EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 June 2016
EMA/493970/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

ILARIS

International non-proprietary name: canakinumab

Procedure No. EMEA/H/C/001109/II/0043

Note

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

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List of abbreviations

ACR	American College of Rheumatology
ADA	Anti-drug antibody
AE	Adverse event
ALT	Alanine aminotransferase
AOSD	Adult-onset Still's disease
AST	Aspartate aminotransferase
CAPS	cryopyrin-associated periodic syndrome
CHAQ	Child Health Assessment Questionnaire
CHMP	Committee for Medicinal Products for Human Use
CP	Clinical pharmacology
CRP	C-reactive protein
DAS28	Disease Activity Score
DMARD(s)	Disease-modifying anti-rheumatic drug(s)
EMA	European Medicines Agency
FAS	Full analysis set
FDA	Food and Drug Administration
FO	First order
HLT	High level term
HLGT	High level group terms
ICH	International Conference on Harmonisation
IL-1	Interleukin-1
IL-1α	Interleukin-1 alpha
IL-1β	Interleukin-1 beta
MAH	Marketing Authorization Holder
MAS	Macrophage activation syndrome
MedDRA	Medical Dictionary for Regulatory Activities
NSAID	Non-steroidal anti-inflammatory drug
PD	Pharmacodynamics
PK	Pharmacokinetics
PSUR	Periodic safety update report
PT	Preferred term (for AE)
RA	Rheumatoid arthritis
RMP	rRsk management plan
s.c.	Subcutaneous
SAE	Serious adverse event
SJIA	Systemic juvenile idiopathic arthritis
SmPC	Summary of Product Characteristics
SOC	System organ class
TNF-α	Tumor necrosis factor-alpha
VPC	Visual predictive check

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 8 December 2015 an application for a variation.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II, IIIA and IIIB

Extension of Indication to amend the Systemic Juvenile Idiopathic Arthritis (SJIA) indication to include treatment of active Still's disease including Adult-Onset Still's Disease (AOSD) in patients aged 2 years and older who have responded inadequately to previous therapy with non-steroidal anti-inflammatory drugs (NSAIDs) and systemic corticosteroids; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated and the Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to bring the Product Information in line with the latest QRD template. An updated RMP version 10 was provided as part of the application.

The requested variation proposed amendments to the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0141/2013 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0141/2013 was completed.

The PDCO issued an opinion on compliance for the PIP.

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

The MAH received Scientific Advice from the CHMP on 23 April 2015. The advice pertained to clinical aspects 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 Mueller-Berghaus Co-Rapporteur: Outi Mäki-Ikola

Timetable	Actual dates
Submission date	8 December 2015
Start of procedure	3 January 2016
CHMP Co-Rapporteur Assessment Report	25 February 2016
CHMP Rapporteur Assessment Report	25 February 2016
PRAC Rapporteur Assessment Report	3 March 2016
PRAC members comments	9 March 2016
Updated PRAC Rapporteur Assessment Report	10 March 2016
PRAC Outcome	17 March 2016
CHMP members comments	22 March 2016
Updated CHMP Rapporteurs' joint Assessment Report	23 March 2016
Request for supplementary information (RSI)	1 April 2016
CHMP Rapporteurs' joint response Assessment Report	23 May 2016
PRAC Rapporteur response Assessment Report	25 May 2016
PRAC members comments	31 May 2016
Updated PRAC Rapporteur response Assessment Report	2 June 2016
PRAC Outcome	9 June 2016
CHMP members comments	13 June 2016
Updated CHMP Rapporteurs' joint response Assessment Report	17 June 2016
Updated PRAC Rapporteur response Assessment Report	23 June 2016
Opinion	23 June 2016

2. Scientific discussion

2.1. Introduction

Canakinumab (Ilaris) is a fully human monoclonal anti-human interleukin-1 beta (IL-1 beta) antibody of the IgG1/κ isotype. 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.

Ilaris has been authorised since 23 October 2009 and is available in two pharmaceutical forms: 150 mg powder for solution for injection and 150 mg powder and solvent for solution for injection. The current therapeutic indications are Cryopyrin-Associated Periodic Syndromes (CAPS), Systemic Juvenile Idiopathic Arthritis (SJIA), and Gouty Arthritis.

Ilaris was approved in 11 October 2013 for the treatment of active 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 (Procedure No. EMEA/H/C/001109/II/0026). Ilaris can be given as monotherapy or in combination with methotrexate. The recommended dose of Ilaris for SJIA patients with body weight ≥7.5 kg is 4 mg/kg (up to a maximum of 300 mg) administered every four weeks via subcutaneous injection.

The scope of this variation is to amend the approved SJIA indication to include the over-arching medical condition, "Still's disease". This includes patients with paediatric onset SJIA and those who experience onset of disease in adulthood (and are more commonly ascribed as having adult-onset Still's disease or AOSD). The proposed new indication is: the treatment of active Still's disease including Adult-Onset Still's Disease (AOSD) and Systemic Juvenile Idiopathic Arthritis (SJIA) in patients aged 2 years and older who have responded inadequately to previous therapy with non-steroidal anti-inflammatory drugs (NSAIDs) and systemic corticosteroids. Ilaris can be given as monotherapy or in combination with methotrexate.

AOSD and SJIA are both rare auto-inflammatory disorders for which there are no definitive diagnostic tests, and whose diagnoses is based on defined clinical criteria and age at onset. AOSD occurs worldwide, affecting both men and women, with estimated incidence rates of 0.16, 0.22 and 0.4 cases per 100,000 persons in France, Japan, and Norway, respectively (Gerfaud-Valentin et al 2014a).The two disorders share many features including the clinical signs and symptoms at onset, the serious complications that may arise, the involvement of specific cytokines and defects in the function of natural killer (NK) cells profile in the underlying pathology, and the clinical response to specific anti-cytokine therapies. AOSD and SJIA both have cytokine-driven pathologies, with a central role for interleukin-1 (IL-1).

No formal studies of the use of canakinumab in the treatment of AOSD were submitted. To support the modified indication, the MAH provided a review of the existing scientific literature, demonstration of similar biomarker and gene expression profiles in SIJA and AOSD patients, and extrapolation of paediatric pharmacokinetics to the adult population to support the dosing recommendation. Furthermore, pooled analyses of data from the clinical development program for SJIA was submitted, in which efficacy and safety were summarized by the age of the patients, intended to show that the efficacy and safety of canakinumab in older adolescents and young adults are consistent with those in younger patients.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity / environmental risk assessment

The applicant did not submit any environmental risk assessment (ERA) studies in accordance with the CHMP Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00) which states that proteins are unlikely to result in significant risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

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.

- Tabular overview of clinical studies

Study Number	Status	Location
Studies in active Still's disease including Adult Onset Still's Disease (AOSD) and Systemic Juvenile Idiopathic Arthritis (SJIA)		
CACZ885A2203	Completed	France, Italy, Netherlands, United Kingdom
CACZ885G1301	Ongoing	Japan
CACZ885G2301	Completed	Argentina, Austria, Belgium, Brazil, Canada, France, Germany, Greece, Hungary, Israel, Italy, Netherlands, Norway, Peru, Poland, Spain, Sweden, Switzerland, Turkey, United Kingdom, United States
CACZ885G2301E1	Completed	Argentina, Austria, Belgium, Brazil, Canada, France, Germany, Greece, Hungary, Israel, Italy, Netherlands, Peru, Poland, Russia, Spain, Sweden, Switzerland, Turkey, United Kingdom, United States
CACZ885G2305	Completed	Argentina, Belgium, Brazil, France, Germany, Greece, Hungary, Israel, Italy, Netherlands, Peru, Poland, Spain, Sweden, Switzerland, Turkey, United Kingdom, United States
CACZ885G2306	Ongoing	Austria, Belgium, Brazil, Canada, France, Germany, Hungary, Israel, Italy, Netherlands, Poland, Russia, Spain, Sweden, Turkey, United States
CACZ885GDE01T	Ongoing	Germany
CACZ885GFR01	Ongoing	France
Studies in cryopyrin associated periodic syndrome (CAPS)		
CACZ885A2102	Completed	France, Germany, India, Spain, United Kingdom
CACZ885D2201	Completed	United States
CACZ885D2304	Completed	France, Germany, India, United Kingdom, United States
CACZ885D2306	Completed	Belgium, France, Germany, India, Italy, Spain, Turkey, United Kingdom, United States
CACZ885D2308	Completed	Japan

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 patients with gouty arthritis and SJIA (variations EMEA/H/C/001109/II/10 and EMEA/H/C/001109/ II/26, respectively).

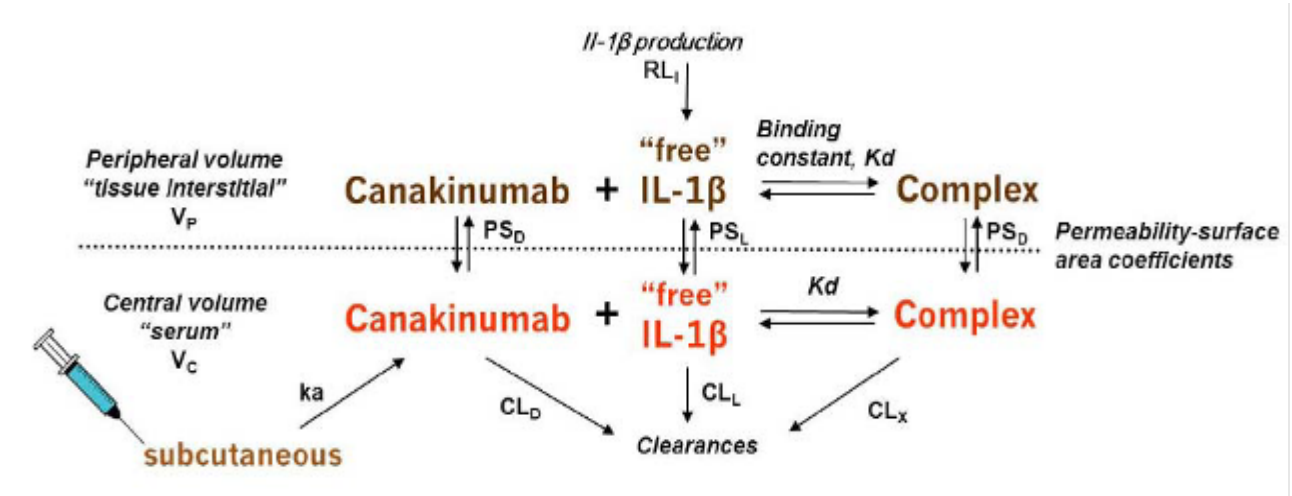
Canakinumab population PK/PD (pop-PK/PD) model was first submitted and assessed in 2008 in the MAA dossier; PD refers here to binding of canakinumab to IL-1β. The model has been slightly updated in subsequent variation applications, but the base model and modelling methods have remained the same. The pop-PK/PD model was last assessed in variation II/26 (extension of indication - SJIA; CHMP positive opinion on 25/07/2013), using pooled data from studies A2203, G2305, G2301 and G2301E1. The dataset included 201 unique SJIA patients with ages ranging from 2 to < 20 years and body weight ranging from 9.3 to 102.6 kg. Canakinumab and total IL-1β plasma concentration-time data were adequately described by the population-based PK-Binding model

An overview of the model is provided here; please refer to the EPAR of variation II/26 for a detailed description and assessment.

The mathematical model of the binding of canakinumab (ACZ885) to IL-1β is characterized by the equilibrium reaction of the binding of canakinumab to IL-1β which can occur either in the tissue interstitial fluid space, where IL-1β is released, or in the plasma. The model also includes diffusion-exchange of canakinumab and IL-1β between the peripheral and plasma compartments, plus elimination rates for free canakinumab, free IL-1β and the canakinumab-IL-1β complex from the plasma space. It is assumed that the elimination of the complex is at the same rate of that for canakinumab due to the small molecular mass of IL-1β and hence the lack of steric hindrance for binding of the complex to the FcRn "Brambell" receptor. The model describes the measured kinetics of both canakinumab and the observed increase in the biomarker total IL-1β in both the plasma and peripheral compartments.

A schematic diagram of the model is depicted in **Figure 1**.

Figure 1. PK-Binding Model for canakinumab and IL-1β



Extrapolation of paediatric pharmacokinetic and selected efficacy data to the adult population to support the dosing recommendation

The objective was to evaluate the pharmacokinetics and exposure-response relationships by age groups to support extrapolation of the efficacy of canakinumab in SJIA to the adult population of AOSD patients.

For that purpose, the SJIA pooled dataset used originally during the evaluation of canakinumab in SJIA (variation EMEA/H/C/001109/II/26) was updated by including the data from the completion of the cohort 1 and the cohort 2 from study CACZ885G2301E1.

The pooled dataset used for the population PK included studies in SJIA as well as various other disease populations (e.g., CAPS, Gouty Arthritis, Rheumatoid Arthritis, Japanese Healthy Volunteer, Non-Japanese Healthy Volunteer, and Psoriasis), totaling 28 clinical studies including their extensions. Descriptions of the SJIA studies (A2203, G2305, G2301, and G2301E1) are given below.

CACZ885A2203 was a multicenter, open label, uncontrolled, 2-stage, dose ranging study (0.5 – 9 mg/kg) to evaluate the safety, tolerability, immunogenicity, pharmacokinetics and efficacy of repeated doses of canakinumab given s.c. in paediatric subjects with active SJIA (at least 2 joints with active arthritis [ACR definition]; spiking, intermittent fever and CRP > 50mg/L). 23 pediatric patients and young adults (aged 4 to 20 years) were enrolled in the study with duration up to 30 months. The study consisted of a 15-day screening period, a run-in period of maximum 72 hours, a treatment period consisting of two different stages (stage 1 and stage 2) during which patients were repeatedly dosed upon relapse with canakinumab with a baseline evaluation prior to each drug administration and an observation period following each drug administration in order to evaluate the response to treatment and time to relapse. In stage 1, patients were treated on an mg/kg basis; an analysis using the PK-Flare model was performed at the end of stage 1 to determine the fixed dose(s) to be used in stage 2. Blood samples in stage 1 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 had completed two cycles of remission. No samples were taken in stage 2.

CACZ885G2305 was a randomized, double-blind, placebo-controlled study evaluating the short term 4-week acute efficacy of canakinumab in SJIA patients using the American College of Rheumatology (ACR) Pediatric 30 criteria. Patients (≥2 to < 20 years of age) with active SJIA were randomized to receive either placebo or canakinumab 4mg/kg (maximum 300 mg) as a single s.c. injection. The primary endpoint was response as determined by a minimum adapted ACR30 at Day 15. Blood samples for canakinumab and total IL-1β were collected on Day 1, 3, 15 and 29; including cases of flare.

CACZ885G2301 was a randomized, double-blind, placebo-controlled, withdrawal study of flare prevention by canakinumab in patients with active SJIA. The study consisted of two major parts with two independent primary endpoints, Part I was an open-label study period consisting of 4 subparts (Ia to Id). Part Ia addressed responder identification, Part Ic steroid tapering. Each part was followed by a 4-week period (Ib and Id) to observe the sustainability of response and then ability to maintain response during steroid withdrawal. Canakinumab was administered subcutaneously at a dose of 4 mg/kg every 4 weeks. Maximum duration of Part I was 32 weeks, corresponding to maximum of 8 injections of canakinumab. Part II was a randomized, double-blind, placebo-controlled, withdrawal-design period which aimed to confirm the maintenance of the initially observed non-controlled efficacy of canakinumab. The administered drug was either canakinumab at 4 mg/kg every 4 weeks or matching placebo injections. The study ended when 37 independent flare events had occurred(subsequent flares from the same subject in Part II were not included in the count as part of the stopping rule). Blood samples were collected at Day 1, 3, 15, 29, 57, end of Part Ic (or start of Part Id) visit, every 6 months during Part II, end of Part II visit and in case of flares.

CACZ885G2301E1 was an open label umbrella extension study designed to demonstrate the long-term safety in patients (cohort 1) from previous studies (G2305 and G2301) as well as in canakinumab naïve patients (cohort 2). Dosing and safety assessments occurred every 4 weeks, whereas efficacy was assessed every 12 weeks. Serum canakinumab and total IL-1β concentrations were collected every 6 months.

Analysis datasets:

In the updated dataset there were 6125 PK and IL-1ß observations in the SJIA subset, as compared with 3306 in the previous analysis.

A separate dataset containing only SJIA pooled studies was created, which contained additional variables including the time records for DAS28, CRP as well as placebo data. It was used to derive post-hoc predicted values from the model.

Baseline demographic variables previously identified to affect the PK properties of canakinumab exposure are summarized for SJIA studies in **Table 1** and graphical distributions of bodyweight, age and albumin are shown in **Figure 2**.

Table 1. Baseline demographic summaries for SJIA studies

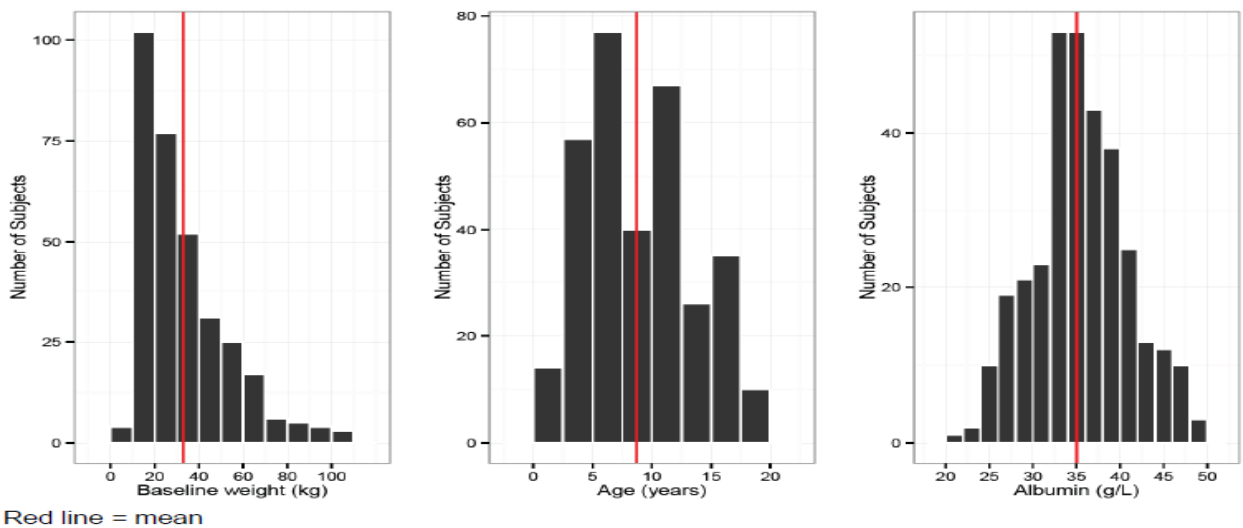
Study	N	Weight (kg)	Age (years)	Albumin (g/L)	Gender M/F
A2203	23	33.7 ± 18.5 (13.6-90.6)	9.5 ± 4.2 (4-19)	36.0 ± 3.7 (29-46)	12/11
G2305*	84	34.8 ± 22.3 (10.8-102.6)	9.0 ± 4.7 (2-19)	34.5 ± 5.5 (23-49)	34/50
G2301	177	33.1 ± 21.2 (9.3-102.6)	8.6 ± 4.4 (1-19)	34.5 ± 5.6 (21-49)	79/98
G2301E1	270	33.3 ± 19.9 (9.2-102.6)	8.8 ± 4.5 (1-19)	35.2 ± 5.4 (20-49)	114/156
G2301E1 Cohort 1	147	33.6 ± 21.8 (9.3,102.6)	8.7 ± 4.4 (1-19)	34.4 ± 4.9 (25-49)	66/81
G2301E1 Cohort 2	123	32.9 ± 17.5 (9.2,86.9)	9 ± 4.5 (2-19)	36.1 ± 5.8 (20-48)	48/75
SJIA POOL	326	32.8 ± 19.7 (9.2-102.6)	8.7 ± 4.5 (1-19)	35 ± 5.4 (20-49)	138/188

For weight, age and albumin, each cell shows the mean ± standard deviation (SD), and the range. For gender (M=males, F=females), numbers of patients are given.

