NOVARTIS

Global Clinical Development - General Medicine

ACZ885/Canakinumab

Clinical Trial Protocol CACZ885G1301 / NCT02396212

# An open label, single-arm, active-treatment, efficacy and safety study of canakinumab (ACZ885) administered for at least 48 weeks in Japanese patients with Systemic Juvenile Idiopathic Arthritis (SJIA)

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| Authors: | [redacted] |
| Document type: | Clinical Trial Protocol |
| EUDRACT number: | Not applicable |
| Version number: | v00 (Original protocol) |
| Development phase: | III |
| Release date: | 12-Nov-2014 |


**Clinical Trial Protocol Template Version 2.0, November, 2013**

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## List of abbreviations

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| ACR | American College of Rheumatology |
| AE | adverse event |
| ALT | alanine aminotransferase |
| AST | aspartate aminotransferase |
| BCG | Bacillus Calmette-Guerin |
| BP | blood pressure |
| CHAQ© | Child Health Assessment Questionnaire |
| CFR | US Code of Federal Regulations |
| CPO | Country Pharma Organization |
| CRF | Case Report/Record Form (paper or electronic) |
| CRO | Contract Research Organization |
| CRP | C-Reactive Protein |
| CS | Corticosteroids |
| CSR | Clinical Study Report |
| CTC | Common Toxicity Criteria |
| DS&E | Drug Safety & Epidemiology |
| ECG | Electrocardiogram |
| eCRF | Electronic case report/record form |
| EDC | Electronic Data Capture |
| FAS | Full Analysis Set |
| GCP | Good Clinical Practice |
| HBc | Hepatitis B core |
| HBs | Hepatitis B surface |
| HBsAg | Hepatitis B surface antigen |
| HCV | Hepatitis C Virus |
| HIV | Human Immunodeficiency Virus |
| HLH | Hemophagocytic lymphohistiocytosis |
| IB | Investigator Brochure |
| ICH | International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use |

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| IEC | Independent Ethics Committee |
| Ig | Immunoglobulin |
| IL | Interleukin |
| IL-1 | Interleukin-1 |
| IL-1β | Interleukin-1 beta |
| ILAR | International League Against Rheumatism |
| IRB | Institutional Review Board |
| IRT | Interactive Response Technology |
| i.v. | intravenous(ly) |
| i.v. Ig | Intravenous immunoglobulin |
| JIA | Juvenile Idiopathic Arthritis |
| LFT | Liver function test (raised serum transaminases and/or bilirubin levels) |
| LLN | Lower Limit of Normal |
| LOQ | Limit of Quantification |
| MAS | Macrophage Activation Syndrome |
| MedDRA | Medical dictionary for regulatory activities |
| OC/RDC | Oracle Clinical/Remote Data Capture *Delete if NOVDD* |
| MTX | Methotrexate |
| NSAID | Non-Steroidal Anti-Inflammatory Drug |
| PD | Pharmacodynamic |
| PK | Pharmacokinetics |
| PPD | Purified Protein Derivative |
| PRINTO | Paediatric Rheumatology International Trials Organisation |
| PSW | Premature Subject Withdrawal |
| QF | Quantiferon |
| REB | Research Ethics Board |
| s.c. | subcutaneous(ly) |
| SAA | Serum Amyloid A |
| SAE | Serious Adverse Event |
| SJIA | Systemic Juvenile Idiopathic Arthritis |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |

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| TB | Tuberculosis |
| TNF | Tumor Necrosis Factor |
| ULN | Upper Limit of Normal |
| VAS | Visual Analog Scale |
| WHO | World Health Organization |

## Glossary of terms

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| Assessment | A procedure used to generate data required by the study |
| Active arthritis (as per ACR) | 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 |
| Adapted ACR Pediatric 30 | Improvement from baseline of at least 30% in at least 3 of response variables 1 to 6 **and** no intermittent fever, i.e. body temperature ≤ 38°C, in the preceding week (variable 7), with no more than one variable 1-6 worsening by more than 30% |
| Adapted ACR Pediatric 50 | Improvement from baseline of at least 50% in at least 3 of response variables 1 to 6 **and** no intermittent fever, i.e. body temperature ≤ 38°C, in the preceding week (variable 7), with no more than one variable 1-6 worsening by more than 30% |
| Adapted ACR Pediatric 70 | Improvement from baseline of at least 70% in at least 3 of response variables 1 to 6 **and** no intermittent fever, i.e. body temperature ≤ 38°C, in the preceding week (variable 7), with no more than one variable 1-6 worsening by more than 30% |
| Adapted ACR Pediatric 90 | Improvement from baseline of at least 90% in at least 3 of response variables 1 to 6 **and** no intermittent fever, i.e. body temperature ≤ 38°C, in the preceding week (variable 7), with no more than one variable 1-6 worsening by more than 30% |
| Adapted ACR Pediatric 100 | Improvement from baseline of at least 100% in at least 3 of response variables 1 to 6 **and** no intermittent fever, i.e. body temperature ≤ 38°C, in the preceding week (variable 7), with no more than one variable 1-6 worsening by more than 30% |
| Adapted ACR Pediatric response variables | The below response variables will be assessed for the Adapted ACR Pediatric 30, 50, 70, 90, 100:<br>1. Physician's Global Assessment of disease activity on a 0-100 mm VAS from 0 mm = no disease activity to 100 mm = very severe disease activity.<br>2. Parent's or patient's (if appropriate in age) Global Assessment of Subject's overall well-being on a 100 mm VAS from 0 mm= very well to 100 mm= very poor.<br>3. Functional ability: Childhood Health Assessment Questionnaire (CHAQ)<br>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)<br>5. Number of joints with limitation of motion<br>6. Laboratory measure of inflammation: CRP (mg/L)<br>7. Absence of intermittent fever due to SJIA (body temperature ≤ 38°C only for several hours during the day) during the preceding week |
| Assessment | A procedure used to generate data required by the study |
| Clinical remission on | At least 6 months (24 weeks) of inactive disease on medication |

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| medication | |
| Cohort | A group of newly enrolled patients treated at a specific dose and regimen (i.e. treatment group) at the same time |
| Control drug | Any drug (an active drug or an inactive drug, such as a placebo) which is used as a comparator to the drug being tested in the trial |
| Dose level | The dose of drug given to the patient (total daily or weekly etc.) |
| Enrollment | Point/time of patient entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol) |
| Epoch | A portion of the study which serves a specific purpose. Typical Epochs are: screening/recruitment, wash-out, treatment, and follow-up |
| Inactive disease | No joints with active arthritis; no fever (body temperature ≤ 38°C) due to SJIA, no rheumatoid rash, serositis, splenomegaly, hepatomegaly or generalized lymphadenopathy attributable to SJIA; normal CRP (or, if elevated, not attributable to SJIA); a Physician's Global Assessment of disease activity indicating no disease activity (i.e. score ≤ 10 mm); adapted from Wallace, Ruperto, and Giannini 2011. |
| Investigational drug | The drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug" or "investigational medicinal product." |
| Investigational treatment | All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls.<br>This *includes* any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination.<br>Investigational treatment generally *does not include* protocol-specified concomitant background therapies when these are standard treatments in that indication |
| Medication number | A unique identifier on the label of each investigational/study drug package in studies that dispense medication using an IRT system |
| Patient number | A number assigned to each patient who enrolls in the study. When combined with the center number, a unique identifier is created for each patient in the study. |
| Premature patient withdrawal | Point/time when the patient exits from the study prior to the planned completion of all study treatment administration and/or assessments; at this time all study treatment administration is discontinued and no further assessments are planned, unless the patient will be followed for progression and/or survival |
| Protocol | A written account of all the procedures to be followed in a trial, which describes all the administrative, documentation, analytical and clinical processes used in the trial. |
| Randomization number | A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment |
| SJIA Flare | Defined by at least 1 of the following:<br>1. Reappearance of fever not due to infections (>38°C lasting for at least 2 days) AND/ OR |

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| | 2. Flare according to the JIA pediatric criteria for flare (all criteria must be met):<br>≥ 30% worsening in at least 3 of the 6 Adapted ACR Pediatric response variables and<br>≥ 30% improvement in not more than 1 of the 6 Adapted ACR Pediatric response variables<br>If the Physician or Parent Global Assessment is one of the 3 Adapted ACR Pediatric response variables used to define SJIA Flare, worsening of ≥20 mm must be present.<br>If the number of active joints or joints with limitation of motion is one of the 3 Adapted ACR Pediatric response variables used to define flare, worsening in ≥ 2 joints must be present.<br>If CRP is used to define flare, CRP must be > 30 mg/L. |
| Stop study participation | Point/time at which the patient came in for a final evaluation visit or when study drug was discontinued whichever is later |
| Study drug/ treatment | Any single drug or combination of drugs administered to the patient as part of the required study procedures; includes investigational drug (s), active drug run-ins or background therapy |
| Study treatment discontinuation | Point/time when patient permanently stops taking study/investigational treatment for any reason; may or may not also be the point/time of premature patient withdrawal |
| Subject Number | A number assigned to each patient who enrolls into the study |
| Variable | A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study |

## Protocol summary

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| Protocol number | CACZ885G1301 |
| Title | An Open-label, single-arm, active-treatment, efficacy and safety study of canakinumab (ACZ885) administered for at least 48 weeks in Japanese patients with Systemic Juvenile Idiopathic Arthritis (SJIA) |
| Brief title | Study of efficacy and safety of canakinumab in Japanese patients with SJIA |
| Sponsor and Clinical Phase | Novartis<br>III |
| Investigation type | Biological |
| Study type | Interventional |
| Purpose and rationale | The purpose of this study is to evaluate efficacy and safety for canakinumab administered for at least 48 weeks in Japanese patients with SJIA |
| Primary Objective(s) | • To evaluate the efficacy of canakinumab, defined as the proportion of patients who achieved adapted ACR Pediatric 30 criteria at Week 8<br>• To evaluate the proportion of patients with canakinumab treatment who were able to taper corticosteroids successfully at Week 28 |
| Secondary Objectives | • To evaluate the efficacy (percentage of patients who met the adapted ACR Pediatric 30/50/70/90/100 criteria) of canakinumab over time<br>• To evaluate the components of adapted ACR Pediatric criteria of canakinumab over time<br>• To evaluate the proportion of patients who had flare with canakinumab treatment over time<br>• To evaluate the proportion of patients who achieved inactive disease (with and without duration of morning stiffness) with canakinumab treatment over time<br>• To evaluate the change C-reactive protein (CRP) levels with canakinumab treatment over time<br>• To evaluate the proportion of patients with canakinumab treatment who were able to taper corticosteroids successfully over time |

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| | • To evaluate corticosteroids dose reduction with canakinumab treatment over time<br>• To evaluate the safety and tolerability of canakinumab<br>• To evaluate the pharmacokinetics (PK)/pharmacodynamics (PD) of canakinumab<br>• To evaluate the immunogenicity of canakinumab |
| Study design | This is an open label, single-arm active treatment, efficacy and safety study of canakinumab 4 mg/kg every 4 weeks administered for at least 48 weeks in Japanese patients with SJIA until canakinumab is approved for SJIA in Japan or Novartis terminates the study. |
| Population | The study population will consist of male and female patients (≥2 to <20 years of age) with a confirmed diagnosis of SJIA. |
| Inclusion criteria | • Parent's or legal guardian's written informed consent and child's assent, if appropriate.<br>• Male and female patients aged ≥ 2 to < 20 years at the time of the screening visit.<br>• Confirmed diagnosis of SJIA as per ILAR definition (Petty, et al. 2004) that must have occurred at least 3 months prior to enrollment with an onset of disease < 16 years of age:<br>  • Arthritis in one or more joints, with or preceded by fever of at least 2 weeks duration that is documented to be daily/quotidian for at least 3 days and accompanied by one or more of the following:<br>  – Evanescent non-fixed erythematous rash,<br>  – Generalized lymph node enlargement,<br>  – Hepatomegaly and/or splenomegaly,<br>  – Serositis<br>• Active disease at the time of baseline defined as follows:<br>  • At least 2 joints with active arthritis (using ACR definition of active joint),<br>  • Documented spiking, intermittent fever (body temperature > 38°C) for at least 1 day during the screening epoch and within 1 week before first canakinumab dose,<br>  • CRP > 30 mg/L(3 mg/dL) (normal range < 10 mg/L(1 mg/dL)) |

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| | • Negative chest X-ray and IFN-γ ELISPOT (T-SPOT) test at screening or within 4 weeks prior to the screening visit. Patients with a positive TB screening test are eligible to participate in the study if (1) active TB is ruled out and (2) the patient is willing and able to complete a minimum of 4 weeks of latent TB treatment prior to initiating treatment with canakinumab (Day 1) and (3) the patient is willing to continue and complete the latent TB treatment (according to local guidelines) in parallel with study treatments. In the absence of local guidelines the US CDC guidelines for treatment of latent TB must be followed i.e. INH treatment for 9 months. Patients diagnosed with active TB should be referred for treatment as deemed appropriate and are not eligible to participate in this study.<br>• No concomitant use of second line agents such as disease-modifying and/or immunosuppressive drugs will be allowed with the exception of:<br>  • Stable dose of methotrexate (maximum of 20 mg/m$^2$/week) for at least 4 weeks prior to the baseline visit, and folic/folinic acid supplementation (according to standard medical practice of the center),<br>  • Stable dose of no more than one non-steroidal anti-inflammatory drug (NSAID) for at least 1 week prior to the baseline visit,<br>  • Stable dose of systemic corticosteroid treatment ≤ 1.0 mg/kg/day (maximum 60 mg/day for children over 60 kg) in 1-2 doses per day of oral prednisone (or equivalent) for at least 3 days prior to baseline |
| Exclusion criteria | • Pregnant or nursing (lactating) female patients, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test (> 5 mIU/ mL) at screening visit<br>• For female patients ages 2 to <18 years: female patients of childbearing potential who do not agree to abstinence or, if sexually active, do not agree to the use of contraception as defined in Section 6.5.9<br>• For female patients of child-bearing potential who are ≥18 years of age, defined as all females physiologically capable of becoming pregnant, unless they are using effective methods of contraception during administration of study treatment. Effective contraception methods for this age group mentioned |

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| | in Section 4.2<br>• History of hypersensitivity to study drug or to biologics.<br>• History/evidence of active macrophage-activation syndrome (MAS) within the last 6 months<br>• With active or recurrent bacterial, fungal or viral infection at the time of enrollment, including patients with evidence of Human Immunodeficiency Virus (HIV) infection, Hepatitis B and Hepatitis C infection. Patients with resolved/previous hepatitis B infection (a negative HBs antigen, but a positive anti-HBs antibody and/or anti-HBc antibody). Patients with a negative HBs antigen and positive anti-HBs and/or anti-HBc antibody due to previous hepatitis B vaccination and not because of a previous hepatitis B infection can be included.<br>• With underlying metabolic, renal, hepatic, infectious or gastrointestinal conditions which in the opinion of the investigator immunocompromises the patient and/ or places the patient at unacceptable risk for participation in an immunomodulatory therapy. |
| Investigational and reference therapy | • Canakinumab 4 mg/kg every 4 weeks (q4wks) |
| Efficacy assessments | • Adapted ACR pediatric criteria<br>• Physician's global assessment of disease activity (VAS)<br>• Parent's or patient's global assessment of subject's overall well-being<br>• CHAQ®<br>• Parent's or patient's assessment of pain (VAS)<br>• Joint counts with active arthritis<br>• Joints counts with limitation of motion<br>• C-reactive protein (CRP)<br>• Intermittent fever assessment<br>• Flare<br>• Inactive disease<br>• Steroid tapering |
| Safety assessments | • Physical examination<br>• Vital signs<br>• Height and weight<br>• Clinical assessment of serositis, splenomegary,hepatomegary and lymphadenopathy<br>• Senography of spleen and liver<br>• Laboratory evaluation (hematology, clinical chemistry, |

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| | urinalysis)<br>• Local tolerability(subcutaneous injection)<br>• ECG<br>• Pregnancy<br>• Macrophage activation syndrome |
| Other assessments | • PK<br>• PD<br>• Immunogenicity<br>• [redacted]<br>• TB risk |
| Data analysis | The primary efficacy variable are the proportion of patients who achieve a minimum adapted ACR Pediatric 30 criteria at week 8 and the proportion of patients with canakinumab treatment who were able to taper corticosteroids successfully at Week 28. Frequency tables with the number and percentage of patients who achieved a minimum adapted ACR pediatric 30 criteria at Week 8 and patients who were able to taper corticosteroids successfully at Week 28 will be provided based on the FAS. All of the efficacy results will be presented in a descriptive manner. |
| Key words | Canakinumab, SJIA, Japanese patients, Efficacy, safety |

# 1 Introduction

## 1.1 Background

Systemic Juvenile Idiopathic Arthritis (SJIA) is a unique subset of Juvenile Idiopathic Arthritis (JIA) that occurs in children 16 years of age and younger, and accounts for approximately 4 − 17% of JIA (Ravelli and Martini 2007). In contrast to other JIA subtypes where the female population is affected more commonly, SJIA equally affects males and females. The peak age of disease onset lies between 18 months and 2 years (Symmons, et al 1996), but SJIA may occur in children of any age and, rarely, in young adults too (Woo 2006). In Japan, an estimated SJIA prevalence was determined to be 11.3 in 100,000 children based on a study of 2,893 JIA patients (Takei and Kato 2008). In another publication, the percentage of JIA patients with SJIA was found to be 41.7% (Takei, Yamashita, and Kato 2008).

