A prospective, open-label, multicenter, post-authorization, efficacy and safety study of subcutaneous anakinra in Chinese patients with Systemic Juvenile Idiopathic Arthritis (SJIA) and Adult-Onset Still's Disease (AOSD).

Final Protocol Number: Sobi.ANAKIN-304

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Sponsor: Swedish Orphan Biovitrum AB (publ), SE 112 76 Stockholm, Sweden

Type of Study: **Therapeutic Use, Phase 4**

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Investigator statement

I have read the protocol entitled "A prospective, open-label, multicenter, post-authorization, efficacy and safety study of subcutaneous anakinra in Chinese patients with systemic juvenile idiopathic arthritis (SJIA) and adult-onset Still's disease (AOSD)" and the accompanying current investigator's brochure (IB). I agree to conduct the clinical investigation in compliance with the Final Protocol, Version 2.1, 20 Jan 2025, the International Council for Harmonisation (ICH) harmonised guideline E6(R2): Guideline for Good Clinical Practice (GCP) (1), applicable regulatory/government regulations, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki (2). I will not implement any changes to study procedures or conduct without prior approval from the sponsor and, when applicable, the Independent Ethics Committee/Institutional Review Board and Regulatory Authority. I will supervise any individual or party to whom I delegate study-related duties and functions conducted at the study site and ensure qualification of individuals or parties who perform delegated tasks.

I agree to maintain the confidentiality of this study protocol, as described on the title page. Further, I will not publish results of the study without authorization from Swedish Orphan Biovitrum AB (publ).

Signature of Principal Investigator	Date
Printed Name of Principal Investigator	

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1 Synopsis

STUDY IDENTIFIERS	
Title of study:	**A prospective, open-label, multicenter, post-authorization, efficacy and safety study of subcutaneous anakinra in Chinese patients with systemic juvenile idiopathic arthritis (SJIA) and adult-onset Still's disease (AOSD).**
Clinical study number:	Sobi.ANAKIN-304
Type of study:	Therapeutic use, Phase 4
STUDY OBJECTIVES	
Primary objective:	The primary objective is to evaluate the efficacy of anakinra in Chinese patients with Still's disease (SJIA and AOSD) at Week 4.
Secondary objective(s):	To evaluate the efficacy of anakinra in Chinese patients with Still's disease (SJIA and AOSD) over time. To evaluate the safety of anakinra in patients with Still's disease. To evaluate the pharmacokinetic of anakinra in patients with Still's disease.
STUDY ENDPOINTS	
Primary endpoint:	American College of Rheumatology (ACR) 30 response at Week 4 with absence of fever attributable to the disease during the 7 days preceding Week 4 visit. **Definition of ACR30 response:** An improvement of ≥ 30% from baseline to Week 4, in at least 3 of any 6 variables of the ACR core set listed below, with no more than 1 variable worsening by > 30%. 1. Physician global assessment of disease activity (visual analogue scale; VAS). 2. Patient/parent global assessment of overall well-being (VAS). 3. Number of joints with active arthritis. 4. Number of joints with limitation of motion. 5. Assessment of physical function (Child health assessment questionnaire; CHAQ / Stanford health assessment questionnaire; SHAQ). 6. C-reactive protein (CRP) (mg/L). **Definition of fever:** Body temperature ≥ 38.0 °C attributable to the disease. **Definition of active arthritis**: Joint with swelling. In absence of swelling, limitation of range of motion accompanied by either pain on motion or tenderness not due to deformity.
Secondary endpoints supporting the primary objective:	Absence of fever during the 7 days preceding Week 4. Absence of rash during the 7 days preceding Week 4. ACR50, ACR70, and ACR90 response with absence of fever during the 7 days preceding the visit at Week 4. Change from baseline in physician global assessment of disease activity (VAS) to Week 4. Change from baseline in patient/parent global assessment of overall well-being (VAS) to Week 4. Change from baseline in patient/parent global assessment of disease related pain (VAS) to Week 4.

