Efficacy and safety of canakinumab in patients with Still's disease: exposure-response analysis of pooled systemic juvenile idiopathic arthritis data by age groups

E. Feist[1], P. Quartier[2], B. Fautrel[3,4], R. Schneider[5], P. Sfriso[6], P. Efthimiou[7], L. Cantarini[8], K. Lheritier[9], K. Leon[10], C.S. Karyekar[10], A. Speziale[9]

[1]Charité-Universitätsmedizin, Berlin, Germany; [2]Paris-Descartes University, IMAGINE Institute, Necker-Enfants Malades Hospital, Assistance Publique Hopitaux de Paris, France; [3]UPMC-GRC 08, Pierre Louis Institute of Epidemiology and Public Health, Paris, France; [4]AP-HP, Pitie Salpetriere Hospital, Rheumatology Department, Paris, France; [5]University of Toronto and The Hospital for Sick Children, Toronto, Canada; [6]University of Padova, Padova, Italy; [7]New York University School of Medicine, New York, USA; [8]University of Siena, Siena, Italy; [9]Novartis Pharma AG, Basel, Switzerland; [10]Novartis Pharmaceuticals Corporation, East Hanover, USA.

Abstract

Objective

To describe the efficacy, safety, and exposure-response relationship of canakinumab in a subgroup of patients with systemic juvenile idiopathic arthritis (SJIA) aged ≥16 years, representative of adult-onset Still's disease (AOSD) patients, and to compare this subgroup with those of children and young adolescents with SJIA by pooling clinical data collected during the development programme of canakinumab.

Methods

Safety and efficacy data on canakinumab-treated patients were pooled from 4 SJIA studies (NCT00426218, NCT00886769, NCT00889863, and NCT00891046). In the majority of patients, canakinumab was administered at 4 mg/kg every 4 weeks. Efficacy parameters (adapted American College of Rheumatology [aACR] paediatric and juvenile idiopathic arthritis [JIA] ACR responses), quality of life, C-reactive protein levels, safety, and exposure-response relationship were assessed over 12 weeks in 3 age groups (children 2–<12, young adolescents 12–<16 and older adolescents and young adults ≥16 years).

Results

Efficacy outcomes were analysed in 216 children, 56 young adolescents and 29 older adolescents and young adults. Efficacy parameters across 3 age groups were largely comparable. At Day 15, at least 50% of patients from each age group exhibited aACR ≥70 and ACR responses. The safety profile of canakinumab was similar across age groups. One death was reported.

Conclusions

Pooled analyses from SJIA studies indicate that older adolescents and young adults SJIA patients show similar efficacy, safety, and exposure-response relationship on a weight-based dosing regimen as observed in children and adolescent SJIA patients. These analyses suggest that canakinumab may be an effective therapy in young adults with Still's disease.

Key words

adult-onset Still's disease, adolescent rheumatology, autoinflammatory conditions, biological therapies, juvenile idiopathic arthritis

Eugen Feist, MD
Pierre Quartier, MD
Bruno Fautrel, MD, PhD
Rayfel Schneider, MBBCh, FRCPC
Paolo Sfriso, MD, PhD
Petros Efthimiou, MD
Luca Cantarini, MD, PhD
Karine Lheritier, PhD
Karolynn Leon, MD
Chetan S. Karyekar, MD
Antonio Speziale, MD

Please address correspondence to:
Dr Eugen Feist,
Department of Rheumatology and Clinical Immunology,
Charité-Universitätsmedizin,
Chariteplatz 1,
10117 Berlin, Germany.
E-mail: Eugen.Feist@charite.de

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Competing interests
E. Feist received research support and honoraria for consultation from Abbvie, BMS, Lilly, Novartis, Pfizer, Roche, Sanofi and works as an investigator in clinical trials.
P. Quartier received grant/research support from AbbVie, Novartis, Pfizer, and Chugai-Roche; is a consultant for AbbVie, Novartis, Pfizer, Sobi, Roche Novimmune and Sanofi; and is a speaker bureau for AbbVie, Novartis, Sobi, and Roche.
B. Fautrel is a consultant for AbbVie, Biogen, BMS, Celgène, Hospira, Janssen, Lilly, MSD, Nordic Pharma, Pfizer, Roche, Sobi, and UCB. Received research grants from AbbVie, MSD, and Pfizer.
R. Schneider received grant/research support from Novartis and is a consultant for Novartis, Novimmune and Sobi.
P. Sfriso participated in advisory board meetings of Novartis.
P. Efthimiou is a consultant for Novartis.
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K. Lheritier, K. Leon, C.S. Karyekar and A. Speziale are employees of Novartis.