SJIA is a serious, potentially disabling form of arthritis associated with systemic symptoms such as fever, anemia, rash, leukocytosis, elevated erythrocyte sedimentation rate and acute-phase proteins, a phenotype comparable in some features to Muckle-Wells syndrome.

SJIA is heterogeneous in its severity, the disease-progression can take the following courses: (i) monocyclic course (42%), with remission within 2–4 years; (ii) relapsing course (polycyclic course 7%), characterized by flares of systemic features and mild arthritis; (iii) persistent disease (51%) with arthritis, which is usually more prominent after the regression of systemic features and typically lasting for several years (Woo 2006).

Predictors of poor outcome include the presence of systemic features 6 months after onset, thrombocytosis, and the presence of polyarthritis with hip involvement (Woo 2006). The mortality rate from SJIA has been shown to be higher (standardized mortality rate in SJIA in the United States population at 1.8 [95% CI, 0.66 – 3.92) than the mortality rate associated with other subtypes of JIA (Hashkes, et al 2010).

The main causes of SJIA-related death included Macrophage Activation Syndrome (MAS), infection and, rarely, myocardial insufficiency (Woo 2006). Children with severe SJIA who are inadequately treated also have an increased incidence of amyloidosis (1.4% to 9%, Svantesson, et al 1983) compared to other JIA subtypes. Other potential complications of SJIA and affecting the prognosis include malnutrition, growth retardation, and other growth disturbances, as well as osteoporosis, joint deformity, limited or poor school performance possibly related to school absence, and physical disability. Literature with pediatric rheumatologists treating these patients highlight the challenge to provide effective therapy to limit the serious disability and also the potential for death of these children during a flare of their disease (Carrasco, Smith and Lovell 2004). Although a minority of patients does well with non-steroidal anti-inflammatory drugs (NSAIDs), most patients require oral and/ or systemic corticosteroids (CS) and methotrexate (MTX) for prolonged periods to treat the systemic manifestations and arthritic features, respectively. Corticosteroids treatment results in significant morbidity, including but not limited to vertebral compression fractures, cataracts and severe growth retardation. (Sarnes et al. 2011) Intravenous gamma globulin, cyclosporine

and thalidomide have also been used to treat refractory cases. Most SJIA patients do not respond well to anti-tumor necrosis factor (TNF) therapy.

Several lines of evidence show that interleukin-1 (IL-1) plays a pivotal role in the pathogenesis of SJIA (Dinarello 2005, _Pascual et al 2005,_Verbsky and White 2004). The major roles of IL-1 in SJIA are: (i) fever induction (increase in prostaglandin E2 via synthesis of cycloxygenase-2 production in the hypothalamic vascular network); (ii) stimulate endothelial receptors causing rashes (iii) increases the circulating IL-6 (via stimulation of endothelial receptors) thereby induces several acute phase proteins (increase in erythrocyte sedimentation rate (ESR)) and increases platelet production, which results in thrombocytosis; (iv) on the bone marrow to increase mobilization of granulocyte progenitors and mature neutrophils, resulting in peripheral neutrophilia; and (v) decreased response to erythropoietin, which causes anemia (Dinarello 1996).

Furthermore, sera from patients with systemic disease induced more IL-1 secretion compared with patients with only active arthritis (Dinarello 2005). Therefore, it can be argued, that blocking IL-1 could prevent various systemic effects including IL-6 mediated reactions. In line with this, Pascual et al 2005 showed that serum from SJIA patients induces the transcription of innate immunity genes (fibronectin; 17-fold), including IL-1 in healthy peripheral blood mononuclear cells (PBMCs). These findings prompted the use of anakinra (an IL-1 receptor antagonist) in the treatment of SJIA patients (Vastert et al 2014, Quartier et al 2011, Pascual et al 2005, Verbsky, and White 2004) and the results were encouraging. Based on the mounting clinical evidence of the effectiveness of IL-1 inhibitors in the treatment of SJIA, the ACR issued updated treatment guidelines for SJIA in which IL-1 inhibitors are recommended as first line therapy in patients with an overall physician disease activity assessment of >5 (scale of 1-10) and in patients with active arthritis involving > 4 joints and a global assessment of ≤5 (Ringold et al 2013). They also recommend them for patients with continued disease activity after treatment with 2 weeks of corticosteroid monotherapy or NSAID monotherapy > 4 weeks.

Canakinumab (ACZ885) is a high-affinity fully human monoclonal anti-human interleukin-1β (IL-1β) antibody of the IgG1/κ isotype. Canakinumab is designed to bind to human IL-1β blocking the interaction of this cytokine to its receptors, thus functionally neutralizing the bioactivity of this cytokine, without preventing binding of the natural inhibitor, IL-1Ra nor binding of IL-1α to the IL-1 receptors. IL-1β is recognized as one of the principal pro-inflammatory cytokines, in a variety of inflammatory conditions (Dinarello 1996, Dinarello 2005).

Canakinumab, as a potent neutralizer of IL-1β, is expected to treat the underlying structural features of arthritis (inflammation, bone and cartilage degradation), as well as providing relief of the symptoms in at least a subset of patients with these forms of arthritis.

Canakinumab has a half-life of approximately 21-28 days. The longer half-life compared to that of anakinra (6 hours) and rilonacept (8-9 days) may well be a convenient and potent treatment option for SJIA patients in need of infrequent administration. As of May 2014, canakinumab has been approved for the treatment of SJIA in the European Union (for patients ≥2 years of age with poor response to NSAIDs and systemic CS and may be used with and

without concomitant MTX), the United States (for patients ≥2 years of age) and 9 other countries including Canada and Switzerland.

To date, four clinical studies (CACZ885A2203, CACZ885G2305, CACZ885G2301, and CACZ885G2301E1) have been performed by Novartis to evaluate canakinumab as a potential therapeutic agent to treat patients with SJIA. CACZ885A2203 was a proof of concept dose ranging study that showed 59% patients responded, achieving an adapted ACR pediatric 50 or better, and four patients (18%) had inactive disease. (Ruperto, et al. 2012) CACZ885G2305 was the first pivotal study conducted with a primary objective to assess the initial efficacy of canakinumab with respect to the adapted ACR Pediatric criteria in patients with SJIA and active systemic manifestations. The proportion of patients who had an adapted ACR padiatric 30 at Day 15 was significantly higher in the canakinumab group compared with the placebo group (83.7% vs. 9.8%). (Ruperto, et al 2012). CACZ885G2301 was the second pivotal study conducted in SJIA which showed that canakinumab reduced the risk of flare by 64% and prolonged the time to flare compared to placebo (Ruperto, et al 2012). Additionally, 44.5% of patients on CS at study entry successfully tapered their corticosteroid dose within 5 months, and 33% of patients were able to discontinue the corticosteroid.

In addition, canakinumab has demonstrated no effect on induction and persistence of antibody response after vaccination with unadjuvanted influenza and the alum-adjuvanted MenC vaccine in healthy subjects (Chioato, et al 2009).

No Japanese patients with SJIA were included in the four clinical studies described above. Consequently, this study will evaluate the efficacy and safety of canakinumab in Japanese patients with SJIA.

### 1.2 Purpose

This is a phase III study designed to provide efficacy and safety data for canakinumab administered for at least 48 weeks as subcutaneous (s.c.) injection every 4 weeks (q4wk) in Japanese patients with Systemic Juvenile Idiopathic Arthritis (SJIA). Interim analysis (IA) data at Week 28 and 48 from this study will support a registration submission of canakinumab in the indication of SJIA in Japan.

Beyond Week 48, the study allows patients to continue canakinumab treatment until it is approved for SJIA and is commercially available for clinical use in Japan or Novartis terminates the study.

## 2 Study objectives

### 2.1 Primary objective(s)

- To evaluate the efficacy of canakinumab, defined as the proportion of patients who achieved a minimum adapted ACR Pediatric 30 criteria at Week 8
- To evaluate the proportion of patients with canakinumab treatment who were able to taper corticosteroids successfully at Week 28

## 2.2 Secondary objectives

- To evaluate the efficacy (percentage of patients who met the adapted ACR Pediatric 30/50/70/90/100 criteria) of canakinumab over time
- To evaluate the components of adapted ACR Pediatric criteria of canakinumab over time
- To evaluate the proportion of patients who had flares with canakinumab treatment over time
- To evaluate the proportion of patients who achieved inactive disease (with and without duration of morning stiffness) with canakinumab treatment over time
- To evaluate the change in C-reactive protein (CRP) levels with canakinumab treatment over time
- To evaluate the proportion of patients with canakinumab treatment who were able to taper corticosteroids successfully over time
- To evaluate corticosteroids dose reduction with canakinumab treatment over time
- To evaluate the safety and tolerability of canakinumab
- To evaluate the pharmacokinetics (PK)/pharmacodynamics (PD) of canakinumab
- To evaluate the immunogenicity of canakinumab

# 3 Investigational plan

## 3.1 Study design

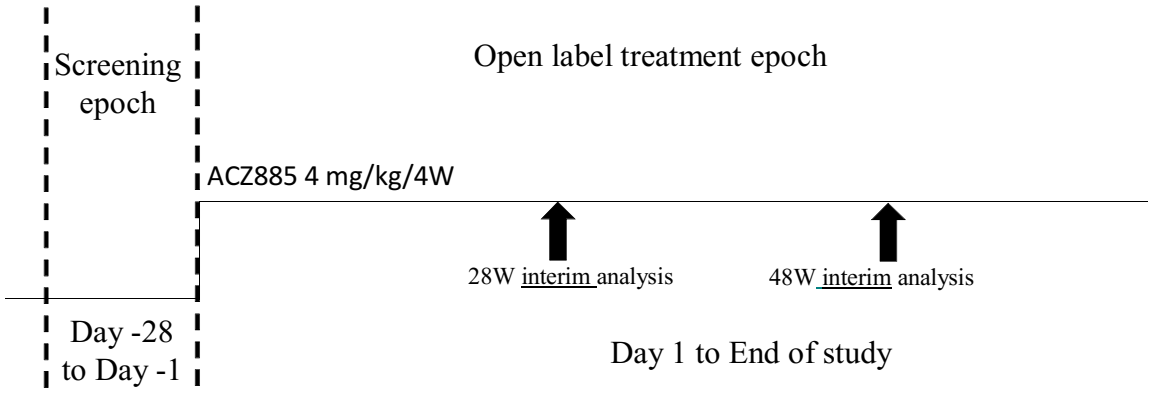
This is an open label, single-arm active treatment, efficacy and safety study of canakinumab 4 mg/kg every 4 weeks administered for at least 48 weeks in Japanese patients with SJIA until canakinumab is approved for SJIA in Japan and commercially available or until Novartis terminates the study. Approximately 20 patients will be enrolled in the study.

The study will consist of two distinct study epochs as outlined below (see also Figure 3-1):

- Screening epoch: Day -28 to Day -1
- Open label treatment epoch: Day 1 to approval and commercially available or study termination

Two interim analyses are planned at Week 28 and Week 48 to support the registration dossier in Japan.

**Figure 3-1 Study design**




### 3.1.1 Screening epoch

Eligible patients will enter the screening epoch to assess whether the patients will be eligible to enter the next epoch. Patients may be required to visit the study site multiple times to complete all assessments, which also include tuberculosis screening

### 3.1.2 Treatment epoch

Eligible patients will enter an open label treatment epoch with the baseline evaluation conducted on Day 1. Patients will be administered canakinumab 4 mg/kg (maximum dose is 300 mg) every 4 weeks during this epoch without any dose adjustments allowed until it is approved for SJIA in Japan and commercially available or until Novartis terminates the study.

Patients who do not meet a minimum adapted ACR Pediatric 30 criteria by Week 12 will be discontinued from the study.

## 3.2 Rationale of study design

This study is designed to evaluate the efficacy and safety of canakinumab in a Japanese SJIA population. A randomized blinded trial is not feasible in Japan due to the limited number of patients available for study in the target population and the symptomatology of the disease.

## 3.3 Rationale of dose/regimen, route of administration and duration of treatment

The PK analysis between Japanese and non-Japanese revealed no ethnic differences.

Based on the efficacy and safety data generated from the pivotal trials, CACZ885G2305, CACZ885G2301, and CACZ885G2301E1, the same dose of 4 mg/kg every 4 weeks was chosen as the dose for this study. The pivotal trials showed that canakinumab treatment resulted in a clinically meaningful response in a large percentage of patients, a significantly reduced risk of experiencing a disease flare with continued canakinumab administration and an ability to successfully reduce or eliminate concomitant corticosteroid dose in a significant proportion of patients. One year (48 weeks) of canakinumab treatment was chosen as an

appropriate time period to evaluate long-term safety and efficacy in the context of existing data from the pivotal studies listed above.

## 3.4 Rationale for choice of comparator

Not applicable.

## 3.5 Purpose and timing of interim analyses/design adaptations

Two interim analyses will be performed during the study: One will be at Week 28, to support the registration dossier and the second will be at Week 48.

## 3.6 Risks and benefits

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

SJIA continues to be associated with significant morbidity and mortality (up to 14%) (Batthish et al 2005). The main causes of death include infection, MAS, and rarely, myocardial insufficiency (Woo 2006). Many children with SJIA never achieve long-term remission. Inflammation can lead to joint damage within 2 years. Up to 50-70% of SJIA patients have active arthritis as adults, and 30-40% can have long-term disabilities. Some need major surgery or joint replacement (Hashkes and Laxer 2005). Since 2000, tocilizumab, an IL-6 inhibitor, has been the only approved therapy for SJIA in Japan. . Consequently, a high unmet medical need exists to develop additional treatment options which have different unique mechanisms of action.

To date, the data generated from the clinical trials involved with canakinumab in patients with SJIA have shown an acceptable benefit risk profile. Canakinumab treatment has demonstrated strong efficacy (84% response rate at Day 15 with 33% having with inactive disease; 45% successfully reduced steroid dose and a 64% reduced risk for a SJIA flare with continued canakinumab) and an acceptable safety profile including infections, gastrointestinal disorders along with skin and musculo skeletal disorders as possible adverse events (Ruperto, et al 2011).

In the Phase III canakinumab SJIA program, the most frequent adverse effects included infections, mostly non-serious of mild to moderate severity, although serious infections were observed. The most frequently reported (>10%) infections affected the upper respiratory tract (nasopharyngitis, upper respiratory tract infection, rhinitis and pharyngitis) and the gastrointestinal tract (gastroenteritis). Serious adverse events were most commonly related to disease flares or associated with MAS.

Macrophage activation syndrome is a well-known serious and potentially fatal condition associated with SJIA. The most common triggers of MAS are infections and disease flare.

Based on the available Phase III data, canakinumab neither increases nor decreases the risk of developing MAS in SJIA; however, MAS is considered to be a potential risk and therefore the clinical signs and symptoms should be carefully monitored by investigators. Occurrence of other risks, e.g. infections, neutropenia, thrombocytopenia and malignancies are also required to be carefully monitored by the investigator.

Neutropenia occurred in 6.0% of patients, but there was no evidence of any increased rate of infection among these patients. The small proportion of patients (4%) with low platelet counts had no evidence of bleeding-related AEs.

Local tolerability at the site of subcutaneous injection will also be evaluated at all administration visits and at the end of study (EOS) visit in all patients in case of any local reaction, and at each clinical visit until this has disappeared.

Canakinumab offers a new therapeutic option for patients who do not respond to standard therapy. Canakinumab enables patients to control their disease and reduce their use of steroids, a main cause of impaired growth and fractures in SJIA children.

The risk to subjects in this trial will be minimized by compliance with the eligibility criteria, close clinical monitoring, and adherence to the protocol guidelines for dose administration/reduction/interval prolongation/discontinuation.

# 4 Population

The study population will consist of male and female patients (≥2 to <20 years of age) with a confirmed diagnosis of SJIA.