Secondary endpoint(s):	To evaluate efficacy of anakinra in Chinese patients with Still's disease over time. • Absence of fever during the 7 days preceding each visit. • Absence of rash during the 7 days preceding each visit. • ACR30, ACR50, ACR70, and ACR90 response with absence of fever during the 7 days preceding each visit. • Change from baseline in physician global assessment of disease activity (VAS). • Change from baseline in patient/parent global assessment of overall well-being (VAS). • Change from baseline in patient/parent global assessment of disease related pain (VAS). • Change from baseline in CRP, ferritin, and white blood cells count. Occurrence of inactive disease • Proportion of patients who reach inactive disease at Week 8 and at the following respective visits up to Week 48. To evaluate the safety of anakinra in patients with Still's disease. • Occurrence of adverse events (AEs) (serious adverse events [SAEs] and non-serious AEs, deaths, and AEs leading to study drug discontinuation) at all study visits up to Week 52. • Vital signs changes over time, including blood pressure, heart rate, body weight. Changes of height in pediatric patients from baseline to Weeks 4, 12, 24, 40, and 48. • Laboratory safety assessment changes over time, and occurrence of abnormal laboratory values at all study visits up to Week 48. To evaluate the pharmacokinetic of anakinra in patients with Still's disease. • Anakinra serum concentration at Baseline, Week 2 and Week 4 visits.

STUDY DESIGN AND METHODS

Study design:	This is a prospective, open-label, multicenter, efficacy and safety study of anakinra in Chinese patients with Still's disease (SJIA and AOSD). The study consists of a 48-Week treatment period with anakinra followed by a 4-Week period to evaluate safety of anakinra after the last dose of investigational medicinal product (IMP). The study is divided into three parts: screening, treatment period, and safety follow-up, and will be performed in China.
Number of patients planned:	The study will recruit a total of 60 patients (expected allocation is 30 SJIA and 30 AOSD).
Diagnosis and main criteria for inclusion:	A patient must fulfill all the following criteria in order to be included in the study: 1. Informed consent form signed by the patient or a legal guardian representative. 2. Male or female patients, 8 months of age or older with a body weight ≥ 10 kg. 3. Diagnosis of Still's disease. 4. Criteria for diagnosis of Still's disease: a. If < 16 years of age at disease onset, the diagnosis is made according to international league for associations of rheumatology (ILAR) criteria for SJIA.

b. If ≥ 16 years of age at disease onset, the diagnosis is made according to Yamaguchi criteria for AOSD.

5. Active disease confirmed by the following three signs and symptoms:
   a. Active arthritis in ≥ 1 joint.
   b. CRP > 30 mg/L.
   c. At least one fever episode attributable to the disease within one week before enrollment.
   Definition of fever: Body temperature ≥ 38.0 °C attributable to the disease
6. Background treatment with stable dose of ≤ 1 mg/kg/d (Max 60 mg/d) of oral prednisolone or equivalent for at least 3 days prior to enrollment is permitted.
7. If currently on methotrexate (MTX) treatment, the dose must be stable for at least 4 weeks prior to enrollment. Maximum dose allowed is 20 mg/m^2/week. If the patient discontinued MTX prior to enrollment, the discontinuation is required to be at least 4 weeks prior to enrollment.
8. Female patients of childbearing potential and male patient with female partner of childbearing potential must use an effective method of contraception during the study (abstinence being a possible option). A negative pregnancy test prior to enrollment is also required.
9. In case of use of oral contraception, women should have been stable on the same brand (or generic equivalent) for a minimum of 3 months before taking study treatment.
10. Negative tuberculosis screening confirmed at the Screening visit by the Mantoux Tuberculin skin test (TST) using purified protein derivative (PPD), or by Interferon-Gamma-Release Assays (IGRAs) e.g., QuantiFERON® TB Gold Plus (QFT-Plus) or TSpot-® (TB Test) within 8 weeks prior to enrollment. Negative results must be complemented by the medical history, physical examination, and Chest X-Ray. Patients presenting positive TST or IGRA, with or without active or clinical suspicion of latent tuberculosis, are not eligible to enter the study.

    Previously vaccinated for Tuberculosis patients: IGRA positive patients are not eligible to enter the Study; TST positive patients with an induration of 15 mm and more are also not eligible to enter the study, TST positive patients (with an induration less than 15 mm) are also not eligible to enter the study, unless an IGRA test is subsequently performed and provides a negative result.