*2 patients received only placebo (excluded from req_mt14426.csv)

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 to the total from individual SJIA studies.

Figure 2. Histograms for bodyweight, age and albumin at baseline for SJIA studies



Figures 3 and **4** show respectively the canakinumab and IL-1β concentrations versus time relative to previous dose on a log-scale in the various studies included in this analysis.

Figure 3. Canakinumab concentrations vs. time by study

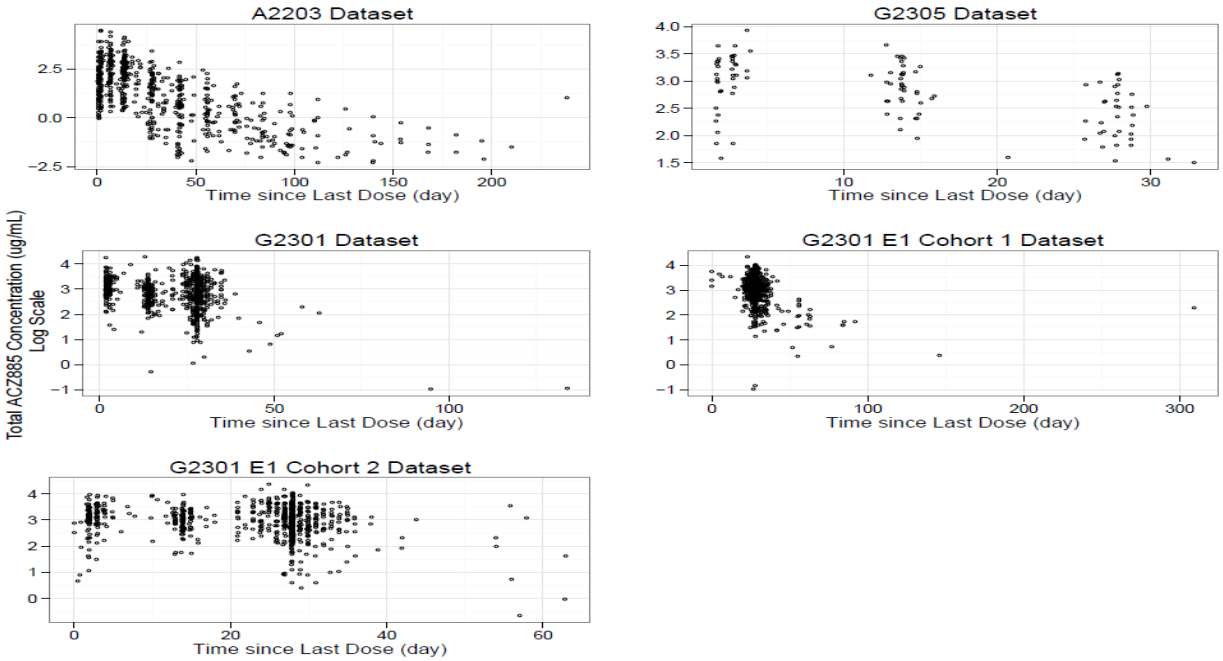
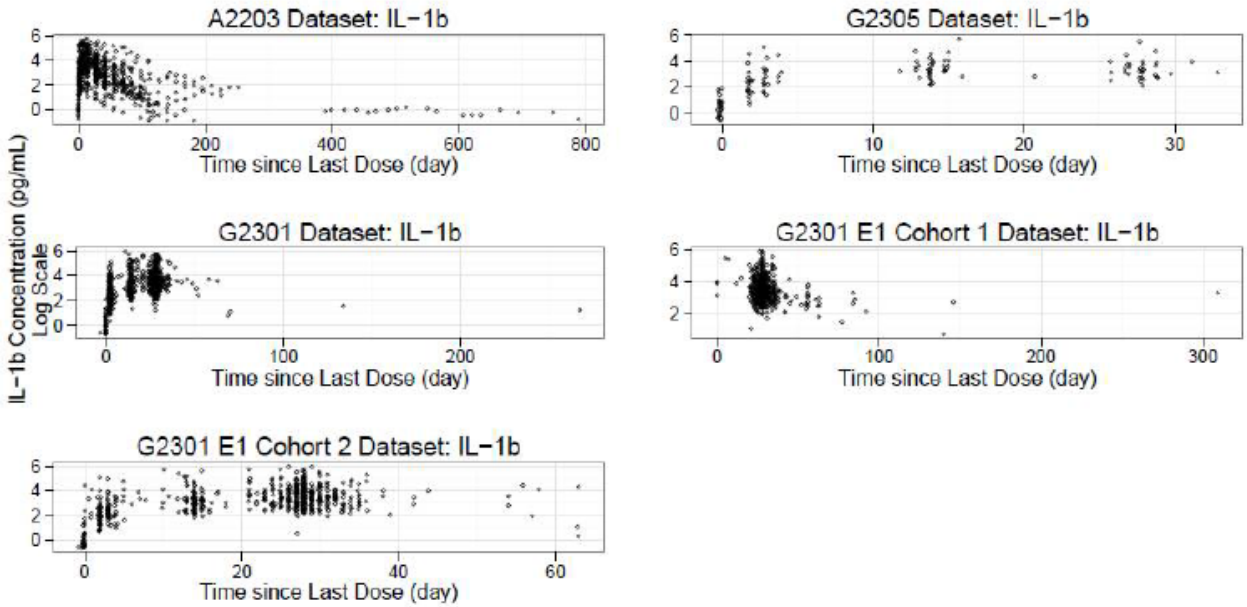


Figure 4. IL-1β concentrations vs. time by study



2.3.3. Pharmacodynamics

2.3.3.1. Primary and secondary pharmacology

Canakinumab for treatment of adult onset Still's disease to achieve reduction of arthritic manifestation (CONSIDER) – (CACZ885GDE01T): Integrated Summary Report: statistical analysis and data interpretation of transcript and protein biomarkers in comparison to CACZ885G2305 and CACZ885G2301.

The aim of this study was the comparison of disease-related dysregulation of blood cell transcripts between SJIA and AOSD patients to address the question how similar the diseases are on a molecular level, and analyse the behaviour of canakinumab responsive genes identified in SJIA in a comparison of AOSD and healthy subjects.

Baseline blood samples for genetic and biomarker analyses were collected from 17 healthy volunteers and subjects participating in 3 studies: two from previous studies in SJIA (CACZ885G2305 and CACZ885G2301) and a further study in AOSD (CACZ885GDE01T) which was designed to investigate the efficacy of canakinumab in patients with AOSD.

Exploratory biomarker results

Table 2. *Overview of Biomarkers measurements*

Study	Biomarker Analyte / technology	Matrix
CACZ885GDE01T (AOSD)	mRNA / Affymetrix DNA microarray	Whole blood
CACZ885GDE01T (AOSD)	mRNA / Affymetrix DNA microarray	PBMCs
CACZ885GDE01T (AOSD)	IL6, IL18 protein	Plasma
CACZ885G2305 combined with CACZ885G2301 (SJIA)	mRNA / Affymetrix DNA microarray	Whole blood

Comparison of disease dysregulated genes in AOSD and SJIA

In order to estimate the level of similarity between SJIA and AOSD, the MAH performed, for each of these two diseases, a comparison of baseline (prior to canakinumab treatment) gene expression with that in group of healthy controls (paediatric for SJIA and adult for AOSD).

mRNA was isolated from whole blood samples and analysed using gene arrays. Based on the resulting list of robustly expressed genes, the MAH performed a Wilcoxon test ($p<0.05$, fold change≥ 1.5) to identify genes with differential expression in disease.

Some common functional themes observed in the list of upregulated genes between the two diseases were neutrophil activation and antibacterial functions (CD177, BPI, OLFM4), regulation of IL1-beta synthesis (CARD16) and proteolysis (MMP8, CASP5, CARD8, CARD16, SERPING1).

In order to generate a quantitative estimate of the overlap between transcriptional dysregulation in AOSD and SJIA the MAH determined the intersections of up- or down-regulated genes from the AOSD to healthy comparison and a previously performed SJIA to age matched healthy control comparison.

Of 110 probesets with at least 3-fold upregulation in AOSD, 72 (66%) were at least 1.5-fold upregulated in SJIA and 35 (32%) were at least 3-fold upregulated in SJIA. This analysis did not show a 100% concordance, as 38 probesets showed a < 1.5-fold difference, or did not reach statistical significance.

Supervised analysis of published SJIA-related gene signatures in PBMCs of AOSD patients and healthy subjects

As no internal data on the gene expression in PBMCs of SJIA patients was available, a supervised visualisation of published gene lists in the AOSD-healthy comparison of PBMC gene expression was performed. For this purpose selected publications which included comparisons between healthy and SJIA patients were chosen, using PBMC samples and microarry technology to increase the comparability between the internal and external datasets.

The results for the probesets (Probe IDs, Affymetrix IDs) from Fall et al 2007 are shown in **Table 3**.

Table 3. Gene expression profiling for macrophage activation syndrome in SJIA-innate immune gene cluster

Description	Common name	Probe ID	P	Fold change†
Solute carrier family 25 member 37	MSCP	226179_at	3.41×10^{-8}	1.82
Elastase 2, neutrophil	ELA2	206871_at	1.88×10^{-6}	2.81
Resistin	RETN	220570_at	1.10×10^{-6}	2.95
Hypothetical protein MGC17301	MGC17301	227055_at	9.92×10^{-5}	2.00
Eukaryotic translation initiation factor 2c, 2	EIF2C2	225827_at	8.48×10^{-5}	2.00
Ubiquitin-specific protease 32	USP32	211702_s_at	3.68×10^{-6}	2.02
Peptidoglycan recognition protein 1	PGLYRP1	207384_at	2.33×10^{-7}	2.34
Inhibin $_{A}$	INHBA	227140_at	0.0042	6.49
Bactericidal/permeability increasing protein	BPI	205557_at	4.82×10^{-5}	8.72
Ribonuclease, RNase A family 3	RNASE3	206851_at	0.000271	5.83
Secretory leukocyte protease inhibitor	SLPI	203021_at	2.82×10^{-5}	5.08
Carcinoembryonic antigen–related cell adhesion molecule 6	CEACAM6	203757_s_at	8.88×10^{-5}	8.16
Myeloperoxidase	MPO	203949_at	3.75×10^{-5}	4.53
Carcinoembryonic antigen–related cell adhesion molecule 1	CEACAM1	209498_at	0.000342	2.68
Haptoglobin	HP	206697_s_at	4.43×10^{-6}	2.93
Haptoglobin-related protein	HPR	208470_s_at	2.02×10^{-6}	2.98
Suppressor of cytokine signaling 3	SOCS3	206359_at	5.52×10^{-6}	1.26
Adrenomedullin	ADM	202912_at	5.31×10^{-6}	1.85
Family with sequence similarity 20, member A	FAM20A	241981_at	6.26×10^{-9}	2.35
Membrane-spanning 4 domain, subfamily A, member 4	MS4A4A	1555728_a_at	1.04×10^{-7}	1.71

For 16 of these 20 probesets (80%), a differential expression between peripheral blood mononuclear cells (PMBCs) of AOSD patients and healthy subjects with p-values below 0.05 was observed. All of these were regulated in the same direction as described for SJIA.

Supervised analysis of a SJIA canakinumab response signature in AOSD patients at baseline and in healthy subjects

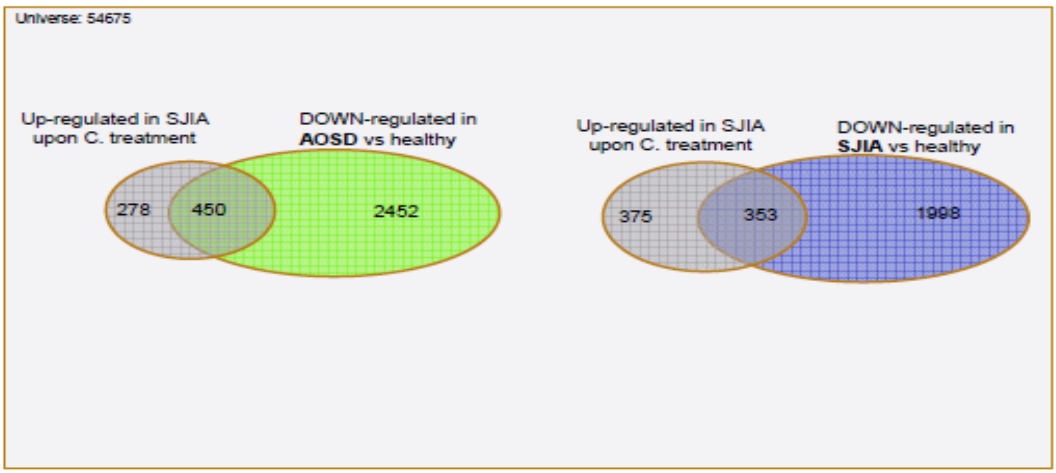
The overlap of SJIA canakinumab responsive genes with AOSD dys-regulated genes was actually slightly larger than the overlap with SJIA dys-regulated genes: 480 of 577 (83%) genes down-regulated by canakinumab in SJIA were also up-regulated in AOSD, relative to healthy while 443 of these 577 genes (77%) were also up-regulated in SJIA (**Figure 5**).

Figure 5. Intersections of canakinumab downregulated genes (SJIA) and disease up-regulated genes (AOSD or SJIA)

Genes *down*-regulated in SJIA post-Canakinumab treatment versus genes *up*-regulated at baseline in SJIA and AOSD relative to healthy subjects.

Similarly, 450 of 728 (62%) %) genes up-regulated by canakinumab in SJIA were also down-regulated in AOSD, relative to healthy while 353 of these 728 genes (49%) were also down-regulated in SJIA (**Figure 6)**.

Figure 6. Intersections of canakinumab upregulated genes (SJIA) and disease down-regulated genes (AOSD or SJIA)



Genes *up*-regulated in SJIA post-Canakinumab treatment versus genes *down*-regulated at baseline in SJIA and AOSD relative to healthy subjects.

Protein markers in AOSD

Plasma levels of two central pro-inflammatory cytokines IL-6 and IL-18 were assessed for baseline samples of AOSD patients and compared to previously obtained values in healthy controls and other inflammatory conditions (**Table 4**).

Table 4. IL-6 and IL-18 levels in patients with different inflammatory conditions and healthy subjects

Indication	IL-6 mean (pg/ml)	IL-6 median (pg/ml)	IL-18 mean (pg/ml)	IL-18 median (pg/ml)
CAPS/NOMID	31.5	2.1	579.6	467.4
CAPS/Muckle-Wells	11.1	4.1	376.4	342.2
AOSD	30.8	19.6	23292	8390
SJIA	157.0	57.2	16994.6	8865.1
RA		5.9		324
Healthy	1.2		194	

2.3.4. PK/PD modelling

The previously developed PK-binding-model for canakinumab was used to generate individual predicted canakinumab and IL-1β-concentrations for patients who were not included in the previous submission.

This was done by fixing model parameters at their final estimated values (**Table 5**, initially included in EMEA/H/C/1109/II/0026 submission for SJIA) and updating post-hoc predictions without running the fitting algorithm.

Table 5. Final estimates of model parameters for SJIA patients

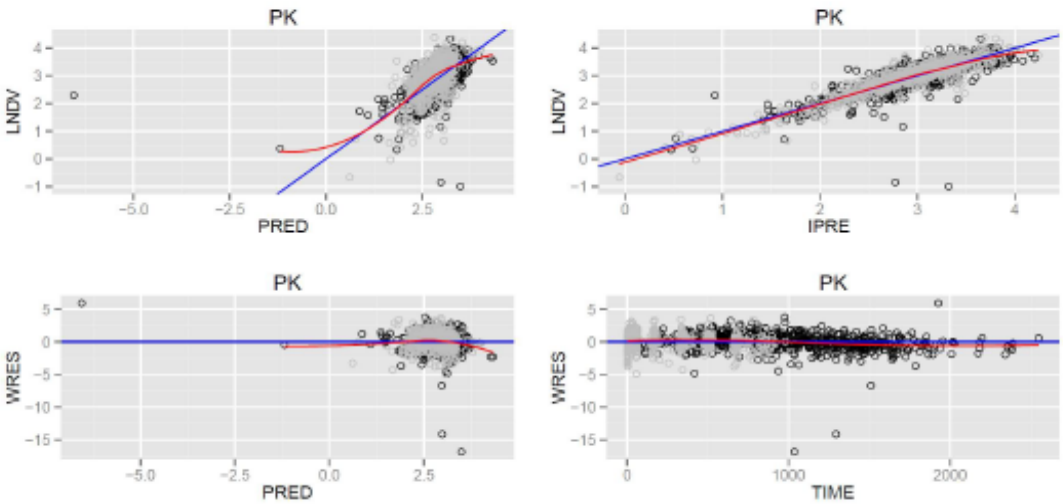
Parameter [units]	Population mean θ ± SE (%RSE) [95% Confidence Interval]	Inter-individual variance ω^2 ± SE (%RSE) [95% Confidence Interval]	Coefficient of Variation (CV)	Shrinkage
Canakinumab parameters				
ACZ Clearance – 70 kg (CL_D, L/day at 43 g/L albumin)	0.196 ± 0.0148 (7.55%) [0.167 – 0.225]	0.131 ± 0.00934 (7.13%) [0.113 – 0.149]	36.2%	9.30%
ACZ Clearance – 33 kg (CL_D, 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)*	0.295 ± 0.015 (5.1%)	0.195 ± 0.0421 (21.6%) [0.112 – 0.278]	44.2%	38.9%
Bioavailability (F1, %)*	68.9 ± 3.65 (5.3%)			
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%

* cell product type D

To assess the ability of the model to predict data from study CACZ885G2301E1, plots of observed versus (population and individual) predicted values, and residuals versus population predicted values and time, were produced for canakinumab (**Figure 7**) and IL-1ß (**Figure 8**).

Figure 7. Canakinumab model diagnostic plots for study CACZ885G2301E1



Top row: Observed canakinumab concentration (LNDV, ug/mL) versus population (PRED) and individual (IPRE) predictions, on log-scale.

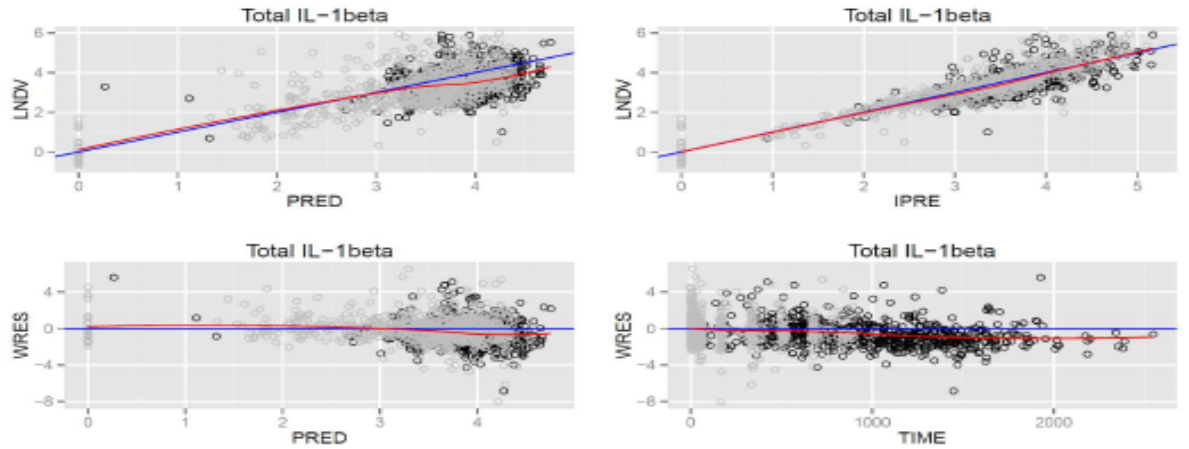
Bottom row: Weighted residuals versus population predictions and weighted residual versus time in days.