## 4.1 Inclusion criteria

Patients eligible for inclusion in this study have to fulfill all of the following criteria:

1. Parent's or legal guardian's written informed consent and child's assent, if appropriate.
2. Male and female patients aged ≥ 2 to < 20 years at the time of the screening visit.
3. Confirmed diagnosis of SJIA as per ILAR definition (Petty, et al. 2004) that must have occurred at least 3 months prior to enrollment with an onset of disease < 16 years of age:
    a. Arthritis in one or more joints, with or preceded by fever of at least 2 weeks duration that is documented to be daily/quotidian for at least 3 days and accompanied by one or more of the following:
        i. Evanescent non-fixed erythematous rash,
        ii. Generalized lymph node enlargement,
        iii. Hepatomegaly and/or splenomegaly,
        iv. Serositis

4. Active disease at the time of baseline defined as follows:
    a. At least 2 joints with active arthritis (using ACR definition of active joint);
    b. Documented spiking, intermittent fever (body temperature > 38°C) for at least 1 day during the screening epoch and within 1 week before first canakinumab dose;
    c. CRP > 30 mg/L(3 mg/dL) (normal range < 10 mg/L(1 mg/dL))
5. Negative chest X-ray and INF-γ ELISPOT (T-SPOT) test at screening or within 4 weeks prior to the screening visit. Patients with a positive TB screening test are eligible to participate in the study if (1) active TB is ruled out and (2) the patient is willing and able to complete a minimum of 4 weeks of latent TB treatment prior to initiating treatment with canakinumab (Day 1) and (3) the patient is willing to continue and complete the latent TB treatment (according to local guidelines) in parallel with study treatments. In the absence of local guidelines the US CDC guidelines for treatment of latent TB must be followed i.e. INH treatment for 9 months. Patients diagnosed with active TB should be referred for treatment as deemed appropriate and are not eligible to participate in this study.
6. No concomitant use of second line agents such as disease-modifying and/or immunosuppressive drugs will be allowed with the exception of:
    a. Stable dose of methotrexate (maximum of 20 mg/m$^2$/week) for at least 4 weeks prior to the baseline visit, and folic/folinic acid supplementation (according to standard medical practice of the center);,
    b. Stable dose of no more than one non-steroidal anti-inflammatory drug (NSAID) for at least 1 week prior to the baseline visit;
    c. Stable dose of systemic corticosteroid treatment ≤ 1.0 mg/kg/day (maximum 60 mg/day for children over 60 kg) in 1-2 doses per day of oral prednisone (or equivalent) for at least 3 days prior to baseline

## 4.2 Exclusion criteria

Patients fulfilling any of the following criteria are not eligible for inclusion in this study. No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

1. Pregnant or nursing (lactating) female patients, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test (> 5 mIU/ mL) at screening visit
2. For female patients ages 2 to <18 years: female patients of childbearing potential who do not agree to abstinence or, if sexually active, do not agree to the use of contraception as defined in Section 6.5.9
3. Female patients of child-bearing potential who are ≥18 years of age, defined as all females physiologically capable of becoming pregnant, unless they are using effective methods of

contraception during administration of study treatment. Effective contraception methods for this age group include:

- Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
- Male sterilization (at least 6 m prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject
- Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/ vaginal suppository
- Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception
- Placement of an intrauterine device (IUD) or intrauterine system (IUS)

In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment. Reliable contraception should be maintained throughout the study.

4. History of hypersensitivity to study drug or to biologics.
5. History / evidence of active macrophage-activation syndrome (MAS) within the last 6 months.
6. With active or recurrent bacterial, fungal or viral infection at the time of enrollment, including patients with evidence of Human Immunodeficiency Virus (HIV) infection, Hepatitis B and Hepatitis C infection. Patients with resolved/previous hepatitis B infection (a negative HBs antigen, but a positive anti-HBs antibody and/or anti-HBc antibody). Patients with a negative HBs antigen and positive anti-HBs and/or anti-HBc antibody due to previous hepatitis B vaccination and not because of a previous hepatitis B infection can be included.
7. Any of the risk factors for tuberculosis (TB) such as:
   - History of any of the following: residence in a congregate setting (e.g. jail or prison, homeless shelter, or chronic care facility), substance abuse (e.g. injection or noninjection); health-care workers with unprotected exposure to patients who are at high risk of TB or patients with TB disease before the identification and correct airborne precautions of the patient, or
   - Close contact (i.e. share the same air space in a household or other enclosed environment for a prolonged period (days or weeks, not minutes or hours)) with a person with active pulmonary TB disease within the last year
   - Evidence of Latent TB (positive T-SPOT) but unwilling or unable to complete a minimum of 4 weeks of latent TB treatment before initiating treatment with canakinumab (Day 1).

8. With underlying metabolic, renal, hepatic, infectious or gastrointestinal conditions which in the opinion of the investigator immunocompromises the patient and/ or places the patient at unacceptable risk for participation in an immunomodulatory therapy.
9. With neutropenia (absolute neutrophil count < 1500/$mm^3$) at screening.
10. History or current diagnosis of ECG abnormalities indicating significant risk of safety for patients participating in the study such as:
    - Concomitant clinically significant cardiac arrhythmias, e.g., sustained ventricular tachycardia, and clinically significant second or third degree AV block without a pacemaker
    - History of familial long QT syndrome or known family history of Torsades de Pointes
11. With significant medical conditions, which in the opinion of the Investigator will exclude the patient from the study (can be discussed on a case by case basis with Novartis).
12. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin or in-situ cervical cancer), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.
13. Clinical evidence of liver disease or liver injury as indicated by abnormal liver function tests at screening such as AST, ALT, GGT, alkaline phosphatase, or serum bilirubin (must not exceed twice the upper limit value of the normal range for age).
    Exception: Patients who exceed this limit after initiating latent TB treatment may be eligible for participation in this study pending confirmation with Novartis.
14. Presence of moderate to severe impaired renal function as indicated by clinically significantly abnormal creatinine (≥ 1.5 x upper normal limit [ULN]) or abnormal urinary constituents (e.g., albuminuria) at screening. Evidence of urinary obstruction or difficulty in voiding at screening.
15. Use of the following therapies:
    - Anakinra within 24 hours prior to Baseline visit
    - Rilonacept within 1 week prior to Baseline visit
    - Abatacept within 10 weeks prior to the Baseline visit
    - Tocilizumab within 3 weeks prior to Baseline visit
    - Etanercept within 4 weeks prior to Baseline visit
    - Adalimumab within 8 weeks prior to the Baseline visit
    - Infliximab within 12 weeks prior to the Baseline visit
    - Rituximab within 26 weeks prior to the Baseline visit
    - Leflunomide within 4 weeks prior to the Baseline visit. Documentation of a completion of a full cholestyramine elimination treatment after most recent leflunomide use will be required.
    - Thalidomide within 4 weeks prior to the Baseline visit
    - Cyclosporine within 4 weeks prior to the Baseline visit

- Intravenous immunoglobulin (i.v. Ig) within 8 weeks prior to the Baseline visit
- 6-Merceptopurine, azathioprine, cyclophosphamide, or chlorambucil within 12 weeks prior to the Baseline visit
- Dapsone, mycophenolate mofetil within 3 weeks prior to the Baseline visit
- Growth hormone within 4 weeks prior to the Baseline visit
- Corticosteroids (oral prednisone (or equivalent)) > 1.0 mg/kg/day (or greater than the maximum of 60 mg/day for children over 60 kg) for at least 3 days prior to the Baseline visit
- Intra-articular, peri-articular or intramuscular corticosteroid injections within 4 weeks prior to the Baseline visit
- Any other investigational biologics or any canakinumab treatment within 8 weeks prior to the Baseline visit
- Any other investigational drugs, other than investigational biologic treatment, within 30 days (or 3 months for investigational monoclonal antibodies) or 5 half-lives prior to the Baseline visit, whichever is longer

16. Live vaccinations within 3 months prior to the start of the study. Killed or inactivated vaccines may be permitted according to the investigator's discretion.
17. Donation or loss of blood (amount depending on age and weight, 10-20% or more of volume, within 8 weeks prior to first administration, or longer if required by local regulation.
18. Family and social conditions rendering regular medical assessment not possible.
19. Any organ transplant recipient, or patient currently listed for imminent transplant (i.e. patients on an administrative transplant waiting list will not be excluded), or admitted for any transplantation.
20. History of drug or alcohol abuse within the 12 months prior to administration.

# 5 Treatment

## 5.1 Protocol requested treatment

### 5.1.1 Investigational treatment

Patients will receive canakinumab 4 mg/kg (maximum dose is 300 mg) administered subcutaneously every 4 weeks at the study center throughout the study. Study drug dose adjustment and/or interruptions are not permitted, except per the need for changes in patient size/weight.

ACZ885 150 mg: Active canakinumab in individual 2 mL glass vials, each containing 150 mg canakinumab liquid in vial.

Sites will provide a 5% dextrose solution for subcutaneous injection as needed for canakinumab dilution purposes only, for patients requiring a dose less than 15 mg.

The maximal total single dose of canakinumab allowed is 300 mg, which is administered as two subcutaneous 150 mg injections once every 4 weeks.

Novartis will provide canakinumab until study completion.

### 5.1.2 Additional study treatment

No additional treatment beyond investigational treatment is requested for this trial.

## 5.2 Treatment arms

All patients will receive canakinumab as open-label study medication.

Patients will be administered canakinumab 4 mg/kg every 4 weeks. The maximal total single dose of canakinumab allowed is 300 mg. Any patient who requires a dose greater than a single dose of 150 mg (patients > 37.5 kg) will require two s.c. injections.

## 5.3 Treatment assignment

Eligible patients with signed informed consent will be assigned to canakinumab treatment.

## 5.4 Treating the patient

### 5.4.1 Patient numbering

Each patient is uniquely identified in the study by a combination of his/her center number and patient number. The center number is assigned by Novartis to the investigator site. Upon signing the informed consent form, the patient is assigned a patient number by the investigator (composed of the center number and patient number). At each site, the first patient is assigned patient number 1, and subsequent patients are assigned consecutive numbers (e.g., the second patient was assigned patient number 2; the third patient is assigned patient number 3, etc.). The assigned patient number should be entered in the field labeled “Subject ID” on the EDC data entry screen. Once assigned to a patient, a patient number will not be reused. If the patient failed to be enrolled for any reason, the reason for not being enrolled will be entered on the Screening Log, and the Demography eCRF should be completed.

Each patient is uniquely identified by a Subject Number which is composed by the site number assigned by Novartis and a sequential number assigned by the investigator. Once assigned to a patient, the Subject Number will not be reused.

Upon signing the informed consent form, the patient is assigned the next sequential number by the investigator. The site should select the CRF book with a matching Subject Number from the EDC system to enter data.

If the patient fails to be treated for any reason, Sponsor must be notified within 2 days that the patient was not treated. The reason for not being treated will be entered on the Screening Epoch Study Disposition CRF.

### 5.4.2 Dispensing the investigational treatment

Study drug will be supplied to each study site by Novartis as open labeled bulk medication.

Each study site will be supplied by Novartis with investigational treatment in packaging of identical appearance.

Patient will be administered canakinumab 4 mg/kg every 4 weeks.

### 5.4.3 Handling of study treatment

#### 5.4.3.1 Handling of investigational treatment

Investigational treatment must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designees have access. Upon receipt, all investigational treatment should be stored according to the instructions specified on the labels. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis CPO Quality Assurance.

Medication labels will be in Japanese and comply with the legal requirements of Japan. They will include storage conditions for the investigational treatment but no information about the patient except for the medication number.

The investigator must maintain an accurate record of the shipment and administration of investigational treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused investigational treatment, packaging, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

#### 5.4.3.2 Handling of other study treatment

Not applicable.

### 5.4.4 Instructions for prescribing and taking study treatment

The s.c. injections of investigational treatment may be administered into the patient's arm or thigh. Detailed instructions on the preparation and administration of the study drug will be described in the Pharmacist Manual and provided to each site.

All patients will receive a first open-label canakinumab 4 mg/kg s.c. at Baseline (Day 1). Following Baseline, patients will receive injections every 4 weeks until canakinumab is approved for SJIA in Japan and commercially available or until Novartis terminates the study.

The maximal total single dose of canakinumab allowed is 300 mg. Any patient who requires a dose greater than 150 mg (patients > 37.5 kg) will require two s.c. injections.

All dosages administered to the patient and all dose changes during the study must be recorded on the Dosage Administration Record CRF

### 5.4.5 Permitted dose adjustments and interruptions of study treatment

Study treatment dose adjustments and/or interruptions are not permitted, however, if for any reason a change in dose is administered, it must be recorded on the Dosage Administration Record CRF.

### 5.4.6 Steroid tapering

Patients using concomitant corticosteroids at study entry may begin to reduce their corticosteroid dose to the lowest possible dose/discontinuation beginning at Week 8 until the End of Study.

All changes in corticosteroid doses should be made in the appropriate concomitant medication eCRF.

**Rules for steroid tapering:**

- Corticosteroid tapering is encouraged and permitted to occur beginning at Week 8 if it is the investigator's judgment that a patient's SJIA disease activity is stable and has not worsened.
- As shown in Table 5-1, for oral prednisone (or equivalent) doses > 0.1 mg/kg/day, the dose should be tapered at 0.1 mg/kg of oral prednisone (or equivalent) per week. If and when the oral prednisone (or equivalent) dose is at 0.1 mg/kg/day, the dose should be reduced to 0.05 mg/kg/day of oral prednisone (or equivalent) for 1 week, then to 0.05 mg/kg/every 48 hours for the next 2 weeks and then discontinued.
- If it is the investigator's judgment that a patient's SJIA disease activity worsens during steroid tapering then the patient must return to the immediate prior dose (or higher if deemed necessary by the investigator) and may not resume steroid dose tapering for at least 2 weeks.

**Table 5-1 Steroid tapering guideline**

| Prednisone (or equivalent) dose | Amount of reduction |
|---|---|
| > 0.1 mg/kg/day | Taper at 0.1 mg/kg per week until at dose of 0.1 mg/kg/day |
| 0.1 mg/kg/day | Taper to dose of 0.05 mg/kg/day for 1 week |
| ≤ 0.05 mg/kg/day | Alternate administration days (i.e. take dose every 48 hours) for 2 weeks and then discontinue |

### 5.4.7 Rescue medication

Rescue medication will not be allowed during the course of the study. Please see Section 5.4.6 for details on corticosteroid tapering.

### 5.4.8 Concomitant treatment

The investigator should instruct the patient to notify the study site about any new medications he/she takes after patient was enrolled into the study. All medications, procedures and

significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient enrolled into the study must be recorded.

### 5.4.9 Prohibited Treatment

No concomitant use of second line agents such as disease-modifying and/or immunosuppressive drugs will be allowed with the exception of:

- Systemic steroid treatment ≤ 1.0 mg/kg/day (maximum 60 mg/day for children over 60 kg) in 1-2 doses of oral prednisone (or equivalent). The steroid dose should be stable until Week 8. Beginning at the Week 8 visit, steroid dose tapering should be attempted as per steroid tapering guidelines (Section 5.4.6).
- Stable dose of methotrexate (maximum of 20 mg/m$^2$/ week) and folic/folinic acid supplementation (according to standard medical practice of the center).
- Stable dose of no more than one NSAID.

**Table 5-2 Prohibited treatment**

| Medication | Action to be taken |
|---|---|
| Anakinra | discontinue study treatment |
| Tocilizumab, abatacept, rilonacept, rituximab and any other biologics (investigational or marketed) | discontinue study treatment |
| Etanercept, adalimumab, infliximab, or any TNF inhibitor (investigational or marketed) | discontinue study treatment |
| Leflunomide, thalidomide, cyclosporine, or i.v. immunoglobulin (i.v. Ig) | discontinue study treatment |
| 6-Merceptopurine, azathioprine, cyclophosphamide, or chlorambucil | discontinue study treatment |
| Dapsone or mycophenolate mofetil | discontinue study treatment |
| Growth hormone | discontinue study treatment |
| Intra-articular, peri-articular or intramuscular corticosteroid injections | discontinue study treatment |
| Any other investigational non-biological drugs | discontinue study treatment |
| Live vaccination | discontinue study treatment |

Note: Live vaccination is NOT allowed after screening and until after 3 months following the last study dose. Killed or inactivated vaccines may be permitted according to the investigator's discretion.

It is recommended not to initiate biologic treatment until 3 months after the last dose of study drug. Therefore, biologic treatment should not be used any time during study participation.

Patients should remain on their current medication wherever possible for the duration of the study. All prescription medications and significant non-drug therapies (including physical therapy and blood transfusions) taken within one month, and over-the-counter drugs (including vitamins) taken within 14 days prior to the start of and throughout the study must be recorded on the Concomitant Medications/ Non-Drug Therapies page of the eCRF.

Medication entries for corticosteroids, methotrexate and NSAIDs should be specific to trade name, the dose and unit, the frequency and route of administration, the start and discontinuation date and the reason for therapy. Medication entries for all other treatments should be specific to trade name, the start and discontinuation date, and the reason for therapy.

The investigator should instruct the patient to notify the study site about any new medications he/she takes after the start of the study drug. All medications and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient starts treatment with study drug must be listed on the Concomitant medications/Significant non-drug therapies eCRF.

### 5.4.10 Discontinuation of study treatment

Patients may voluntarily discontinue study treatment for any reason at any time.

Study treatment *must* be discontinued under the following circumstances:

- If, on balance the investigator believes that continuation would be detrimental to the patient's well-being.
- Use of prohibited treatment as per Table 5-2.
- Any severe or serious adverse event that is not compatible with administration of study medication, including adverse events that require treatment with an unacceptable co-medication.
- Onset of malignancy.
- Occurrence of uncontrolled life-threatening infection.
- Pregnancy.
- Patients who do not meet the adapted ACR Pediatric 30 criteria by Week 12.
- Patients with non-response (defined as Adapted ACR Pediatric <30) at two consecutive visits at any time in the study beginning at Week 12 must be discontinued.
- Any other protocol deviation that results in a significant risk to the patient's safety.