Main criteria for exclusion:

The presence of any of the following will exclude a subject from inclusion in the study

1. Previous enrollment to this study
2. Participation in another clinical interventional study 30 days prior to enrollment.
3. Treatment with an investigational drug within 5 half-lives prior to enrollment.
4. Previous or current treatment with anakinra, or any other IL-1 inhibitor, except for canakinumab. Previous treatment with canakinumab is allowed if canakinumab was discontinued for reasons other than lack of efficacy and after a washout period of minimum 130 days (Refer to Exclusion Criteria 5). Patients who have discontinued canakinumab because of insufficient effect, refractory disease or toxicities are not allowed to be enrolled in the study

5. Use of the following therapies prior to enrollment:
   - Narcotic analgesics within 24 hours prior to enrollment.
   - Dapsone within 1 week prior to enrollment or etanercept within 2 weeks prior to enrollment.
   - Intraarticular, intramuscular, or intravenous administration of glucocorticoids within 72h (3 days) prior to enrollment, or intravenous immunoglobulin within 4 weeks prior to enrollment.
   - Leflunomide, infliximab or adalimumab within 8 weeks prior to enrollment.
   - Thalidomide within 72h (3 days) prior to enrollment, cyclosporine within 5 weeks prior to enrollment, tacrolimus hydrate within 2 weeks prior to enrollment, mycophenolate mofetil within 1 week prior to enrollment, 6-mercaptopurine within 48h (2 days) prior to enrollment, azathioprine within 72h (3 days) prior to enrollment, cyclophosphamide within 96h (4 days) prior to enrollment, chlorambucil within 48h (2 days) prior to enrollment, JAK inhibitors within 5 half-lives prior to enrollment, or any other immunosuppressant within 12 weeks prior to enrollment.
   - Tocilizumab within 4 weeks prior to enrollment or any other immunomodulatory medication within 5 half-lives prior to enrollment.
   - Rituximab within 26 weeks prior to enrollment.
   - Canakinumab within 130 days prior to enrollment.
6. Live vaccines within 4 weeks prior to enrollment.
7. Known presence or suspicion of active, chronic or recurrent bacterial, fungal or viral infections, including but not limited to tuberculosis, human immunodeficiency virus (HIV) infection, coronavirus disease (Covid-19) infection, hepatitis B or C infection at baseline.
8. Clinical evidence of liver disease or liver injury as indicated by presence of abnormal liver tests:
   a. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 5 x upper limit of normal (ULN), or
   b. AST or ALT > 3 x ULN and elevated bilirubin > 2 x ULN.
9. Presence of severe chronic kidney disease (CKD) stages 4 and 5 (estimated creatinine clearance < 30 mL/min/1.73m^2).
10. Presence of neutropenia (ANC < 1.5 x 10^9/L).
11. Presence of thrombocytopenia (platelets count < 100 x 10^9/L).
12. Presence or suspicion of macrophage activation syndrome (MAS) at baseline.
13. A diagnosis of MAS within the last 2 months prior to enrollment.
14. History of malignancy within 5 years prior to enrollment. Exceptions are basal cell skin cancer, carcinoma-in-situ of the cervix, or low-risk prostate cancer after curative therapy.
15. Known hypersensitivity to E. Coli-derived proteins, or any components of anakinra.
16. Pregnant or lactating women.
17. Foreseeable inability to cooperate with given instructions or study procedures.
18. Presence of any medical, psychological condition, or laboratory result that in the opinion of the investigator can interfere with the patient's ability to comply with the protocol requirements, or make the patient not appropriate for inclusion to the study and treatment with IMP.