The red line through the points in each plot is a local regression (loess in R).

The blue line is the identity line (top row) or horizontal line y=0 (bottom row).

Black dots = G2301E1 cohort 1 / Grey dots = G2301E1 cohort 2

Figure 8. Total IL-1ß model diagnostic plots for study CACZ885G2301E1



Top row: Observed IL-1β concentration (LNDV, ug/mL) versus population (PRED) and individual (IPRE) predictions, on log-scale.

Bottom row: Weighted residuals versus population predictions and weighted residual versus time in days.

The red line through the points in each plot is a local regression (loess in R).

The blue line is the identity line (top row) or horizontal line y=0 (bottom row).

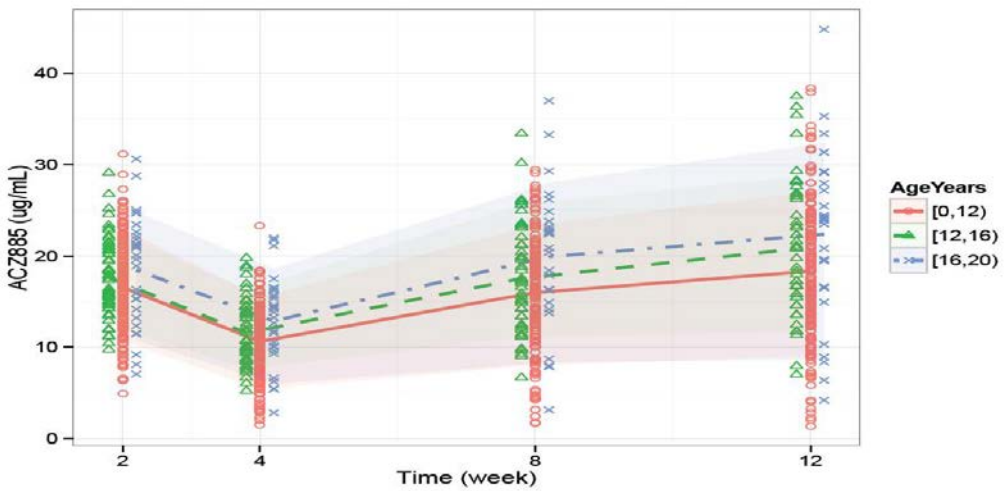
Black dots = G2301E1 cohort 1 / Grey dots = G2301E1 cohort 2

The final population-based PK-Binding model was then used for simulating the predicted steady-state exposures and PK post-hoc at the time of 12-weeks efficacy (DAS28 and CRP) measurements.

Extrapolation of pediatric PK data to the adult population

Predicted canakinumab concentrations with dosage 4 mg/kg every 4 weeks for the three age groups defined in the SJIA population are displayed **in Figure 9**.

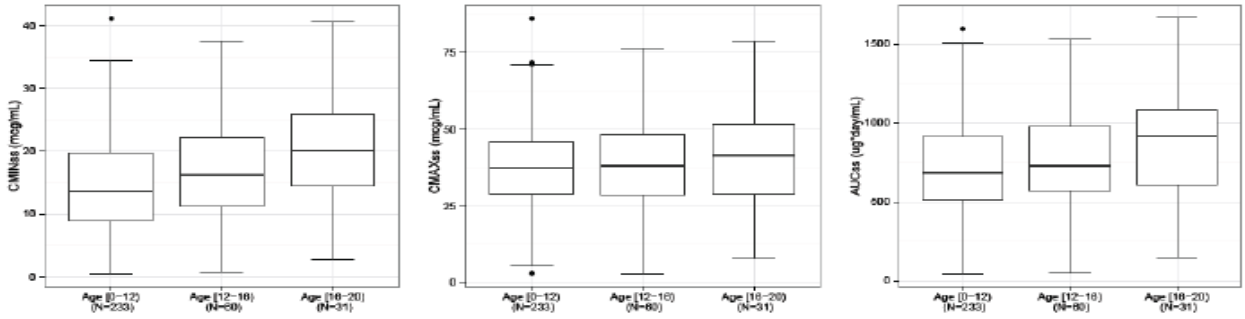
Figure 9. Predicted canakinumab concentrations over the first 12 weeks (4 mg/kg every 4 weeks)



Dashed Line = Median. Shaded area = 80% ranges (10th and 90th percentiles)

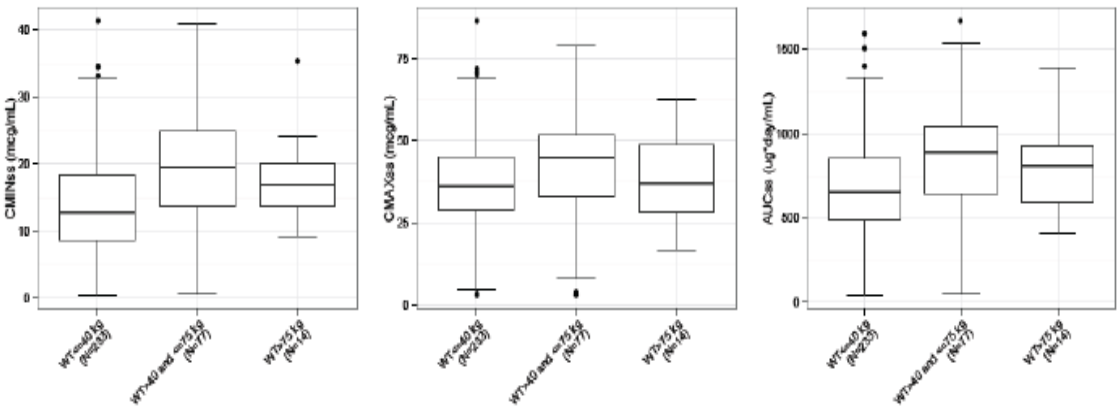
Steady-state exposure metrics were also derived (CMINss, CMAXss, AUCss). **Figures 10** and **11** show canakinumab exposure in SJIA patients of various age and weight categories, using different simulated metrics of exposure at steady state (CMINss, CMAXss, AUCss). Positive trends in median exposure were seen with increasing age or weight, but distributions overlap significantly and can be considered comparable overall, consistent with previous observations in the SJIA population.

Figure 10. Simulated steady-state exposure of canakinumab for SJIA patients stratified by age



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. Dots represent the outliers.
N represents the number of subjects.

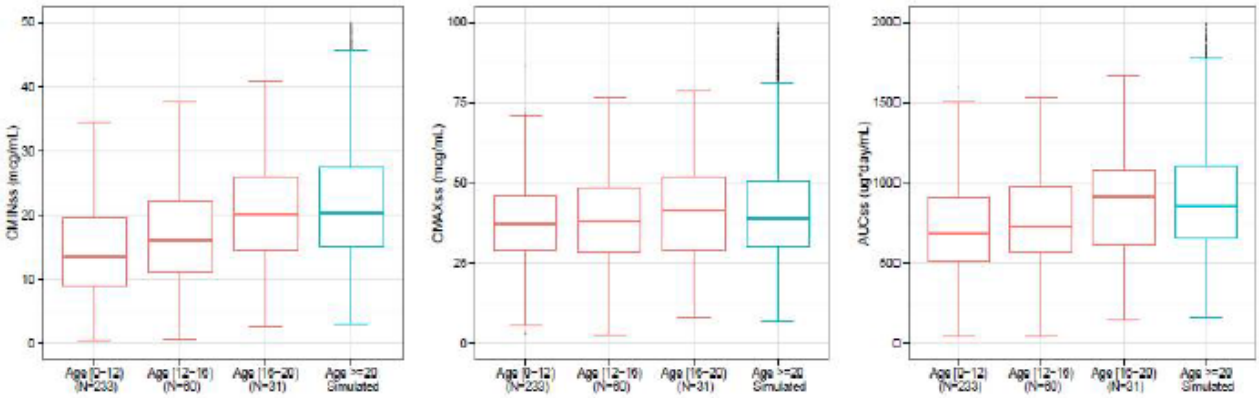
Figure 11. Simulated steady-state exposure of canakinumab for SJIA patients stratified by bodyweight



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

In addition, PK exposure metrics from SJIA patients were compared with those from a simulated population of "SJIA-like" adult patients. For this purpose, demographic data (age, weight) from all CAPS and Gout patients above 20 years of age (n=913 patients) were selected from the pooled dataset; their median age was 51 years (range 20-91) and median weight was 91 kg (range 19-171). Steady-state metrics (CMINss, CMAXss, AUCss) were simulated for approximately 10000 patients using these demographic data and assuming all received the dosing regimen recommended in SJIA. The results from these simulations are illustrated in **Figure 12**. In this figure, for each PK metric the same boxplots from **Figure 10**, representing the SJIA clinical study population, are presented alongside an additional boxplot for the simulated population of "SJIA-like" adults (age ≥ 20).

Figure 12. Simulated steady-state exposure of canakinumab for SJIA patients stratified by age including patients above 20 years of age



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. Dots represent the outliers.

N represents the number of subjects.

IL-1-beta levels in AOSD, in response to anti-IL-1 treatment and comparison to the data available in SJIA

Higher levels of IL-1beta have been observed in 2 out of 4 AOSD patients compared with controls, as reported by Kötter et al 2007, **Table 6**.

Table 6. Laboratory data before and after Anakinra treatment, Kötter et al 2007

	Before & After Anti-IL-1 Treatment				
	Patient 1	**Patient 2**	**Patient 3**	**Patient 4**	*Normal Ranges*
Systemic markers:					
CRP (mg/dL)	13.6→0.17	29.23→0.15	13.84→0.55	5.64→0.26	*<0.5*
ESR (mm/h)	30→2	79→8	80→4	13→5	*<10*
Ferr (µg/dL)	9.6→1.3	1,418→1.8	165→84.4	7.1→3.4	*1-30,50 (F, M)*
Leuko (/µL)	22,940→7,400	17,880→4,260	16,150→6,410	14,660→7,390	*4,000 – 9,500*
Pro-inflammatory cytokines:					
IL-1β (pg/mL)	0.27→0.15	2.11→0.41	2.53→ 0.83	0.23→0.34	*<0.5*
IL-6 (pg/mL)	0→0	5.7→0	134→4	2.4→0	*<15*
TNF-α (pg/mL)	8.5→0	15.4→7.7	13.5→ 5	8.5→0	*<8*
IL-18 (pg/mL)	2,122→1,007	>12,500→649	>12,500→1,540	3,699→1,540	*36 – 275*
IL-1RA (pg/mL)	939→>30,000	ND→>30,000	8,628→>30,000	1,076→>30,000	*<1,500*

CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, Ferr = ferritin, Leuko = leucocyte counts
Source: Kötter et al 2007

In another publication (Fitzgerald et al. 2005) it has been demonstrated that patients with refractory AOSD exhibit higher IL-1alpha, IL-1beta, IL-1RA, IL-6, and IL-18 serum levels prior to the first injection of an anti-IL-1 treatment. Regarding serum IL-1beta kinetics in other auto-inflammatory disorders successfully treated with IL-1 blockade treatments, the authors concluded that circulating levels of IL-1β represent a "spillover" effect from the respective cytokine levels at the end organ. Therefore, attribution of a causative role for IL-1β in disease should not be solely based on circulating levels but rather on clinical responses to agents that reduce IL-1 activities.

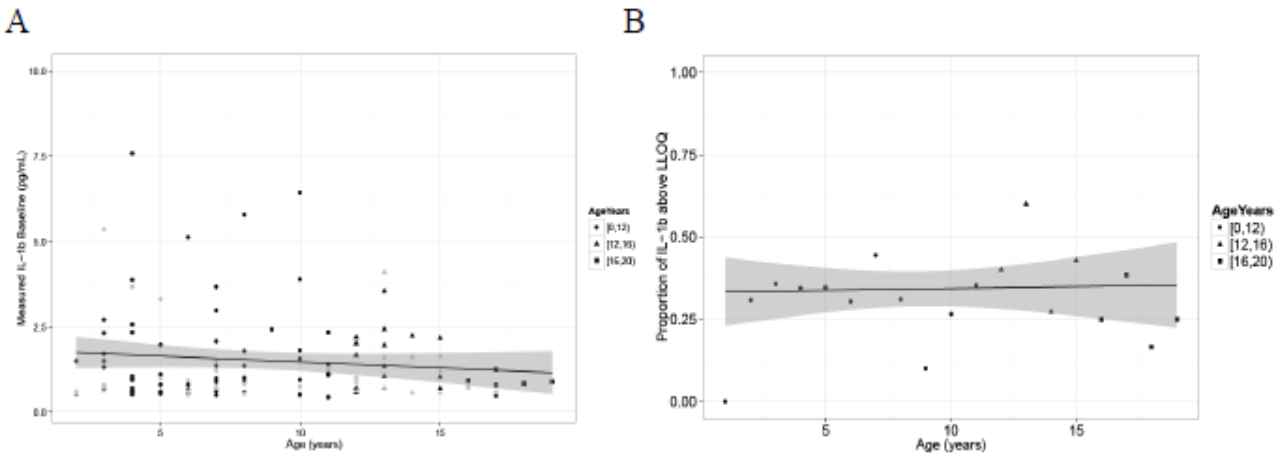
Enhanced responses to anti IL-1 treatments in AOSD patients with active disease has been reported across single case reports, smaller or larger patient series, clinical trials, national surveys.

From one meta-analysis including data from 134 patients, drawn from the above described studies, surveys and case reports (Hong et al. 2014) it was demonstrated that IL-1 inhibition is effective not just in inducing remission but also in allowing steroid dose reduction in AOSD patients, while being well-tolerated and not increasing the risks of adverse events.

Lequerré et al. (2008), a study in 15 patients treated with IL-1 blockade, suggested that IL-1 inhibition might be more effective in AOSD patients whose systemic symptoms predominate over the chronic arthritic symptoms. However, in another report (Kontzias and Efthimiou 2012), AOSD patients with severe systemic and articular manifestations and poor response to short acting anti IL-1 compounds were successfully treated with canakinumab postulating that complete remission in AOSD, in terms of both systemic and articular manifestations, may be dependent on a more sustained IL-1 suppression with a long-acting IL-1 inhibitor.

Patients from the phase 2, phase 3 and extension studies (CACZ885A2203; CACZ885G2305; CACZ885G2301; CACZ885G2301E), in which the observed IL-1β levels were above the lower limit of quantitation (LLOQ; 0.5 pg/mL) at baseline were measured across age groups (**Figure 13**, panel A). Panel B in the same Figure shows the proportion of values per age-year that were above LLOQ.

Figure 13. Measured IL-1β at baseline and proportion of values above the lower limit of quantitation versus age



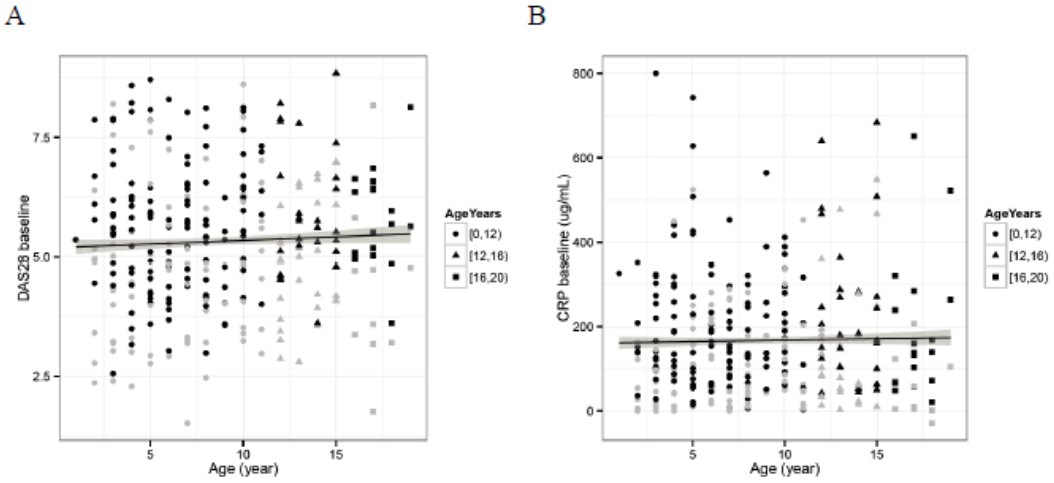
Grey dots = G2301E1 cohort 2 (panel A)

Line = Linear Regression (shaded area = 95% confidence limits)

Extrapolation of efficacy data from SJIA to AOSD

Efficacy measurements (DAS28 and CRP) were plotted versus the corresponding predicted concentrations of canakinumab for the assessment by age groups. **Figure 14** shows individual DAS28 (panel A) and CRP (panel B) values at baseline versus age.

Figure 14. Baseline DAS28 and CRP versus age

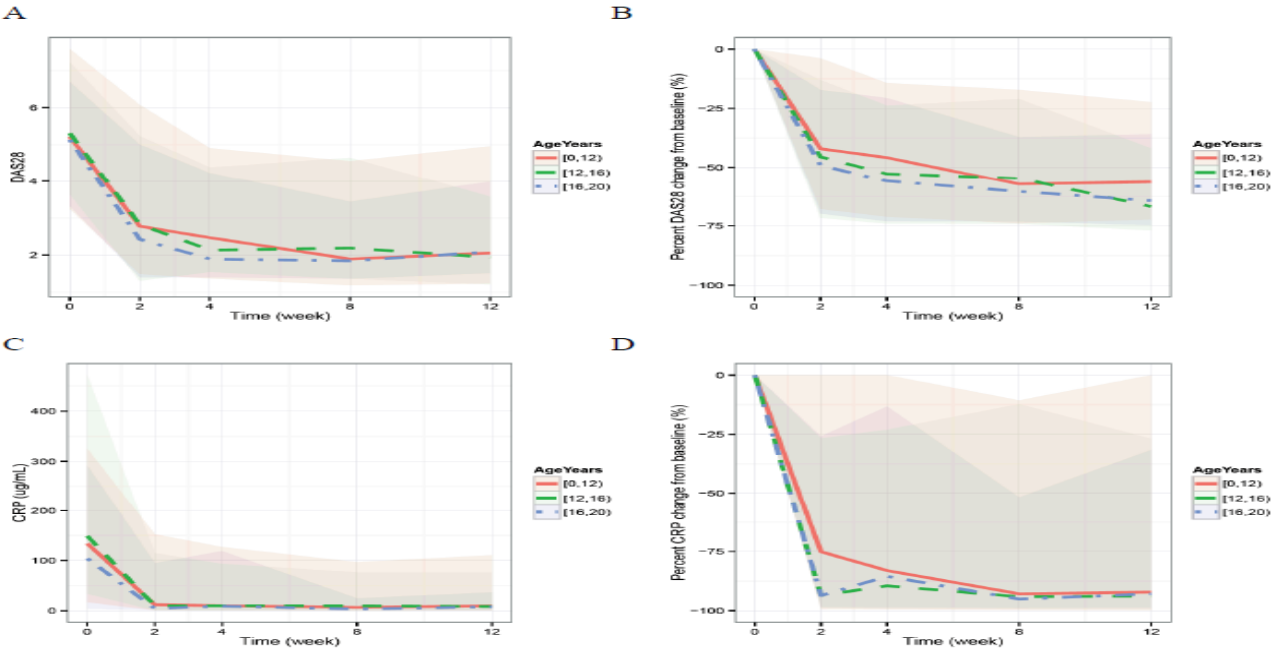


Grey dots= G2301E1 cohort 2

Line = Linear Regression (shaded area = 95% confidence limits)

Figure 15 displays the median time course for DAS28 (panel A: absolute change, panel B: percent change) and CRP (panel C: absolute change, panel D: percent change) over the first 12 weeks of treatment for the three age groups.

