130	0.099
PARM	CLL [L/day/kg]			
MEAN	0.412	0.172	0.122	0.347
STD	0.305	0.132	0.103	0.292
%CV	73.94	77.02	83.99	84.13
MEDIAN	0.333	0.130	0.105	0.269
MIN	0.014	0.036	0.024	0.014
MAX	1.927	0.741	0.426	1.927
2.5P	0.075	0.063	0.033	0.054
97.5P	1.202	0.400	0.358	1.156
PARM	RLI [ng/day/kg]			
MEAN	0.557	0.234	0.151	0.468
STD	0.556	0.208	0.112	0.510
%CV	99.78	88.83	74.09	109.04
MEDIAN	0.357	0.165	0.136	0.307
MIN	0.042	0.061	0.023	0.023
MAX	3.173	0.980	0.430	3.173
2.5P	0.096	0.063	0.034	0.064

GROUP	WGT ≤ 40 kg	WGT > 40 and ≤ 70 kg	WGT > 70 kg	ALL
N	149	39	13	201
97.5P	2.287	0.761	0.390	2.006
PARM	KD [nM]			
MEAN	1.565	1.541	1.598	1.563
STD	0.558	0.560	0.520	0.554
%CV	35.65	36.32	32.56	35.42
MEDIAN	1.497	1.507	1.572	1.502
MIN	0.384	0.178	0.977	0.178
MAX	3.384	3.752	3.164	3.752
2.5P	0.574	0.470	1.040	0.488
97.5P	3.004	2.509	2.768	3.007

Due to high shrinkage, other parameters are not presented.

Model- based predictions

Simulated Steady-state Exposure of Canakinumab in SJIA population

Using the individual post-hoc estimates of the PK parameters (eg, CLD, VD, VP), individual estimates of steady-state exposure of area under the plasma concentration-time curve (AUCss), peak (CMAXss) and trough (CMINss) concentrations were simulated using the population based PK-Binding model for only the SJIA patients pooled from the Phase2a (A2203) and Phase3 (G2305, G2301, G2301E1) studies.

The model prediction showed comparable exposures across the different age groups where their overall average (±SD) for CMINss, CMAXss and AUCss were 14.68±8.80 µg/mL, 36.50±14.92 µg/mL and 696.09±326.55 µg*day/mL, respectively.

A higher median of exposure for CMINss (19 versus 11.4 µg/ml) and AUCss (880 versus 594 µg*day/mL) for the higher bodyweight group (> 40 kg) than lower bodyweight group (≤ 40 kg) was observed.

Absorption and absolute bioavailability

After single dose s.c. administration of canakinumab, peak serum levels were reached by approximately 2 days.

The absolute bioavailability of canakinumab after s.c. administration was estimated using population PK-binding model. The rate and extent of absorption were independently estimated for the 4 product types (see table below), with product D as the current available marketed drug. Bioavailability and absorption rate constants of the product types were similar, ranging from 62-72% and 0.25-0.30 d-1, respectively. The absolute bioavailability of canakinumab (mean ± SE) for Product Types A, B, C, D were 62.2 ± 3.72, 64.1 ± 3.49, 72.5 ± 3.83, and 68.9 ± 3.65%, respectively. Based on the relative bioavailability of D/C of 0.95 ± 0.002 (mean ± SEM), it can be concluded that there is no apparent difference in the two product types.

Table 13. Absorption rate and bioavailability parameters for all product types (mean ± SE) based from their typical values

Parameter [units]	Product Type A	Product Type B	Product Type C	Product Type D
Logit bioavailability	0.499 ± 0.159	0.578 ± 0.152	0.968 ± 0.192	0.796 ± 0.171
Bioavailability (%)*	62.2 ± 3.72	64.1 ± 3.49	72.5 ± 3.83	68.9 ± 3.65
Relative bioavailability*		0.984 ± 0.0653 (B/A)	1.114 ± 0.0238 (C/B)	0.952 ± 0019 (D/C)
Absorption rate constant (k_a, 1/d)	0.252 ± 0.017	0.244 ± 0.027	0.213 ± 0.016	0.295 ± 0.015

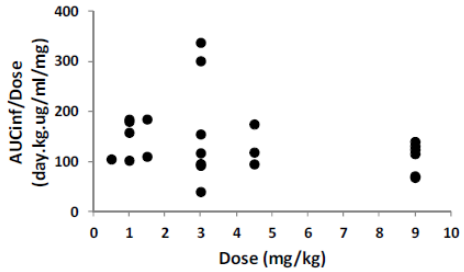
*Logit transformation: F = exp(X)/(1+exp(X))

The s.c. bioavailability estimates of canakinumab of approximately 60-70% is comparable to the bioavailability estimates of other IgG monoclonal antibodies.

Dose proportionality and time dependencies

Canakinumab exhibited dose proportionality in CAPS patients. In Study A2203, sJIA patients received s.c. administration of 0.5, 1.0, 1.5, 3.0, 4.5 or 9.0 mg/kg canakinumab and PK parameters were obtained by non-compartmental analysis. As shown in Figure 3-2, dose normalized AUCinf values remained unchanged with increasing dose within the dose range studied. Thus, dose proportionality can also be concluded for the sJIA population.

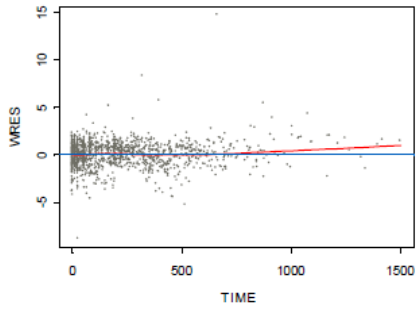
Figure 6. Canakinumab dose proportionality in SJIA patients [A2203]



There was no indication of changes in canakinumab pharmacokinetic properties over time as supported by the population PK-binding model. Single dose pharmacokinetics of canakinumab in SJIA subjects was studied in A2203 whereas only sparse samples were collected from multiple dose phase III clinical studies. While a direct comparison is not possible, the AUC0-inf value after single dose obtained from A2203 study based on fewer subjects are comparable to the steady state AUCtau obtained from the

PopPK analysis. Figure 3-3 shows a plot of the weighted residuals versus time for canakinumab following multiple dosing from the population PK-binding model, with the assumption of time-invariant PK. The values were randomly distributed around zero value and show no directional shift, suggesting the time-independent PK assumption in the model is valid. This is consistent with the results reported in the original CAPS submission.

Figure 7. Weighted Residual versus time: Single dose and multiple dose in SJIA



Source: [ACZ885 SJIA PPK modeling Report, Figure 10-1]

Special populations

Patients versus healthy subjects

The pharmacokinetic parameters of canakinumab in SJIA patients and from various other patient population and healthy subjects were estimated by the PK-binding model.

The clearance of canakinumab was not overly impacted by patient population or disease. There was little difference between the SJIA clearance and that of other patient populations; at most 10-24% difference for non-Japanese healthy volunteer (slower clearance) and Rheumatoid Arthritis (higher clearance).

Gender

A total of 111 female and 90 male subjects were included in SJIA clinical studies. No gender-related difference was observed in any of the PK parameters of canakinumab after correction for body weight.

Race

A total of 6 Asians, 9 black, 173 Caucasians and 13 others were included in SJIA clinical studies. While the number of patients from other races was small, there was no indication of race effect on PK parameters.

Body Weight

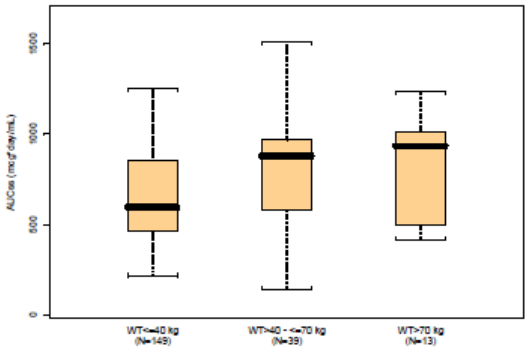
Clearance is the main parameter of interest as it is the determinant of overall systemic exposure (AUC=F*DOSE/CL). It is known that clearance increased with body weight based on the principle of allometry and provides a rational for bodyweight-based dosing to ensure comparable exposures (AUC) in patients with broad range of bodyweights.

Serum clearance of canakinumab and its volumes of distribution were dependent on body weight in an allometric relationship. The exponent was approximately 0.823 ± 0.0367 for clearance with a formula CLD = 0.106× (BW/33 kg)$^{0.823}$.

Canakinumab clearance versus body weight relation has the allometric exponent of 0.823 (95% CI: 0.751 – 0.895), which is less than 1. While the effect of body weight can be eliminated by body weight based dosing if the allometric exponent is equal to one, the effect of body weight on canakinumab pharmacokinetics was nonetheless minimized when the dose was given on body weight basis, with only

a slightly lower body-weight normalized clearance at higher body weight. When stratified by weight, a higher exposure was observed for AUCss for the higher bodyweight group (>40 kg) (see figure below). However, it must be noted that the range of exposures overlap entirely with each other.

Figure 8. Steady-state exposures of canakinumab for SJIA patients stratified by bodyweight



Source: [ACZ885 SJIA PPK Modeling Report-Figure 5-5]

Age

SJIA patients from all four SJIA clinical trials were included to assess the PK exposure across the age group of 2- <20 years. Thus the database in the PK-binding model included 201 SJIA patients, out of which 24 were of age 2-3, 40 subjects were age 4-5, 86 were between 6-11, and 51 were 12 and above. Demographic data for SJIA studies are summarized in the table below.

Table 14. Demographic data for SJIA studies

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)	37.9 ± 4.6 (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 will not match the total from each of the individual SJIA studies

Source: [ACZ885 SJIA PPK Modeling Report, Table 3-1]

The key pharmacokinetic parameters such as canakinumab clearance and volume of distribution were plotted by age after correction for the subject's body weight.

The body-weight normalized canakinumab clearance showed a slight trend when plotting versus age across different disease indications containing adult populationor in SJIA pediatric studies alone. No significant difference can be found in exposure as represented by AUCss across all the age groups from 2 to <20 years old, including age group 2 to <4.

Impaired renal function

There were no severely renal impaired subjects included in the SJIA studies. Since canakinumab is a human IgG immunoglobulin with large molecular size (~150 kDa), little intact immunoglobulin can be filtered by the kidney, hence little antibody is expected to be excreted in the urine.

In CAPS, clearance values of four subjects with moderate to end stage renal insufficiency were similar to mean clearance values in patients with normal renal function [SCPS original CAPS submission].

In gout, the mean serum clearance of canakinumab was found to be 16% and 22% lower for gouty arthritis patients with mild (CrCl: 50–80 mL/min) and moderate (CrCl: 30–<50 mL/min) renal impairment, respectively, than in those with normal renal function (CrCl > 80 mL/min).

Impaired hepatic function

No formal study has been performed with canakinumab in patients with impaired hepatic function as it is known that the majority of IgG elimination occurs via intracellular catabolism, following fluid-phase or receptor medicated endocytosis.

Pharmacokinetic interaction studies

No formal clinical drug interaction studies or in vitro metabolism/drug interaction studies between canakinumab and other medicinal products have been performed. Since macromolecules such as canakinumab are primarily eliminated via intracellular catabolism, the effect of drug interactions through cytochrome P450 system on pharmacokinetics of canakinumab is not expected.

It is reported that the synthesis of CYP450 enzymes is suppressed by increased levels of cytokines (e.g., IL-1, IL-6, TNF-alpha) during chronic inflammation (Aitken and Morgan 2007, Sunman et al 2004, Chaluvadi et al 2009). Anti-cytokine antibodies such as canakinumab that target and neutralize these proinflammatory cytokines or their receptors are capable of restoration of CYP450 enzymes to normal levels (Ashino et al 2007). This is clinically relevant for CYP450 substrates with a narrow therapeutic index where the dose is individually adjusted. On initiation of canakinumab in patients being treated with this type of medicinal product, therapeutic monitoring of the effect or of the active substance concentration should be performed and the individual dose of the medicinal product adjusted as necessary.

2.3.3. Pharmacodynamics

Mechanism of action

Canakinumab binds with high affinity specifically to human IL-1 beta and neutralises the biological activity of human IL-1 beta by blocking its interaction with IL-1 receptors, thereby preventing IL-1 beta-induced gene activation and the production of inflammatory mediators.

Primary pharmacology

Canakinumab binding to human IL-1β results in the formation of a canakinumab-IL-1β complex. As the complex is cleared slower than the free IL-1β, an increase in total IL-1β is observed indicating successful binding, which is observed in SJIA patients measured from all SJIA clinical trials.

The binding parameters were estimated by the PK-binding model and reported below as mean ± SEM (see table below). The clearance of IL-1β was calculated to be 6.22 L/day in SJIA patients, with a terminal half-life of 4.2 days. The production rate of IL-1β is 8.05 ± 0.913 ng/day. The ability of canakinumab to bind to IL- 1β is captured by the apparent in vivo dissolution constant, Kd, with a population estimate of 1.5 ± 0.264 nM.

PD parameter estimates of canakinumab in SJIA patients

Parameter [units]	mean ± SEM (%RSE)
Clearance for ligand (CL_L, L/d)	6.22 ± 0.907 (14.6%)
Production rate of ligand (R_{LI}, ng/d)	8.05 ± 0.913 (11.3%)
Binding constant (K_d, nM)	1.5 ± 0.264 (17.6%)

Source: [ACZ885 SJIA PPK Modeling Report, Table 9-1]

The clearance of IL-1β was substantially (75-302%) higher in all other indications than that in SJIA, while the IL-1β production rate (RLI) in all other indications was in general lower than that in SJIA by 0.5 – 40%. Specifically, the IL-1β clearance was 75.5% higher in CAPS than that in SJIA, and the production rate in CAPS was only 22% higher (see table below). The slower clearance and higher production rate of IL-1β in SJIA is considered by the applicant to indicate the possible need for a higher dose.

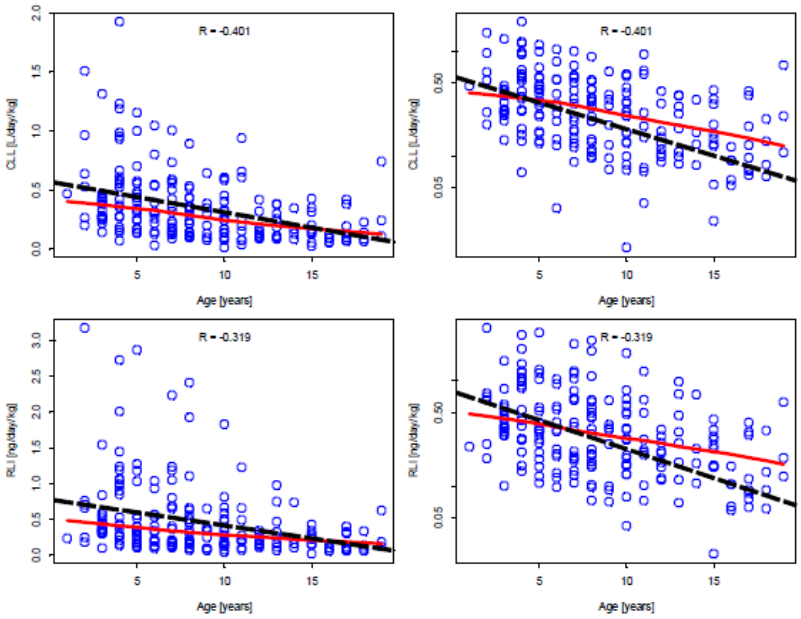
Table 15. Deviation of PD Parameters from SJIA Patients for Other Study Populations (displayed as percentage of SJIA Typical Value)

	CL_L (%)	R_{LI} (%)
Healthy Volunteers, Japanese	231 ± 81.9	-40.1 ± 6.19
Healthy Volunteers, Non-Japanese	159 ± 73.2	-37.8 ± 7.26
Asthma	302 ± 97.9	-24.0 ± 9.0
Rheumatoid Arthritis	177 ± 39.3	-29.9 ± 13.4
CAPS	75.5 ± 26	22.4 ± 14.9
Psoriasis	177 ± 73.9	-12.3 ± 14.0
Gouty Arthritis	83.9 ± 27.1	-0.51 ± 10.7

Source: [ACZ885 SJIA PPK Modeling Report, Table 9-5]

The figure below shows the relationship between age and the body weight normalized IL-1β clearance, as well as the IL-1β production rate. There is a modest trend of higher IL-1β production rate (RLI) and clearance (CLL), resulting a modest higher overall turnover of IL- 1β in younger children.

Figure 9. Body weight normalized IL-1β production rate and clearance by age



Top Row: Linear (left) and log (right) scale of normalized bodyweight IL-1β clearance.
Bottom Row: Linear (left) and log (right) scale of normalized bodyweight IL-1β production rate. Solid red line is loess smooth line and dotted line is linear regression fitting.

Source: [ACZ885 SJIA PPK Modeling Report - Figure 5-3]

Secondary pharmacology

Influence on other biomarkers

No information is given whether determinations of other biomarkers than IL-1ß were conducted in the sJIA studies.

During the single dose study in the CAPS population the soluble serum biomarkers TNFa, IL-6, IL-1ra (IL-1 receptor antagonist), sIL-1R (soluble IL-1 receptor) and sCTX (C-terminal cross-linking telopeptide of type I collagen) had been determined in order to explore the influence of IL-1ß blockade

on other cytokines/biomarkers involved. It was observed that IL-6 and IL-1ra returned from high baseline levels to the normal range and remained within normal limits during the long lasting clinical response, while levels of IL-1R, TNF-alpha and sCTX did not change.

During the pivotal CAPS study (CACZ885D2304) also IL-1ra and IL-6, and additionally IL-18, MMP-1 and MMP-3 were measured: In Part I (single SC dose of 150 mg), IL-6 levels tended to decrease following the first injection with canakinumab. In Part II of the study, IL-6 levels tended to remain low in the canakinumab treatment group, while in placebo treated group, levels of this cytokine tended to rise. IL-1ra and IL-18 levels did not change in Parts I and II. Data on MMP-1 and MMP-3 were too sparse at the time of this report to allow analysis.

Influence on effectiveness of vaccination

The use of live vaccines was prohibited in the SJIA studies. Study A2106 (previously submitted in gouty arthritis dossier) evaluated the efficacy of influenza and meningococcal vaccination in healthy adult volunteers exposed to canakinumab 300 mg s.c. This study found no effect of canakinumab administration on development of antibody response after vaccination. The ongoing study D2307 is evaluating the protective antibody levels following immunization with inactivated (killed) vaccines, and the safety of canakinumab with concomitant vaccination in children aged ≤4 years with CAPS. The planned actions highlight routine pharmacovigilance activities resulting in the cumulative review in each PSUR.

Pharmacodynamic interactions with other medicinal products

Canakinumab binds to and neutralizes the activity of human IL-1β, a proinflammatory cytokine. Hence, any other biologic drugs targeting the immune system (for example, TNF blockers, anakinra, rituximab, abatacept, tozilizumab) may lead to a synergistic immune suppression. Therefore, concomitant therapy with such biologics is prohibited.

Immunogenicity

Canakinumab is a human recombinant protein. The potential for development of antibodies to canakinumab has been assessed in SJIA clinical studies and the results are summarized in this section.

Anti-canakinumab antibodies (ADAs) were tested in serum of pediatric patients following single or multiple administrations of canakinumab. Assessments were done at multiple time points during the treatment phase depending on the study design but always included a baseline pre-dose measurement, and an end of study sample. Collection of additional samples in case of anaphylaxis was implemented in all the SJIA clinical study protocols. A sample for measurement of canakinumab concentration was taken concomitantly with the one for testing immunogenicity to facilitate correct interpretation of the immunogenicity data.

Results across the studies

In the SJIA population, a total of 14 unique patients had anti-canakinumab antibodies detected in at least 1 sample out of 196 patients in SJIA clinical program who contributed to immunogenicity testing. Of these 14 patients, 8 had anti-canakinumab antibodies only at baseline, while 6 had post-treatment anti-canakinumab antibodies, representing an incidence of 3.1% (6/196) of positive anti-canakinumab antibodies in canakinumab treated SJIA patients. None of the patients had neutralizing antibodies.

Of the 6 patients who had post-treatment anti-canakinumab antibodies, only one patient met definition of persistent positive immunogenicity and in this patient there was no evidence of loss of efficacy or reported allergy/hypersensitivity AE. This patient also had negative anticanakinumab antibody testing afterwards with continued canakinumab dosing.

There was no evidence of change of drug levels, IL-1β binding or loss of efficacy in any of the 6 post-treatment immunogenicity positive patients. One SJIA patient with post-treatment anti-canakinumab antibodies had an AE (mild eyelid edema) suggestive of hypersensitivity within a plausible time to onset. This AE was successfully treated with an antihistamine and the patient remained in the study without clinical relapse and no antibodies detected afterwards upon re-treatment. No anaphylactic or anaphylactoid reactions or SAE related to immunogenicity were reported. AEs potentially related to immunogenicity were mostly mild and were mainly injection site reactions, rash and urticaria events which did not recur upon redosing with canakinumab. There was no evidence of immune-related loss of efficacy either by direct antibody detection or by indirect evidence of decreased canakinumab levels or target binding.

In addition to the SJIA integrated immunogenicity analysis, a similar report was written about analysis performed in the canakinumab CAPS and Gouty arthritis clinical programs. The incidence of positive anti-canakinumab antibodies was 3/194 (1.5%) in CAPS and 17/799 (2.1%) in Gouty arthritis. In the immunogenicity report, information on relationships between immunogenicity, PK and IL-1β binding, and safety and efficacy in these patient populations is also reported

In summary, canakinumab showed low immunogenicity. The incidence of treatment related anti-canakinumab antibodies was 3.1% in SJIA patients. No patient had neutralizing antibodies. In one case the presence of anti-canakinumab antibodies was linked to a mild hypersensitivity AE. No anaphylactic or anaphylactoid reactions or SAE related to immunogenicity were reported.

2.3.4. PK/PD modelling

Exposure-efficacy relationship

PK-flare model for dose selection

Exposure-efficacy response relationship was initially explored in SJIA patients in study A2203. A non-linear mixed effect PK-flare model was fitted to the Phase II data. The PK-flare model establishes a relationship between drug concentrations (exposure) and primary clinical manifestation of the disease-that is a flare. The PK-flare model allowed estimation of the critical flare concentration, *Ki*, at which there is a 50:50 probability of clinical relapse (flare) and was determined to be 2 µg/mL (74% CV).

The PK-flare model was used to perform simulations for the probability of relapse (flare) for SJIA patients given doses from 1-7 mg/kg administered s.c.. The metric was the proportion of patients relapsing (flaring) at the end of 4 weeks (Table 3-6). At a dose of 4 mg/kg s.c., the median percentage of patients predicted to relapse within 4 weeks was estimated at 6% (95% CI, 1–21%). The median percentage of patients predicted to relapse at 3 mg/kg or 2 mg/kg was approximately 11% or 18%, respectively. The incremental efficacy gain between 4 and 7 mg/kg was not considered large enough considering the wide confidence intervals to justify higher dosing.

Based on these data, a fixed dose regimen of monthly canakinumab at 4 mg/kg up to a maximum 300 mg s.c. injection was chosen as the recommended dose, to ensure low probability of relapse in majority of patients.

Table 16. Projected percent of patients relapsing by 4 weeks post single dose in Study A2203

Dose	% Patients relapsing	
	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

Projections were calculated by simulating 100 trials with 100 patients per trial using the PK-flare model, then summarizing the range of results. The simulations included both variability between patients and the uncertainty (SEM) in the estimates of the PK and flare parameters

Source: [Study A2203 Modeling Report-Table 5-1]

Simulated Concentration of Canakinumab at the Visit Time of Flare in SJIA Patients

Simulated concentrations of canakinumab at flare for the combined SJIA pooled studies showed a wide distribution ranging from 0 to 41µg/mL, with the median predicted concentration centered at 5.8 µg/mL.

There is a statistical difference (p-value < 0.0001, unpaired t-test) in the concentration at flare versus no flare.

The predicted mean concentration at flare for combined SJIA pooled studies was determined to be 8.1 ± 9.1 µg/mL (112% CV) whereas predicted mean concentration at no flare was 14.5 ± 10.4 µg/mL (72% CV). Comparison across the different studies showed differences in the mean predicted concentration at flare for studies 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).

Examination of the mean predicted trough concentration at flare in all SJIA studies or for only the Phase 3 studies with and without exclusion of LLOQ was statistically significant from the mean predicted trough concentration at no flare (Phase 3 studies: 13.1 ± 8.68 µg/mL (flare) vs 16.9 ± 9.53 µg/mL (no flare); p-value < 0.0001).

Table 17. Summary of Canakinumab Concentration at Flare and No Flare for Different SJIA Studies

STUDY	A2203*		G2305*		G2301*		G2301E1*		SJIA POOL*		PHASE3 ONLY*	
FLARE	YES	NO	YES	NO	YES	NO	YES	NO	YES	NO	YES	NO
N	132	528	34	47	94	1374	77	1125	337	3074	205	2546
MEAN	4.77	7.27	0.53	9.31	11.59	14.94	12.93	17.58	8.11	14.50	10.26	16.00
STD	7.48	8.94	1.77	5.80	9.29	10.83	8.78	8.81	9.08	10.39	9.38	10.04
%CV	156.9	123.0	336.6	62.3	80.2	72.5	67.9	50.1	112.0	71.7	91.4	62.7
MEDIAN	1.26	3.86	0.00	9.52	10.30	14.17	10.66	16.08	5.76	13.11	8.86	14.76
MIN	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.09	0.00	0.00	0.00	0.00
MAX	37.77	52.85	7.99	21.11	40.76	65.91	39.36	58.33	40.76	65.91	40.76	65.91
2.5P	0.01	0.15	0.00	0.00	0.00	0.00	0.00	4.67	0.00	0.01	0.00	0.01
97.5P	28.46	33.07	5.55	20.00	34.10	40.75	34.63	38.05	33.33	38.84	34.37	39.35
p-value	0.0032		0.0001		0.0035		0.0001		0.0001		0.0001	

Reanalyzed Excluding LLOQ Values (< 0.2 ug/mL)

STUDY	A2203*		G2305*		G2301*		G2301E1*		SJIA POOL*		PHASE3 ONLY*	
FLARE	YES	NO	YES	NO	YES	NO	YES	NO	YES	NO	YES	NO
N	114	506	3	39	84	1241	74	1125	275	2911	161	2405
MEAN	5.51	7.58	5.96	11.22	12.97	16.54	13.45	17.58	9.93	15.31	13.06	16.94
STD	7.80	9.00	1.76	4.33	8.87	10.18	8.55	8.81	9.11	10.08	8.68	9.53
%CV	141.7	118.8	29.6	38.6	68.4	61.6	63.6	50.1	91.7	65.9	66.4	56.3
MEDIAN	1.95	4.10	5.03	10.63	10.96	15.50	10.82	16.08	8.30	13.83	10.83	15.69
MIN	0.20	0.20	4.86	3.60	0.28	0.20	1.41	1.09	0.20	0.20	0.28	0.20
MAX	37.77	52.85	7.99	21.11	40.76	65.91	39.36	58.33	40.76	65.91	40.76	65.91
2.5P	0.25	0.29	4.87	3.70	0.40	0.56	3.31	4.67	0.29	0.57	0.99	1.11
97.5P	30.09	33.28	7.84	20.24	34.58	41.04	34.73	38.05	34.53	39.32	34.72	40.38
p-value	0.0235		0.0448		0.0018		0.0001		0.0001		0.0001	

*Statistically significant (p-value < 0.05) by unpaired t-test for predicted concentration at flare versus no flare. N represents the total number of flare or no flare records. Assessment for flare (and/or no flare) is usually at each study visit before dose administration subsequently is trough measurement except in A2203 that considered dosing upon relapse as flares.

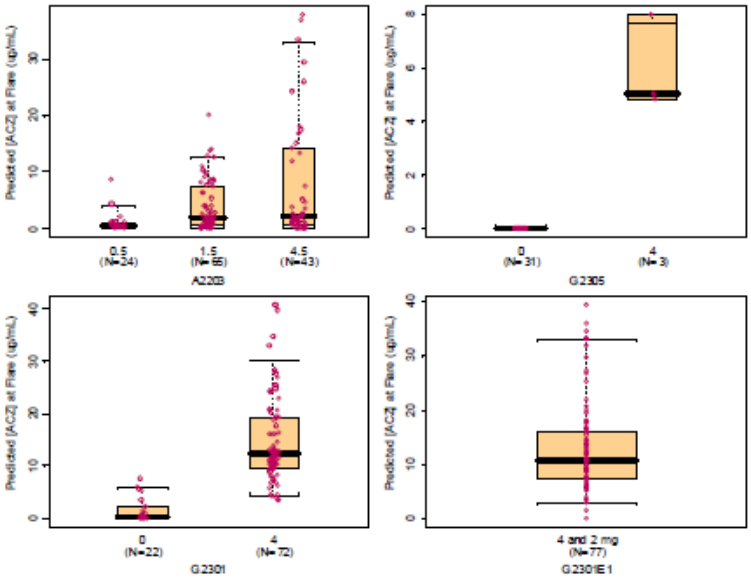
Note: Bottom table excludes LLOQ values (< 0.2 µg/mL). "SJIA POOL" summarizes results combining all SJIA studies whereas "PHASE3 ONLY" excludes Phase2a dose-ranging A2203 study due to differences in sample collections for flare and no flare. Subjects in G2305 are randomized to either placebo or 4 mg/kg canakinumab treatment group. Subjects in G2301 and G2301E1 are initially treated on 4 mg/kg.

Script: CACZ885G/pool/pkpd_002/Splus/sjia/scripts/SumStat-PKFLARE.ssc

Source: CACZ885G/pool/pkpd_002/nonmem/SJIAsubm/PKBIND02/simulation/PKFLARE-03b/exports/ → FlareExposureSummStat.csv

To further understand how the exposures of canakinumab for the different SJIA studies may prevent flares, the figure below subsets each study by treatment arms.

Figure 10. Comparison of Predicted Concentration at Flare by Treatment for Different SJIA Studies



Top panel is boxplots of A2203 (left) dose-ranging study with 0.5, 1.5 and 4.5 mg/kg of canakinumab treatment whereas G2305 (right) is a double-blind study where subjects are randomized to either placebo (no canakinumab –"0") or treated arm (4 mg/kg canakinumab –"4").

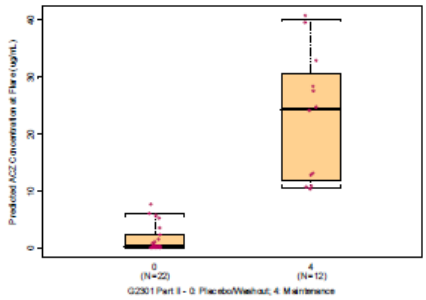
Bottom panel is G2301 (left) study where subjects enrolled are maintained on 4 mg/kg canakinumab in part I with the possibility in part II to be randomized to the placebo arm. G2301E1 (right) is the long-term extension study where some subjects could reduce canakinumab dose from 4 mg/kg to 2 mg/kg during the course of the trial.

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. Points are the individual estimated predictions. N represents the total number of flare records. Assessment for flare (and/or no flare) is usually at each study visit before dose administration subsequently is trough measurement except in A2203 that considered dosing upon relapse as flares.

For G2305 efficacy study where SJIA patients are randomized to either placebo or 4 mg/kg s.c of canakanimab, a difference in trough concentration at flare versus no flare is observed. Higher incidence of flares in the placebo group is seen (31 total number of flares vs 3 total number of flares in canakinumab treatment). Similar findings were seen for G2301 for those treated and randomized to placebo group.

Further separation of part I and part II in G2301 was done where Figure 5-10 shows a boxplot of only G2301 Part II for placebo versus maintenance; a 2-fold higher incidence of flares occurred in comparison to the treated group maintained on 4 mg/kg of canakinumab. The predicted trough concentration at flare for the placebo group (or washout period) in part II of G2301 showed majority of subjects with an estimated null canakinumab concentration at flare. Estimated mean trough concentration at flare for Part II of G2301 excluding LLOQ (see table below) was statistically different from the mean predicted trough concentration at no flare (12.9 ± 13 µg/mL vs 18.1 ± 12.3 µg/mL).

Figure 11. Predicted Flare Concentration at Trough in G2301 Part II by Treatment



Subjects in part II of G2301 are randomized to either maintained on 4 mg/kg of canakinumab ("4") or placebo ("0"). 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. Points are the individual estimated predictions. N represents the total number of flare records. Assessment for flare is usually at each study visit before dose administration subsequently is trough measurement.

Table 18. Summary of Canakinumab Trough Concentration at Flare and No Flare for G2301 Part II: Prevention of Flare

	All Part II		Exclude LLOQ	
FLARE	YES	NO	YES	NO
N (LLOQ)	34 (10)	707 (133)	24 (0)	574 (0)
MEAN	9.12	14.70	12.90	18.09
STD	12.40	13.20	13.02	12.38
%CV	135.98	89.81	100.92	68.42
MEDIAN	2.87	15.03	8.96	18.72
MIN	0.00	0.00	0.28	0.20
MAX	40.76	65.41	40.76	65.41
2.5P	0.00	0.00	0.28	0.33
97.5P	39.77	44.75	40.07	45.88
p-value	0.0160		0.0451	

Statistically significant (p-value < 0.05) by unpaired t-test for predicted concentration at flare versus no flare between individual parts in G2301. PartII: randomized to maintenance (4 mg/kg of canakinumab) or placebo (washout). N refers to total number of flare or no flare records collected. Assessment for flare (and/or no flare) is usually at each study visit before dose administration subsequently is trough measurement. Lower limit of quantitation (LLOQ) refers to the number of LLOQ (<0.2 µg/mL) samples.

Stratifying by age and bodyweight group, the predicted concentration of canakinumab at the visit time for the assessment of flare was comparable among the groups ranging from 7 to 13 µg/mL.Assuming this predicted concentration of canakinumab at flare (ranging from 7 to 13 µg/mL) is a closer value of Ki at steady-state, sufficient exposure is covered by 4 mg/kg s.c dosage. The average steady-state trough and peak level for canakinumab in SJIA patients are 15 µg/mL and 37 µg/mL, respectively. Subsequently, 4 mg/kg s.c admininstered every 4 weeks maintained steady-state trough levels above predicted concentration at flare.

In conclusion, the few flares that do occur are expected as the PK-Flare model had projected at 4 mg/kg s.c dose, a 6% probability of relapse to take place. More than 95% of subjects administered 4 mg/kg s.c dose of canakinumab had their steady-state trough levels above the previous estimated *Ki*.

Simulated Concentration of free IL-1ß at the Visit Time of Flare in SJIA Patients

It is interesting to note that those that do flare, not only have lower concentration of canakinumab but also slightly higher predicted level of free IL-1β than that predicted at no flare. This was a consistent trend observed in all SJIA studies.

Predicted free IL-1β at flare were comparable across the age groups with median value of 0.87 pg/mL suggesting minimal difference in IL-1β level at the concentration at flare. Of note, the lower bodyweight group (≤ 40 kg) had a 20% higher predicted free IL-1β for both flare and no flare.

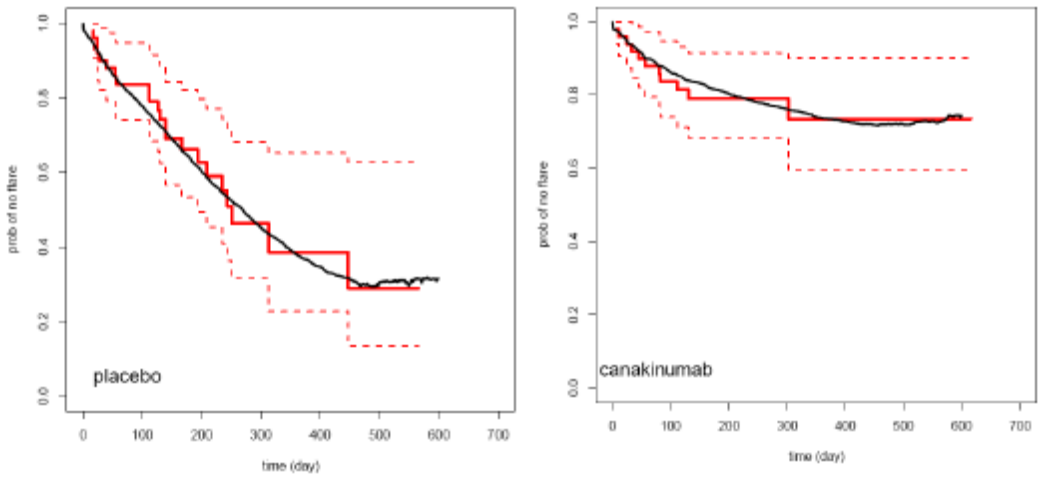
PK-hazard model based on G2301 part II data

The exposure- efficacy response analysis of canakinumab in SJIA patients were performed with the data from G2301 Part II. The analysis was to assess whether 4 mg/kg every 4 weeks dosing regimen is appropriate for SJIA patients and provided insights into where this dose (4 mg/kg every 4 weeks) lies within the broader dose response relationship.

Study G2301 Part II employed a withdrawal design for patients randomized to placebo (see above). Together with the patients in canakinumab arm, the data set provided a wide range of canakinumab concentrations that enabled estimation of an exposure-flare reduction relationship. The incidents of flare in Study G2301 part II were modeled as a time-varying (non-homogeneous) Poisson process, implemented as a discrete hazard model. Canakinumab was postulated to suppress the background hazard of flare in a concentration-dependent manner, with an inhibitory Emax model linking canakinumab concentration to the flare hazard reduction. In the discrete hazard model, the time-varying flare hazard function takes into account both the disease severity of a patient and the therapeutic effect from canakinumab, including the flare rate per week. For canakinumab exposure, the dosing history was used to calculate the weekly average canakinumab concentration of each patient using the PK binding model.

The final model was a heterogeneous background hazard model which reflected a small portion of high hazard patients. The model was able to capture the observed Kaplan-Meier curves of both the placebo and canakinumab arms well (Figure 3-8). The only significant covariate retained in the discrete hazard model were baseline steroid dose at the end of Part I of the study, no other covariates (age, daily steroid usage and baseline ACR strata) offered further improvement to the hazard model. In contrast to the pre-defined statistical analysis, the exposure-flare reduction relationship takes into account the protective effect of residual canakinumab concentrations for placebo patients during the initial period of the withdrawal design. This model-based analysis is potentially more sensitive than the pre-defined statistical analysis. The model demonstrates that canakinumab decreases significantly ($p<0.001$) the risk of flare with potentially full suppression in a concentration-dependent manner, where median IC50 was estimated to be 3.27 µg/ml (Range: 0.529-7.27 µg/ml).

Figure 12. Observed Kaplan-Meier and point-wise median of 500 simulated Kaplan-Meier curves or flaring for placebo (left) and canakinumab (right) base on the heterogeneous background hazard model



Red solid lines are observed Kaplan-Meier curves; red dashed lines are their 95% confidence intervals; Black solid lines are model predicted Kaplan-Meier curves.
Source: [ACZ885 SJIA Hazard Modeling Report -Figure 5-1]

Based on the final parameters estimated from the exposure-hazard model, simulations of canakinumab exposure-flare reduction relationship in SJIA was performed (see tables below). Trial simulations suggested that at the end of 12 months, the probability of flare was 63% (90% CI: 55% to 71%) for the placebo arm. For the treatment arms ranging from 1 mg/kg to 6 mg/kg canakinumab, the probabilities of flare were 37%, 30%, 26%, 24%, 22%, 21%. Specifically, 4 mg/kg dose reduces flare rate over placebo by 39% at the end of 12 months, consistent with the clinical observed data.

Greater than 4 mg/kg dose would provide only marginal gain in flare reduction over 6 and 12 months, while less than 4 mg/kg dose would significantly increase risk to experience a flare over 6 and 12 months. The results support 4 mg/kg as an appropriate dose in preventing flare events in patients.

Table 19. Model predicted flare rate by canakinumab dose in 6 months

Table 3-7	Model predicted flare rate by canakinumab dose in 6 months						
	Canakinumab dose (mg/kg)						
	0	1	2	3	4	5	6
Median rate	37%	26%	22%	20%	18%	16%	15%
90% CI	(29,44)%	(21,32)%	(17,27)%	(15,25)%	(13,23)%	(12,21)%	(11,20)%
% improvement over 4mg/kg	-103%	-44%	-23%	-11%	0%	10%	17%
odds ratio over 4mg/kg	2.626	1.601	1.294	1.139	1.000	0.879	0.804

Table 20. Model predicted flare rate by canakinumab dose in 12 months

Table 3-8	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

Source: [ACZ885 SJIA Hazard Modeling Report –Table 5-2 & Table 5-3]

Exposure-safety relationship

Potential relationships between canakinumab exposure and various adverse events as well as the clinically notable abnormalities in laboratory parameters were explored.

The analyses were based on the data from the canakinumab treatment groups in two Phase III studies in SJIA, Study G2305 and Study G2301 (Part I only). Canakinumab exposure was estimated by popPK binding model. The AE included in this analysis were abdominal pain, cough, headache, infection, MAS, pyrexia, SAE of infection, and vomiting; laboratory parameters were hemoglobin levels, platelet counts, absolute neutrophil counts or absolute WBC counts; as well as AST, ALT, estimated creatinine clearance and total cholesterol.

In the combined population of these 2 studies, patients received up to 8 s.c. doses of 4 mg/kg canakinumab, given at 4-week intervals. The total treatment duration was divided into 8 periods based on the timing of canakinumab administration, which allowed analysis of trends over time on treatment. Estimated canakinumab exposure data were available for 188 patients, although the number of patients declined over time. The average canakinumab concentration was lower in the early dosing periods since the time to steady state was approximately 110 days.

The distribution of the canakinumab exposure (average concentration) for subjects with and without adverse and laboratory abnormality event were displayed in each of Periods 1 to 8.

The average canakinumab concentration was similar between patients who had AEs and those who did not have AEs in each of the 8 studied dosing periods. In patients who experienced adverse events of abdominal pain, cough, headache, infection, MAS, fever, and vomiting, canakinumab concentrations were similar to those who did not have the events.

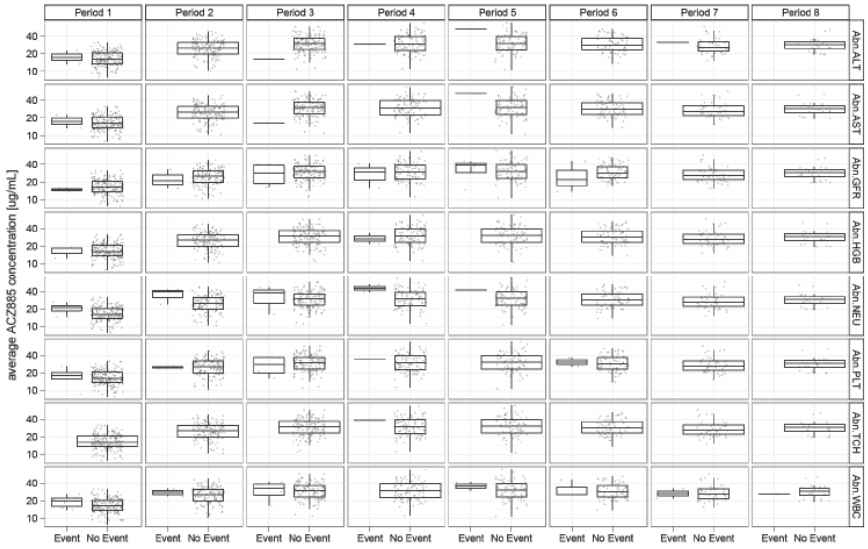
The relationship between canakinumab exposure and longitudinal incidence of events was graphically investigated by line plots presenting the time course of the individual estimated canakinumab concentration and the individual estimated canakinumab concentration at the time of first event (in the period) if any. AEs did not occur at peak canakinumab concentrations. This was also the case for infection SAEs. These findings suggest that there was no relationship between canakinumab

concentration and AEs, but should be interpreted cautiously given the small number of events in some cases.

Similarly, canakinumab concentrations in patients who had notable laboratory abnormalities (of liver function parameters ALT and AST; estimated creatinine clearance; hemoglobin levels, platelet counts or absolute WBC counts) were similar to those in patients without such abnormalities, and there was no particular trends with respect to the time course of canakinumab concentrations in patients with abnormalities. This suggests that there was no relationship between canakinumab concentration and these abnormal laboratory values.