Test product; dose and mode of administration:	The investigational medicinal product anakinra is delivered as a sterile solution for injection, pre-filled in a single-use glass syringe with the strength 100 mg. The total volume of injection is 0.67 mL and the concentration of anakinra in the solution is 150 mg/mL. Pediatric and adult patients weighing ≥ 50kg will receive 100 mg anakinra per day by subcutaneous injection. Pediatric and adult patients weighing < 50 kg should be dosed by body weight with a starting dose of anakinra of 1 to 2 mg/kg/day (with a max of 100 mg/day). If patients receiving 1 mg/kg/d are not responding at Week 1, the dose will be escalated to 2 mg/kg/day. If at the appreciation of the investigator, a patient < 16 years old with a body weight below 50 kg, is not responding sufficiently to anakinra treatment at Week 4 visit, the dose will be adjusted according to actual body weight (rounded to the nearest kg) and will be increased up to 4 mg/kg/day with a max of 200 mg/day or the continuation of anakinra will be considered by the investigator.
Reference product; dose and mode of administration:	Not applicable
Duration of treatment(s):	The treatment period is 48 weeks
Determination of sample size:	The sample size is based on feasibility and practical considerations rather than statistical. However, assuming an expected ACR30 response rate of at least 75%, the planned sample size ensures at least 80% probability that the observed response rate in each patient population is ≥ 70%
Statistical methods:	Safety and efficacy analyses will be conducted on the “All treated analysis set” which will comprise all patients who received at least one dose of IMP. Results will be presented by descriptive statistics only. The primary endpoint and other categorical endpoints will be evaluated by counts and proportions with corresponding 95% confidence intervals. Continuous data will be summarized using descriptive statistics; n, mean, standard deviation, 95% confidence intervals, median, minimum, and maximum.

2 List of Abbreviations and definitions

Term	Definition
ACR	American College of Rheumatology
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANA	Antinuclear antibodies.
ANC	Absolute neutrophil count
AOSD	Adult-onset Still's disease
AST	Aspartate aminotransferase
$AUC_{0-\infty}$	Area under the plasma concentration-time curve from zero to infinity
CAPS	Cryopyrin-associated periodic syndromes
CARRA	Childhood Arthritis and Rheumatology Research Alliance
CDASH	Clinical data acquisition standards harmonization
CDE	Center for Drug Evaluation
CDISC	Clinical data interchange standards consortium
CHAQ	Child health assessment questionnaire
CKD	Chronic kidney disease
CL	Plasma clearance
C_{max}	Maximum plasma concentration
COVID	Coronavirus Disease
CPK	Creatine phosphokinase
CRF	Case report form
CRO	Contract research organization
CRP	C-reactive protein
CSR	Clinical study report
DIRA	Deficiency of interleukin-1 receptor antagonist
DRESS	Drug reaction with eosinophilia and systemic symptoms
E. Coli	Escherichia Coli
eCRF	Electronic case report form
EEA	European economic area

e.g.	Exempli gratia (for example)
EMA	European Medicines Agency
Enrollment	Defined as the start of the Baseline visit
ESR	Erythrocyte sedimentation rate
EU	European union
EudraCT	European union drug regulating authorities of Clinical Trials
FAS	Full analysis set
FDA	Food and drug administration (US regulatory authority)
FMF	Familial Mediterranean fever
GCP	Good clinical practice
GDPR	General data protection regulation
GPV	Global Pharmacovigilance & Patient Safety
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HRQoL	Health-related quality of life
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
iDMC	Independent data monitoring committee
i.e.	id est (that is)
IEC	Independent ethics committee
IgM-RF	Immunoglobulin M-Rheumatoid factor
IGRA	Interferon-gamma-release assay
IL-1	Interleukin-1
IL-6	Interleukin-6
IL-1α	Interleukin-1 alpha
IL-1β	Interleukin-1 beta
IL-1Ra	Interleukin-1 receptor antagonist
ILAR	International League for Associations of Rheumatology
IMP	Investigational medicinal product

IRB	Institutional review board
IRS	Interactive response system
ISR	Injection site reaction
i.v.	Intravenous
JIA	Juvenile idiopathic arthritis
LDH	Lactate dehydrogenase
LOCF	last observation carried forward
MAS	Macrophage activation syndrome
MTX	Methotrexate
NOMID	Neonatal onset multisystem inflammatory disease
NSAID	Non-steroidal anti-inflammatory drug
PASS	Post-authorization safety study
PFS	Pre-filled syringe
PK	Pharmacokinetic
PPD	Purified protein derivative
PROM	Patient reported outcome measure
PT	Preferred term
RA	Rheumatoid arthritis
RCT	Randomized Controlled Trial
RF	Rheumatoid factor
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Safety analysis set
s.c	subcutaneous
SHAQ	Stanford health assessment questionnaire
SJIA	Systemic juvenile idiopathic arthritis
Sobi	Swedish Orphan Biovitrum AB (publ)
SOC	System organ class
SOP	Standard operating procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{1/2}$	Half-life
TEAE	Treatment-emergent adverse event