Figure 15. Time course of DAS28 and CRP during the first 12 weeks of treatment

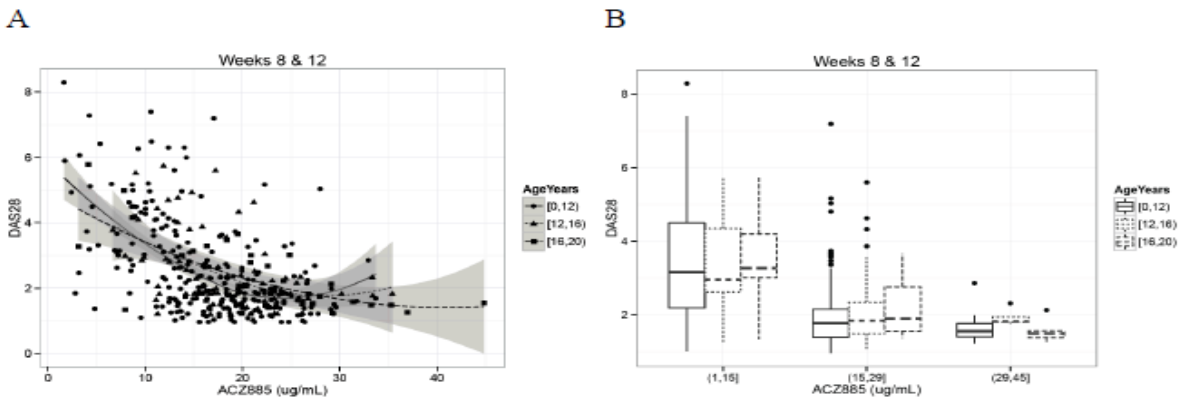


Dashed Lines = Medians

Shaded areas = 80% ranges (10th and 90th percentiles)

Individual DAS28 scores at week 8 and 12 are depicted versus age in **Figure16, panel A**. Lines indicate loess smooth curves (with 95% confidence intervals as shaded areas). Another representation is given in panel B, where data in each age group were summarized by boxplots in 3 concentration groups with bins of equal width (≤15, 15-29, and >29 mcg/mL).

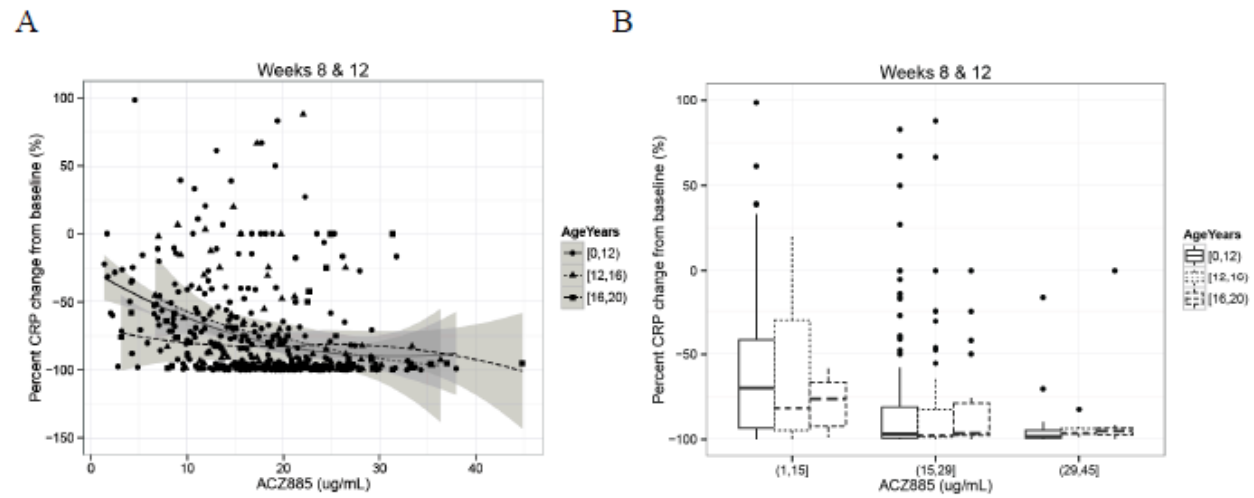
Figure 16. DAS28 versus predicted canakinumab concentrations



Panel A: Lines = Loess curves (shaded area = 95% confidence limits)

Panel B: 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. Dots represent the outliers.

Figure 17. Percent CRP change from baseline versus predicted canakinumab concentrations



Panel A: Lines = Loess curves (shaded area = 95% confidence limits)

Panel B: 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. Dots represent the outliers.

2.3.5. Discussion on clinical pharmacology

Pharmacokinetics

Kinetics of canakinumab and IL-1β in SJIA patients < 20 years of age were described by a population-PK/PD model, which was previously assessed in variation II/26. The CHMP concluded at the time that canakinumab and total IL-1β plasma concentration-time data were adequately described by the population-based PK-Binding model. The data analysed at the time have been supplemented with PK data from additional SJIA patients; these data were used for external validation of the population PK model and supported the conclusion that the model can acceptably predict exposures in a new dataset.

In the updated SJIA data set, distributions of age (1-19y), weight (9.2 – 102.6 kg) covered wide ranges. Age distribution was quite homogenous around the mean (8.7y). Regarding weight, the majority had a body

weight between 10-30 kg which is lower than the population mean (32.8 kg). Only a few subjects > 70 kg were included. Around 40 subjects (12.3 %) in the age range of 15-20 years contributed data for the population PK analysis.

A positive trend in median exposure (AUC, Cmax, Cmin,ss) was seen with increasing age or weight (up to 75 kg) which is consistent with the observation of a slight decrease in body-weight-normalized Clearance with increasing age in the previous SJIA population PK modeling analysis.

The approved dosage of canakinumab in SJIA is 4 mg/kg (up to 300 mg for patients ≥75 kg) every 4 weeks. Overall the pharmacokinetics of canakinumab in young adult SJIA patients aged 16 to 20 years were similar to those in patients less than 16 years of age. Predicted canakinumab steady state exposures at a dose level of 4 mg/kg (maximum 300 mg) in patients over the age of 20 years were comparable to those in SJIA patients younger than 20 years of age.

Likewise, typical exposure tended to increase with body weight up to 75 kg and level or slightly decrease in subjects from 75 to 102 kg. Prior data indicate that canakinumab pharmacokinetics is similar across different disease populations when comparing their bodyweight normalized clearance.

Steady-state metrics (CMINss, CMAXss, AUCss) were simulated for approximately 10,000 patients using the demographic data from all CAPS and Gout patients above 20 years of age (n=913 patients) and assuming all received the dosing regimen recommended in SJIA. Predicted exposure in “SJIA-like” adult patients was nearly identical to that observed in young adult SJIA patients.

Plots of observed versus (population and individual) predicted values, and residuals versus population predicted values and time showed that that the previous model could adequately and without bias describe the totality of canakinumab concentration data in study CACZ885G2301E1.

The model was also able to predict IL-1ß concentrations with little bias up to approximately two years after starting canakinumab therapy, (but showed trends of over-prediction for longer-term IL-1ß data). However, this was not deemed of particular concern by the CHMP as for the present graphical exploration as focus was on the first 12 weeks of treatment and only canakinumab concentrations were used.

According to the prediction for “adult SJIA patients”, a higher variability in exposure may be expected in adults weighing in excess of 75 kg. The CHMP recommended that the MAH provides further data which expected in this regard through PK samples which will be collected and analyzed in the ongoing clinical trial of the use of canakinumab in the treatment of AOSD (study CACZ885GDE01T).

Pharmacodynamics

The comparison of disease dysregulated genes in AOSD and SJIA did not show a 100% concordance as 38 probesets showed a < 1.5-fold difference, or did not reach statistical significance. However, this could be explained by the inherent small technical variation in sampling, mRNA preparation, and chip performance, but also by biological variation. The latter might be attributed, e.g., to the age difference in the SJIA and AOSD study population or to inter-subject variability. However, the overall alteration of the blood transcript profile in both patient populations is highly similar, indicating a strong concordance between SJIA and AOSD at the molecular/cellular level.

The analysis of a SJIA canakinumab response signature in AOSD patients at baseline and in healthy subjects indicated that the vast majority of transcripts which show an immediate response (day 3) to canakinumab in SJIA are amongst the dysregulated genes in AOSD patients, suggesting a concordance in IL-1β dependent pathology.

Published data have also demonstrated that anti-IL-1 treatment is able to normalize or improve markers of systemic inflammation, and normalize levels of key circulating pro-inflammatory cytokines such as IL- 1β and its downstream cytokines such as TNF-α, IL-18, and IL-6.The applicant provided data in order to demonstrate similar genetic profiles and similar clinical responses to anti-IL-1 agents in AOSD patients compared to SJIA patients.

Elevated levels of pro-inflammatory cytokines IL-6 and IL-18 were found in baseline samples of AOSD patients which are comparable to previously observed elevated levels of these proteins in SJIA patients. The levels were elevated in SJIA and AOSD in comparison to healthy volunteers and patients with rheumatoid arthritis. The levels also appeared higher in comparison to the NOMID- or MWS-phenotypes of CAPS. The mean levels of IL-6 protein were found to be approximately 26-fold elevated in AOSD patients while mean IL-18 levels were even 120-fold higher than in healthy subjects. These findings are again consistent with previous observations of strongly elevated levels of these proteins in SJIA patients. In contrast, elevation of these pro-inflammatory proteins – in particular IL-18 - is much less pronounced in patients with other auto-inflammatory conditions like NOMID/CAPS or Muckle-Wells.

The data submitted overall indicate that both SJIA and AOSD have cytokine-driven pathologies, with a central role for IL-1.

Extrapolation of efficacy data from SJIA to AOSD

Observed response (DAS28 scores and CRP levels) to canakinumab was similar in all three age groups in SJIA patients <20 years of age. Likewise, exposure-response relationships were similar for all the age groups. It is reasonable to assume that the efficacy in the age group 16 to 20 years of age is comparable to the efficacy in subjects > 20 years of age. As SJIA and AOSD share same pathogenetic mechanisms, it is reasonable to assume that the exposure-response relationship can be extrapolated to the AOSD population.

Individual DAS28 scores at week 8 and 12 also indicated a consistent concentration-response relationship for all three age groups.

Concentration-response relationships were also comparable with respect to CRP change from baseline and based on the available data it is reasonable to expect similar exposure-response relationships in AOSD patients.

2.3.6. Conclusions on clinical pharmacology

Overall, the population PK analyses using all available data from SJIA patients support extrapolation of canakinumab PK from pediatric (SJIA) to adult (AOSD) patients. It can be expected that both populations would be exposed to a similar range of canakinumab exposures with the currently recommended dosing regimen for SJIA.

2.4. Clinical efficacy

A pooled analyses of data from the clinical development program for SJIA was conducted in order to show that the efficacy and safety of canakinumab in older ‘adult’ SJIA patients (≥16 years) are consistent with those in younger patients.

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

Efficacy data up to 12 weeks of exposure from the SJIA studies G2305, G2301 (excluding patients from the study A2203 who rolled over into G2301), and G2301E1 were submitted in support of this application the analysis; only data from canakinumab-treated patients were included (Full analysis set); data from patients who received placebo in study G2305 were excluded.

A brief outline of the design of these studies is included in Section 2.3.2 of this report.

Definition of subgroups for efficacy analysis

The following age subgroup categories were defined:

- Childhood SJIA: 2 - <12 years old
- Adolescent SJIA: 12 - <16 years old
- Adults: ≥16 years old

Patients were divided in age subgroups at the time of their enrolment into the study.

The demographic and disease characteristics at baseline are shown in **Table 7**.

Table 7. Baseline demographic and disease characteristics by age group from studies G2305, G2301 and G2301E1 for patients treated with canakinumab (Full analysis set)

		2 to <12 years N = 216	12 to <16 years N = 56	≥16 years N = 29
Sex - n (%)	Male	91 (42.1)	22 (39.3)	13 (44.8)
	Female	125 (57.9)	34 (60.7)	16 (55.2)
Age (years)	Mean (SD)	6.3 (2.71)	13.3 (1.18)	17.1 (0.95)
	Median (Min–Max)	6.0 (1-11)	13.0 (12-15)	17.0 (16-19)
Race - n/N (%)	Caucasian	190 (88.0)	46 (82.1)	26 (89.7)
	Black	5 (2.3)	5 (8.9)	1 (3.4)
	Asian	3 (1.4)	2 (3.6)	1 (3.4)
	Other	18 (8.3)	3 (5.4)	1 (3.4)
Ethnicity - n/N (%)	Hispanic/Latino	27 (12.5)	5 (8.9)	2 (6.9)
	Chinese	1 (0.5)	0	1 (3.4)
	Indian (subcontinent)	0	1 (1.8)	0
	Mixed Ethnicity	7 (3.2)	2 (3.6)	2 (6.9)
	Other	181 (83.8)	48 (85.7)	24 (82.8)
Weight (kg)	Mean	23.49	52.89	64.00
Height (cm)	Mean	114.3	152.4	164.0
BMI (kg/m^2)	Mean (SD)	17.17 (2.727)	22.15 (5.252)	23.67 (5.496)
Disease duration (n/%)	≤6 months >6 months to <4 years ≥4 years	48 (22.2) 119 (55.1) 49 (22.7)	6 (10.7) 23 (41.1) 27 (48.2)	1 (3.4) 8 (27.6) 20 (69.0)
Level of C-reactive protein at baseline (standardized in mg/L)	Mean (SD)	164.54 (137.217)	190.06 (170.271)	143.83 (154.389)
	Median	133.90	149.00	104.70
	Min–Max	0.0-800.0	3.0-683.3	1.6-651.2
Steroid (oral) free at BL	Yes, n (%)	70 (32.4)	21 (37.5)	11 (37.9)
Prednisone (oral) equivalent dose at baseline (mg/kg/day)	n	146	35	18
	Mean (SD)	0.700 (1.6263)	1.753 (6.0669)	0.271 (0.2653)
	Median	0.375	0.200	0.185
	Min–Max	0.02-12.50	0.05-27.00	0.02-1.00
NSAID free at baseline	Yes, n (%)	95 (44.0)	26 (46.4)	17 (58.6)
Methotrexate free at BL	Yes, n (%)	100 (46.3)	34 (60.7)	17/29 (58.6)
Physician's global assessment of disease activity (VAS, mm)	Mean (SD)	62.1 (20.94)	61.5 (21.05)	64.4 (17.82)
	Median	64.0	62.5	63.0
	Min–Max	1-100	1-100	28-100
Parent's / Patient's global assessment of overall well being (VAS, mm)	n	216	55	29
	Mean (SD)	56.1 (27.69)	56.3 (24.85)	57.4 (27.20)
	Median (Min–Max)	60.0 (0-100)	60.0 (0-98)	59.0 (0-98)
Number of active joints	Mean (SD)	13.0 (12.85)	13.8 (13.07)	12.5 (14.56)
	Median (Min–Max)	8.0 (0-66)	8.0 (2-55)	8.0 (0-58)
Number of joints with limitation of motion	Mean (SD)	12.2 (13.02)	13.0 (13.34)	12.0 (15.26)
	Median (Min–Max)	7.0 (0-62)	7.5 (0-55)	7.0 (0-56)

BL = baseline; VAS = visual analogue scale; BMI = Body Mass Index: BMI (kg/m^2) = weight(kg)/[(height(cm)/100)^2]. Based on baseline values of height and weight
C-reactive protein level standardized to the range 0-10 mg/L and measured pre-dose.

Efficacy variables

Adapted American College of Rheumatology (ACR) Pediatric 30/50/70/90/100 response
Responses were defined as improvement from baseline of at least 30%/50%/70%/90%/ 100% in at least 3 of the response variables 1 to 6 (see below) and no intermittent fever, i.e. body temperature ≤ 38°C, in the preceding week (variable 7), with no more than one variable of 1-6 worsening by more than 30%.

Adapted ACR Pediatric 30, 50, 70, 90, 100 response variables (ACR components):

1. Physician's Global Assessment of disease activity on a 0-100 mm visual analog scale (VAS) from 0 mm = no disease activity to 100 mm = very severe disease activity.

2. Parent's or patient's (if appropriate by age) Global Assessment of patient's overall wellbeing on a 100 mm VAS from 0 mm = very well to 0-100 mm = very poor.

3. Functional ability: Childhood Health Assessment Questionnaire (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: C-reactive protein (CRP; standardized mg/L)

7. Absence of intermittent fever due to SJIA (body temperature ≤ 38°C only for several hours during the day) during the preceding week ACR 30 responder: response according to the adapted ACR Pediatric 30 criteria (yes/no), and similarly, for ACR 50, ACR 70, ACR 90 and ACR 100.

Juvenile Idiopathic Arthritis (JIA) ACR 30/50/70/90/100 response

Improvement from baseline of at least 30%/50%/70%/90%/100% in at least 3 of the response variables 1 to 6 (see above) with no more than one of the ACR core components (variables 1- 6) worsening by more than 30%. An ACR response is derived if the underlying criteria are fully conclusive for the overall measure and set to missing otherwise, as outlined in **Table 8**.

Table 8. Calculation of ACR 30/50/70/90/100 criteria

Priority	Number of criteria worsening >30%	Number of criteria improving >30%/50%/70%/90%/100%	Number of missing criteria	Adapted ACR Pediatric 30/50/70/90/100 responder
1	≥2			No
2	≤1	≥3	0	Yes
2	≤1	<3	0	No
3	0	0	≤2	No
3	0	1	≤1	No
3	0	≥3	≤1	Yes
3	1	0	≤2	No
3	1	1	≤1	No

If one of the response variables 1 to 6 (Physician's Global Assessment, Parents or patient's Global Assessment, numbers of active joints, number of joints with limitation of motion, CRP, CHAQ) is 0 at baseline and greater than 0 at a later visit then worsening is taken as 100%.

C-reactive protein normalization

CRP levels were measured at local laboratories and CRP values were therefore standardized to a normal range of 0-10 mg/L. CRP (standardized in mg/L) was categorized as 'Normal' if the value was <10 mg/L and as 'Elevated' otherwise. Due to some issues with standardization, some values could be negative. These were set to missing.

Childhood Health Assessment Questionnaire, CHAQ

- CHAQ was used to assess physical ability and functional status of patients as well as quality of life. The disability dimension consists of 20 multiple choice items concerning difficulty in performing eight common activities of daily living; dressing and grooming, arising, eating, walking, reaching, personal hygiene, gripping and activities. Patients choose from four response categories, ranging from 'without any difficulty' (score 0) to 'unable to do' (score 3).
- Within each of the 8 categories, only the item indicating the most severe impairment contributed to the category score.
- If the patient required the use of aids, devices, or help from another to accomplish any of the activities in an associated category, then the score for that category was assigned the value 2, unless the score was already 3 (i.e. the scores of 0 or 1 were increased to 2).
- From the scores for each category, a Standard Disability Index (SDI) was computed by summing the computed scores for each category and dividing by the number of categories answered.
- The SDI was not computed if the patient did not have the scores for at least 6 categories. This SDI is the CHAQ score, which was used in the statistical analyses of this instrument. The range for this score is (0, 3).
- The 'Other' option was excluded in the calculation of the CHAQ score.

Other endpoints

Inactive disease was defined as no joints with active arthritis; no fever (body temperature ≤38°C), no rheumatoid rash, serositis, splenomegaly, hepatomegaly or generalized lymphadenopathy attributable to JIA; normal ESR or CRP; a Physician's Global Assessment of disease activity indicating no disease activity (i.e. best possible score ≤10 mm).