Patients who had low neutrophil counts (post-baseline values of < 0.9 x LLN) had higher canakinumab concentrations than subjects who had neutrophil counts that remained within the normal range. This is consistent with a known pharmacodynamic effect of canakinumab.

Figure 13. Distribution of the individual average ACZ885 concentrations for subjects with and without laboratory abnormality event by period



2.3.5. Discussion on clinical pharmacology

Pharmacokinetics

Four studies (studies [A2203], [G2305], [G2301], and [G2301E]) contributed sparse PK data from SJIA patients at the age of 1-19 years. Single dose PK after 4 mg/kg canakinumab in SJIA patients could not be determined properly due to sparse data, especially with regard to Cmax and Tmax. However, from AUC estimations dose proportionality can also be assumed in this population. Tmax appeared to be earlier (2.6 days) in SJIA patients than in former populations (7d). Even though determination of Tmax is imprecise due to sparse sampling this observation could plausibly be related to a faster absorption rate in children, since a clear relationship between ka and age has been found in the population PK analysis.

The NONMEM dataset used for the PK-Binding model derived previously including other disease populations (eg, CAPS, Gouty Arthritis, Rheumatoid Arthritis, Japanese Healthy Volunteer, Non-Japanese Healthy Volunteer, and Psoriasis) was updated with the sparse PK data of the additional SJIA studies totalling 28 clinical studies including their extensions. Canakinumab and total IL-1β plasma concentration-time data were adequately described by the population-based PK-Binding model. However, predictability for the IL-1ß data was much lower than for the canakinumab concentration

data. Also predictability for rate of absorption (and thus Cmax and Tmax) is low due to lack of observed data in the early time range. Therefore, individual estimates of the model parameters Cmax, Tmax and IL-1ß have to be interpreted with caution. Based on the population PK analysis the PK properties of canakinumab relevant to SJIA population were estimated as follows:

All covariate-parameter relationships formerly identified (bodyweight on clearance and the two volumes of distribution, allometrically scaled with weight, plus serum albumin on clearance and age on the subcutaneous drug absorption rate) were confirmed to be statistically significant (p-value < 0.0001), confirming the importance of these covariates in the population-based PK-Binding model. Potential relationships between all PK parameters and continuous covariates (eg age, weight, height, scr) and categorical covariates (gender, Race, Ethnicity) were graphically assessed. No apparent relationship was evident for the PK parameters and the other tested covariates.

The covariate effect of Albumin on canakinumab clearance in SJIA patients is low, the effect of body weight on CL and V and of age on absorption rate is more relevant.

Serum clearance of canakinumab and its volumes of distribution were dependent on bodyweight. The estimated serum clearance of canakinumab was 0.106 ± 0.00689 L/day in SJIA patients (typical value at mean body weight of 33 kg from SJIA clinical trials). The corresponding volume of distribution at steady state was 3.21 L.

Canakinumab clearance versus body weight relation has the allometric exponent of 0.823 (95% CI: 0.751 – 0.895), which is less than 1. Therefore, the effect of body weight on canakinumab pharmacokinetics was not completely compensated when the dose was given on body weight basis. A slightly lower body-weight normalized clearance at higher body weight leads to a higher exposure (AUCss) for the higher bodyweight groups (> 40 kg).

A clear inverse relationship is observed between absorption rate and age. This means that absorption is faster the younger the patients are. This is reflected by an apparently smaller Tmax observed than in adults. Whether this might be accompanied by a higher bioavailability in younger children was not investigated, but estimations of steady state exposure by age do not indicate a big effect.

Following subcutaneous administration of canakinumab (product type D), the estimated absolute bioavailability (F) in SJIA patients was 68.9 ± 3.65% which was similar to other formulations applied and to the observed value in CAPS patients (63-70%).

After repeated administration of 4 mg/kg every 4 weeks s.c., the accumulation ratio of canakinumab was 1.6 fold in SJIA patients. The overall predicted mean (±SD) for Cmin,ss, Cmax,ss and AUC,ss were 14.7±8.8 µg/mL, 36.5 ± 14.9 µg/mL and 696.1 ± 326.5 µg.day/mL, respectively.

A lower (30-40%) median of exposure for Cmin,ss (11.4 versus 19 µg/ml) and AUCss (594 versus 880 µg*day/mL) for the lower bodyweight group (≤40 kg) than higher bodyweight group (> 40 kg) was estimated.

As expected from the selected dosing regimen, the predictions confirm that steady state exposure of canakinumab in sJIA patients is higher than that obtained in CAPS children or adults after administration of 150 mg/2 mg/kg 8weekly. This population reaches the highest steady state levels of canakinumab observed so far in studied populations, resulting in about twice the exposure of adult CAPS patients after 150 mg s.c. 8-weekly (Cmax,ss: 22,4 µg/ml, AUC8w,ss: 704 µg*day/ml).

The estimated terminal half-life was 22 days, which is consistent with the value estimated in CAPS or gouty arthritis patients (26 days). Time to steady state is expected to be approximately 110 days (5 half-lives) which means that after about 4 months (4 dose intervals) steady state should be reached. There was no indication of changes in pharmacokinetic properties over time.

Canakinumab pharmacokinetics is similar across different disease population including asthma, rheumatoid arthritis, CAPS, gout and SJIA when comparing their bodyweight normalized clearance. Final parameter estimates for IL-1ß kinetics differ between the populations.

The data provided indicate that there is no disease effect in the PK of canakinumab. CL values at 70 kg BW are comparable in all populations. The absolute number of male and female patients in the data pool of sJIA patients was sufficient for testing gender as a category covariate. No indication for a gender effect was seen.

It cannot be excluded that canakinumab potentially increases the clearance of CYP450 metabolized drugs via IL-1 neutralisation. Potential interactions with drugs eliminated by CYP450 enzyme are addressed in the RMP and appropriately labeled in the Product in formation.

Pharmacodynamics:

As expected from former trials with canakinumab in other populations an increase in total IL-1β indicating successful binding is observed in SJIA patients from all SJIA clinical trials.

From sparse IL-1ß data in all studies by means of the PK binding model values were estimated for binding affinity (Kd about 1nM) and for the half-life of free IL-1ß (4 days) which are comparable to that estimated in CAPS patients. A slower clearance and higher production rate of un-complexed IL-1ß was estimated for SJIA patients compared to other populations. The IL-1β clearance rate in CAPS was 75.5% higher than that of SJIA, suggesting higher levels of IL-1β in SJIA patients which might be a possible reason for the need for a higher dose. In younger children with SJIA, there was a modest trend of higher production rate and clearance of IL-1β, resulting in a modest higher overall turnover of IL-1β.

No data are available on either the effects of live vaccination or the secondary transmission of infection by live vaccines in patients receiving Ilaris. Therefore the SmPC state that live vaccines should not be given concurrently with Ilaris unless the benefits clearly outweigh the risks.

There is a potential risk of interaction between canakinumab and other drugs blocking IL-1 (e.g. anakinra) and drugs blocking TNF. This has been addressed in the RMP/SmPC accordingly.

Immunogenicity

Canakinumab showed low immunogenicity. The incidence of treatment related anti-canakinumab antibodies was 3.1% (6/196) in SJIA patients which is similar to that observed in CAPS (3/194; 1.5%) and in Gouty arthritis (17/799; 2.1%). No patient had neutralizing antibodies. One SJIA patient with post-treatment anti-canakinumab antibodies had an AE (mild eyelid edema) suggestive of hypersensitivity within a plausible time to onset. No anaphylactic or anaphylactoid reactions or SAE related to immunogenicity were reported.

Exposure-response relationships:

Efficacy

The range of predicted canakinumab concentrations at flare in all SJIA studies is extremely large (from zero to up 41 µg/mL), almost as wide as those predicted for no flare (from zero up to 60 µg/mL).

However, the mean estimated trough concentration at flare was statistically lower than the mean estimated trough concentration at no flare in phase 3 clinical studies (13.1 ± 8.68 µg/mL vs 16.9 ± 9.53 µg/mL; p-value < 0.0001).

There is a (weak) relationship between canakinumab plasma concentrations and probability of flare and a Ki (concentration for 50% flare probability) of 2 µg/mL was estimated which is comparable to

that estimated for the CAPS population. More than 95% of subjects administered 4 mg/kg s.c dose of canakinumab had their steady-state trough levels above Ki.

By means of this model it was predicted that at a dose of 4 mg/kg s.c., the median percentage of patients predicted to relapse within 4 weeks was estimated at 6% (95% CI, 1–21%). The median percentages of patients predicted to relapse were much higher at 2 mg/kg and 3 mg/kg, and were approximately 11% and 18%, respectively. The efficacy improvement between 4 and 7 mg/kg was marginal.

An exposure-hazard model based on G2301 Part II data demonstrated that canakinumab decreased significantly ($p<0.001$) the risk of flare with potentially full suppression in a concentration-dependent manner (IC50 = 3.27 (range: 0.530, 7.27) µg/ml). The baseline steroid dose at the end of part I of the study had significant influence on risk of flare.

The exposure-hazard model predicted that the 4mg/kg dose reduced flare rate over placebo by ~39% at the end of 12 months, consistent with the clinical data observed. The model predicted that greater than 4mg/kg dose would provide only marginal improvement in flare reduction over 6 and 12 months, while doses less than 4mg/kg dose would significantly increase risk to experience a flare over 6 and 12 months.

Safety

There was a lack of an exposure-safety relationship for the AEs evaluated including Cough, Headache, Infection, MAS, Pyrexia, SAE infection. Except for infection, the observation was based on limited AE incidence.

Subjects with neutropenia had higher canakinumab levels than subjects without neutropenia. The "IC50 parameter for the neutrophil loss" was estimated to be about 9.1 ug/mL being about 2.5 to 3 times higher than the "IC50 parameter for the freedom of flares" equal to 3.27 ug/mL derived from the PK-hazard model. The majority of SJIA patients has Ctrough values > 9.1 µg/mL. Neutrophil values of less than 90% of the LLN mainly occurred at concentrations of 30ug/mL and above. This is comparable with the IC90 for efficacy. Dosing with canakinumab 4 mg/kg reduces the neutrophils levels from approximately 2-32* 109/L at baseline to 1-16*109/L at steady state (5% reach > grade 2). Thus, there is a narrow but acceptable window of discrimination between efficacy and safety. Information and precautions with regards to this side effect is appropriately reflected in the product information (see also discussion on safety).

2.3.6. Conclusions on clinical pharmacology

The data provided on pharmacokinetics, pharmacodynamics and on PK / PD modelling are considered appropriate to support the proposed extension of the indication to the treatment of active Systemic Juvenile Idiopathic Arthritis (SJIA) in patients aged 2 years and older who have responded inadequately to previous therapy with non-steroidal anti-inflammatory drugs (NSAIDs) and systemic corticosteroids. Ilaris can be given as monotherapy or in combination with methotrexate.

2.4. Clinical efficacy

2.4.1. Dose response study

Study A2203

This was a multi-center, open label, repeated dose range finding study to evaluate the safety, tolerability, immunogenicity, pharmacokinetics and efficacy of Canakinumab, a fully human

antiinterleukin- 1β (anti-IL-1β) monoclonal antibody, given subcutaneously in pediatric subjects with active SJIA.

Detailed description of the study and the assessment of data can be found in in the pharmacokinetic chapter (2.3.2) of this report and in the chapter on PK/PD modelling (2.3.4).

2.4.2. Main studies

Study G2305

A randomized, double-blind, placebo controlled, single-dose study to assess the initial efficacy of canakinumab (ACZ885) with respect to the adapted ACR pediatric 30 criteria in patients with Systemic Juvenile Idiopathic Arthritis (sJIA) and active systemic manifestations.

Methods

Study participants

Patients were randomized in a total of 40 centers in 18 (EU and non EU) countries. Male or female patients aged 2 to <20 years with a confirmed diagnosis of sJIA as per International League Against Rheumatism (ILAR) definition at least 2 months prior to enrollment with an 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 study drug administration; and 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 was allowed with the exception of:

- Stable dose of methotrexate (maximum of 20 mg/ m2/ week) for at least 8 weeks prior to the screening visit, and folic/folinic acid supplementation (according to standard medical practice of the center)
- 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 glucocorticoid 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 randomization.

Treatments

Patients received a s.c. injection of canakinumab (4 mg/kg) or placebo on Day 1. The maximal 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 s.c. injections.

Patients who did not show clinical improvement prior to Day 15 as well as those who did not achieve an adapted ACR pediatric 30 criteria (ACR30) at Day 15 were discontinued from the study.

Objectives

The primary objective of the study was to show superiority of canakinumab compared to placebo with regards to the primary variable.

Outcomes/endpoints

The primary objective of the study was to demonstrate that the proportion of patients who met the adapted ACR Pediatric 30 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 ACR Pediatric 30/50 criteria at Day 29
- Efficacy (% of patients who meet the adapted ACR Pediatric 50 criteria) of canakinumab as compared to placebo 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 analog scale (VAS) in the Childhood Health Assessment Questionnaire (CHAQ) by Day 15/29
- Efficacy of canakinumab as compared to placebo to show clinical signs of response (% of patients who have body temperature ≤ 38°C) at Day 3.
- Effect of treatment with canakinumab as compared to placebo with respect to the adapted ACR Pediatric 70/90/100 criteria at Day 29
- Effect of treatment with canakinumab as compared to placebo with respect to the adapted ACR Pediatric 70/90/100 criteria at Day 15
- 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

Efficacy assessments consisted of the adapted ACR Pediatric response (components shown below), parent's or patient's assessment of pain based on the 0-100 mm VAS in the CHAQ© and the CHQ-PF50.

The adapted ACR Pediatric 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 well-being 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)
7. Absence of intermittent fever due to sJIA during the preceding week

The degree of adapted ACR pediatric response was assessed by a standardized procedure at PRINTO or PRCSG. The adapted ACR Pediatric 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 (i.e., 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%

X-ray (radiograph) of the hands and wrists (both sides)

Patients (volunteers who consented at Screening) with an affected hand and/or wrist had articular x-rays of both hands and wrists (left and right side) performed. (Note: Assessed at baseline only. The purpose was to have a baseline for patients who may have rolled over into study CACZ885G2301 or CACZ885G2301E1.)

Monitoring of sexual maturation (Tanner stages)

Physical development in children, adolescents and adults from 6 – 20 years of age was monitored by the Tanner stages (also known as the Tanner scale). (Note: Assessed at baseline only. The purpose was to have a baseline for patients who may have rolled over into study CACZ885G2301 or CACZ885G2301E1.)

Sample size

The planned sample size was 122 patients (61 patients per treatment group). The anticipated sample size for the interim analysis was 84 patients. Anticipating responder rates of 60% for the active group and 30% for the placebo group, it was calculated that with 122 (61 per group) patients Fisher's exact test would have about 90% power to detect this difference when applying a type I error of 2.5% (one-sided).

A total of 84 patients were randomized (43 to canakinumab and 41 to placebo), treated, and all are included in the efficacy and safety analysis populations.

Randomisation

Patients were centrally randomized in an 1:1 ratio (canakimumab:placebo) stratified by number of active joints (≤ 26 / >26), non-responder to anakinra (yes / no), and level of current corticosteroid use (≤ 0.4 mg/kg / > 0.4 mg/kg).

Blinding (masking)

This was a double-blind, randomized study. The following blinding methods were used:

1. Randomization data were kept strictly confidential until the time of unblinding, and were not accessible by anyone else involved in the study with the exception of the independent, unblinded qualified study person at the investigator's site who prepared the study medication.
2. The identity of the canakinumab/placebo treatments were concealed by the use of study drugs in form of syringes filled with reconstituted canakinumab solutions that were all identical in appearance, but the actual canakinumab (or placebo) vials with lyophilisate were supplied "open-label"

Statistical methods

Superiority of canakinumab over placebo with regard to ACR30 response at day 15 was to be assessed by means of a Cochran-Mantel-Haenszel (CMH) test adjusted for the stratification factors at randomisation. For the primary analysis, patients who discontinued due to any reason prior day 15 were considered non-responders. Homogeneity across strata was assessed by means of a Breslow & Day test.

If the primary objective was achieved, secondary endpoints were to be assessed according to a pre-specified hierarchy to evaluate superiority of canakinumab over placebo. In order to control the overall Type I error rate testing had to stop as soon as statistical significance failed for the first time. Categorical variables were to be analysed by means of a CMH test, continuous variables by means of ANCOVA models. All efficacy analyses were to be based on the full analysis set (FAS) of all randomized patients who received at least one dose of study drug.

In general data were described by statistical characteristics (continuous variables: mean, standard deviation, median, minimum, maximum, 25% and 75% quantiles; categorical variables: absolute and relative frequencies) stratified for treatment. Treatment differences were described by point estimates and their 95%-confidence intervals.

According protocol amendment 4, a pre-planned interim analysis was performed after 84 patients had achieved the primary endpoint. Based on an error spending function approximating O'Brien-Fleming boundaries it was calculated that for the primary analysis an alpha level of 0.00697 was to be applied at interim to protect the overall false positive rate of the trial at 0.025. The alpha level to be used for testing the secondary parameters (0.01612) was based on an adjustment according Pocock.

Results

Participant flow

A total of 84 patients were randomized, 43 to canakinumab and 41 to placebo (Table 10-1). The only reported reason patients discontinued from the study was unsatisfactory therapeutic effect. A majority of patients in the placebo group discontinued from the study for this reason (90.2%) while only 14.0% of patients in the canakinumab group discontinued for this reason. There were no discontinuations due to safety reasons.

Table 21. Patient disposition by treatment (Randomized set)

	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)

Source: Table 14.1-1.1

The primary reason for discontinuation as given by the investigator on the study completion eCRF was summarized.

Recruitment

First patient screened: 22-Jul-2009

Early termination date: 18-Jan-2011 (upon recommendation by Data Monitoring Committee)

Last patient completed: 02-Dec-2010

Conduct of the study

There are five protocol amendments, however, Amendment 2 was retracted before implementation (see below). Previous sections of this report describe the study conduct as amended. The key features of each amendment are summarized below:

Protocol Amendment 1 was written to change 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 was written to ensure 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 CACZ885G2305 placebo or canakinumab patients to study CACZ885G2301 or CACZ885G2301E1, respectively, if they did not maintain a minimum adapted ACR Pediatric 30 response after Day 15.

Protocol Amendment 4 was written to implement an interim analysis.

Protocol Amendment 5 was written to describe the implementation of an adjudication committee for MAS and the follow-up to be conducted on MAS cases that are identified in the study.

No other changes in study conduct occurred.

Protocol deviations

The proportion of patients with any protocol deviation was higher in the canakinumab group (79.1%) compared with the placebo group (53.7%).

The three most common protocol deviations were the following:

• Body temperature not taken orally or rectally: 11 (25.6%) vs. 5 (12.2%)

• Missing hematology value: 10 (23.3%) vs. 6 (14.6%)

• Missing important safety evaluation (ECG, vital signs): 7 (16.3%) vs. 4 (9.8%)

Protocol deviations for exclusion from a per protocol analysis were pre-defined although a per protocol analysis was not planned nor performed. Three patients in each treatment group had this type of protocol deviation: patient was not discontinued despite not meeting the adapted ACR 30 pediatric criteria at Day 15.

There was one protocol deviation that was not captured: Patient 0147/00007 in the placebo group did not have a CRP level >30 mg/L at baseline (as required by the inclusion criteria). However, this deviation did not exclude the patient from any analysis. In addition, protocol deviations for two patients in the canakinumab group and three patients in the placebo group identified in Amendment 1 to the initial CSR (14-Nov-2011) have been incorporated in this CSR.

One additional type of protocol deviation was identified before database re-lock: urine protein ≥ 2+ (considered moderately to severely impaired) at study entry. One patient had this protocol deviation (0020/00001). These additional protocol deviations had no impact on the analyses.

Baseline data

The majority of patients were Caucasian and female, and the average age was 9 years. The youngest patients in the entire population (i.e., those patients 2-<4 years of age) were all in the canakinumab group. There was a lower number of patients aged 6 - <12 years in the canakinumab group compared with the placebo group. Baseline demographics were otherwise generally comparable for the two treatment groups.

Table 22. Demographic and background characteristics by treatment (Full analysis set)

	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

Source: Table 14.1-3.1

Age is calculated at Visit 1 using date of birth.
Body Mass Index: BMI (kg/m^2) = weight (kg) / [(height (cm) / 100)^2].

Key baseline disease characteristics are provided in the table below.

Table 23. Diseases history and baseline characteristics (Full analysis set)

	ACZ885 N=43	Placebo N=41	Total N=84
Body temperature (°C)			
n	43	41	84
Mean	37.295	37.224	37.261
S.D.	0.8059	0.8552	0.8261
Median	37.100	37.100	37.100
Min-Max	36.10 – 39.10	34.90 – 39.20	34.90 – 39.20
Time of sJIA diagnosis to study entry (days)			
n	29	27	56
Mean	1146.3	1309.3	1224.9
S.D.	1051.13	1316.43	1178.33
Median	857.0	728.0	822.5
Min-Max	68 – 3696	100 – 5357	68 – 5357
Presence of systemic signs after the first 6 months of disease – n (%)			
No	7 (16.3)	6 (14.6)	13 (15.5)
Yes	33 (76.7)	34 (82.9)	67 (79.8)
Missing	3 (7.0)	1 (2.4)	4 (4.7)
CRP (standardized) at baseline (mg/L)			
n	43	41	84
Mean	192.501	156.676	175.015
S.D.	156.9332	122.7990	141.6128
Median	141.290	136.939	140.645
Min-Max	20.63 – 800.00	0.68 – 656.60	0.68 – 800.00
No. of flares in previous year			
n	40	40	80
Mean	2.4	3.7	3.1
S.D.	1.93	3.71	3.01
Median	2.0	2.0	2.0
Min-Max	0 – 8	0 – 15	0 – 15
Physician's global assessment of disease activity (VAS) (mm)			
n	43	41	84
Mean	65.3	65.7	65.5
S.D.	19.09	19.55	19.20
Median	67.0	66.0	66.5
Min-Max	25 – 100	21 – 99	21 – 100
Patient's (or parent's) global assessment of patient's overall wellbeing (VAS) (mm)			
n	43	41	84
Mean	62.9	55.6	59.3
S.D.	24.56	31.81	28.39
Median	63.0	61.0	63.0
Min-Max	7 – 100	0 – 100	0 – 100

Patient's pain intensity (VAS) (mm)			
n	43	41	84
Mean	69.7	60.9	65.4
S.D.	19.49	25.77	23.06
Median	73.0	67.0	71.5
Min-Max	20 – 100	9 – 96	9 – 100
CHAQ score			
n	43	41	84
Mean	1.6686	1.5091	1.5908
S.D.	0.73592	0.78431	0.75957
Median	1.6250	1.5000	1.6250
Min-Max	0.000 – 3.000	0.125 – 3.000	0.000 – 3.000
CHQ-PF50 physical score for 5-18 years old			
n	28	35	63
Mean	16.9190	14.8079	15.7462
S.D.	13.35216	13.03674	13.11329
Median	19.2116	18.1338	18.3415
Min-Max	-4.506 – 38.073	-4.477 – 39.223	-4.506 – 39.223
CHQ-PF50 psychosocial score for 5-18 years old			
n	28	35	63
Mean	40.5087	44.4871	42.7189
S.D.	9.49647	11.81653	10.94604
Median	39.9951	44.9334	43.6967
Min-Max	22.784 – 57.383	17.654 – 64.691	17.654 – 64.691
No. of active joints			
n	43	41	84
Mean	15.8	12.4	14.1
S.D.	15.25	12.18	13.86
Median	10.0	7.0	8.0
Min-Max	2 – 58	2 – 55	2 – 58
No. of active joints– n (%)			
≤ 26 active joints	34 (79.1)	36 (87.8)	70 (83.3)
> 26 active joints	9 (20.9)	5 (12.2)	14 (16.7)
No. of joints with limitation of motion			
n	43	41	84
Mean	14.3	12.4	13.4
S.D.	15.03	12.93	13.99
Median	8.0	6.0	6.5
Min-Max	0 – 54	0 – 55	0 – 55
Prednisone equivalent dose (mg/kg/day)			
n	31	28	59
Mean	0.384	0.865	0.612
S.D.	0.2465	2.7840	1.9231
Median	0.340	0.205	0.270
Min-Max	0.02 – 1.00	0.09 – 15.00	0.02 – 15.00
Prednisone equivalent dose – n (%)			
No prednisone use	12 (27.9)	13 (31.7)	25 (29.8)
>0 - ≤ 0.4 mg/kg/day oral prednisone (or equivalent)	21 (48.8)	20 (48.8)	41 (48.8)
> 0.4 mg/kg/day oral prednisone (or equivalent)	10 (23.3)	8 (19.5)	18 (21.4)

Source: Table 14.1-3.2, Table 14.2-2.5, Table 14.2-2.22

n.a. = not available

The majority of patients had no prior use of anakinra (63.1% of patients overall). Of those who had used anakinra before, most had taken it within the previous week (21 of 31 patients overall). Approximately half of the patients with prior use discontinued anakinra for reasons other than lack of efficacy or tolerability (16 of 31 patients overall). There were no relevant differences between the two treatment groups in the prior use of anakinra.

- Prior use of tocilizumab, etanercept, abatacept, and adalimumab:

- Thirteen (30.2%) patients in the canakinumab group and 15 (36.6%) patients in the placebo group had prior use of etanercept; all had discontinued use due to lack of efficacy.
- One (2.3%) patient in the canakinumab group and 2 (4.9%) patients in the placebo group had prior use of tocilizumab; the drug had been discontinued for either lack of efficacy or lack of tolerability.
- Three (7.0%) patients in the canakinumab group and 4 (9.8%) patients in the placebo group had prior use of adalimumab and in all cases it had been discontinued due to lack of efficacy.
- No patients in either treatment group reported prior use of abatacept.

Most patients had a relevant past or current medical history/condition (62.8% canakinumab vs. 75.6% placebo). The most common medical histories by system organ class (i.e., ≥15.0% in either group) for canakinumab vs. placebo, respectively, were infections and infestations (37.2% vs. 29.3%), gastrointestinal disorders (20.9% vs. 26.8%), musculoskeletal and connective tissue disorders (18.6% vs. 17.1%), skin and subcutaneous tissue disorders (20.9% vs. 12.2%), and blood and lymphatic system disorders (9.3% vs. 17.1%). The most common histories by preferred term (i.e., ≥10.0% in either group) were varicella (11.6% vs. 2.4%) and anemia (4.7% vs. 14.6%). The profile of medical histories was as expected for this patient population.

Numbers analysed

All randomized patients were included in the Safety Set and Full Analysis Set populations.

Outcomes and estimation

Primary efficacy results

The primary efficacy variable was the proportion of patients who responded to treatment at Day 15 according to the adapted ACR Pediatric 30 criteria (ACR30). The two treatment groups were compared using the Cochran-Mantel-Haenszel test adjusting for stratification factors: number of active joints (≤ 26, > 26), non-responder to anakinra (yes or no if either responder to anakinra or never exposed to anakinra), and level of current corticosteroid use (≤ 0.4 mg/kg oral prednisone [or equivalent] or > 0.4 mg/kg oral prednisone [or equivalent]). The proportion of patients who had an ACR30 at Day 15 was higher 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 (odds ratio of 62.29; p<0.0001).

Table 24. Responders to treatment according to the adapted ACR Pediatric 30 criteria at Day 15: Comparison between treatment groups (Full Analysis Set)

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)			

Source: Table 14.2-1.4

Comparison of treatment groups using Cochran-Mantel-Haenszel (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.
* Indicates a statistically significant difference between the treatments. A one-sided test was conducted with significance level 0.00697 as determined by O'Brien-Fleming boundaries for an overall false positive rate of the trial at 0.025.

The primary analysis was repeated using an unstratified Fisher's exact test. The results revealed similar findings; the odds ratio was 47.57, in favour of canakinumab; the difference in proportions was -73.96% (CI: -88.26,-59.67) (p<0.0001). The response to treatment according to the adapted ACR Pediatric 30 criteria at Day 15 was summarized by stratification variable, age category, and gender. In general, response to canakinumab was consistent across these subgroups including the youngest patients (2-<4 years of age). In fact, 7/9 (77.8%) of the patients in the youngest age category had an ACR70 or higher at Day 15 or Day 29.

Corticosteroid usage at baseline 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. Note that the proportion of responders to canakinumab in the >26 joints category was lower (6/9 or 66.7%) but this may have been due to the low number of patients in the category overall. The proportion of responders in the ≤26 joints category was 88.2% (30/34 patients).There were a total of 6 patients in the canakinumab group and 3 patients in the placebo group who had previously used and discontinued anakinra due to lack of efficacy. Of these patients, 5/6 (83.3%) in the canakinumab group were ACR responders at Day 15 (2 with ACR50, 1 with ACR70, and 2 with ACR100); all 3 patients in the placebo group were non-responders at Day 15.

Secondary efficacy results

A closed testing procedure was performed for secondary efficacy variables. Each of the steps in the closed testing procedure was satisfied, as shown in the table below.

Closed testing procedure on secondary endpoints (Full analysis set)

Criteria	Time point	Statistical significance according to closed testing procedure (1)
ACR 30	Day 29	Yes
ACR 50	Day 29	Yes
ACR 50	Day 15	Yes
Patient's pain intensity (0–100mm VAS)	Day 29	Yes
Patient's pain intensity (0–100mm VAS)	Day 15	Yes
Proportion of patients who have body temperature ≤ 38°C	Day 3	Yes
ACR 70	Day 29	Yes
ACR 90	Day 29	Yes
ACR 100	Day 29	Yes
ACR 70	Day 15	Yes
ACR 90	Day 15	Yes
ACR 100	Day 15	Yes
CHQ-PF50 physical score for 5–18 years old	Over time	Yes
CHQ-PF50 psychosocial score for 5–18 years old	Over time	Yes
CHAQ disability score	Over time	Yes

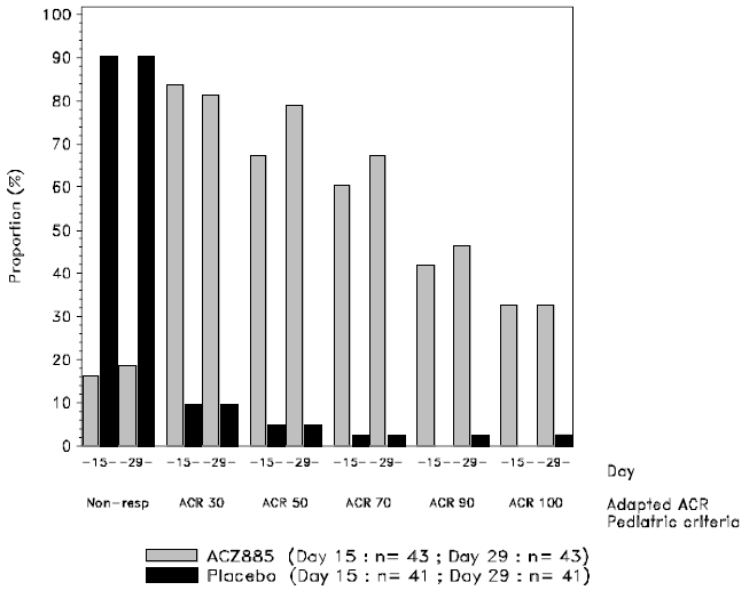
Source: Table 14.2-2.1

(1) One sided test with significance level 0.01612, based on the Pocock method with one interim analysis, to protect the overall false positive rate of the trial at 0.025.

Response according to adapted ACR pediatric criteria

The percentage of responders to treatment according to the adapted ACR pediatric criteria is shown in Figure 11-1. A majority of the canakinumab group achieved a minimum ACR70 at Day 15 (60.5%) and at Day 29 (67.4%) compared with one placebo patient (2.4%) at this ACR level at the same time points. There was a much higher proportion of patients in the canakinumab group at each ACR level at Day 15 or 29 in comparison to patients in the placebo group. In the canakinumab group, there was a small decline in the proportion of patients who had an ACR30 from Day 15 to Day 29, an increase in the proportion of patients with an ACR50, 70, or 90 from Day 15 to Day 29, and the proportion of patients with an ACR100 (33%) remained stable between Day 15 and Day 29.

Figure 14. Percentage of responders to treatment according to the adapted ACR Pediatric criteria, by visit, criteria and treatment (Full analysis set)



Source: Table 14.2-1.1, Table 14.2-2.3, Table 14.2-2.4
Only patients with measurements at the specific visit were included.

In addition to the significance of canakinumab versus placebo demonstrated for ACR30 at Day 15, the proportion of patients with an ACR30 at Day 29 or an ACR50, 70, 90, or 100 at Days 15 or 29 was significantly higher in the canakinumab group compared to the placebo group (all, odds ratios >22; p≤0.0001) (see table below).

Table 25. Responders to treatment according to the adapted ACR Pediatric criteria: Comparison between treatment groups, by visit (Full analysis set)

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)			

Source: Table 14.2-2.4

NotEst = not estimable
Comparison of treatment groups using Cochran-Mantel-Haenszel (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.
* Indicates a statistically significant difference between the treatments. A one-sided test was conducted with significance level 0.01612 as determined by the Pocock method for an overall false positive rate of the trial at 0.025.

Adapted ACR pediatric criteria response variables

Physician's global assessment of disease activity

The physician's global assessment of disease activity using a 0-100 mm VAS is the first response variable in the adapted ACR pediatric criteria. At baseline, the median values were 67.0 mm for canakinumab and 66.0 mm for placebo. Patient's response to canakinumab was apparent as early as day 3 at which time the median change from baseline was -25.0 mm for canakinumab (n=42) vs. -2.5 mm for placebo (n=38). At Day 15, the median change was -40.0 mm for canakinumab (n=43) vs. -2.0 mm for placebo (n=25). At Day 29, the median change was -43.0 mm for canakinumab (n=38) vs. -17.0 mm for placebo (n=7). The median percent changes from baseline were approximately -50%, -69%, and -83% for canakinumab vs. -3%, -5%, and -38% for placebo at Days 3, 15, and 29, respectively.

Note that the number of patients in the placebo group decreased over time due to early discontinuation from the study for unsatisfactory therapeutic response.

The physician's global assessment of disease activity was also summarized by response to treatment, ACR criteria, age category and gender. In general, the results were consistent for all ACR responders at Day 15 regardless of gender and age (including the youngest of patients). In the youngest age category (2-<4 years of age), the median changes from baseline for canakinumab were -40.0 mm (n=9), -42.0 mm (n=9), and -56.0 mm (n=7) and the median percent changes from baseline were approximately -80%, -93%, and -96% at Days 3, 15, and 29, respectively. There were no patients in the placebo group in the youngest age category.

Patient's global assessment of patient's overall well being

The patient's (or parent's) global assessment of the patient's overall well-being using a 0-100 mm VAS is the second response variable in the adapted ACR pediatric criteria.

At baseline, the median values were 63.0 mm for canakinumab and 61.0 mm for placebo. At Day 15, the median change was -36.0 mm for canakinumab (n=43) vs. 2.0 mm for placebo (n=25). At Day 29, the median change was -49.5 mm for canakinumab (n=38) vs. -11.0 mm for placebo (n=7). This represented a median -73% and -91% change from baseline for canakinumab vs. 1% and -17% for placebo at Days 15 and 29, respectively. Note that the number of patients in the placebo group decreased over time due to early discontinuation from the study for unsatisfactory therapeutic response.

The patient's (or parent's) global assessment of the patient's overall well-being was also summarized by response to treatment, ACR criteria, age category, and gender. In general, the results were consistent for all ACR responders at Day 15 regardless of gender and age (including the youngest of patients). In the youngest age category (2-<4 years of age), the median changes from baseline for canakinumab were -27.0 mm (n=9) and -61.0 mm (n=7) representing median -94% and -97% changes from baseline at Days 15 and 29, respectively. There were no patients in the placebo group in the youngest age category.

Number of active joints

The number of joints with active arthritis is the fourth response variable in the adapted ACR pediatric criteria. At baseline, the median number was higher for canakinumab vs. placebo (10 vs. 7). At Day 15, the median number decreased by 6 for canakinumab (n=43) vs. none for placebo (n=41). At Day 29, the median number decreased by 5 for canakinumab (n=38) vs. 1 for placebo (n=7). These decreases represent median -67% and -86% changes from baseline for canakinumab vs. 0% and -32% for placebo at Days 15 and 29, respectively. Note that the number of patients in the placebo group decreased over time due to early discontinuation from the trial for unsatisfactory therapeutic response.

The number of joints with active arthritis was also summarized by response to treatment, ACR criteria, age category, and gender. In general, the results were consistent for all ACR responders at Day 15 regardless of gender and age (including the youngest of patients). In the youngest age category (2-<4 years of age), the median number of joints with active arthritis decreased from baseline by 5 at Day 15 (n=9) and 4 at Day 29 (n=7), which equated to a median -100% change from baseline at both time points (i.e., the median number of active joints post baseline at the two time points was 0). There were no patients in the placebo group in the youngest age category.

Number of joints with limited range of motion

The number of joints with a limited range of motion is the fifth response variable in the adapted ACR pediatric criteria. At baseline, the median number was higher for canakinumab vs. placebo (8 vs. 6). At Day 15, the median number had decreased by 5 for canakinumab (n=43) vs. none for placebo (n=41). At Day 29, the median number decreased by 4.5 for canakinumab (n=38) vs. 1 for placebo (n=7). The median percent changes from baseline were approximately -73% and -83% for canakinumab vs. 0% and -33% for placebo at Days 15 and 29, respectively. Note that the number of patients in the placebo group decreased over time due to early discontinuation from the study for unsatisfactory therapeutic response. The number of joints with a limited range of motion was also summarized by response to treatment, ACR criteria, age category, and gender. In general, the results were consistent for all ACR responders at Day 15 regardless of gender and age (including the youngest of patients). In the youngest age category (2-<4 years of age), the median number of joints with limited range of motion decreased from baseline by 4 at both Days 15 (n=9) and Day 29 (n=7), and the median percent change from baseline was -100% at both time points. There were no patients in the placebo group in the youngest age category.

C-reactive protein (CRP)

CRP level is the sixth response variable in the adapted ACR pediatric criteria. CRP values were standardized to a normal range of 0-10 mg/L. At baseline, median CRP values were 141.3 mg/L for canakinumab and 136.9 mg/L for placebo. Patient's response to canakinumab was apparent as early as Day 3 at which time the median change from baseline was -76.7 mg/L for canakinumab vs. -7.4 mg/L for placebo. At Day 15, the median change was -100.0 mg/L for canakinumab (n=43) vs. 5.7 mg/L for placebo (n=25). At Day 29, the median change was -132.0 mg/L for canakinumab (n=39) vs. -15.0 mg/L for placebo (n=7). The median percent changes from baseline were approximately -55%, -91%, and -91% for canakinumab vs. -4%, 5%, and -13% for placebo at Days 3, 15, and 29, respectively. Note that the number of patients in the placebo group decreased over time due to early discontinuation from the study for unsatisfactory therapeutic response.

Fever at Day 3

All patients in the canakinumab group had a normal body temperature at Day 3 compared to 86.8% of patients in the placebo group. The difference between the two treatment groups was statistically significant (p=0.0098).

Pain intensity (0-100 mm VAS) as part of CHAQ

At baseline, the patient's mean pain intensity was 69.7 mm for canakinumab and 60.9 mm for placebo. At Day 15, the mean change was -50.0 mm for canakinumab (n=43) vs. 4.5 mm for placebo (n=25). At Day 29, the mean change was -56.9 mm for canakinumab (n=38) vs. -11.4 mm for placebo (n=7). The mean percent changes from baseline were approximately -69% and -80% for canakinumab vs. 40% and -27% for placebo at Days 15, and 29, respectively. Note that the number of patients in the placebo group decreased over time due to early discontinuation from the study due to unsatisfactory therapeutic response. A comparison between the treatment groups showed that the LS means in overall pain intensity were statistically significantly lower in the canakinumab treatment group compared with the placebo group at Days 15 and 29 (both, p<0.0001).

CHQ-PF50

Health-related quality of life was assessed in patients aged 5-18 years old using the CHQPF50. At baseline, the median CHQ-PF50 physical score was 19.2 for canakinumab (n=28) and 18.1 for placebo (n=35). At Day 15, the median change was 17.7 for canakinumab (n=28) vs. 1.2 for placebo (n=22). At Day 29, the median change was 23.5 for canakinumab (n=26) vs. 13.5 for placebo (n=6). Note that the number of patients in the placebo group decreased over time due to early discontinuation from the study for unsatisfactory therapeutic response.

For the CHQ-PF50 psychosocial score, the baseline median value was 40.0 for canakinumab (n=28) and 44.9 for placebo (n=35). At Day 15, the median change was 7.2 for canakinumab (n=28) vs. -0.7 for placebo (n=22). At Day 29, the median change was 8.8 for canakinumab (n=26) vs. 2.1 for placebo (n=6). Note that the number of patients in the placebo group decreased over time due to early discontinuation from the study for unsatisfactory therapeutic response. A comparison between the treatment groups showed that the LS mean changes from baseline over time in the CHQ-PF50 physical and psychosocial scores were both statistically significantly higher in the canakinumab treatment group compared with the placebo group (both, p<0.005).

CHAQ disability score

The CHAQ functional ability score is the third response variable in the adapted ACR pediatric criteria. At baseline, the median values were 1.6 for canakinumab and 1.5 for placebo. At Day 15, the median change was -1.0 for canakinumab (n=43) vs. -0.1 for placebo (n=25). At Day 29, the median change was -1.1 for canakinumab (n=38) vs. 0.1 for placebo (n=7). Note that the number of patients in the placebo group decreased over time due to early discontinuation from the study for unsatisfactory therapeutic response. The minimal clinical important difference (MCID) for improvement cited to be -0.19 (Brunner, et al 2005) was well exceeded at Day 15 in the canakinumab group, and further clinical improvement was seen at Day 29. The improvement observed at Days 15 and 29 exceeded the MCID by a factor of 5.

A comparison between the treatment groups showed that the LS mean change from baseline over time in the CHAQ© disability score was significantly greater in the canakinumab treatment group compared with the placebo group (p=0.0002). The estimated difference of -0.69 shows a treatment effect over the course of the study that is approximately 3.6 times (range of 1.7 to 5.5 times) the cited MCID of -0.19 (Brunner, et al 2005).

In general, the results were consistent for all ACR responders at Day 15 regardless of gender and age (including the youngest of patients). In the youngest age category (2-<4 years of age), the median changes from baseline for canakinumab were -1.0 (n=9) and -0.75 (n=7). There were no patients in the placebo group in the youngest age category.

Ancillary analyses

EQ-5D or EQ-5D proxy

Health-related quality of life was explored over time by use of the EQ-5D (for patients ≥ 12 years of age) and EQ-5D proxy (for patients 8 - 11 years of age. The numbers of patients with data at baseline and Day 29 were 22 in the canakinumab group and 25 in the placebo group. The proportions of patients who had “some health problems” at baseline and “no health problems” at Day 29 in the canakinumab (n=20) vs. placebo group (n=4) for the following domains were: mobility (59.1% vs. 4.0%), self-care (45.5% vs. 4.0%), usual activities (45.5% vs. 4.0%), pain discomfort (40.9% vs. 4.0%), and anxiety depression (22.7% vs. 4.0%). Overall, the results were consistent with those of the CHAQ.

PDSS

The level of sleepiness was explored over time by use of the PDSS for patients 11-15 years of age. The number of patients with data is low overall, and no patients in the placebo group had data at Day 29. Mean values at baseline were 18.0 in the canakinumab group (n=7) and 14.0 in the placebo group (n=6). At Day 29, the mean change from baseline was -4.3 in the canakinumab group (n=6).

Flare

The occurrence of flare was an assessment during the course of the study, but it was not an endpoint of the study. Some patients will roll over into the longer term studies CACZ885G2301 and CACZ885G2301E1, and flare will be evaluated further in those studies.

The assessment was made in relation to the previous visit.

Three patients in the canakinumab group flared, and the flare occurred at the last study visit (i.e., end of the study visit). At the time of the flare, two of the patients were ACR non-responders and the third was an ACR90 responder.

- 0051/00002 (ACR50 responder at Day 15; non-responder at end of the study [Day 29])
- 0040/00002 (ACR100 responder at Day 15; ACR90 responder at end of the study [Day 30])
- 0083/00001 (ACR90 responder at Day 15; non-responder at end of the study [Day 29])

Of these three patients, Patient 0040/00002 is the only one who flared and who also had an ACR responder status at Day 29 (ACR90). At that time point, the physician's global assessment had worsened, CRP increased dramatically, the number of active joints increased (to 2 compared to 0 at Day 15), and the number of joints with limited range of motion increased (to 3 compared to 0 at Day 15). Unlike ACR calculation, flare calculation was compared to the previous visit (i.e., Day 15). Thirty-one patients in the placebo group flared. With the exception of one patient, all of these patients were non-responders at the time of the flare.