Introduction

Still's disease presents in paediatric and adult patients as a disease continuum with similar pathophysiology and is denoted as systemic juvenile idiopathic arthritis (SJIA) and adult-onset Still's disease (AOSD), respectively (1-2). SJIA and AOSD are both rare systemic inflammatory diseases that share similar clinical symptoms including spiking fever, skin rash, arthralgia or arthritis, myalgia, hepatosplenomegaly, lymphadenopathy, serositis and laboratory findings with acute-phase response, hyperferritinemia and leukocytosis (3-5).

SJIA and AOSD have cytokine-driven pathologies wherein interleukin-1 (IL-1) plays a key role (1). The pathophysiology of these diseases is complex due to abnormal activation of the innate immune response with induction of a cytokine cascade (Th1) (6-7) and elevation of IL-8, IL-6, tumour necrosis factor (TNF)-α, and IL-17, which are downstream of IL-1β and IL-18 (1). The key role of IL-1β in SJIA was established in studies that analysed patterns of gene transcription in peripheral blood mononuclear cells (PBMCs) (8-11). In addition, IL-1β is elevated in the serum of SJIA and AOSD patients (1, 12).

Blockade of the IL-1 pathway is an effective therapeutic strategy against these inflammatory diseases (13-15). Canakinumb is a monoclonal antibody specifically targeting IL-1β. Two pivotal clinical studies have reported the efficacy of canakinumab in treating active SJIA (13, 16). Moreover, case reports on successful use of canakinumab in treatment of AOSD have been published (14, 17-19). The objective of the present analysis was to describe the efficacy, safety, and exposure-response relationship of canakinumab in a subgroup of SJIA patients ≥16 years of age (older adolescents and young adults), who are considered as representative of AOSD patients, and to compare this patient subgroup with those of children and young adolescents with SJIA using a pooled analysis of the pivotal SJIA studies of canakinumab.

Materials and methods

Study design and patient population

This was a pooled subgroup analysis wherein data on canakinumab-treated patients were pooled from 4 SJIA studies, study designs for which have been published earlier (13, 16, 20). Brief description of the 4 studies is provided (Supplementary figure). Study 1 (NCT00886769) was a phase 3, randomised, double-blind, placebo-controlled study conducted in SJIA patients who received either single subcutaneous (s.c.) doses of canakinumab at 4 mg/kg (maximum of 300 mg) or placebo. Study 2 (NCT00889863), a phase 3 pivotal study, included two parts: Part I was an open-label, steroid-tapering study in which patients with SJIA received s.c. canakinumab 4 mg/kg (maximum dose of 300 mg) every 4 weeks, for up to 8 months. Part II was a double-blind, placebo-controlled study that assessed flare prevention. Study 3 (NCT00891046) was a phase 3, open-label extension study, that enrolled SJIA patients who had received canakinumab in either Study 1 or Study 2 (Cohort 1) with an additional cohort of canakinumab-naïve patients (Cohort 2). Patients in both the cohorts were treated with s.c. canakinumab 4 mg/kg every 4 weeks for 12 weeks and were included in pooled efficacy analyses. The study continued up to Week 217 with the possibility to reduce the dose to 2 mg/kg every 4 weeks in patients who were steroid free. For Cohort 2 patients, no dose reduction could occur until 6 months of treatment. Study 4 (NCT00426218) was a phase 2, multicenter, open-label, uncontrolled, 2-stage, dose-ranging study (0.5–9 mg/kg) that evaluated the safety, tolerability, immunogenicity, pharmacokinetics, and efficacy of repeated doses of canakinumab in patients with active SJIA.

Common inclusion criteria (with some differences among studies) were as follows: patients diagnosed with SJIA using the International League Against Rheumatism (ILAR) classification criteria (21) confirmed at least 2 months before enrolment and disease onset at <16 years of age, with at least 2 joints with active arthritis, documented spiking, intermittent fever for at least 1 day during the screening period and C-reactive protein (CRP) levels >30 mg/L (13, 16, 20). Patients were excluded if they were diagnosed with an active macrophage acti-

vation syndrome (MAS) within the previous 6 months, had received treatment with another biologic agent or disease-modifying drug (without a washout of ≥5 half-lives), had active tuberculosis, human immunodeficiency virus, or hepatitis B or C infection, or had received live-virus vaccination within 3 months before enrolment (13, 16).

Assessment and outcome measures

• *Efficacy assessments*

Data from patients who had received at least one dose of 4 mg/kg canakinumab in 3 studies (Study 1, 2 and 3) were pooled and included in the analysis for efficacy outcomes. Canakinumab treated patients were retrospectively categorised in the 3 groups based on age at the time of enrolment: 2 to <12 years (children), 12 to <16 years (young adolescents) and ≥16 years (older adolescents and young adults, representing AOSD population). Efficacy data up to 12 weeks of exposure were analysed, as this duration constituted data from canakinumab treated patients on a stable dose, without adjustment of other impactful comedication including steroids (Study 2). Patients were evaluated for improvement in efficacy outcome measures including adapted American College of Rheumatology (aACR) paediatric responses (ACR30/50/70/90/100 response criteria), defined as absence of fever plus improvements of ≥30%, ≥50%, ≥70%, ≥90%, and 100%, respectively, from baseline in at least three of the six response variables and >30% worsening in no more than one of the six variables (13, 16), and juvenile idiopathic arthritis (JIA) ACR 30/50/70/90/100 responses, defined as improvements of ≥30%, ≥50%, ≥70%, ≥90%, and 100%, respectively from baseline in at least three of the six variables with no more than one of the six variables worsening by >30%.