All patients who discontinue will complete an EOS visit, be discontinued from the trial and be treated as per standard local medical practice (see also Section 7.2.2 for information on SAE reporting following the last dose of study medication).

If premature withdrawal from the study occurs for any reason, the investigator must make every effort to determine the primary reason for a patient's premature withdrawal from the study and record this information on the Study Phase Completion page.

Patients who are prematurely withdrawn from the study will not be replaced.

### 5.4.11 Withdrawal of consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time.

Withdrawal of consent occurs only when a patient does not want to participate in the study anymore and does not want any further visits or assessments and does not want any further study related contacts and does not allow analysis of already obtained biologic material.

If a patient withdraws consent, the investigator must make every effort (e.g. telephone, e-mail, letter) to determine the primary reason for this decision and record this information on the Withdrawal of Informed Consent page. Study treatment must be discontinued and no further assessments conducted. All biological material that has not been analyzed at the time of withdrawal must not be used. Further attempts to contact the patient are not allowed unless safety findings require communicating or follow-up.

### 5.4.12 Loss to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw, the investigator should show "due diligence" by contacting the patient, family or family physician as agreed in the informed consent and by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc. A patient should not be formally considered lost to follow-up until his/her scheduled end of study visit would have occurred.

### 5.4.13 Emergency breaking of assigned treatment code

Not applicable for this open-label study.

### 5.4.14 Study completion and post-study treatment

All patients are expected to complete an End-of-Study (EOS) visit at the completion of the treatment epoch (or at the close of the study) unless discontinued from the study prematurely, for any reason. The assessments for the EOS visit are marked in the assessment schedule (Section 6).

Information on the date the subject last took drug, the subject's completion or discontinuation of the study and the reason for discontinuation of the study will be recorded on the Study Phase Completion page.

The investigator also must provide follow-up medical care for all patients who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care. This care may include initiating another treatment outside of the study as deemed appropriate by the investigator.

Premature subject withdrawal (PSW) will occur when patients discontinue from the study at any time.

Following Week 48, the study will allow patients to continue treatment with canakinumab until it has been approved for SJIA in Japan and commercially available or until Novartis terminates the study. In case Novartis decides due to an emerging unfavourable benefit/risk profile or is asked by Health Authorities to stop the development of canakinumab, a compassionate use or patient access program cannot be pursued.

### 5.4.15 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible and treated for a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure

that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing the Institutional Review Board/Independent Ethics Committee (IRBs/IECs) of the early termination of the trial.

# 6 Visit schedule and assessments

Table 6-1 lists all of the assessments and indicates with an "x" when the visits are performed.

Patients should be seen for all visits on the designated day as close to it as possible.

At a minimum, patients will be contacted for safety evaluations during the 30 days following the last administration of study treatment documentation of attempts to contact the patient should be recorded in the source documentation.

**Table 6-1 Assessment schedule**

| Epoch | Screening | Open label treatment | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit | 1 | 101 | 102 | 103 | 104 | 105 | 106 | 107 | 108 | 109 | 110 | 111 | 112 | 113 | 114 | 115 | 116, 117, … | 199 and/or PSW |
| Week | -4 | 1 | 1 | 2 | 4 | 8 | 12 | 16 | 20 | 24 | 28 | 32 | 36 | 40 | 44 | 48 | Every 4 weeks | EOS[1] |
| Day | -28 to -1 | 1 | 3 | 15 | 29 | 57 | 85 | 113 | 141 | 169 | 197 | 225 | 253 | 281 | 309 | 337 | | |
| Informed consent | X | | | | | | | | | | | | | | | | | |
| Demography | X | | | | | | | | | | | | | | | | | |
| Inclusion/ Exclusion criteria | X | X | | | | | | | | | | | | | | | | |
| Relevant medical history/Current medical conditions | X | | | | | | | | | | | | | | | | | |
| Prior/Concomitant medications/Significant non-drug therapies | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Clinical assessment for serositis, splenomegaly, hepatomegaly, and lymphadenopathy* | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Sonography of spleen and liver[2] | | X | | | | | | | | | | | | | | X | | X |
| Chest X-ray | X | | | | | | | | | | | | | | | | | |
| T-SPOT test | X | | | | | | | | | | | | | | | | | |

| Epoch | Screening | Open label treatment | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit | 1 | 101 | 102 | 103 | 104 | 105 | 106 | 107 | 108 | 109 | 110 | 111 | 112 | 113 | 114 | 115 | 116, 117, … | 199 and/or PSW |
| Week | -4 | 1 | 1 | 2 | 4 | 8 | 12 | 16 | 20 | 24 | 28 | 32 | 36 | 40 | 44 | 48 | Every 4 weeks | EOS[1] |
| Day | -28 to -1 | 1 | 3 | 15 | 29 | 57 | 85 | 113 | 141 | 169 | 197 | 225 | 253 | 281 | 309 | 337 | | |
| TB Risk Assessment | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Physical examination | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Body height | X | X | | | | | X | | | X | | | | | | X | | X |
| Body weight | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Body temperature (axillary, oral or rectal) | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Intermittent fever assessment* | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Rheumatoid rash assessment* | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Inactive disease assessment* | | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Blood pressure/Pulse rate | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| ECG evaluation | X | | | | | | | | | X | | | | | | X | X[3] | X |
| Physician's global assessment of disease activity (VAS)[4]* | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| CHAQ©* | | X | | X | X | X | X | X | X | X | X | X | X | X | X | X | X[5] | X |

| Epoch | Screening | Open label treatment | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit | 1 | 101 | 102 | 103 | 104 | 105 | 106 | 107 | 108 | 109 | 110 | 111 | 112 | 113 | 114 | 115 | 116, 117, … | 199 and/or PSW |
| Week | -4 | 1 | 1 | 2 | 4 | 8 | 12 | 16 | 20 | 24 | 28 | 32 | 36 | 40 | 44 | 48 | Every 4 weeks | EOS[1] |
| Day | -28 to -1 | 1 | 3 | 15 | 29 | 57 | 85 | 113 | 141 | 169 | 197 | 225 | 253 | 281 | 309 | 337 | | |
| Joint count with active arthritis* | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Joint count with limitation of motion* | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Adapted ACR pediatric response assessment[6]* | | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X[5] | X |
| Assessment of morning stiffness* | | X | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Hematology, Blood chemistry, Urinalysis | X | X[7] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Hepatitis B & C and HIV exam | X | | | | | | | | | | | | | | | | | |
| CRP (analyzed at local)* | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Pregnancy test (for females of childbearing potential) | X (serum) | X (urine) | | | | | | | | | | | | | | X (urine) | | X (urine) |
| PK (ACZ885)[8, 9, 10] | | X | X | X | X | | X | | | X | | | X | | | X | X[5] | X |
| PD (total IL-1β)[8] | | X | X | X | X | | X | | | X | | | X | | | X | X[5] | X |
| Immunogenicity[8,9,10] | | X | | | | | | | | X | | | | | | X | X[3] | X |

| Epoch | Screening | Open label treatment | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit | 1 | 101 | 102 | 103 | 104 | 105 | 106 | 107 | 108 | 109 | 110 | 111 | 112 | 113 | 114 | 115 | 116, 117, … | 199 and/or PSW |
| Week | -4 | 1 | 1 | 2 | 4 | 8 | 12 | 16 | 20 | 24 | 28 | 32 | 36 | 40 | 44 | 48 | Every 4 weeks | EOS[1] |
| Day | -28 to -1 | 1 | 3 | 15 | 29 | 57 | 85 | 113 | 141 | 169 | 197 | 225 | 253 | 281 | 309 | 337 | | |
| [redacted] | | | | | | | | | | | | | | | | | | |
| Administration of study drug | | X | | | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Drug administration record | | X | | | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Dispense diary | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Collect and check diary | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Adverse events | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Local tolerability | | X | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Epoch disposition | X | | | | | | | | | | | | | | | | | X |

EOS = End of study

* Data will be entered into the tablet device and transferred by the central vendor into the clinical database. Adapted ACR Pediatric response, inactive disease, and flare will be calculated by tablet device.

1. All patients are expected to complete an EOS visit upon completion / close of the study or upon discontinuing from the study prematurely.
2. Sonography of the spleen and/or liver should be done whenever there is a new finding or a suspected worsening from the clinical assessment.
3. Assessment should be performed every 24 weeks
4. In order to prevent bias, the physician's global assessment of disease activity (VAS) should be completed prior to the investigator reviewing the parent/subject's assessment of disease activity (which is completed as part of CHAQ).
5. Assessments should be performed every 12 weeks.
6. ACR calculation should be performed at any time during the study when the investigator suspects a worsening of the patient's SJIA. An unscheduled visit may be necessary.
7. Hematology and clinical chemistry does not need to be performed at Visit 101, if screening lab was performed within 7 days from Visit 101.

8. Sample should be obtained pre-dose.
9. Sample should be obtained in cases of flare.
10. In case of anaphylactic reaction, a sample will be taken at the time of event and 8 weeks later.

## 6.1 Information to be collected on screening failures

Patients screened at Visit 1 and who will not be enrolled at Visit 101 (Day 1) are considered screening failures. All patients who have signed informed consent but not entered into the next epoch will have the study completion page for the screening epoch, demographics, inclusion/exclusion, and serious adverse event (SAE) data collected. Adverse events that are not SAEs will be followed by the investigator and collected only in the source data.

## 6.2 Patient demographics/other baseline characteristics

Investigators will have the discretion to record abnormal test findings on the medical history CRF whenever in their judgment, the test abnormality occurred prior to the informed consent signature.

At screening (Visit 1), patient demographic and baseline characteristic data to be collected on all patients include: date of birth, age, sex, race, ethnicity. Relevant medical history/current medical conditions data includes data until study drug administration. Where possible, diagnoses and not symptoms should be recorded.

Confirmed diagnosis of SJIA as per ILAR definition (Petty, et al 2004) with the date of disease onset and history and diagnosis of SJIA will be recorded on the relevant eCRF page at Screening (Visit 1).

### 6.2.1 Hepatitis screen, HIV screen

In order to exclude an active infection such as hepatitis or HIV infection, all patients will undergo appropriate testing at the Screening visit.

Patients will be screened for HBsAg, anti-HBs antibody, and anti-HBc antibody. Screening for Hepatitis C will be based on HCV antibodies. A copy of the lab report must be placed in the patient's file.

Evaluation for HIV seropositivity will be performed, and if positive, confirmation by a second technique available at the laboratory site, e.g., Western blot. Appropriate subject counseling will be made available by the investigator in the event of a positive finding. Notification of state and federal authorities, as required by law, will be the responsibility of the investigator. A copy of the lab report must be placed in the patient's file.

### 6.2.2 Tuberculosis Screen

Tuberculosis screen will be performed at screening before the first dose of study medication to evaluate an eventual infection with tuberculosis.

#### 6.2.2.1 Chest X-ray

A chest X-ray must be performed as part of TB screening for all patients at the Screening Visit. In cases where a negative result is available within 4 weeks prior to screening and the

investigator has no suspicion of change in the patient's TB risk in the interval, an additional chest X-ray test is not required at Screening.

#### 6.2.2.2 Interferon-γ (IFN-γ) response assay (IFN-γ ELISPOT assay)

IFN-γ response assay using the IFN-γ ELISPOT (T-SPOT) test must be performed for all patients at the Screening Visit. In cases where a negative result is available within 4 weeks prior to screening and the investigator has no suspicion of infection since the negative T-SPOTtest (e.g., the patient has not been exposed to any external factors that might have caused an infection), an additional T-SPOT test is not required at Screening.

The T-SPOT blood-based assay is specific for Mycobacterium tuberculosis and is not influenced by previous BCG vaccination or exposure to other Mycobacteria species. This test, in contrast to the PPD skin test, is insensitive to a booster effect since the subject is not exposed to any antigen. The assay measures the production of interferon-gamma and puts it into relation to a negative and a positive control sample. Further information is given by (Manuel and Kumar 2008). Details about sample processing are described in the central laboratory manual.

Patients with a negative T-SPOT will be eligible for study entry. In case of a positive T-SPOT test result, the investigator will, according to local guidance, perform a TB workup to evaluate the patient for active / latent TB infection (Note: A repeat TB [T-SPOT or PPD] test should not be performed as part of the TB workup). Patients with active TB should be referred for treatment as deemed appropriate and are not eligible to participate in this study. Patients with latent TB are eligible for participation in the study upon completing a minimum of 4 weeks of treatment (according to local guidelines) for latent TB, provided that the patient is willing to continue and complete the treatment (according to local guidelines) in parallel with study treatment. In case of an indeterminate T-SPOT test result, one repeat T-SPOT test may be performed. If the result of the repeat test is also indeterminate, for the purpose of this study, the patient will be handled as if the test result was positive (i.e., the investigator should perform a TB workup as per local guidelines). Any significant findings will be recorded in the Relevant Medical History/Current Medical Conditions section of the eCRF as necessary.

## 6.3 Treatment exposure and compliance

Any deviations from the protocol regarding the administration of study medication must be described on the Dose Administration Record eCRF.

Concomitant medications/ non-drug therapy before the first dose of study medication and after start of study drug will be collected, including medication name and reason.

Compliance is expected to be 100% since study drug will be administered by the investigator or study personnel.

## 6.4 Efficacy

### 6.4.1 Adapted ACR Pediatric criteria

The adapted ACR Pediatric 30 criteria will be used to determine efficacy defined as improvement from baseline of at least 30% in at least 3 of response variables 1 to 6 **and** no intermittent fever (i.e. axillary, oral, or rectal body temperature ≤ 38°C) in the preceding week (variable 7), with no more than one variable 1-6 worsening by more than 30%.

The adapted ACR Pediatric response variables listed below will be assessed at Baseline (Day 1), Day 15, Day 29, and then at every scheduled administration visit thereafter until Week 48. Adapted ACR Pediatric response variables will be measured every 12 weeks until the End of study.

1. Physician's Global Assessment of disease activity on a 0-100 mm VAS
2. Parent's or Patient's (if appropriate in age) Global Assessment of Patient's overall well-being based upon the 0-100 mm VAS in the CHAQ©
3. Functional ability: CHAQ©
4. Number of joints with active arthritis
5. Number of joints with limitation of motion
6. Laboratory measure of inflammation: CRP (mg/L)
7. Absence of intermittent fever due to SJIA during the preceding week.

The adapted 'ACR Pediatric 50', 'ACR Pediatric 70', 'ACR Pediatric 90' and 'ACR Pediatric 100' criteria will be used as additional efficacy assessments, i.e. an improvement ≥ 50%, ≥ 70%, ≥ 90%, or = 100% in at least 3 of 6 response variables **and** no intermittent fever in the preceding week (variable 7) with no more than one variable 1-6 worsening by more than 30%.

The degree of adapted ACR Pediatric response, flare and inactive disease will be assessed by a standardized procedure.

Note the definition of flare is defined by at least 1 of the following:

1. Reappearance of SJIA-related (e.g. not due to infection) fever (>38°C) lasting for at least 2 consecutive days AND/OR
2. Flare according to the JIA pediatric criteria for flare (all criteria must be met):
    - ≥ 30% worsening in at least 3 of the 6 response variables and
    - ≥ 30% improvement in at not more than 1 of the 6 response variables
        - if the Physician or Parent Global Assessment is one of the 3 response variables used to define flare, worsening of ≥ 20 mm must be present,
        - if the number of active joints or joints with limitation of motion is one of the 3 response variables used to define flare, worsening in ≥ 2 joints must be present
        - if CRP is used to define flare, CRP must be > 30 mg/L

Inactive disease is defined as meeting all of the following:

- No joints with active arthritis;
- No fever (body temperature ≤ 38°C);
- No rheumatoid rash, serositis, splenomegaly, hepatomegaly or generalized lymphadenopathy attributable to JIA;
- Normal CRP;
- Physician's Global Assessment of disease activity score ≤ 10 mm (Wallace, Ruperto, and Giannini 2004)

#### 6.4.1.1 Physician's global assessment of disease activity (VAS)

The physician will rate the patient's current condition on a 0-100 mm VAS (Appendix 4), ranging from no disease activity (0 mm) to very severe disease activity (100 mm), at Baseline (Day 1), Day 3, Day 15, Day 29 and then at all subsequent administration visits and End of study. Scores on the 100-mm linear scale will be measured to the nearest millimeter from the left and the value will be entered on the Tablet device. To enhance objectivity, the physician must not be aware of the specific parent's or patient's global assessment of patient's overall well-being, when performing his own assessment on that patient.

#### 6.4.1.2 Childhood Health Assessment Questionnaire (CHAQ)

The childhood health assessment questionnaire, CHAQ© (Appendix 5), will be 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 other "activities". Subjects choose from four response categories, ranging from 'without any difficulty' to 'unable to do'.