Inactive disease

Inactive disease was included in the assessments during the course of the study, but it was not an endpoint of the study. Some patients will roll over into the longer term studies CACZ885G2301 and CACZ885G2301E1, and inactive disease will be evaluated further in those studies. At Day 15, 14 (32.6%) patients in the canakinumab group had inactive disease; 13 of these had an ACR100 and 1 had an ACR90. Twelve of the 14 patients continued to have inactive disease at Day 29. One additional patient who had active disease at Day 15 had inactive disease at Day 29 when ACR status went from ACR90 to ACR100. No patients in the placebo group had inactive disease.

Study G2301

A randomized, double-blind, placebo controlled withdrawal study of flare prevention of canakinumab (ACZ885) in patients with Systemic Juvenile Idiopathic Arthritis (sJIA) and active systemic manifestations.

Methods

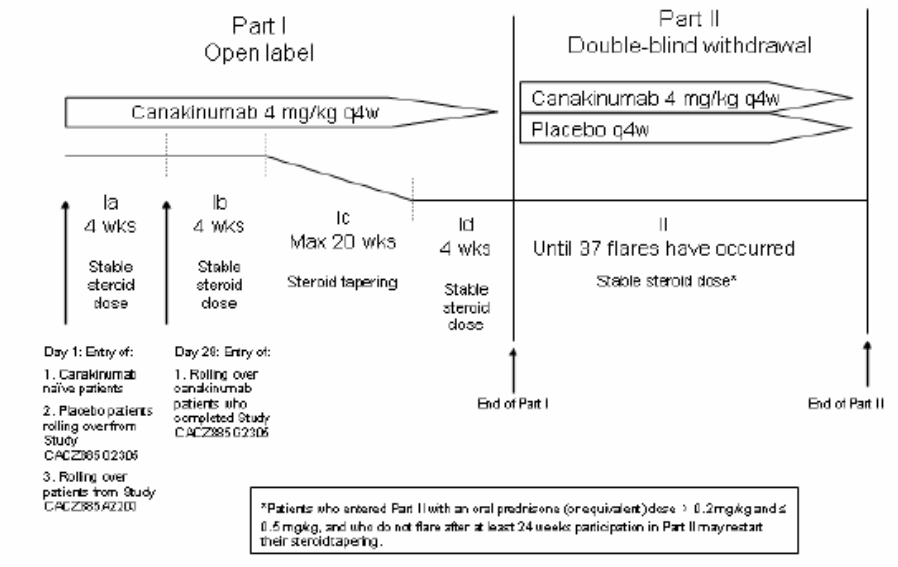
This was a multicentre two-part study with an open-label, single-arm active treatment (Part I) followed by a randomized, double-blind, placebo-controlled, event-driven withdrawal design (Part II). In Part I, patients received a single dose of canakinumab (4 mg/kg) subcutaneously (s.c.) every 4 weeks. Part I had four subparts. Parts Ia and Ib aimed 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 stabilize patients on an achieved steroid dose before entering Part II (withdrawal period). In Part II, patients were randomized to canakinumab or placebo in a 1:1 ratio, and received a s.c. injection of canakinumab (4 mg/kg) or placebo every 4 weeks.

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 actual median duration for all patients in Part I was approximately 16 weeks (maximum of 33.3 weeks).

The average planned duration of Part II was estimated to be 75 weeks resulting in an average total study duration of 109 weeks. The actual median duration in Part II was approximately 31.6 weeks in the canakinumab group (maximum of 88.1 weeks) and 23.4 weeks in the placebo group (maximum of 81 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.

Figure 15. Study design



Part I (open-label treatment period)

Part I was an open-label, active treatment period to identify canakinumab-treated patients who met the adapted ACR Pediatric 30 criteria (ACR30) at Day 15, and to allow for patients who continued to maintain a minimum ACR30 response at Day 57 to taper their steroid dose. The maximum duration of Part I was 32 weeks, corresponding to a maximum of 8 doses of canakinumab. Part I had 4 subparts: Ia to Id.

- Parts Ia and Ib aimed to induce and maintain at least an ACR30 response without steroid tapering.
- Parts Ic aimed to reduce steroid dose prior to the potentially long duration of Part II and to evaluate steroid tapering in responders.
- Parts Id was designed to stabilize patients on an achieved steroid dose before entering Part II (withdrawal period).

Part Ia

Once patient eligibility was confirmed at screening, patients entered Part Ia and received the first dose of canakinumab (4 mg/ kg) s.c. on Day 1. The duration of Part Ia was 4 weeks.

In brief, rollover patients eligible to enroll in Part Ia were the following:

- placebo patients from CACZ885G2305;
- canakinumab patients in CACZ885G2305 who did not complete the study or who were non-responders at Day 15; or
- patients who completed study CACZ885A2203 and flared ≥ 6 months after their last canakinumab dose

No steroid dose tapering was allowed. Steroid doses were to remain stable for the full duration of Part Ia.

Patients who met the ACR30 criteria at Day 15 continued in the study. Patients who did not maintain a minimum ACR30 response between Day 15 and Day 29 were discontinued from the study but were eligible to enter the extension study CACZ885G2301E1.

Part Ib

Patients who completed Part Ia and continued to meet at least an ACR30 entered Part Ib on Day 29. The duration for Part Ib was 4 weeks. Canakinumab patients who completed CACZ885G2305 and continued to meet a minimum adapted ACR30 were allowed to rollover into the study. No tapering of steroids was allowed. Steroid doses were to remain stable for the full duration of Part Ib. Patients who were steroid free and who completed Part Ib were able to enter Part Id directly.

Patients who did not maintain a minimum ACR30 response between Day 29 and Day 57 during Part Ib were discontinued from the study but were eligible to enter the extension study CACZ885G2301E1.

Part Ic (steroid tapering)

Patients who completed Part Ib and who entered the study using an oral steroid entered Part Ic and were observed for up to 20 weeks for their ability to taper/eliminate concomitant oral steroid use while maintaining an ACR30 response. Patients entering the study steroid-free could advance directly to Part Id.

Rules for steroid tapering were as follows

- Steroid tapering was initiated if the patient had achieved a minimum adapted ACR 50 and no fever.
- For oral prednisone (or equivalent) doses > 0.1 mg/kg/day, the dose was tapered at 0.1 mg/kg of oral prednisone (or equivalent) per week. If and when the oral prednisone (or equivalent) dose was at 0.1 mg/kg/day, the dose was reduced to 0.05 mg/kg/day of oral prednisone (or equivalent) for 1 week, then to 0.05 mg/kg/every 48 hours for the next 2 weeks and then discontinued.

Patients who did not maintain a minimum ACR30 response were discontinued from the study, but were eligible to enter the extension study CACZ885G2301E1 unless the loss of the ACR30 response was considered a consequence of steroid tapering.

Patients eligible for entry into Part Id and Part II were the following:

- 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.

Patients who were unable to reduce their steroid dose to qualify for Part Id and Part II were discontinued from the study, but were eligible to enter the extension study CACZ885G2301E1. Patients who were able to taper off of steroids prior to completing Part Ic and who maintained a minimum ACR30 entered Part Id.

Part Id

Steroid-free patients who completed Part Ib and patients who completed Part Ic entered Part Id, the duration of which was 4 weeks. No tapering of steroids was allowed. Steroid doses were to remain stable for the full duration of Part Id.

Patients who did not maintain a minimum ACR30 response were withdrawn from Part Id, but were eligible to enter the extension study CACZ885G2301E1. The purpose of Part Id was to ensure that patients had received at least 12 weeks of treatment with canakinumab prior to entering Part II, and

that patients who were on steroids were on a stable steroid dose for at least 4 weeks prior to entering Part II.

Part II (withdrawal period)

Patients who continued to meet at least an ACR30 at the end of Part I were randomized to either canakinumab or placebo in a ratio of 1:1. Patients received an s.c. injection of study drug (canakinumab 4 mg/kg or placebo) on the first day of Part II and thereafter every 4 weeks.

Randomization 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 Pediatric response reached at the end of Part Id (two strata: > adapted ACR Pediatric 50 criteria met [e.g., ACR70, 90 or 100], ≤ adapted ACR Pediatric 50 criteria met [e.g., ACR 30 or 50]).

Steroid doses were to remain stable for the first 24 weeks of treatment in Part II (i.e., no steroid tapering was allowed).

- Patients who were on ≤ 0.2 mg/kg oral prednisone (or equivalent) maintained their steroid dose for the first 24 weeks as well as the remainder of Part II.
- Patients on an oral prednisone (or equivalent) dose > 0.2 mg/kg and ≤ 0.5 mg/kg and no flare after at least 24 weeks participation could re-start steroid tapering. Patients who flared per definition or who did not maintain a minimum ACR30 response at any time during Part II, even if due to steroid tapering, were discontinued from Part II. They were eligible to enroll in the extension study CACZ885G2301E1.

Patients who flared per definition or who discontinued from the study while in Part II were counted as having a flare event in the primary analysis.

Patients who maintained a status of inactive disease for at least 24 weeks in Part II and then discontinued could enter the extension study CACZ885G2301E1 (e.g., to taper their steroids).

Study participants

Male or female patients aged 2 to <20 years with a confirmed diagnosis of sJIA as per International League Against Rheumatism (ILAR) definition at least 2 months prior to enrollment with an 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 study drug administration; and 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 was allowed with the exception of:

- Stable dose of methotrexate (maximum of 20 mg/ m2/ week) for at least 8 weeks prior to the screening visit, and folic/folinic acid supplementation (according to standard medical practice of the center)
- 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 randomization.

Treatments

In Part I, patients received a single dose of canakinumab (4 mg/kg) subcutaneously (s.c.) every 4 weeks. In Part II, patients received a single dose of canakinumab (4 mg/kg) or placebo s.c. every 4 weeks.

Objectives

The primary objective of the study in Part I was to assess if monthly canakinumab 4 mg/kg allowed tapering of steroids in at least 25% of patients. The main objective in part II was to demonstrate that the time to flare was longer with canakinumab than with placebo.

Outcomes/endpoints

Primary objective(s)

For Part I of the study, the primary objective is to assess if canakinumab allowed tapering of steroids as per protocol in at least 25% of the patients.

For Part II of the study, the primary objective is to demonstrate that the time to flare was higher with canakinumab than with placebo.

Secondary objectives

For Part I of the study, the secondary objectives are:

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

For Part II of the study, the secondary objective is:

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

For both Parts I and II of the study the secondary objectives are:

- 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©)
- To evaluate 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)
- To evaluate the safety, tolerability and immunogenicity of canakinumab
- To evaluate the pharmacokinetics (PK) / pharmacodynamic (PD) of canakinumab

Efficacy assessments consisted of the ability to taper steroids, flare events, the adapted ACR Pediatric response (components shown below), 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 variable for Part I was the proportion of patients who were on oral steroids at entry into Part I and who were able to taper oral steroid as per protocol, from start of Part I to end of Part Ic.

The primary efficacy variable for Part II was the time to a flare event in Part II. Flare events included flares as well as discontinuations from Part II of the study (for any reason other than inactive disease for at least 24 weeks in Part II).

Sample size

Anticipating a flare rate of 25% for the active group and 70% for the placebo group at week 24 and reasonable assumptions about the distribution of flares (exponential and a mixture of Weibull and exponential), it was calculated that 37 events were to be observed in order for a log-rank test (with 1-sided type I error 0.025) to detect such a difference in favour of the active treatment with 90% power. It was estimated that about 10% of the patients entering part I were steroid free and that 90% qualified for tapering steroids before entering part II. Among the steroid free patients, 60% were expected to respond to treatment with canakinumab in part I, 45% of patients on steroids entering part I qualify for steroid tapering, out of these patients 60% would successfully taper. Anticipating an overall 10% dropout rate, these assumptions resulted in about 214 patients to be enrolled into part I of the study in order to achieve about 58 patients to be randomized into the withdrawal part (part II) of the study.

Randomisation

Part II of the study has a randomized, double-blind, placebo-controlled, event-driven withdrawal design.

Patients were centrally randomized into part II of the trial in an 1:1 ratio (canakimumab:placebo) stratified for oral prednisone dose at the end of part I (≤ 0.4 mg/kg / > 0.4 mg/kg) and degree of adapted ACR Pediatric response at the end of part I (> ACR50 / ≤ ACR50).

Blinding (masking)

Part I was an open-label, active treatment period.

Part II is a double-blind, randomized, event-driven treatment period. The following blinding methods were used:

1. Randomization data were kept strictly confidential until the time of unblinding, and were not accessible by anyone else involved in the study with the exception of the independent, unblinded pharmacist/nurse/physician or authorized personnel at the investigator's site who prepared the study medication.
2. The identity of the canakinumab/placebo treatments were concealed by the use of study drugs in form of syringes filled with reconstituted canakinumab solutions that were all identical in appearance, but the actual canakinumab (or placebo) vials with lyophilisate were supplied "open-label".

Statistical methods

The confirmatory analysis was done for part II of the study. The primary (null-) hypothesis of shorter time to first flare in the canakinumab group (compared to placebo), versus the alternative of a prolonged time to flare under canakinumab (compared to placebo) was tested by means of a log-rank test stratified for the randomization strata applying a (one-sided) type I error of 0.025. In addition a COX-regression model (using randomisation strata as explorative variables) was used to calculate the hazard ration (HR) including the corresponding 95%-CI.

If the primary objective was achieved, all secondary endpoints in part II were assessed in a closed testing procedure according to a pre-defined hierarchy to evaluate the superiority of canakinumab over placebo. Testing was continued as long as each test showed statistical significance at the 2.5% level. The efficacy analyses were performed on the population of all subjects entering study part II who received a least one dose of study drug during this study part.

The data from the open-label, active treatment (part I) were analysed descriptively.

The Full Analysis Set (FAS) for Part I (Full Analysis Set I) consisted of all patients who received at least one dose of study drug in Part I.

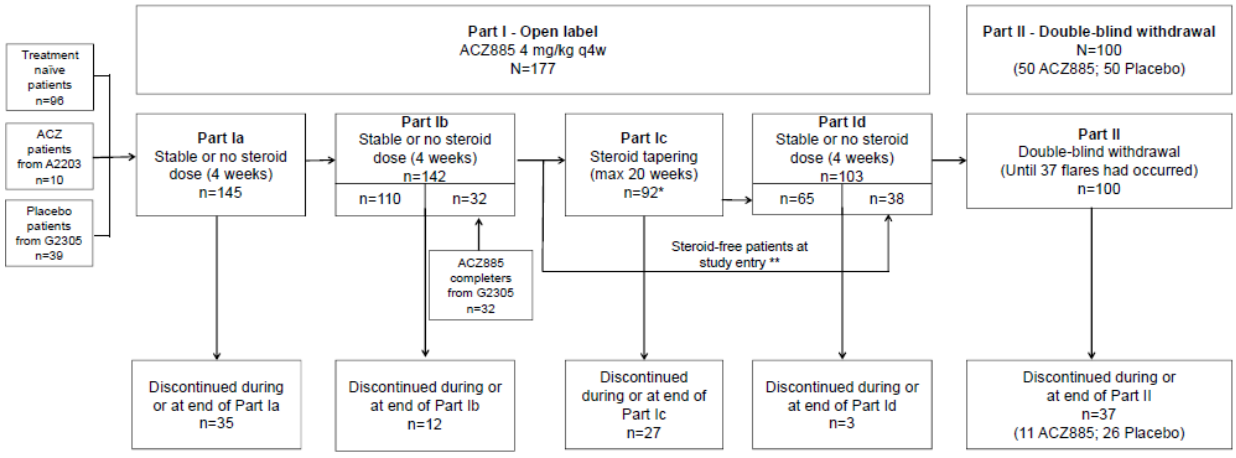
The FAS for Part II (Full Analysis Set II) consisted of all randomized patients who received at least one dose of study drug in Part II. Following the intent-to-treat principle, patients were analyzed according to the treatment they were assigned to at randomization in Part II.

There was no Per-Protocol Analysis Set.

Results

Participant flow

Figure 16. **Patient flow diagram (Safety Set I and Safety Set II)**



* Patients who were using steroids at study entry and met ACR30 criteria at the end of Part Ib could enter Part Ic
** Patients who were steroid free at study entry could enter Part Id directly without entering/completing Part Ic

Source: Table 10-1, Table 10-2, Table 14.1-3.5, Listing 16.2.4-2.1

Part I

A total of 177 patients entered Part I of the study.

Patients entered the study at Part Ia (135 treatment-naïve patients [including 96 who had no prior study participation and 39 patients who had received placebo in CACZ885G2305 and 10 patients who

had participated in study CACZ885A2203) or Part Ib (32 patients who had received canakinumab in study CACZ885G2305 and completed the study). Ninety-two patients using a steroid at baseline entered Part Ic and 103 patients entered Part Id.

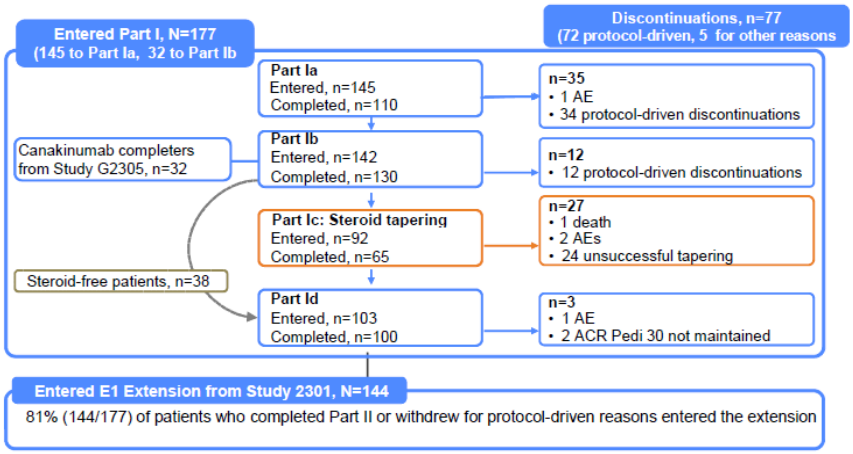
Table 26. Patient disposition in Part I (Safety Set I)

Disposition Reason	ACZ885 N=177 n (%)
Entered Part I	177
Completed Part I	100 (56.5)
Continued to Part II	100 (56.5)
Discontinued during or at end of Part I	77 (43.5)
Reason for discontinuation during or at end of Part I	
Death	1 (0.6)
Adverse event(s)	4 (2.3)
Unsatisfactory therapeutic effect	72 (40.7)
Entered Part Ia	145
Completed Part Ia	117 (80.7)
Continued to next Part	110 (75.9)
Discontinued during or at end of Part Ia	35 (24.1)
Reason for discontinuation during or at end of Part Ia	
Adverse event(s)	1 (0.7)
Unsatisfactory therapeutic effect	34 (23.4)
Entered Part Ib (1)	142
Completed Part Ib	131 (92.3)
Continued to next Part	129 (90.8)
Discontinued during or at end of Part Ib	12 (8.5)
Reason for discontinuation during or at end of Part Ib	
Unsatisfactory therapeutic effect	12 (8.5)
Entered Part Ic	92
Completed Part Ic	65 (70.7)
Continued to next Part	65 (70.7)
Discontinued during or at end of Part Ic	27 (29.3)
Reason for discontinuation during or at end of Part Ic	
Death	1 (1.1)
Adverse event(s)	2 (2.2)
Unsatisfactory therapeutic effect	24 (26.1)
Entered Part Id	103
Completed Part Id	100 (97.1)
Continued to next Part	100 (97.1)
Discontinued during or at end of Part Id	3 (2.9)
Reason for discontinuation during or at end of Part Id	
Adverse event(s)	1 (1.0)
Unsatisfactory therapeutic effect	2 (1.9)

Source: Table 14.1-1.1

The primary reason for discontinuation as given by the investigator on the study completion eCRF was summarized.
Number of patients entering a study part is used as denominator for relative frequencies of that part.
(1) Includes patients from study G2305 who enter Part Ib. Patients who discontinued during or at end of Part Ib and patients who continued to next Part do not add up to all patients who entered Part Ib as the "Study Phase (Ib) completion" page on the eCRF was not filled in for Patient 93/101.

Figure 17. Disposition of patients (Study G2301 Part 1)



Source: [SCE-Table 3-5], [Study G2301-Table10-1] (part I) and [Study G2301E1-Section 10] (extension)

The primary reason for discontinuation from Part I of the study was unsatisfactory therapeutic effect for 72 (40.7%) patients. All 72 patients were withdrawn by the investigator for protocol-driven, efficacy-related reasons (i.e., no initial response at Day 15 [n=27] or loss of response after Day 15 [n=15], steroid tapering failure [n=26], and pre-protocol Amendment 1, i.e., CRP ≥10mg/L [n=2] or flare [n=2])

Most of the 72 patients (46, 63.9%) were studied further after entry into the extension study. Note that patients who discontinued for failure to achieve an initial response at Day 15 in Part Ia were not allowed by protocol to enter the extension.

Part II

A total of 100 patients entered the randomized, double-blind withdrawal period in **Part II** (50 in each treatment group) and 63 completed (i.e., had no flare event) Part II (78% canakinumab; 48% placebo) (Table 10-2). Patients were considered to have completed the study if they either i) achieved 24 consecutive weeks of inactive disease or ii) were still active in Part II at the time of study closure (i.e., 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.

One patient, in the placebo group, was discontinued due to a protocol deviation (unblinding due to serious adverse event of gastrointestinal viral infection) (Patient 0042/00101).

Table 27. Patient disposition in Part II (Safety Set II)

Disposition Reason	ACZ885 N=50 n (%)	Placebo N=50 n (%)	Total N=100 n (%)
Randomized in Part II	50	50	100
Completed Part II	39 (78.0)	24 (48.0)	63 (63.0)
Discontinued during Part II	11 (22.0)	26 (52.0)	37 (37.0)
Reason for discontinuation during Part II			
Adverse event(s)	0 (0.0)	4 (8.0)	4 (4.0)
Unsatisfactory therapeutic effect	11 (22.0)	20 (40.0)	31 (31.0)
Subject withdrew consent	0 (0.0)	1 (2.0)	1 (1.0)
Protocol deviation	0 (0.0)	1 (2.0)	1 (1.0)

Source: Table 14.1-1.2

The primary reason for discontinuation as given by the investigator on the study completion eCRF was summarized.
Number of randomized patients is used as denominator for relative frequencies.

Recruitment

First patient enrolled: 06-Jul-2009

Last patient completed: 12-Sep-2011

Conduct of the study

The study protocol was amended seven times. Previous sections of this report describe the study conduct as amended. The key features of each amendment are summarized below:

Protocol Amendment 1 was written to change 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 CACZ885G2305 and CACZ885A2203 studies was changed so that the requirement of intermittent fever and CRP > 30 mg/L would not be applicable.

Protocol Amendment 2 was written to ensure patients from study CACZ885A2203 could continue to receive continuous treatment in subsequent phase III studies provided that the patient did not meet the discontinuation criteria of CACZ885A2203 or the safety discontinuation criteria of CACZ885G2301.

Protocol Amendment 3 was written to ensure 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 CACZ885G2305 placebo patients to the CACZ885G2301 study if they did not maintain a minimum ACR30 response between Days 15 and 29; and to clarify the handling of CACZ885A2203 rollover patients when there was a gap of at least 6 months between the patient's last dose in CACZ885A2203 and entry into CACZ885G2301. 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 was written to describe the implementation of 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 was written to introduce the possibility performing an interim analysis, (which, in finality, was not performed). This amendment also adjusted the statistical hypothesis in the statistical methods section for Part I to be fully aligned with the objective. These amendments were not considered to have affected the interpretation of study results as they were minor and occurred prior to study unblinding.

No other changes in study conduct occurred.

Changes in planned analysis

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 randomization) 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 improvement 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 vs. that of the investigator-calculated prednisone equivalent dose in the clinical database.

Protocol deviations – Part I (open-label treatment)

The majority of patients had at least one protocol deviation in Part I (72.3%), most of which were minor. Protocol deviations for exclusion from a per protocol analysis were pre-defined although a per protocol analysis was not planned nor performed. A total of 8 (4.5%) patients had this type of protocol deviation: 4 patients with loss in ACR response (after an initial response) who were not discontinued, 2 patients for whom steroid tapering was not initiated (based on investigator's judgment) although they were 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.

Protocol deviations – Part II (double-blind placebo withdrawal period)

The number of patients with at least one protocol deviation in Part II is 31 (62%) in the canakinumab group and 33 (66%) in the placebo group. Protocol deviations for exclusion from a per protocol analysis were not planned nor performed.

Baseline data

Demographic and other baseline characteristics – Part I (open-label treatment)

Baseline demographics of patients entering Part I are shown in the table below. Most (85.3%) were Caucasian, gender was distributed comparably (45% male, 55% female), and the average age was 8.7 years with a large proportion of patients aged 6-11 years (43%).

Table 28. Demographics (Full analysis set)

	ACZ885 N=177
Sex - n (%)	
Male	79 (44.6)
Female	98 (55.4)
Age (years)	
n	177
Mean	8.7
S.D.	4.46
Median	8.0
Min–Max	1, 19
Age groups - n (%)	
2 - <4 years	21 (11.9)
4 - <6 years	32 (18.1)
6 - <12 years	76 (42.9)
12 - <20 years	48 (27.1)
>= 20 years	0 (0.0)
Predominant Race - n (%)	
Caucasian	151 (85.3)
Black	7 (4.0)
Asian	6 (3.4)
Native American	1 (0.6)
Pacific Islander	0 (0.0)
Other	12 (6.8)
BMI (kg/m2)**	
n	167
Mean	18.98
S.D.	4.878
Median	17.35
Min–Max	13.1, 41.3

Source: Table 14.1-3.1

Age group 2 - <4 years includes one patient who was 1 year old at date of screening and 2 years old at date of first study dose.

Body Mass Index: BMI (kg/m**2) = weight(kg)/[(height(cm) /100)**2].

Disease history of patients entering Part I is shown in the table below.

Table 29. Disease history and baseline characteristics (Full analysis set)

	ACZ885 N=177
Body temperature (°C)	
n	177
Mean	37.175
S.D.	0.8448
Median	37.100
Min–Max	35.10, 39.50
Pattern of onset of arthritis in the first 6 months of disease	
Polyarthritis	133 (75.1%)
Oligoarthritis	35 (19.8%)
Monoarthritis	3 (1.7%)
No arthritis	6 (3.4%)
Pattern of onset of arthritis after the first 6 months of disease	
Polyarthritis	141 (79.7%)
Oligoarthritis	25 (14.1%)
Monoarthritis	1 (0.6%)
No arthritis	2 (1.1%)
Presence of systemic signs after the first 6 months of disease - n (%)	
No	23 (13.0)
Yes	148 (83.6)
Missing	6 (3.4)
Time from sJIA diagnosis to study entry (days)	
n	124
Mean	1123.8
S.D.	1098.91
Median	757.0
Min–Max	56, 5367
CRP at baseline (standardized in mg/L)	
n	177
Mean	198.43
S.D.	146.629
Median	160.000
Min–Max	3.3, 742.0
Number of flares in the past 12 months – n (%)	
0	13 (7.3)
1	56 (31.6)
2	35 (19.8)
3 to 5	40 (22.6)
6 to 10	14 (7.9)
11 to 15	7 (4.0)
Continuous flare (>15 or indefinable)	7 (4.0)
Missing	5 (2.8)
Oral steroid free at baseline - n (%)	
No	128 (72.3)
Yes	49 (27.7)
Oral prednisone equivalent dose at baseline (mg/kg/day)	

	ACZ885 N=177
n	128
Mean	0.369
S.D.	0.2750
Median	0.270
Min–Max	0.02, 1.00
Oral prednisone equivalent dose at baseline - n (%)	
no prednisone	49 (27.7)
>0 to <=0.4 mg/kg/day oral prednisone (or equivalent)	83 (46.9)
>0.4 mg/kg/day oral prednisone (or equivalent)	45 (25.4)
Methotrexate-free at baseline – n (%)	
No	93 (52.5)
Yes	84 (47.5)
NSAID-free at baseline – n (%)	
No	117 (66.1)
Yes	60 (33.9)
Physician's global assessment of disease activity (VAS*) (mm)	
n	177
Mean	66.5
S.D.	18.89
Median	70.0
Min–Max	12, 100
Patient's/parent's assessment of overall wellbeing (VAS*) (mm)	
n	176
Mean	60.7
S.D.	25.64
Median	63.5
Min–Max	0, 100
Number of active joints	
n	177
Mean	14.9
S.D.	13.65
Median	10.0
Min–Max	0, 66
Number of active joints - n (%)	
<=26	143 (80.8)
>26	34 (19.2)
Number of joints with limitation of motion	
n	177
Mean	14.7
S.D.	14.35
Median	9.0
Min–Max	0, 62

Source: Table 14.1-3.3

C-reactive protein level standardized to the range 0-10 mg/L.

* assessed on a 100mm scale (100 representing the worst score)

Prior use of biologic drugs, specifically anakinra, tocilizumab, etanercept, abatacept, and adalimumab:

- A total of 83 (46.9%) patients had prior use of anakinra; the drug had been discontinued for lack of efficacy (n=37, 20.9%), lack of tolerability (n=20, 11.3%), or for "other" reason. Thirty-seven (20.9%) reported being a non-responder.
- A total of 58 (32.8%) patients had prior use of etanercept; in most cases (n=56, 31.6%) it had been discontinued due to lack of efficacy with a few cases for "other" reason. Fiftysix (31.6%) reported being a non-responder.
- A total of 10 (5.6%) patients had prior use of tocilizumab; the drug had been discontinued for either lack of efficacy or lack of tolerability
- A total of 9 (5.1%) patients had prior use of adalimumab and all had discontinued due to lack of efficacy
- No patients reported prior use of abatacept

Most patients had a relevant past or current medical history/condition coming into Part I of the study (80.2%). The most common histories by preferred term (i.e., ≥5.0%) were anemia (10.7%), varicella (9.6%), pyrexia (8.5%), arthralgia (7.9%), cough (7.9%), eczema (7.9%), histiocytosis hematophagic (preferred term for MAS) (6.8%), rash (5.6%), hypertension (5.1%), and abdominal pain (5.1%). The more common events were reported in a similar or slightly higher percentage of the patients who were taking oral steroids at study entry. The profile of medical histories was as expected for this patient population.

Demographic and other baseline characteristics – Part II (double-blind withdrawal period)

Baseline demographics and disease characteristics of patients randomized into Part II are shown in Table 11-5 and Table 11-6, respectively. Demographics were similar between treatment groups although fewer patients were 4-5 years old in the canakinumab group (10%) compared to the placebo group (22%) and more patients were 6-11 years old in the canakinumab group (48%) compared to the placebo group (36%).

Disease history was broadly similar between the two treatment groups with the following exceptions:

- The median time from sJIA diagnosis to study entry (~2.7 years for canakinumab vs. ~1.8 years for placebo)
- 2 or more flares in the 12 months prior to study entry (58% of canakinumab patients vs. 40% of placebo patients)
- The presence of systemic signs after the first 6 months of disease (90% of canakinumab patients vs. 72% of placebo patients)

Comparability between the two treatment groups showed no significant differences for any baseline demographic or disease characteristic.

Table 30. Demographic according to randomization in Part II (Full analysis set)

	ACZ885 N=50	Placebo N=50	Total N=100
Sex - n (%)			
Male	22 (44.0)	23 (46.0)	45 (45.0)
Female	28 (56.0)	27 (54.0)	55 (55.0)
Age (years)			
n	50	50	100
Mean	9.1	9.0	9.1
S.D.	4.18	4.76	4.45
Median	8.0	8.0	8.0
Min–Max	2, 18	3, 19	2, 19
Age groups - n (%)			
2 - <4 years	5 (10.0)	5 (10.0)	10 (10.0)
4 - <6 years	5 (10.0)	11 (22.0)	16 (16.0)
6 - <12 years	24 (48.0)	18 (36.0)	42 (42.0)
12 - <20 years	16 (32.0)	16 (32.0)	32 (32.0)
>= 20 years	0 (0.0)	0 (0.0)	0 (0.0)
Predominant Race - n (%)			
Caucasian	41 (82.0)	42 (84.0)	83 (83.0)
Black	2 (4.0)	1 (2.0)	3 (3.0)
Asian	3 (6.0)	2 (4.0)	5 (5.0)
Other	4 (8.0)	5 (10.0)	9 (9.0)
BMI (kg/m2)**			
n	47	48	95
Mean	19.91	18.73	19.31
S.D.	5.955	4.499	5.275
Median	18.11	17.32	17.47
Min–Max	13.8, 41.3	13.1, 34.2	13.1, 41.3

Source: Table 14.1-3.2

Body Mass Index: BMI (kg/m**2) = weight(kg)/[(height(cm) /100)**2].

Table 31. Disease history and baseline characteristics according to randomization in Part II (Full analysis set)

	ACZ885 N=50	Placebo N=50	Total N=100
Body temperature (°C)			
n	50	50	100
Mean	37.258	37.172	37.215
S.D.	0.9174	0.9046	0.9075
Median	37.050	37.050	37.050
Min–Max	35.10, 39.40	35.50, 39.50	35.10, 39.50
Pattern of onset of arthritis in the first 6 months of disease			
Polyarthritis	36 (72.0)	36 (72.0)	72 (72.0)
Oligoarthritis	11 (22.0)	12 (24.0)	23 (23.0)
Monoarthritis	2 (4.0)	0 (0.0)	2 (2.0)
No arthritis	1 (2.0)	2 (4.0)	3 (3.0)
Pattern of onset of arthritis after the first 6 months of disease			
Polyarthritis	37 (74.0)	36 (72.0)	73 (73.0)
Oligoarthritis	11 (22.0)	8 (16.0)	19 (19.0)
Monoarthritis	1 (2.0)	0 (0.0)	1 (1.0)
No arthritis	0 (0.0)	1 (2.0)	1 (1.0)
Presence of systemic signs after the first 6 months of disease - n (%)			
No	4 (8.0)	11 (22.0)	15 (15.0)
Yes	45 (90.0)	36 (72.0)	81 (81.0)
Missing	1 (2.0)	3 (6.0)	4 (4.0)
Time from sJIA diagnosis to study entry (days)			
n	36	39	75
Mean	1349.8	973.2	1154.0
S.D.	1102.57	1110.01	1115.15
Median	1000.0	658.0	806.0
Min–Max	136, 4517	56, 5367	56, 5367
CRP at baseline (standardized in mg/L)			
n	50	50	100
Mean	182.79	182.19	182.49
S.D.	164.772	141.225	152.675
Median	120.65	148.60	137.90
Min–Max	6.0, 651.2	5.6, 742.0	5.6, 742.0
Number of flares in the past 12 months			
0	4 (8.0)	6 (12.0)	10 (10.0)
1	14 (28.0)	23 (46.0)	37 (37.0)
2	9 (18.0)	6 (12.0)	15 (15.0)
3 to 5	11 (22.0)	7 (14.0)	18 (18.0)
6 to 10	5 (10.0)	6 (12.0)	11 (11.0)
11 to 15	2 (4.0)	1 (2.0)	3 (3.0)
Continuous flare (>15 or indefinable)	2 (4.0)	0 (0.0)	2 (2.0)

Missing	3 (6.0)	1 (2.0)	4 (4.0)
Oral steroid free at baseline - n (%)			
No	32 (64.0)	30 (60.0)	62 (62.0)
Yes	18 (36.0)	20 (40.0)	38 (38.0)
Oral prednisone equivalent dose at baseline (mg/kg/day)			
n	32	30	62
Mean	0.292	0.353	0.321
S.D.	0.2546	0.2571	0.2555
Median	0.200	0.270	0.260
Min–Max	0.02, 1.00	0.03, 0.97	0.02, 1.00
Oral prednisone equivalent dose at baseline* - n (%)			
no prednisone	18 (36.0)	20 (40.0)	38 (38.0)
>0 to <=0.4 mg/kg/day oral prednisone (or equivalent)	25 (50.0)	22 (44.0)	47 (47.0)
>0.4 mg/kg/day oral prednisone (or equivalent)	7 (14.0)	8 (16.0)	15 (15.0)
Methotrexate-free at baseline – n (%)			
No	28 (56.0)	26 (52.0)	54 (54.0)
Yes	22 (44.0)	24 (48.0)	46 (46.0)
NSAID-free at baseline – n (%)			
No	28 (56.0)	32 (64.0)	60 (60.0
Yes	22 (44.0)	18 (36.0)	40 (40.0)
Physician's global assessment of disease activity (VAS) (mm)			
n	50	50	100
Mean	60.0	64.7	62.4
S.D.	21.12	17.81	19.58
Median	60.0	66.0	63.0
Min–Max	12, 100	25, 100	12, 100
Patient's/Parent's assessment of overall wellbeing (VAS) (mm)			
n	50	49	99
Mean	58.1	60.5	59.3
S.D.	24.28	26.20	25.15
Median	63.0	60.0	62.0
Min–Max	0, 95	0, 98	0, 98
Number of active joints			
n	50	50	100
Mean	10.5	11.6	11.1
S.D.	11.19	10.72	10.92
Median	7.0	7.5	7.0
Min–Max	2, 48	0, 43	0, 48
Number of active joints - n (%)			
<=26	45 (90.0)	45 (90.0)	90 (90.0)
>26	5 (10.0)	5 (10.0)	10 (10.0)
Number of joints with limitation of motion			
n	50	50	100
Mean	10.8	12.3	11.6
S.D.	12.60	12.20	12.36
Median	6.0	7.0	6.5
Min–Max	0, 56	0, 47	0, 56

Source: Table 14.1-3.4
C-reactive protein level standardized to the range 0-10 mg/L.

Numbers analysed

All enrolled patients (N=177) were included in the Part I safety and full analysis sets.

All randomized patients (N=100) were included in the Part II safety and full analysis sets.

Outcomes and estimation

Analysis of efficacy – Part I

Primary efficacy results – Part I (open-label treatment)

The primary objective of Part I of the study was to assess if canakinumab allowed tapering of steroids as per protocol in at least 25% of the patients who entered the study taking a steroid. The objective was achieved as 44.5% of the 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) (Table 11-7).

Of those patients who entered Part Ic taking an oral steroid, 62% (57/92) were able to successfully taper their steroid dose.

Table 32. Oral steroid tapering in Part I (Full analysis set I)

	Patients taking oral steroids at entry of study Part	ACZ885 N=177 Able to taper oral steroids			
Study Part	m (%)		n (n/m %)	90% exact CI	p-value(1)
Part I	128 (72.3)	No	71 (55.5)	(47.8, 62.9)	
		Yes	57 (44.5)	(37.1, 52.2)	<.0001 *
Part Ic	92 (52.0)	No	35 (38.0)	(29.6, 47.1)	
		Yes	57 (62.0)	(52.9, 70.4)	

Source: Table 14.2-1.1

Patients on oral steroids at study entry who do not enter Part Ic are considered steroid tapering failures.
Ability to taper oral steroids: Yes if dose reduced from start of Part I to end of Part Ic from > 0.8 mg/kg/day to ≤ 0.5 mg/kg/day, or from ≥ 0.5 mg/kg/day and ≤ 0.8 mg/kg/day by at least 0.3 mg/kg, or from any initial dose to ≤ 0.2 mg/kg/day, while maintaining a minimum adapted ACR 30 pediatric criterion.
(1) p-value from exact one-sided binomial test for percentage of patients able to taper steroids ≥ 25%.
* Statistically significant on one-sided significance level 0.05. (Statistical analysis not performed for subgroup of patients on steroids at Part Ic entry.)

The primary analysis was repeated including only those patients who were taking steroids >0.2 mg/kg/day at study entry and the results were consistent. Of the 78 patients in this subcategory, 34 (43.6%) were able to successfully taper their steroid regimen according to the protocol-defined criteria (p=0.0003; 90% CI: 34.0, 53.5).

Novartis calculated the prednisone equivalent daily dose as an exploratory evaluation. The results of a post hoc sensitivity analysis were similar to those of the a priori analysis shown in Table 11-7: 43.8% of the 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: 36.3, 51.4).

Secondary efficacy results – Part I (open-label treatment)

Steroid reduction

Of the 128 patients taking oral steroids at study entry,

- 92 (71.9%) had a minimum ACR50 response at the end of Part Ib; of these, 87 were eligible to enter Part Ic and taper steroids
- 10 (7.8%) had a maximum ACR30 response at the end of Part Ib; of these, 4 were eligible to enter Part Ic and taper steroids
- 26 (20.3%) were non-responders at the end of Part Ib and were ineligible to enter Part Ic and taper steroids. However, 1 of the 26 non-responders did enter Part Ic (protocol deviation). This patient (0034/00106) who was not a successful steroid taperer, was still a non-responder at the end of Part Ic and was then discontinued from the study.

The number of patients who were steroid free or who had an oral steroid dose at a level of > 0mg/kg and ≤ 0.2 mg/kg or > 0.2 mg/kg at the end of Part Ic is shown in the table below.

About one-half of the patients who entered Part I taking oral steroids had an oral steroid dose ≤ 0.2 mg/kg at the end of Part Ic (66/128, 51.6%); the majority of these patients were steroid free (42/66, 63.6%).

The majority of the patients who entered Part Ic taking oral steroids had an oral steroid dose ≤0.2 mg/kg at the end of Part Ic (66/92, 71.7%), and the majority of these patients were steroid free (42/66, 63.6%).

Table 33. Oral steroid dose at end of Part Ic (Full analysis set)

	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)

Source: Table 14.2-2.1

(1) Oral prednisone equivalent dose.
Last observation (in Part Ic) carried forward was used.

The level of steroid tapering achieved in successful steroid taperers is provided in the table below. Most of the patients who entered the study taking oral steroids at baseline were taking < 0.5 mg/kg/d.

Table 34. Level of steroid tapering in successful steroid taperers (Full analysis set I)

Patients taking oral steroids at study entry (N=128)		Patients taking oral steroids at start of Part Ic (N=92)		Successful steroid taperers at end of Part Ic (N=57)	
Steroid dose at baseline	n (%)	Steroid dose at baseline	n (%)	Steroid dose at end of Part Ic	n (%)
> 0.8 mg/kg/d	14 (10.9)	> 0.8 mg/kg/d	10 (10.9)	>0 and ≤ 0.5 mg/kg/d	1 (1.8)
				Steroid free	3 (5.3)
≥ 0.5 - ≤ 0.8 mg/kg/d	22 (17.2)	≥ 0.5 - ≤ 0.8 mg/kg/d	18 (19.6)	Reduced by ≥ 0.3 mg/kg/d	11 (19.3)
				Steroid free	4 (7.0)
< 0.5 mg/kg/d	92 (71.9)	< 0.5 mg/kg/d	64 (69.6)	>0 and ≤ 0.2 mg/kg/d	8 (14.0)
				Steroid free	34 (59.6)
Any dose	128 (100)	Any dose	92 (100)	>0 and ≤ 0.2 mg/kg/d	12 (21.0)
				Steroid free	41 (71.9)

Source: Listing 16.2.6-1.1, Table 14.2-2.1, Table 14.2-2.3

As shown in Table 11-8, a total of 66 patients were either steroid free (n=42) or on a low dose of steroids (≤0.2 mg/kg/day) (n=24) at the end of Part Ic. Of these 66, a total of 53 patients were successful steroid taperers (see table above). Therefore, a total of 13 patients were either steroid free (n=1) or on a low dose of steroids (n=12) at the end of Part Ic, yet they were not among the group of successful steroid taperers. The reasons may have included the following:

patients were not eligible for steroid tapering (including not having a qualifying CRP level as required prior to Protocol Amendment 5 or not having a minimum ACR50 at the end of Part Ic), tapering was not initiated at the investigator's discretion, or an ACR measurement was not available at the end of Part Ic.

For the 57 patients who achieved successful steroid tapering at the end of Part Ic, the median baseline dose was 0.27 mg/kg/day, and the median change from baseline was -0.26 mg/kg/day, a median percentage change of -100% (see table below).