28-point Disease Activity Score (DAS-28) CRP at Baseline, Day 15, Day 29, Day 57, Day 85

Outcomes and estimation

The main efficacy parameters are summarised for Day 15 and Day 85 in **Table 9**.

Table 9. Summary of efficacy response at Days 15 and 85, by efficacy parameter and age group from studies G2305, G2301 and G2301E1 for patients treated with canakinumab (Full analysis set)

		Age group		
Efficacy endpoint	**Time point**	**2 to <12 years N = 216**	**12 to <16 years N = 56**	**≥16 years N = 29**
ACR pediatric response				
Missing assessment	Day 15	6/216 (2.8%)	3/56 (5.4%)	2/29 (6.9%)
Non-Responders		52/216 (24.1%)	6/56 (10.7%)	2/29 (6.9%)
ACR≥ 30		158/216 (73.1%)	47/56 (83.9%)	25/29 (86.2%)
ACR≥ 70		109/216 (50.5%)	33/56 (58.9%)	19/29 (65.5%)
ACR 100		46/216 (21.3%)	15/56 (26.8%)	4/29 (13.8%)
Missing assessment	Day 85*	8/133 (6.0%)	3/27 (11.1%)	0/18 (0.0%)
Non-Responders		35/133 (26.3%)	4/27 (14.8%)	3/18 (16.7%)
ACR≥ 30		90/133 (67.7%)	20/27 (74.1%)	15/18 (83.3%)
ACR≥ 70		77/133 (57.9%)	18/27 (66.7%)	13/18 (72.2%)
ACR 100		42/133 (31.6%)	8/27 (29.6%)	4/18 (22.2%)
Number of active joints				
Median (range)	Baseline	n=216 8.0 (0 - 66)	n=56 8.0 (2 - 55)	n=29 8.0 (0 - 58)
Change from baseline	Day 15	n=211 -4.0 (-39 - 26)	n=54 -6.5 (-39 - 0)	n=28 -6.5 (-22 - 0)
Change from baseline	Day 85	n=100 -5.0 (-50 - 5)	n=20 -9.5 (-43 - -2)	n=16 -8.0 (-30 - -2)
Number of joints with limitation of motion				
Median (range)	Baseline	n=216 7.0 (0 - 62)	n=56 7.5 (0 - 55)	n=29 7.0 (0 - 56)
Change from baseline	Day 15	n=211 -3.0 (-34 - 28)	n=54 -4.0 (-36 - 13)	n=28 -5.0 (-19 - 0)
Change from baseline	Day 85	n=100 -5.0 (-49 - 5)	n=20 -8.0 (-37 - 3)	n=16 -6.5 (-29 - 2)
C-reactive protein levels				
Median (range)	Baseline	n=216 133.9 (0.0 - 800.0)	n=56 149.0 (3.0 - 683.3)	n=28 104.7(1.6 - 651.2)
Change from baseline	Day 15	n=211 -70.0 (-790.0 - 180.0)	n=55 -96.7 (-630.0 - 30.0)	n=26 76.5 (-649.8 - 0.0)
Change from baseline	Day 85	n=168 -98.3 (-707.0 - 312.0)	n=45 -102.0 (-630.0 - 33.3)	n=23 -113.3 (-649.4 - 4.0)
Physician's Global Assessment of disease activity				
Median (range)	Baseline	n=216 64.0 (1 - 100)	n=59 62.5 (1 - 100)	n=29 63.0 (28 - 100)
Change from baseline	Day 15	n=210 -37.0 (-94 - 37)	n=55 -46.0 (-96 - 11)	n=28 -50.5 (-78 - -9)
Change from baseline	Day 85	n=100 -55.0 (-98 - 6)	n=20 -70.0 (-100 - -23)	n=16 -67.5 (-85 - -18)
CHAQ disability score				
Median (range)	Baseline	n=216 1.63 (0.0 - 3.0)	n=55 1.75 (0.0 - 3.0)	n=29 1.63 (0.0 - 2.8)
Change from baseline	Day 15	n=209 -0.50 (-3.0 - 2.1)	n=54 -0.63 (-2.9 - 0.3)	n=27 -0.75 (-2.3 - 1.5)
Change from baseline	Day 85	n=100 -1.00 (-2.8 - 0.6)	n=20 -1.75 (-2.9 - 0.0)	n=16 -1.13 (-2.8 - 0.1)

ACR pediatric response is calculated as improvement from baseline
*ACR response was not collected at day 85 for G2301E1 cohort 2 patients, therefore patients from G2301E1 Cohort 2 are excluded from the denominator at day 85.
ACR=American College of Rheumatology, CHAQ= Child Health Assessment Questionnaire

DAS-28 (CRP) scores by age group showed similar changes in at Day 15 (median changes from baseline were -2.10 in the 2 to <12 years age group, -2.53 in the 12 to <16 years age group, and -2.37 in the adult subgroup). Median changes from baseline at Day 85 were also similar between the 12 to <16 years and adult age groups (-3.76 and - 3.50, respectively), but smaller in the 2 to <12 years age group (-2.64).

The proportion of patients with inactive disease is shown by age group and time point in **Table 10**.

Table 10. Proportion of patients with inactive disease, by age group and time point from studies G2305, G2301 and G2301E1 for patients treated with canakinumab (Full analysis set)

		Patients with inactive disease n/N (%)		
Timepoint		2-<12 years N = 216	12-<16 years N = 56	≥16 years N = 29
Day 15	Missing	5/216 (2.3)	2/56 (3.6)	1/29 (3.4)
	Yes	40/216 (18.5)	18/56 (32.1)	6/29 (20.7)
	No	171/216 (79.2)	36/56 (64.3)	22/29 (75.9)
Day 29	Missing	22/216 (10.2)	2/56 (3.6)	1/29 (3.4)
	Yes	61/216 (28.2)	18/56 (32.1)	12/29 (41.4)
	No	133/216 (61.6)	36/56 (64.3)	16/29 (55.2)
Day 57	Missing	41/216 (19.0)	5/56 (8.9)	3/29 (10.3)
	Yes	71/216 (32.9)	20/56 (35.7)	15/29 (51.7)
	No	104/216 (48.1)	31/56 (55.4)	11/29 (37.9)
Day 85*	Missing	36/133 (27.1)	7/27 (25.9)	2/18 (11.1)
	Yes	32/133 (24.1)	10/27 (37.0)	8/18 (44.4)
	No	65/133 (48.9)	10/27 (37.0)	8/18 (44.6)

n= number of patients who satisfy the criteria
Inactive disease is defined as no joints with active arthritis; no fever (body temperature ≤38 °C.), no rheumatoid rash, serositis, splenomegaly, hepatomegaly or generalized lymphadenopathy attributable to SJIA; normal CRP; a Physician's Global Assessment of disease activity indicating no disease activity (i.e. score ≤10 mm).
*Data were not available for G2301E1 Cohort 2 patients at Day 85 thus patients from G2301E1 Cohort 2 are excluded from the denominator at Day 85.

2.4.2. Discussion on clinical efficacy

In this pooled analysis submitted data from 301 patients were included. Of these, 29 patients were ≥16 at the time point of enrolment. This age group is in the main focus for the assessment of possible extrapolation from child data to adult efficacy and safety.

The baseline demographics and disease criteria did not differ in the three evaluated age cohorts; especially the severity of disease at baseline was very balanced between younger patients and the oldest cohort. No significant trend with age was seen in baseline values of IL-1β, C-reactive protein (CRP) and Disease Activity Score (DAS28) in SJIA patients.

The MAH presented a comparison of efficacy results in the three age groups (2->12 n=216, 12->16 n=56, ≥ 16n=29) for the ACR pediatric response, number of active joints, number of joints with limitation of motion, CRP levels , Physician' s global assessment of disease activity, and CHAQ disability score.

No major differences were observed in these clinically relevant efficacy endpoints between younger age groups and older age groups. A trend could of a slightly better response on treatment in the older age group ≥16.

Adapted ACR pediatric 30 response at Day 15 was achieved by 158/216 (73.1%) of subjects in the 2 - <12 years old group, 47/56 (83.9%) of subjects in the 12 - <16 years old group, and 25/29 (86.2%) of subjects in the ≥16 years old group. The corresponding JIA ACR 30 responses at Day 15 were 78.2%, 83.9% and 86.2%, respectively. The treatment was highly effective and the onset of response was rapid in all age groups, as ACR70 (both adopted ACR pediatric and JIA ACR) responses were reached by over half of the patients by Day 15.

The efficacy was well maintained in all age groups up to Day 85, with adapted ACR 30 responses of 67.7%, 74.1% and 83.3% in the age groups of 2 - <12 years, 12 - <16 years and ⩾16 years, respectively. The adapted ACR 100 pediatric responses were highest at Day 57 (31.5%, 33.9% and 34.5% in the age groups, respectively).

Changes from baseline in the seven ACR components were consistently similar or slightly greater in the ⩾ 16 years age group. Median CRP values were less than 10 mg/L, i.e., normal by Day 15 in the eldest age group, and within the normal range in all age groups by Day 57. Overall, similar or better responses were seen in the two older age groups compared to the youngest patients <12 years of age.

All 3 age groups also showed similar changes in DAS-28 (CRP) at Day 15 (median changes from baseline were -2.10 in the 2 - <12 years age group, -2.53 in the 12 - <16 years age group, and -2.37 in the ≥16 years age group). Median changes from baseline at Day 85 were also similar between the 12 - <16 years and ≥16 years age groups (-3.76 and - 3.50, respectively), but smaller in the 2 - <12 years age group (-2.64).

Treatment effect was sustained over the prolonged assessment period until day 85 also in each of the three age groups.

These results are supportive for the proposed change of indication to allow treatment in adults newly diagnosed with AOSD. However, as the subset of young adult SJIA patients aged 16 to 20 years which closer resmbles AOSD patients, the CHMP recommended that the MAH ensures that the results of a multicentre, placebo-controlled, 12-week, investigator-intiated trial of the efficacy, safety and tolerability of canakinumab in 68 AOSD patients is ongoing (ACZ885GDE01T/ NCT02204293) are submitted to the CHMP as soon as these are available.

2.4.3. Conclusions on the clinical efficacy

The results of the pooled analysis of 12 weeks efficacy data divided in three age groups are supportive for the proposed change of indication for the treatment of adults newly diagnosed with AOSD.

2.5. Clinical safety

Introduction

For this submission, analyses previously conducted for the SJIA submission were re-run using appropriate age cut-offs, in order to show whether safety are similar between children, adolescents and adults. The safety pooling datasets previously used for the SJIA submission were updated with data from study G2301E1.

For the previous SJIA submission, data from studies A2203, G2305 (canakinumab group only), G2301, and G2301E1 Cohort 1 (data up to 31-May-2012) were pooled to create one pooled database for safety. For the current analysis, complete data from G2301E1 were added, meaning complete data from Cohort 1 (roll-over patients from G2301 and G2305) and Cohort 2 (canakinumab-naïve patients at the start of the study).

Age subgroup categories were defined as follows:
- Childhood: 2-<12 years old
- Adolescent: 12-<16 years old
- Adult: ≥16 years old

Patient exposure

The difference between the SJIA pooled safety population ('Safety Set, **Table 11**) and the pooled efficacy population is the addition of Study A2203 containing a total of 23 patients. This dose-finding study had a differing dose regimen compared to the other three included studies, dosing upon relapse rather than at

prescribed regular intervals. The Safety set also contained non-canakinumab naïve patients unlike the FAS. Disease features were comparable among age groups, except for the expected shorter duration of disease in children.

Table 11. Overall duration of exposure, pooled SJIA population (Safety set)

	Age group		
	2-<12 years N=233	12-<16 years N=60	≥16 years N=31
Overall duration (days)			
n	233	60	31
Mean	804.2	637.3	888.8
Median	728.0	542.0	757.0
(Min–Max)	3-2661	5-1743	16-1938
Patient-years exposure	513.0	104.7	75.4
Overall duration – n (%)			
≥1 day	233 (100.0)	60 (100.0)	31 (100.0)
≥ 12 weeks	192 (82.4)	53 (88.3)	28 (90.3)
≥ 24 weeks	173 (74.2)	47 (78.3)	25 (80.6)
≥ 36 weeks	166 (71.2)	43 (71.7)	23 (74.2)
≥ 48 weeks	158 (67.8)	41 (68.3)	22 (71.0)
≥ 96 weeks	131 (56.2)	28 (46.7)	20 (64.5)
≥ 144 weeks	76 (32.6)	11 (18.3)	12 (38.7)
≥ 192 weeks	68 (29.2)	5 (8.3)	11 (35.5)

SJIA Studies A2203, G2305, G2301, G2301E1. The exposure was calculated without adjusting for possible gaps between enrollment of patients in different studies.

Table 12 shows the numbers of canakinumab doses in each age group.

Table 12. Number of doses of canakinumab (Safety Set)

	Age group		
	2-<12 years N=233	12-<16 years N=60	≥16 years N=31
Number of canakinumab doses			
n	233	60	31
Mean	27.5	21.8	30.3
(S.D.)	22.01	16.84	23.77
Median	26.0	17.5	26.0
(Min–Max)	1-75	1-63	1-67

SJIA Studies A2203, G2305, G2301, G2301E1. Placebo doses administered to patients in part II of G2301 are included in the count.

Median exposure in the SJIA patients was lower (542 days) in the 12 to <16 years age group than in the 2 to <12 years age group (728 days) and the ⩾ 16 years age group (757 days).

Adverse events

Adverse events in the SJIA population are presented by primary SOCs and age group in **Table 13**.

Table 13. Adverse events by primary System Organ Class and Age Group (Safety Set)

	n (%) patients		
Primary system organ class	2-<12 years N = 233	12-<16 years N = 60	≥16 years N = 31
No. of patients with at least 1 AE	202 (86.7)	53 (88.3)	27 (87.1)
Infections and infestations	176 (75.5)	42 (70.0)	23 (74.2)
Gastrointestinal disorders	122 (52.4)	32 (53.3)	18 (58.1)
Musculoskeletal and connective tissue disorders	119 (51.1)	33 (55.0)	16 (51.6)
Skin and subcutaneous tissue disorders	108 (46.4)	25 (41.7)	13 (41.9)
Respiratory, thoracic and mediastinal disorders	98 (42.1)	25 (41.7)	10 (32.3)
General disorders and administration site conditions	91 (39.1)	22 (36.7)	14 (45.2)
Injury, poisoning and procedural complications	71 (30.5)	17 (28.3)	5 (16.1)
Nervous system disorders	64 (27.5)	24 (40.0)	12 (38.7)
Investigations	55 (23.6)	15 (25.0)	9 (29.0)
Blood and lymphatic system disorders	44 (18.9)	15 (25.0)	8 (25.8)
Eye disorders	30 (12.9)	7 (11.7)	2 (6.5)
Ear and labyrinth disorders	22 (9.4)	7 (11.7)	4 (12.9)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	22 (9.4)	4 (6.7)	3 (9.7)
Immune system disorders	19 (8.2)	1 (1.7)	3 (9.7)
Psychiatric disorders	18 (7.7)	6 (10.0)	5 (16.1)
Hepatobiliary disorders	15 (6.4)	6 (10.0)	3 (9.7)
Metabolism and nutrition disorders	15 (6.4)	5 (8.3)	1 (3.2)
Reproductive system and breast disorders	11 (4.7)	5 (8.3)	7 (22.6)
Vascular disorders	11 (4.7)	4 (6.7)	4 (12.9)
Renal and urinary disorders	10 (4.3)	6 (10.0)	1 (3.2)
Cardiac disorders	9 (3.9)	5 (8.3)	1 (3.2)
Endocrine disorders	3 (1.3)	1 (1.7)	0 (0.0)
Congenital, familial and genetic disorders	1 (0.4)	1 (1.7)	0 (0.0)
Social circumstances	1 (0.4)	0 (0.0)	0 (0.0)

Primary system organ classes are sorted by descending frequency in the 2-<12 years age group.
A patient with multiple occurrences of an AE is counted only once in the AE category.

Adverse events by preferred term

AEs by preferred term are presented for the SJIA population. The most frequent AEs (reported for at least 5% of patients in any age group) are shown for each age group in **Table 14**.

Table 14. Most common adverse events (at least 10% in any age group) by preferred term and age group (Safety Set)

	n (%) patients		
Preferred term	2-<12 years N = 233	12-<16 years N = 60	≥16 years N = 31
Cough	70 (30.0)	13 (21.7)	6 (19.4)
Pyrexia	69 (29.6)	14 (23.3)	8 (25.8)
Nasopharyngitis	68 (29.2)	18 (30.0)	13 (41.9)
Upper respiratory tract infection	62 (26.6)	9 (15.0)	6 (19.4)
Rhinitis	58 (24.9)	8 (13.3)	10 (32.3)
Vomiting	56 (24.0)	12 (20.0)	3 (9.7)
Juvenile idiopathic arthritis	55 (23.6)	17 (28.3)	6 (19.4)
Abdominal pain	51 (21.9)	9 (15.0)	7 (22.6)
Gastroenteritis	50 (21.5)	9 (15.0)	5 (16.1)
Arthralgia	49 (21.0)	17 (28.3)	8 (25.8)
Diarrhoea	48 (20.6)	9 (15.0)	7 (22.6)
Headache	45 (19.3)	17 (28.3)	9 (29.0)
Oropharyngeal pain	42 (18.0)	10 (16.7)	5 (16.1)
Pharyngitis	39 (16.7)	2 (3.3)	1 (3.2)
Pain in extremity	34 (14.6)	8 (13.3)	3 (9.7)
Eczema	32 (13.7)	6 (10.0)	2 (6.5)
Rash	32 (13.7)	4 (6.7)	4 (12.9)
Abdominal pain upper	30 (12.9)	6 (10.0)	8 (25.8)
Bronchitis	25 (10.7)	2 (3.3)	0 (-)
Nausea	20 (8.6)	12 (20.0)	9 (29.0)
Respiratory tract infection	16 (6.9)	4 (6.7)	4 (12.9)
Histiocytosis haematophagic	13 (5.6)	7 (11.7)	3 (9.7)
Influenza	13 (5.6)	4 (6.7)	4 (12.9)
Arthritis	12 (5.2)	7 (11.7)	1 (3.2)
Viral upper respiratory tract infection	12 (5.2)	2 (3.3)	4 (12.9)
Back pain	10 (4.3)	9 (15.0)	2 (6.5)
Joint swelling	10 (4.3)	2 (3.3)	4 (12.9)
Rhinorrhoea	9 (3.9)	1 (1.7)	5 (16.1)
Urinary tract infection	8 (3.4)	6 (10.0)	5 (16.1)
Sinusitis	8 (3.4)	0 (-)	4 (12.9)
Folliculitis	2 (0.9)	0 (-)	4 (12.9)

Preferred terms are sorted by descending frequency in the 2 to <12 age subgroup.
A patient with multiple occurrences of an AE is counted only once in the AE category.

Exposure adjusted incidence rates of the most common AEs are presented for the SJIA population by SOC in **Table 15**.