This questionnaire should be completed by the parent (or, for patients 18 years and older, the questionnaire will be completed together by both the patient and parent) on an electronic tablet device according to schedules in (Baseline (Day 1) Day 15, Day 29 and then at all subsequent administration visits until Week 48, every 12 weeks after Week 48, and End of study).

A detailed tablet device Site Manual describing the administrative procedures of the CHAQ questionnaire will be given to the sites.

Completed questionnaires will be reviewed and examined by the investigator, before the clinical examination, for responses which may indicate potential AEs or SAEs. If AEs or SAEs are confirmed, then the physician must record the events as per instructions given in Section 7.1 and Section 7.2 of the protocol. Investigators should not encourage the patients and/or parents to change the responses reported in the PRO questionnaires.

#### 6.4.1.2.1 Parent's or patient's global assessment of patient's overall well-being

The parent's or patient's global assessment of patient's overall well-being will be assessed on the VAS that is part of the CHAQ©. The VAS scale ranges from 0-100 mm, from very well (0 mm) to very poor (100 mm) at Baseline (Day 1), Day 15, Day 29 and then at all subsequent administration visits and End of study.

Scores on the 100-mm linear scale will be measured to the nearest millimeter from the left.

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

The parent's or patient's assessment of pain will be assessed on the VAS that is part of the CHAQ©. The VAS scale ranges from 0-100 mm, from no pain (0 mm) to very severe pain (100 mm) at Baseline (Day 1) Day 15, Day 29 and then at all subsequent administration visits and End of study.

Scores on the 100-mm linear scale will be measured to the nearest millimeter from the left.

### 6.4.1.3 Joint counts with active arthritis

The number of joints with active arthritis using the ACR definition will be assessed at Baseline (Day 1), Day 3, Day 15, Day 29 and then at all subsequent administration visits and End of study. 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.

For there to be consistency between the joint assessments, it is strongly recommended that the same evaluator perform these assessments at all visits.

### 6.4.1.4 Joint counts with limitation of motion

The number of joints with limitation of motion will be assessed at Baseline (Day 1), Day 3, Day 15, Day 29 and then at all subsequent administration visits and End of study.

For there to be consistency between the joint assessments, it is strongly recommended that the same evaluator perform these assessments at all visits.

### 6.4.1.5 C-reactive protein (CRP)

C-reactive protein will be determined in serum at Screening, Baseline (Day 1), all following visits and End of study in order to identify the presence of inflammation, to determine its severity, and to monitor response to treatment.

Analytes will be measured at the local lab, including during unscheduled visit for flares.

The actual sample collection date and time and result will be entered on the tablet device.

### 6.4.1.6 Patient diary

A diary will be dispensed to the patient at each visit to record any occurrence of fever until one day after resolution. The diary is also used to collect information pertaining to corticosteroid use and tapering/discontinuation information, if any.

The completed diary will be collected and reviewed at each visit.

#### 6.4.1.7 Intermittent fever assessment

The absence or presence of intermittent fever due to SJIA (oral, rectal, or axillary body temperature > 38°C only for several hours during the day) will be assessed at Baseline (Day 1), all following visits and End of study.

#### 6.4.1.8 Rheumatoid rash assessment

The absence or presence of a rheumatoid rash will be collected (based on physical exam findings) at the every visit and used to evaluate Inactive Disease status.

#### 6.4.1.9 Assessment of duration of morning stiffness

The absence or presence of patient-reported morning stiffness, attributable to SJIA, lasting at least 15 minutes will be assessed at Day 1, Day 29 and every visit thereafter and used to evaluate an alternate definition of Inactive disease.

### 6.4.2 Steroid tapering

Patients using concomitant corticosteroids at study entry may begin to reduce their corticosteroid dose to the lowest possible dose/discontinuation beginning at Week 8 until the End of Study as detailed in section 5.4.6 of the protocol.

### 6.4.3 Appropriateness of efficacy assessments

After publication by Giannini et al (1997) and Ruperto et al (1998), the definition of improvement for JIA as per efficacy variables described in Section 6.4.1 was adopted by the FDA and EMEA as the primary outcome for all clinical trials involving children with JIA, and was subsequently officially recognized by the ACR and was renamed the 'ACR Pediatric 30'.

Assessment of CRP was added because it is a clinical response variable to identify the presence of inflammation. Fever was added because it is indicative of the systemic feature of SJIA.

## 6.5 Safety

### 6.5.1 Physical examination

A complete physical examination will be performed at Screening, Baseline (Day 1), all following visits and End of study. It will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological.

Information for all physical examinations must be included in the source documentation at the study site. Significant findings that are present prior to signing informed consent must be included in the Medical History part of the eCRF. Significant findings made after signing informed consent which meet the definition of an AE must be recorded on the AE part of the eCRF.

### 6.5.2 Vital signs

Vital signs will be assessed at Screening, Baseline (Day 1), and at all subsequent visits including End of study. This will include measurement of patient's body temperature, blood pressure (BP) and pulse.

Body temperature (axillary, oral, or rectal) will be measured by the Investigator at each visit. In addition, parent or patient will measure patient's body temperature axillary, orally or rectally during occurrence of fever and record it in the patient's diary from the start until one day after resolution.

Systolic and diastolic BP and radial pulse rate will be assessed after the patient has rested in the supine position for at least 3 minutes. BP should be assessed on the same arm each time measurements are taken. These data will be recorded in the eCRF.

Measurement of BP in the pediatric population should be done with the appropriate cuff size (see Appendix 1, Table 13-1 for more details) and toward the end of the scheduled visit, thereby avoiding an increase in blood pressure which could be due to a white coat effect. Moreover, the investigator should check whether the pediatric patient is calm before taking the blood pressure reading.

**At the baseline visit, a triplicate blood pressure measuring technique will be implemented.** Systolic and diastolic blood pressure will be measured three times. The repeat sitting measurements will be made at 1-2 min intervals and the mean of the three measurements will be used.

Clinically notable vital signs are defined in Appendix 1.

### 6.5.3 Height and weight

Height will be measured in centimeters (cm) at Screening, Baseline (Day 1), Day 85, Day 169, Day 337 and End of study. Height should be measured using the same technique at each visit and the patient should be measured without shoes or hat.

Body weight (in indoor clothing, but without shoes) will be measured to the nearest 0.1 kilogram (kg) at Screening, Baseline (Day 1), and all subsequent visits including End of study.

### 6.5.4 Clinical assessment of serositis, splenomegaly, hepatomegaly and lymphadenopathy

Clinical assessment of serositis, splenomegaly, hepatomegaly, and generalized lymphadenopathy attributable to SJIA will be performed at Screening, Baseline (Day 1) and all subsequent visits including End of study.

The tablet device will contain information related to the clinical assessment of serositis, splenomegaly, hepatomegaly, and generalized lymphadenopathy: date and time of assessment, overall interpretation (normal, clinically insignificant abnormality, clinically significant abnormalities which need to be specified further), type of serositis, anatomic sites of lymphadenopathy.

Significant findings that are present prior to signing informed consent must be included in the Relevant medical history/ Current medical condition eCRF. Significant findings made after signing informed consent which meet the definition of an AE must be recorded in the AE eCRF summary page.

#### 6.5.4.1 Sonography of spleen and liver

Sonography of spleen and liver will be performed at Baseline (Day 1), Day 337 and End of study. In addition, a sonography of the spleen and/or liver should be done based on clinical judgment whenever there is a new finding or a suspected worsening of the clinical assessment that is done at each visit. Original sonography print-outs must be placed in the patient's file.

The eCRF will contain the date of sonography, the overall interpretation (normal, clinically insignificant abnormality, clinically significant abnormalities which need to be specified further).

### 6.5.5 Laboratory evaluations

A central laboratory will be used in this study which is also capable to evaluate laboratory data for children. Central laboratory information, including collection, shipment of samples and reporting of results, may be found in the laboratory manual provided to the sites.

Blood volume for pediatric patients will be reduced and is specified in the central laboratory manual.

The investigator will evaluate the clinical significance of each laboratory value outside of the reference range. This decision should be based upon the nature and degree of the observed abnormality. The investigator may choose to repeat any abnormal result ONCE, in order to rule out laboratory error. "NCS" will be entered on the original laboratory sheet to the right of all laboratory values which are outside the reference range, but are judged "not clinically significant." The physician making these assessments should date and initial each form. Values which are considered clinically significant and/or study drug related will be noted on the respective Central Lab Assessment eCRF page with reference to the date, study day, and hour if applicable. A copy of each laboratory report must be placed in the patient's file. Clinically relevant deviations of laboratory test results occurring during or at completion of the study must be reported and discussed with Novartis. Repeated evaluations are mandatory until normalization or until the change is no longer clinically relevant. In case of doubt, Novartis must be contacted.

Clinically notable laboratory findings are defined in Appendix 1.

#### 6.5.5.1 Hematology

Hemoglobin, hematocrit, red blood cell (RBC) count, red blood cell morphology, white blood cell (WBC) count with differential, and platelet count will be measured at Screening, Baseline (Day 1), and all subsequent visits, including End of study.

Hematology does not need to be performed at Baseline (Day 1), if screening lab was performed within 7 days from baseline.

#### 6.5.5.2 Clinical chemistry

Albumin, alkaline phosphatase, total and differentiated bilirubin, calcium, chloride, cholesterol, creatinine, creatinine kinase (CK), aspartate aminotransferase (AST), alanine aminotransferase (ALT), α-amylase, gamma-glutamyltransferase (GGT), glucose, sodium, potassium, inorganic phosphorous, total protein, lactate dehydrogenase (LDH), lipase, triglycerides, magnesium, urea or blood urea nitrogen (BUN), uric acid, ferritin and fibrinogen will be measured at Screening, Baseline (Day 1), and all subsequent visits, including End of study.

Ferritin and fibrinogen will be also measured in cases of flare or suspicion of MAS by the investigator.

Clinical chemistry does not need to be performed at Baseline (Day 1), if screening lab was performed within 7 days from baseline.

#### 6.5.5.3 Urinalysis

Urine sample will be obtained for semi-quantitative 'dipstick' measurements of specific gravity, pH value, protein, glucose, bilirubin, ketones, leukocytes, and blood at Screening, Baseline (Day 1), all subsequent visits including End of study.

In case blood and/or leukocytes, and/or protein show traces/values in the 'dipstick' evaluation at the site, a macroscopic and microscopic examination including RBC, WBC, and casts will be performed at the central lab. If casts are noted, the type is to be specified on the relevant Central Lab Assessment eCRF (a note should be attached to the line referring to the urinalysis collection field).

### 6.5.6 Local tolerability (subcutaneous injection)

Local tolerability at the site of subcutaneous injection will be evaluated by a physician at each administration visit starting from Day 1 after study drug administration and, in case of any local reaction, at each clinical visit until it has disappeared.

If a local injection site reaction AE is reported, detailed information in terms of severity (none, mild, moderate, severe) for key individual signs and symptoms of the reaction will be recorded in the eCRF.

### 6.5.7 Macrophage Activation Syndrome (MAS)

Occurrence of biologic features of MAS such as hemorrhages, central nervous system dysfunction, hepatomegaly, serum fibrinogen level < 2.5 g/L, cytopenia, hypertriglyceridemia, decreased platelet count, increased aspartate transaminase, hyperferritinemia (Ravelli, Magni-Manzoni and Pistorio 2005) must be carefully monitored by the investigator. Significant findings which meet the definition must be recorded in the Adverse Event eCRF for subsequent adjudication by the MAS Adjudication Committee.

See Section 8.5.1 for the description of the MAS Adjudication Committee.

### 6.5.8 Electrocardiogram (ECG)

ECG will be parformed at Baseline (Day 1), Day 169, Day 337 and End of study.

ECGs must be recorded after 10 minutes rest in the supine position to ensure a stable baseline. The preferred sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs, and blood. The Fridericia QT correction formula (QTcF) should be used for clinical decisions.

Single 12 lead ECGs are collected. The original ECGs, appropriately signed, should be collected and archived at the study site.

Each ECG tracing should be labeled with study number, subject initials, subject number, date and time, and filed in the study site source documents. For any ECGs with subject safety concerns, two additional ECGs should be performed to confirm the safety finding. Clinically significant ECG findings at baseline must be discussed with the sponsor before administration with investigational treatment.

Clinically significant abnormalities should be recorded on the relevant section of the medical history/Current medical conditions/AE CRF / e(CRF) page as appropriate.

### 6.5.9 Pregnancy and assessments of fertility

Serum and urine pregnancy test will be performed for all females of child-bearing potential according to the schedule in Table 6-1 Assessment schedule.

This includes female adolescents who are menarchal or who become menarchal during the study.

All menarchal girls and their parents/caregivers should be informed about the potential risks of pregnancy and the need to prevent pregnancy during the study.

It is important to be sensitive in introducing this issue, as understanding and comprehension of puberty, sexual activity, pregnancy and contraception is influenced by age, as well as factors such as precocity, socio(educational) economic and familial background. These discussions with the patient and her parents/caregivers are therefore best performed by investigators familiar with the adolescent and her family and should be guided by requirements of the local regulatory authorities. These discussions should take into account the socio-economic, cultural factors and religious beliefs of the adolescent participant and her family. The investigator should also discuss the management of the pregnancy test results with the patient and her parents/caregivers. The privacy of the adolescent should be considered in accordance with the local law and ethics.

Additional pregnancy tests may be performed at the investigator’s discretion during the study.

If a pregnancy tests positive, the patient must be discontinued from the trial and followed up according to Section 7.5.

**For female patients <18:**

Female patients of child-bearing potential, who are or might become sexually active, must be informed of the need to prevent pregnancy during the study. At a minimum, the acceptable effective contraception is:

- Barrier method: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/ vaginal suppository .
- Use of established oral, injected or implanted hormonal methods of contraception**,** intrauterine device (IUD) or intrauterine system (IUS)

The decision on the contraceptive method should be reviewed at least every 3 months to evaluate the individual need and compatibility of the method chosen.

**For female patients aged ≥18**

Female patients of child-bearing potential, who are ≥18 years of age, must be informed of the need to prevent pregnancy during the study. Please refer to Section 4.2 for effective contraception methods for this age group.

A serum pregnancy test is required at Screening. Urine pregnancy tests will be performed at Day 1 (Baseline) and at the EOS visit.

Patients becoming pregnant must be discontinued from study drug and followed up to determine outcome mentioned in Section 7.5. However, a patient may choose to remain in the study should she become pregnant, and be followed according to the protocol-defined study visits.

### 6.5.10 Appropriateness of safety measurements

The safety assessments selected are standard for this indication/patient population.

## 6.6 Other assessments

### 6.6.1 Pharmacokinetics

Canakinumab concentrations will be assessed in serum at Baseline (Day 1), Day 3, Day 15, Day 29, Day 85, Day 169, Day 253, Day 337, every 12 weeks after Day 337, End of study, and in case of flare. Please note that at administration visits, sample should be obtained pre-dose.

In case of an anaphylactic reaction after injection should occur, a sample will be taken at the time of the event and 8 weeks later.

#### 6.6.1.1 PK Blood Collection

All blood samples will be taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein. It is important to note that the volume of blood sampling will be adapted to the age of the child according to clinical practice at the investigator site.

For each scheduled PK sample, 2 mL of blood will be drawn into a plain barrier tube to obtain 1 mL serum. (Note the indicated blood volume will apply for children >16 years of age. For younger children, a minimum of 1 mL of blood can be drawn in order to obtain 0.5 mL of

serum). The sample will be allowed to clot during 45 minutes at room temperature. The serum will be obtained by refrigerated centrifugation at approximately 2500 g for 10 minutes.

The sample will be split into two aliquots to be transferred into polypropylene screw-cap tubes. Serum tubes will be frozen within 90 minutes of venipuncture and kept at ≤ -18°C pending shipment on dry ice. One of the two serum samples is to be kept at the study site as a backup while the other one will be shipped to the analytical center.

For a detailed description of blood sampling schema, please refer to the Blood Collection Log in Appendix 4. All samples will be given a unique sample number (as listed in Appendix 4).

The actual sample collection date and time will be entered on the PK blood collection page of the eCRF. Sampling problems will be noted in the Notes field of the eCRFs.

#### 6.6.1.2 PK analytical method(s)

Analytes, media and methods: ACZ885 in serum by competitive ELISA, limit of quantification (LOQ) at 100 ng /mL.

Details of the analytical methods to assess canakinumab in serum will be described in the bioanalytical data report.

#### 6.6.1.3 PK sample handling, labeling and shipment instructions

##### 6.6.1.3.1 Sample labeling

The sample for the pharmacokinetic profile will be labeled as follows:

PK

Study Code: CACZ885G1301

Patient Number:

PK Collection Number:

Sample Number:

Date/ Study Day:

Required Time:

Labels will be provided to the investigator with all label information preprinted on the label.

The actual sample collection date and exact time will be entered on the PK Blood Collection Log eCRF page. Sampling problems will be noted on the PK Blood Collection Log eCRF (a note should be attached to the line referring the PK blood collection field).