ACR response (aACR or JIA ACR) variables included: number of joints with active arthritis, number of joints with limitation of motion, normalised CRP values (normal range of 0-10 mg/L), physician's global assessment of disease activity (on a 100-mm visual-analog scale, with higher scores indicating more disease activity), parent's global assessment of patient's overall well-being (on a 100-mm visual-analogue scale, with higher scores indicating worse overall well-being), Childhood Health Assessment Questionnaire (CHAQ disability score; on a scale of 0 to 3, with higher scores indicating greater disability), absence of intermittent fever due to SJIA (body temperature ≤38°C) during the preceding week, and 28-point disease activity score (DAS-28) CRP (based on number of tender and swollen joints from a 28 joints list) at Day 15 and Day 85.

• *Safety*

Safety data of patients were collected from all 4 SJIA studies. Safety assessments included collection of data on adverse events (AEs), AEs leading to discontinuation, serious adverse events (SAEs), and AEs of special interest. Safety events were described for the 3 subgroups defined post hoc.

• *Pharmacokinetics and exposure-response analysis*

To compare adequacy of dosing and exposure in older adolescents and young adults compared with children and young adolescents, drug concentration data of patients were pooled from all 4 SJIA studies for pharmacokinetic analysis. Serum samples of patients were collected at baseline and during treatment. Population pharmacokinetics and exposure-response modeling were performed with dose, age, and weight as covariates. Pharmacokinetics concentrations in different age groups of SJIA patients over 12 weeks of treatment were predicted using pharmacokinetics modeling. Steady-state exposure metrics, including trough concentration (C_{MINss}), peak concentration (C_{MAXss}), and area under the plasma concentration-time curve (AUC_{ss}) were derived from the model for the 3 age sub groups.

Statistical analysis

Efficacy and safety data were analysed using SAS v. 9.2 statistical package with predetermined age cut-offs to compare the efficacy and safety among the different age groups. Continuous variables were summarised by mean, standard deviation (SD), median, minimum, and maximum. Categorical variables were summarised by absolute frequencies and percentages. Baseline characteristics were summarised using descriptive statistics. No formal statistical testing was performed to assess efficacy differences between subgroups.

Results

Demographic and baseline characteristics

A total of 301 patients were analysed for efficacy outcomes including 216 children (age, 2 to <12 years), 56 young adolescents (age, 12 to <16 years) and 29 older adolescents and young adults (age, ≥16 years). Baseline demographic and disease characteristics by age group are summarised in Table I. Overall, the baseline characteristics were well balanced across all age groups. Gender distribution was similar in each age group. Most patients were Caucasian and approximately one-third of the patients were steroid-free. The pattern of arthritis was similar across all age groups, except the proportion of patients with polyarthritis was higher in older adolescents and young adults. Systemic features after initial 6 months of disease were seen more frequently in older adolescents and young adults.

Efficacy outcomes

The efficacy parameters across the 3 age groups were largely comparable. aACR paediatric responses to canakinumab treatment were rapid in all age groups; at Day 15, at least 50% of patients in each age group had aACR ≥70 responses (Fig. 1). The response seen at Day 15 was maintained or improved over time until at Day 85 (Fig. 1). Similar results were observed for JIA ACR responses. At Day 15, at least 50% of patients from each age group (51.4%, 58.9% and 65.5 % for children, young adolescents and older adolescents and young adults, respectively) had JIA ACR ≥70 responses and showed improvements (57.9%, 66.7% and 66.7% for children, young adolescents and older adolescents and young adults, respectively) at Day 85.

Table II shows changes over time in ACR variables and clinical features for the patients. At baseline, the median

Table I. Baseline demographic and disease characteristics by age group (efficacy set).