Table 35. Change from baseline in oral steroid dose (mg/kg/day) to end of Part Ic in successful steroid taperers (Full analysis set I)

Time point	Statistics	Baseline value	Post-baseline	Change from baseline	
				Change	Percentage
End of Part Ic					
	n	57	57	57	57
	Mean	0.344	0.045	-0.299	-90.08
	S.D.	0.2714	0.1002	0.2412	18.433
	Median	0.270	0.000	-0.260	-100.00
	Min , Max	0.02 , 1.00	0.00 , 0.48	-0.97 , -0.02	-100.0 , -38.9

Source: Table 14.2-2.2
(1) Last observation carried forward has been used.
Oral prednisone equivalent dose is evaluated.
Only patients with a value at both baseline and end of Part Ic are included.
Reduction from baseline: Change = (end of Part Ic value - baseline value).
Percentage = (Change / baseline value) * 100.

Effect on body temperature

At Day 3 of Part Ia, nearly all of the patients with body temperature measurements had no fever (≤38° C) (139/141, 98.6%). The mean baseline body temperature for all 177 patients in Part I was 37.18°C.

Response according to adapted ACR pediatric criteria

At Day 15 in Part Ia, 81.3% were responders, 58.3% had a minimum ACR70, and 18.0% had an ACR100.

At Day 29 (end of Part Ia/beginning of Part Ib), 88.8% were responders, 68.8% had a minimum ACR70, and 30.6% had an ACR100.

At Day 57 (end of Part Ib), 94.3% were responders, 78.7% had a minimum ACR70, and 38.3% had an ACR100.

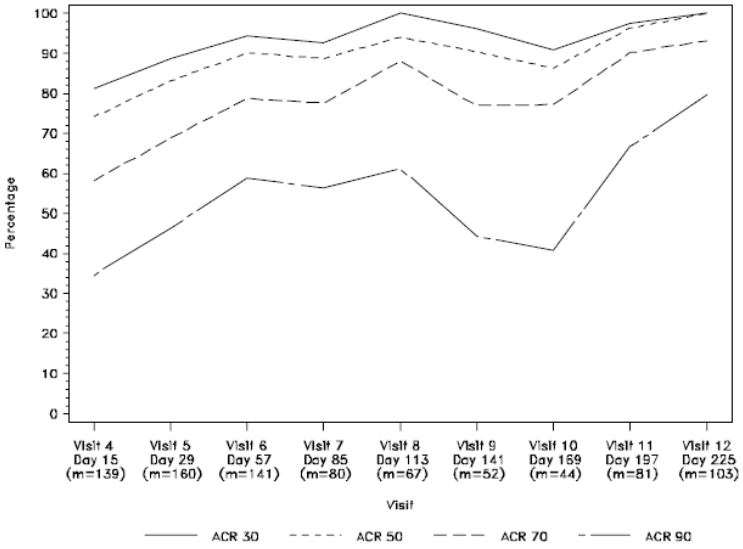
The time spent in Part Ic, the steroid tapering phase of the study, varied depending on the success of oral steroid tapering. If successful, a patient would continue to Part Id; if not, the patient remained in Part Ic for the maximum time allotted (20 weeks). In general, during Part Ic, the proportion of patients with a minimum ACR30/50/70/90 response remained fairly stable, however, the proportion with a minimum ACR100 decreased over time (e.g., from 28.8% [23/80] at Day 85 to 15.9% [7/44] at the last Part Ic visit, Day 169). (Note that the number of patients with data decreased over time in Part Ic.)

At the end of Part Id (Day 225), 100% were responders, 93.2% had a minimum ACR70, and 55.3% had an ACR100.

At the end of Part I (last assessment available): 77.1% were responders, 64.6% had a minimum ACR70, and 34.3% had an ACR100.

The minimum ACR response achieved over time in Part I is shown graphically in the figure below.

Figure 18. Mininum ACR pediatric response level achieved in Part I, by visit (Full analysis set I)



Approximately 30-40% of the patients with a minimum ACR50 or ACR70 had elevated CRP levels during the course of the study.

About 50% of the 65 patients who achieved a minimum ACR50 or ACR70 and had a normalized CRP in Part I did so within 15 and 16 days, respectively. A total of 37 patients had previously used and discontinued anakinra due to lack of efficacy. Of the 37 patients, 5 entered Part Ib directly from CACZ885G2305 and were responders at Day 15 of that study. Of the remaining 32 patients, 19 (59.4%) were responders at Day 15 of this study (2 with ACR30, 4 with ACR50, 7 with ACR70, 2 with ACR90 and 4 with ACR100), 11 were non responders and 1 had a missing assessment (patient 40/110 as discontinued at Day 4).

The level of adapted ACR pediatric response was assessed at the time of the visit by a standardized procedure at PRINTO/PRCSG. These data were recalculated by Novartis after database lock when it could be assured that the data had been verified. Relevant differences in ACR response in Part I of the study were the following:

- Five patients who were ACR responders per PRINTO/PRCSG were non-responders (0059/00101, 0060/00102, 0040/00119, 0040/00103, 0040/00116), and two patients who were non-responders per PRINTO/PRCSG were ACR responders (0040/00108 and 0207/00101) at one or more visits following Novartis' recalculation.

CHAQ

The CHAQ functional ability score is the third response variable in the adapted ACR pediatric criteria. At baseline, the median CHAQ score was 1.8.

From the beginning of Part Ia to the start of Part Ic, the median change from baseline showed a strong improvement starting at Day 15 (-0.6, -54.4%) with further improvement at Day 57 (-1.0, -80.7%).

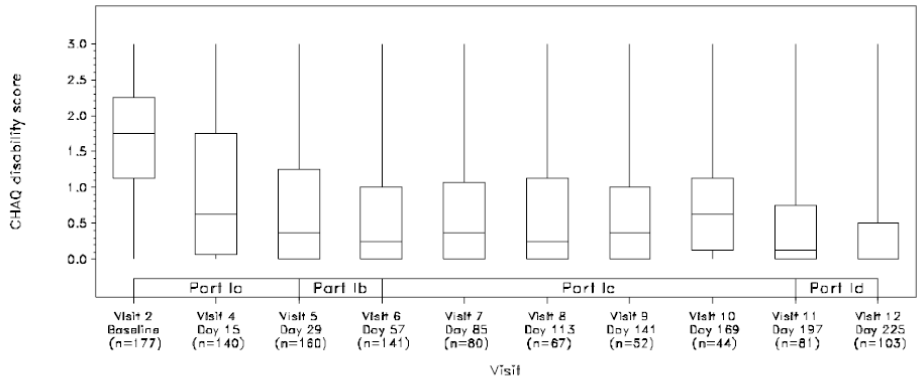
During Part Ic (steroid tapering), the level of improvement seen earlier in the study decreased, as reflected by the median change from baseline at Day 85 (-0.9 [-75.0% improvement]) and at Day 169 (-0.8 [-61.5% improvement]), which would be expected as a result of the design of this portion of the study.

At the end of Part Id (Day 225), the median change from baseline was -1.3 (-100%) showing resumption of continued CHAQ score improvement for responders to canakinumab treatment.

For each time point shown, the median change from baseline showed a treatment effect that was several times the cited minimal clinical important difference (MCID) of -0.19 (Brunner, et al 2005). The median change from baseline at the end of Part I of -0.9 (-79.4%) indicates a treatment effect that is approximately 4.6 times the MCID.

The degree of improvement seen with canakinumab treatment in the CHAQ disability score in Part I is show graphically over time in the figure below.

Figure 19. CHAQ disability score in Part I. by visit (Full analysis set I)



Source: Figure 14.2-1.3
Only patients with a value at both baseline and the respective post-baseline time point are included.
Boxes were drawn between quartiles with median line crossing. Whiskers expand to minimum or maximum.
Patients who discontinue had an additional measurement shown at the end of the part they discontinued.

- From the beginning of Part Ia to the start of Part Ic, the percentage of patients showing a MCID of improvement was high and increased with continued canakinumab treatment (103/140 [73.6%] at Day 15 to 118/141 [83.7%] at Day 57).
- During Part Ic (steroid tapering), a MCID of improvement was seen consistently in ≥80% of patients (e.g., 65/80 [81.3%] at Day 85, 58/67 [86.6%] at Day 113, 43/52 [82.7%] at Day 141, and 38/44 [86.4%] at Day 169).
- At the end of Part Id (Day 225), the percentage of patients showing an MCID of improvement relative to baseline was 91/103, 88.3%.
- At the end of Part I (last assessment available), 135/175 patients (77.1%) showed an MCID of improvement in the CHAQ disability score.

CHQ-PF50

Health-related quality of life was assessed in patients aged 5-18 years old using the CHQPF50.

For the CHQ physical health score:

- From the beginning of Part Ia to the start of Part Ic, the median change from baseline showed an improvement starting at Day 15 (14.0 [+46.8%]) that increased over time (23.3 [+75.5%] at Day 57).
- During Part Ic, an improved score was evident despite the intervention of steroid tapering (median changes from baseline of 26.1 (+80.8%) at Day 141 and 25.2 (+78.5%) at Day 197).
- At the end of Part Id (Day 225), the median change from baseline was 25.1 (+94.0%).

- At the end of Part I (last assessment available), the median change from baseline was 21.8 (+74.0%).

For the CHQ psychosocial health score:

- From the beginning of Part Ia to the start of Part Ic, the median change from baseline showed an improvement starting at Day 15 (5.5 [+11.9%]) that increased over time (9.8 [+21.3%] at Day 57).
- During Part Ic, an improved score was maintained despite the intervention of steroid tapering (median changes from baseline of 14.2 [+32.0%] at Day 141 and 11.9 [+29.2%] at Day 197).
- At the end of Part Id (Day 225), the median change from baseline was 11.8 (+30.6%).
- At the end of Part I (last assessment available), the median change from baseline was 8.2 (+21.7%).

Analysis of efficacy – Part II

Part II of the study was a double-blind withdrawal treatment period. Patients were randomized in Part II to canakinumab or placebo in a 1:1 ratio. It should be kept in mind that patients in the placebo group had received canakinumab in Part I of the study.

Primary efficacy results – Part II (double-blind withdrawal period)

The primary objective of Part II was to demonstrate that the time to flare was higher with canakinumab than with placebo. Patients who flared per definition or who discontinued from the study while in Part II (for any reason other than inactive disease were counted as having a flare event in the primary analysis. A total of 6 patients discontinued from Part II for reasons other than flare or lack of efficacy (loss of ACR response), and they all were in the placebo group: 4 due to adverse events, 1 due to protocol deviation (unblinding due to SAE), and 1 due to withdrawal of consent.

The study achieved the primary objective of Part II. The probability to experience a flare event in Part II was lower for canakinumab treatment compared with placebo treatment (see table below). This corresponds to a statistically significant relative risk reduction to flare of 64% (hazard ratio of 0.36; 95% CI: 0.17 to 0.75; p=0.0032). The median time to flare, which was 236 days for the placebo group, was not observed for the canakinumab group as less than 50% of patients experienced a flare event in Part II.

Table 36. Survival analysis of time to flare in Part II (Full analysis set II)

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

Source: Table 14.2-1.3

Log-rank test adjusted for stratification factors prednisone (or equivalent) dose and ACR 70 Pediatric response reached at the end of Part Id.

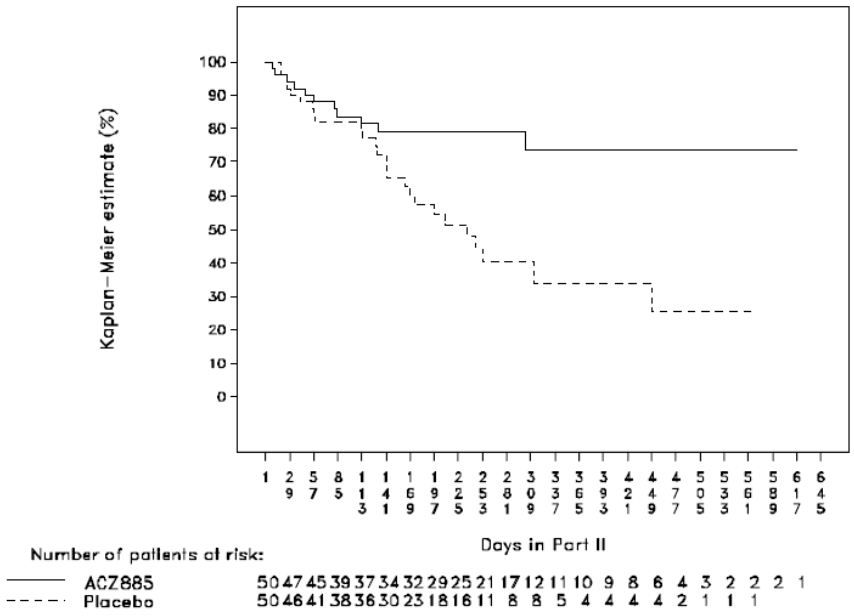
Patients who discontinued the study while in Part II were counted as flared unless they discontinued because of inactive disease for at least 24 weeks in Part II.

Not est. = Not estimable.

* Statistically significant on one-sided significance level 0.025.

The figure below shows that in the first 4 months in Part II, the probability to flare was similar in both treatment groups. Beyond 4 months, the rate of flare remained constant for the placebo group whereas only a few flares were observed in the canakinumab group.

Figure 20. Kaplan-Meier estimates of the probability to stay flare free in Part II, by treatment (Full analysis set II)



Source: Table 14.2-1.4

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.

The source table displays the Kaplan-Meier estimates of the probability to flare and the figure displays the probability not to flare: 1-probability to flare.

The primary analysis was repeated whereby patients discontinuing the study for any reason (with the exception of flare) were censored at the time of study discontinuation. The results showed a non-significant relative risk reduction to flare of 49% with canakinumab treatment relative to placebo (hazard ratio of 0.51; 95% CI: 0.23 to 1.12; p=0.0445).

Secondary efficacy results – Part II (double-blind withdrawal period)

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

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

1. Maintenance of adapted ACR Pediatric 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, as shown in the table below.

Table 37. Closed testing procedure on secondary endpoints in Part II (Full analysis set II)

Criteria	Statistical significance according to closed testing procedure (1)
Survival analysis of time to worsening in ACR level	Yes
CHAQ disability score: Repeated measures ANCOVA	No
CHQ-PF50 physical health score: Repeated measures ANCOVA	-
CHQ-PF50 psychosocial health score: Repeated measures ANCOVA	-

Source: Table 14.2-2.20

(1) One-sided test with significance level 0.025, adjusted for multiple testing.

Maintenance of efficacy

A survival analysis of the time to worsening in ACR level in Part II is shown in the table below. 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). This satisfies the requirement for the success of the 1st endpoint in the closed testing procedure. The median time to worsening in ACR level, which was 141 days for the placebo group, could not be observed for the canakinumab group as less than 50% of patients experienced a worsening in ACR level in Part II.

Table 38. Survival analysis of time to a worsening in ACR level during Part II

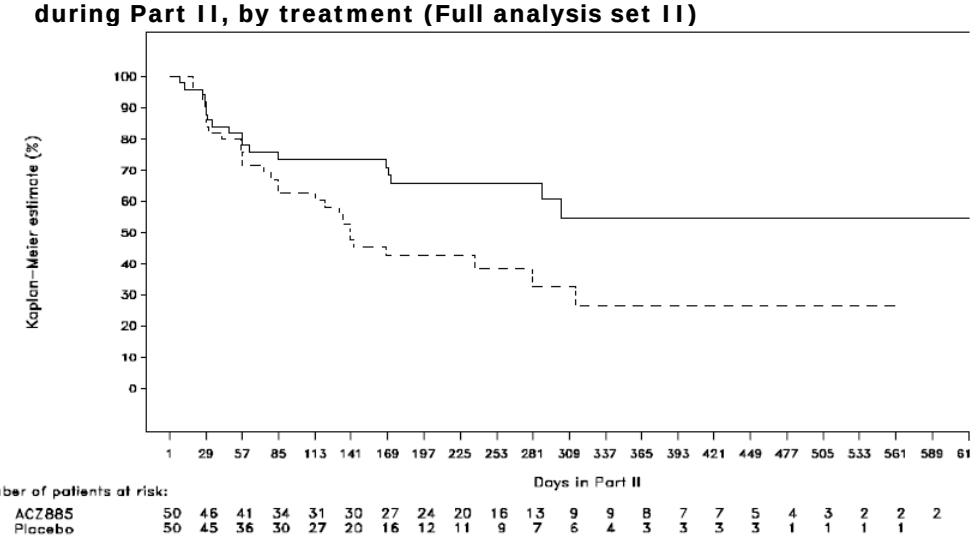
			Kaplan-Meier estimate	Stratified log-rank test	
Treatment	n	Number of events	Median in days (95% CI)	Hazard ratio to Placebo (95% CI)	One-sided p-value
ACZ885	50	18	Not est. (171.0, Not est.)	0.49 (0.27, 0.90)	0.0131*
Placebo	50	29	141.0 (85.0, 281,0)		

Source: Table 14.2-2.18

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

The figure below shows that in the first 2 months in Part II, the probability not to worsen (i.e., maintain ACR response) was similar for both treatment groups. Beyond 2 months, the probability of patients to maintain their ACR response was greater with canakinumab vs. placebo.

Figure 21. Kaplan-Meier estimates of the probability not to worsen in ACR response during Part II, by treatment (Full analysis set II)



Source: Table 14.2-2.19

The source table displays the Kaplan-Meier estimates of the probability to worsen and the figure displays the probability not to worsen (1-probability to worsen).

The level of adapted ACR pediatric response was assessed at the time of the patient visit by a standardized procedure at PRINTO/PRCSG in agreement with Novartis. These data were recalculated by Novartis after database lock when it could be assured that the data had been verified. There was one relevant difference in ACR response in Part II:

- One placebo patient (0115/00101) was an ACR responder per PRINTO/PRCSG and a non-responder following Novartis' recalculation (at one visit).

CHAQ disability score

The CHAQ functional ability score is the third response variable in the adapted ACR pediatric criteria. At the beginning of Part II, the median value at baseline in the CHAQ score was 0 for canakinumab and

0.1 for placebo. At the end of Part II (last assessment available), the median change from the start of Part II was 0 for both groups. A comparison between the treatment groups showed there was no difference between canakinumab and placebo in the LS mean change from the start of Part II over time in Part II in the CHAQ© disability score (p=0.4571) (see table below). The requirements for the success of the 2nd endpoint were not met, and, therefore, the 4-step closed testing procedure stops here.

Table 39. Change in CHAQ disability score in Part II: Repeated measures ANCOVA, by treatment (Full analysis set II)

Treatment	n	LS Mean	Standard Error	Difference to Placebo	95% CI	One-sided p-value
ACZ885	50	0.1184	0.17592	-0.0073	(-0.1407, 0.1260)	0.4571
Placebo	50	0.1258	0.18241			

Source: Table 14.2-2.9

Repeated measures ANCOVA with treatment group, visit day, prednisone (or equivalent) dose and adapted ACR 70 Pediatric response reached at the end of Part Id as covariates.

* Statistically significant on one-sided significance level 0.025.

The number of patients showing a MCID of improvement (decrease ≥ 0.19) or worsening (increase ≥ 0.13) in the CHAQ disability score from the beginning of Part II showed little difference between the treatment groups as far as a MCID of improvement, but there were more patients with a MCID of worsening in the placebo group vs. the canakinumab group. At the end of Part II (last assessment available), 7/50 (14.0%) patients in the canakinumab group and 6/50 (12.0%) patients in the placebo group showed a MCID of improvement, while 9/50 (18.0%) patients in the canakinumab group showed a MCID of worsening compared to 16/50 (32.0%) patients in the placebo group.

The results of a repeated measures logistic model on improvement and worsening in the CHAQ disability score from the beginning of Part II showed no significant differences between the treatment groups for an MCID of either improvement or worsening.

CHQ-PF50

Health-related quality of life was assessed in patients aged 5-18 years old using the CHQPF50.

- At the start of Part II, the median CHQ-PF50 physical score was 50.0 for canakinumab (n=40) and 50.8 for placebo (n=38). At the end of Part II, the median change from the start of Part II was 1.4 for canakinumab (n=39) vs. -3.1 for placebo (n=37).
- For the CHQ-PF50 psychosocial score, the median value at the start of Part II was 57.5 for canakinumab (n=40) and 55.4 for placebo (n=38). At the end of Part II, the median change from the start of Part II was 0.1 for canakinumab (n=39) vs. -1.1 for placebo (n=37).

A comparison between the treatment groups showed that the LS mean changes from the start of Part II over time in the CHQ-PF50 physical and psychosocial scores were numerically higher in the canakinumab treatment group compared with the placebo group but the differences were not statistically significant (see table below).

Table 40. Change in CHQ-PF50 scores in part II: Repeated measures ANCOVA by parameter and treatment (Full analysis set II – patients aged 5-18 years)

Parameter	Treatment	n	LS Mean	Standard Error	Difference to Placebo	95% CI	One-sided p-value
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			

Source: Table 14.2-2.13
Repeated measures ANCOVA change from start of Part II with treatment group, visit day, prednisone (or equivalent) dose and adapted ACR 70 Pediatric response reached at the end of Part Id as covariates.
* Statistically significant on one-sided significance level 0.025.

Ancillary analyses

Part I (open-label treatment)

Adapted ACR pediatric criteria response variables

Physician's global assessment of disease activity

The physician's global assessment of disease activity using a 0-100 mm VAS is the first response variable in the adapted ACR pediatric criteria.

At baseline, the mean value was 66.5 mm (n=177).

- From the beginning of Part Ia to the start of Part Ic, the mean change from baseline showed improvement starting at Day 3 (-33.0 mm [-51.0%], n=136) that increased over time to -53.0 mm (-83.1%) at Day 57 (n=141).
- During Part Ic, improvement was evident despite the intervention of steroid tapering (e.g., mean changes from baseline of -58.1 mm [-83.7%] at Day 85 [n=80], -59.4 mm [-84.6%] at Day 113 [n=67], -56.9 mm [-80.3%] at Day 141 [n=52], and -56.4 mm [-78.0%] at Day 169 [n=44]).
- At the end of Part Id (Day 225), the mean change from baseline was -57.9 mm (-92.4%) (n=103).
- At the end of Part I (last assessment available), the mean change from baseline was -48.2 mm (-73.5%) (n=177).

Parent's or patient's global assessment of patient's overall well-being as part of the CHAQ

The parent's or patient's global assessment of patient's overall well-being using a 0-100 mm VAS is the second response variable in the adapted ACR pediatric criteria.

The overall VAS scores at baseline and changes from baseline at each visit are similar to those reported for the physician's global assessment of disease activity.

At baseline, the mean value was 60.7 mm (n=176).

- From the beginning of Part Ia to the start of Part Ic, the mean change from baseline showed improvement starting at Day 15 (-33.4 mm [-51.7%], n=138) that increased over time (-45.6 mm [-74.1%] at Day 57, n=140).
- During Part Ic, improvement was evident despite the intervention of steroid tapering (e.g., mean changes from baseline of -43.6 mm [-71.0%] at Day 85 [n=79], -43.7 mm [-73.4%] at Day 113 [n=66], -44.6 mm [-68.7%] at Day 141 [n=51], and -48.4 mm [-70.5%] at Day 169 [n=43]).

- At the end of Part Id (Day 225), the mean change from baseline was -51.7 mm [-86.0%] (n=102).
- At the end of Part I (last assessment available), the mean change from baseline was -39.8 mm [-60.8%] (n=174).

Number of active joints

The number of joints with active arthritis is the fourth response variable in the adapted ACR pediatric criteria. At baseline, the median number of active joints was 10 (n=177).

- From the beginning of Part Ia to the start of Part Ic, the median change from baseline showed a modest decrease in the number of active joints starting at Day 15 (-6 [-75%] at Day 15 [n=139] and -6 [-92.5%] at Day 57 [n=141]).
- During Part Ic, a modest decrease in the number of active joints was apparent despite the intervention of steroid tapering (e.g., median changes from baseline of -8 [-87.1%] at Day 85 [n=80], -7 [-90.9%] at Day 113 [n=67], -8 [-87.2%] at Day 141 [n=52], and -9 [-89.5%] at Day 169 [n=44]).
- At the end of Part Id (Day 225), the median change from baseline was -6 [-100%] (n=103).
- At the end of Part I (last assessment available), the median change from baseline was -7 [-88.1%] (n=177).

Number of joints with limited range of motion

The number of joints with a limited range of motion is the fifth response variable in the adapted ACR pediatric criteria. The overall numbers and changes from baseline in the number of joints with limited range of motion were similar to those reported for the number of active joints. At baseline, the median number of joints with limited range of motion was 9 (n=177).

- From the beginning of Part Ia to the start of Part Ic, the median change from baseline showed a modest decrease in the number of joints with limited range of motion starting at Day 15 (-5 [-63.9%] at Day 15 [n=139] and -6 [-87.5%] at Day 57 [n=141]).
- During Part Ic, a modest decrease in the number of joints with limited range of motion was apparent despite the intervention of steroid tapering (e.g., median changes from baseline of -7 [-79.6%] at Day 85 [n=80], -7 [-85.0%] at Day 113 [n=67], -7 [-78.7%] at Day 141 [n=52], and -8 [-71.4%] at Day 169 [n=44]).
- At the end of Part Id (Day 225), the median change from baseline was -6 [-100%] (n=103).
- At the end of Part I (last assessment available), the median change from baseline was -5 [-83.3%] (n=177).

C-reactive protein (CRP)

CRP level is the sixth response variable in the adapted ACR pediatric criteria. CRP values were standardized to a normal range of 0-10 mg/L. At baseline, the median CRP value was 160.0 mg/L (n=177).

- From the beginning of Part Ia to the start of Part Ic, the absolute median CRP values decreased over time, starting at Day 3 (73.3 mg/L at Day 3 to 10.0 mg/L at Day 57). The median change from baseline was -86.0 mg/L (-50.6%) at Day 3 (n=141) and -129.0 mg/L (-94.3%) at Day 57 (n=140).

- During Part Ic, absolute median CRP values remained low despite the intervention of steroid tapering (e.g., 10.3 mg/L at Day 85, 15.0 mg/L at Day 113, 21.5 mg/L at Day 141, and 23.1 mg/L at Day 169). The median changes from baseline were -115.1 mg/L (-92.2%) at Day 85 (n=80), -124.2 mg/L (-87.5%) at Day 113 (n=67), -103.0 mg/L (-81.1%) at Day 141 (n=52), and -95.0 mg/L (-75.5%) at Day 169 (n=44).
- At the end of Part Id (Day 225), the absolute median CRP value was 5.5 mg/L. The median change from baseline at Day 225 was -127.6 mg/L (-96.8%) (n=103).
- At the end of Part I (last assessment available), the absolute median CRP value was 17 mg/L. The median change from baseline at the end of Part I was -114.8 mg/L (-87.4%) (n=177).

Pain intensity (0-100 mm VAS) as part of CHAQ

At baseline, the mean value was 66.7 mm (n=176).

- From the beginning of Part Ia to the start of Part Ic, the mean change from baseline showed a high degree of decrease in pain starting at Day 15 (-42.0 mm [-59.0%] at Day 15 [n=139] and -53.5 mm [-80.5%] at Day 57 [n=140]).
- During Part Ic, the decreased level in pain was still evident despite the intervention of steroid tapering (e.g., mean changes from baseline of -53.4 mm [-79.4%] at Day 85 [n=79], -53.8 mm [-81.9%] at Day 113 [n=66], -53.2 mm [-82.8%] at Day 141 [n=51], and -50.9 mm [-77.0%] at Day 169 [n=43]).
- At the end of Part Id (Day 225), the mean change from baseline was -56.2 mm (-88.8%) (n=102).
- At the end of Part I (last assessment available), the mean change from baseline was -46.4 mm (-67.9%) (n=174).

The number of patients showing a ≥ 20 mm decrease in pain on VAS:

- From the beginning of Part Ia to the start of Part Ic, the percentage of patients showing this level of decrease in pain was high and increased with continued canakinumab treatment (109/139 [78.4%] at Day 15 to 128/140 [91.4%] at Day 57).
- During Part Ic, this level of decrease in pain was seen consistently in ≥83% of patients despite the intervention of steroid tapering (e.g., 68/79 [86.1%] at Day 85, 60/66 [90.9%] at Day 113, 45/51 [88.2%] at Day 141, and 36/43 [83.7%] at Day 169).
- At the end of Part Id (Day 225), the percentage of patients showing this level of decrease in pain was 95/102 (93.1%).
- Overall during Part I (maximum decrease), 152/174 patients (87.4%) showed ≥ 20 mm decrease in pain.

Part II (double-blind withdrawal period)

Adapted ACR pediatric criteria response variables

Physician's global assessment of disease activity

The physician's global assessment of disease activity using a 0-100 mm VAS is the first response variable in the adapted ACR pediatric criteria. The median value was 0 mm at the start of Part II for both treatment groups (n=50 for each group). At the end of Part II (last assessment available), the median change from the start of Part II was 0 mm for canakinumab and 0.5 mm for placebo (n=50 for each group.

Parent's or patient's global assessment of patient's overall well being

The parent's or patient's global assessment of the patient's overall well-being using a 0-100 mm VAS is the second response variable in the adapted ACR pediatric criteria. The median value was 2.0 mm for both canakinumab and placebo at the start of Part II (n=50 for each group). At the end of Part II (last assessment available), the median change from the start of Part II was 0 mm for canakinumab and 1.0 mm for placebo (n=50 for each group).

Number of active joints / number of joints with limited range of motion

The number of joints with active arthritis is the fourth response variable and the number of joints with a limited range of motion is the fifth response variable in the adapted ACR pediatric criteria. At the start of Part II, the median number of both variables was 0 for both treatment groups (n=50 for each group). At the end of Part II (last assessment available), the median change from the start of Part II was also 0 for both variables for both treatment groups (n=50 for each group).

C-reactive protein (CRP)

CRP level is the sixth response variable in the adapted ACR pediatric criteria. The median value for CRP (standardized in mg/L) was 5.0 mg/L for canakinumab and 7.9 mg/L for placebo at the start of Part II (n=50 for each group). At the end of Part II (last assessment available), the absolute median values were 5.0 mg/L for canakinumab and 17.9 mg/L for placebo. The median change from the start of Part II was 0 mg/L for canakinumab and 2.1 mg/L for placebo (n=50 for each group).

Pain intensity (0-100 mm VAS) as part of CHAQ

The median value was 1.0 mm at the start of Part II for both treatment groups (n=50 for each group). At the end of Part II (last assessment available), the median change from the start of Part II was 0 mm for both treatment groups (n=50 for each group).

A comparison between the treatment groups showed a greater decrease in the parent's or patient's assessment of pain from the start of Part II in canakinumab group (LS mean change of -7.1 mm in the canakinumab group vs. -3.6 mm in the placebo group), but the difference was not significant (p=0.0536). Overall during Part II (maximum decrease), 5 (10.0%) patients in the canakinumab group and 1 (2.0%) patient in the placebo group showed a ≥ 20 mm decrease in pain on VAS from the beginning of Part II.

Exploratory efficacy results – Part I (open-label treatment)

EQ-5D or EQ-5D proxy

Health-related quality of life was explored over time by use of the EQ-5D (for patients ≥ 12 years of age) and EQ-5D proxy (for patients 8 - 11 years of age).

The mean EQ-5D state of health score at baseline was 41.9 (n=96). The mean change from baseline was 39.2 at Day 57 (n=76), 42.9 at Day 197 (n=40), 43.8 at Day 225 (n=54), and 35.3 at the end of Part 1 (last assessment available) (n=92).

The median EQ-5D utility score at baseline was 0.25 (n=96). The median change from baseline was 0.45 at Day 57 (n=77), 0.45 at Day 197 (n=40), 0.48 at Day 225 (n=54), and 0.41 at the end of Part 1 (last assessment available) (n=93).

Pediatric Daytime Sleepiness Scale (PDSS)

The level of sleepiness was explored over time in Part I by use of the PDSS for patients 11-15 years of age. The mean value at baseline was 16.4 (n=33). The mean change from baseline was -4.3 at Day 57 (n=26), -5.1 at Day 197 (n=14), -3.6 at Day 225 (n=21), and -2.5 at the end of Part 1 (last assessment available) (n=33).

Growth velocity

Although the impact of treatment with canakinumab on growth velocity was an exploratory objective for Part I, this endpoint was evaluated in patients with the longest time duration in the study, i.e., in Part II.

Physical development based on Tanner scale

Although the observation period was small, no unexpected effects on physical development were seen.

Exploratory efficacy results – Part II (double-blind withdrawal period)

Inactive disease

Over Part II, Kaplan-Meier estimates showed that the median time to inactive disease from the start of Part II was 30.0 days for canakinumab vs. 33.0 median days for placebo. Although there was no significant difference between the two treatment groups, the hazard ratio was >1 indicating a treatment benefit in favor of canakinumab (hazard ratio of 1.26; p=0.1446). Of note is that approximately one-half of the patients entering Part II already had inactive disease at the start of Part II (26 patients in the canakinumab group and 27 patients in the placebo group). At the end of Part II, the proportion of patients who had inactive disease was higher in the canakinumab group (31/50, 62.0%) compared with the placebo group (17/50, 34.0%). A statistically significantly higher likelihood of inactive disease was seen with canakinumab treatment compared with placebo (CMH test: odds ratio of 3.4 (95% CI: 1.5, 8.0); p=0.0020).

Patients were considered to have completed the study if they achieved 24 consecutive weeks of inactive disease. Twenty patients in the canakinumab group and two patients in the placebo group had at least 24 weeks of inactive disease during Part II and remained in the study.

Growth velocity

Part II of the study was chosen to evaluate growth as it was the longer of the two observation periods of the study. The impact of treatment with canakinumab on growth velocity was evaluated at an exploratory level and results should interpreted with caution due to the limited number of patients available to observe changes in height and the limited and varied time of observation. In addition, multiple factors such as age during the observation period, onset of puberty, nutritional status, concomitant medications, etc, influence a child's growth and would need to be taken into consideration.

Canakinumab appeared to have no negative affect on height as reflected by a small but positive increase in the median change from baseline in height percentile at the end of the study (+2.09) demonstrate that for the canakinumab group, the largest changes in height percentiles occurred in the two lowest categories. The percentage of patients in the canakinumab group who entered the study in the lowest height percentile category (20th percentile) was 51%; at the end of the study, the percentage had decreased to 39%. The percentage of patients in the canakinumab group in the 20th to <40th percentile category increased from 22% at baseline to 31% at the end of Part II.

All of other higher height percentile categories increased slightly by a few percentages. For those in the placebo group, there was essentially no change between baseline and the end of study height percentile categories.

The changes seen in weight and BMI percentiles were similar to those for height.

Physical development based on Tanner scale

No unexpected effects on physical development were seen.

Joint erosions

The impact of treatment with canakinumab on the progression of joint erosions in the affected hand and/or wrist by x-ray is an exploratory objective for Part II (in a subset of volunteer patients). However, this endpoint will be evaluated at the pooled level, rather than the individual study level.

EQ-5D or EQ-5D proxy

Health-related quality of life was explored over time by use of the EQ-5D (for patients ≥ 12 years of age) and EQ-5D proxy (for patients 8 - 11 years of age).

EQ-5D state of health score

At the start of Part II, the median EQ-5D state of health score was 90.0 for canakinumab (n=28) and 95.0 for placebo (n=25). At the end of Part II, the median change from the start of Part II was 1.5 for canakinumab and -4.0 for placebo.

A comparison of the LS mean changes from the start of Part II showed no significant difference between the treatment groups in the EQ-5D state of health score at the end of Part II (estimated difference of 9.60; 95% CI: -5.40, 24.59; p=0.1017).

EQ-5D utility score

At the start of Part II, the median EQ-5D utililty score was 1.0 for canakinumab (n=28) and 0.85 for placebo (n=25). At the end of Part II, the median change from the start of Part II was 0 for both canakinumab and placebo.

A comparison of the LS mean changes from the start of Part II showed no significant difference between the treatment groups in the EQ-5D utility score at the end of Part II (estimated difference of 0.12; 95% CI -0.05, 0.28; p=0.0869)

Pediatric Daytime Sleepiness Scale (PDSS)

The level of sleepiness was explored over time by use of the PDSS for patients 11-15 years of age. The number of patients with data is low overall. At the start of Part II, the median PDSS score was 14.0 in the canakinumab group (n=12) and 11.0 in the placebo group (n=11). At the end of Part II, the median change from the start of Part II was 2.0 in the canakinumab group and 0.5 in the placebo group.

A comparison of the LS mean changes from the start of Part II showed no significant difference between the treatment groups at the end of Part II (estimated difference of 0.3; 95% CI: -5.5, 6.1; p=0.5403).

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 41. Summary of Efficacy for trial ACZ885G2305

Title: A randomized, double-blind, placebo controlled, single-dose study to assess the initial efficacy of canakinumab (ACZ885) with respect to the adapted ACR Pediatric 30 criteria in patients with Systemic Juvenile Idiopathic Arthritis (sJIA) and active systemic manifestations		
Study identifier	ACZ885G2305	
Design	A randomized, double-blind, placebo controlled, single-dose study	
	Duration of main phase: Duration of run-in phase: Duration of extension phase:	4 weeks not applicable not applicable
Hypothesis	Superiority	
Treatment groups	Canakinumab	Canakinumab 4mg/kg. 4 weeks, 43 patients randomised
	Placebo	Placebo. 4 weeks, 41 patients randomised

Endpoints and definitions	Primary endpoint	ACR30 at day 15	The proportion of patients who responded to treatment at Day 15 according to the adapted ACR Pediatric 30 criteria. The adapted ACR Pediatric 30 criteria were used to determine responders defined as: improvement from baseline of at least 30% in at least 3 of the response variables 1 to 6 and no intermittent fever (i.e., body temperature ≤ 38°C) in the preceding week (variable 7), with no more than one variable 1-6 worsening by more than 30%. The below response variables were assessed: 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 using the ACR definition (The ACR definition of active arthritis is any joint with swelling, or in the absence of swelling, limitation of motion accompanied by either pain on motion or tenderness not due to deformity) 5. Number of joints with limitation of motion 6. Laboratory measure of inflammation: CRP (standardized to a normal range of 0-10 mg/L) 7. Absence of intermittent fever due to sJIA during the preceding week Patients who did not respond or discontinued due to any reason before Day 15 were considered as non-responders.

	Key Secondary endpoint (secondary endpoints assessed in a closed testing procedure)	1. ACR30 at day 29 2. ACR50 at day 29 3. ACR50 at day 15 4. Pain at day 29 5. Pain at day 15 6. Temperature ≤ 38°C 7. ACR70 at day 29 8. ACR90 at day 29 9. ACR100 at day 29 10. ACR70 at day 15 11. ACR90 at day 15 12. ACR100 at day 15 13. CHQ-PF50 physical score CHQ-PF50 psychosocial score 14. CHAQ disability score	1. Proportion of patients achieving the adapted ACR Pediatric 30 criteria at Day 29 2. Proportion of patients achieving the adapted ACR Pediatric 50 criteria at Day 29 3. Proportion of patients achieving the adapted ACR Pediatric 50 criteria at Day 15 4. Patient's pain intensity assessed on a 0–100 mm VAS by Day 29 5. Patient's pain intensity assessed on a 0–100 mm VAS by Day 15 6. Absence of fever (proportion of patients who have body temperature ≤ 38°C) at Day 3 7. Proportion of patients achieving the adapted ACR Pediatric 70 criteria at Day 29 8. Proportion of patients achieving the adapted ACR Pediatric 90 criteria at Day 29 9. Proportion of patients achieving the adapted ACR Pediatric 100 criteria at Day 29 10. Proportion of patients achieving the adapted ACR Pediatric 70 criteria at Day 15 11. Proportion of patients achieving the adapted ACR Pediatric 90 criteria at Day 15 12. Proportion of patients achieving the adapted ACR Pediatric 100 criteria at Day 15 13. Change in HRQoL over time by use of the CHQ-PF50 for 5–18 years old 14. Change in disability over time by use of the CHAQ®

Database lock	3 August 2012		
Results and analysis			
Analysis description	**Primary analysis**		
Analysis population and time point description	Full analysis set – timepoint: at day 15		
Descriptive statistics and estimate variability	Treatment group	ACZ885	Placebo
	Number of patients	43	41
	ACR30 at day 15 - n (%)	36 (83.7%)	4 (9.8%)
Effect estimate per comparison	ACR30 at day 15	Comparison groups	ACZ885 vs Placebo
		Cochran-Mantel-Haenszel test- estimated odds ratio	62.29

		95% CI	[12.68, 306.07]
		P-value	<0.0001
Notes			
Analysis description	**Key Secondary analysis**		
Analysis population and time point description	Full analysis set – timepoint: at day 29		
Descriptive statistics and estimate variability	Treatment group	ACZ885	Placebo
	Number of patients	43	41
	ACR30 at day 29 - n (%)	35 (81.4%)	4 (9.8%)
Effect estimate per comparison	ACR30 at day 29	Comparison groups	ACZ885 vs Placebo
		Cochran-Mantel-Haenszel test-estimated odds ratio	62.29
		95% CI	[12.68, 306.07]
		P-value	<0.0001
Analysis population and time point description	Full analysis set – timepoint: at day 29		
Descriptive statistics and estimate variability	Treatment group	ACZ885	Placebo
	Number of patients	43	41
	ACR50 at day 29 - n (%)	34 (79.1%)	2 (4.9%)
Effect estimate per comparison	ACR50 at day 29	Comparison groups	ACZ885 vs Placebo
		Cochran-Mantel-Haenszel test-estimated odds ratio	106.76
		95% CI	[16.26, 701.10]
		P-value	<0.0001
Analysis population and time point description	Full analysis set – timepoint: at day 15		
Descriptive statistics and estimate variability	Treatment group	ACZ885	Placebo
	Number of patients	43	41
	ACR50 at day 15 - n (%)	29 (67.4%)	2 (4.9%)

Effect estimate per comparison	ACR50 at day 15	Comparison groups	ACZ885 vs Placebo
		Cochran-Mantel-Haenszel test-estimated odds ratio	58.00
		95% CI	[10.13, 332.13]
		P-value	<0.0001
Analysis population and time point description	Full analysis set – timepoint: at day 29		
Descriptive statistics and estimate variability	Treatment group	ACZ885	Placebo
	Number of patients	38	7
	Patient's pain intensity (0-100 mm VAS)- LSM (Standard error)	20.6 (5.59)	62.5 (9.70)
Effect estimate per comparison	Patient's pain intensity (0-100mm VAS)	Comparison groups	ACZ885 vs Placebo
		ANCOVA – estimated difference of LSM	-41.86
		95% CI	[-59.81, -23.90]
		P-value	<0.0001
Analysis population and time point description	Full analysis set – timepoint: at day 15		
Descriptive statistics and estimate variability	Treatment group	ACZ885	Placebo
	Number of patients	43	25
	Patient's pain intensity (0-100 mm VAS)- Least square mean (LSM) (Standard error)	20.3 (5.08)	66.7 (6.35)
Effect estimate per comparison	Patient's pain intensity (0-100 mm VAS)	Comparison groups	ACZ885 vs Placebo
		ANCOVA – estimated difference of LSM	-46.42
		95% CI	[-57.72, -35.13]
		P-value	<0.0001
Analysis population and time point description	Full analysis set – timepoint: at day 3		
Descriptive statistics and estimate variability	Treatment group	ACZ885	Placebo
	Number of patients	43	38

	Temperature ≤ 38 °C - n (%)	43 (100%)	33 (86.8%)
Effect estimate per comparison	Temperature ≤ 38 °C	Comparison groups	ACZ885 vs Placebo
		Cochran-Mantel-Haenszel test-estimated odds ratio	Not estimable
		95% CI	Not estimable
		P-value	0.0098
Analysis population and time point description	Full analysis set – timepoint: at day 29		
Descriptive statistics and estimate variability	Treatment group	ACZ885	Placebo
	Number of patients	43	41
	ACR70 at day 29 - n (%)	29 (67.4%)	1 (2.4%)
Effect estimate per comparison	ACR70 at day 29	Comparison groups	ACZ885 vs Placebo
		Cochran-Mantel-Haenszel test-estimated odds ratio	105.27
		95% CI	[12.01, 922.79]
		P-value	<0.0001
Analysis population and time point description	Full analysis set – timepoint: at day 29		
Descriptive statistics and estimate variability	Treatment group	ACZ885	Placebo
	Number of patients	43	41
	ACR90 at day 29 - n (%)	20 (46.5%)	1 (2.4%)
Effect estimate per comparison	ACR90 at day 29	Comparison groups	ACZ885 vs Placebo
		Cochran-Mantel-Haenszel test-estimated odds ratio	40.64
		95% CI	[5.24, 315.19]
		P-value	<0.0001
Analysis population and time point description	Full analysis set – timepoint: at day 29		
Descriptive statistics and estimate variability	Treatment group	ACZ885	Placebo
	Number of patients	43	41

	ACR100 at day 29 - n (%)	14 (32.6%)	1 (2.4%)
Effect estimate per comparison	ACR100 at day 29	Comparison groups	ACZ885 vs Placebo
		Cochran-Mantel-Haenszel test-estimated odds ratio	22.67
		95% CI	[2.80, 183.21]
		P-value	0.0001
Analysis population and time point description	Full analysis set – timepoint: at day 15		
Descriptive statistics and estimate variability	Treatment group	ACZ885	Placebo
	Number of patients	43	41
	ACR70 at day 15 - n (%)	26 (60.5%)	1 (2.4%)
Effect estimate per comparison	ACR70 at day 15	Comparison groups	ACZ885 vs Placebo
		Cochran-Mantel-Haenszel test-estimated odds ratio	86.81
		95% CI	[10.23, 736.72]
		P-value	<0.0001
Analysis population and time point description	Full analysis set – timepoint: at day 15		
Descriptive statistics and estimate variability	Treatment group	ACZ885	Placebo
	Number of patients	43	41
	ACR90 at day 15 - n (%)	18 (41.9%)	0
Effect estimate per comparison	ACR90 at day 15	Comparison groups	ACZ885 vs Placebo
		Cochran-Mantel-Haenszel test-estimated odds ratio	Not estimable
		95% CI	Not estimable
		P-value	<0.0001
Analysis population and time point description	Full analysis set – timepoint: at day 15		
Descriptive statistics and estimate variability	Treatment group	ACZ885	Placebo
	Number of patients	43	41

	ACR100 at day 15 - n (%)	14 (32.6%)	0
Effect estimate per comparison	ACR100 at day 15	Comparison groups	ACZ885 vs Placebo
		Cochran-Mantel-Haenszel test- estimated odds ratio	Not estimable
		95% CI	Not estimable
		P-value	<0.0001
Analysis population and time point description	Full analysis set (for 5–18 years old patients)– timepoint: over time		
Descriptive statistics and estimate variability	Treatment group	ACZ885	Placebo
	Number of patients	28	34
	CHQ-PF50 physical score- LSM Change from baseline (Standard error)	16.9 (3.46)	4.9 (3.97)
Effect estimate per comparison	CHQ-PF50 physical score	Comparison groups	ACZ885 vs Placebo
		Repeated measures ANCOVA – estimated difference of LSM	12.07
		95% CI	[4.65, 19.48]
		P-value	0.0012
Analysis population and time point description	Full analysis set (for 5–18 years old patients) – timepoint: over time		
Descriptive statistics and estimate variability	Treatment group	ACZ885	Placebo
	Number of patients	28	34
	CHQ-PF50 psychosocial score- LSM Change from baseline (Standard error)	6.2 (2.15)	-1.1 (2.49)
Effect estimate per comparison	CHQ- psychosocial score	Comparison groups	ACZ885 vs Placebo
		Repeated measures ANCOVA – estimated difference of LSM	7.28
		95% CI	[2.61, 11.94]
		P-value	0.0017
Analysis population and time point description	Full analysis set – timepoint: over time		

Descriptive statistics and estimate variability	Treatment group	ACZ885	Placebo
	Number of patients	43	41
	CHAQ disability score-LSM Change from baseline (Standard error)	-0.9 (0.15)	-0.2 (0.20)
Effect estimate per comparison	CHAQ disability score	Comparison groups	ACZ885 vs Placebo
		Repeated measures ANCOVA – estimated difference of LSM	-0.69
		95% CI	[-1.05, -0.32]
		P-value	0.0002
Notes	A closed testing procedure was performed for secondary efficacy variables. Each of the steps in the closed testing procedure was satisfied.		