Tel	Telephone
t_{max}	Time to maximum plasmatic concentration
TNF	Tumor necrosis factor
TST	Tuberculin skin test
ULN	Upper limit of normal
USA	United states of America
VAS	Visual analogue scale

3 Ethics

3.1 Independent ethics committee and/or institutional review board

It is the responsibility of the investigator to obtain approval of the study protocol, possible amendments, and the written patient information and informed consent form (ICF) from the Independent Ethics Committee/Institutional Review Board (IEC/IRB). The investigator should file all correspondence with the IEC/IRB. Copies of IEC/IRB correspondence and approvals should be forwarded to the Contract research organization (CRO).

3.2 Ethical conduct of the study

This study will be conducted in compliance with this protocol, the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) (1) , applicable regulatory requirements, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki (2).

3.3 Patient information and consent

It is the responsibility of the investigator to give each patient (or the patient's acceptable representative or parent/guardian) prior to any study-related activities, full and adequate verbal and written information regarding the objective and procedures of the study and the possible risks involved. The patients, and if applicable, their legally authorized representative or parent/guardian must be informed about their right to withdraw from the study at any time without prejudice. The written patient information and/or ICF must not be changed without prior discussion with Swedish Orphan Biovitrum AB (Sobi). Before any revisions are implemented, the revised written patient information and/or ICF, and assent (where applicable) must be approved by the IEC/IRB.

It is the responsibility of the investigator to obtain signed informed consent/assent from all patients prior to any study-related activities. The patients should receive a copy of the written information and the signed ICF, and assent (where applicable).

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained.

If approved by the IEC/IRB, the task of obtaining informed consent can be delegated to an appropriately qualified site staff although the responsibility and the oversight of the procedure remains with the Investigator.

If approved by the IEC/IRB, the consent process can be conducted remotely, outside of the study site without physical presence of the site personnel, for example by sending the patient information, ICF, and assent (where applicable) to the patient's home and answering questions via phone.

If remote consenting is used the Investigator should have methods in place to ensure that the informed consent process allows patients to ask questions and to prevent fraudulent use of remote/electronic signatures. Irrespective of where the consent process takes place, on-site or

remotely, the responsibility for obtaining informed consent remains with the Investigator and the study personnel to which responsibility has been appropriately delegated.

If a female study participant or a female partner of a male participant becomes pregnant during the study period a separate consent form should be obtained before collecting any details on the pregnancy, its outcome, and the birth and health of the baby, if required per local regulations.

4 Introduction

4.1 Background

In 1897, the English physician Sir George Frederic Still described a form of polyarthritis in children with a unique constellation of symptoms that included chronic arthritis, adenopathy, splenomegaly, and fever. Initially called Still's disease, it is now also known as systemic juvenile idiopathic arthritis (SJIA). The diagnosis is based on its typical features and an age at onset of less than 16 years (3).

About the same time as G. F. Still's case description, the first adult patient exhibiting the same symptoms was reported. Later in 1971, E. G. Bywaters described 14 adult patients with the same symptoms as those seen in the pediatric Still's disease, establishing the diagnosis of adult onset Still's disease (AOSD) (4).

Systemic juvenile idiopathic arthritis (SJIA) and adult-onset Still's disease (AOSD) are rare systemic disorders, and their pathogenesis is still not completely understood, but is believed to be of autoinflammatory nature. Laboratory and clinical observations suggest an inappropriate activation of the innate immune system, with hypersecretion of the proinflammatory cytokines interleukin-1 (IL-1) and interleukin-6 (IL-6). They share common clinical manifestations such as daily spiking fever, typical transient cutaneous rash, arthritis, lymphadenopathy, hepatosplenomegaly, and serositis. They also share similar biological manifestations such as high erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), platelet, and neutrophil counts (5). The two diseases also share the increased risk for macrophage activation syndrome (MAS); a severe, potentially fatal complication (6, 7, 8). It is well known that SJIA and AOSD are one single disease representing an age continuum of a single biologic disease entity (5, 9-17). The principal difference between SJIA and AOSD is the patient's age at the time of the disease onset.