Characteristic	Children N=216	Young adolescents N=56	Older adolescents and young adults N=29
Female, n (%)	125 (57.9)	34 (60.7)	16 (55.2)
Age, mean (SD), years	6.3 (2.71)	13.3 (1.18)	17.1 (0.95)
Caucasian, n (%)	190 (88.0)	46 (82.1)	26 (89.7)
Disease duration, n (%)			
≤6 months	48 (22.2)	6 (10.7)	1 (3.4)
>6 months to < 4 years	119 (55.1)	23 (41.1)	8 (27.6)
≥4 years	49 (22.7)	27 (48.2)	20 (69.0)
Patients on steroid, n (%)	146 (67.6)	35 (62.5)	18 (62.1)
Patients on NSAID, n (%)	121 (56.0)	30 (53.6)	12 (41.4)
Patients on methotrexate, n (%)	116 (53.7)	22 (39.3)	12 (41.4)

Children (2 – <12 years), young adolescents (12 – <16 years), older adolescents and young adults (≥16 years).
N: total number of patients in each age group; n: number of patients in each category of baseline characteristics.
NSAID: non-steroidal anti-inflammatory drugs; SD: standard deviation.

number of active joints was 8.0 in each age group. At Day 15, the median number of active joints ranged from 1 to 2 and at Day 85 medians ranged from 0 to 0.5 in all age groups. At Day 15, median percentage changes of active joints from baseline were -69.80 in children, -88.20 in young adolescents and -90.90 in older adolescents and young adults. At Day 85, median percentage changes from baseline were -100.00 in children, -100.00 in young adolescents and -98.10 in older adolescents and young adults, respectively. The median changes in the number of joints with limitation of motion were greater in young adolescents and older adolescents and young adults than in children. At Day

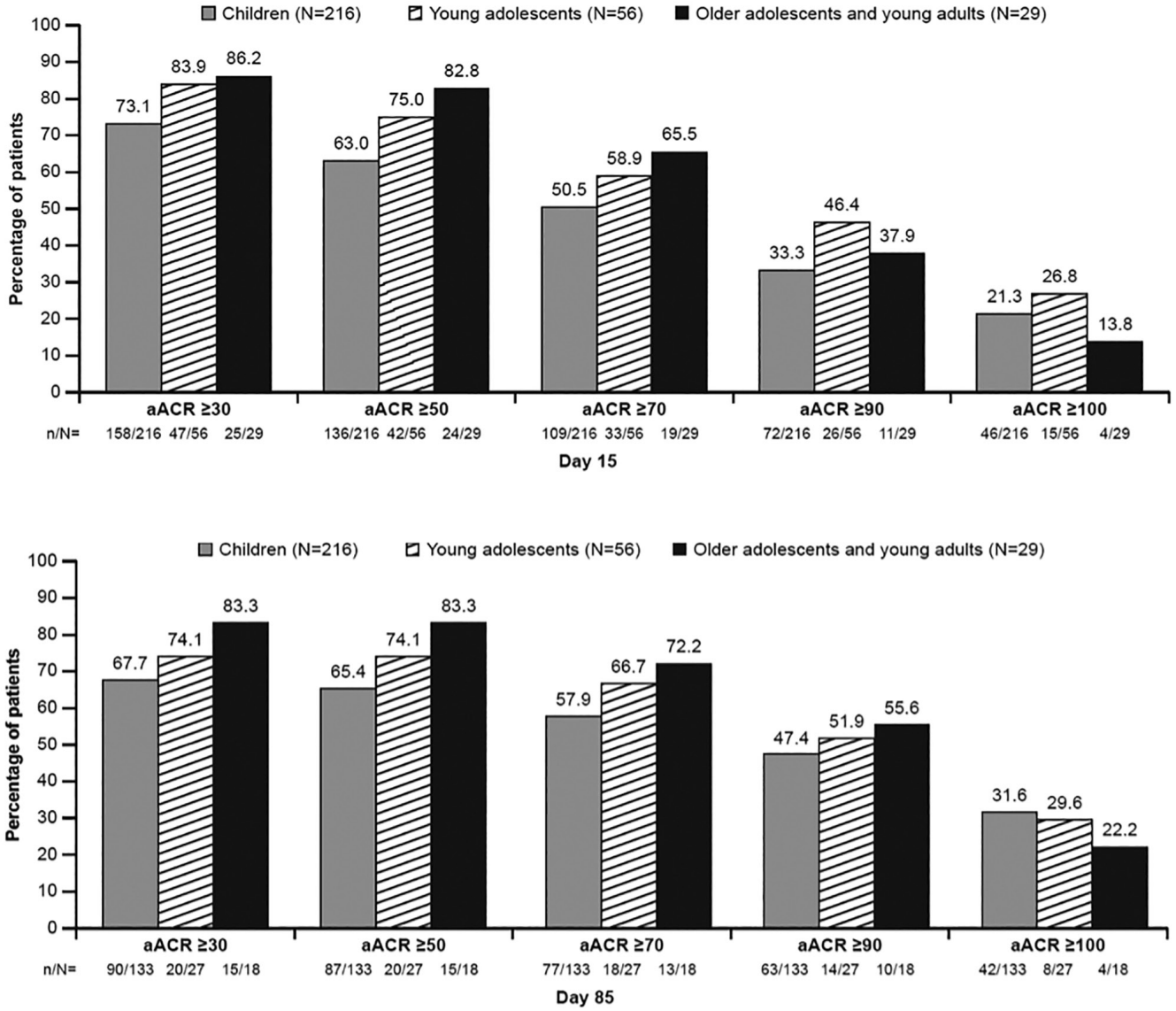

Fig. 1. Response to treatment by age groups (efficacy set). Number of patients decreased at Day 85 because in one of the pooled studies, ACR assessments were not available in Cohort 2 patients at Day 85. ACR: American College of Rheumatology.