##### 6.6.1.3.2 Shipment of pharmacokinetic samples to Central Laboratory

All pharmacokinetic specimens will be kept at ≤ -18°C until shipment.

Samples have to be packed according to the ICAO/IATA-Packing-Instructions in an insulated box. To guarantee that the samples remain deep frozen during transport, use about 10 kg of

dry ice per box which will keep the samples frozen during the whole duration of the transport (air freight).

For each shipment, all PK samples are to be entered in the shipping log which can be found in the central laboratory manual. The original document will be retained at the site in the Investigator's file, and a copy of the PK Samples Shipping Log page must be included with the package of PK samples shipped.

All samples from the site should be shipped to the central laboratory (please refer to central laboratory manual for more details).

### 6.6.2 Pharmacodynamic (PD) assessments

Total IL-1β (sum of IL-1β free and bound to canakinumab) will be assessed. Please note that sample should be obtained pre-dose.

Total IL-1β samples will be collected at visits: Baseline (Day 1), Day 3, Day 15, Day 29, Day 85, Day 169, Day 253, Day 337, every 12 weeks after Day 337 and End of study. Please note that at administration visits, the sample should be obtained pre-dose

#### 6.6.2.1 PD Blood collection

All blood samples will be taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein.

For each scheduled PD (total IL-1β) sample, 3 mL of blood will be drawn into a plain barrier tube, to obtain 1.5 mL serum. (Note the indicated blood volume will apply for children >16 years of age. For younger children, a minimum of 1.5 mL blood can be drawn in order to obtain 0.7 mL of serum). The sample will be allowed to clot during 45 minutes at room temperature. The serum will be obtained by refrigerated centrifugation at approximately 2500 g for 10 minutes. The sample will be split into two aliquots to be transferred into freezer-proof polypropylene screw-cap tubes. Serum tubes will be frozen within 90 minutes of venipuncture and kept at ≤ -18°C pending shipment on dry ice. One of the two serum samples is to be kept at the study site as a backup while the other one will be shipped to the central lab.

For a detailed description of blood sampling schema, please refer to the Blood Log in Appendix 3.

The actual sample collection date and exact time will be entered on the PD Blood Collection eCRF page. Sampling problems will be noted on the PD Blood Collection Log eCRF (a note should be attached to the line referring the PD blood collection field).

#### 6.6.2.2 PD analytical method(s)

Analytes, media and methods: total IL1β in serum by ELISA, limit of quantification at 1 pg/mL.

PD parameters: Total IL-1β in serum, this being the sum of free and ACZ885 bound.

Details of the analytical methods to assess total IL-1β in serum will be described in the bioanalytical data report.

#### 6.6.2.3 PD sample handling, labeling and shipment instructions

##### 6.6.2.3.1 Sample labeling

The serum tube samples for the PD profile will be labeled as follows:

PD

Study Code: CACZ885G1301

Patient Number:

Sample Number:

Date / Study Day:

Required Time:

Labels will be provided to the investigator with all label information preprinted on the label.

For each shipment, the same procedure described in Section 6.6.1.3.2 has to be followed.

### 6.6.3 Immunogenicity assessments

Anti-canakinumab antibodies concentrations will be assessed in serum at Baseline (Day 1), Day 169, Day 337, every 24 weeks after Day 337, and at the End of study.

In case of an anaphylactic reaction after injection should occur, a sample will be taken at the time of the event and 12 weeks later.

#### 6.6.3.1 Immunogenicity blood collection

For each scheduled immunogenicity sample, 2 mL of blood will be drawn into a plain barrier tube, to obtain 1 mL serum (Note the indicated blood volume will apply for children > 16 years of age. For younger children, all efforts should be made to obtain not less than 1 mL of whole blood to obtain 500 µL serum). The blood sample will be allowed to clot during 45 minutes at room temperature. The serum will be obtained by centrifugation at approximately 2500 g for 10 minutes. The sample will be split into two aliquots to be transferred into freezer-proof polypropylene screw-cap tubes. Serum tubes will be frozen within 90 minutes of venipuncture and kept at ≤ -18°C pending shipment on dry ice. One of the two serum samples is to be kept at the study site as a backup while the other one will be shipped to the central lab.

For a detailed description of blood sampling schema, please refer to the Blood Collection Log in Appendix 3.

An immunogenicity positive patient at end of study should be followed up until back to baseline.

The actual sample collection date and exact time will be entered on the Immunogenicity Blood Collection eCRF page. Sampling problems will be noted on the Immunogenicity Blood

Collection eCRF (a note should be attached to the line referring the immunogenicity blood collection field).

#### 6.6.3.2 Immunogenicity sample handling, labeling and shipment instructions

##### 6.6.3.2.1 Sample labeling

The samples for the immunogenicity profile will be labeled as follows:

Anti-ACZ885 Detection

Study Code: CACZ885G1301

Patient Number:

Sample Number:

Date / Study Day:

Required Time:

Labels will be provided to the investigator with all label information preprinted on the label.

For each shipment, the same procedure described in Section 6.6.1.3.2 has to be followed.

#### 6.6.3.3 Analytical method(s)

Immunogenicity will be analyzed using a Bridging MSD assay with acid dissociation. Details of the analytical method to assess anti-ACZ885 antibodies in serum will be described in bioanalytical data report.

PK data are required for all immunogenicity sampling time points to interpret the data.

### 6.6.5 TB Risk Assessment

At every scheduled post-screening visit, the investigator will perform a clinical evaluation of TB infection risk based on medical history and physical exam.

A worksheet will be provided to help guide investigators in assessing the patient's TB risk, which may be used in the source documents, and which will include but not be limited to the following questions:

- Has the patient been exposed to someone with known TB since the last visit?
- Has the patient experienced any of the following symptoms since the last visit?
  - Unexplained persistent cough

- Unexplained fever
- Unexplained night sweats
- Unexplained weight loss

If, in the clinical judgment of the investigator, TB infection risk has changed, the patient will be referred for a TB workup per local guidelines.

Based on the outcome of the TB workup, the investigator will ensure proper treatment as per local guidelines and document all screening / diagnostic tests performed and medications prescribed documented in the clinical database.

The change in TB infection risk and outcome of TB workup will be recorded in the clinical database. Diagnoses of latent or active TB after initiation with canakinumab treatment will be reported as AEs.

# 7 Safety monitoring

## 7.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (i.e., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject *after providing written informed consent* for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments.

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms,
- they are considered clinically significant,
- they require therapy.

Clinically significant abnormal laboratory values or test results should be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in patient with underlying disease. Investigators have the responsibility for managing the safety of individual patient and identifying adverse events. Alert ranges for labs and other test abnormalities are included in Appendix 1.

Adverse events should be recorded in the Adverse Events CRF under the signs, symptoms or diagnosis associated with them, accompanied by the following information.

- the severity grade
  - mild: usually transient in nature and generally not interfering with normal activities

  - moderate: sufficiently discomforting to interfere with normal activities
  - severe: prevents normal activities
- its relationship to the study treatment (no/yes)
- its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved should be reported.
- whether it constitutes a serious adverse event (SAE - See section 7.2 for definition of SAE)
- action taken regarding study treatment

All adverse events should be treated appropriately. Treatment may include one or more of the following:

  - no action taken (i.e. further observation only)
  - study treatment dosage adjusted/temporarily interrupted
  - study treatment permanently discontinued due to this adverse event
  - concomitant medication given
  - non-drug therapy given
  - patient hospitalized/patient's hospitalization prolonged
- its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug can be found in the Investigator Brochure (IB) or will be communicated between IB updates in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

The investigator should also instruct each patient to report any new adverse event (beyond the protocol observation period) that the patient, or the patient's personal physician, believes might reasonably be related to study treatment. This information should be recorded in the investigator's source documents and if the AE meets the criteria of an SAE, it must be reported to Novartis.

## 7.2 Serious adverse events

### 7.2.1 Definition of SAE

An SAE is defined as any adverse event (appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s) or medical conditions(s) which meets any one of the following criteria:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity

- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (specify what this includes)
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
  - social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, i.e. defined as an event that jeopardizes the patient or may require medical or surgical intervention.

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Life-threatening in the context of a SAE refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe (see Annex IV, ICH-E2D Guideline).

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse (see Annex IV, ICH-E2D Guideline).

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

All AEs (serious and non-serious) are captured on the CRF, SAEs also require individual reporting to DS&E as per section 7.2.2.

### 7.2.2 SAE reporting

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until 8 weeks after the last study visit must be reported to Novartis within 24 hours of learning of its occurrence. Any SAEs experienced after the 30 days period should only be reported to Novartis if the investigator suspects a causal relationship to study treatment.

Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted within 24 hours of the investigator receiving the follow-up information. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs (*either initial or follow up information)* is collected and recorded on the paper Serious Adverse Event Report Form. The investigator must assess the relationship to *each specific component of study treatment (if study treatment consists of several drugs)* complete the SAE Report Form in English or Japanese, and send the completed, signed form by fax within 24 hours after awareness of the SAE to the local Novartis Drug Safety and Epidemiology Department. The telephone and fax number of the contact persons in the local department of Drug Safety and Epidemiology, specific to the site, are listed in the investigator folder provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site. Follow-up information should be provided using a new paper SAE Report Form stating that this is a follow-up to a previously reported SAE

Follow- up information provided should describe whether the event has resolved or continues, if and how it was treated, whether the treatment code was broken or not and whether the patient continued or withdrew from study participation. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the investigational treatment a Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same investigational treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

## 7.3 Liver safety monitoring

To ensure patient safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

The following two categories of abnormalities / adverse events have to be considered during the course of the study:

- Liver laboratory triggers, which will require repeated assessments of the abnormal laboratory parameter
- Liver events, which will require close observation, follow-up monitoring and completion of the standard base liver CRF pages

Please refer to Table 14-1 in Appendix 2 for complete definitions of liver laboratory triggers and liver events.

For the liver laboratory trigger:

- Repeating the liver function test (LFT) within the next week to confirm elevation.

These LFT repeats should be performed using the central laboratory if possible. If this is not possible, then the repeats can be performed at a local laboratory to monitor the safety of the patient. Repeats laboratory should then be performed at central laboratory as soon as possible. If a liver event is subsequently reported, any local LFTs previously conducted that are associated with this event should be reported on the Liver CRF pages.

For the liver events:

- Repeating the LFT to confirm elevation as appropriate
- Discontinuation of the investigational drug if appropriate
- Hospitalization of the patient if appropriate
- A causality assessment of the liver event via exclusion of alternative causes (e.g., disease, co-medications)
- An investigation of the liver event which needs to be followed until resolution.

These investigations can include serology tests, imaging and pathology assessments, hepatologist's consultancy, based on investigator's discretion. All follow-up information, and the procedures performed should be recorded on appropriate CRF pages, including the liver event overview CRF pages.

## 7.4 Renal safety monitoring

To ensure patient safety and enhance reliability in determining the nephrotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of renal events has to be followed.

The following two categories of renal adverse events have to be considered during the course of the study:

1. Serum event:

- Confirmed (after $\geq$ 24h) increase in serum creatinine of $\geq$ 25% compared to baseline during normal hydration status

2. Urine event:

- Doubling in the urinary albumin-creatinine ratio (ACR) or urinary protein-creatinine ratio (PCR) (if applicable).

Every renal laboratory trigger or renal event as defined in Table 7-1 should be followed up by the investigator or designated personnel at the trial site as summarized below.

**Table 7-1 Specific Renal Alert Criteria and Actions**

| Serum Event | |
|---|---|
| Serum creatinine increase<br>25 – 49% compared to baseline | Confirm 25% increase after 24-48h<br>Follow up within 2-5 days |
| Acute Kidney Injury: Serum creatinine increase ≥ 50% compared to baseline | Follow up within 24-48h if possible<br>Consider drug interruption<br>Consider patient hospitalization /specialized treatment |
| **Urine Event** | |
| New dipstick proteinuria ≥ 1+<br>Albumin- or Protein-creatinine ratio increase ≥ 2-fold<br>Albumin-creatinine ratio (ACR) ≥ 30 mg/g or ≥ 3 mg/mmol;<br>Protein-creatinine ratio (PCR )≥ 150 mg/g or >15 mg/mmol | Confirm value after 24-48h<br>Perform urine microscopy<br>Consider drug interruption / discontinuation |
| New dipstick glucosuria ≥ 1+ not due to diabetes | Blood glucose (fasting)<br>Perform serum creatinine, ACR |
| New dipstick hematuria ≥ 1+ not due to trauma | Urine sediment microscopy<br>Perform serum creatinine, ACR |

For all renal events:

1. Document contributing factors in the CRF: co-medication, other co-morbid conditions, and additional diagnostic procedures performed
2. Monitor patient regularly (frequency at investigator's discretion) until either:
   - Event resolution: sCr within 10% of baseline or protein-creatinine ratio within 50% of baseline, or
   - Event stabilization: sCr level with ±10% variability over last 6 months or protein-creatinine ratio stabilization at a new level with ±50% variability over last 6 months.

## 7.5 Pregnancy reporting

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on the Pharmacovigilance Pregnancy Form and reported by the investigator to the local Novartis Drug Safety and Epidemiology Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment.

Any SAE experienced during the pregnancy and unrelated to the pregnancy must be reported on a SAE form.

# 8 Data review and database management

## 8.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and CRFs with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of patient records, the accuracy of entries on the (e)CRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis CRA organization. Additionally, a central analytics organization may analyse data & identify risks & trends for site operational parameters, and provide reports to Novartis Clinical Teams to assist with trial oversight.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the patient's file.

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients will be disclosed.

## 8.2 Data collection

Designated investigator staff will enter the data required by the protocol into the OC/RDC system. Designated investigator site staff will not be given access to the system until they have been trained.

Automatic validation procedures within the system check for data discrepancies during and after data entry and, by generating appropriate error messages, allow the data to be confirmed or corrected online by the designated investigator site staff. The Investigator must certify that the data entered into the electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive copies of the patient data for archiving at the investigational site.

## 8.3 Database management and quality control

Novartis staff (or CRO working on behalf of Novartis) review the data entered into the CRFs by investigational staff for completeness and accuracy and instruct the site personnel to make

any required corrections or additions. Queries are sent to the investigational site using an electronic data query.

Designated investigator site staff is required to respond to the query and confirm or correct the data. If the electronic query system is not used, a paper Data Query Form will be faxed to the site. Site personnel will complete and sign the faxed copy and fax it back to Novartis staff that will make the correction to the database. The signed copy of the Data Query Form is kept at the investigator site.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Concomitant procedures, non-drug therapies and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Laboratory samples will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

The occurrence of relevant protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis Development management.

Subjects/Investigators will use an electronic tablet device to enter PRO and other study data, as indicated in Section 6. This data will be processed centrally and the results will be sent electronically to Novartis (or designee). A tablet device Site Manual will be provided for instructions related to tablet data entry.

## 8.4 Data Monitoring Committee

Not applicable

## 8.5 Adjudication Committee

Three independent adjudication committees have been formed on a program level and will review pertinent data from this trial. They will review unblinded safety data from ongoing trials.

### 8.5.1 MAS Adjudication Committee

An independent Adjudication Committee will review and adjudicate information on all potential cases of MAS. Potential cases will be identified through systematic database search of specified adverse event terms and/or (abnormal) laboratory criteria specified by the MAS adjudication committee. The Committee will review cases as they are identified. A report of the adjudication outcome will be provided to the Sponsor.

As part of the adjudication process, a request for supplemental data collection will be sent to the investigator (as needed). If biological specimens (e.g. bone marrow aspirate, bronchoalveolar lavage, etc.) were collected as part of customary diagnostic workup, samples, such as tissue slides, may be requested by the committee for their review and/or for

specialized analysis such as immunohistochemical staining for biomarkers associated with MAS. As part of follow-up, additional blood specimens for biomarker analyses may also be collected. Patients and parents will provide written informed consent for providing additional specimens.

The MAS Adjudication Committee Charter provides detail on the committee composition, adjudication process, database AE and laboratory criteria search terms, and supplemental data package. The outcome of the adjudication will be reported on the MAS Adjudication CRF.

The MAS Adjudication Committee Charter is available upon request.

### 8.5.2 Infections Adjudication Committee

The Infections Adjudication Committee (IAD) will review and adjudicate, on a program-wide basis, information related to clinically meaningful infections as detailed in the IAD charter (e.g. infections classified as serious adverse events; infections which were treated with i.v. antibiotics; and infections classified as a potential opportunistic infection regardless of seriousness assignment or treatment).

The outcome of the adjudication will be reported on the Infections Adjudication CRF.

The Infections Adjudication Committee Charter is available upon request.

### 8.5.3 Malignancies Adjudication Committee

The Malignancies Adjudication Committee will review and adjudicate, on a program-wide basis, information related to all reported malignant events. The outcome of the adjudication will be reported on the Malignancies Adjudication CRF.

The Malignancies Adjudication Committee Charter is available upon request.

# 9 Data analysis

Data summaries will be presented. Continuous variables will be summarized by mean, standard deviation, median, minimum, maximum, and number of patients with non-missing data. Categorical variables will be summarized by absolute frequencies and percentages.