If symptoms appear during the late teens, it appears arbitrary whether a diagnosis of SJIA or AOSD is used. Therefore, we will refer to Still's disease as the overarching name when describing the disease in both the pediatric and adult populations.

Anakinra is an IL-1 blocking agent with a short half-life (approximately 6 hours) which allows quick modification or withdrawal of treatment should untoward effects occur. Therefore, it is an advantage to be able to quickly terminate IL-1 blocking therapy in case of infections or other clinical reasons for discontinuation. Existing publications indicate that IL-1 inhibitor treatment early in the disease course is beneficial since it is particularly efficacious in treating the systemic symptoms, which are prominent early during the disease progression (18, 19, 20). Early treatment with an IL-1 inhibitor may also reduce the risk for a later development of arthritis (21),

and enable tapering of glucocorticoids to avoid the risk of dependency and the associated risks of osteoporosis, diabetes, serious infections, and growth disturbances in children (22, 23).

Anakinra is considered to be a good candidate for the treatment of SJIA and AOSD and an alternative treatment to the currently approved therapies in China.

To date, non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, methotrexate (MTX), and IL-1/IL-6 inhibitors are used in the treatment of Still's disease. In the USA and Canada, the long acting IL-1 inhibitor canakinumab and the IL-6 inhibitor tocilizumab are approved for the treatment of SJIA. In Europe both anakinra and canakinumab are approved for treatment of Still's disease, including SJIA and AOSD.

In both the consensus treatment plans developed by the Childhood Arthritis and Rheumatology Research Alliance (CARRA) (24, 25) and the treatment pathways published by the American College of Rheumatology (ACR) (26), anakinra is presented as an alternative first line treatment for patients with SJIA. This reflects how important a short-acting IL-1 blocking therapy is for the treatment of the disease. IL-1 and IL-6 blocking therapies are also included as treatment options in the published treatment recommendations for AOSD (27, 28).

Anakinra is a recombinant human IL-1 receptor antagonist (IL-1Ra) that blocks the biological activity of cytokine IL-1 (IL-1α and IL-1β) by competitively inhibiting its binding to the IL-1 type I receptor and thereby controlling active inflammation. Anakinra has a short half-life and is self-administered as a daily subcutaneous injection.

Anakinra is currently approved for the treatment of SJIA in Australia (2015) and in Still's disease (including SJIA and AOSD) in the EU/EEA (2018), Great Britain, and Russia (2021), Saudi Arabia (2022) and China (2024). It is also approved for treatment of rheumatoid arthritis (RA) in the US (2001), in the EU/EEA and Canada (2002), Australia (2003), and Israel (2011), Great Britain (2021), Russia (2022), and Saudi Arabia (2022). In addition, it is approved for all subtypes of cryopyrin associated periodic syndromes (CAPS) in the EU/EEA (2013), Israel and Australia (2014), Great Britain, Russia (2021), Saudi Arabia (2022) and China (2023), and for the most severe form of CAPS, i.e., neonatal onset multisystem inflammatory disease (NOMID) in the USA (2012) and Canada (2017). Anakinra is also approved for the treatment of the familial Mediterranean fever (FMF), in the EU/EEA, Australia, and Israel (all 2020), in Great Britain and Russia (2021), in Saudi Arabia (2022) and in China (2023). The US FDA approved anakinra for the treatment of deficiency of interleukin-1 receptor antagonist (DIRA) in 2020. Anakinra is approved for the treatment of coronavirus disease 2019 (COVID-19) in adult patients with pneumonia in the EU/EEA (2021), Russia and Saudi Arabia (2022).

In the currently available safety information, there are no relevant differences in the safety profile between pediatric and adult patients. Neither are there any relevant differences in the safety profile of patients with Still's disease compared to patients with other indications for anakinra treatment. However, post-marketing reports describing hepatic events and events of MAS are over-represented in patients with Still's disease, especially in pediatric patients.