Table 42. Summary of Efficacy for trial ACZ885G2301

Title: A randomized, double-blind, placebo controlled, withdrawal study of flare prevention of canakinumab (ACZ885) in patients with Systemic Juvenile Idiopathic Arthritis (sJIA) and active systemic manifestations		
Study identifier	ACZ885G2301	
Design	This two-part study consisted of an open-label, single-arm active treatment in Part I followed by a randomized, double-blind, placebo controlled, event-driven withdrawal design in Part II.	
	Duration of Part I : Duration of Part II:	Up to 32 weeks Until 37 flare events occurred
Hypothesis	Superiority	
Treatment groups	Part I	
	Canakinumab (ACZ885)	Canakinumab 4mg/kg q4wk. Duration: up to 32 weeks Enrolled: 177
	Part II	
	Canakinumab (ACZ885)	Canakinumab 4mg/kg q4wk. Duration: Until 37 flares occurred, Randomised: 50
	Placebo	Placebo q4wk. Duration: Until 37 flare events occurred Randomised: 50

Endpoints and definitions	Co-Primary endpoints	Part I: Oral Steroid tapering Part II: Time to Flare event	The proportion of patients who entered Part I on an oral steroid who successfully tapered steroid at the end of Part 1c as per protocol. Time to flare event defined as at least 1 of the following: • Reappearance of fever (>38°C, lasting for at least 2 consecutive days) not due to an infection • Flare according to the JIA pediatric criteria for flare (all criteria must have been met): • ≥ 30% worsening in at least 3 of the first 6 ACR response variables • ≥ 30% improvement in not more than 1 of the first 6 ACR response variables For Part II, the flare assessment was made at each visit in relation to the start of Part II. For the primary analysis, flare events included (disease) flares as well as discontinuations from Part II of the study for any reason other than inactive disease.
	Key Secondary endpoints	Part II	The following secondary endpoints were assessed in a closed testing procedure: 1. Maintenance of adapted ACR Pediatric 30/50/70/90/100 criteria during Part II (Time to a worsening in ACR level) 2. Change in disability over time by CHAQ© 3. Change in HRQoL over time by CHQ-PF50© (PhS and PSs)
Database lock	7 August 2012		
Results and analysis			
Analysis description	**Primary analysis**		
Analysis population and time point description	Full analysis set in part I – at the end of Part I		
Descriptive statistics and estimate variability	Treatment group	ACZ885	
	Number of patients taking oral steroid dose at baseline	128	
	Patients who successfully tapered their steroid dose as per protocol at the end of Part Ic-n (%)	57 (44.5%)	
Effect estimate per	Oral steroid	ACZ885	

comparison	tapering	Exact one-sided binomial test for percentage of patients able to taper steroids ≥ 25%.	44.5%
		90% CI	[37.1, 52.2]
		P-value	<0.0001
Analysis population and time point description	Full analysis set in Part II		
Descriptive statistics and estimate variability	Treatment group	ACZ885	Placebo
	Number of patients	50	50
	Number of flare events	11	26
Effect estimate per comparison	Time to flare event	Comparison groups	ACZ885 vs Placebo
		Stratified log-rank test-Hazard ratio	0.36
		95% CI	[0.17,0.75]
		P-value	0.0032
Notes			
Analysis description	**Key Secondary analysis**		
Analysis population and time point description	Full analysis set in Part II		
Effect estimate per comparison	Time to a worsening in ACR level	Comparison groups	ACZ885 vs Placebo
		Stratified log-rank test-Hazard ratio	0.49
		95% CI	[0.27,0.90]
		P-value	0.0131
Analysis population and time point description	Full analysis set in Part II – timepoint: over time in Part II		
Descriptive statistics and estimate variability	Treatment group	ACZ885	Placebo
	Number of patients	50	50
	CHAQ disability score-LS Mean (Standard error)	0.1184 (0.1759)	0.1258 (0.1824)
Effect estimate per comparison	CHAQ disability score	Comparison groups	ACZ885 vs Placebo

		Repeated measures ANCOVA – estimated difference of LSM	-0.0073
		95% CI	[-0.1407, 0.4571]
		P-value	0.4571
Analysis population and time point description	Full analysis set in Part II (patients aged 5-18 years) – timepoint: over time in Part II		
Descriptive statistics and estimate variability	Treatment group	ACZ885	Placebo
	Number of patients	39	37
	CHQ-PF50 psychosocial score- LSM Change from start of part II (Standard error)	2.5 (1.88)	-0.5 (1.86)
Effect estimate per comparison	CHQ- psychosocial score	Comparison groups	ACZ885 vs Placebo
		Repeated measures ANCOVA – estimated difference of LSM	3.0
		95% CI	[-0.2, 6.1]
		P-value	0.0328
Analysis population and time point description	Full analysis set in part II (patients aged 5-18 years) – timepoint: over time in part II		
Descriptive statistics and estimate variability	Treatment group	ACZ885	Placebo
	Number of patients	39	37
	CHQ-PF50 physical health score- LSM Change from start of part II (Standard error)	3.9 (2.54)	-0.3 (2.53)
Effect estimate per comparison	CHQ- physical health score	Comparison groups	ACZ885 vs Placebo
		Repeated measures ANCOVA – estimated difference of LSM	4.2
		95% CI	[-0.1, 8.4]
		P-value	0.0280

Analysis performed across trials (pooled analyses and meta-analysis)

Data from 178 subjects of the phase III trials G2305, G2301 and G2301E1 (not complete, data up to interim database lock 10-Aug-2012) were pooled on an individual level because most patients were enrolled in more than one study (i.e., these patients were reported once). Patients from the study A2203 who rolled over into G2301 were excluded. The aim of the combined efficacy analyses is to

evaluate the 12-week efficacy of canakinumab in canakinumab treatment naïve patients in various subgroups based on demographic and baseline disease parameters and characterize specific patient groups.

Study populations

The main combined demographic and baseline disease characteristics of patients in the 12- week efficacy pooled group (see table below) generally matched those of the contributing studies, i.e., patients with active disease, often severe and considered to have a poor prognosis. Patients were predominantly Caucasian (84.8%) and 56.2% female, with a mean age of 8.5 years. Twenty-four (13.5%) of the patients were aged 2-<4 years.

Table 43. Demographic and baseline disease characteristics – 12 weeks efficacy pooled group (Full analysis set)

Parameter	Category/statistic	ACZ885 N=178
Gender - n (%)	Male	78 (43.8)
	Female	100 (56.2)
Age (years)	n	178
	Mean (SD)	8.5 (4.55)
	Median	8.0
	Min-Max	1-19
Age group - n (%)	2 -< 4 years	24 (13.5)
	4 -< 6 years	35 (19.7)
	6 -< 12 years	74 (41.6)
	12 -< 20 years	45 (25.3)
Race - n (%)	Caucasian	151 (84.8)
	Black	9 (5.1)
	Asian	6 (3.4)
	Other	12 (6.7)
Time of SJIA diagnosis to study entry (days)	n	178
	Mean (SD)	1265.1 (1204.09)
	Median	868.5
	Min-Max	52-5686
C-reactive protein at baseline (standardized in mg/L)	n	178
	Mean (SD)	200.5 (151.3)
	Median	157.9
	Min-Max	3-800
Number of active joints	n	178
	Mean (SD)	15.4 (14.1)
	Median	10.0
	Min-Max	0-66
Number of joints with limitation of motion	n	178
	Mean (SD)	14.7 (14.6)
	Median	9.0
	Min-Max	0-62
Steroid dose at baseline (standardized in mg/kg/day)	n	130
	Mean (SD)	0.381 (0.278)
	Median	0.285
	Min-Max	0.02-1.00
Steroid free at baseline - n (%)	No	130 (73.0)
	Yes	48 (27.0)

C-reactive protein level standardized to a normalized range of 0-10 mg/L
Source: [SCE Appendix 1-Table 3.3-1c]

Pooled study participation and withdrawals from the phase III program for the 12-week efficacy pooled group are shown in Table 3-10. The majority (81.5%) of patients completed 12 weeks participation. The main reason for discontinuation from the phase III program was unsatisfactory therapeutic effect (16.9%).

Table 44. Patient participation and withdrawals – 12 weeks efficacy pooled group (Full analysis set)

Table 3-10 Patient participation and withdrawals – 12-week efficacy pooled group (Full analysis set)

	ACZ885 N=178 n (%)
Completed 12 weeks	
Yes	145 (81.5)
No*	33 (18.5)
Reason for discontinuation	
Adverse event(s)	1 (0.6)
Unsatisfactory therapeutic effect	30 (16.9)

Discontinuation status of a patient is the status at Day 85 in the last study the patient enrolled.
*Some patients completed a study and did not enter a subsequent study. These are not counted as discontinuations.
Source: [SCE Appendix 1-Table 3.1-1c]

Adapted ACR pediatric response / criteria components

A clinically relevant, fast response to canakinumab treatment was seen in the 12-week pooled efficacy group as demonstrated by the adapted ACR pediatric response at Day 15 and 29. Further, maintenance of that response was seen at Day 57 and 85 (Table 3-26). A minimum ACR30 response was sustained over time. An improvement in response was also seen over time, particularly at the ACR90 and ACR100 level. The proportion of patients who achieved a status of "inactive disease" in the 12-week efficacy pooled group was 20.2% at Day 15, 25.8% at Day 29, 30.3% at Day 57, and 28.1% (50/178) at Day 85 (Table 3-26).

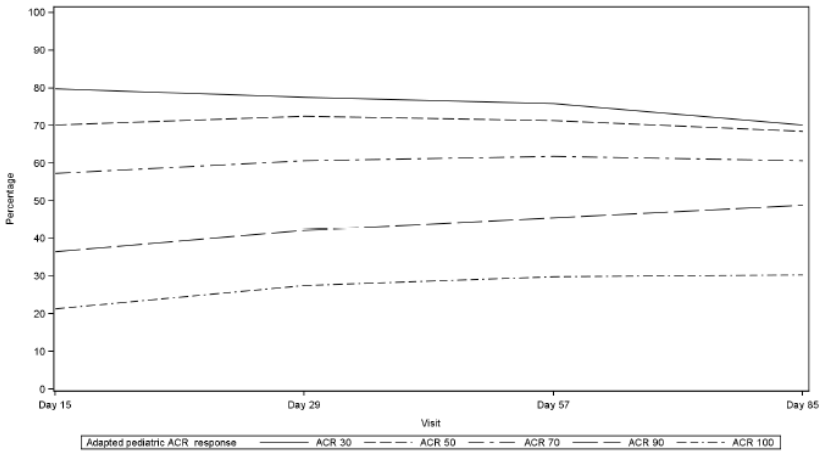
Median changes (median % changes) (improvements) from baseline in the adapted ACR pediatric criteria response components 1 through 6 and a high proportion of patients with an absence of fever in the preceding week (component 7) were seen in the 12-week pooled efficacy group at Day 15 and Day 29, including improvement in both arthritic and systemic measurements of SJIA. The 12-week combined efficacy data also shows improvements in ACR components that extend beyond Day 29, at Day 57 and 85.

Table 45. Adapted ACR pediatric response and inactive disease status achieved at Day 15, 29, 57, and 85 in the 12-week efficacy pooled group (Full analysis set)

	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)

Patients who discontinued the phase III program before Week 12 are counted as non-responders after discontinuation.
Source: [SCE Appendix 1-Table 3.6-1c, Table 3.6-16c]

Figure 22. Adapted ACR pediatric response versus time – 12 week efficacy pooled group (Full analysis set)



Source: [SCE Appendix 1-Figure 3.6-1c]

Table 46. ACR response variables 1-7 (12 week pooled data)

		Baseline, Change from baseline	
		All patients, N=178	
		n	
1: Physician's assess. of disease activity (mm)		***178***	***70.0***
Day 15	Median change (median % change)	174	-46.0 (-75%)
Day 29		158	-51.0 (-87%)
Day 57		142	-55.0 (-91%)
Day 85		134	-58.0 (-96%)
2: Parent/patient assess. of overall well-being (mm)		***178***	***63.0***
Day 15	Median change (median % change)	173	-35.0 (-67%)
Day 29		157	-44.0 (-85%)
Day 57		142	-47.0 (-88%)
Day 85		134	-46.5 (-92%)
3: CHAQ disability score (mm)		***178***	***1.8***
Day 15	Median change (median % change)	174	-0.8 (-56%)
Day 29		157	-0.9 (-69%)
Day 57		141	-1.0 (-80%)
Day 85		134	-1.0 (-85%)
4: Joints with active arthritis (n)		***178***	***10.0***
Day 15	Median change (median % change)	174	-6.0 (-75%)
Day 29		158	-6.5 (-81%)
Day 57		142	-6.5 (-91%)
Day 85		134	-7.0 (-100%)
5: Joints with limited range of motion (n)		***178***	***9.0***
Day 15	Median change (median % change)	174	-5.0 (-65%)
Day 29		158	-5.0 (-76%)
Day 57		142	-5.0 (-87%)
Day 85		134	-6.0 (-86%)
6: CRP (mg/L)		***178***	***157.9***
Day 15	Median change (median % change)	175	-103.0 (-82%)
Day 29		159	-115.0 (-88%)
Day 57		132	-129.0 (-95%)
Day 85		132	-121.4 (-94%)
7: No intermittent fever in last week n (%)		***178***	***11 (6.2%)***
Day 15	No fever - n (%)	175	152 (87%)
Day 29		159	148 (93%)
Day 57		132	128 (97%)
Day 85		134	131 (98%)

CHAQ = Child Health Assessment Questionnaire
CRP values were standardized to a normal range of 0-10 mg/L
baseline = median value at baseline, median change (median % change) = changes relative to baseline
Source: [SCE-Table 3-27]

The majority of patients in the 12-week efficacy pooled group with a maximum ACR30 response at Day 15 maintained their response (≥ACR30) beyond Day 15: Day 29 (13/17, 76.5%), Day 57 (14/16, 87.5%), and Day 85 (11/14, 78.6%). Moreover, most of these patients improved beyond Day 15, i.e.,

they achieved an ACR50 response or greater: Day 29 (11/17, 64.7%), Day 57 (11/16, 68.8%), and Day 85 (11/14, 78.6%). The majority of patients with a maximum ACR70 response at Day 15 also maintained their response (≥ACR70) beyond Day 15: Day 29 (33/37, 89.2%), Day 57 (31/37, 83.8%), and Day 85 (30/36, 83.3%). Many of these patients continued to improve beyond Day 15, i.e., achieved an ACR90 or ACR100 response at Day 29 (15/37, 40.5%), Day 57 (18/37, 48.6%), and Day 85 (21/36, 58.3%).

A large proportion of patients achieve an ACR70 by Day 16 of treatment (58%). The proportion increases to 82% by Day 71.

The probability of a patient to lose an ACR30 response after an initial response at Day 15 increases to 7.8% at Day 16, 10.6% at Day 43, and 15.4% at Day.

CHAQ clinically meaningful change

A high proportion of patients in the 12-week efficacy pooled group showed an improvement in the CHAQ disability score (based on the cited minimal clinically important difference by Brunner et al 2005, defined as a decrease ≥ 0.19 from baseline): 72.5% at Day 15, 71.3% at Day 29, 67.4% at Day 57, and 64.6% at Day 85.

CRP normalization

Almost all of the patients (172/175, 98.3%) had an elevated CRP (> 10 mg/L) at baseline. The proportions of patients with a CRP that was elevated at Day 15 and Day 29 were similar (62.9% and 60.4%, respectively). The proportions decreased to 43.9% and 45.8% at Day 57 and Day 85, respectively.

Parent's or patient's assessment of pain (VAS)

Summary statistics for the parent's or patient's assessment of pain using a 0-100 mm VAS as part of the CHAQ are provided for the 12-week pooled group in. Improvements in pain on VAS were observed starting at Day 15, with small further improvements seen over time. At baseline, the mean value was 67.1 mm (n=178). The mean changes (mean % changes) from baseline were -44.5 mm (-61.7%) at Day 15 (n=174), -51.4 mm (-73.4%) at Day 29 (n=157), -53.3 mm (-79.6%) at Day 57 (n=142), and -55.2 mm (-83.0%) at Day 85 (n=134).

Comparison of results in subpopulations

Clinically relevant, fast and sustained responses to canakinumab treatment as demonstrated by the adapted ACR pediatric criteria were seen across subgroups of age (including the youngest of patients, 2-<4 years of age, as well as patients 2, 3, and 4 years of age) gender, race, body weight, disease duration, active disease joint count, baseline oral steroid level, prior reported treatment (anakinra, steroids [oral or i.v.], methotrexate, or NSAIDs), as well as concomitant therapy (oral steroids and/or methotrexate) consistent with the overall efficacy seen in the 12-week efficacy pooled group.

Methods of subgroup analysis in the pooled group

Data on ACR pediatric response criteria were pooled from the two pivotal studies G2305 and G2301 and the long-term extension study G2301E1 (12-week efficacy pooled group) to better evaluate the efficacy of canakinumab in various subgroups. Comparisons were made both within and across the respective subgroups. Analysis of the 12-week efficacy pooled group was performed for the following subgroups based on baseline characteristics:

- Age (2-<4, 4-<6, 6-<12, 12-<20 years)
- Age 2, 3, 4 (2 years, 3 years, 4 years)

- Gender (male, female)
- Race (Caucasian, other)
- Body weight (≤40, >40-<75, ≥75 kg)
- Disease duration (≤ 6, >6 months to <4 years, ≥ 4 years) since date of diagnosis at baseline
- Baseline oral steroid level (0, >0-≤ 0.4, >0.4 mg/kg/day)
- Number of joints with active arthritis (≤10, >10)
- Previous exposure to anakinra (exposed and discontinued due to lack of efficacy, exposed and discontinued for other reasons, never exposed)
- Previous reported steroid (oral or i.v.) use
- Previous reported MTX use
- Previous reported NSAID use
- Previous reported steroid (oral or i.v.), MTX, or NSAID use
- Canakinumab and other therapies (canakinumab monotherapy; canakinumab and steroids [oral or i.v.); canakinumab and MTX; canakinumab, steroids [oral or i.v.] and MTX)

The efficacy endpoint evaluated in the subgroup analyses was the proportion of adapted ACR30/50/70/90/100 responders at Day 15, Day 29, Day 57, and Day 85.

Analysis was also performed for the following subgroups based on outcome during treatment phase:

- CRP (standardized in mg/L) at Day 15 ('Normal' if the value is < 10 mg/L and as 'Elevated' else).
- Patients who completed 12 weeks treatment (without missing ACR assessments)

Demographic factors

Age

Clinically relevant, fast and sustained responses to canakinumab treatment as demonstrated by the adapted ACR pediatric criteria were seen across the age groups at Days 15, 29, 57, and 85.

Gender

Clinically relevant, fast and sustained responses to canakinumab treatment as demonstrated by the adapted ACR pediatric criteria were seen for both genders at Days 15, 29, 57 and 85.

Race

Clinically relevant, fast, and sustained responses to canakinumab treatment as demonstrated by the adapted ACR pediatric criteria were seen at Days 15, 29, 57, and 85 for both Caucasians and non-Caucasians with no relevant differences in response rates seen between the two groups. Note that the number of patients who were Caucasian was large (n=151) in comparison to those who were non-Caucasian (n=27).

Body weight

Clinically relevant, fast, and sustained responses to canakinumab treatment as demonstrated by the adapted ACR pediatric criteria were seen at Day 15 and Day 29 across the body weight groups although response rates were generally higher for patients weighing > 40 kg compared to patients

weighing ≤ 40 kg. Note that the number of patients who weighed > 40 kg was small (n=46) in comparison to those who weighed ≤ 40 kg (n=132).

Baseline disease factors

Disease duration

Clinically relevant, fast and sustained responses to canakinumab treatment as demonstrated by the adapted ACR pediatric criteria were seen at Day 15, 29, 57 and 85 in the 12-week pooled efficacy group for patients with ≤ 6 or > 6 months disease duration.

Number of joints with active arthritis

Clinically relevant, fast and sustained responses to canakinumab treatment as demonstrated by the adapted ACR pediatric criteria were seen at Day 15, 29, 57 and 85 in the 12-week pooled efficacy group for patients with ≤10 or >10 active joints. 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

Clinically relevant, fast and sustained responses to canakinumab treatment as demonstrated by the adapted ACR pediatric criteria were seen at Day 15, 29, 57 and 85 in the 12-week pooled efficacy group regardless of baseline oral steroid use/dose. In general, ACR response rates were higher for steroid-free patients compared with those using oral steroids at baseline, and those in the higher oral steroid dose level category (>0.4 mg/kg/day) had lower response rates compared to those on lower steroid doses (≤0.4 mg/kg/day), a trend that was more apparent the higher the ACR response level achieved.

Previous exposure to other therapies

Clinically relevant, fast and sustained responses to canakinumab treatment as demonstrated by the adapted ACR pediatric criteria were seen at Day 15, 29, 57 and 85 in the 12-week pooled efficacy group in subgroups of previous exposure to other therapies, consistent with the overall efficacy seen in the 12-week efficacy pooled group.

Previous exposure to anakinra, tocilizumab

Clinically relevant, fast and sustained responses to canakinumab treatment as demonstrated by the adapted ACR pediatric criteria were seen at Day 15, 29, 57 and 85 regardless of previous anakinra exposure. ACR response rates were generally lower in patients who discontinued anakinra due to lack of efficacy compared with patients who discontinued anakinra for other reasons or patients who were never exposed to anakinra. Note that the numbers of patients who discontinued anakinra due to lack of efficacy (n=32) is small in comparison to those who were never exposed (n=100).

Prior reported steroid use

Clinically relevant, fast and sustained responses to canakinumab treatment as demonstrated by the adapted ACR pediatric criteria were seen at Day 15, 29, 57 and 85 regardless of prior reported steroid (oral and/or i.v.) use. Response rates were generally comparable for patients with or without prior use although there is some variability between the two groups at higher ACR response levels (ACR70, ACR90, ACR100) suggesting that those without prior steroid use have higher response rates compared to those with prior use. Patients requiring steroids, however, tend to have a more severe disease state than those not requiring steroids. The number of patients with no prior use is small (n=31) compared to those with prior use (n=147).

Prior reported MTX use

Clinically relevant, fast and sustained responses to canakinumab treatment as demonstrated by the adapted ACR pediatric criteria were seen at Day 15, 29, 57 and 85 regardless of prior reported MTX treatment (Table 3-40). Response rates were generally comparable for patients with or without prior MTX use although there is some variability between the two groups at higher ACR response levels (ACR70, ACR90, ACR100) suggesting that those without prior MTX use have higher response rates compared to those with prior use. Patients requiring MTX, however, tend to have a more severe disease state than those not requiring MTX.

Prior reported NSAID use

Clinically relevant, fast and sustained responses to canakinumab treatment as demonstrated by the adapted ACR pediatric criteria were seen at Day 15, 29, 57 and 85 regardless of prior NSAID use. Response rates were generally comparable for patients with or without prior NSAID use although there is some variability between the two groups at higher ACR response levels (ACR70, ACR90, ACR100) suggesting that those without prior NSAID use have higher response rates compared to those with prior use. The number of patients with no prior use is small (n=45) compared to those with prior use (n=133).

Prior reported steroid, MTX, or NSAID use

Clinically relevant, fast and sustained responses to canakinumab treatment as demonstrated by the adapted ACR pediatric criteria were seen at Day 15, 29, 57 and 85 regardless of prior reported steroid (oral and/or i.v.), MTX, or NSAID use. Response rates were generally comparable for patients with or without prior use although there is some variability between the two groups at higher ACR response levels (ACR70, ACR90, ACR100) suggesting that those without prior steroid use have higher response rates compared to those with prior use. Patients requiring steroids, however, tend to have a more severe disease state than those not requiring steroids. The number of patients with no prior use is very small (n=6) compared to those with prior use (n=172).

Canakinumab and concomitant therapies

Clinically relevant, fast and sustained responses to canakinumab treatment as demonstrated by the adapted ACR pediatric criteria were seen at Day 15, 29, 57 and 85 in subgroups of concomitant therapy use, consistent with the overall efficacy seen in the 12-week efficacy pooled group.

ACR30 response rates were higher in patients who used canakinumab monotherapy as well as canakinumab+steroids+MTX compared with canakinumab+steroids and canakinumab+MTX. For the higher ACR categories (ACR70-ACR100), response rates were higher in patients who used canakinumab monotherapy compared to all three other concomitant use subcategories, and the response rates were lowest in patients using canakinumab+steroids+MTX. The number of patients who used canakinumab+MTX was small (n=19) as well as for those who used canakinumab monotherapy (n=29) in comparison to those who used canakinumab+steroids (n=52) and canakinumab+steroids+MTX (n=78).

Outcome during treatment phase

Clinically relevant, fast and sustained responses to canakinumab treatment were seen at Day 15, 29, 57 and 85 in patients whose CRP normalized (<10 mg/L) or was elevated (≥10 mg/L) at Day 15, consistent with the overall efficacy seen in the 12-week efficacy pooled group. ACR response rates were generally lower for patients with an elevated CRP at Day 15 compared with those whose CRP was normal at Day 15, a trend that was more apparent the higher the ACR response level achieved.

Selected demographic and baseline disease characteristics in the 12-week efficacy pooled group are summarized by CRP normalization at Day 15 in Table 3-45. Patients who had an elevated CRP at Day 15 tended to be female (59.5%) and of a lower weight (≤40 kg, 80.2%) compared to those with a normal CRP at Day 15 (48.4% female and 64.1% weighing ≤40 kg). Those whose CRP levels did not normalize at Day 15 also appeared to have a more active disease state at baseline as they had higher values in ACR components, and a higher proportion were receiving MTX, steroids, or NSAIDs at baseline.

Table 47. Comparison of selected baseline characteristics by CRP normalization at Day 15 in the 12-week efficacy pooled group (Full analysis set)

	ACZ885 (N=178)	
Baseline characteristic	**Normal CRP (<10 mg/L) at Day 15 m=64**	**Elevated CRP (≥ 10 mg/L) at Day 15 m=111**
Females – n (%)	31 (48.4)	66 (59.5)
Mean/median age (years)	8.9/8.0	8.2/8.0
Age group – n (%)		
2-<4 years	7 (10.9)	17 (15.3)
4-<6 years	14 (21.9)	19 (17.1)
6-<12 years	24 (37.5)	50 (45.0)
12-<20 years	19 (29.7)	25 (22.5)
Body weight group – n/m (%)		
≤40 kg	41/64 (64.1)	89/111 (80.2)
>40 - <75 kg	16/64 (25.0)	19/111 (17.1)
≥75 kg	7/64 (10.9)	3/111 (2.7)
Disease duration group – n/m (%)		
≤ 6 months	12/64 (18.8)	15/111 (13.5)
> 6 months to < 4 years	31/64 (48.4)	60/111 (54.1)
≥ 4 years	21/64 (32.8)	36/111 (32.4)
Median (range) CRP at baseline (standardized in mg/L)	115.7 (3.3-651.2)	192.5 (8.9-800.0)
Mean physician's global assessment of disease activity (VAS)	62.6	70.1
Mean parent's/patent's global assessment of overall well-being (VAS)	58.1	62.2
Mean parent's/patient's global assessment of pain (VAS)	65.8	67.8
Mean CHAQ score	1.5	1.8
Number of active joints group – n/m (%)		
≤10	44/64 (68.8)	45/111 (40.5)
>10	20/64 (31.3)	66/111 (59.5)
Mean number of joints with limited range of motion	7.9	18.8
Steroid use at baseline - n/m (%)	41/64 (64.1)	88/111 (79.3)
MTX use at baseline – n/m (%)	32/64 (50.0)	63/111 (56.8)
NSAID use at baseline – n/m (%)	35/64 (54.7)	77/111 (69.4)
Canakinumab and other therapies – n/m (%)		
Canakinumab monotherapy	17/64 (26.6)	11/111 (9.9)
Canakinumab and steroids	15/64 (23.4)	37/111 (33.3)
Canakinumab and MTX	6/64 (9.4)	12/111 (10.8)
Canakinumab and steroids and MTX	26/64 (40.6)	51/111 (45.9)

Source: [SCE Appendix 1-Table 3.3-1c17]

Clinical studies in special populations

There were no dedicated trials in special patient populations.

Supportive study

Long-term efficacy data

Study G2301E1, an extension study to the 2 pivotal studies G2305 and G2301, provided further data to confirm the long-term efficacy and safety of canakinumab 4 mg/kg every 4 weeks. The study is ongoing and the results presented here are of an IA including data up to the time of interim database lock, 10-Aug-2012.

The median duration in the study at the time of interim database lock was 49 weeks (range 3- 144 weeks). All of the 147 patients received at least one dose of 4 mg/kg; 33 patients (22.4%) received 1-4 doses, 19 patients (12.9%) received 5-8 doses, 30 patients (20.4%) received 9-12 doses, and 28 patients (19.0%) received 13-16 doses. The remainder of patients received 17 or more doses.

Study G2301E1 enrolled patients who previously participated in studies G2301 or G2305. Patients were randomized to canakinumab or placebo in study G2301 Part II; both canakinumab and placebo patients were allowed to enter study G2301E1. In study G2305, patients who had been randomized to canakinumab were allowed to enter study G2301E1. Patients were allocated into 1 of 4 analysis groups according to their status at the end of their participation in the previous study. The rate of discontinuation due to unsatisfactory therapeutic effect was highest in Group 3 (47.5%) compared to the other groups (Group 1: 15.2%; Group 2: 1.6%; and Group 4: 18.2%). The patients in Group 3 entered the extension study from study G2301 Part I as steroid tapering failures and as such had a comparatively poorer prognosis.

In general, baseline demographic and characteristics were similar for the 4 analysis groups. The majority of patients were Caucasian, and slightly more than half were female. The mean age was 9.5 years. Patients in Group 2 came into the extension study from study G2301 Part II with a minimum ACR30 response, and as such their level of disease was less active in comparison to the 3 other groups (e.g., lower CRP, lower number of affected joints, and less need for steroids).

Exploratory efficacy: Response according to adapted ACR pediatric criteria in study G2301E1

Most of the patients who entered the extension study as non-responders regained their responder status at Month 3 (25/40, 62.5%). A substantial proportion achieved a minimum ACR70 (18/25, 72%), ACR90 (12/25, 48%), or ACR100 (7/25, 28%).

Group 1 comprises 33 patients who discontinued prematurely due to flare from study G2301 Part II. Of the 33, 10 had been randomized to canakinumab and 23 had been randomized to placebo at the start of Part II.

Approximately half of the 33 patients (48.5%) were ongoing and 5 (15.2%) completed 96 weeks of the study at the time of IA database lock. Five patients (15.2%) discontinued due to unsatisfactory therapeutic effect, four (12.1%) discontinued due to AEs, one patient (3.0%) discontinued due to a protocol deviation, and two patients (6.1%) withdrew consent.

Even though these patients flared in study G2301 Part II, most who entered as a nonresponder were able to regain their response in the extension study. At Month 3, 12/17 patients (70.6%) who entered the extension as a non-responder achieved a minimum ACR30 response and 10 (58.8%) had a minimum ACR70 response. At Month 6, 10/13 (76.9%) had a minimum ACR70. At the time of interim database lock, 10/17 patients (58.8%) had a minimum ACR70.

Group 2 comprises 63 patients who were minimum ACR30 responders at the time study G2301 Part II completed. Of the 63, 39 had been randomized to canakinumab and 24 had been randomized to placebo at the start of Part II. The majority of the 63 patients (93.7%) in this group were ongoing at the time of IA database lock. Four patients (6.3%) discontinued the study. One patient discontinued due to an adverse event (AE), and another patient due to an unsatisfactory therapeutic effect. Two patients' condition no longer required study drug.

A large majority achieved a minimum ACR30 response at Month 3 (62/63, 98.4%) as well as maintained an ACR90 response or better throughout the study until interim database lock (60/63, 95.2%).

Group 3 comprises 40 patients defined as steroid tapering failures in study G3201 Part I (includes patients who did not reach Part Ic). All 40 patients received canakinumab treatment in Part I. Approximately one-quarter of the 40 patients (27.5%) were ongoing and six patients (15.0%) completed 96 weeks of the study at the time of IA database lock. Unsatisfactory therapeutic effect led to the discontinuation of 19/40 patients (47.5%). Two patients (5.0%) discontinued prematurely due to AEs and two patients (5.0%) withdrew consent.

At Month 3, 9/16 (56.3%) who entered the extension as a non-responder achieved a minimum ACR30 response. At Month 6, 8/9 (88.9%) had a minimum ACR30 response.

Group 4 is a mixed group of 11 patients who did not fulfill the criteria for any of the other analysis groups. Of the 11 patients, 8 came from study G2301, 3 came from study G2305, and all had previously received canakinumab treatment. Less than half of the 11 patients (36.4%) were ongoing and four patients (36.4%) completed 96 weeks of the study at the time of IA database lock. Only two patients (18.2%) discontinued prematurely due to unsatisfactory therapeutic effect and one patient (9.1%) withdrew consent.

Of the 6 patients who were non-responders at extension study entry, 4 (66.7%) achieved a minimum ACR30 response at Month 3; all had a minimum ACR70 response.

Exploratory efficacy: canakinumab dose reduction in study G2301E1

Canakinumab dose reduction in extension study G2301E1 from 4 mg/kg to 2 mg/kg was permitted in steroid-free patients only when the treating physician requested it and Novartis agreed that this was within study design and protocol allowance.

Twenty-six patients received at least three consecutive 2 mg/kg doses (no patient received only two consecutive reduced doses). The mean/median number of reduced doses received was 10/9 and the mean/median number of days of exposure to the reduced dose was 268/224.5. The age of the 26 patients ranged from 4 to 19 years and eight were aged 4 to 6 years. All 26 patients had an ACR100 throughout the time the reduced dose was given. No patient who received a reduced canakinumab dose discontinued from the study due to unsatisfactory therapeutic effect.

Exploratory efficacy: Steroid reduction in study G2301E1

Steroid tapering was optional in extension study G2301E1 and was permitted only if the patient had a minimum ACR50 response and no fever. The mean and median steroid levels decreased from baseline of the extension study to the time of interim database lock (last observation), and some patients successfully tapered or eliminated their steroid dose.

Overall, 69 patients entered the extension study on oral steroids. Twenty of these (29.0%) were steroid-free and 13 (18.8%) were able to successfully reduce their steroid dose at the time of interim database lock. Twenty-seven (39.1%) did not attempt tapering and 9 (13.0%) failed an attempt at steroid tapering. Details by analysis group are as follows:

Group 1: Twelve of the 33 patients (36.4%) in this group were on oral steroids upon entering the extension study. Of the 12, 2 (16.7%) successfully tapered their steroid dose and 4 (33.3%) were steroid-free at interim database lock. One patient (8.3%) was unsuccessful and 5 (41.7%) did not attempt tapering. The median steroid dose at extension study baseline was 0.195 mg/kg/day; the median percent change from baseline to interim database lock was −21%.

Group 2: Nine of the 63 patients (14.3%) in this group were on oral steroids upon entering the extension study. Of the 9, 1 patient (11.1%) successfully tapered their steroid dose and 4 (44.4%) was steroid-free at interim database lock. Four patients (44.4%) did not attempt tapering. The median steroid dose at extension study baseline was 0.080 mg/kg/day; the median percent change from baseline to interim database lock was −75%.

Group 3: All 40 patients in this group were on steroid treatment upon entering the extension study. Seven of the 40 (17.5%) successfully tapered their dose and 10 (25%) were steroid-free at interim database lock. Seven (17.5%) patients were unsuccessful in tapering and 16 (40%) patients did not attempt steroid tapering. The median steroid dose at extension study baseline was 0.380 mg/kg/day; the median percent change from baseline to interim database lock was −24%.

Group 4: Eight of the 11 (72.7%) patients in this group were on oral steroids at study entry. Of the 8, 3 (37.5%) successfully tapered their steroid dose and 2 (25.0%) were steroid free at the time of interim database lock. One was unsuccessful in tapering and two did not attempt tapering. The median steroid dose at extension study baseline was 0.355 mg/kg/day; the median percent change from baseline to interim database lock was −16%.

Exploratory efficacy: Inactive disease in study G2301E1

Many patients were able to achieve a status of “inactive disease” during the extension study, particularly in patients who were ACR responders at the completion of study G2301 Part II (Group 2). Over all patients, 65/130 (50.0%) had inactive disease at Month 3, and 76/146 (52.1%) had inactive disease at the time of interim database lock (last observation).

Details by analysis group are as follows:

Group 1: At Month 3, 12 of 29 patients assessed (41.4%) met the criteria for inactive disease. At the time of interim database lock, 14 of 33 patients assessed (42.4%) met the criteria.

Group 2: At Month 3, 47 of 63 patients assessed (74.6%) met the criteria for inactive disease. At interim database lock, 54 of 63 patients assessed (85.7%) met the criteria.

Group 3: At Month 3, 4 of 30 patients assessed (13.3%) met the criteria for inactive disease. At interim database lock, 5 of 40 patients assessed (12.5%) met the criteria.

Group 4: At Month 3, 2 of 8 patients assessed (25.0%) met the criteria for inactive disease. At interim database lock, 3 of 10 patients assessed (30.0%) met the criteria.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The dose finding study provided useful information regarding the appropriate dose for the pivotal studies. The chosen dose of 4 mg/kg every 4 weeks is supported by the results of study A2203.

Study G2305 is a randomized, double-blind, placebo controlled, single-dose study to assess the initial efficacy of canakinumab (ACZ885) with respect to the adapted ACR Pediatric 30 criteria in patients with Systemic Juvenile Idiopathic Arthritis (sJIA) and active systemic manifestations.

The study plan and design of the pivotal study G2305 is appropriate to assess the efficacy and safety of canakinumab in the described target population. The numbers of protocol deviations are rather high. 34 of 43 (79%) canakinumab treated patients had a protocol deviation and 22 of 41 (53.7%) placebo treated patients.

The objectives and endpoints of study G2305 are sufficient to assess efficacy of a short term treatment to observe effect on signs and symptoms of systemic juvenile idiopathic arthritis.

Study G2301 is a randomized, double-blind, placebo controlled withdrawal study of flare prevention of canakinumab (ACZ885) in patients with Systemic Juvenile Idiopathic Arthritis (sJIA) and active systemic manifestations.

The study design of the second pivotal trial G2301 was discussed with the CHMP during a scientific advice procedure in 2008. This design was modified to include steroid tapering in part I, and part II was adapted to be event driven. The inclusion and exclusion criteria are adequate to include the target population with active sJIA.

The objectives and endpoints of this multicenter two part study G2301 are appropriate to allow the assessment of clinically meaningful efficacy and safety in the target population. The major aim of the study was to evaluate whether monthly canakinumab 4 mg/kg allowed for steroid tapering in at least 25% of patients (Part I) and to demonstrate that time to flare was longer with canakinumab than with placebo (Part II).

The rate of protocol deviations in both parts of the study is high with 72.3% in Part I and 64% in Part II. The relevant protocol deviations include missing body temperatures, missing hematology values, missing biochemistry values, missing ECGs etc. The deviations are not considered major and are therefore not expected to bias results.

Efficacy data and additional analyses

G2305

The baseline patient- and disease characteristics show a balanced treatment population. However, all children of the very low age group are in the canakinumab group. Disease characteristics are typical for patients with moderate active SJIA. Regarding the prior use of anakinra and other DMARDs there were no major differences between the two treatment groups.

The primary endpoint of the study was met as the proportion of patients who had an ACR30 at Day 15 was higher 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 (odds ratio of 62.29; $p<0.0001$).

The use of corticosteroids at baseline had no influence on the efficacy of canakinumab.

The results of the response to treatment according to the adapted ACR pediatric criteria are showing a statistically significant difference in the treatment effect of canakinumab compared to placebo at all time points. The numbers of ACR responders are increasing between day 15 and day 29 and even do not decline for ACR100 responders. All individual ACR components, reflecting systemic and joint symptoms, showed improvements towards normal levels. 30% of canakinumab patients had inactive disease after 4 weeks treatment.

These data demonstrate a clinically relevant statistically significant superiority of canakinumab compared to placebo.

Secondary endpoints and exploratory analyses give consistent results.

G2301

Baseline characteristics, disease characteristics and data on prior use of biologic DMARS represent a typical patient population of children with active systemic juvenile idiopathic arthritis. The profile of medical history and prior medication is as expected. Patients baseline and disease characteristics are well balanced in the canakinumab and placebo treatment group. There were slightly more patients 6-11 years old in the canakinumab group.

Part I of the study met its primary endpoint as 44.5% of the patients were able to taper their steroid dose. This result is clinically important as frequent long term use of corticosteroids is accompanied by severe and major side effects especially in children ($p<0.0001$; 90% CI: 37.1, 52.2).

128 patients entered Part I of the study taking oral steroids. At the end of part Ic 42 patients were steroid free (32.8%). 66/128 patients (51.6%) had an oral steroid dose of ≤0.2 mg/kg at the end of Part Ic. Therefore treatment with canakinumab showed the ability to taper the oral use of corticosteroids.