Table 15. Exposure adjusted incidence rate of adverse events in SJIA patients by primary system organ class (Safety Set)

System organ class Preferred term	No. of events/Rate per 100 patient-years 2-<12 years N=233 Total exposure 513.426 pt-years	 12-<16 years N=60 Total exposure 104.769 pt-years	 ≥16 years N=31 Total exposure 75.439 pt-years
Any AE	4376 (852.3)	835 (797.0)	525 (695.9)
Infections and infestations	1282 (249.7)	164 (156.5)	145 (192.2)
Gastrointestinal disorders	618 (120.4)	104 (99.3)	77 (102.1)
Musculoskeletal and connective tissue disorders	507 (98.7)	161 (153.7)	58 (76.9)
Respiratory, thoracic and mediastinal disorders	458 (89.2)	54 (51.5)	39 (51.7)
Skin and subcutaneous tissue disorders	295 (57.5)	58 (55.4)	37 (49.0)
General disorders and administration site conditions	257 (50.1)	56 (53.5)	27 (35.8)
Nervous system disorders	246 (47.9)	68 (64.9)	39 (51.7)
Injury, poisoning and procedural complications	188 (36.6)	30 (28.6)	17 (22.5)
Investigations	145 (28.2)	38 (36.3)	26 (34.5)
Blood and lymphatic system disorders	86 (16.8)	24 (22.9)	15 (19.9)
Eye disorders	54 (10.5)	10 (9.5)	2 (2.7)
Ear and labyrinth disorders	47 (9.2)	11 (10.5)	6 (8.0)
Immune system disorders	29 (5.6)	1 (1.0)	3 (4.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	26 (5.1)	5 (4.8)	5 (6.6)
Vascular disorders	26 (5.1)	5 (4.8)	7 (9.3)
Psychiatric disorders	23 (4.5)	11 (10.5)	6 (8.0)
Hepatobiliary disorders	23 (4.5)	6 (5.7)	3 (4.0)
Metabolism and nutrition disorders	23 (4.5)	6 (5.7)	2 (2.7)
Reproductive system and breast disorders	13 (2.5)	8 (7.6)	8 (10.6)
Cardiac disorders	13 (2.5)	5 (4.8)	1 (1.3)
Renal and urinary disorders	12 (2.3)	8 (7.6)	2 (2.7)
Endocrine disorders	3 (0.6)	1 (1.0)	0 (-)
Congenital, familial and genetic disorders	1 (0.2)	1 (1.0)	0 (-)
Social circumstances	1 (0.2)	0 (-)	0 (-)

Studies A2203, G2305, G2301, G2301E1
Primary system organ classes are sorted alphabetically
n = Number of events
The incidence rate per 100 patient-years is 100 times (total number of occurrence of events divided by patient-years), calculated per SOC level
Patient-years is the total time at risk in years. It is the sum of all patient's times at risk, i.e. duration of exposure is calculated from the onset start day to the last exposure day
Source: Table 2.1-10a1

Serious adverse event / deaths / other significant events

Deaths

In the SJIA population, one patient died in Study G2301 in the 12-16 years age group due to pulmonary hypertension that was associated with macrophage activation syndrome (MAS). In addition, one patient from Cohort 1 of Study G2301E1 died approximately 3 months after discontinuation from the study.

Other serious adverse events

The most common SAEs (more than 1 patient in any age group) are summarized in **Table 16**.

Table 16. Serious adverse events by system organ class, most common preferred term (more than 1 patient in any age group) and age group (Safety set)

	n (%) patients		
System organ class Preferred term	**2-<12 years** **N = 233**	**12-<16 years** **N = 60**	**≥16 years** **N = 31**
Patient with at least 1 SAE	81 (34.8)	25 (41.7)	9 (29.0)
Infections and infestations			
Total	36 (15.5)	12 (20.0)	3 (9.7)
Cytomegalovirus infection	0 (-)	0 (-)	2 (6.5)
Gastroenteritis	5 (2.1)	3 (5.0)	0 (-)
Gastrointestinal viral infection	2 (0.9)	0 (-)	0 (-)
Lymph node abscess	2 (0.9)	0 (-)	0 (-)
Pharyngitis	2 (0.9)	0 (-)	0 (-)
Pneumonia	5 (2.1)	1 (1.7)	0 (-)
Scarlet fever	2 (0.9)	0 (-)	0 (-)
Subcutaneous abscess	2 (0.9)	0 (-)	0 (-)
Varicella	5 (2.1)	0 (-)	0 (-)
Musculoskeletal and connective tissue disorders			
Total	28 (12.0)	9 (15.0)	5 (16.1)
Arthralgia	2 (0.9)	1 (1.7)	0 (-)
Juvenile idiopathic arthritis	21 (9.0)	7 (11.7)	4 (12.9)
Polyarthritis	2 (0.9)	0 (-)	0 (-)
Blood and lymphatic system disorders			
Total	21 (9.0)	8 (13.3)	4 (12.9)
Anaemia	2 (0.9)	0 (-)	0 (-)
Histiocytosis haematophagic	12 (5.2)	7 (11.7)	3 (9.7)
Leukopenia	2 (0.9)	1 (1.7)	1 (3.2)
Lymphadenitis	4 (1.7)	0 (-)	0 (-)
Lymphadenopathy	4 (1.7)	1 (1.7)	0 (-)
Thrombocytopenia	2 (0.9)	0 (-)	0 (-)
Gastrointestinal disorders			
Total	11 (4.7)	3 (5.0)	2 (6.5)
Abdominal pain	5 (2.1)	0 (-)	1 (3.2)
Nausea	2 (0.9)	0 (-)	0 (-)
General disorders and administration site conditions			
Total	11 (4.7)	6 (10.0)	1 (3.2)
Drug ineffective	0 (-)	2 (3.3)	0 (-)
Pyrexia	7 (3.0)	5 (8.3)	1 (3.2)
Investigations			
Total	9 (3.9)	1 (1.7)	1 (3.2)
Alanine aminotransferase increased	2 (0.9)	0 (-)	0 (-)
Aspartate aminotransferase increased	2 (0.9)	0 (-)	0 (-)
C-reactive protein increased	2 (0.9)	0 (-)	0 (-)
Hepatic enzyme increased	4 (1.7)	0 (-)	0 (-)
Skin and subcutaneous tissue disorders			
Total	9 (3.9)	3 (5.0)	0 (-)
Dermatitis allergic	2 (0.9)	1 (1.7)	0 (-)
Rash	3 (1.3)	0 (-)	0 (-)
Injury, poisoning and procedural complications			
Total	7 (3.0)	2 (3.3)	0 (-)
Post procedural haemorrhage	2 (0.9)	0 (-)	0 (-)
Traumatic fracture	2 (0.9)	0 (-)	0 (-)
Respiratory, thoracic and mediastinal disorders			
Total	6 (2.6)	2 (3.3)	0 (-)
Hepatobiliary disorders			
Total	5 (2.1)	1 (1.7)	0 (-)
Hepatitis	2 (0.9)	1 (1.7)	0 (-)

System organ class Preferred term	n (%) patients 2-<12 years N = 233	 12-<16 years N = 60	 ≥16 years N = 31
Injury, poisoning and procedural complications			
Total	7 (3.0)	2 (3.3)	0 (-)
Post procedural haemorrhage	2 (0.9)	0 (-)	0 (-)
Traumatic fracture	2 (0.9)	0 (-)	0 (-)
Respiratory, thoracic and mediastinal disorders			
Total	6 (2.6)	2 (3.3)	0 (-)
Hepatobiliary disorders			
Total	5 (2.1)	1 (1.7)	0 (-)
Hepatitis	2 (0.9)	1 (1.7)	0 (-)
Nervous system disorders			
Total	4 (1.7)	3 (5.0)	0 (-)
Paraesthesia	2 (0.9)	0 (-)	0 (-)
Cardiac disorders			
Total	2 (0.9)	3 (5.0)	0 (-)
Pericarditis	0 (-)	2 (3.3)	0 (-)
Immune system disorders			
Total	2 (0.9)	0 (-)	0 (-)
Drug hypersensitivity	2 (0.9)	0 (-)	0 (-)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Total	2 (0.9)	0 (-)	0 (-)
Psychiatric disorders			
Total	2 (0.9)	1 (1.7)	0 (-)
Renal and urinary disorders			
Total	2 (0.9)	1 (1.7)	0 (-)
Vascular disorders			
Total	1 (0.4)	0 (-)	0 (-)
Haematoma	1 (0.4)	0 (-)	0 (-)
Reproductive system and breast disorders			
Total	0 (-)	1 (1.7)	0 (-)

Primary system organ classes are sorted by descending frequency in the 2-<12 years age group.
A patient with multiple occurrences of an AE is counted only once in the AE category.
A subject with multiple AEs within a primary system organ class is counted only once in the total row.

The total exposure-adjusted rate of SAEs was lowest in the adult age group are presented in **Table 17**.

Table 17. Exposure adjusted incidence rate of most frequent serious adverse events in SJIA patients by primary system organ class (Safety Set)

System organ class	No. of events/Rate per 100 patient-years 2-<12 years N=233 Total exposure 513.426 pt-years	 12-<16 years N=60 Total exposure 104.769 pt-years	 ≥16 years N=31 Total exposure 75.439 pt-years
Any SAE	238 (46.4)	78 (74.4)	23 (30.5)
Infections and infestations	66 (12.9)	15 (14.3)	3 (4.0)
Musculoskeletal and connective tissue disorders	37 (7.2)	12 (11.5)	10 (13.3)
Blood and lymphatic system disorders	32 (6.2)	10 (9.5)	6 (8.0)
Investigations	20 (3.9)	1 (1.0)	1 (1.3)
Gastrointestinal disorders	17 (3.3)	6 (5.7)	2 (2.7)
General disorders and administration site conditions	14 (2.7)	8 (7.6)	1 (1.3)
Skin and subcutaneous tissue disorders	10 (1.9)	5 (4.8)	0 (-)
Injury, poisoning and procedural complications	10 (1.9)	2 (1.9)	0 (-)
Hepatobiliary disorders	8 (1.6)	1 (1.0)	0 (-)
Respiratory, thoracic and mediastinal disorders	7 (1.4)	4 (3.8)	0 (-)
Nervous system disorders	5 (1.0)	5 (4.8)	0 (-)
Renal and urinary disorders	3 (0.6)	1 (1.0)	0 (-)
Cardiac disorders	2 (0.4)	3 (2.9)	0 (-)

Psychiatric disorders	2 (0.4)	3 (2.9)	0 (-)
Immune system disorders	2 (0.4)	0 (-)	0 (-)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (0.4)	0 (-)	0 (-)
Vascular disorders	1 (0.2)	0 (-)	0 (-)
Reproductive system and breast disorders	0 (-)	2 (1.9)	0 (-)

Studies A2203, G2305, G2301, G2301E1
Primary system organ classes are sorted by frequency in the 2 - <12 years age group
n = Number of events
The incidence rate per 100 patient-years calculated per SOC level is (total number of events divided by patient-years) x 100
Patient-years is the total time at risk in years. It is the sum of all patient's times at risk, i.e. duration of exposure is calculated from the onset start day to the last exposure day

Laboratory findings

Hematology

Changes from baseline in absolute neutrophil count, direct platelet count, hemoglobin and white blood cell count were summarized by age group (data not shown). The changes observed were consistent with the known safety profile and mechanism of action of canakinumab. There were no clinically meaningful differences in changes from baseline across age groups.

Clinical chemistry

Changes from baseline in aspartate transaminase (AST), alanine transaminase (ALT), creatinine clearance, total bilirubin, total cholesterol and triglycerides in the SJIA population were summarized (data not shown). There were no clinically meaningful differences in changes from baseline across age groups.

Discontinuation due to adverse events

Table 18 summarizes AEs leading to discontinuation in SJIA patients by age group.

Table 18. Adverse events leading to study drug discontinuation by age group (Safety Set)

	n (%) patients		
Preferred term	**2-<12 years N = 233**	**12-<16 years N = 60**	**≥16 years N = 31**
At least one AE	26 (11.2)	10 (16.7)	6 (19.4)
Histiocytosis haematophagic	9 (3.9)	2 (3.3)	2 (6.5)
Juvenile idiopathic arthritis	7 (3.0)	3 (5.0)	4 (12.9)
Hepatitis	2 (0.9)	0 (-)	0 (-)
Polyarthritis	2 (0.9)	0 (-)	0 (-)
Pneumonia	1 (0.4)	1 (1.7)	0 (-)
Anaemia	1 (0.4)	0 (-)	0 (-)
Lymphadenitis	1 (0.4)	0 (-)	0 (-)
Uveitis	1 (0.4)	0 (-)	0 (-)
Oral disorder	1 (0.4)	0 (-)	0 (-)
Hepatocellular injury	1 (0.4)	0 (-)	0 (-)
Hepatomegaly	1 (0.4)	0 (-)	0 (-)
Measles	1 (0.4)	0 (-)	0 (-)
C-reactive protein increased	1 (0.4)	0 (-)	0 (-)
Hepatic enzyme increased	1 (0.4)	0 (-)	0 (-)
Platelet count increased	1 (0.4)	0 (-)	0 (-)
White blood cell count increased	1 (0.4)	0 (-)	0 (-)
Anaplastic large cell lymphoma T- and null-cell types	1 (0.4)	0 (-)	0 (-)
Superior sagittal sinus thrombosis	1 (0.4)	0 (-)	0 (-)
Respiratory failure	1 (0.4)	0 (-)	0 (-)

Preferred term	n (%) patients 2-<12 years N = 233	12-<16 years N = 60	≥16 years N = 31
Rash	1 (0.4)	0 (-)	0 (-)
Rash maculo-papular	1 (0.4)	0 (-)	0 (-)
Pyrexia	0 (-)	2 (3.3)	0 (-)
Coagulopathy	0 (-)	1 (1.7)	0 (-)
Pancytopenia	0 (-)	1 (1.7)	0 (-)
Pericarditis	0 (-)	1 (1.7)	0 (-)
Colitis	0 (-)	1 (1.7)	0 (-)
Vomiting	0 (-)	1 (1.7)	0 (-)
Serositis	0 (-)	1 (1.7)	0 (-)
Oesophageal candidiasis	0 (-)	1 (1.7)	0 (-)
Sepsis	0 (-)	1 (1.7)	0 (-)
Serum ferritin increased	0 (-)	1 (1.7)	0 (-)
Stenotrophomonas test positive	0 (-)	1 (1.7)	0 (-)
Intracranial pressure increased	0 (-)	1 (1.7)	0 (-)
Seizure	0 (-)	1 (1.7)	0 (-)
Somnolence	0 (-)	1 (1.7)	0 (-)
Polyuria	0 (-)	1 (1.7)	0 (-)
Pulmonary embolism	0 (-)	1 (1.7)	0 (-)
Pulmonary hypertension	0 (-)	1 (1.7)	0 (-)
Urticaria	0 (-)	1 (1.7)	0 (-)
Hypertension	0 (-)	1 (1.7)	0 (-)

Studies A2203, G2305, G2301, G2301E1
A subject with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment

Important Identified Risks and Important Potential Risks

The Important Identified Risks and Important Potential Risks defined in the canakinumab Risk Management Plan (RMP) were also assessed by age group. Among the important identified risks, the proportions of patients with infection AEs were similar across all three age groups. On the basis of the data available, patients aged ≥16 years do not appear to be at higher risk of opportunistic infections than younger patients. There were no patients with AEs corresponding to the identified risk "Neutropenia" in the ≥16 years age group. Events corresponding to the identified risk "Thrombocytopenia" appeared to be slightly less common in the ≥16 years age group, (9.7%) than in the 2 - <12 years age group (17.6%), although the proportion of patients with such events in the 12 - <16 years age group was lower (5.0%). The proportion of patients with at least 1 event corresponding to the identified risk "Leukopenia" appeared to be lower in the ≥16 years age group. There were no patients in the ≥16 years age group with events corresponding to the identified risk "Long-term effect on kidney function". Adverse events corresponding to the identified risk "Musculoskeletal pain and arthralgia", i.e. in the SOC "Musculoskeletal and connective tissue disorders" were reported in similar proportions of patients (51 to 55%) in each age group.

Among the important potential risks, the proportions of patients with AEs corresponding to the potential risk "Immunogenicity/allergenicity" were similar in all age groups, namely 24/233 (10.3%) in the 2 - <12 years age group, 10/60 (16.7%) in the 12 - <16 years age group, and 3/31 (9.7%) in the ≥16 years age group. No events corresponding to the potential risk "Autoimmunity reactions" were identified for any age group. There were 2 malignancies, both in the 2 - <12 age group. The ≥16 years age group appeared to have a higher rate than the other age groups of AEs identified by a broad initial screen as corresponding to the potential risk "Drug induced liver injury (DILI, hepatic transaminases and bilirubin elevations)", with 9/31 (29.0%) of patients having at least 1 such AE, compared with 35/233 (15.0%) of the 2 - <12 years age group and 10/60 (16.7%) of the 12 - <16 years age group. The difference appeared to be largely due to higher rates of laboratory abnormalities reported as AEs in the ≥16 years age group. The differences are probably exaggerated by the small sample size of the ≥16 years age group, with ALT increased and bilirubin increased reported for 3 and 2 patients, respectively. None of the patients with these AEs in the ≥16 years age group had severe events.

The proportion of patients with events corresponding to the potential risk "Disorders of lipoprotein metabolism" appeared to be higher in the ≥16 years age group 2/31 (6.5%) than in the younger age groups. For the potential risk "Vertigo/dizziness", the ≥16 years age group had a higher total rate of events (4/31, 12.9%) than the younger age groups, i.e. 3.4% in the 2 - <12 years age group and 5.0% in the 12 - <16 years age group). Of note, the SmPC already contains advice regarding driving and use of machinery in affected patients. There were no reports of events corresponding to the potential risk of "Canakinumab-immunosuppressants combination therapy toxicity" in any age group. Macrophage activation syndrome, identified by the MedDRA preferred term histiocytosis haematophagic, was reported in 13/233 (5.6%) of the 2 - <12 years age group, 7/60 (11.7%) of the 12 - <16 years age group and 3/31 (9.7%) of the ≥16 years age group; corresponding exposure-adjusted rates were 2.9, 6.7 and 6.6 events per 100 patient-years. No AEs corresponding to the potential risk of "Pulmonary complications: pulmonary hypertension and interstitial lung disease" were reported in patients aged ≥16 years.

Integrated immunogenicity report for patients with SJIA treated with canakinumab

This integrated immunogenicity report (IIR) summarizes data from the canakinumab SJIA development program, from clinical trials completed prior to 30 June 2015.

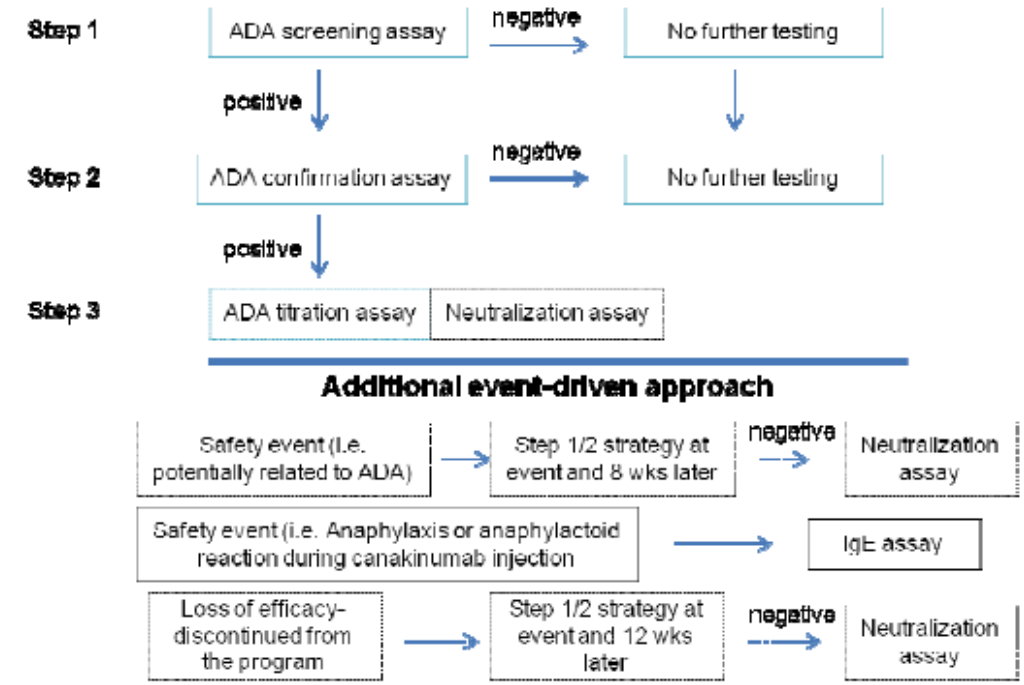
The IIR also describes the methodology and results of a revised assay to detect anti-canakinumab antibodies, which was used for samples from Study ACZ885G2301E1 (including re-testing of samples tested using the previous assay).