Table II. Changes over time in ACR variables and DAS28-CRP by age groups (efficacy set).

	Baseline			Day 15			Day 85		
	Children N=216	Young adolescents N=56	Older adolescents and young adults N=29	Children N=216	Young adolescents N=56	Older adolescents and young adults N=29	Children N=216	Young adolescents N=56	Older adolescents and young adults N=29
Number of active joints	n=216	n=56	n=29	n=211	n=54	n=28	n=100	n=20	n=16
Median (range)	**8.0 (0 - 66)**	**8.0 (2 - 55)**	**8.0 (0 - 58)**	**2.0 (0 - 59)**	**1.5 (0 - 43)**	**1.0 (0 - 53)**	**0.0 (0 - 40)**	**0.0 (0 - 12)**	**0.5 (0 - 23)**
Number of joints with limitation of motion	n=216	n=56	n=29	n=211	n=54	n=28	n=100	n=20	n=16
Median (range)	**7.0 (0 - 62)**	**7.5 (0 - 55)**	**7.0 (0 - 56)**	**2.0 (0 - 65)**	**2.0 (0 - 43)**	**1.5 (0 - 55)**	**1.0 (0 - 67)**	**1.0 (0 - 33)**	**1.0 (0 - 55)**
C-reactive protein levels, (mg/L)	n=216	n=56	n=28	n=211	n=55	n=26	n=168	n=45	n=23
Median (range)	**133.90 (0.0 - 800.0)**	**149.00 (3.0 - 683.3)**	**104.70 (1.6 - 651.2)**	**12.00 (0.0 - 633.3)**	**10.00 (0.0 - 436.7)**	**4.50 (0.6 - 182.2)**	**9.75 (0.0 - 386.7)**	**8.40 (0.0 - 458.3)**	**7.80 (0.8 - 110.6)**
Score for physician's global assessment of disease activity (mm,VAS)	n=216	n=56	n=29	n=210	n=55	n=28	n=100	n=20	n=16
Median (range)	**64.0 (1 - 100)**	**62.5 (1 - 100)**	**63.0 (28 - 100)**	**18.0 (0 -100)**	**10.0 (0 - 97)**	**12.0 (0 - 76)**	**2.5 (0 - 100)**	**3.0 (0 - 47)**	**3.5 (0 - 72)**
Score for parent's global assessment of patient's overall well-being (mm,VAS)	n=216	n=55	n=29	n=209	n=54	n=27	n=99	n=20	n=16
Median (range)	**60.0 (0 - 100)**	**60.0 (0 - 98)**	**59.0 (0 - 98)**	**20.0 (0 - 100)**	**17.0 (0 - 89)**	**10.0 (0 - 89)**	**5.0 (0 - 98)**	**2.0 (0 - 95)**	**6.5 (0 - 80)**
CHAQ disability score	n=216	n=55	n=29	n=209	n=54	n=27	n=99	n=20	n=16
Median (range)	**1.63 (0.0 - 3.0)**	**1.75 (0.0 - 3.0)**	**1.63 (0.0 - 2.8)**	**0.63 (0.0 - 3.0)**	**0.13 (0.0 - 2.9)**	**0.38 (0.0 - 2.6)**	**0.25 (0.0 - 3.0)**	**0.06 (0.0 - 2.1)**	**0.25 (0.0 - 2.6)**
Absence of intermittent fever due to SJIA, % (n/m)	**21.9** (47/215)	**21.4** (12/56)	**13.8** (4/29)	**85.8** (181/211)	**96.4** (53/55)	**96.4** (27/28)	**97.0** (164/169)	**97.9** (47/48)	**100** (25/25)
DAS28-CRP	n=216	n=55	n=28	n=208	n=53	n=26	n=91	n=20	n=15
Median (range)	**5.220 (1.52 - 8.71)**	**5.310 (2.80 - 8.84)**	**5.135 (1.76 - 8.17)**	**2.775 (0.96 - 8.45)**	**2.850 (1.16 - 8.54)**	**2.420 (1.25 - 7.49)**	**2.050 (0.96 - 7.19)**	**1.935 (1.03 - 5.60)**	**2.080 (1.37 - 5.79)**

Children (2 – <12 years), young adolescents (12 – <16 years), older adolescents and young adults (≥16 years).
N: total number of patients in each age group; n: number of patients assessed for ACR variables; m: number of patients with an assessment in the time period; ACR: American College of Rheumatology; CHAQ: Childhood Health Assessment Questionnaire; DAS-28: disease activity score (28-point); SJIA: systemic juvenile idiopathic arthritis; VAS: visual analogue scale.