## 9.1 Analysis sets

The following populations will be defined for this trial:

The Full Analysis Set (FAS) will consist of all patients who received at least one dose of study drug.

The Safety set will consist of all patients who received at least one dose of study drug and had at least one post-baseline safety assessment.

## 9.2 Patient demographics and other baseline characteristics

Demographic and baseline characteristics will be summarized descriptively for the Safety set.

Any significant prior or active medical condition at the time of signing informed consent will be coded using the MedDRA dictionary. These medical conditions will be summarized by primary system organ class and preferred term.

## 9.3 Treatments

The exposure to study drug (number of injections) and duration of exposure (days) will be summarized and listed for the Safety set.

The number and percentage of patients taking prior medication, concomitant medication will be summarized by preferred term and Anatomical Therapeutic Classification (ATC) class for the Safety set. In addition, non-drug therapies will be summarized.

## 9.4 Analysis of the primary variable(s)

### 9.4.1 Variable(s)

The co-primary efficacy variables are the proportion of patients who achieve a minimum adapted ACR Pediatric 30 criteria at Week 8 and the proportion of patients who are able to taper corticosteroids successfully at Week 28. The analysis of the co-primary efficacy variables will be based on the FAS.

### 9.4.2 Statistical model, hypothesis, and method of analysis

Frequency tables with the number and percentage of patients achieving a minimum adapted ACR pediatric 30 criteria at Week 8 and patients able to taper corticosteroids successfully at Week 28 will be provided.

With a small number of patients in this study, the efficacy results will be presented in a descriptive manner. Neither a statistical model nor a statistical hypothesis is defined.

### 9.4.3 Handling of missing values/censoring/discontinuations

For the analyses of adapted ACR pediatric 30/50/70/90/100 criteria at Week 8, missing response will be imputed with non-responder regardless of the reason for missing data (non-responder imputation). This imputation method will be also applied to the analyses of adapted ACR pediatric 30/50/70/90/100 criteria by visit up to Week 8. After Week 8, no imputation will be applied.

For the analysis of corticosteroid tapering at Week 28, the last observation carried forward (LOCF) approach will be applied. If patients early discontinued before Week 8, they will be considered corticosteroid tapering failures. After Week 28, no imputation will be applied.

For the other efficacy analyses, missing values will not be imputed. The percentage will be calculated based on the number of patients with an assessment at the visit.

### 9.4.4 Supportive analyses

NA.

## 9.5 Analysis of secondary variables

### 9.5.1 Efficacy variables

All efficacy endpoints will be summarized using the FAS.

#### Adapted ACR pediatric criteria

Subjects will be classified into the following categories to characterize their magnitude of efficacy response: Non-Responder (< minimum adapted ACR Pediatric30), achieved minimum adapted ACR Pediatric 30, achieved minimum adapted ACR Pediatric 50, achieved minimum adapted ACR Pediatric 70, achieved minimum adapted ACR Pediatric 90, and achieved minimum adapted ACR Pediatric 100.

A frequency table with the number and percentage of patients in each category will be presented by visit.

#### Components of the adapted ACR pediatric criteria

For the following ACR individual components, summary statistics for the observed values and the change/percent change from baseline will be provided by visit.

- Physician's Global Assessment of disease activity on a 0-100 mm VAS from 0 mm = no disease activity to 100 mm = very severe disease activity.
- Parent's or patient's (if appropriate in age) Global Assessment of Subject's overall well-being on a 0-100 mm VAS from 0 mm= very well to 100 mm= very poor in the CHAQ©.
- Functional ability: Childhood Health Assessment Questionnaire (CHAQ©)
- Number of joints with active arthritis using the ACR definition
- Number of joints with limitation of motion
- Standardized CRP (mg/ L)

Number of patients having fever will be described by visit.

#### Flare

A frequency table with the number and percentage of patients who had flare will be presented by visit.

#### Inactive Disease

Inactive disease is defined in two ways. In the first, it 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 JIA; normal CRP; a Physician's Global Assessment of disease activity indicating no disease activity ≤ 10 mm. In the second, duration of morning stiffness ≤15 minutes will be added to the first definition.

A frequency table with the number and percentage of patients achieving inactive disease (with and without duration of morning stiffness) will be presented using two definitions.

### Parent's or patient's assessment of pain (VAS from CHAQ©)

Summary statistics for the observed values and the change/percent change from baseline will be provided by visit.

### Steroid tapering from Week 8

The number and percentage of patients who were able to taper corticosteroids successfully over time will be provided.

In addition to the primary efficacy variable, patients will be classified into three categories: steroid free, reached a steroid dose >0 - ≤ 0.2 mg/kg, or did not reach a steroid dose ≤ 0.2 mg/kg (>0.2 mg/kg). The number and percentage of patients in each category will be provided.

Summary statistics for the percent change from Week 8 in corticosteroids dose over time will be provided.

## 9.5.2 Safety variables

All Safety endpoints will be summarized using the Safety set.

### Adverse events

Adverse events will be coded using the MedDRA dictionary that provides the primary system organ class and preferred term information.

Adverse events will be summarized by presenting, the number and percentage of patients having any adverse event, having any adverse event in each primary system organ class and having each individual adverse event based on the preferred term. All other information collected (e.g. severity, relationship to study drug) will be tabulated and listed as appropriate. Adverse events will also be summarized by SMQ. Adverse event analyses will be adjusted for study treatment exposure.

Deaths, serious adverse events, and adverse events leading to discontinuation of study drug will be summarized by primary system organ class and preferred term and listed.

Of note, the statement that a patient had no adverse events (AE) also constitutes a safety assessment.

### Macrophage Activation Syndrome (MAS)

The number and percentage of patients having this special adverse event will be presented. MAS will be presented by the preferred terms Histiocytosis haematophagic and Lymphohistiocytosis.

### Vital signs and ECG

Vital signs and ECG data will be summarized by presenting descriptive statistics for the absolute values and changes from baseline. All information collected will be listed by patient and abnormal values (see Appendix 1) will be flagged.

### Laboratory evaluations

Laboratory data will be summarized in the same way as vital signs. In addition, shift tables based on normal ranges and incidence rates of notable abnormalities (see Appendix 1) will be presented.

### Special assessments

For the special assessments like serositis, splenomegaly, hepatomegaly, lymphadenopathy, sonography of spleen and liver, the overall interpretation (normal, clinically insignificant abnormality, clinically significant abnormality) will be summarized descriptively by shift tables. Further specified clinically significant abnormalities will be listed.

## 9.5.3 Resource utilization

No resource / healthcare utilization will be collected on patients entered into this study.

## 9.5.4 Tolerability

Local injection site tolerability will be assessed by injection site reaction adverse events (separately from the adverse event page). Each patient will be classified into one of the following four categories (based on AE ATC grade):

1. No local injection site reaction AEs at any time in the trial.
2. A mild local injection site reaction (grade 1) AE reported on at least one occasion but no moderate or severe/potentially life threatening local injection site reaction AEs reported.
3. A moderate local injection site reaction (grade 2) AE reported on at least one occasion but no severe/potentially life threatening local injection site reaction AE reported.
4. A severe (grade 3) or potentially life threatening (grade 4) local injection site reaction AE observed on at least one occasion.

The number and percentage of patients in each category will be presented.

## 9.5.5 Health-related Quality of Life

Changes in health-related quality of life will be measured using the CHAQ©.

Descriptive statistics for the absolute values and the changes from baseline will be used to summarize patient responses on the, CHAQ© Questionnaires, total score and by domain.

Descriptive statistics for patients achieving a clinically meaningful change from baseline will presented.

## 9.5.6 Pharmacokinetics

A mixed effects modeling approach will be used to characterize the PK of canakinumab and its binding to IL-1β using a previously established target-mediated drug disposition model. Data from this study will be pooled with historical data from 31 clinical studies, including SJIA and non SJIA populations and a total of 1933 patients [ACZ885 SJIA Modeling Report]. Deviations of selected model parameters (clearance of canakinumab and IL-1β, production

rate of IL-1β, dissociation constant for binding) between Japanese and non-Japanese SJIA patients will be quantified. Quality of individual fits to the Japanese SJIA dataset will be assessed, and individual model parameters (post-hoc estimates) will be obtained for each patient.

Results will be presented in a separate modeling report from the final CACZ885G1301 clinical study report.

#### 9.5.6.1 Pharmacokinetic variables

All subjects who have evaluable PK and PD parameters will be included in the data analysis. Summary statistics (e.g. mean, standard deviation) and individual subject listing of serum concentration measurements of canakinumab at the assigned time points will be provided as surrogates of systemic exposure

### 9.5.7 PK/PD

Refer to Pharmacokinetics section.

## 9.6 Interim analyses

Two cut-off analyses will be performed on the safety and efficacy data during the study:

One will be at week 28, to support the registration dossier and the other will be at week 48 to supplement the dossier with long-term safety data.

## 9.7 Sample size calculation

No statistical sample size calculation was performed.

Due to the rarity of the condition, the availability of an approved treatment in Japan, and the inclusion/exclusion criteria of this study, it is expected that approximately 20 patients will enroll in this study.

# 10 Ethical considerations

## 10.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

## 10.2 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative(s) of the

patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC approval.

Women of child bearing potential should be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

### 10.2.1 Child Assent

In pediatric patients (< 20 years of age) parental permission and, whenever possible, child assent is needed instead of the procedure for informed consent used for research involving adults. In general, one or both parents or a guardian must be provided with the information ordinarily required for informed consent, so that they may decide whether to allow the child to participate, and children capable of assent must also express their willingness to participate. These forms will be submitted for IRB/IEC/REB approval.

## 10.3 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution should obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements) and any other written information to be provided to patients. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

## 10.4 Publication of study protocol and results

Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and

finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

# 11 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of patients should be administered as deemed necessary on a case by case basis. Under no circumstances should an investigator collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and health authorities, where required, it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

## 11.1 Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC prior to implementation. Only amendments that are intended to eliminate an apparent immediate hazard to patients may be implemented immediately provided the Health Authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in section 7 Safety Monitoring should be followed.

# 12 References

Batthish M, Schneider R, Ramanan AV, et al (2005) What does "active disease" mean? Patient and parent perceptions of disease activity in the systemic arthritis form of juvenile idiopathic arthritis (SO-JIA). Rheumatology; 44: 796-99.

Carrasco R, Smith JA, Lovell D (2004) Biologic agents for the treatment of juvenile rheumatoid arthritis: current status. Pediatric Drugs; 6(3):137-46.

Chioato A., Noseda E., Felix S. D., Stevens M., Del Giudice G., Fitoussi S., et al (2009) Efficacy of Influenza and Meningococcal Vaccinations in Healthy Subjects Exposed to Canakinumab 300 mg s.c.: Preliminary Study Results [abstract]. Arthritis Rheum 2009; 60 Suppl 10:801

Consolaro A, Ruberto N, Bazso A, et al (2009) Development and validation of a composite disease activity score for juvenile idiopathic arthritis. Arthritis Rheum; 61(5):658-666.

Dinarello CA (1996) Biologic basis for interleukin-1 in disease. Blood; 87(6):2095-147. Review.

Dinarello CA (2005) Blocking IL-1 in systemic inflammation. J Exp Med; 201(9):1355-9.

Feld LG and Corey H (2007) Hypertension in childhood. Pediatric in review; 28: 283-98.

Giannini EH, Ruperto N, Ravelli A, et al (1997) Preliminary definition of improvement in juvenile arthritis. Arthritis Rheum; 40(7):1202-9.

Hashkes PJ, Laxer RM (2005) Medical Treatment of Juvenile Idiopathic Arthritis. JAMA; 294(13); 1671-84.

Hashkes PJ, Wright BM, Lauer MS et al. Mortality outcomes in pediatric rheumatology in the US. Arthritis Rheum 2010; 62(2): 599-608.

Lovell DJ, Giannini EH, Kimura Y (2006) Preliminary Evidence for Bioactivity of IL-1 trap (Rilonacept), A long Acting IL-1 Inhibitor, in Systemic Juvenile Idiopathic Arthritis (SJIA) [abstract]. ACR Congress; 718.

Pascual V, Allantaz F, Arce E, et al (2005) Role of interleukin-1 (IL-1) in the pathogenesis of systemic onset juvenile idiopathic arthritis and clinical response to IL-1 blockade. J Exp Med; 201(9):1479-86.

Petty RE, Southwood TR, Manners P, et al (2004) International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. J Rheumatol; 31:390-2.

Ravelli A, Martini A (2007) Juvenile idiopathic arthritis. Lancet; 369:767–78.

Ravelli A, Magni-Manzoni S, Pistorio A (2005) Preliminary diagnostic guidelines for macrophage activation syndrome complicating systemic juvenile idiopathic arthritis. J Pediatr; 146(5):598-604. Review.

Ringold S, Weiss P, Beukelman T, et al. (2013) 2013 Update of the 2011 American College of Rheumatology Recommendations for the Treatment of Juvenile Idiopathic Arthritis, Arthritis Rheum; 65(10):2499–2512.

Ruperto N, Quartier P, Wulffraat N, et al (2012) A phase II, Multicenter, Open-label study evaluating dosing and preliminary safety and efficacy of canakinumab in systemic juvenile idiopathic arthritis with active systemic features. Arthritis Rheum; 64: 557-67.

Ruperto N, Brunner HI, Quartier P et al (2012) Two randomized trials of canakinumab in systemic juvenile idiopathic arthritis. N Engl J Med; 367: 2396-406.

Ruperto N, Ravelli A, Falcini F, et al. (1998) Performance of the preliminary definition of improvement in juvenile chronic arthritis patients treated with methotrexate. Italian Pediatric Rheumatology Study Group. Ann Rheum Dis; 57(1):38-41.

Svantesson H, Akesson A, Eberhardt K et al (1983) Prognosis in juvenile rheumatoid arthritis with systemic onset. A follow-up study. Scand J Rheumatol; 12:139-44.

Symmons D, Jones M, Osborne J, et al (1996) Pediatric rheumatology in the United Kingdom. Data from the British Pediatric Rheumatology Group. National Diagnostic Register. J Rheumatol; 23:1975-80.

Schwartz GJ, Munoz A, Schneider MF, et al (2009) New equations to estimate GFR in children with CKD. J Am Soc Nephrol; 20: 629–37.

Takei S, Kato T (2008) Estimation of disease prevalence of juvenile rheumatoid arthritis JIA by capture-recapture method. Study related to creation of database for pediatric chronic disease and integration of registration system by utilizing the research projects into treatment for pediatric chronic specific diseases (Article in Japanese). Research reports in the Health and Labor Sciences Research Grant in 2007 (Child and family general research projects). 129-33. (available upon request)

Takei S, Yamashita S, Kato T (2008) Secondary investigations of juvenile rheumatoid arthritis JIA by utilizing pediatric chronic data (Article in Japanese). Research reports in the Health and Labor Sciences Research Grant (Child and family general research projects). 102-13. (available upon request)

Vastert S, Jager W, Noordman B et al (2014) Effectiveness of first-line treatment with recombinant interleukin-1 receptor antagonist in steroid-naïve patients with new-onset systemic juvenile idiopathic arthritis. Arthritis Rheum ; 66: 1034-43.

Verbsky JW, White AJ (2004) Effective Use of the Recombinant Interleukin 1 Receptor Antagonist Anakinra in Therapy Resistant Systemic Onset Juvenile Rheumatoid Arthritis. J Rheumatol; 31:2071-5.

Wallace C, Ruperto N, Giannini E (2004) Preliminary criteria for clinical remission for select categories of juvenile idiopathic arthritis. The Journal of Rheumatology; 31(11): 2290-2294.

Wallace CA, Giannini EH, Huang B, et al (2011) American College of Rheumatology provisional criteria for defining clinically inactive disease in select categories of juvenile idiopathic arthritis. Arthritis Care Res 63;929-936.

Woo P (2006) Systemic juvenile idiopathic arthritis: diagnosis, management, and outcome. Nat Clin Pract Rheumatol; 2(1):28-34.

# 13 Appendix 1: Clinically notable laboratory values and vital signs

The following defined notable laboratory or vital sign abnormalities, except creatinine clearance, will be communicated at the same time as they are sent to investigators to Novartis. Novartis will determine if further consultations with Investigator(s) are appropriate.