The ACR pediatric response levels gained during the treatment time show a robust and prolonged treatment effect with even improved efficacy after longer treatment.

The results of the CHAQ disability score indicate a clinically meaningful improvement over the period of Part I of the study. The fact that a MCID of improvement was even seen during the time of steroid tapering is reassuring and supports the overall efficacy of canakinumab treatment.

Nearly the same results as for the CHAQ score can be seen for the quality of live assessment using the CHQ-PF50 tool. Improvement in quality of live was maintained despite steroid tapering supporting the efficacy of canakinumab.

Results of the assessment of adapted ACR pediatric criteria response variables are equally showing improvement with canakinumab treatment in all variables.

The results of the exploratory endpoints in Part I support the efficacy of canakinumab in the target population.

The primary endpoint of Part II, time to flare, was met for canakinumab treatment. The risk to experience a disease flare was 64% reduced with canakinumab compared to placebo ($p=0.0032$). It is further shown that the probability to experience a disease flare is similar for placebo and canakinumab in the first four month of treatment. After this time point the rate of flares was much lower in the canakinumab group than in the placebo group.

The results of the secondary endpoint assessing maintenance of efficacy based on a survival analysis of the time to worsening in ACR level in Part II are showing a reduced probability of worsening in ACR level for the canakinumab group. This result is statistically significant with a one-sided p-value of 0.0131.The probability not to worsen in the ACR levels is in the first two month identical for placebo and canakinumab treatment and diverges from this time point on in favor of canakinumab treatment.

The results of the CHAQ disability score in Part II of the study do not show in this randomized withdrawal setting a statistically significant difference in the treatment groups. At the end of the treatment period a slight superiority of prolonged canakinumab treatment could be assumed. Keeping in mind that all of the 100 patients starting Part II are ACR30 responders and were treated with canakinumab already for a longer time these results are comprehensible.

The results of the change in CHQ-PF50 scores in Part II are not showing any difference in treatment of placebo or canakinumab during the withdrawal period. As explained above this might be due to the fact that all patients were already treated with canakinumab in Part I and a possibly prolonged

treatment effect and therefore the treatment/withdrawal time in Part II was too short to produce a meaningful difference.

The results of the adapted ACR pediatric response criteria variables are of descriptive character. A trend for sustained efficacy in the canakinumab group compared to reduced effect of placebo treatment (tendency for resuming disease activity) can be seen. However, the differences are too small to be of any statistical significance.

The results of the exploratory endpoints of Part II of the study are supportive to demonstrate prolonged efficacy of canakinumab treatment in this sensitive patient population.

Importantly, at the end of Part II, the proportion of patients who had inactive disease was higher in the canakinumab group (31/50, 62.0%) compared to the placebo group (17/50, 34.0%). A statistically significantly higher likelihood of inactive disease was seen with canakinumab treatment compared with placebo (CMH test: odds ratio of 3.4 (95% CI: 1.5, 8.0); p=0.0020). Furthermore, canakinumab treatment seems to have a small positive effect on the growth velocity as demonstrated by increase in the median change from baseline in height percentile at the end of the study (+2.09). For patients in the placebo group, no change between baseline and the end of study height percentile categories could be demonstrated. The changes seen in weight and BMI percentiles were similar to those for height.

The 12 week pooled efficacy data show a sustained treatment effect over time. A proportion of 58% of patients achieve an ACR70 by Day 16 of treatment. The proportion of patients in the pooled group who achieved a status of inactive disease at day 85 was 28% (50/178).

In the secondary endpoint analysis of the pooled data it is shown that treatment with canakinumab over the time of 12 weeks leads to a slight increase of response in the different criteria apart from CHAQ. The improvement of CHAQ disability score decreases over time.

The MAH performed a number of different **subgroup analysis** with data from 178 patients in the 12 week pooled group of studies G2305, G2301, and G2301E1. The chosen efficacy endpoint for this subgroup analysis is appropriate.

Response to canakinumab treatment as demonstrated by the adapted ACR pediatric criteria was seen across subgroups of age (including the youngest of patients, 2-<4 years of age, as well as patients 2, 3, and 4 years of age) gender, race, and body weight consistent with the overall efficacy seen in the 12-week efficacy pooled group. A response to canakinumab treatment was also seen in subgroups of disease duration, active joint count, and baseline oral steroid level and in all other assessed subgroups.

The response rates for patients with a lower joint count were generally higher compared to those with a higher joint count.

ACR response rates were higher for steroid-free patients compared with those using oral steroids at baseline, and those in the higher oral steroid dose level category (>0.4 mg/kg/day) had lower response rates compared to those on lower steroid doses (≤0.4 mg/kg/day), a trend that was more apparent the higher the ACR response level achieved.

ACR response rates were generally lower in patients who discontinued anakinra due to lack of efficacy compared with patients who discontinued anakinra for other reasons or patients who were never exposed to anakinra. Response rates were generally comparable for patients with or without prior steroid use, although there is some variability between the two groups at higher ACR response levels (ACR70, ACR90, ACR100) suggesting that those without prior steroid use have higher response rates compared to those with prior use. The same effect can be seen for prior MTX use and prior DMARDs use. Patients requiring these medications, however, tend to have a more severe disease state than those not requiring MTX, steroids and DMARDs.

Study G2301E1, an extension study to the 2 pivotal studies G2305 and G2301, provided further data to confirm the long-term efficacy and safety of canakinumab 4 mg/kg every 4 weeks.

The presented data is complex due to the different treatment regimens and treatment durations. Of the 147 patients assessed at time of the interim analysis 76 (52.1%) had inactive disease.

In general the efficacy data of the long term extension study support the results gained from the two pivotal trials.

69 patients entered the extension study on oral steroids. Twenty of these (29.0%) were steroid-free and 13 (18.8%) were able to successfully reduce their steroid dose at the time of interim database lock. Twenty-seven (39.1%) did not attempt tapering and 9 (13.0%) failed an attempt at steroid tapering. These results are seen as very important in light of the paediatric population and the possible side effects of long term steroid therapy. The study showed that even patients with no initial ACR30 response were able to gain this response and were further able to reduce their steroid dose. Overall, data from the extension study G2301E1 show that canakinumab treatment is effective in the target population with sJIA over longer time periods.

2.4.4. Conclusions on the clinical efficacy

The efficacy of canakinumab in treating SJIA was demonstrated in 2 pivotal phase III studies. The efficacy criteria, sample size and duration of exposure are appropriate.

Overall, data from the two pivotal studies and the extension study show that canakinumab treatment is effective in the target population with sJIA, allows steroid dose reduction and tapering in an important proportion of paediatric patients, can induce inactive disease, and efficacy is maintained over longer time period (so far median treatment duration 49 weeks).

2.5. Clinical safety

2.5.1. Introduction

Approximately 2,500 subjects have been treated with Ilaris in blinded and open-label clinical trials in patients with CAPS, gouty arthritis or other IL-1 beta mediated diseases, and healthy volunteers. The cumulative patient exposure since the first launch of the product is estimated to be approximately 1284 patient-treatment-years (PTY).

As part of a specific obligation (SO) at the initial MA a CAPS registry was initiated and data collection is ongoing with 232 CAPS patients enrolled (cut-off 30 June 2012). According to the assessment the safety profile was comparable to the known profile and no new potential safety concerns were identified.

From the third annual re-assessment (16 October 2012) safety data from 175 CAPS patients in completed clinical trials is available. The most frequently reported adverse events included upper respiratory tract infections and nasopharyngitis across all CAPS studies. Dose and duration of treatment apparently had no impact on the type or frequency of adverse events.

The RMP version 5.0 includes Macrophage Activation Syndrome (MAS) as a risk under potential off-label pediatric use in patients with SJIA since MAS is specific to SJIA. The Investigator Brochure and the patient informed consent include detailed information on MAS events. For the approved indication (CAPS), the risk of MAS has adequately been addressed in the RMP.

The safety database for the new indication claimed encompasses:

- 3 completed SJIA studies A2203, G2305 and G2301,
- interim report from the ongoing extension Study G2301E1. Patients from both G2305 and G2301 could be eligible to enter into this open-label extension trial

Patient exposure

For the current submission 201 SJIA patients, with 301 patient-years of exposure were treated in the 1 Phase II and 3 Phase III clinical trials. Of these, 130 patients received treatment of at least 48 weeks duration, with 78 being treated for at least 96 weeks. Median duration of exposure was 617 days (minimum 4, maximum 1829 days). The median number of doses given was 22 with a minimum of 1 and maximum of 49.

Study A2203

Detailed description of the study and the assessment of data can be found in in the pharmacokinetic chapter (2.3.2) of this report and in the chapter on PK/PD modelling (2.3.4).

Table 48. Overall exposure by treatment duration [n(%)]

	ACZ885			All
	0.5 mg/kg	1.5 mg/kg	4.5 mg/kg	treatments
Exposure duration	N=5	N=10	N=11	N=23
2 - < 4 months	1 (20)		1 (9)	1 (4)
4 - < 6 months	2 (40)	2 (20)	5 (46)	9 (39)
6 - < 8 months		1 (10)		
8 - <10 months	1 (20)			
10 - <12 months		1 (10)		1 (4)
12 - <24 months		2 (20)	5 (46)	5 (22)
24 months or more	1 (20)	4 (40)		7 (30)

Patients who were re-enrolled into a different treatment group are counted in the 'All treatments' column only once, with the disposition information of the last enrollment. Source: PT-Table 14.3-6.1

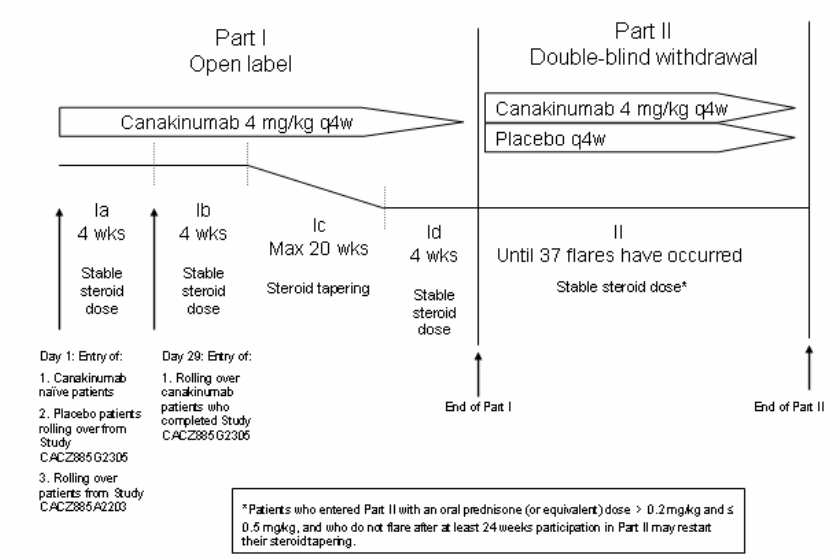
All patients who entered Stage II of the study received a dose of 4 mg/kg. Single doses were given when a patient relapsed; 10 patients received treatment in Stage II (1 in Cohort I, 5 in Cohort II and 4 in Cohort III). The number of doses received in Stage I ranged from 1 to 11 and in Stage II ranged from 1 to 8.

Study G2305

This double-blind, placebo-controlled, multi-centre (40 centres in 18 countries) single dose, 29-day Phase III trial enrolled 84 SJIA patients (43 canakinumab and 41 placebo) aged 2-20 years. Total patient-years exposure in 43 canakinumab patients was 3.25 and in 41 placebo patients it was 1.20.

Study G2301

This was a two-part Phase III study with an open-label, single-arm active treatment (Part Ia, b, c, d) followed by a randomized, double-blind, placebo-controlled, event-driven withdrawal design (Part II).



- **Part I** encompassed **177 patients**; all of which received a single dose of canakinumab (4 mg/kg) subcutaneously (s.c), with a maximum total single dose of 300 mg every 4 weeks. The median duration of **exposure in Part I was 113 days**. 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
- **Part II** enrolled **100 patients** (50 verum and 50 placebo) who received a single dose of canakinumab (4 mg/kg) or placebo s.c. every 4 weeks. The median duration of exposure in Part II was higher in the canakinumab group than in the placebo group (221.5 vs. 163.5 days), as more patients in the placebo group discontinued early from Part II due to unsatisfactory therapeutic effect. **The total patient-years exposure in Part II was 31.84 years for the canakinumab group and 24.78 years for the placebo group.** 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% vs. 28.0%), also related to the higher rate of discontinuation in placebo patients.

Study G2301E1

Study G2301E1 is an ongoing open label extension study to characterize the long-term safety and efficacy in patients from previous studies G2305 and G2301. All patients who demonstrated at minimum adapted ACR pediatric 30 response at Day 15 from their originating study were eligible to participate. An interim analysis performed with a cut-off date of Aug 10, 2012 included **147 patients** who had a median 343 days (range: 3 to 144 weeks) of exposure. **Total exposure was 156 patient years.**

Concomitant medication

In general 166/201 patients (82.6%) had had previous steroid treatment. At baseline 169 (84.1%) were using MTX or oral steroids.

Study A2203

All 23 patients received concomitant treatment (mainly NSAIDs, prednisone, antibiotics, Vitamin D). No prohibited medications were administered. The majority of the patients (19 out of 23) were under concomitant steroid treatment at baseline and 16 patients had used anakinra.

Study G2305

Patients had to be off any previous biologic agent for an appropriate washout period, but could be on a stable dose of methotrexate and/or corticosteroid at a prednisone equivalent dose of ≤1.0mg/kg/day. The majority of patients had taken (and discontinued) medications prior to the start of study drug (79.1% canakinumab vs. 75.6% placebo). The most common of these medications (i.e., ≥10.0% of patients in either group) were anakinra (32.6% vs. 31.7%), etanercept (23.3% vs. 17.1%), prednisone (23.3% vs. 7.3%), prednisolone (16.3% vs. 22.0%), methylprednisolone (14.0% vs. 12.2%), methotrexate (16.3% vs. 12.2%), and ibuprofen (4.7% vs. 17.1%).

Study G2301

- **Part I**

177 patients (128 on corticosteroids; 49 steroid-free) entered Part 1. The most frequently used other prior medications (≥15%) were anakinra (35.6%), prednisone (20.3%), etanercept (17.5%), prednisolone (16.9%) and methotrexate (16.9%).

Nearly all patients (175/177; 98.9%) took a concomitant medication on or after the start of study drug in Part I. Concomitant steroids were used by 74.0% of patients in Part I and consisted primarily of prednisone (36.2%) and prednisolone (28.8%). Over half of patients (54.2%) used concomitant methotrexate or methotrexate sodium. Concomitant NSAIDs were used by 72.9% of patients and consisted mainly of ibuprofen, indomethacin and naproxen.

- **Part II**

Most of the 100 patients took a concomitant medication on or after the start of study drug in Part II, with no meaningful difference between the treatment groups (94.0% canakinumab vs. 92.0% placebo). Concomitant use of steroids was reported more frequently for the placebo group (30.0%) than the canakinumab group (16.0%), with prednisolone (10.0% canakinumab and 12.0% placebo) as the most common steroid. Over half of patients in both treatment groups used concomitant methotrexate or methotrexate sodium (58.0% canakinumab and 52.0% placebo). Concomitant NSAIDs, mainly ibuprofen, indomethacin and naproxen, were used by a greater proportion of placebo patients (70.0%) than canakinumab patients (58.0%).

Study G2301E1

Most patients (97.3%) were taking at least one concomitant medication on or after the start of study drug. Concomitant steroid medications were taken by 57.1% of patients; concomitant methotrexate medications were taken by 56.5% of patients and concomitant NSAIDs were taken by 66.7% of patients. Concomitant medications used by ≥10% of patients were indomethacin (16.3%), paracetamol (40.1%), ibuprofen (31.3%), naproxen (17.7%), prednisone (23.1%), prednisolone (22.4%), methylprednisolone (19.7%), folic acid (40.8%), methotrexate (45.6%), methotrexate sodium (11.6) amoxicillin (12.9%), omeprazole (30.6%), and ergocalciferol (10.9%).

Adverse events

General

A total of 171/200 (85.1%) experienced adverse events. The most often affected system organ classes (SOCs) were infections and infestations (71.1%), followed by gastrointestinal disorders, (52.7%), musculoskeletal and connective tissue disorders (41.8%), and respiratory, thoracic and mediastinal disorders (38.3%). This sequence was the same when adjusted by exposure (see below).

The most frequently reported AEs by preferred term were nasopharyngitis (29.4%), cough (25.9%), pyrexia (25.9%), vomiting (22.9%), diarrhea (22.4%), upper respiratory tract infection (22.4%) and headache (20.9%).

Severity

Most AEs were of mild or moderate intensity; with 16.9% of SJIA patients having severe AEs (this compares to the data on severe AEs in CAPS children at 15.6%). AEs of gastrointestinal disorders were mainly mild; 3.0% of SJIA children had severe events. AEs of infections and infestations were also mainly mild or moderate, with 6.0% of SJIA children having severe events. Among the most frequent AEs, there were no cases of severe nasopharyngitis, cough or upper respiratory tract infection.

Exposure-adjusted incidence rates

Exposure-adjusted incidence rates of AEs in total did not increase over time on treatment (1684.1 vs. 802.2 AEs per 100 patient years for first 4 weeks vs. after 48 weeks), suggesting that undesirable effects do not increase with continued canakinumab therapy.

Most specific AEs showed either decreasing rates or no clear pattern of change over time. The only AEs showing slight increases in rate over time were musculoskeletal events (preferred terms juvenile arthritis, pain in extremity, and arthralgia).

The incidence rate of SAEs did not increase with time (199.0 vs. 39.9 per 100 patient years in first 4 weeks vs. after 48 weeks), suggesting there is no progression of undesirable effects or immune suppression with continued use of canakinumab. There was no indication that a severe AE outcome (deaths) increased over time.

Exposure-adjusted AEs and SAEs over time by SOC in SJIA

AEs (N=201) n (n/100 patient years)				SAEs (N=201) n (n/100 patient years)			
0-<4 weeks	4-<24	24-<48	≥48	0-<4 weeks	4-<24	24-<48	≥48
All events							
237 (1684.1)	700 (1142.0)	606 (961.4)	1306 (802.2)	28 (199.0)	57 (93.0)	39 (61.9)	65 (39.9)
Infections & infestations							
63 (447.7)	203 (331.2)	152 (241.2)	380 (233.4)	8 (56.8)	9 (14.7)	5 (7.9)	27 (16.6)
Gastrointestinal disorders							
52 (369.5)	121 (197.4)	83 (131.7)	203 (124.7)	5 (35.5)	5 (8.2)	4 (6.3)	3 (1.8)

arranged by AE frequency in first period, n/100 patient years = incidence per 100 years of patient exposure
Source: [SCS Table 2-5] (AEs), [SCS-Table 2-18] (SAEs)

Table 49. Comparison of exposure adjusted AE between SJIA and CAPS (Incidence rate per 100 patient-years)

Primary system organ class	SJIA pediatric Canakinumab N=201	CAPS pediatric Canakinumab N=77
Exposure in patient-years	**301.199**	**93.522**
-Any primary system organ class	2849 (945.9)	796 (851.1)
Infections and infestations	798 (264.9)	223 (238.4)
Gastrointestinal disorders	459 (152.4)	89 (95.2)
Musculoskeletal and connective tissue disorders	286 (95.0)	41 (43.8)
Respiratory, thoracic and mediastinal disorders	272 (90.3)	67 (71.6)
Skin and subcutaneous tissue disorders	200 (66.4)	56 (59.9)
Nervous system disorders	181 (60.1)	57 (60.9)
General disorders and administration site conditions	180 (59.8)	58 (62.0)
Investigations	109 (36.2)	67 (71.6)
Injury, poisoning and procedural complications	108 (35.9)	48 (51.3)
Eye disorders	52 (17.3)	19 (20.3)
Blood and lymphatic system disorders	39 (12.9)	10 (10.7)
Ear and labyrinth disorders	25 (8.3)	17 (18.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	26 (8.6)	2 (2.1)
Psychiatric disorders	20 (6.6)	11 (11.8)
Cardiac disorders	13 (4.3)	1 (1.1)
Hepatobiliary disorders	14 (4.6)	0
Reproductive system and breast disorders	11 (3.7)	6 (6.4)
Vascular disorders	13 (4.3)	9 (9.6)
Metabolism and nutrition disorders	15 (5.0)	6 (6.4)
Renal and urinary disorders	12 (4.0)	5 (5.3)
Immune system disorders	14 (4.6)	1 (1.1)
Endocrine disorders	2 (0.7)	0
Congenital, familial and genetic disorders	0	1 (1.1)
Pregnancy, puerperium and perinatal conditions	0	1 (1.1)
Surgical and medical procedures	0	1 (1.1)

Plasma canakinumab levels and AEs

Plasma canakinumab levels were not higher in patients with selected AEs (e.g., infection, MAS, pyrexia, SAE of infection and abdominal pain) compared to those without these AEs. There was no clear relation of time of AEs to peak plasma levels.

Study A2203

All patients experienced at least one AE, (22/23 in Stage I and 11/11 in Stage II). In general the most common AEs were upper respiratory tract infections, rhinitis, nasopharyngitis, pharyngitis, tonsillitis and gastroenteritis.

Stage I (n= 23)

A total of 19 patients (83%) had gastrointestinal disorders, whereby abdominal pain/ upper abdominal pain (47.8%) and vomiting (35%) were the most common AEs, mainly experienced by patients in the 1.5 and 4.5 mg/kg groups, followed by nausea and diarrhoea in 4 patients each (17%). Sixteen patients (69%) were classified as having an infection, these were mainly rhinotracheitis, gastroenteritis, nasopharyngitis, and URTI.

General disorders and administration site conditions were experienced by 13 patients (57%). Pyrexia (30%) was a common AE with the rate increasing with increasing dose; this was followed by cough, headache and rhinitis (26% each) which were mainly experienced by patients in the 1.5 mg/kg group. Cardiac arrhythmia and pericarditis was experienced by 1 patient, both were SAEs

Stage II (n=11)

The majority of the patients 73% (8/11) were listed in the SOC “infections and infestations”, these were mainly gastroenteritis (27%) and influenza (18%).

Gastrointestinal disorders were also high and observed in 7/11 (64%), mainly diarrhoea (3/11; 27 %) There are 2 cases of rectal hemorrhage and one of anal erosion and one of haematochezia. (see SAEs) Respiratory disorders were common (54%; mainly cough). One case of MAS and 1 syncope occurred (see MAS and SAE below)

Severity of AEs

Most of AEs were of mild to moderate severity, unrelated to study drug and did not lead to discontinuation.

Study G2305

A total of 24/43 patients (55.8%) had AEs in the canakinumab group vs. 16/41 (39%) in the placebo group.

The most commonly affected primary system organ classes were infections and infestations (30.2% vs. 12.2% in placebo group; primarily nasopharyngitis, upper respiratory tract infection, and bronchitis), gastrointestinal disorders at (16.3% vs 4.9%; primarily diarrhea, abdominal pain), skin and subcutaneous tissue disorders (14.0% vs. 2.4%; primarily maculo-papular rash), and nervous system disorders (primarily headache). Other AEs occurred in individual patients in both groups, without a distinct pattern or signal emerging. MAS occurred in one patient each of both verum and placebo groups.

Severity of AEs

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.

AEs requiring significant additional therapy were found more often in the canakinumab group (39.5% vs. 19.5%); additional therapy was primarily required for infections, gastrointestinal disorders and skin disorders

AEs by age group

In general, there were no significant differences amongst the age categories in the canakinumab group with respect to frequency or nature of AEs, however, the youngest age category (i.e., 2-<4 years of age) had a relatively lower proportion of patients reporting AEs compared with other age categories, as well as compared with the overall population.

In the canakinumab group, AEs were reported for:

4/9 (44.4%) patients in the 2-<4 age group, (vs. 0 in the placebo group)

5/8 (62.5%) patients in the 4-<6 age group, (vs. 3/7 (42.9%))

8/14 (57.1%) patients in the 6-<12 group, (vs. 11/22 (50.0%))

7/12 (58.3%) patients in the >12 age group. (vs. 2/12 (16.7%)).

AEs by gender

The reporting frequency of AEs was generally comparable for the two genders. In the canakinumab group, AEs were reported for 9/16 (56.3%) male patients and 15/27 (55.6%) female patients. In the placebo group, AEs were reported for 6/18 (33.3%) male patients and 10/23 (43.5%) female patients. Of the common reported AEs, infections and infestations AEs were seen at a comparable rate in the two genders, while gastrointestinal disorders (f=22.2% vs. m= 6.3%) and skin (f= 18.5 vs. m= 6.3%) AEs were seen more often in females, and neurological disorder AEs were seen more often in males (f=3.7% vs. m=18.8%)

Study G2301

- **Part I**

A total of 78.0% (138/177) of patients experienced an AE during Part I. The most commonly affected primary SOCs were infections and infestations (54.8%; primarily nasopharyngitis, upper respiratory tract infection and rhinitis), gastrointestinal disorders (29.4%; primarily vomiting, abdominal pain and diarrhea), and respiratory, thoracic and mediastinal disorders (20.9%; primarily cough), skin and subcutaneous disorders (18.6%; primarily eczema), followed by musculoskeletal and connective tissue disorders (16.4%, primarily arthralgia) general and administration disorders (15.8%, primarily pain in extremity) and nervous system disorders (15.8%; primarily headache). The most frequent AEs by preferred term were nasopharyngitis (15.3%), headache (13.0%) and cough (11.3%). MAS was reported in 4 (2.3%) patients (see below).

Severity of AEs Part I

The majority of AEs were either mild (51.4%) or moderate (21.5%) in severity. Nine (5.1%) patients had a severe AE. Of these patients, 5 had multiple severe events. Four (2.3%) patients had hematophagic histiocytosis (MAS); all 4 cases were reported as severe AEs and as SAEs and were adjudicated by the independent MAS Adjudication Committee (MASAC). Most severe AEs were also reported as SAEs, except for the following 3 events:

  - increased serum ferritin (patient 0057/00101); this patient had an SAE of traumatic fracture;
  - anxiety (patient 0115/00109); this patient had multiple severe AEs / SAEs including MAS;
  - pyrexia (patient 0510/00101); this patient had 2 other severe AEs / SAEs.

- **Part II**

A total of 50 patients participated in Part II (50 in the verum and 50 in the placebo group). AEs occurring in Part II of the study were reported for 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 primary SOC in Part II (54.0% canakinumab and 38.0% placebo) and consisted predominantly of nasopharyngitis, upper respiratory tract infection and rhinitis.

In the canakinumab group, arthralgia (24.0%) was the most frequently reported AE by preferred term followed by cough (16.0%), and nasopharyngitis and pyrexia (both 14.0%). In the placebo group, the most frequently reported AEs were nasopharyngitis and rhinitis (both 14.0%), followed by cough (12.0%), and arthralgia, pyrexia and upper respiratory tract infection (each 10.0%). MAS was reported in 1 (2.0%) patient in the placebo group.

Severity of AEs Part II

In both verum and placebo treatment groups, the majority of AEs occurring were mild (36.0% canakinumab vs. 34.0% placebo) or moderate (34.0% vs. 28.0%) in severity. Severe AEs were reported in 5 (10.0%) patients on canakinumab and 3 (6.0%) patients on placebo, and 3 of these patients (1 canakinumab and 2 placebo) had multiple severe AEs.

One patient (0011/00101) who was randomized to placebo after previously receiving canakinumab experienced 9 severe AEs in Part II, all associated with hematophagic histiocytosis (MAS) which was reported 5 months after entering Part II and 192 days since the last canakinumab dose in Part I. Most severe AEs were also reported as SAEs, except for the following 4 events:

- rash papular (patient 0094/00102 randomized to canakinumab),
- arthralgia (patient 0135/00101 randomized to canakinumab),
- coagulopathy (patient 0011/00101 randomized to placebo); this patient had multiple severe AEs / SAEs,
- pruritus (patient 0042/00101 randomized to placebo); this patient had multiple severe AEs / SAEs

Exposure- adjusted AEs Part II

The incidence of adverse events was adjusted to the exposure (rate per 100 patient days) to account for the unequal exposure in the verum and placebo arms and the overall rate was found to be similar in both groups; in the canakinumab group (n= 50) there were 272 adverse events (= 2.34 / 100 patient days) and 229 in the placebo group (= 2.53 / 100 patient days). However, some differences were noticeable:

The canakinumab group had a higher exposure-adjusted incidence of musculoskeletal and connective tissue disorders (0.42 canakinumab vs. 0.19 placebo), particularly arthralgia (0.15 vs. 0.06) and back pain (0.09 vs. 0.00); and gastrointestinal disorders (0.36 vs. 0.25) such as abdominal pain (0.12 vs. 0.06) compared with the placebo group.

AEs that were more frequent in the placebo group compared with the canakinumab group included infections and infestations (0.63 placebo vs. 0.59 canakinumab), such as nasopharyngitis (0.15 vs. 0.09) and rhinitis (0.17 vs. 0.05); nervous system disorders (0.27 vs. 0.08), primarily headache (0.24 vs. 0.04); investigations (0.14 vs. 0.09); respiratory, thoracic and mediastinal disorders (0.25 vs. 0.18); and skin and subcutaneous tissue disorders (0.27 vs. 0.19).

Study G2301E1

Most patients (128/147; 87.1%) experienced at least one AE.

Exposure adjusted (per 100 patient days) incidence rates for adverse events were calculated. The system organ class (SOC) with the highest 100-day exposure adjusted incidence rate was infections and infestations (0.632; mainly nasopharyngitis (0.105), rhinitis (0.075), upper respiratory tract infection (0.083), and gastroenteritis (0.047)). The SOCs with the next highest incidence rates were gastrointestinal disorders (0.342; mainly vomiting, diarrhoea, abdominal pain), followed by musculoskeletal and connective tissues disorders (0.253; mainly arthralgia, juvenile arthritis) and respiratory, thoracic and mediastinal disorders (0.239; mainly cough).

Severity of AEs

Most patients experienced AEs that were considered mild (40.8%) or moderate (32.0%) 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, hematophagic histiocytosis (2 patients in each, 1.4%); and juvenile arthritis (7 patients, 4.8%).

Adverse events that required significant additional therapy

A total of 112 patients (76.2%) experienced AE(s) that required significant additional therapy. The most commonly affected SOCs (≥10%) in this category were infections and infestations (55.1%), musculoskeletal and connective tissue disorders (29.3%), gastrointestinal disorders (23.8%), respiratory, thoracic and mediastinal disorders (19.0%), general disorders and administration site conditions (17.0%), skin and subcutaneous disorders (17.0%), injury, poisoning and procedural complications (13.6%), nervous system disorders (12.9%).

Adverse drug reaction (ADRs)

General

Potential ADRs were identified by the applicant as AE terms that were either listed ADRs in the CDS, or showed higher rates than placebo.

The main ADRs of the 2 pivotal studies identified from AE reports, their rates of occurrence and frequency category are shown in the table below (see table below).

Table 50. Adverse drug reactions identified in phase III SJIA trials

	Study G2301			Study G2305		Frequency category
	Part I	Part II				
	Canakinumab n=177	Canakinumab n=50	Placebo n=50	Canakinumab n=43	Placebo n=41	
Infections and infestations (e.g. nasopharyngitis (viral), upper resp. tract infect. pneumonia, rhinitis, etc.)	97 (54.8%)	27 (54.0%)	19 (38.0%)	13 (30.2%)	5 (12.2%)	very common
Gastrointestinal disorders						
Abdominal pain (upper)	25 (14.1%)	8 (16.0%)	6 (12.0%)	3 (7.0%)	1 (2.4%)	very common
Skin and subcutaneous						
Injection site reactions						
mild	19 (10.7%)	6 (12.0%)	2 (4.0%)	0	3 (7.3%)	very common
moderate	2 (1.1)	1 (2.0)	0	0	0	common

Source: [SCS-Table 2-30]

Study A2203

A total of 14/23 (60.8%) patients had ADRs:

- 2 patients with 3 ADRs of vertigo in (2x mild, 1x moderate)
- 1 patient with 1 mild ADR of myalgia and costal pain
- 1 patient with 1 mild ADR of injection site urticaria.
- 1 patient with a moderate hematoma
- 1 patient with a moderate case of EBV infection
- 1 patient with mild abdominal pain and headache
- 1 patient with prolonged, moderate APTT, mild gastroenteritis and mild vaso-vagal collapse.
- 2 patients with molluscum contagiosum, one thereof also with mild buccal candiosis

- 2 patients with mild nausea, one case of diarrhoea.
- 1 patient with mild fever (2x) and hot flushes (2x) and erythema (2x),
- 1 patient with mood irritability

Study G2305

AEs suspected to be related to study medication (by the investigator) were reported in 5/43 /patients (11.6%) in the canakinumab group and 1/41 patient (2.4%) in the placebo group. In the canakinumab group, the suspected AEs were

- 1 patient with bronchopneumonia, rash maculo-papular, MAS, hepatitis, neutropenia, and leukopenia,
- 1 patient with allergic edema,
- 1 patient with headache and varicella,
- 1 patient with dizziness,
- 1 patient with pruritus

In the placebo group, the suspected related AEs were fatigue and thirst in 1 patient.

Study G2301

- **Part I (only canakinumab)**

Adverse drug reactions were reported in 30/177 (16.9%) patients. Infections and infestations (8 patients, 4.5%) and gastrointestinal disorders (6 patients, 3.4%) were the most commonly affected SOCs of drug-related AEs. Most drug-related AEs by preferred term occurred in 1 or 2 patients, except for hematophagic histiocytosis (4 patients) and headache (3). Gastrointestinal non-specific inflammation and dysfunctional conditions were the most frequently reported Standardized MedDRA Query (SMQ) category (25.4%), followed by 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%).

- **Part II (canakinumab vs placebo)**

Adverse drug reactions were reported in 13/50 (26.0%) patients in the canakinumab group and 6/50 (12.0%) in the placebo group. The most common drug-suspected AEs 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 predominant SOCs of drug-related AEs were 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%).

The two treatment groups had similar incidences and types of Standardized MedDRA Query (SMQs) reported, except for oropharyngeal disorders which were more frequent in the canakinumab group than in the placebo group (24.0% vs. 12.0%), particularly with respect to oropharyngeal infections (16.0% vs. 6.0%). Hepatic disorders, consisting entirely of liver-related investigations, were reported with comparable frequency between the treatment groups (8.0% canakinumab vs. 10.0% placebo).

Study G2301E1

Adverse events that were suspected to be related to study drug were experienced by 34/147 patients (23.1%). Suspected events that were experienced by more than 1 patient were upper respiratory tract infection (5 patients, 3.4%); hematophagic histiocytosis and juvenile arthritis (4 patients in each, 2.7%); cough and nasopharyngitis (3 patients in each, 2.0%); neutropenia, leukopenia, influenza-like illness, pyrexia, oral candidiasis, skin papilloma, abdominal pain, conjunctivitis, oral herpes, and injection site erythema (2 patients in each, 1.4%).

Adverse events of special interest

- **Macrophage activation syndrome (MAS)**

Background information

In rheumatology, MAS is most strongly associated with the systemic form of juvenile idiopathic arthritis (SJIA). In fact, it accounts for much of the morbidity and mortality seen in this disease. About 10% of the patients with SJIA develop overt life-threatening MAS [S Sawhney, Arch Dis Child 2001;85:421–426; retrospective study in (n=143) mainly SJIA, nine developed MAS, 2 thereof died], and this may occur at any time point during the course of SJIA. (Adapted from: Grom A. Current Opinion in Rheumatology 2010,22:561–566 and S. Davì, A. An international consensus survey of diagnostic criteria for macrophage activation syndrome in systemic juvenile idiopathic arthritis,"J. Rheum., vol. 38, no. 4, pp. 764–768, 2011.)

The diagnosis of MAS is challenging because it is a syndrome defined by a constellation of signs and symptoms that evolve rapidly and can be similar to both active SJIA and sepsis.

MAS is a severe, potentially fatal condition associated with excessive activation and expansion of macrophages and T cells (mainly CD8+) leading to an overwhelming inflammatory reaction.

A fall in the ESR and platelet count, particularly in a combination with persistently high CRP and increasing levels of serum D-dimer and ferritin, should raise a suspicion of impending MAS. In MAS, serum IL-18 levels are elevated out of proportion compared with other cytokines. This is in distinct contrast to in other diseases such as rheumatoid arthritis. In healthy individuals IL-18 levels are in the realm of 100 pg/mL, in diseases with systemic inflammation the levels rarely exceed 300 pg/mL, whereas in MAS IL-18 can be in the nanogram per milliliter range.

MAS can be confirmed by evidence of macrophage hemophagocytosis in the bone marrow. An infective trigger may herald the onset of MAS in predisposed patients. Multisystem involvement is a poor prognostic sign.

The main clinical manifestations of MAS include fever, hepatosplenomegaly, lymphadenopathy, severe cytopenias, liver dysfunction, and coagulopathy consistent with disseminated intravascular coagulation. The pathognomonic feature of MAS is the expansion of well differentiated macrophages exhibiting hemophagocytic activity. These macrophages are typically found in bone marrow or lymph nodes, but they may infiltrate almost any organ in the body and may account for many of the systemic features of this syndrome, including cytopenias and coagulopathy.

Occult MAS

In a controlled study by Behrens et al (Behrens E. J Rheumatol 2007;34:1133–8) they investigated the prevalence of "occult MAS" in children with SJIA by reviewing bone marrow aspirates (BMA).

Patients diagnosed with SJIA who underwent bone marrow aspiration were identified retrospectively. Patients admitted with a diagnosis of fever of unknown origin and discharged with a diagnosis other than SJIA or malignancy, and who had a BMA, were identified as controls. The BMA were reviewed by a

single hematopathologist for evidence of MAS, ranging from activated macrophages to frank hemophagocytic cells.

Eight of 15 (53%) patients with SJIA had BMA suggestive of MAS. Two of 15 patients (13%) were diagnosed clinically with MAS. Three patients (20%) were noted to have frank hemophagocytosis, only one of whom was diagnosed with MAS clinically. There were no statistically significant differences in the laboratory values for the patients with and without evidence of MAS on BMA. There was no evidence of increased macrophage activity or hemophagocytosis in any of the control BMA. Occult MAS appears to be common in patients with SJIA who undergo BMA. This suggests that macrophage activation may be integral to the pathogenesis of SJIA, with implications for treatment.(adapted from: Behrens E. J Rheumatol 2007;34:1133–8)

Reported cases of MAS in canakinumab SJIA studies

Reported cases of MAS were reviewed and adjudicated by an independent MAS adjudication committee (MASAC).

According to the study report MAS was reported in 12 patients (10 canakinumab and 2 placebo), including two (1 canakinumab and 1 placebo patient) with a fatal outcome:

- 1 in **Study A2203** (1 canakinumab)
- 2 in **Study G2305** (1 canakinumab (prior bronchopneumonia) and 1 placebo)
- 5 in **Study G2301** (4 canakinumab and 1 placebo)
- 4 in **Study G2301E1** (4 canakinumab; *possibly 8 see CHMP's comment below*)

In 3 of these patients, the diagnosis of MAS was confirmed by the demonstration of hemophagocytic macrophages in the bone marrow.

Corticosteroid (CS) dose reduction

Corticosteroid (CS) dose reduction was part of the protocol design of study G2301 (Part Ic) and was allowed at the discretion of the investigator in the extension study G2301E1.

Since in clinical practice MAS may be triggered by a flare of the disease brought on by aggressive steroid taper, the possibility that steroid dose reduction might have been a contributing factor in some patients was considered in the analysis. Overall, CS tapering did not appear to increase the risk of MAS. Of the 12 reported AEs of MAS, 8 of the patients had entered the program on a concomitant corticosteroid and of these, 7 reduced their corticosteroid dose or completely discontinued it during the trial. Only two of these patients had reduced their corticosteroid dose within short period prior to MAS.

- Patient 510_101 from study G2301 had MAS reported on the same day as her first CS dose reduction. She also had a confirmed acute EBV infection which was the likely trigger.
- Patient 145_201 in study G2301E1 had CS dose reduction on Days 59-164 and MAS on Day 198. The last CS dose change was a dose increase in response to increased SJIA activity approximately 3 weeks after completing part IC in study G2301 when he had an ACR100.

In addition to steroid taper during the study, in many patients steroid dose reduction had been performed just prior to the study entry to meet certain eligibility criteria (i.e presence of systemic features, CRP >3 mg/dL etc.). Of the six patients who developed MAS within 90 days of entering the study, only one (Patient G2301 82_00103) had a steroid dose reduction (from 0.83 mg/kg/day to 0.6 mg/kg/day) within 7 days prior to the entry.

Time adjusted rate of Reported MAS

Table 51. Time adjusted rate of Reported probable or possible MAS in the Canakinumab SJIA Clinical Program

	SJIA Clinical Program		
	Canakinumab	Placebo	Difference canakinumab – placebo (95% confidence interval)
Number of adjudicated Probable or Possible MAS cases	12	2	
Patient-years exposure (yrs)	276	26	
Rate of adjudicated Probable or Possible MAS / 100 pt-yrs	4.3	7.7	-3.4 (-14.3, 7.6)

Clinical program included studies: CACZA2203, CACZG2305, CACZG2301, CACZG2301E1.
Data provided by and sourced on file at Novartis with a adjudication data cut-off date of May 31, 2012.
AE= adverse event. MASAC= MAS Adjudication Committee.

Study A2203

One case (2/5210) was identified and adjudicated by the MASAC as having MAS. The 4 year-old male patient developed fever and polyarthralgia, hepatosplenomegaly. The SJIA flare may have triggered the further MAS development.

Study G2305

A total of 6 events were identified for adjudication by the MASAC, 2 in the canakinumab group and 4 in the placebo group. However, only one case in each group was supported by clinical and laboratory features but without histological confirmation or meeting the formal HLH criteria.

Study/ Patient ID Age(yr)/ Sex/ Race	Study Day of event[1]	No. of canakinumab doses taken before event	Days from last canakinumab dose and MAS event	Baseline SJIA meds[2]	History of MAS[3]	Reason for adjudication	Outcome	MASAC Adjudication	MASAC comments	No. of canakinumab and/or placebo doses after event	Disposition status
G2305/ 0132_00001 15/M/Ca	Day 3	0 (1 placebo dose)	0	CS, NSAID	Yes	**Lab:** Ferritin ≥2000 µg/L	Normalized in G2301	Unlikely MAS	SJIA disease activity	6 canakinumab, then 1 placebo, then 2 canakinumab	continues
G2305/ 0508_00002 5/F/Ca	Day 4	0 (1 placebo dose)	0	MTX, NSAID	None	**AE:** Hepatomegaly **Lab:** Ferritin ≥2000 µg/L	Hepatomegaly resolved, Normalized in G2301	Unlikely MAS	SJIA disease activity	3 canakinumab, then 1 placebo, then 1 canakinumab	DC: AE (SJIA flare)
G2305/ 0051_00005 15/F/As	Day 3	0 (1 placebo dose)	0	None	None	AE: MAS **Lab:** Ferritin ≥2000 µg/L; Thrombocytopenia	Full recovery	Probable MAS	None	14 canakinumab	Continues
G2305/ 0060_00002 11/M/Ca	Day 3	0 (1 placebo dose)	0	NSAID	None	**Lab:** Ferritin ≥2000 µg/L	Decrease of ferritin in G2301	Unlikely MAS	Underlying disease (SJIA)	20	Continues
G2305/ 0082_00004 14/M/Ca	Day 3	1	2	None	Yes	AE: MAS **Lab:** Ferritin ≥2000 µg/L	Full recovery	Probable MAS	None	0	Completed G2305 but did not enter G2301
G2305/ 0130_00001 18/F/Ca	Day 29	1	28	None	None	**Lab:** Leukopenia; Thrombocytopenia	Normalized in G2301	Unlikely MAS	IL-1 inhibition causing neutropenia. Lab error for thrombocytopenia	1 canakinumab, then 21 placebo, then 6 canakinumab	Continues

Study G2301

Of the 30 patients who were initially identified by the MASAC, 3 cases were adjudicated as probable and 2 as possible MAS (=5). Two deaths occurred: one patient (11/101) had received 8 canakinumab doses, then 6 doses of placebo (15/F/Bl; Day 390), the other patient 11/109; 13/M/bl; Day 64 had received 3 doses of canakinumab.

Study G2301E1

All patients were on canakinumab in the open-label extension study; of the 11 patients who were initially identified by the MASAC, 3 cases were adjudicated as probable and 3 as possible MAS (=6).