15, medians in all age groups ranged from 1.5 to 2.0 and at Day 85 median values were same (1 in each age group) (Table II). The changes in DAS-28 (CRP) scores were similar in all 3 age groups at Day 15; median changes from baseline were -2.10 in children, -2.53 in young adolescents, and -2.37 in older adolescents and young adults. Median changes from baseline at Day 85 were also similar between young adolescents and older adolescents and young adults (-3.76 and -3.50, respectively), but smaller in children (-2.64). Absence of fever was seen early in all 3 groups. By Day 15, absence of intermittent fever was observed in 85.8%-96.4% of patients, with minimal difference between age groups. The median CRP levels rapidly decreased from baseline to Day 15 and remained low at Day 85 in all age groups (Table II). The median values of physician's global assessment of disease activity, parent's or patient's global assessment of patient's overall wellbeing and CHAQ disability score decreased in all age groups at Day 15 and Day 85 (Table II).

Safety

In total, 324 patients were analysed for safety including 233 children, 60 young adolescents and 31 older adolescents and young adults. The mean (SD) number of doses administered were 27.5 (22.01), 21.8 (16.84) and 30.3 (23.77) in children, young adolescents and older adolescents and young adults, respectively. Table III summarises AEs by age groups. The most commonly reported AEs in children, young adolescents and older adolescents and young adults were infections and infestations, gastrointestinal disorders, and musculoskeletal and connective tissue disorders (Table III). Infections of the upper respiratory tract were among the most frequent AEs in all age groups, notably nasopharyngitis, upper respiratory tract infection, rhinitis (less frequent in the young adolescents), and cough (more common in children). Liver injury (hepatic transaminases and bilirubin elevations) was reported as a study drug-related AE in 35 (15.0%) children, 10 (16.7%) young adolescents and 9 (29.0%) older adolescents and young adults. One patient (13-year-old male) from the young adolescents group died because of pulmonary hypertension that was associated with MAS. SAEs were most commonly related to the underlying disease, such as flares or worsening of disease. The two most common SAEs in all 3 age groups were flare of SJIA and histiocytosis haematophagic, also known as MAS (Table III). The MAS events were approximately twice as common in older ado-

Table III. Summary of adverse events and serious adverse events (safety set)[#].

	Children, n (%) N=233	Young adolescents, n (%) N=60	Older adolescents and young adults, n (%) N=31
AEs (at least 1)	202 (86.7)	53 (88.3)	27 (87.1)
AEs leading to study drug discontinuation	26 (11.2)	10 (16.7)	6 (19.4)
AEs most common			
Infections and infestations*	176 (75.5)	42 (70.0)	23 (74.2)
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)
Gastrointestinal disorders*	122 (52.4)	32 (53.3)	18 (58.1)
Vomiting	56 (24.0)	12 (20.0)	3 (9.7)
Abdominal pain	51 (21.9)	9 (15.0)	7 (22.6)
Diarrhoea	48 (20.6)	9 (15.0)	7 (22.6)
Nausea	20 (8.6)	12 (20.0)	9 (29.0)
Musculoskeletal and connective tissue disorders*	119 (51.1)	33 (55.0)	16 (51.6)
Juvenile idiopathic arthritis	55 (23.6)	17 (28.3)	6 (19.4)
Arthralgia	49 (21.0)	17 (28.3)	8 (25.8)
Arthritis	12 (5.2)	7 (11.7)	1 (3.2)
Skin and subcutaneous tissue disorders	108 (46.4)	25 (41.7)	13 (41.9)
Eczema	32 (13.7)	6 (10.0)	2 (6.5)
Rash	32 (13.7)	4 (6.7)	4 (12.9)
Respiratory, thoracic and mediastinal disorders	98 (42.1)	25 (41.7)	10 (32.3)
Cough	70 (30.0)	13 (21.7)	6 (19.4)
Oropharyngeal pain	42 (18.0)	10 (16.7)	5 (16.1)
Rhinorrhoea	9 (3.9)	1 (1.7)	5 (16.1)
General disorders and administration site conditions[§]	91 (39.1)	22 (36.7)	14 (45.2)
Injury, poisoning and procedural complications[α]	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)
AEs of special interest			
Thrombocytopenia	41 (17.6)	3 (5.0)	3 (9.7)
Neutropenia	11 (4.7)	2 (3.3)	0
Transaminase elevation	4 (1.7)	0	1 (3.2)
Opportunistic infections	3 (1.3)	4 (6.7)	1 (3.3)
Hepatitis	2 (0.9)	1 (1.7)	1 (3.2)
Irritable bowel syndrome	1 (0.4)	0	0
SAE (at least 1)[β]	81 (34.8)	25 (41.7)	9 (29.0)
Juvenile idiopathic arthritis	21 (9.0)	7 (11.7)	4 (12.9)
Histiocytosis haematophagic (MAS)	12 (5.2)	7 (11.7)	3 (9.7)
Pyrexia	7 (3.0)	5 (8.3)	1 (3.2)
Gastroenteritis	5 (2.1)	3 (5.0)	0
Cytomegalovirus infection	0	0	2 (6.5)