The strategy used to detect immunogenicity takes into consideration not only the results of ADA assays, but also other potential effects of immunogenicity, including effects on drug exposure/pharmacokinetics (changes in drug clearance); pharmacodynamic effects (changes in drug target binding); efficacy (impaired response to treatment); and some adverse events.

Methods and analysis

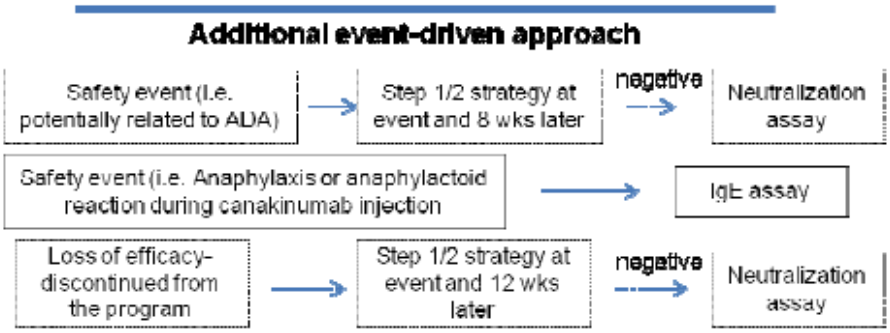
In 2010, the MAH developed a new assay for anti-canakinumab ADA detection with higher sensitivity, i.e. a bridging MSD assay. This bridging MSD assay was further improved by adding an acidic dissociation step to reach a better drug tolerance and used for clinical sample analysis from 2014.

Table 19. Flowchart of the immunogenicity testing strategy – original and as of October 2010



Dotted line shows the immunogenicity strategy as of October 2010, which include titration assay and neutralizing antibody assay.

Since there was no Anaphylaxis or anaphylactoid reaction during canakinumab injection in any of the clinical studies, IgE assay was not yet performed for samples collected.



Dotted line shows the immunogenicity strategy as of October 2010, which include titration assay and neutralizing antibody assay.

Since there was no Anaphylaxis or anaphylactoid reaction during canakinumab injection in any of the clinical studies, IgE assay was not yet performed for samples collected.

Observations of post-treatment ADAs were classified in three categories: transient, persistent or other:

- Transient: single ADA positive time-point(s) followed by ADA negative time-point(s)
- Persistent: two or more consecutive ADA positive time-points for an interval that spans >16 weeks
- Other: Patients with only one sample collected; patients with at least 2 samples collected at an interval <16 weeks due to study design; and other patients that do not fit into the definitions above of transient and persistent.

Results

The SJIA clinical program included a total of 324 canakinumab treated patients, with 281 patients receiving more than 1 dose of canakinumab. A total of 319 patients in the SJIA clinical program contributed to immunogenicity testing, and a total of 16 patients had ADA detected, per the assay used in each study. Out of these 16 patients, 11 patients had ADA detected at baseline only and thus are not considered as treatment-induced, while 5 had post-treatment ADA with no baseline ADA detected, representing an incidence of 1.6% (5/319) of positive ADA in canakinumab-treated SJIA patients (see **Table 20**).

Table 20. Summary overview of ADA incidence in SJIA program

		Post-treatment ADA			
	Baseline ADA	Transient	Persistent	Other	Neutralizing ADA
N	11	5	0	0	0

Of the post-treatment ADA patients, all were classified as having transient antibodies, as they occurred at single visits in all cases (**Table 21**). No neutralizing antibodies were detected in any of the SJIA patients. Since no events of anaphylaxis or anaphylactoid reactions were reported, IgE testing was not performed in any of the SJIA studies.

There were no obvious safety or efficacy clinical consequences for the patients who had ADA detected (**Table 21).**

In the 5 subjects who had post-treatment anti-drug antibody detected, the impact of ADA formation on the pharmacokinetics of canakinumab and IL-1β-canakinumab binding, as measured by total IL-1β, was examined. At the times when antibodies were detected, the observed trough canakinumab concentrations were comparable to other trough concentrations when there were no positive ADAs detected. This suggests no apparent impact of ADA formation on canakinumab pharmacokinetics. There was also no apparent impact of ADA formation on total IL-1β concentrations.

Table 21. ADA test results by time in SJIA patients with positive post-treatment anti-drug antibody titers (Safety data set)

Study Day	Canakinumab (µg/mL)	Total IL-1β (pg/mL)	ADA titer	Positive ADA	AE potentially related to immunogenicity[1]	Loss of Efficacy[2]
G2301-0131-00101/G2301E1-0131-00202; 17 years, male						
G2301					No	No
BL	0	0.51		No		
197	34.1	17.4		No		
225	32.7	14.4		NA		
283	NA	NA		No		
344	NA	NA		No		
367	NA	NA		No		
393	NA	NA		No		
477	NA	NA		No		
505	NA	NA		No		
533	NA	NA		No		
611	NA	NA		No		
633	NA	NA		No		
694	NA	NA	NR	Yes		
G2301E1					No	No
BL	NA	NA	NR	Yes		
171	20.7	22.5		No		
344	20.9	23.8		No		
428	20.2	14.4		No		
G2301-0023-00101/G2301E1-0023-00201; 6 years, female						
G2301					No	No
BL	0	0.0		No		
196	5.89	106	0.535	Yes		
G2301E1					No	Yes, Day 309*
BL	5.89	106	0.535	Yes		
169	8.25	86.1		No		
316	34.6	225		No		
G2301-0093-00102/G2301E1-0093-00202; 11 years, male						
G2301					No	No
BL	0	0.0		No		
193	14.3	55.5	0.768	Yes		
218	25.1	149		NA		
269	NA	NA		No		
297	39.2	141		No		
G2301E1					No	No
BL	39.2	141		No		
220	6.7	30		No		
371	30.2	56.4		No		
553	32.5	38.2		No		
776	14.1	16.4		No		
932	31.2	28		No		
1031	30.5	23.5		No		
1127	34.0	26.6		No		
1183	44.4	24.2		No		
G2301-513-00101/ G2301E1-0513-00201; 14 years, male						
G2301					No	No
BL	NA	NA	NA	NA		
198	9.96	39.80	0.857	Yes		
G2301E1					No	No
BL	9.96	39.80	0.857	Yes		
181	26.5	29.1		No		
377	22.5	22.1		No		
576	8.55	13.5		No		

756	29.4	20.5		No		
G2301-115-00108/G2301E1-0115-00203; 15 years, male						
G2301					No	No
BL	0	0.0		No		
187	13.1	35.3		No		
G2301E1					Eyelid oedema, Day 225	No
340	15.8	60.4	0.78	Yes		
512	22.7	40.2		No		
680	24.7	45.8		No		
764	20.4	39.7		No		
848	25.6	32.4		No		
1016	16.5	58.3		No		
1184	15.2	32.8		No		
1352	14.4	49.5		No		
1488	22.3	74.9		No		

Day is Day in the study at the time of measurement; counts restart in extension study
BL: baseline
NR: not reported
NA: not available
[1]As defined in Section 4.4 and described in Section 5.4
[2]As defined in Section 4.2 and described in Section 5.2
*Patient discontinued due to lack of efficacy, last dose on G2301E1 Day 309
Source: [Study G2301-Listing 16.2.6-1.13, Listing 16.2.6-1.14, Listing 16.2.8-1.4], [Study G2301E1-Listing 16.2.6-1.15, Listing 16.2.8-1.4, Listing 16.2.8-1.4], Table 5.4, Table 5.5

A total of 35 patients met the definition of loss of efficacy because they 1) showed initial response (≥adapted pediatric ACR30) on Day 15 in the study where they received their first dose of canakinumab; and 2) subsequently discontinued the program due to unsatisfactory therapeutic effect after becoming a non-responder at least 1 time point. These patients were assessed separately for ADA as well as indirect evidence of antibody production post-treatment.

Of the 35 patients with loss of efficacy, 32 had no ADA detected at any time, and 2 had ADA detected at baseline only. One patient had post-treatment ADA detected, at a single visit with 2 subsequent negative ADA assessments (including at the time of discontinuation); this patient discontinued due to unsatisfactory therapeutic effect over 300 days after the visit with positive ADA. AEs potentially related to immunogenicity/allergenicity: A total of 37 patients (24 aged 2 - <12 years, 10 aged 12 - <16 years, and 3 aged ≥16 years) and 51 AEs were retrieved using the search criteria. No anaphylaxis or anaphylactoid reaction AEs were reported. Three of the 37 patients experienced serious adverse events. SAEs in two of these patients (toxic skin eruption; and severe rash) were not considered as potentially related to immunogenicity/allergenicity due to canakinumab, as they had more plausible alternative explanations; immunogenicity/allergenicity could not be excluded as a possible cause in the third patient (urticaria and pyrexia), even though the SAE did not occur within 24 hours of a canakinumab dose.

Of the 37 patients with an AE potentially related to immunogenicity reported, 9 experienced a total of 10 AEs that qualified as immunogenicity-related (as previously defined). None of these 10 events were serious, and none led to study discontinuation. All 10 of the AEs were reported as mild. Of the 10 events, 7 resolved in between 1 and 51 days (resolution date not provided in 3 events). No action was taken in 2 events and 8 required concomitant medications. Of note, one patient experienced mild eyelid oedema and ADA were detected 83 days later. No ADA were detected at any time point in any other patient with potential allergenicity/immunogenicity AEs.

Post marketing experience

As reported in [PSUR 12] (cut-off date 30 Jun 2015) the estimated cumulative exposure from marketing experience was approximately 7000 patient treatment years (PTY) to cut off date 30 Jun 2015. Data are available from approximately 10,000 patients who are estimated to have been treated with canakinumab.

No new or changing safety signals have been identified in the reporting interval of this PSUR (PSUR 12; 01 Jan 2015 to 30 Jun 2015). The safety data remain in accord with the previous cumulative experience.

2.5.1. Discussion on clinical safety

The safety pooling dataset includes complete data from study G2301E1, including Cohort 1 with roll-over patients from G2301 and G2305 and cohort 2 with canakinumab-naïve patients. Similar to the efficacy analysis, analysis of safety has been performed in the age categories of children (2 - <12 years old), adolescents (12 - <16 years old) and adults (≥16 years old).

The pooled safety set consists of 324 patients. Exposure was greater in the younger age groups which is comprehensible. Patient number in the oldest age group is limited to 31 participants.

The important identified risks of canakinumab in the treatment of SJIA are infections, opportunistic infections, neutropenia, drug induced liver injury, decreased estimated creatinine clearance and proteinuria, and musculoskeletal pain and arthralgia.

The most frequent adverse events reported were in all three age groups infections and infestations, musculoskeletal and connective tissue disorders and gastrointestinal disorders. There was some variation between age groups in exposure-adjusted total rates of AEs across the SOCs, but no clear pattern could be distinguished caused also by the rather low patient number.

Some differences in frequency between age groups can be seen but overall the safety profile in older patients compared to younger age groups is balanced.

The exposure adjusted incidence rate of adverse events allows a better overview of the safety profile in the three age groups. The overall rate of AEs is the lowest in the oldest population. Differences in some of the preferred terms can be seen, which is often a result of the disease incidence in the age groups.

In the SJIA population, one patient died in Study G2301 due to pulmonary hypertension that was associated with macrophage activation syndrome (MAS). In addition, one patient from Cohort 1 of Study G2301E1 died approximately 3 months after discontinuation from the study.

In the first described death, a relationship to canakinumab treatment cannot be ruled out totally. The second death in a 10 year old female, non-responder to canakinumab, occurred 3 month after discontinuation of study drug and is regarded as not related.

SAEs were reported less frequently in the ≥16 years age group (9 patients; 29%, vs. 34.8% in the 2 - <12 years age group and 41.7% in the 12 - <16 years age group). Cytomegalovirus (CMV) infection was reported in 2 patients in this group vs. none in the younger patients. CMV infection is an identified risk (opportunistic infection). Cases of another identified risk, MAS (Histiocytosis haematophagic), were reported in all age groups, with slightly higher frequency in the older age groups (9.7-11.7%, vs. 5.2% in the 2 - <12 years age group).

The exposure adjusted incidence rates of serious adverse events suggest that the rate of AEs and SAEs is decreasing in the oldest age group, with the exception of musculoskeletal and connective tissue disorders. Otherwise, incidence rates of SAEs are rather balanced in the three age groups. Exposure-adjusted incidence rates of juvenile idiopathic arthritis and MAS tended to be higher in older age groups. These SAEs, along with cytomegalovirus infection, were the only SAEs that were more frequent in the ≥ 16 year age group. Serious adverse events, and in particular serious infections, were less frequent in patients aged ≥ 16 years.

Assessment of laboratory findings did not show any clinically relevant differences in changes from baseline across the three age groups.

Within the ≥16 years age group, the Important Identified Risks and Important Potential Risks were generally reported in similar or smaller numbers compared to the younger age groups, except for AEs corresponding to the potential risks of “Drug induced liver injury”, “Disorders of lipoprotein metabolism” and

"Vertigo/dizziness". Among laboratory findings (see above), the ≥16 years age group tended to show less increase in liver enzymes (ALT and AST) and more increase in bilirubin levels. None of the events were severe and there may also be some uncertainty due to the relatively small number of subjects in the highest age group. Regarding dizziness/vertigo, the SmPC section 4.7 already contains information regarding this AE and the corresponding advice regarding ability to drive and use machines.

The 2015 integrated immunogenicity report for SJIA is an update of the previous report from 2012. The updated report includes final data from Study ACZ885G2301E1 and overall data from 324 patients, of whom 319 provided immunogenicity data.

Immunogenicity data were not divided into the age groups due to the low numbers of detected ADA. Overall, 16 of the 319 patients contributing to immunogenicity testing in the SJIA clinical program had anti-canakinumab antibodies. Among the 16 patients, 11 patients had baseline positive ADA and 5 patients (1.6%) had post-treatment ADA. The post-treatment ADAs occurred at a single occasion and the titers were low. There were no apparent efficacy or safety related clinical consequences. No effect of antibody development on clinical efficacy was detected. No change in the immunogenicity profile of canakinumab is apparent. No SmPC update regarding immunogenicity has been proposed by the MAH and this is acceptable. The proportions of patients who discontinued due to AEs were higher in the older age groups. The most common AEs leading to discontinuation in all age groups were juvenile idiopathic arthritis , which is probably related to the background indication of the patients and MAS. These were both most common in the ≥16 year age group and were the only AEs that led to discontinuation in this age group.

MAS is an AE of great concern Still's disease and is monitored intensively through the Macrophage Activation Syndrome Adjudication Committee (MASCAC) which independently reviews evaluate pre-specified AEs or laboratory values that could potentially indicate MAS, and then adjudicates all cases identified through a search of the SJIA clinical program and the global safety databases. In the future, cases in AOSD patients will also be monitored in this way. However, so far, no signal for a higher incidence of MAS with canakinumab treatment has been seen.

Furthermore, considering that the new indication is likely to increase the use of canakinumab in women of child bearing potential it was considered appropriate to expand on the current wording in the SmPC relating to concurrent use of canakinumab and live vaccines. A new warning in section 4.6 has been introduced recommending against the administration of live vaccines to newborn infants exposed to canakinumab *in utero* for 16 weeks following the mother's last dose of Ilaris before childbirth. The patient alert card has been updated accordingly, to remind women who received canakinumab during pregnancy of the importance to inform the baby's healthcare professional before any vaccinations are given to their newborn infant.

Overall no difference in the safety profile in older patients compared to younger age groups could be detected. However, as the subset of of young adult SJIA patients aged 16 to 20 years, which most closely resembles the AOSD patients, the CHMP recommended that the MAH ensures that the results of a multi-centre, placebo-controlled, 12 week trial of the efficacy, safety and tolerability of canakinumab in 68 AOSD patients is ongoing (ACZ885GDE01T/ NCT02204293) are submitted to the CHMP as soon as these are available.

2.5.2. Conclusions on clinical safety

The safety profile of canakinumab does not differ in great extent between younger and older age groups with the diagnose SJIA. The analysis of the available safety data in patients with SJIA provides sufficient evidence that a similar safety profile can be expected for AOSD patients.

Review of the existing scientific literature in support of the extrapolation from SJIA to AOSD

Review of the existing scientific literature was performed to demonstrate:

(i) that SJIA and AOSD represent pediatric and adult-onset variants of the Still's disease continuum with superimposable clinical and laboratory features, particularly with respect to the central role of IL-1 in their pathology;

(ii) that IL-1 inhibition is an effective strategy in the treatment of Still's disease including SJIA and AOSD.

Assessment of the results of this literature search allowed identification of 28 references that were relevant to the topic of the relationship of SJIA and AOSD. Publications reporting the use of IL-1 inhibition in the treatment of AOSD were also identified, and after excluding abstracts of congress presentations where data were available from full, peer-reviewed publications this search revealed 72 publications that provided relevant information on the use of IL-1 blockade, namely anakinra and rilonacept, in the treatment of AOSD.

As AOSD is a very rare disease (Gerfaud- Valentin et al 2014a), the number of relevant publications was relatively small, but sufficient to allow assessment of both topics.

Relationship between SJIA and AOSD

As expressed in several reviews of AOSD, the condition is generally considered to be either the same disease as SJIA (but occurring in adults), or to belong to a disease continuum that includes SJIA. The original description of AOSD by Bywater (1971) acknowledges this, in that the similarity of the adult cases in the series to cases of Still' s disease (i.e. SJIA) led to the naming of the condition. One review of the pathogenesis of AOSD (Jamilloux et al 2015a) included a direct comparison with SJIA, and summarized the available evidence from a small number of publications that compared various aspects of the two conditions. These studies have generally concluded that the two conditions are at least closely related, and that where differences exist (as noted by Pay et al (2006) and Sobieska et al (1998), see Section 5) these may be due to differences between adults and children in the expression of the same disease process, a conclusion shared by Jamilloux et al (2015a). While there remains some debate as to the degree of identity between AOSD and SJIA, the central role of IL-1 in the immunopathology of AOSD (as in SJIA) is well-established, as discussed in a number of reviews (Kadavath and Efthimiou 2015, Jamilloux et al 2015a, Jamilloux et al 2015b, Maria et al 2014, Gerfaud-Valentin et al 2014a), and, as described below, demonstrated by the impressive efficacy of IL-1 inhibition in the treatment of this condition.

IL-1 inhibition in the treatment of AOSD

Treatment of AOSD with IL-1 inhibitors has been widely reported in the literature. The most studied IL-1 inhibitor is anakinra, which was developed earlier than rilonacept and canakinumab (the first report of its use in this condition (Rudinskaya and Trock 2003) was published in 2003); most publications describing the use of IL-1 inhibition in the treatment of AOSD therefore cover anakinra. A controlled study, several surveys and case series, a meta-analysis including data from over 100 patients (Hong et al 2014), and numerous case reports provide evidence that inhibition of IL-1 is highly effective in relieving both systemic and, to a lesser extent, articular symptoms of AOSD. While systemic symptoms resolved rapidly, joint symptoms resolved more slowly and persisted in some cases. In some cases, corticosteroid and/or methotrexate could be tapered or stopped while maintaining remission.