Patient ID[1]	Age/Sex/Race	Event (preferred term) or lab abnormality	Study day onset-resolution	Adjudication outcome
0215/00201	5/M/Ca	Ferritin ≥1000µg/L Elevated transaminases Leukopenia and/or thrombocytopenia	Day 176-201	Possible MAS
0060/00202	14/F/Ca	Leukopenia and/or thrombocytopenia	Day 01-continuing	Unlikely MAS
0202/00201	13/F/As	Suspected MAS	Day 43-continuing	**Probable MAS**
0070/00205	9/F/Ca	Ferritin ≥1000µg/L Elevated transaminases	Day 140-152	Possible MAS
0145/00201	7/M/Ca	MAS	Day 35-39	**Probable MAS**
0506/00201	8/F/Ca	Ferritin ≥2000µg/L	Day 29-continuing	Unlikely MAS
0200/00203	5/F/Ca	Macrophage activated syndrome (parvovirus infection)[2]	Day 192-201	Unlikely MAS
0057/00201	9/F/Ca	Ferritin ≥2000µg/L	Day 143-171	Unlikely MAS
0011/00201	13/F/Bl	Leukopenia and/or thrombocytopenia	Day 113-169	Unlikely MAS
0021/00202	18/F/As	Leukopenia and/or thrombocytopenia	Day 373-400	Possible MAS
0145/00202	11/M/Ca	MAS	Day 209-217	**Probable MAS**

<u>MAS cases identified outside the SJIA clinical program</u>

Search of the most currently available data from the FDA AERs database (data cut-off date of March 31, 2012) performed by Novartis identified 13 patients with reported MAS. This group includes all patients with MAS reported as an AE in the clinical study program (up to that date). Novartis estimated that as of March 31, 2012, thirty patients with SJIA had been prescribed Ilaris outside a canakinumab clinical study. It is not known how close this estimation is to the true number since the diagnosis of SJIA is tracked differently in various countries and in some countries, including the United States, the physician diagnostic code for SJIA does not exist making it difficult to determine the true diagnosis. Nevertheless, based on the 3 MAS reports among all SJIA patients treated with canakinumab outside a clinical study, an estimated crude incidence in this group was determined to be 10% (3/30).

Of the 3 cases identified outside the clinical program, one was adjudicated to be probable MAS, the two other cases were categorized as “unlikely”, both of these resulted in death (see table below).

Study/Patient ID Age(yr)/ Sex/ Race	No. of canakinumab doses taken before event	Days from last canakinumab dose and MAS event	Maintence meds[2]	History of MAS[3]	Reason for adjudication	Outcome	MASAC Adjudication	No. of canakinumab doses after event
(GB 74952) 10/M/UNK	4	53	CS, MTX,	Yes	AE: MAS	Death	Unlikely MAS	0
(FR 49147) 48/F/UNK[1]	2	12	CS, MTX	None	AE: MAS	Full recovery	Probable MAS	0
(US 24124) 13/F/UNK	5	33[2]	None	None	AE: Sepsis, seizures; resp. failure	Death	Unlikely MAS	0

Data provided by and sourced on file at Novartis with a adjudication data cut-off date of May 31, 2012.
AE= adverse event, UNK = Unknown, CS= corticosteroid, IV IgG = intravenous immunoglobulin G, MTX= methotrexate, NA= not available.
[1]Patient had Adult Onset Stills Disease. The number of subjects with AOSD receiving canakinumab is not known.
[2] MAS was not reported for this patient. Reason for adjudication was "death" and not MAS.

Infections

As expected from the mode of action of canakinumab , the incidence of infections was higher in the canakinumab arm compared to in the placebo arm (see Study G2305). There was 1 fatal outcome of sepsis from an untreated urinary tract infection more than 2 years after receiving the last canakinumab dose in a SJIA trial (see Deaths below).

There were SAEs of infections in 30/201 patients (15%), 2 patients (1%) discontinued due to the SAE infection. No single serious infection preferred term occurred in more than 2 (1%) of SJIA patients, patients, except gastroenteritis and varicella, both in 4 (2%) of patients.

Potential opportunistic or unusual infections were prospectively defined as systemic herpes or fungal infections, or those caused by toxoplasma, mycobacterium, aspergillus, pneumocystis, or cryptococcus pathogens, polyoma or cytomegalovirus, and Kaposi sarcoma. In a prospective search for these terms, cases potentially suggestive of an opportunistic infection were identified but not medically confirmed. One patient was being treated for a serious streptococcal infection and was found to have asymptomatic toxoplasmosis. This was not considered to be an opportunistic infection.

Infection rates compared to CAPS

Table 52. Infections related to death, SAEs, withdrawal in SJIA and CAPS

	Patients with events N (%)		Events N (per 100 years exposed)	
	SJIA pediatric N=201	CAPS pediatric N=77	SJIA pediatric Pat. yrs. = 301.2	CAPS pediatric Pat. yrs. = 93.5
Any Infections & infest. AEs	143 (71.1)	62 (80.5)	798 (264.9)	223 (238.4)
Deaths	1	0	-	-
SAEs	30 (14.9)	10 (13.0)	49 (16.3)	14 (15.0)
SAE discontinuations	2 (1.0)	0	-	-

Pat. yrs = patient years of exposure
Source: [SCS-Table 2-10] (deaths), [SCS Appendix 1-Table 2.1-10a] (exp-adj AEs), [SCS Appendix 1-Table 2.1-3a] (SAEs), [SCS Appendix 1-Table 2.1.6a (SAEs, dis.), [SCS Appendix 1-Table 2.1-11a] (exp.-adj. SAEs)

Serious adverse event / deaths / other significant events

Deaths

General

There were 4 deaths in SJIA patients; none were considered related to canakinumab by the reporting investigator.

Three of the four deaths occurred a considerable time after the last dose of canakinumab (4 months to 2 years). The fourth patient died after developing MAS approximately 3 weeks after the last dose of canakinumab, after severe gastroenteritis and subsequent pulmonary hypertension.

Study A2203

No deaths occurred either during the study or the follow-up period.

However a death was reported for a female patient, 2.25 years after the last injection of study medication. The cause of death was pneumococcal sepsis (encephalitis)

Study G2301E1

No patients died during the study.

However, one patient (0115/00201), a 9-year old female Caucasian, discontinued from the study due to unsatisfactory therapeutic effect and died due to disease progression approximately 3 months after discontinuing from the study.

Study G2305

No deaths occurred during the study.

Study G2301

- **Part I**

One patient died during Part I. Patient 0115/00109, a 13-year-old Black male, experienced an SAE of severe adenovirus gastroenteritis on Day 40 which resolved on Day 57. He then experienced SAEs of pulmonary hypertension, pyrexia, increased serum ferritin and interstitial lung disease on Day 62. Two days later, on Day 64, the patient was diagnosed with MAS. This case was adjudicated by the MASAC as clinically consistent with MAS with either histologic confirmation or meets current formal hemophagocytic lymphohistiocytosis (HLH) guideline criteria. The patient received 3 doses of study drug (Day 1 in Part Ia, Day 31 in Part Ib and Day 59 in Part Ic). He discontinued treatment due to the SAEs and died on Day 81 due to pulmonary hypertension which occurred in association with MAS.

- **Part II**

No deaths occurred on treatment during Part II.

However, one patient in the placebo group died about 1 month after receiving the sixth dose of placebo in Part II. This death was not included in the clinical database because the patient had discontinued the study 2 days before death (1 month after sixth and last placebo dose), but it was reported to the safety database. Patient 0011/00101, a 15-year-old Black female randomized to placebo in Part II, died on Day 399 (31-Jul-2011) approximately 1 month after receiving the sixth and last dose of placebo on Day 365 (27-Jun- 2011) and 2 days after discontinuing the study due to MAS. The patient received 8 doses of canakinumab in Part I and 6 doses of placebo in Part II. She was initially hospitalized with acute nephrolithiasis which was treated conservatively and then discharged in good condition. Four months later, she experienced SAEs of renal colic, cardiac arrest, pneumonia, sepsis (urosepsis), septic shock, a small intracranial hemorrhage and MAS.

Serious Adverse Events (SAEs)

General

Serious adverse events occurred in 30.8% of SJIA patients (62.7 SAEs per 100 patient-years exposure). Infection SAEs affected 14.9% of patients in total (16.3 SAEs per 100 patient-years

exposure). No specific infection SAE affected more than 2 (1%) patients, except for gastroenteritis and varicella, both occurring in 4 (2%) of patients.

	SJIA pediatric Canakinumab N=201 n (%)	CAPS pediatric Canakinumab N=77 n (%)
Any primary system organ class	**62 (30.8)**	**14 (18.2)**
Infections and infestations	30 (14.9)	10 (13.0)
Musculoskeletal and connective tissue disorders	24 (11.9)	0 (0)
General disorders and administration site conditions	12 (6.0)	1 (1.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	11 (5.5)	0
Gastrointestinal disorders	10 (5.0)	0
Blood and lymphatic system disorders	6 (3.0)	0
Investigations	6 (3.0)	1 (1.3)
Respiratory, thoracic and mediastinal disorders	6 (3.0)	0
Skin and subcutaneous tissue disorders	5 (2.5)	0
Cardiac disorders	4 (2.0)	0
Nervous system disorders	4 (2.0)	0
Injury, poisoning and procedural complications	4 (2.0)	1 (1.3)
Hepatobiliary disorders	3 (1.5)	0
Psychiatric disorders	3 (1.5)	0
Renal and urinary disorders	2 (1.0)	1 (1.3)
Immune system disorders	1 (0.5)	0
Vascular disorders	1 (0.5)	0
Ear and labyrinth disorders	0	2 (2.6)
Eye disorders	0	1 (1.3)
Pregnancy, puerperium and perinatal conditions	0	1 (1.3)
Surgical and medical procedures	0	1 (1.3)
Congenital, familial and genetic disorders	0	0
Social circumstances	0	0

Study A2203

In total 13 patients (10 in Stage I and 3 in Stage II) had an SAE, two of these patients had SAEs suspected to be related to study drug. All patients continued in the study.

Two patients had SAEs that were suspected to be related study drug:

Patient 5210 (1.5 mg/kg), a 5 year old, Caucasian male had an EBV infection of moderate severity in period 4 of Stage I. This patient was noted to have a viral illness prior to receiving his sixth injection after a relapse on day 347 of the study. He experienced persistent fever, arthritis and severe anemia with initial reticulopenia and hepatitis following this injection and was admitted to hospital 11 days after the injection where a serological test was found to be positive for Ign EBV. His condition improved and the patient continued in the study receiving a further injection in Stage I and 7 injections in Stage II of the study.

Patient 5408 (at 1.5mg/kg dose level), a 12 year old, Caucasian female experienced moderate hematoma, moderate prolonged APTT, mild gastroenteritis and mild syncope in period 1 of Stage II, all of which were suspected to be related to study drug. This patient had received 4 injections in Stage I prior to receiving the first injection in Stage II on study day 355. The patient reported pain in the right calf muscle 38 days after this injection; she had no thrombosis or fever. An ultrasound showed a hematoma in the right calf. Five days later the patient had a vasovagal collapse and was hospitalized and she was found to have a prolonged APTT. The patient also developed gastroenteritis. The patient was discharged 3 days later. She completely recovered from the gastroenteritis and all other symptoms had improved. The patient continued in the study receiving a further 7 injections in Stage II.

Study G2305

A total of four patients had SAEs, two in each treatment group. Of these, two patients had MAS, one in each treatment group. Three of the patients had serious infections: bronchopneumonia (canakinumab; bronchopneumonia may have triggered MAS), varicella (canakinumab; child had been vaccinated), and gastroenteritis (placebo). No SAEs led to discontinuation, and all resolved without sequelae.

Patient ID	Age/sex/race	Study day	SAE(s) (preferred term)	Severity / relationship
Canakinumab				
0082/00004*	14/M/Ca	13	Bronchopneumonia	Mild/susp
		13	Hepatitis	Moderate/susp
		20	Histiocytosis hematophagic	Moderate/susp
		28	Leukopenia	Mild/susp
		28	Neutropenia	Mild/susp
		28	Rash maculo-papular	Mild/susp
0083/00001	4/M/Ca	4	Varicella	Moderate/susp
Placebo				
0023/00001	6/M/Ca	10	Gastroenteritis	Mild/not susp
0051/00005**	15/F/As	3	Histiocytosis hematophagic	Mild/not susp

Study G2301

- **Part I**

SAEs were reported in 15 (8.5%) patients (one of whom is the patient who died) and led to study drug discontinuation in 5 (2.8%) patients. Serious infections were the most commonly reported class of SAEs (7 patients, 4.0%) and consisted of single events with no predominance of organ class or pathogen. Four (2.3%) patients had MAS (preferred term hematophagic histiocytosis); whereby two of these patients had both MAS and a serious infection. The four remaining patients had other disorders (hepatitis, abdominal pain, medical device complication and arthritis)

- **Part II**

SAEs were reported in 6 patients in each of the two treatment groups (i.e. 12.0% each) and led to study drug discontinuation in 3 (6.0%) patients on placebo and none on canakinumab. Two (4.0%) patients in each treatment group had a serious infection. One patient in the placebo group had MAS. The SOC “investigations” (mainly hepatic enzymes increased) was increased in the verum group compared to the placebo group (4% vs. 0).

Study G2301E1

A total of 30 patients (20.4%) experienced at least 1 SAE.

Infection and infestations were seen in 15/147 (10.2%; varicella (3, 2%) and gastroenteritis (2, 1.4%) were the only infections reported in more than 1 patient as an SAE; the others were CMV infection, device related sepsis, febrile infection, gastrointestinal infection, impetigo, parvovirus infection, peritonitis, pharyngitis streptococcal, pneumonia, pseudocroup, scarlet fever, septic shock, tonsillitis streptococcal, toxoplasmosis (*see section on infections above*), varicella, wound infection, yersinia infection).

Musculoskeletal / connective tissue disorders were observed in 15/147 (10.2%); 13/15 were SJIA-related AEs). 4 patients experienced pyrexia, 4 patients (2.7%) (*or possibly 8 patients -see MAS discussion above*) experienced MAS.

Laboratory findings

General

Hematology

Hematolgy summary data from all SJIA paediatric pooled (A2203, G2305, G2301, G2301E1 up to G2301E1 interim analysis database lock, also compared to CAPS).

Parameter Notable criterion	SJIA pediatric N=201 n/Total (%)	CAPS pediatric N=77 n/Total (%)
Absolute Eosinophils		
≥1.1 x ULN	75/200 (37.5)	18/75 (24.0)
Absolute Lymphocytes		
< LLN	46/200 (23.0)	4/75 (5.3)
Absolute Neutrophils		
≤ 0.9 x LLN	27/200 (13.5)	3/75 (4.0)
< $1x10^9$/L	12/200 (6.0)	1/75 (1.3)
Hemoglobin		
≥ 20 g/L decrease from baseline	17/197 (8.6)	2/76 (2.6)
< 100 g/L (if ≥16 years) or < 85 g/L (if <16 years)	17/200 (8.5)	1/76 (1.3)
Platelets		
< LLN	19/200 (9.5)	1/76 (1.3)
< $100x10^9$/L	8/200 (4.0)	0/76 (0.0)
WBC (Total)		
≤ 0.8 x LLN	33/200 (16.5)	1/76 (1.3)
≥ 1.2 x ULN	23/200 (11.5)	7/76 (9.2)
Absolute Neutrophils		
G1:<LLN – 1.5 x 10^9/L	11/200 (5.5)	2/75 (2.7)
G2:<1.5 – 1.0 x 10^9/L	38/200 (19.0)	2/75 (2.7)
G3:<1.0 – 0.5 x 10^9/L	11/200 (5.5)	1/75 (1.3)
G4:<0.5 x 10^9/L	1/200 (0.5)	0/75 (0.0)
Hemoglobin		
G1:< LLN – 100 g/L	35/200 (17.5)	9/76 (11.8)
G2:< 100 – 80 g/L	26/200 (13.0)	4/76 (5.3)
G3:< 80 – 65 g/L	11/200 (5.5)	0/76 (0.0)
G4:< 65 g/L	2/200 (1.0)	0/76 (0.0)
Platelets		
G1:<LLN – 75.0 x 10^9/L	18/200 (9.0)	1/76 (1.3)
G2:<75.0 – 50.0 x 10^9/L	1/200 (0.5)	0/76 (0.0)
G3:<50.0 – 25.0 x 10^9/L	0/200 (0.0)	0/76 (0.0)
G4:<25.0 x 10^9/L	1/200 (0.5)	0/76 (0.0)
WBC (Total)		
G1:<LLN – 3.0 $x10^9$/L	69/200 (34.5)	3/76 (3.9)
G2:<3.0 – 2.0 $x10^9$/L	12/200 (6.0)	1/76 (1.3)
G3:<2.0 – 1.0 $x10^9$/L	3/200 (1.5)	0/76 (0.0)
G4:<1.0 $x10^9$/L	0/200 (0.0)	0/76 (0.0)

Eosinophils

There was no clear relationship between patients with elevated eosinophil counts and increased rate of hypersensitivity reactions. AEs related to atopy or allergy were reported in temporal association with the elevated eosinophil counts in 11 patients, but there were no such AEs in 54 patients. Ten patients

had AEs related to atopy or allergy, but which did not occur within a short time (42 days) of the abnormal eosinophil counts.

Neutrophils

An increased rate of infections was not observed among the patients with low neutrophil counts. 38 patients had a Grade 2 neutrophil count; thereof 18 had infections (mostly mild, no severe infections). Three of the 11 SJIA patients with Grade 3 neutrophil counts had infection AEs that occurred within 42 days of the low neutrophil count. The one patient with a Grade 4 absolute neutrophil count did not have any infection AEs reported at or near the time the abnormality was reported.

Platelets

The 8 patients (4.0%) with low platelet counts (<100 x 10^9/L) did not have bleeding-related AEs.

Canakinumab exposure and hematological abnormalities

Canakinumab predicted exposure data were available for 188 patients, although the numbers declined over time. Canakinumab concentrations in patients with notable abnormalities of hemoglobin levels, platelet counts or absolute WBC counts were similar to those in patients without such abnormalities. Patients who had low neutrophil counts (post-baseline values of < 0.9 x LLN) had higher canakinumab concentrations than subjects who had neutrophil counts that remained within the normal range.

Clinical Chemistry

In canakinumab-treated SJIA patients, elevations of serum transaminases (ALT and/or AST)

occurred in approximately 41% of patients, whereby 37.8% had at least one elevated alanine aminotransferase (ALT) value, 34.3% had an elevated aspartate aminotransferase (AST) value, 10.0% had an elevated alkaline phosphatase value, and 1.5% had an elevated bilirubin value. No cases met the definition of Hy's Law.

In canakinumab-treated patients, an apparent ≥25% decrease in estimated creatinine clearance was recorded in 14.6% of patients.

One patient (0.5%) had an elevated cholesterol value of ≥1.5×ULN and one (0.5%) had a notable triglyceride value of ≥5.7 mmol/L.

These laboratory changes were not associated with clinical sequelae, and none of them resulted in study discontinuation.

Laboratory values: comparison between verum and placebo groups

Decreased white blood cell counts (WBC) ≤ 0.8 × LLN were reported in 5 (10.4%) patients on canakinumab and 2 (4.0%) on placebo. Decreased absolute neutrophils counts (ANC) to <1x109/L were reported in 3 (6.0%) patients on canakinumab and 1 (2.2%) on placebo. One case of ANC counts <0.5x109/L was observed with canakinumab and none with placebo. Mild decreases (<LLN and >75x109/L) in platelet counts, which were transient were observed in 3 (6.3%) patients on canakinumab and 1 (2.0%) on placebo.

Notably high ALT and/or AST values >3×ULN were reported in 2 (4.1%) patients on canakinumab and 1 (2.0%) on placebo.

Table 53. Notable clinical chemistry parameters in SJIA and CPAS patients

Parameter Notable criterion	SJIA pediatric N=201 n/Total (%)	CAPS pediatric N=77 n/Total (%)
Alanine transaminase (ALT)(SGPT)		
> ULN	76/201 (37.8)	3/76 (3.9)
> 3 x ULN	18/201 (9.0)	0/76 (0.0)
> 5 x ULN	11/201 (5.5)	0/76 (0.0)
> 8 x ULN	6/201 (3.0)	1/76 (1.3)
> 10 x ULN	4/201 (2.0)	1/76 (1.3)
Aspartate transaminase (AST)(SGOT)		
> ULN	69/201 (34.3)	4/76 (5.3)
> 3 x ULN	12/201 (6.0)	0/76 (0.0)
> 5 x ULN	5/201 (2.5)	1/76 (1.3)
> 8 x ULN	2/201 (1.0)	1/76 (1.3)
> 10 x ULN	1/201 (0.5)	0/76 (0.0)
Alkaline phosphatase		
≥ ULN	20/201 (10.0)	9/76 (11.8)
≥ 1.5 x ULN	7/201 (3.5)	5/76 (6.6)
≥ 2 x ULN	2/201 (1.0)	4/76 (5.3)
> 3 x ULN	1/201 (0.5)	0/76 (0.0)
≥ 5 x ULN	0/201 (0.0)	0/76 (0.0)
> 3 x ULN and total bilirubin > 2 x ULN	0/201 (0.0)	0/76 (0.0)
< 2 x ULN and total bilirubin > 2 x ULN and ALT or AST > 3 x ULN	0/201 (0.0)	0/76 (0.0)
Gamma-Glutamyltransferase (GGT)		
≥ ULN	24/201 (11.9)	5/76 (6.6)
≥ 3 x ULN	4/201 (2.0)	1/76 (1.3)
≥ 5 x ULN	2/201 (1.0)	1/76 (1.3)
Total Bilirubin		
> ULN	3/201 (1.5)	1/76 (1.3)
> 1.5 x ULN	2/201 (1.0)	0/76 (0.0)
> 2 x ULN	2/201 (1.0)	0/76 (0.0)
> 2 x ULN and ALT or AST > 3 x ULN	0/201 (0.0)	0/76 (0.0)
> 2 x ULN and ALT or AST > 5 x ULN	0/201 (0.0)	0/76 (0.0)
> 2 x ULN and ALT or AST > 10 x ULN	0/201 (0.0)	0/76 (0.0)
Total Cholesterol		
≥ 1.5 x ULN	1/201 (0.5)	1/76 (1.3)
Triglycerides		
≥ 5.7 mmol/L	1/201 (0.5)	0/76 (0.0)
Protein urine dipstick		
≥ ++ (if ≥ 16 years), ≥ Trace (if < 16 years)	75/175 (42.9)	10/64 (15.6)
Creatinine (serum)		
≥ 1.5 x ULN	2/201 (1.0)	0/76 (0.0)
Creatinine Clearance		
≥ 25% decrease from baseline with 2 consecutive values	29/199 (14.6)	4/74 (5.4)

Study A2203

All of the patients had at least one clinical laboratory test result outside of the normal range at some point during the study. Generally these either occurred only at one or two time points with no consistency for any variable or the values were out of range at screening and/or baseline and remained so throughout the study. The majority of patients had low albumin values and low hemoglobin values throughout the study.

Study G2305

Newly occurring post-baseline notable hematology abnormalities

	ACZ885 N=43 n (%)			Placebo N=41 n (%)		
	Total	n	%	Total	n	%
Hemoglobin						
< 85 g/L (for < 16 years) or < 100 g/L (for ≥ 16 years)	42	3	(7.1)	41	3	(7.3)
≥ 20 g/L decrease from baseline	42	0	(0.0)	41	1	(2.4)
Platelet count						
< LLN	42	2	(4.8)	38	1	(2.6)
White blood cells						
≤ 0.8 x LLN	42	1	(2.4)	41	0	(0.0)
≥ 1.2 x ULN	42	2	(4.8)	41	4	(9.8)
Absolute neutrophils						
≤ 0.9 x LLN	42	2	(4.8)	41	0	(0.0)
≥ 1.2 x ULN	42	1	(2.4)	41	1	(2.4)
Absolute eosinophils						
≥ 1.1 x ULN	42	8	(19.0)	41	2	(4.9)
Absolute lymphocytes						
< LLN	42	5	(11.9)	41	3	(7.3)
≥ 1.1 x ULN	42	1	(2.4)	41	0	(0.0)

Source: Table 14.3-2.6

LLN: lower limit of the normal range. ULN: upper limit of the normal range.
Total = number of patients with evaluation criterion; n = number of patients meeting the criterion (i.e., who are abnormal)

Newly occurring post-baseline notable Clinical chemistry abnormalities

Parameter and criterion	ACZ885 N=43 n (%)			Placebo N=41 n (%)		
	Total	n	%	Total	n	%
Albumin						
< LLN	43	4	(9.3)	41	4	(9.8)
ALT						
> 3 x ULN	43	1	(2.3)	41	0	(0.0)
> 5 x ULN	43	1	(2.3)	41	0	(0.0)
> 8 x ULN	43	1	(2.3)	41	0	(0.0)
> 10 x ULN	43	1	(2.3)	41	0	(0.0)
AST						
> 3 x ULN	43	1	(2.3)	41	0	(0.0)
> 5 x ULN	43	1	(2.3)	41	0	(0.0)
> 8 x ULN	43	1	(2.3)	41	0	(0.0)
> 10 x ULN	43	1	(2.3)	41	0	(0.0)
ALT or AST						
> 3 x ULN	43	1	(2.3)	41	0	(0.0)
> 5 x ULN	43	1	(2.3)	41	0	(0.0)
> 8 x ULN	43	1	(2.3)	41	0	(0.0)
> 10 x ULN	43	1	(2.3)	41	0	(0.0)
> 3 x ULN and total bilirubin > 2 x ULN	43	0	(0.0)	41	0	(0.0)
> 5 x ULN and total bilirubin > 2 x ULN	43	0	(0.0)	41	0	(0.0)
> 10 x ULN and total bilirubin > 2 x ULN	43	0	(0.0)	41	0	(0.0)
> 3 x ULN and total bilirubin > 2 x ULN and alkaline phosphatase < 2 x ULN	43	0	(0.0)	41	0	(0.0)
Alkaline phosphatase						
> 1.5 x ULN	43	0	(0.0)	41	0	(0.0)
Total bilirubin						
> ULN	43	0	(0.0)	41	0	(0.0)
Gamma-glutamyltransferase						
> 3 x ULN	43	0	(0.0)	41	0	(0.0)
Creatinine (serum)						
≥ 1.5 x ULN	43	0	(0.0)	41	0	(0.0)
Creatinine clearance (1)						
≥ 25% decrease from baseline	43	2	(4.7)	40	0	(0.0)
Potassium						
≤ 3.5 mmol/L (for < 16 years) or ≤ 3.0 mmol/L (for ≥	43	1	(2.3)	41	0	(0.0)

16 years)						
≥ 5.5 mmol/L	43	0	(0.0)	41	0	(0.0)
Magnesium						
≤ 0.7 mmol/L (for < 16 years) or ≤ 0.5 mmol/L (for ≥ 16 years)	43	0	(0.0)	41	1	(2.4)
≥ 1.2 mmol/L (for < 16 years) or ≥ 1.5 mmol/L (for ≥ 16 years)	43	0	(0.0)	41	0	(0.0)
Sodium						
≤ 130 mmol/L	43	0	(0.0)	41	1	(2.4)
≥ 150 mmol/L	43	0	(0.0)	41	0	(0.0)
Calcium						
< LLN (for ≥ 16 years)	6	0	(0.0)	4	0	(0.0)
≥ 1.2 ULN (for ≥ 16 years)	6	0	(0.0)	4	0	(0.0)
Urine protein dipstick						
≥ Trace (for < 16 years) or ≥ ++ (for ≥ 16 years)	28	3	(10.7)	32	6	(18.8)

Study G2301

- **Part I** Newly occurring post-baseline notable hematology abnormalities(Part I)

	ACZ885 N=177		
	Total	n	(%)
Hemoglobin			
< 85 g/L (for < 16 years) or < 100 g/L (for ≥16 years)	176	6	(3.4)
≥ 20 g/L decrease from baseline	174	5	(2.9)
Platelet count (direct)			
< LLN	176	11	(6.3)
WBC (total)			
≤ 0.8 x LLN	176	17	(9.7)
≥ 1.2 x ULN	176	11	(6.3)
Absolute Neutrophils (Seg. + Bands)			
≤ 0.9 x LLN	176	10	(5.7)
≥ 1.2 x ULN	176	15	(8.5)
Absolute Eosinophils			
≥ 1.1 x ULN	176	46	(26.1)
Absolute Lymphocytes			
< LLN	176	24	(13.6)
≥ 1.1 x ULN	176	2	(1.1)

Newly occurring post-baseline notable Clinical chemistry abnormalities (Part I)

Two parameters are noteworthy:

- a decrease in creatinine clearance (> 25% from baseline) in 28/177 patients (16%) and
- protein positive in the urine in 40 (28.2%)
- In **Part II**

Newly occurring post-baseline notable hematology abnormalities (Part II)

	ACZ885 N=50			Placebo N=50		
	Total	N	(%)	Total	n	(%)
Hemoglobin						
< 85 g/L (for < 16 years) or < 100 g/L (for ≥ 16 years)	48	0		50	1	(2.0)
≥ 20 g/L decrease from baseline	48	1	(2.1)	49	0	
Platelet count (direct)						
< LLN	48	3	(6.3)	50	1	(2.0)
WBC (total)						
≤ 0.8 x LLN	48	5	(10.4)	50	2	(4.0)
≥ 1.2 x ULN	48	0		50	3	(6.0)
Absolute Neutrophils (Seg. + Bands)						
≤ 0.9 x LLN	48	6	(12.5)	50	1	(2.0)
≥ 1.2 x ULN	48	0		50	6	(12.0)
Absolute Eosinophils						
≥ 1.1 x ULN	48	10	(20.8)	50	16	(32.0)
Absolute Lymphocytes						
< LLN	48	4	(8.3)	50	2	(4.0)
≥ 1.1 x ULN	48	1	(2.1)	50	0	

Newly occurring post-baseline notable Clinical chemistry abnormalities (Part II)

- protein positive in the urine in 19 (48.7%) patients in the canakinumab group and in 9 placebo patients (23.1%)

Study G2301E1

Newly occurring post-baseline notable hematology abnormalities

	ACZ885 N=147		
	Total	n	(%)
Hemoglobin			
< 85 g/L (for < 16 years) or < 100 g/L (for ≥ 16 years)	146	5	(3.4)
≥20 g/L decrease from baseline	140	9	(6.4)
Platelet count (direct)			
< LLN	146	9	(6.2)
WBC (total)			
≤0.8 x LLN	146	18	(12.3)
≥ 1.2 x ULN	146	11	(7.5)
Absolute Neutrophils (Seg. + Bands)			
≤0.9 x LLN	146	16	(11.0)
≥1.2 x ULN	146	18	(12.3)
Absolute Eosinophils			
≥1.1 x ULN	146	44	(30.1)
Absolute Lymphocytes			
< LLN	146	22	(15.1)
≥1.1 x ULN	146	2	(1.4)

Antibodies

Six (3.1%) of SJIA patients had positive anti-canakinumab binding antibodies, none were neutralizing and they were not associated with the development of any immunogenicity-associated AEs that indicated hypersensitivity or the presence of any allergic reactions or other clinical sequelae.

Furthermore no real loss of efficacy cases could be observed within CAPS and gouty arthritis. Changes in drug clearance were also analysed as potential early signals of anti-drug antibodies (ADA) which could lead to loss of efficacy. The model-based parameters provided no evidence of unusual pharmacokinetic or pharmacodynamic behaviour in subjects that were identified as ADA positive.

Vital signs

Table 54. Vital signs: Incidence of newly occurring notable abnormalities in placebo-controlled SJIA studies G2305 and G2301-Part II (Safety set)

Parameter Notable criterion	Study G2305 Canakinumab N=42 n (%)	Study G2305 Placebo N=41 n (%)	Study G2301-Part II Canakinumab N=50 n (%)	Study G2301-Part II Placebo after Canakinumab N=49 n (%)
Systolic BP				
≥ 25% decrease from baseline	2 (4.8)	0	1 (2.0)	5 (10.2)
≥ 25% increase from baseline	2 (4.8)	0	7 (14.3)	5 (10.2)
Notable high systolic BP value	5 (11.9)	3 (7.3)	14 (28.0)	10 (20.4)
Diastolic BP				
≥ 25% decrease from baseline	5 (11.9)	5 (12.2)	7 (14.3)	8 (16.3)
≥ 25% increase from baseline	7 (16.7)	3 (7.3)	11 (22.4)	11 (22.4)
Notable high diastolic BP value	9 (21.4)	3 (7.3)	9 (18.0)	2 (4.1)
Pulse				
Notable clinically significant increase from baseline	6 (14.3)	6 (14.6)	0 (0)	1 (2.0)
Notable clinically significant decrease from baseline	0	0	3 (6.0)	0 (0)

Safety in special populations

There were no dedicated trials in special patient populations (e.g. renal / hepatic impairment).

The company has been requested to provide an analysis of AEs by age group and gender (as done for Study G2305) in Studies A2203, G2301 and G2301E1 (see AEs above) .

Safety related to drug-drug interactions and other interactions

No drug-drug interaction studies were performed. In the SPC under Section 4.5 the following is stated:

An increased incidence of serious infections has been associated with administration of another IL-1 blocker in combination with TNF inhibitors. Use of Ilaris with TNF inhibitors is not recommended because this may increase the risk of serious infections.
The expression of hepatic CYP450 enzymes may be suppressed by the cytokines that stimulate chronic inflammation, such as IL-1 beta. Thus, CYP450 expression may be reversed when potent cytokine inhibitory therapy, such as canakinumab, is introduced. This is clinically relevant for CYP450 substrates with a narrow therapeutic index where the dose is individually adjusted. On initiation of canakinumab in patients being treated with this type of medicinal product, therapeutic monitoring of the effect or of the active substance concentration should be performed and the individual dose of the medicinal product adjusted as necessary.

No data are available on either the effects of live vaccination or the secondary transmission of infection by live vaccines in patients receiving Ilaris. Therefore, live vaccines should not be given concurrently with Ilaris unless the benefits clearly outweigh the risks. Should vaccination with live vaccines be indicated after initiation of Ilaris treatment, the recommendation is to wait for at least 3 months after the last Ilaris injection and before the next one.

Discontinuation due to adverse events

The rate of discontinuation due to AEs was 9.5%, mainly due to SJIA flares (4.5%) or to MAS (2.5%). This rate is higher than in the CAPS population where discontinuations due to AEs were only 3.9%. The nature of AEs leading to discontinuation covered all SOCs and their main preferred terms as described under adverse events.

Study A2203

In general, a total of 6/23 patients (26.1%) discontinued the study mainly due to unsatisfactory therapeutic effect (21.7%).

Most of AEs were of mild to moderate severity, unrelated to study drug and did not lead to discontinuation.

Study G2305

No patient discontinued study treatment due to adverse events.

Study G2301

- **Part I**

Five (2.8%) patients experienced at least one AE during Part I that led to discontinuation of study drug:

  - Patient 0115/00109 did not complete Part I due to death from pulmonary hypertension (see deaths above)
  - Two patients (0034/00107 and 0510/00101) discontinued due to hematophagic histiocytosis (MAS). The MAS was adjudicated by the MASAC as some clinical features of MAS, but with alternative explanation (drug reaction) for patient 0034/00107 and as clinically consistent with MAS with either histologic confirmation or having met the current formal HLH guideline criteria for patient 0510/00101
  - Patient 0020/00104 discontinued due to increased C-reactive protein, increased liver enzymes (alkaline phosphatase was 507 U/L on Day 57), increased platelet count and increased WBC count.
  - Patient 0120/00102 discontinued due to juvenile arthritis (sJIA exacerbation).

- **Part II**

Six (12.0%) patients in the placebo group and none in the canakinumab group discontinued study treatment during Part II due to an AE. The 6 placebo patients who discontinued due to an AE in Part II were as follows:

  - Patient 0011/00101 had multiple AEs leading to death: cardiac arrest, pneumonia, sepsis (urosepsis), septic shock, a small intracranial hemorrhage and MAS (see deaths above).
  - Patient 0042/00101 had multiple AEs leading to discontinuation: maculopapular rash, oral disorder, measles, pneumonia, and respiratory failure (distress). All events were also reported as SAEs.
  - Patient 0081/00103 discontinued due to juvenile arthritis (acute sJIA exacerbation/flare). This event was also reported as an SAE.
  - Patient 0040/00111 discontinued due to non-serious rash (worsening due to sJIA/flare).
  - Patient 0115/00107 discontinued due to non-serious vomiting.
  - Patient 0148/00103 discontinued due to non-serious uveitis.

Study G2301E1

A total of 9/147 (6.1%) patients experienced AEs that resulted in discontinuation of study drug

Eight of these patients were also SAEs. The events that led to discontinuation were juvenile arthritis/arthralgia (7 patients; 4.8%) and histiocytosis haematophagic (2 patients, 1.4%); hepatobiliary disorders (1.4%), splenomegaly, pericarditis, abdominal pain and pyrexia in one patient each.

2.5.2. Discussion on clinical safety

Approximately 2,500 subjects have been treated with Ilaris in blinded and open-label clinical trials in patients with CAPS, gouty arthritis or other IL-1 beta mediated diseases, and healthy volunteers. The cumulative patient exposure since the first launch of the product is estimated to be approximately 1284 patient-treatment-years (PTY).

For the current submission 201 SJIA patients, with 301 patient-years of exposure were treated for a median of 617 days (minimum 4, maximum 1829 days) with a median number of 22 doses (minimum 1 and maximum 49). This exposure is considered an adequate dataset for the extension of indication. The median duration of exposure is acceptable given the chronic nature of SJIA. However, the median duration may be too short to correctly assess the rate of occurrence of rarer and infrequent events such as MAS. Thus the applicant will perform a post authorisation registry to capture long-term data and provide new information on possible correlations as outlined in the RMP.

The safety database for SJIA encompasses 3 completed studies A2203, G2305 and G2301, and an interim report from the ongoing extension Study G2301E1.

Prior to this submission the main identified canakinumab risks included serious infections, neutropenia and thrombocytopenia. In addition, following the 4th PSUR (1 Jan 2011 – 30 Jun 2011) the concern with regard to an increased frequency of Macrophage Activation Syndrome (MAS) in patients with SJIA was raised.

In the SJIA pooled population, 85.1% of patients experienced at least 1 AE. The most often affected system organ classes (SOCs) in SJIA studies were infections and infestations (71.1%), followed by gastrointestinal disorders, (52.7%), musculoskeletal and connective tissue disorders (41.8%), and respiratory, thoracic and mediastinal disorders (38.3%). This sequence was the same when adjusted by exposure. The most frequently reported AEs by preferred term were nasopharyngitis (29.4%), cough (25.9%), pyrexia (25.9%), vomiting (22.9%), diarrhea (22.4%), upper respiratory tract infection (22.4%) and headache (20.9%).

Most AEs were of mild or moderate intensity; with 16.9% of SJIA patients having severe AEs (this compares to the data on severe AEs in CAPS children at 15.6%). AEs of gastrointestinal disorders were mainly mild, only 3.0% of SJIA children and no CAPS children having severe events. AEs of infections and infestations were mainly mild or moderate, with 6.0% of SJIA children and 7.8% of CAPS children having severe events.

In general plasma canakinumab levels were not higher in patients with selected AEs (e.g., infection, MAS, pyrexia, SAE of infection and abdominal pain) compared to those without these AEs. In contrast more adverse events were seen in the studies on SJIA than in the studies on other indications which could be due to the higher dose applied in this indication. Canakinumab dose reduction from 4 mg/kg to 2 mg/kg in steroid free patients was permitted in the extension study G2301E1 on the request of the treating physician. Twenty-six patients, aged 4 – 19 years, received at least three consecutive 2 mg/kg doses. All 26 patients had an ACR100 throughout the time the reduced dose was given. No

patient who received a reduced canakinumab dose discontinued from the study due to unsatisfactory therapeutic effect.

While the number of patients successfully reducing canakinumab dose is limited to date, a reasonable conclusion can be drawn from the available data that dose reduction can be achieved in some patients.

To gain more insight on canakinumab dose reduction, the MAH 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.

In general the ADRs mirror the main AEs as listed above (i.e. infections and gastrointestinal disorders) In Study G2301 for the SOC infections ADRS were seen in ~ 55% of the patients (vs. 38% in the placebo group) and in 30% in the 4-week study G2301 (compared to 12% in the corresponding placebo group). In Study G2301 for the SOC gastrointestinal disorders ADRS were seen in ~ 14-16% of the patients (vs. 12% in the placebo group) and in 7% in the 4-week study G2301 (compared to 2.4% in the corresponding placebo group). Infections, gastroenteritis and abdominal pain are included as adverse drug reactions (ADR) in the SmPC. Infections including gastrointestinal infections is an identified risk of canakinumab treatment and included in the RMP with appropriate pharmacovigilance activities and risk minimization measures.

There were 4 deaths in SJIA patients; none were considered related to canakinumab by the reporting investigator. Three of the four deaths occurred a considerable time after the last dose of canakinumab (4 months to 2 years). The fourth patient died after developing MAS approximately 3 weeks after the last dose of canakinumab, after severe gastroenteritis and subsequent pulmonary hypertension. As the occurrence of gastroenteritis or other infections are increased under canakinumab this in turn could have triggered the further sequence of events. The SmPC includes appropriate warning statements with regards to an increased incidence of serious infections and infection is followed as an important identified risk in the RMP.

After an in-depth review of the 8 pulmonary complication AEs identified by SMQs and SOC reviews of the SJIA and CAPS pediatric pooled populations, all except chronic bronchitis (2 AEs in one patient) were single events. Four events were complications of MAS or SJIA flare.

The available patient population is too small to draw any firm conclusions toward a direct link between canakinumab and pulmonary complications. There is an unconfirmed signal for increased incidence of pulmonary complications in SJIA patients treated with IL-1 inhibitors. To closely monitor these events in the remit of the RMP pulmonary complications were made as potential risk.

Serious adverse events occurred in approximately a third of SJIA patients (62.7 SAEs per 100 patient-years exposure). Infection SAEs affected 14.9% of patients in total (16.3 SAEs per 100 patient-years exposure). No specific infection SAE affected more than 2 (1%) patients, except for gastroenteritis and varicella, both occurring in 4 (2%) of patients. With the exception of MAS and musculoskeletal disorders the SAE profile (but not the frequencies) was similar between the SJIA and CAPS pediatric populations. Overall more patients had SAEs in SJIA than in CAPS (30.8% vs. 18.2 %).

Infections are a known risk for canakinumab, as well as for the class of anti-IL-1 therapies. When adjusted for exposure (per 100 patient years), there was a slight increase in infections in the SJIA population compared to CAPS (264.9 vs 238.4 respectively). The nature of the infections did not seem to undergo major changes from those previously described and opportunistic infections were not a concern. The role of canakinumab in the development of infection is unclear; however, infection is an identified risk for canakinumab and included in the RMP with appropriate risk minimization measures. In addition, warning statements in the PI makes prescribers and patients aware about the increased risk of infections.

The main difference between the SJIA and the CAPS population is the occurrence of MAS. All cases were adjudicated by the MASAC. When comparing the occurrence of MAS in the canakinumab and placebo groups across the different trials and adjusting this to 100 patient-years (4.3 vs. 7.7 respectively), there does not seem to be an increase in MAS in the canakinumab group.

This calculation is, however, fraught with difficulty given the small numbers in the placebo group and a tenth of the exposure years. In addition the background incidence of MAS is difficult to estimate from the mainly uncontrolled/retrospective reports in the literature.

No definite conclusion can be made about a possible increase of MAS in SJIA patients treated with canakinumab. In a planned Pharmachild registry the applicant committed to capture AEs of special interest in subjects with SJIA, such as MAS as outlined in the RMP. Within this registry the applicant will also provide 3 years of analysis on patients for all of the identified and potential risks.

A further reason of concern is founded on the absence of treatment naïve patients as a consequence of the withdrawal design of Study G2301. The withdrawal design is in accordance with EMA recommendations to obtain data for an optimal efficacy assessment. In case adverse events show an unequal distribution across the study groups of part II (as occurred in G2301), external validity may be questioned. To address this issue, the MAH opened enrolment of the extension study G2301E1 to new canakinumab-naïve patients and extended the study end date to June 2014 to allow for additional collection of long-term efficacy and safety data as outlined in the RMP.