[#]Mean durations of exposure were 804.2, 637.3 and 888.8 days for children, young adolescents and older adolescents and young adults, respectively.
*AEs by most commonly affected system organ class.
[§]In this category, commonly reported events (>2% in any age group) were pyrexia, fatigue, asthenia, drug ineffective, malaise, non-cardiac chest pain, peripheral swelling, influenza-like illness, feeling hot, and oedema.
[α]In this category, commonly reported events (>2% in any age group) were arthropod bite, arthropod sting, contusion, fall, joint injury, hand fracture, ligament sprain, limb injury, skin abrasion, procedural pain, road traffic accident, and toxicity to various agents.
[§]Investigations primarily included increase of aspartate aminotransferase, alanine aminotransferase, blood triglycerides, C-reactive protein, hepatic enzyme, blood fibrinogen, gamma-glutamyltransferase, serum ferritin, and blood bilirubin.
[β]SAEs ≥5% in any age group, SAEs were not related to study drug treatment.
AE: adverse events; SAEs: serious adverse events; MAS: macrophage activation syndrome; N: total number of patients in each age group.

lescents and young adults and young adolescents compared with children (Table III). Analysis of MAS events showed that there was no increase in the rate MAS events in patients on canakinumab. Laboratory data collected by patient age group did not show any notable differences in safety and tolerability in adult patients as compared with younger patients (children and young adolescents).

Pharmacokinetics and exposure-response relationship by age groups

Pharmacokinetics analyses were conducted in 233 children, 60 young adolescents, and 31 older adolescents and young adults. Fig. 2 shows canakinumab exposure in SJIA patients from various age groups using different simulated metrics of exposure at the steady state (C_{MINss}, C_{MAXss}, and AUC_{ss}). Steady-state canakinumab exposure showed positive trends in median exposure with increasing patient age, but the distributions significantly overlapped and were comparable across all age groups.

Discussion

Canakinumab has a well-established efficacy and safety profile in SJIA patients and is approved for its treatment in many countries. Canakinumab was recently also approved in Europe for treatment of AOSD patients.

We conducted this subgroup-analysis of pooled SJIA studies of canakinumab to evaluate the efficacy, safety, and pharmacokinetics of canakinumab in different age groups of SJIA patients including children, young adolescents, and older adolescents and young adults. This pooled analysis suggests that canakinumab has similar efficacy in older adolescents and young adults, comparable to its efficacy in children and young adolescents. The consistent clinical benefits observed in older adolescents and young adults, who represent AOSD patients, were based on improvements observed in 3 different domains representing both systemic and arthritic components of the disease, including: clinical, inflammatory laboratory markers and quality of life (QoL) measures.

Clinical endpoints such as ACR criteria, including aACR paediatric responses and JIA ACR responses, improved rapidly and were maintained over 12 weeks of treatment in the 3 different age groups. These improvements were largely consistent across the 3 age groups, with slightly higher responses