IL-1 inhibition as reported in the literature appears to be effective in treating both systemic and articular manifestations of AOSD, even in patients who are refractory to standard therapies and other biologics. Anakinra is the most studied IL-1 inhibitor in AOSD, with many case reports, several case series and a

controlled study, which in total indicate that it is highly effective. Although a smaller body of evidence exists for the use of rilonacept and cankinumab in IL-1 inhibition in AOSD, case reports suggest that they are also effective therapies.

Conclusions

The MAH performed an extensive literature search to evaluate existing data on the relationship between SJIA and AOSD as well as the use of IL-1 inhibition in the treatment of AOSD.

Patients included in the concerned studies, case reports, reviews are over 400, directly comparing AOSD and SJIA, over 430 patients in studies comparing clinical, laboratory or pathological aspects. Furthermore, data from more than 400 patients were presented focusing on the response to IL-1 inhibition in AOSD patients

This literature supports to a great extent the position, that AOSD and SJIA share many common features, are closely related diseases, and even are a disease continuum. Existing differences in the disease expression are explained with children reacting differently as a result of the first encounter of putative antigens with their immune systems.

The results of the presented review are supporting the suggestion that SJIA and AOSD are two entities of the same disease and a disease continuum with different expressions in different ages of onset.

The literature research focusing on the effect of IL-1 inhibition in AOSD supports the conclusion that IL-1 inhibition is an effective instrument to reduce clinical signs and symptoms of AOSD, leads to normalization of laboratory parameters, and allows in many patients the clinically meaningful tapering of corticosteroids.

Most evidence regarding the effect of IL-1 inhibition in AOSD relates to the use of anakinra, however case reports for treatment with canakinumab suggest a similar magnitude of efficacy.

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

The next data lock point will be 30 June 2016.

The annex II related to the PSUR refers to the EURD list which remains unchanged.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 10.1 could be acceptable if the applicant implements the changes to the RMP as described in the PRAC endorsed PRAC Rapporteur assessment report.

The CHMP endorsed this advice.

The applicant implemented the changes in the RMP as requested by PRAC.

The CHMP endorsed the Risk Management Plan version 10.2 with the following content:

Safety concerns

Important identified risks	Infections Opportunistic infections Neutropenia DILI (Hepatic transaminase and bilirubin elevations) (for Still's disease) Decreased estimated creatinine clearance and proteinuria (for Still's disease) Musculoskeletal pain and arthralgia (for Still's disease)
Important potential risks	Immunogenicity/allergenicity Autoimmunity reactions Malignancy DILI (Hepatic transaminase and bilirubin elevations) (for CAPS and gouty arthritis) Disorders of lipoprotein metabolism Canakinumab – immunosuppressants combination therapy toxicity (for CAPS and Still's disease) Increased uric acid levels (for gouty arthritis) Macrophage activation syndrome (MAS) (for Still's disease) Pulmonary complications: pulmonary hypertension and interstitial lung disease (for Still's disease) Eosinophilia (for Still's disease) Interactions with vaccines Pharmacodynamic interactions Interactions with drugs eliminated by CYP450 enzymes
Missing information	Pregnancy and lactation Long term effect on kidney function Effects on growth (for CAPS and Still's disease) Long term safety data Long term efficacy (for CAPS and Still's disease)

Pharmacovigilance plan

Study/activity Type, title and category (1-3)	**Objectives**	**Safety concerns addressed**	**Status**	**Date for submission of interim or final Reports (planned or actual)[1]**
Study ACZ885D2401: CAPS Registry β-Confident: Clinical Outcomes and Safety: A Registry Study of Ilaris (canakinumab) Patients): An open-label, long-term, prospective, observational study to monitor the safety and effectiveness of Ilaris in CAPS patients (Category 2)	To provide real life incidence data	• Infections • Opportunistic infections • Neutropenia • Immunogenicity/ allergenicity • Autoimmunity reactions • Malignancy • Disorders of lipoprotein metabolism • DILI (Hepatic transaminase and	Ongoing	Final study report Q3 2016

Study / activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status	Date for submission of interim or final Reports (planned or actual)[1]
		bilirubin elevations) • Canakinumab – immunosuppressants combination therapy toxicity (for CAPS and Still's disease) • Interactions with vaccines • Missing information: Pregnancy and lactation • Missing information: Long term effect on kidney function • Missing information: Effects on growth (For CAPS and Still's disease) • Missing information: Long term safety data (for CAPS) • Missing information: Long term efficacy (for CAPS)		
Study ACZ885H2401: Gouty arthritis Registry A registry study to evaluate the safety and tolerability of canakinumab or standard of care treatment (SoC) in a real world setting in patients with gouty arthritis and acute flares (Category 3)	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 • Malignancy • Disorders of lipoprotein metabolism • DILI (Hepatic transaminase and bilirubin elevations) • Increased uric acid levels (for gouty arthritis) • Interactions with vaccines • Missing information: Pregnancy and lactation • Missing information: Long term effect on kidney function • Missing information: Long term safety data (for gouty arthritis)	Temporarily suspended	

Study / activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status	Date for submission of interim or final Reports (planned or actual)[1]
Study ACZ885G2306: ß-SPECIFIC 4: An open-label study to evaluate efficacy and safety of canakinumab dose reduction or dose interval prolongation in patients with active Systemic Juvenile Idiopathic Arthritis (SJIA) (Category 3)	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	• Musculoskeletal pain and arthralgia (for Still's disease) • Eosinophilia (for Still's disease) • Missing information: Long term safety data (for Still's disease) • Missing information: Long term efficacy (for Still's disease)	Ongoing	Final study report 3Q 2018
Study ACZ885G2403[2]: SJIA registry (Category 3)	To collect prospective safety, tolerability, efficacy, and treatment adherence information on juvenile idiopathic arthritis (JIA) subjects	It is expected that aspects of the following risks will be addressed: • Infections • Neutropenia • Drug-induced liver injury (for Still's disease) • Decreased estimated creatinine clearance and proteinuria (for Still's disease) • Musculoskeletal pain and arthralgia (for Still's disease) • Immunogenicity/allergenicity • Autoimmunity reactions • Malignancy • Disorders of lipoprotein metabolism • Canakinumab – immunosuppressants combination therapy toxicity (for Still's disease) • Pulmonary complications (for Still's disease) • Eosinophilia (for Still's disease) • Pregnancy and lactation • Long-term effects on	Planned	Final study report 1Q 2024

Study / activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status	Date for submission of interim or final Reports (planned or actual)[1]
		kidney function • Long-term effects on growth (for Still's disease) • Long-term efficacy (for Still's disease)		
Infections Adjudication Committee (Category 3)	To independently and blindly review, evaluate and categorize all significant infections events from blinded and controlled studies that may be observed during the canakinumab clinical trials	• Infections • Opportunistic infections	Ongoing	NA
Malignancy Adjudication Committee (Category 3)	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	Ongoing	NA
Macrophage Activation Syndrome Adjudication Committee (MASAC) (Category 3)	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 the global safety databases for these events or changes	Macrophage activation syndrome	Ongoing	NA
Integrated Immunogenicity report (Category 3)	To assess immunogenicity in a comprehensive way, looking at all consequences of it. The report will	• Immunogenicity/ allergenicity • Eosinophilia (for Still's disease)	Ad-hoc in case of submissio n dossiers Ongoing	NA

Study / activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status	Date for submission of interim or final Reports (planned or actual)[1]
	include data on anti-drug 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.			

NA: Not applicable

[1]Due date of study reports is the date of submission to HAs

[2] Since preparation of RMP v9.0, agreement has been reached to change the SJIA registry from being based on the EU Pharmachild registry (Study ACZ885G2401) to being based on the US and Canada CARRA registry (Study ACZ885G2403).

Risk minimisation measures

Safety risk	Routine risk minimization measures	Additional risk minimization measures
Important identified risks		
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)	Patient reminder card HCP information (as per local legislation)
Opportunistic infections	Labeling: SmPC Section 4.4 (Special warnings and precautions for use)	Patient reminder card HCP information (as per local legislation)
Neutropenia	Labeling: SmPC Section 4.4 (Special warnings and precautions for use) and section 4.8 (Undesirable effects)	HCP information (as per local legislation):
DILI (Hepatic transaminase and bilirubin elevations (for Still's disease)	Labeling: SmPC section 4.4 (Special warnings and precautions for use), and section 4.8 (Undesirable effects)	None

Safety risk	Routine risk minimization measures	Additional risk minimization measures
Decreased estimated creatinine clearance and proteinuria (for Still's disease)	Labeling: SmPC section 4.8 (Undesirable effects)	None
Musculoskeletal pain and arthralgia (for Still's disease)	Labeling: SmPC section 4.8 (Undesirable effects)	None.
Important potential risks		
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)	HCP information (as per local legislation)
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
Malignancy	Labeling: SmPC Section 4.4 (Special warnings and precautions for use)	HCP information (as per local legislation)
DILI (Hepatic transaminase and bilirubin elevations (for CAPS and gouty arthritis)	Labeling: SmPC section 4.4 (Special warnings and precautions for use), and section 4.8 (Undesirable effects)	None
Disorders of lipoprotein metabolism	Labeling for Gouty arthritis SmPC section 4.8 (Undesirable effects)	HCP information (as per local legislation)
Canakinumab – immunosuppressants combination therapy toxicity (for CAPS and Still's disease)	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
Increased uric acid levels (for gouty arthritis)	Labeling: SmPC Section 4.8 Undesirable effects	None
Macrophage activation syndrome (for Still's disease)	Labeling: SmPC Section 4.4 (Special warnings and precautions for use)	Patient reminder card HCP information
Pulmonary complications: pulmonary hypertension and interstitial lung disease (for Still's disease)	Upon the emergence of new 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	None
Eosinophilia (for Still's disease)	Upon the emergence of new safety findings related to eosinophilia, as reviewed regularly in the PSUR, appropriate updated risk management activities will be considered.	None

Safety risk	Routine risk minimization measures	Additional risk minimization measures
	No risk minimization measure is considered necessary at this time	
Interactions with 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)	HCP information (as per local legislation)
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
Interactions with drugs eliminated by CYP450 enzymes	Labeling: SmPC Section 4.5 (Interaction with other medicinal products and other forms of interaction)	None
Missing information		
Pregnancy and lactation	Labeling: SmPC Section 4.6 (Fertility, pregnancy and lactation)	HCP information (as per local legislation) Patient reminder card
Long term effect on kidney function	No risk minimization measure is considered necessary at this time	None
Effects on growth (for CAPS and Still's disease)	No risk minimization measure is considered necessary at this time	None
Long term safety data	No risk minimization measure is considered necessary at this time	None
Long term efficacy (for CAPS and Still's disease)	No risk minimization measure is considered necessary at this time	None

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly. Further, the information in section 4.6 of the SmPC has been updated with regard to the administration of live vaccines in newborns exposed in-utero to canakinumab. In addition, the MAH took the opportunity to bring the annexes in line with the latest QRD template.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable for the following reasons:

The changes to the package leaflet are minimal and only extend the scope of an approved paediatric indication to the adult population with no impact on the posology, the mode of administration, the safety profile or on the format/layout of the package leaflet.

3. Benefit-Risk Balance

Benefits

Beneficial effects

A detailed comparison of the efficacy of canakinumab treatment in SJIA patients between three age categories was submitted (2->12 years of age n=216, 12->16 years of age n=56, ≥ 16 years of age n=29). Efficacy results in the three age groups were compared for the ACR pediatric response, number of active joints, number of joints with limitation of motion, CRP, Physician's global assessment of disease activity, and CHAQ disability score.

No major differences were observed in these clinically relevant efficacy endpoints between younger age groups and older age groups. Adapted ACR pediatric 30 response at Day 15 was achieved by 158/216 (73.1%) of subjects in the 2 - <12 years old group, 47/56 (83.9%) of subjects in the 12 - <16 years old group, and 25/29 (86.2%) of subjects in the ≥16 years old group. The corresponding JIA ACR 30 responses at Day 15 were 78.2%, 83.9% and 86.2%, respectively. A trend can be seen to an even slightly better response on treatment in the older age group ≥16.

Treatment effect was sustained over the prolonged assessment period until day 85 also in each of the three age groups, with adapted ACR 30 responses of 67.7%, 74.1% and 83.3% in the age groups of 2 - <12 years, 12 - <16 years and ⩾16 years, respectively. The adapted ACR 100 pediatric responses were 31.6%, 29.6% and 22.2% respectively for the 3 age groups.

Changes from baseline in the seven ACR components were consistently similar or slightly greater in the ≥16 years age group. Median CRP values were less than 10 mg/L, i.e., normal by Day 15 in the eldest age group, and within the normal range in all age groups by Day 57. Overall, similar or better responses were seen in the two older age groups compared to the youngest patients <12 years of age.

All 3 age groups also showed similar changes in DAS-28 (CRP) at Day 15 (median changes from baseline were -2.10 in the 2 - <12 years age group, -2.53 in the 12 - <16 years age group, and -2.37 in the ≥16 years age group). Median changes from baseline at Day 85 were also similar between the 12 - <16 years and ≥16 years age groups (-3.76 and - 3.50, respectively), but smaller in the 2 - <12 years age group (-2.64).

These results are supportive for the proposed change of indication to allow treatment in adults newly diagnosed with AOSD.

Uncertainty in the knowledge about the beneficial effects

No formal studies of the use of canakinumab in the treatment of AOSD have been submitted.

Even though the evaluated efficacy parameters strongly support that canakinumab use is equally effective across younger children, adolescents and adults, all patients randomized to the three pooled studies were diagnosed with SJIA and had their primary diagnosis in childhood. Nevertheless, given the similar genetic profiles and similar clinical responses to anti-IL-1 agents in AOSD and SJIA patients, it is reasonable to expect that the beneficial effects in SJIA will apply to the same extent in AOSD.

Risks

Unfavourable effects

The most frequent adverse events reported were in all three age groups infections and infestations, musculoskeletal and connective tissue disorders and gastrointestinal disorders. There was some variation between age groups in exposure-adjusted total rates of AEs across the SOCs, and even though no clear pattern could be distinguished the overall rate of AEs is the lowest in the oldest population.

MAS which is an AE of concern is monitored intensively through the Macrophage Activation Syndrome Adjudication Committee (MASCAC) which independently reviews adjudicates all cases identified through a search of the SJIA clinical program and the global safety databases events suggestive of MAS.

The overall safety profile of canakinumab remains unchanged for older patients compared to younger age groups.

Uncertainty in the knowledge about the unfavourable effects

Patient number in the oldest age group is limited to 31 participants and therefore, safety data in adult patients is still limited. However, available safety results presented in a literature review, covering paediatric and adult patients do not indicate any new concerns for AOSD patients.

Effects Table

Effects Table for Ilaris in the treatment of Adult Onset Still's disease (data cut-off: 04 August 2014)

Effect	Short Description	Unit	Active 2-12 years	Active 12-16 years	Active ≥16 years	Uncertainties/ Strength of evidence	References
Favourable Effects							
ACR 30[1)]	Patients achieving a 30% response at day 85	%	67.7	74.1	83.3	Data include only a small number of SJIA "adult-like" patients Results consistent through time course	Pooled data from G2305, G2301, and G2301E1
CRP levels	Median change from baseline	mg/L	-98.3	-102.0	-113.3		
Unfavourable Effects							
Infections	Exposure adjusted rate serious adverse events, in Infections and infestations SOC[2)]	IR[(3)] (%)	66 (12.9)	15 (14.3)	3 (4.0)	Data include only a small number of SJIA "adult-like" patients Known risks with canakinumab use, such as MAS and potential risks such as malignancies, cannot be excluded in the AOSD population	Pooled data from A2203, G2305, G230, and G2301E1
Musculo-skeletal and connective tissue disorders	Exposure adjusted rate serious adverse events, in Musculoskeletal and connective	IR (%)	37 (7.2)	12 (11.5)	10 (13.3)		

Effect	Short Description	Unit	Active 2-12 years	Active 12-16 years	Active ≥16 years	Uncertainties/ Strength of evidence	References
	tissue disorders SOC						
Gastro-intestinal disorders	Exposure adjusted rate serious adverse events, in Gastrointestinal disorders SOC	IR (%)	17 (3.3)	6 (5.7)	2 (2.7)		

[1)] ACR: American College of Rheumatology
Response defined as 30% of improvement from baseline of at least 30% in at least 3 of the response variables of the American College of Rheumatology 1 to 6 (see Section 2.4.1 of this report) with no more than one of the ACR core components (variables 1- 6) worsening by more than 30%
[2)] SOC = System Organ Class
[3)] IR = exposure adjusted incidence rate

Benefit-Risk Balance

Importance of favourable and unfavourable effects

AOSD is a rare, debilitating and difficult–to-treat disorder with no approved treatment options.

SJIA and AOSD share many common features, including the clinical signs and symptoms at onset and in the serious complications that may arise. Through the available data from the older SJIA patients, and the literature search focusing on the effect of IL-1 inhibition in AOSD, it can be expected that canakinumab is effective in reducing clinical signs and symptoms of AOSD, leading to normalization of laboratory parameters, and allowing meaningful tapering of corticosteroids.

Like paediatric and juvenile Still's patients, adult-onset patients can also suffer from the rare and potentially fatal complication of macrophage activation syndrome (MAS), and other rare, multi-systemic complications. Other known risks associated with canakinumab use, such as infections and neutropenia or the potential risk of malignancies are expected to apply to AOSD patients. These risks are managed adequately through warnings in the SmPC and educational materials for health-care professionals and patient alert cards.

Benefit-risk balance

Discussion on the Benefit-Risk Balance

This application is based on demonstration of similar biomarker and gene expression profiles in SJIA and AOSD patients, extrapolation of paediatric PK to the adult population to support the dosing recommendation, a review of the existing scientific literature, and pooled analyses of efficacy and safety data by age categories of 301 SJIA patients.

The comparison of disease dysregulated genes in AOSD and SJIA which was performed with gene array analysis showed a strong concordance between the two diseases at the molecular/cellular level. Significantly, the published literature also supports to a great extent the position that AOSD and SJIA share many common features, and are closely related diseases. The population PK analyses using all available

data from SJIA patients support extrapolation of canakinumab PK from pediatric (SJIA) to adult (AOSD) patients. Based on available data, patients within the two populations would be exposed to a similar range of canakinumab level with the currently recommended dosing regimen for SJIA.

The literature research focusing on the effect of IL-1 inhibition in AOSD strongly supports the notion that IL-1 inhibition is effective in reducing clinical signs and symptoms of AOSD and SJIA. Considering the known beneficial effects of canakinumab in the older SJIA patients, a similar positive effect can be reasonably expected for AOSD patients.

No new risks are expected in AOSD patients compared to SJIA, and these are managed satisfactorily through labeling and additional risk management activities.

The similarity of AOSD and SJIA together with the totality of available data from submitted studies in SJIA, are considered to give sufficient support to apply extrapolation of efficacy, PK and safety from the paediatric to the adult population leading to a positive benefit-risk balance for canakinumab in Adult-Onset Still's Disease (AOSD).

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II, IIIA, IIIB and Annex A

Extension of Indication to amend the Systemic Juvenile Idiopathic Arthritis (SJIA) indication to include treatment of active Still's disease including Adult-Onset Still's Disease (AOSD) in patients aged 2 years and older who have responded inadequately to previous therapy with non-steroidal anti-inflammatory drugs (NSAIDs) and systemic corticosteroids; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated and the Package Leaflet has been updated accordingly. Further, the information in section 4.6 of the SmPC has been updated with regard to the administration of live vaccines in newborns exposed in-utero to canakinumab. In addition, the MAH took the opportunity to bring the annexes in line with the latest QRD template and to make a minor correction in the Annex A. An updated RMP version 10.2 was agreed during the procedure.

The variation leads to amendments to the Summary of Product Characteristics, Annex II, Labelling, Package Leaflet, Annex A and to the Risk Management Plan (RMP).