The potential risk of MAS is appropriately mitigated with inclusion of warnings in 4.4. of the SmPC. In addition, the prescription of canakinumab is restricted to specialist physicians experienced in the diagnosis and treatment of SJIA. In order to increase the effectiveness of risk communication and management, physician information will be provided to all prescribing physicians educating them about the early diagnosis, risk factors (e.g. infections and SJIA flare) and treatment of MAS as outlined in the RMP.

An alert card indicating in lay language the potential risk for MAS will be provided to all patients with SJIA receiving canakinumab. The alert card will also request patients to contact their doctors in case of SJIA aggravation or development of an infection.

Lack of efficacy

In Study G2301 Part II the canakinumab group had a higher exposure-adjusted incidence of musculoskeletal and connective tissue disorders (0.42 canakinumab vs. 0.19 placebo), particularly arthralgia (0.15 vs. 0.06) and back pain (0.09 vs. 0.00) compared with the placebo group.

The exposure-adjusted incidence rates have been re-calculated after omitting AEs for which alternative explanations could be identified. In this analysis, combined AEs in both “Joint subgroup” and “Musculoskeletal pain subgroup” were approximately twice more common in the canakinumab group compared to the placebo group, while no statistical difference in the incidence rates was observed. Musculoskeletal pain is listed as a common adverse drug reaction in the SmPC and was made important identified risk in the RMP for canakinumab treatment in SJIA.

Summarising, in the pooled data of all SJIA studies the rate of discontinuation due to AEs was 5.5% and the rate of discontinuation due to unsatisfactory therapeutic event was 31.3%. This unsatisfactory therapeutic outcome is rather high (especially in comparison to CAPS); taken together with the musculoskeletal disorders and additional medication needed for these disorders the benefit is somewhat narrowed.

Approximately 20% of patients did not reach the ACR Pediatric 30 response. Also, there were a number of subjects who initially responded but subsequently lost their response. Thus, there is still a group of patients who do not respond to this anti-IL-1 β targeting therapy.

To minimize the risk of lack of efficacy the SmPC states that continued treatment with Ilaris in patients without clinical improvement should be reconsidered by the treating physician. As outlined in the RMP additional long term data on safety and efficacy in SJIA will be generated by the following activities:

(1)Pharmachild registry; (2) the re-opened first extension to open label study G2301E1; (3) the phase IV dose reduction study.

Laboratory findings

Changes in laboratory parameters in SJIA depend on the activity of the underlying inflammatory state and the type of treatment that ensues. Generally, SJIA patients present with anemia, neutrophilia, and thrombocytosis, but also often have transaminase elevations. Treatment such as canakinumab can revert these changes by reducing the inflammation through reduction of IL-1β, this in turn can result in increases in hemoglobin, reduction of neutrophils and reduction of platelets. Improvements in CRP, ferritin, and fibrinogen were seen with canakinumab treatment compared with placebo consistent with clinical improvement of sJIA.

The most common clinically notable hematology abnormalities relative to upper or lower limit of normal (ULN, LLN) were eosinophil counts ≥1.1 x ULN (37.5% of SJIA patients); lymphocyte counts < LLN (23.0%), WBC counts ≤0.8 x LLN (16.5%) and low hemoglobin (8.5%). Low neutrophil counts (<1.0 x 109/L) occurred in 6.0% of patients, including 1 (0.5%) patient with a CTC Grade 4 neutrophil count (<0.5 x 109/L) on a single assessment.

Neutropenia has already been an identified risk for the other canakinumab approved indications and is appropriately labelled in SmPC. The neutrophil count was the only safety parameter for which a concentration dependency could be observed. The "IC50 parameter for the neutrophil loss" is estimated to be about 9.1 ug/mL. Patients who had low neutrophil counts (post-baseline values of < 0.9 x LLN) had higher canakinumab concentrations than subjects who had neutrophil counts that remained within the normal range. On the other hand, the "IC50 parameter for the freedom of flares" equals to 3.3 ug/mL derived from the PK-hazard model (IC90: 29.4 µg/mL). Thus, there is a narrow but acceptable window of discrimination between efficacy and safety. Predicted steady state values for serum canakinumab in sJIA patients after 4 mg/kg 4-weekly (mean of all ages) are 14.7 (Ctrough,ss) and 36.5 (Cmax,ss) µg/mL. Due to the higher dosing regimen these levels are markedly higher compared to the canakinumab levels in CAPS children <40 kg after the 2 mg/kg 8-weekly dosing regimen (4 and 19.9 µg/mL, respectively). Cmax predictions are highly uncertain due to the lack of PK samples around Cmax in the pivotal studies. An increased rate of infections was not observed among the patients with low neutrophil counts.

The small proportion of patients (4.0%) with low platelet counts (<100 x 109/L) had no evidence of bleeding-related AEs. Thrombocytopenia was already an identified risk for the other canakinumab indications and is appropriately labelled in the PI. Patients with elevated eosinophil counts did not show an increased rate of hypersensitivity reactions. Only a minor part of the patients had concomitant allergies. Eosinophilia was made potential risk in the RMP and cumulative reviews on cases of eosinophilia will be provided in the PSURs.

Leukopenia is a frequent finding in the SJIA population treated with canakinumab. 16.5% of patients had notable leukopenia i.e. WBC equal to or less than 0.8 X LLN. Most events were leukopenia only (70.6%) while 25% comprised of leukopenia and neutropenia and 4.4% of leukopenia, neutropenia and lymphocytopenia.

To balance adequately the risk of the laboratory findings Leukopenia was made identified risk in the RMP for SJIA patients and leukopenia was included within the existing neutropenia warnings in SmPC Section 4.4 and SmPC.

In canakinumab-treated SJIA patients, elevations of serum transaminases (ALT and/or AST) occurred in approximately 41% of patients, whereby 37.8% had at least one elevated alanine aminotransferase (ALT) value, 34.3% had an elevated aspartate, 34.3% had an elevated aspartate aminotransferase (AST) value, 10.0% had an elevated alkaline phosphatase value, and 1.5% had an elevated bilirubin value. Notably high ALT and/or AST values >3×ULN were reported in 2 (4.1%) patients on canakinumab and 1 (2.0%) on placebo. No cases met the definition of Hy's Law.

The MAH analyzed and reviewed hepatic enzymes over time for all studies no clear trends were seen and hepatic values generally remained stable over time. In the placebo controlled Part 2of Study G2301 no definite distinctions could be made between the placebo and verum groups. The magnitude of the difference, compared with the comparator group (placebo or active substance), on the liver parameters of interest was not large enough to suggest a causal relationship however due to the fact that DILI events were observed in several canakinumab clinical trials drug induced liver disease was included as an identified risk in the RMP to be followed up within the Pharmachild SJIA registry and cumulative reviews in coming PSURs.

In the SJIA pooled safety population 29 (14%) patients had at least one notable decreased estimated creatinine clearance and 75 (37%) patients had at least one notable urinary proteinuria but without clinical evidence of genuine renal function deterioration. Eight patients (4%) had both a notable decrease in creatinine clearance and urinary proteinuria simultaneously at least once. Noticeably fewer CAPS vs SJIA paediatric patients had positive testing for proteinuria (15.6% vs 35.6%)."

Decreased creatinine clearance and urinary proteinuria was added to the identified risks in the RMP (to be followed by the Pharmachild registry) and to 4.8 of the SmPC.

2.5.3. Conclusions on clinical safety

SJIA is a serious condition responsible for high childhood mortality and severe morbidity and disability. Taking into consideration that therapeutic options are limited and partially very toxic, the safety profile for canakinumab treatment in SJIA patients is acceptable. Safety concerns are considered adequately balanced with the proposed SmPC and RMP. Further data on identified and potential risks will be provided through the Pharmachild registry and the re-opened first extension to open label study G2301E1. Further the applicant committed to generate efficacy and safety data on dose reduction or dose interval prolongation in SJIA as outlined in the RMP.

2.5.4. PSUR cycle

The PSUR cycle remains unchanged.

The annex II related to the PSUR, refers to the EURD list which remains unchanged.

2.6. Risk management plan

2.6.1. PRAC advice

The CHMP received the following PRAC advice on the submitted Risk Management Plan.

PRAC Advice

Based on the PRAC review of the Risk Management Plan version 7 the PRAC considers by consensus that the risk management system for canakinumab (Ilaris) in the proposed indication of:

Systemic Idiopathic Arthritis (SJIA) in patients aged 2 years and older who have responded inadequately to previous therapy with non-steroidal anti-inflammatory drugs (NSAIDs) and systemic corticosteroids. Ilaris can be given as monotherapy or in combination with methotrexate.

could be acceptable provided an updated risk management plan and satisfactory responses to the questions detailed in this Section are submitted.

This advice is based on the following content of the Risk Management Plan:

Safety concerns

Summary of the Safety Concerns

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

The PRAC considers that the following issues should be addressed:

- Decreased creatinine clearance and urinary proteinuria should be added to the identified risks in the RMP
- DILI should be re-classified from a potential to an identified risk
- Leukopenia should be considered as an additional identified risk in the RMP in addition to the already listed neutropenia
- Pulmonary complications in SJIA should be included in the RMP and classified as identified risk

- Musculoskeletal pain and arthralgia should be considered as an identified risk for the RMP of the SJIA indication
- Eosinophilia in SJIA-patients should be included in the RMP and classified as a potential risk.

Routine risk minimisation measures are Pharmacovigilance activities should be considered to minimise and further characterise these new identified and potential risks which are not included in the RMP.

The PRAC also noted the higher rate of discontinuation due to unsatisfactory therapeutic response in SJIA compared to CAPS. The MAH is therefore requested to present clear guidance for the continuation or withdrawal of Ilaris in non-responding patients with SJIA.

Due to the uncertainties regarding the validity of the tuberculosis screening tests in Ilaris-treated patients the MAH should present a cumulative overview of all events of tuberculosis and all events of positive test results. The analysis should include the Post-marketing experience and the CTs stratified to the indication for Ilaris including the SJIA study program. The type of screening test used (e.g. tuberculin skin test, interferon gamma release assay or chest X-ray) and the outcome should be considered.

Finally, the MAH is asked to include the findings from PK/PD data from the SJIA program in the RMP in order to substantiate the dose dependency of neutropenia in children / adolescents and to remind of the relatively small therapeutic window

Pharmacovigilance plans

On-going and planned studies in the Post-authorisation Pharmacovigilance Development Plan

Study / activity **Type, title and category (1-3)**	**Objectives**	**Safety concerns addressed**	**Status** (planned, started)	**Date for submission of interim or final reports** (planned or actual)
CACZ885D2307 Vaccination study in pediatric CAPS patients.	Provide data on ability of canakinumab treated CAPS patients to mount a protective immune response to childhood vaccinations	Potential interactions: Vaccines	Ongoing	Final study report 24 May 2015
Study CACZ885D2401 Ilaris Registry CAPS	To provide real life incidence data	Infections Neutropenia Opportunistic infections Immunogenicity/ allergenicity Lymphoid organ toxicity Autoimmunity reactions Severe injection site reactions Malignancy	Ongoing	Final study report 24 May 2015

Study / activity **Type, title and category (1-3)**	**Objectives**	**Safety concerns addressed**	**Status** (planned, started)	**Date for submission of interim or final reports** (planned or actual)
		Disorders of lipoprotein metabolism DILI (Hepatic transaminase and bilirubin elevations) Vertigo Canakinumab – immunosupressants combination therapy toxicity (for CAPS and SJIA) Potential interactions: Vaccines Missing information: Pregnancy Missing information: Long term effect on kidney function Missing information: Effects on growth (For CAPS and SJIA)		
Study CACZ885H2401 Ilaris Registry "Gout"	To provide real life incidence data for the safety concerns incl. clinical characteristics, patients at risk (demographic factors, co-medications, concomitant disease).	Infections Opportunistic infections Immunogenicity/ allergenicity Severe injection site reactions Malignancy Disorders of lipoprotein metabolism DILI (Hepatic transaminase and bilirubin elevations) Increased uric acid levels (for gouty arthritis) Potential interactions: Vaccines Missing information: Pregnancy Missing information: Long term effect on	Ongoing	Q4 2016

Study / activity **Type, title and category (1-3)**	**Objectives**	**Safety concerns addressed**	**Status** (planned, started)	**Date for submission of interim or final reports** (planned or actual)
		kidney function Missing information: Long term safety data (for gouty arthritis)		
CACZ885 G2301E1	To provide further long term efficacy and safety data of canakinumab in SJIA patients treated with canakinumab in SJIA pivotal trials.	Long term efficacy Long term safety Immunogenicity/ allergenicity Macrophage Activation Syndrome (for SJIA)	Ongoing	Dec 2014
Phase IV Study (under development): Canakinumab (ACZ885) dose reduction or dose interval prolongation in active Systemic Juvenile Idiopathic Arthritis (SJIA): efficacy and safety study	To explore 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 for inclusion	Long term safety and efficacy of reduced dosing regimen or reduced dosing frequency in patients reaching inactive disease status for 18 months	Planned	TBD
SJIA Pharmachild registry	To collect prospective safety, tolerability, efficacy, and treatment adherence information on juvenile idiopathic arthritis (JIA) subjects exposed to any biologic agents and methotrexate (MTX), according to local standard practice	Infections Neutropenia Thrombocytopenia Opportunistic infections Severe injection site reactions Malignancy Canakinumab – immunosupressants combination therapy toxicity (for CAPS and SJIA) Macrophage activation syndrome (for SJIA) Missing information: Pregnancy	Under discussion	
Infections	To independently and	Infections	Implementation	NA

Study / activity **Type, title and category (1-3)**	**Objectives**	**Safety concerns addressed**	**Status** (planned, started)	**Date for submission of interim or final reports** (planned or actual)
Adjudication Committee	blindly review, evaluate and categorize all significant infections events from blinded and controlled studies that may be observed during the canakinumab clinical trials	Opportunistic infections	of committee	
Malignancy Adjudication Committee	To independently and blindly review, evaluate and categorize all significant reported malignancies events from blinded and controlled studies that may be observed during the canakinumab clinical trials	Malignancy	Implementation of committee	NA
Macrophage Activation Syndrome Adjudication Committee (MASAC)	To independently review, evaluate pre-specified AEs or laboratory values that could potentially indicate MAS, and then adjudicate all cases identified through a search of the SJIA clinical program and SAE databases for these events or changes	Macrophage activation syndrome	Implementation of committee	NA
Integrated Immunogenocity report	To assess immunogenicity in a comprehensive way, looking at all consequences of it. The report will include data on anti-drug	Immunogencity/ allergenicity	Annual update (adhoc in case of submission dossiers)	NA

Study / activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
	antibody (ADA), occurrence of loss of efficacy on repeated treatment, occurrence of loss of exposure, loss of IL-1β capture and immune-related AEs (using the search criteria defined for the potential risks immunogenicity/ allergenicity) related to the above.			

The PRAC, having considered the data submitted, was of the opinion that the proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product. However, the study protocol of the intended study "Canakinumab (ACZ885) dose reduction or dose interval prolongation in active Systemic Juvenile Idiopathic Arthritis (SJIA): efficacy and safety study" should be submitted for detailed assessment as soon as possible.

Risk minimisation measures

Proposal from MAH for risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Identified Risk **Infections**	Labeling: SmPC section 4.3 (Contraindication), section 4.4 (Special warnings and precautions for use), section 4.5 (Interaction with other medicinal products and other forms of interaction) and section 4.8 (Undesirable effects- Summary of the safety profile)	Alert card Physician information (as per local legislation)
Identified Risk **Neutropenia**	Labeling: SmPC Section 4.4 (Special warnings and precautions for use) and section 4.8 (Undesirable effects)	Physician information (as per local legislation)
Identified Risk **Thrombocytopenia**	Labeling: Section 4.8 (Undesirable effects)	None
Potential Risk **Opportunistic infections**	Labeling: SmPC Section 4.4 (Special warnings and	Alert card Physician information (as per

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	precautions for use)	local legislation)
Potential Risk **Immunogenicity/ allergenicity**	Labeling: SmPC Section 4.3 (Contraindications), Section 4.4 (Special warnings and precautions for use) and section 4.8 (Undesirable effects), section 5.1 (Pharmacodynamic properties)	Physician information (as per local legislation)
Potential Risk **Lymphoid organ toxicity**		No AEs of lymphoid organ toxicity have been reported during the clinical program in CAPS and RA patients so far. No risk minimization measure is considered necessary at this time.
Potential Risk **Autoimmunity reactions**		No risk minimization measure is considered necessary at this time. Upon the emergence of new safety findings related to autoimmunity reactions, as reviewed regularly in the PSUR, appropriate updated risk management activities will be considered.
Potential Risk **Severe ISR**	Labeling: SmPC section 4.8 (Undesirable effects)	Physician information (as per local legislation): Injection administration guide in countries guide in all EU member states for CAPS and SJIA.
Potential Risk **Malignancy**	Labeling: SmPC Section 4.4 (Special warnings and precautions for use)	Physician information (as per local legislation)
Potential Risk **Disorders of lipoprotein metabolism**	Labeling for Gouty arthritis SmPC section 4.8 (Undesirable effects)	Physician information (as per local legislation)
Potential Risk **DILI (Hepatic transaminase and bilirubin elevations)**	Labeling: SmPC section 4.4 (Special warnings and precautions for use), and section 4.8 (Undesirable effects)	This risk is adequately addressed and communicated through routine risk minimization activities.
Potential Risk **Vertigo**	Labeling: SmPC Section 4.7 (Effects on ability to drive and use machines) and section 4.8 (Undesirable effects)	None
Potential Risk **Canakinumab – immunosupressants**	Labeling: SmPC Section 4.4 (Special warning and precautions for use) and section	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
combination therapy toxicity (for CAPS and SJIA)	4.5 (Interaction with other medicinal products and other forms of interaction)	
Potential Risk **Increased uric acid levels (for gouty arthritis)**	Labeling: SmPC Section 4.8 Undesirable effects	None
Potential Risk **Macrophage activation syndrome (for SJIA)**	Labeling: SmPC Section 4.4 (Special warnings and precautions for use)	Alert card Physician information
Important potential interactions **Vaccines**	Labeling: SmPC section 4.4 (Special warnings and precautions for use) and section 4.5 (interaction with other medicinal products and other forms of interaction)	Physician information (as per local legislation)
Important potential interactions **Pharmacodynamic interactions**	Labeling SmPC section 4.4 (Special warnings and precautions for use) and section 4.5 (interaction with other medicinal products and other forms of interaction)	None
Important potential interactions **Drugs eliminated by CYP450 enzymes**	Labeling: SmPC Section 4.5 (Interaction with other medicinal products and other forms of interaction)	None
Missing information **Pregnancy**	Labeling: SmPC Section 4.6 (Fertility, pregnancy and lactation)	Physician information (as per local legislation)
Missing information **Long term effect on kidney function**		No risk minimization measure is considered necessary at this time
Missing information **Effects on growth (for CAPS and SJIA)**		No risk minimization measure is considered necessary at this time
Missing information **Long term safety data**		No risk minimization measure is considered necessary at this time
Missing information **Long term efficacy (for CAPS and SJIA)**		No risk minimization measure is considered necessary at this time

The PRAC, having considered the data submitted, was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indications.

Following consideration of the RMP by the PRAC the MAH provided an updated RMP to address the issues that had been identified during the PRAC assessment of the RMP.

This included the following updated tables with the summary of safety concerns and the proposed risk minimisation measures.

Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	Infections Neutropenia Thrombocytopenia DILI (Hepatic transaminase and bilirubin elevations) (for SJIA) Leukopenia (for SJIA) Decreased estimated creatinine clearance and proteinuria (for SJIA) Musculoskeletal pain and arthralgia (for SJIA)
Important potential risks	Opportunistic infections Immunogenicity/allergenicity Lymphoid organ toxicity Autoimmunity reactions Severe injection site reaction Malignancy Disorders of lipoprotein metabolism DILI (Hepatic transaminase and bilirubin elevations) (for CAPS and gouty arthritis) Vertigo Canakinumab – immunosupressants combination therapy toxicity (for CAPS and SJIA) Increased uric acid levels (for gouty arthritis) Macrophage activation syndrome (MAS) (for SJIA) Pulmonary complications:pulmonary hypertension and interstitial lung disease (for SJIA) Eosinophilia (for SJIA) Potential interactions with vaccines Potential pharmacodynamics interactions Potential interactions with drugs eliminated by CYP450 enzymes
Missing information	Pregnancy Long term effect on kidney function Effects on growth (for CAPS and SJIA) Long term safety data Long term efficacy (for CAPS and SJIA)

Summary of Risk Minimisation Measures for Ilaris

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Identified Risk **Infections**	Labeling: SmPC section 4.3 (Contraindication), section 4.4 (Special warnings and precautions for use), section 4.5 (Interaction with other medicinal products and other forms of interaction) and section 4.8 (Undesirable effects- Summary of the safety profile)	Alert card Physician information (as per local legislation)
Identified Risk **Neutropenia**	Labeling: SmPC Section 4.4 (Special warnings and precautions for use) and section 4.8 (Undesirable effects)	Physician information (as per local legislation)
Identified Risk **Thrombocytopenia**	Labeling: Section 4.8 (Undesirable effects)	None
Identified Risk **DILI (Hepatic transaminase and bilirubin elevations (for SJIA)**	Labeling: SmPC section 4.4 (Special warnings and precautions for use), and section 4.8 (Undesirable effects)	None
Identified Risk **Leukopenia (for SJIA)**	Labeling: SmPC section 4.4 (Special warnings and precautions for use), and section 4.8 (Undesirable effects)	None
Identified Risk **Decreased estimated creatine clearance and proteinuria (for SJIA)**	Labeling: SmPC section 4.4 (Special warnings and precautions for use), and section 4.8 (Undesirable effects)	None
Identified Risk **Musculoskeletal pain and arthralgia (for SJIA)**	Labeling: SmPC section 4.8 (Undesirable effects)	None
Potential Risk **Opportunistic infections**	Labeling: SmPC Section 4.4 (Special warnings and precautions for use)	Alert card Physician information (as per local legislation)
Potential Risk **Immunogenicity/ allergenicity**	Labeling: SmPC Section 4.3 (Contraindications), Section 4.4 (Special warnings and precautions for use) and section 4.8 (Undesirable effects), section 5.1 (Pharmacodynamic properties)	Physician information (as per local legislation)
Potential Risk **Lymphoid organ toxicity**	No AEs of lymphoid organ toxicity have been reported during the clinical program in	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	CAPS and RA patients so far. No risk minimization measure is considered necessary at this time.	
Potential Risk **Autoimmunity reactions**	Upon the emergence of new safety findings related to autoimmunity reactions, as reviewed regularly in the PSUR, appropriate updated risk management activities will be considered. No risk minimization measure is considered necessary at this time.	None
Potential Risk **Severe ISR**	Labeling: SmPC section 4.8 (Undesirable effects)	Physician information (as per local legislation): Injection administration guide in countries guide in all EU member states for CAPS and SJIA.
Potential Risk **Malignancy**	Labeling: SmPC Section 4.4 (Special warnings and precautions for use)	Physician information (as per local legislation)
Potential Risk **Disorders of lipoprotein metabolism**	Labeling for Gouty arthritis SmPC section 4.8 (Undesirable effects)	Physician information (as per local legislation)
Potential Risk **DILI (Hepatic transaminase and bilirubin elevations)**	Labeling: SmPC section 4.4 (Special warnings and precautions for use), and section 4.8 (Undesirable effects)	None
Potential Risk **Vertigo**	Labeling: SmPC Section 4.7 (Effects on ability to drive and use machines) and section 4.8 (Undesirable effects)	None
Potential Risk **Canakinumab – immunosupressants combination therapy toxicity (for CAPS and SJIA)**	Labeling: SmPC Section 4.4 (Special warning and precautions for use) and section 4.5 (Interaction with other medicinal products and other forms of interaction)	None
Potential Risk **Increased uric acid levels (for gouty arthritis)**	Labeling: SmPC Section 4.8 Undesirable effects	None
Potential Risk **Macrophage activation syndrome (for SJIA)**	Labeling: SmPC Section 4.4 (Special warnings and precautions for use)	Alert card Physician information
Potential Risk	Upon the emergence of new	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Pulmonary complications: pulmonary hypertension and interstitial lung disease (for SJIA)	safety findings related to pulmonary complications, as reviewed regularly in the PSUR, appropriate updated risk management activities will be considered. No risk minimization measure is considered necessary at this time	
Potential Risk **Eosinophilia (for SJIA)**	Upon the emergence of new safety findings related to eosinophilia, as reviewed regularly in the PSUR, appropriate updated risk management activities will be considered. No risk minimization measure is considered necessary at this time	None
Important potential interactions **Vaccines**	Labeling: SmPC section 4.4 (Special warnings and precautions for use) and section 4.5 (interaction with other medicinal products and other forms of interaction)	Physician information (as per local legislation)
Important potential interactions **Pharmacodynamic interactions**	Labeling SmPC section 4.4 (Special warnings and precautions for use) and section 4.5 (interaction with other medicinal products and other forms of interaction)	None
Important potential interactions **Drugs eliminated by CYP450 enzymes**	Labeling: SmPC Section 4.5 (Interaction with other medicinal products and other forms of interaction)	None
Missing information **Pregnancy**	Labeling: SmPC Section 4.6 (Fertility, pregnancy and lactation)	Physician information (as per local legislation)
Missing information **Long term effect on kidney function**	No risk minimization measure is considered necessary at this time	None
Missing information **Effects on growth (for CAPS and SJIA)**	No risk minimization measure is considered necessary at this time	None
Missing information **Long term safety data**	No risk minimization measure is considered necessary at this	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	time	
Missing information **Long term efficacy (for CAPS and SJIA)**	No risk minimization measure is considered necessary at this time	None

The other issues raised in the PRAC assessment of the RMP were also adequately addressed in the updated RMP provided by the MAH.

The CHMP endorsed this advice without changes.

2.7. Update of the Product information

As a consequence of this new indication sections 4.1, 4.2, 4.4, 4.7, 4.8, 4.9, 5.1 and 5.2 of the SmPC have been updated. Annex II and sections 1, 2, 3 and 4 of the Package Leaflet were updated accordingly.

Particularly, a new warning with regard to Leukopenia and Macrophage activation syndrome has been added to the product information. The Package Leaflet has been updated accordingly.

Changes were also made to the PI to bring it in line with the current Agency/QRD template, SmPC guideline and other relevant guideline(s), which were reviewed by QRD and accepted by the CHMP.

The results of the user consultation with target patient groups on the package leaflet submitted by the MAH show that the package leaflet does not yet meet the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use. The applicant will address the following minor issues concerning the user consultation with target patient group population on the package leaflet:

- To submit an additional reduced readability test (1 round of testing with ten participants) with the next forthcoming type II variation which will affect the content of the package leaflet.

In addition, the list of local representatives in the PL has been revised to amend contact details for the local representatives of Malta and Croatia.

3. Benefit-Risk Balance

Benefits

Beneficial effects

Clinically highly relevant, rapid and sustained efficacy of canakinumab in the treatment of SJIA has been demonstrated. Canakinumab was superior to placebo in achieving the adapted ACR pediatric 30 criteria at Day 15 (83.7% vs. 9.8%; odds ratio of 62.3; 95% CI: 12.7, 306.1, p<0.0001). In the pooled 12-week efficacy data, 79.8% of subjects achieved ACR30 response and 57.3% achieved ACR70 response by Day 15 and maintenance of the response was demonstrated in patients initially responding to treatment. The number of subjects achieving highest ACR responses (ACR90 and ACR100) was increasing with time up to Day 85. Successful steroid tapering was achieved by 44.5% (p<0.0001; 90% CI: 37.1, 52.2). The probability to experience a flare event was lower for canakinumab treatment compared with placebo treatment (relative risk reduction to flare of 64%; hazard ratio of 0.36; 95% CI: 0.17 to 0.75; p=0.0032).

In the ongoing extension study, with the longest follow-up periods between 2 and 3 years, the efficacy of canakinumab was largely maintained.

With regard to the concomitant therapies, patients who used canakinumab monotherapy showed highest response rates based on ACR30-100 criteria; significant responses were also seen in patients with concomitant methotrexate. In addition, relevant responses were seen in the group of patients who discontinued anakinra or tocilizumab due to lack of efficacy.

Uncertainty in the knowledge about the beneficial effects

Approximately 20% of patients did not reach the ACR Pediatric 30 response. It is uncertain how long the treatment should be continued if no rapid clinical response is seen. To minimize this risk of lack of efficacy the SmPC states that continued treatment with Ilaris in patients without clinical improvement should be reconsidered by the treating physician.

There were a number of subjects who initially responded but subsequently lost their response. So far it is not finally assessable if a long term effect will be sustained. As outlined in the RMP additional long term data on safety and efficacy in SJIA will be generated by the following activities:

(1)Pharmachild registry; (2) the re-opened first extension to open label study G2301E1; (3) the phase IV dose reduction study.

It is currently unknown if patients, who achieve inactive or stable, less active disease might be maintained with a lower dose or less frequent dosing schedule long-term. While the number of patients successfully reducing canakinumab dose is limited to date, a reasonable conclusion can be drawn from the available data that dose reduction can be achieved in some patients. This is in so far relevant from a safety perspective as more adverse events were seen in the studies on SJIA than in the studies on other indications which could be due to the higher dose applied in this indication.

To gain more insight on canakinumab dose reduction, the MAH 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.

Risks

Unfavourable effects

In the SJIA pooled population, 85.1% of patients experienced at least 1 AE. The SOCs most frequently affected by AEs were ‘Infections and infestations’ (71.1% of patients); ‘Gastrointestinal disorders’ (52.7%); and ‘Musculoskeletal and connective tissue disorders’ (41.8%). Most AEs were of mild or moderate intensity. In particular, gastrointestinal AEs such as vomiting, diarrhea, abdominal pain, upper abdominal pain and nausea were frequently reported in the SJIA population compared to the CAPS population. Infection is an expected side effect of canakinumab due to its mode of action. Infections including gastrointestinal infections are an identified risk of canakinumab treatment and included in the RMP with appropriate pharmacovigilance activities and risk minimization measures. Gastroenteritis and abdominal pain are included as adverse drug reactions in the SmPC for SJIA.

Serious infections, neutropenia and thrombocytopenia occurred both in the CAPS and SJIA studies but overall more patients had SAEs in SJIA than in CAPS. With the exception of MAS and musculoskeletal disorders the SAE profile (but not the frequencies) was similar between the SJIA and CAPS in this more severely diseased population.

Whereas neutropenia, thrombocytopenia and infection have been already identified risk for the other canakinumab indications and are appropriately labelled in the product information leukopenia is a frequent finding in the SJIA population treated with canakinumab. Leukopenia was made identified risk in the RMP for SJIA patients and the risk is considered adequately mitigated with the inclusion of leukopenia within the existing neutropenia warnings in SmPC Section 4.4. Musculoskeletal pain is listed as a common adverse drug reaction in the SmPC and was made important identified risk in the RMP for canakinumab treatment in SJIA.

Decreased creatinine clearance and urinary proteinuria without renal function deterioration was observed in the SJIA pooled safety population. Noticeably fewer CAPS vs SJIA paediatric patients had positive testing for proteinuria (15.6% vs 35.6%). Decreased creatinine clearance and urinary proteinuria was added to the identified risks in the RMP and to 4.8 of the SmPC concerning the SJIA indication.

MAS was classified under the SOC neoplasma, thus neoplasmas were higher in SJIA than in CAPS solely due to MAS: 8.6 vs. 2.1. MAS may occur spontaneously during a flare of SJIA, or may be triggered by any infectious agent. When comparing the occurrence of MAS in the canakinumab and placebo groups across the different trials and adjusting this to 100 patient-years (4.3 vs. 7.7 respectively), there does not seem to be an increase in MAS in the canakinumab group. However, the role of canakinumab in this setting is still under evaluation; on the one hand canakinumab can trigger infections and thus release a cascade of events leading to MAS. On the other hand by reducing the flares in SJIA, the equation may be balanced in favour of less MAS events. (See next paragraph on “Uncertainty”).

Uncertainty in the knowledge about the unfavourable effects

Macrophage activation syndrome (MAS) is a well-known and potentially fatal complication of SJIA. In the scientific community a clear understanding of the pathogenesis and aetiology of MAS is still lacking. The background incidence of is difficult to estimate due to the fact that robust epidemiological data are missing and thus the role of canakinumab in this setting is hard to calculate. This is further encumbered by the design of the pivotal trial G2301: due to the withdrawal approach (albeit in accordance with EMA recommendations to obtain data for an optimal efficacy assessment) there are no treatment naïve patients to compare to. Study G2305, although placebo controlled, is relatively small and short and therefore also does not suffice. Triggers of MAS include modifications of drug therapy. The role of novel biologic therapies with respect to the risk or the severity of MAS is not fully known and no definite conclusion can be made about a possible increase of MAS in SJIA patients treated with canakinumab. For the granting of a marketing authorisation the potential risk of MAS is appropriately mitigated with inclusion of the appropriate warnings in 4.4. of the SmPC. In addition, the prescription of canakinumab is restricted to specialist physicians experienced in the diagnosis and treatment of SJIA. In order to increase the effectiveness of risk communication and management, physician information will be provided to all prescribing physicians educating them about the early diagnosis, risk factors (e.g. infections and SJIA flare) and treatment of MAS as outlined in the RMP.

An alert card indicating in lay language the potential risk for MAS will be provided to all patients with SJIA receiving canakinumab. The alert card will also request patients to contact their doctors in case of SJIA aggravation or development of an infection. In the planned Pharmachild registry the applicant committed to capture AEs of special interest in subjects with SJIA, such as MAS as outlined in the RMP.

Furthermore the MAH opened enrolment of the extension study G2301E1 to new canakinumab-naïve patients and extended the study end date to June 2014 to allow for additional collection of long-term efficacy and safety data as outlined in the RMP.

As described in the discussion on safety there is an unconfirmed signal for increased incidence of pulmonary complications in SJIA patients treated with IL-1 inhibitors. The available patient population is too small to draw any firm conclusions toward a direct link between canakinumab and pulmonary complications. These events will be closely monitored as potential risk as outlined in the RMP.

DILI events (elevations of serum transaminases) were observed in several canakinumab clinical trials in SJIA patients. The magnitude of the difference, compared with the comparator group (placebo or active substance), on the liver parameters of interest was not large enough to suggest a causal relationship and no cases met the definition of Hy's Law. Drug induced liver disease was included as an identified risk in the RMP and additional information will be provided within the Pharmachild SJIA registry.

Within the planned registry the applicant will provide 3 years of analysis on patients for all of the identified and potential risks.

Benefit-Risk Balance

Importance of favourable and unfavourable effects

Treatment with canakinumab is efficacious regarding ACR response and statistically superior to placebo in a paediatric population with systemic juvenile idiopathic arthritis. Canakinumab administration in this population allows in a statistically significant and clinically important proportion of treated patient a reduction of glucocorticoid treatment. The risk to suffer a disease flare is statistically significant reduced with canakinumab compared to placebo treatment.

These results are seen as clinically very important in a severe childhood disease with restricted treatment options. Especially the possibility for reducing the steroid dose is important in view of long term severe side effects.

A higher number of SAEs and clinically notable abnormalities in laboratory parameters, including haematology and transaminase values were observed in the treatment of SJIA compared to CAPS. An increased rate of infections was not observed among the patients with low neutrophil counts and DILI events did not meet the definition of Hy's Law.

Summarising, in the pooled data of all SJIA studies the rate of discontinuation due to unsatisfactory therapeutic event was 31.3%. Taken together with the musculoskeletal disorders being a common adverse drug reaction in SJIA patient treated with canakinumab and additional medication needed for these disorders the benefit is somewhat narrowed. Furthermore as the efficacy of canakinumab is reliant on the compliance of the patient the importance of gastrointestinal disorders becomes apparent.

Benefit-risk balance

Two pivotal studies demonstrate that treatment with canakinumab is statistically superior to placebo in the defined response variables (e. g. 79.8% ACR30, 70.2% ACR50, 57.3% ACR70, 36.5% ACR90, and 21.3% ACR100; pooled data at Day 15). In study G2305, 32.6% of patients achieved inactive disease at Day 15. All ACR components (including systemic and joint symptoms) moved towards normal. In study G2301 Part I, steroids were eliminated in 32.8% patients and successfully tapered in 44.5%. The risk of experiencing a flare event was 64% lower for canakinumab compared with placebo after the withdrawal of canakinumab treatment (Part II).

Data from the extension study also demonstrate that responses are maintained and often improve with continued therapy, providing a high degree of benefit to the majority of patients.

On the whole a similar safety profile in SJIA was seen when compared to CAPS albeit with higher frequencies of the adverse events mainly in gastrointestinal disorders, infections and respiratory disorders, Creatinine renal clearance decreased and Proteinuria. The risk of these unfavorable effects is appropriately mitigated with the proposed SmPC and RMP.

Furthermore, the applicant committed to provide 3 years of analysis on patients for all of identified and potential risks within the canakinumab RMP, in addition to missing information on pregnancy, long-term safety and efficacy, and the long-term effect of canakinumab on renal function through the planned registry.

The main new potential safety concern is that of MAS, which can be triggered by a SJIA flare or an infection. From the current evaluation it is not possible to reject or confirm any increased risk of MAS events following Ilaris treatment. Precautionary measures as described above are considered to adequately mitigate the risk of MAS and in the planned registry the applicant committed to capture AEs of special interest in subjects with SJIA, such as MAS as outlined in the RMP.

Considering the severity of SJIA, the efficacy of canakinumab outweighs the known and the potential risks of the treatment.

Discussion on the Benefit-Risk Balance

SJIA is a serious, rare condition responsible for high childhood mortality and severe morbidity, including arthritis, joint deformities and systemic manifestations e.g. anaemia, hepatosplenomegaly, lymphadenopathy, serositis, hepatitis, tenosynovitis, stunted growth, which in turn can lead to severe disability. One of the immunological features of SJIA is the increased IL-1 levels.

Many patients are not controlled by current standard treatment with NSAIDs and/or methotrexate and must resort to corticosteroids. Chronic use of high corticosteroid doses leads to additional morbidity, such as growth retardation, osteoporosis, cataracts, cushingoid appearance, increased susceptibility to infections, hypertension and glucose intolerance. MTX is a highly toxic immunosuppressant and can lead to myelosuppression, severe GI disorders, hepato- and neuro- and nephrotoxicity and interstitial pneumonitis. The only other recently approved therapy in SJIA is tocilizumab (an anti-IL-6 monoclonal antibody). So far no comparator studies of tozilicumab versus canakinumab were undertaken.

Canakinumab is a fully human monoclonal anti-IL-1 beta antibody binds with high affinity specifically to human IL-1 beta and neutralises the biological activity of human IL-1 beta by blocking its interaction with IL-1 receptors, thereby preventing IL-1 beta-induced gene activation and the production of inflammatory mediators.

In the current application, canakinumab has shown clinically highly relevant, rapid and sustained efficacy in the treatment of SJIA. Especially the possibility to reduce the corticosteroid dose or to become steroid-free is of utmost importance for the wellbeing and development of these juvenile patients. Administration by subcutaneous injection (e.g. by the parent/ self-injection) will be a practical advantage, in comparison to i.v. infusion (as in tocilizumab treatment) or to daily s.c. injections (as in off-label anakinra treatment). Long term extension data support prolonged efficacy.

Based on AE reporting rates, the overall safety of canakinumab in the SJIA pediatric population was comparable to that in the CAPS population. Exposure adjusted incidence rates of AEs generally decreased over time, including the rate of infections. There were no patients with true opportunistic infections in the SJIA clinical program. The safety profile of the SJIA long-term population was similar to that of the overall SJIA pediatric population, but more data will become available post authorization through the planned registry the extension of the open label study G2301E1 and the planned phase IV dose reduction study.

The MAH is proposing the following wording of the indication: “Ilaris can be given as monotherapy or in combination with methotrexate”. In clinical practice, concomitant methotrexate may be beneficial particularly for patients with severe arthritic symptoms of SJIA. For patients presenting predominantly with systemic symptoms such as fever, monotherapy with canakinumab may be preferable. Initiating a biological treatment in juvenile patients only after the more traditional methotrexate treatment has failed is not considered feasible in the context of SJIA. Some SJIA patients present mainly with systemic symptoms including fever and methotrexate would not be an optimal treatment for these subjects. Hence, the indication as suggested by the MAH is acceptable.

The CHMP considers that Canakinumab has clearly demonstrated its clinically and statistically significant efficacy to support the claimed indication and that the known risks can be appropriately mitigated. The benefits of the treatment outweigh the risks.

The overall benefit risk profile is considered favorable.

4. Recommendations

Final Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends, by the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation(s) accepted		**Type**
C.1.6 a)	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Extension of Indication to include new indication/population for Ilaris for the treatment of active Systemic Juvenile Idiopathic Arthritis (SJIA) in patients aged 2 years and older who have responded inadequately to previous therapy with non-steroidal anti-inflammatory drugs (NSAIDs) and systemic corticosteroids. Ilaris can be given as monotherapy or in combination with methotrexate.

As a consequence sections 4.1, 4.2, 4.4, 4.7, 4.8, 5.1 and 5.2 of the SmPC have been updated. Annex II and sections 1, 2, 3 and 4 of the Package Leaflet were updated accordingly.

Furthermore, the PI is being brought in line with the latest QRD template version 9.0.

In addition, the MAH took the opportunity to include the contact details of the Croatian local representative and to update the contact details of the Maltese local representative in the Package Leaflet.

The requested variation proposed amendments to the SmPC, Annex II and Package Leaflet.

Conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk management plan (RMP)**

The MAH shall perform the required Pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

Additional risk minimisation measures

The Marketing Authorisation Holder (MAH) shall ensure that, prior to launch, all physicians who are expected to prescribe/use Ilaris are provided with a physician information pack containing the following:

- The Summary of Product Characteristics
- Physician information
- Patient Alert Card

The physician information should contain the following key messages:

- The risk of serious infections, including opportunistic bacterial, viral and fungal infections in patients treated with Ilaris;
- The risk of acute injection-related reactions;
- For CAPS patients: the need to instruct patients on proper techniques for self-administration when the patient is willing and capable to do so, and guidance for Health Care Professionals on how to report administration errors;
- The identified or potential risk of immunogenicity that might lead to immune-mediated symptoms. For gouty arthritis patients: highlighting that intermittent therapy or re-exposure after a long treatment-free interval may be associated with an enhanced immune response (or loss of immune tolerance) to Ilaris and thus re-treated patients must be considered at risk of hypersensitivity reactions;
- For chronic therapy in CAPS: the need for Health Care Professionals to perform an annual clinical assessment of patients regarding a potential increased risk for the development of malignancies;
- As treatment with Ilaris should not be initiated in patients with neutropenia, the need to measure neutrophil counts prior to initiating treatment and again after 1 to 2 months. For chronic therapy in CAPS patients or repeated therapy in gouty arthritis patients, it is recommended to assess neutrophil counts periodically during treatment;

- For SJIA patients, the need for Health Care Professionals to be attentive to symptoms of infection or worsening of SJIA, as these are known triggers for macrophage activation syndrome (MAS) which is a known, life-threatening disorder that may develop in patients with rheumatic conditions, in particular SJIA patients. If MAS occurs, or is suspected, evaluation and treatment should be started as early as possible;
- The need to monitor patients for changes in their lipid profiles;
- The unknown safety of Ilaris in pregnant and lactating women, thus the need for physicians to discuss this risk with patients if they become or plan to become pregnant;
- The proper patient management as regards the interaction with vaccination;
- The possibility to include patients in the registry study to facilitate the collection of long term efficacy and safety data;
- The role and use of patient alert card.

Specific Obligation to complete post-authorisation measures for the marketing authorisation under exceptional circumstances

This being an approval under exceptional circumstances and pursuant to Article 14(8) of Regulation (EC) No 726/2004, the MAH shall conduct, within the stated timeframe, the following measures:

Description	Due date
The MAH is requested to provide reports on the ß-Confident registry (CACZ885D2401), which was designed to provide data on long-term safety and effectiveness of Ilaris treatment in paediatric and adult CAPS patients in routine clinical practice. In these reports the MAH is requested to specifically assess cases for whom there is a loss of efficacy (patients reported to have discontinued Ilaris for lack-of-therapeutic response) to determine whether this is due to changes over time in PK/PD or antibody development (where data is available) or in whom a dose adjustment has led to improved therapeutic response (patients with a dose up titration without discontinuation for lack-of-therapeutic response). The MAH is required to provide updates on the recruitment rates and any intermediary results annually within the annual re-assessment. The patients should be included in the Registry until both following conditions are met: 5 years recruitment period and 200 patients included.	Annually within the annual re-assessment

Paediatric data

The CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0108/2012 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.