**Laboratory Criteria**

Newly occurring selected notable laboratory abnormalities in pediatric patients at the time of the assessment:

**Biochemistry**

- Alanine transaminase (ALT)(SGPT):
  - > Upper Limit of Normal (ULN)
  - >3 x ULN
  - >5 x ULN
  - >8 x ULN
  - >10 x ULN
- Aspartate transaminase (AST) (SGOT):
  - >ULN
  - >3 x ULN
  - >5 x ULN
  - >8 x ULN
  - >10 x ULN
- Total Bilirubin (TBL)
  - >ULN,
  - >1.5xULN,
  - > 2xULN
- ALP
  - >ULN
  - >1.5xULN,
  - >2xULN,
  - >3x ULN
  - >5xULN
- ALT and/or AST >3x-, 5x-, 10x ULN accompanied by TBL >2xULN
- ALT or AST >3x ULN and TBL >2x-, and ALP >2 x ULN.
- ALP >3x ULN and TBL >2x ULN

- Gamma-Glutamyltransferase (GGT):
  - >ULN
  - >3 x ULN
  - >5 x ULN
- Creatinine (serum): ≥1.5 x ULN
- Creatinine clearance (Schwartz formula§): ≥ 25% decrease from baseline, ≥3 months in duration
- Protein urine dipstick:
  New protein ≥1+, ≥3 months in duration
- Creatinine clearance (Schwartz formula§): ≥ 25% decrease from baseline, ≥3 months in duration in combination with protein urine dipstick resulting in new protein ≥1+, ≥3 months in duration
- Total Cholesterol: ≥1.5xULN
- Triglycerides: ≥5.7 mmol/L.

§Schwartz formula- Creatinine clearance (mL/min/1.73 m2) was derived using the following formula 0.413 x length (cm) / (serum creatinine (mg/dl) (Schwartz et al. 2009).

For creatinine clearance only, baseline value for the decrease from baseline criterion will be calculated as the average of all values prior to the first dose (i.e. screening and baseline values).

**Hematology**

- Hemoglobin: ≥ 20 g/L decrease from baseline,
  or < 85 g/L for < 16 years of age
  < 100 g/L for ≥ 16 years of age
- Absolute neutrophils:
  Grade 1: <LLN – 1.5 x 10E9/L
  Grade 2: <1.5 – 1.0 x 10E9/L
  Grade 3: <1.0 – 0.5 x 10E9/L
  Grade 4: <0.5 x 10E9/L
- Criteria based on CTC grades for platelet count:
  Grade 1: <LLN – 75.0 x 10E9/L
  Grade 2: <75.0 – 50.0 x 10E9/L
  Grade 3: <50.0 – 25.0 x 10E9/L
  Grade 4: <25.0 x 10E9/L
- Criteria based on CTC grades for WBC:
  G1:<LLN – 3.0 x10E9/L
  G2:<3.0 – 2.0 x10E9/L

G3:<2.0 – 1.0 x10E9/L
G4: <1.0 x10E9/L

- Absolute Lymphocytes: < LLN
- Absolute Eosinophils: ≥ 1.1 x ULN
- Absolute Eosinophils: ≥0.45 x 10E9/L

**Vital Signs**

The following criteria will be used.

Note: The age is the age at the time of the visit.

**Systolic blood pressure (mmHg):**

- High: >ULN and Increased >20 in change from baseline
- Low: <LLN and Decreased >20 in change from baseline
  Reference Ranges:
  - Age 2-5 : LLN=100, ULN=115
  - Age 6-12 : LLN=110, ULN=125
  - Age 13-19: LLN=120, ULN=135

**Diastolic blood pressure (mmHg):**

- High: >ULN and Increased >20 in change from baseline
- Low: <LLN and Decreased >20 in change from baseline
  Reference Ranges:
  - Age 2-5 : LLN=65, ULN=75
  - Age 6-12 : LLN=70, ULN=80
  - Age 13-19: LLN=75, ULN=85

**Pulse (bpm)[§]:**

- High: >ULN and Increased >20 in change from baseline
- Low: <LLN and Decreased >20 in change from baseline
  Reference Ranges:
  - Age 2-5 : LLN=80, ULN=130
  - Age 6-12 : LLN=70, ULN=115
  - Age 13-19: LLN=60, ULN=100

**Note:** Only post-baseline values will be flagged as notable abnormalities

**Table 13-1 Recommended Dimensions for Blood Pressure Cuff Bladders**

| ` | Width [cm] | Length [cm] | Maximum Arm Circumference [cm]* |
|---|---|---|---|

| ` | **Width [cm]** | **Length [cm]** | **Maximum Arm Circumference [cm]*** |
|---|---|---|---|
| Newborn | 4 | 8 | 10 |
| Infant | 6 | 12 | 15 |
| Child | 9 | 18 | 22 |
| Small adult | 10 | 24 | 26 |
| Adult | 13 | 30 | 34 |
| Large adult | 16 | 38 | 44 |
| *calculated so that the bladder can encircle even the largest arm by at least 80% | | | |

Source: Feld LG and Corey H (2007): Hypertension in childhood, Pediatric in Review 28: 283-98

# 14 Appendix 2: Liver event and Laboratory trigger Definitions and Follow-up Requirements

**Table 14-1 Liver Event and Laboratory Trigger Definitions**

| | Definition/ threshold |
|---|---|
| LIVER LABORATORY TRIGGERS | • 3 x ULN < ALT / AST ≤ 5 x ULN<br>• 1.5 x ULN < TBL ≤ 2 x ULN |
| LIVER EVENTS | • ALT or AST > 5 × ULN<br>• ALP > 2 × ULN (in the absence of known bone pathology)<br>• TBL > 2 × ULN (in the absence of known Gilbert syndrome)<br>• ALT or AST > 3 × ULN and INR > 1.5<br>• Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and TBL > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN)<br>• Any clinical event of jaundice (or equivalent term)<br>• ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia<br>• Any adverse event potentially indicative of a liver toxicity * |

**Table 14-2 Follow Up Requirements for Liver Events and Laboratory Triggers**

| Criteria | Actions required | Follow-up monitoring |
|---|---|---|
| Potential Hy's Law case[a] | • Discontinue the study drug immediately<br>• Hospitalize, if clinically appropriate<br>• Establish causality<br>• Complete liver CRF | ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion) |
| ALT or AST | | |
| > 8 × ULN | • Discontinue the study drug immediately<br>• Hospitalize if clinically appropriate<br>• Establish causality<br>• Complete liver CRF | ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion) |
| > 3 × ULN and INR > 1.5 | • Discontinue the study drug immediately<br>• Hospitalize, if clinically appropriate<br>• Establish causality<br>• Complete liver CRF | ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion) |
| > 5 to ≤ 8 × ULN | • Repeat LFT within 48 hours<br>• If elevation persists, continue follow-up monitoring<br>• If elevation persists for *more than 2* | ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion) |

| Criteria | Actions required | Follow-up monitoring |
|---|---|---|
| | *weeks*, discontinue the study drug<br>• Establish causality<br>• Complete liver CRF | |
| > 3 × ULN accompanied by symptoms[b] | • Discontinue the study drug immediately<br>• Hospitalize if clinically appropriate<br>• Establish causality<br>• Complete liver CRF | ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion) |
| > 3 to ≤ 5 × ULN (patient is asymptomatic) | • Repeat LFT within the next week<br>• If elevation is confirmed, initiate close observation of the patient | Investigator discretion<br>Monitor LFT within 1 to 4 weeks |
| ALP (isolated) | | |
| > 2 × ULN (in the absence of known bone pathology) | • Repeat LFT within 48 hours<br>• If elevation persists, establish causality<br>• Complete liver CRF | Investigator discretion<br>Monitor LFT within 1 to 4 weeks or at next visit |
| TBL (isolated) | | |
| > 2 × ULN (in the absence of known Gilbert syndrome) | • Repeat LFT within 48 hours<br>• If elevation persists, discontinue the study drug immediately<br>• Hospitalize if clinically appropriate<br>• Establish causality<br>• Complete liver CRF | ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)<br>Test for hemolysis (e.g., reticulocytes, haptoglobin, unconjugated [indirect] bilirubin) |
| > 1.5 to ≤ 2 × ULN (patient is asymptomatic) | • Repeat LFT within the next week<br>• If elevation is confirmed, initiate close observation of the patient | Investigator discretion<br>Monitor LFT within 1 to 4 weeks or at next visit |
| Jaundice | • Discontinue the study drug immediately<br>• Hospitalize the patient<br>• Establish causality<br>• Complete liver CRF | ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion) |
| Any AE potentially indicative of a liver toxicity* | • Consider study drug interruption or discontinuation<br>• Hospitalization if clinically appropriate<br>• Establish causality<br>• Complete liver CRF | Investigator discretion |

*These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms

[a]Elevated ALT/AST > 3 × ULN and TBL > 2 × ULN but without notable increase in ALP to > 2 × ULN

[b](General) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia

| Criteria | Actions required | Follow-up monitoring |
|---|---|---|
| [c]Resolution is defined as an outcome of one of the following: (1) return to baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death. | | |

# 15 Appendix 3: Blood collection Log

The volume of blood to be collected for lab parameters that will be analyzed by the central laboratory can be found in the central laboratory manual. The blood collection log for PK/PD and immunogenicity samples are shown in Table 15-1.

**Table 15-1 Blood Collection Log for PK/PD and Immunogenicity Samples**

| Day | Pharmacokinetics | | | Pharmacodynamic | | Immunogenicity | |
|---|---|---|---|---|---|---|---|
| Analyte/purpose | Canakinumab | | | Total IL-1β | | | |
| | PK Collection No. | Sample No. | mL[1] | Number | mL[1] | Number | mL[1] |
| Baseline (Day 1) | 1 | 1 | 2 (1) | 101 | 3 (1.5) | 201 | 2 (1) |
| Day 3 | 1 | 2 | 2 (1) | 102 | 3 (1.5) | - | - |
| Day 15 | 1 | 3 | 2 (1) | 103 | 3 (1.5) | - | - |
| Day 29 | 2 | 4 | 2 (1) | 104 | 3 (1.5) | - | - |
| Day 85 | 3 | 5 | 2 (1) | 105 | 3 (1.5) | - | - |
| Day 169 | 4 | 6 | 2 (1) | 106 | 3 (1.5) | 202 | 2 (1) |
| Day 253 | 5 | 7 | 2 (1) | 107 | 3 (1.5) | - | - |
| Day 337 | 6 | 8 | 2 (1) | 108 | 3 (1.5) | 203 | 2 (1) |
| Week 60 | 7 | 9 | 2 (1) | 109 | 3 (1.5) | - | - |
| Week 72 | 8 | 10 | 2 (1) | 110 | 3 (1.5) | 204 | 2 (1) |
| Week 84 | 9 | 11 | 2 (1) | 111 | 3 (1.5) | - | - |
| Week 96 | 10 | 12 | 2 (1) | 112 | 3 (1.5) | 205 | 2 (1) |
| Week 108 | 11 | 13 | 2 (1) | 113 | 3 (1.5) | - | - |
| Week 120 | 12 | 14 | 2 (1) | 114 | 3 (1.5) | 206 | 2 (1) |
| Week 132 | 13 | 15 | 2 (1) | 115 | 3 (1.5) | - | - |
| Week 144 | 14 | 16 | 2 (1) | 116 | 3 (1.5) | 207 | 2 (1) |
| | | | | | | | |
| EOS | 30 | 30 | 2 (1) | 130 | 3 (1.5) | 230 | 2 (1) |
| **Unscheduled Collection:** | | | | | | | |
| Unscheduled 1 | - | 1001 | 2 (1) | 1101 | 3 (1.5) | 1201 | 2 (1) |
| Unscheduled 2 | | 1002 | 2 (1) | 1102 | 3 (1.5) | 1202 | 2 (1) |

EOS = End of Study

1 : Number in brackets represent blood volume for small children less than 16 years of age

# 16 Appendix 4: Physician's global assessment of disease activity (VAS)

Below question will be shown to and will be answered by the physician:

The physician's assessment should be made and recorded without viewing ANY of the patient's assessments. The result of the physician's assessment of the patient's disease activity should be withheld from the patient so as not to influence his/her own assessment.

(*This is the text of the question not taking into account the make-up of the questionnaire pages*)

"Considering all the ways Systemic Juvenile Idiopathic Arthritis (SJIA) affects your patient, how would you rate his or her condition today?"

| | |
|---|---|
| No disease activity<br>0 | Very severe disease activity<br>100 |

# 17 Appendix 5: CHAQ

1990 Original version Singh G et al. 1998 Cross-cultural adapted version Woo P, Murray KJ, Nugent J for PRINTO

For Japanese patients, Japanese version will be provided.

**CHILDHOOD HEALTH ASSESSMENT QUESTIONNAIRE**

In this section we are interested in learning how your child's illness affects his/her ability to function in daily life. Please feel free to add any comments on the back of this page. In the following questions, please tick the one response which best describes your child's usual activities **OVER THE PAST WEEK. ONLY NOTE THOSE DIFFICULTIES OR LIMITATIONS WHICH ARE DUE TO ILLNESS**. If most children at your child's age are not expected to do a certain activity, please mark it as "Not Applicable". **For example, if your child has difficulty in doing a certain activity or is unable to do it because he/she is too young but not because he/she is RESTRICTED BY ILLNESS, please mark it as "NOT Applicable".**

| | Without ANY Difficulty | With SOME Difficulty | With MUCH Difficulty | UNABLE To do | Not Applicable |
|---|---|---|---|---|---|
| **DRESSING & PERSONAL CARE** | | | | | |
| Is your child able to: | | | | | |
| - Dress, including tying shoelaces and doing buttons? | | | | | |
| - Shampoo his/her hair? | | | | | |
| - Remove socks? | | | | | |
| - Cut fingernails? | | | | | |
| **GETTING UP** | | | | | |
| Is your child able to: | | | | | |
| - Stand up from a low chair or floor? | | | | | |
| - Get in and out of bed or stand up in a cot? | | | | | |
| **EATING** | | | | | |
| Is your child able to: | | | | | |
| - Cut his/her own meat? | | | | | |
| - Lift up a cup or glass to mouth? | | | | | |
| - Open a new cereal box? | | | | | |
| **WALKING** | | | | | |
| Is your child able to: | | | | | |
| - Walk outside on flat ground? | | | | | |
| - Climb up five steps? | | | | | |

*** Please tick any AIDS or DEVICES that your child usually uses for any of the above activities:**

- Walking stick
- Walking frame
- Crutches
- Wheelchair
- Devices used for dressing (button hook, zip pull, long-handled shoe horn, etc.)
- Built up pencil or special utensils
- Special or built up chair
- Other (Specify:_____)

*** Please tick any categories for which your child usually needs help from another person BECAUSE OF ILLNESS:**

- Dressing and personal care
- Getting up
- Eating
- Walking

| | | Without ANY Difficulty | With SOME Difficulty | With MUCH Difficulty | UNABLE To do | Not Applicable |
|---|---|---|---|---|---|---|
| 31 | | | | | | |
| 32 | **HYGIENE** | | | | | |
| 33 | Is your child able to: | | | | | |
| 34 | - Wash and dry entire body? | | | | | |
| 35 | - Take a bath (get in and out of bath)? | | | | | |
| 36 | - Get on and off the toilet or potty? | | | | | |
| 37 | - Brush teeth? | | | | | |
| 38 | - Comb/brush hair? | | | | | |
| 39 | **REACH** | | | | | |
| 40 | Is your child able to: | | | | | |
| 41 | - Reach and get down a heavy object such as a large game or books from just above his/her head? | | | | | |
| 42 | - Bend down to pick up clothing or a piece of paper from the floor? | | | | | |
| 43 | - Pull on a jumper over his/her head? | | | | | |
| 44 | - Turn neck to look back over shoulder? | | | | | |
| 45 | **GRIP** | | | | | |
| 46 | Is your child able to: | | | | | |
| 47 | - Write or scribble with pen or pencil? | | | | | |
| 48 | - Open car doors? | | | | | |
| 49 | - Open jars which have been previously opened? | | | | | |
| 50 | - Turn taps on and off? | | | | | |
| 51 | - Push open a door when he/she has to turn a door knob? | | | | | |
| 52 | **ACTIVITIES** | | | | | |
| 53 | Is your child able to: | | | | | |
| 54 | - Run errands and shop? | | | | | |
| 55 | - Get in and out of a car or toy car or school bus? | | | | | |
| 56 | - Ride bike or tricycle? | | | | | |
| 57 | - Do household chores (e.g. wash dishes, take out rubbish, hoovering, gardening, make bed, clean room)? | | | | | |
| 58 | - Run and play? | | | | | |

59 *** Please tick any AIDS or DEVICES that your child usually uses for any of the above activities:**

| | | |
|---|---|---|
| 60 | - Raised toilet seat | - Bathrail |
| 61 | - Bath seat | - Long-handled appliances for reach |
| 62 | - Jar opener (for jars previously opened) | - Long-handled appliances in bathroom |

63 *** Please tick any categories for which your child usually needs help from another person BECAUSE OF ILLNESS:**

| | | |
|---|---|---|
| 64 | - Hygiene | - Gripping and opening things |
| 65 | - Reach | - Errands and chores |

**PAIN:** We are also interested in learning whether or not your child has been affected by pain because of his or her illness.

66 How much pain do you think your child has had because of his/her illness IN THE PAST WEEK?

Place a mark on the line below, to indicate the severity of the pain

67 No pain 0 ├──────────────────────────────────────────┤ 100 Very severe pain

68 **GENERAL EVALUATION:** Considering all the ways that arthritis affects your child, rate how he/she is doing by placing a single mark on the line below.

69 Very well 0 ├──────────────────────────────────────────┤ 100 Very poor