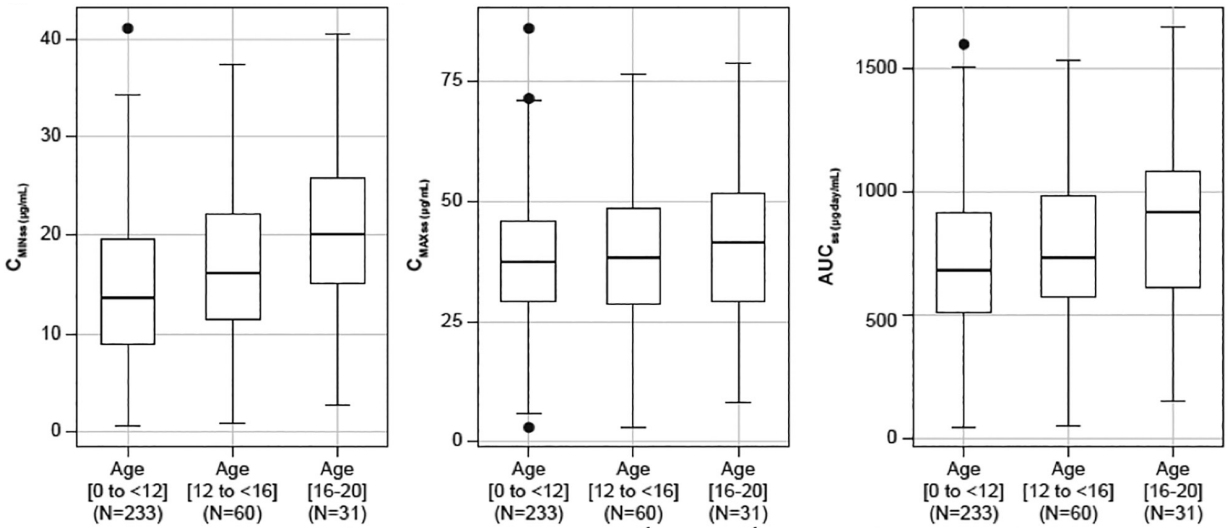

Fig. 2. Simulated steady-state exposure of canakinumab for SJIA patients stratified by age (pharmacokinetic analysis set).
The lower and upper end of boxes represent the 25th and 75th percentiles of distribution, the bold line in the box represents the median, and the whiskers 5th and 95th percentiles of the data. Dots represent the outliers. Age given in years. N: the number of patients; SJIA: systemic juvenile idiopathic arthritis; AUCss: area under the plasma concentration-time curve; CMAXss: peak concentration; CMINss: trough concentration.

seen in older adolescents and young adults. These rapid responses observed at Day 15 were also consistently maintained at Day 85. These findings corroborate previously published reports which showed that response to an IL-1 receptor antagonist treatment was rapid and sustained in AOSD and SJIA patients, suggesting that IL-1 is a key cytokine in pathogenesis of these two diseases (3-4, 13, 22). Furthermore, a rapid and sustained decrease to a similar extent was observed in the 3 age groups in acute phase reactants as well as QoL measures. At Day 85, median CRP values in all age groups were less than 10 mg/L, which were within the normal range. Improvements observed in disability scores were also meaningful at Day 85 and consistent across the 3 age groups. No major differences in other efficacy measures were observed across all age groups. In fact, there was no indication of reduced efficacy with canakinumab in older adolescents and young adults at the 4 mg/kg dose every 4 weeks. These observations are consistent with case reports that have shown that canakinumab was successful in controlling signs and symptoms of AOSD patients refractory to disease-modifying anti-rheumatic drugs and short- to moderate-acting IL-1 blockade (14, 18).

Patients from all three age groups showed broadly similar AE profiles: most frequent AEs included infections of the upper respiratory tract and gastrointestinal AEs. In general, older adolescents and young adults (≥16 years) showed no major differences with respect to AEs *versus* patients from the younger age groups. SAEs in the SJIA population were most commonly related to the underlying disease, such as flares or worsening of disease (JIA) or complications, most notably MAS (histiocytosis haematophagic) or infections. The reported JIA and MAS events were not related to canakinumab treatment.

The results of these analyses support the concept of a Still's disease continuum that includes both a paediatric or juvenile onset (SJIA) and adult onset (AOSD) form. SJIA and AOSD largely share the same pathophysiology and both diseases are highly responsive to IL-1β inhibition. Evidence suggests that SJIA and AOSD are also comparable at the molecular level. Nirmala *et al*. showed that most genes that were down-regulated after canakinumab treatment in patients with SJIA were up-regulated in a majority of patients with active AOSD (2).

A population-based pharmacokinetics-binding model was built to evaluate adequacy of exposure with weight-based dosing of canakinumab in older patients compared to younger patients. The model showed that overall, canakinumab exposures were comparable across all age groups including young adult SJIA patients. The analysis supports extrapolation of the efficacy of canakinumab in SJIA to the adult population of AOSD patients. Furthermore, the data support use of the same dose regimen for treatment of patients with AOSD (canakinumab 4 mg/kg s.c. monthly) as used for SJIA.

There are several limitations to this study. The post-hoc nature of the analysis along with small sample size in the young adult patients limits definitive conclusions. Data was pooled for the first 12 weeks of treatment, which limits long term extrapolation of these results. Finally, small sample size also limits comprehensive understanding of the safety profile of canakinumab in AOSD patients who are older than the age range assessed in this analysis. In this analysis, the mean age of the adult patients was 17.1 years and therefore it does not address treatment with canakinumab across the full age spectrum of AOSD.

Overall, this pooled analysis from SJIA studies indicates that older adolescents and young adults SJIA patients (aged ≥16 years at baseline of treatment considered to represent AOSD) exhibit similar efficacy, safety and exposure-response relationship on a weight-based dosing regimen to children and adolescent SJIA patients. These analy-

ses suggest that canakinumab may be an effective therapy at a dose of 4 mg/kg every 4 weeks in young-adult AOSD patients, as observed in SJIA patients. Further explorations with assessment of canakinumab efficacy in patients with active AOSD are warranted to confirm these findings.

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