Hepatic events, mainly liver enzyme elevations, but also cases of non-infectious hepatitis, have been associated with anakinra. Hepatic events during post-marketing use have mainly been reported in patients with predisposing factors, e.g., history of transaminase elevations before start of anakinra treatment. Hepatic events are common manifestations in Still's disease and have been reported in Still's patients treated with anakinra.

The pharmacokinetics (PK) of anakinra is well characterized in healthy volunteers and rheumatoid arthritis (RA) patients. The bioavailability is high (~95%), time to maximum plasmatic concentration (t_{max}) is about 6 hours and anakinra serum concentrations decline with a half-life ($t_{1/2}$) of 4-6 hours following subcutaneous (s.c.) administration to RA patients. The exposure increases in approximate proportion to dose, accumulation is modest following once daily administration and approximately 80% of anakinra is eliminated by the kidney. In JIA patients, trough anakinra concentrations were lower in the age group 3-6 years compared to older children and in 22 SJIA patients clearance was higher in children with a lower body-weight (29).

In an open-label company-sponsored study, the PK of a single s.c. dose of anakinra (1 mg/kg)was investigated in 15 Chinese adult patients with RA (CSR 20000152). After the injection of anakinra, the t_{max} was reached at 2.00 to 6.00 hours post dose and the mean concentration was 687 ng/mL. Plasma concentration subsequently declined with a mean $t_{1/2}$ value of 3.76 hours and the mean CL/F value was 150 mL/min.

The PK of anakinra in the Chinese patients with RA in this study were compared with the PK of anakinra in non-Chinese RA patients in other studies (0501, 0502, and 990763): study 0501 (anakinra dose 1 and 2 mg/kg s.c.), study 0502 (1 and 2 mg/kg s.c. on Day 1), and study 990763 (100 mg s.c.) (CSR 20000152). When the maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve from zero to infinity ($AUC_{0-\infty}$) values were dose-normalized to 100 mg, the PK for the Chinese patients were comparable to those for non-Chinese patients with RA. It is suggested that there is no clinically relevant difference in systemic PK behaviors between Chinese and non-Chinese and that anakinra is less likely sensitive to ethnic factors from the viewpoint of systemic PK.

For a detailed description of anakinra characteristics, contraindications, warnings and precautions, adverse reactions, and pharmaceutical properties, refer to the Investigator's brochure (IB).

4.2 Study rationale

There is evidence that IL-1 plays an important role in the systemic features of Still's disease and that inhibition of IL-1 (IL-1α and IL-1β) can be an effective treatment strategy for this condition (30, 31, 32). Anakinra is considered to be a good treatment of SJIA and AOSD, and an alternative treatment to the currently approved therapies in China.

This phase 4 clinical study is designed to confirm and generate additional efficacy, safety and PK data of anakinra in Chinese patients with SJIA and AOSD.

4.3 Potential risks and benefits

IL-1 inhibition appears to be of particular importance when systemic symptoms of Still's disease are predominant. Published data demonstrate that anakinra induces a rapid resolution of systemic features, such as fever, rash, and acute phase reactants (20, 33). Another important benefit of anakinra treatment compared to registered biologic treatments in China is the short half-life which enables flexible dosing including fast wash-out.

It seems that most beneficial effects of anakinra are obtained if treatment with anakinra is started early after disease onset, before significant arthritis has developed (20). Partial response to

anakinra has also been reported in some patients with well-established disease at treatment onset (33).

The efficacy of anakinra in adult patients with Still's disease has been evaluated in a meta-analysis conducted by Hong et al. 2014 (34). Anakinra was shown to be effective in remitting the manifestations of AOSD, in reducing the doses of glucocorticoids, and was also well tolerated.

The safety profile of anakinra is well established with the known common risks associated predominantly with injection site reactions (ISRs) as well as known, less common, but more severe risks, such as development of neutropenia and serious infections. The safety profile has been similar across indications, age groups and dose levels, with the exception of ISRs that were more frequent when doses were higher than 100 mg s.c. In Still's disease, increases in liver enzymes are common during disease flares. In addition, patients with Still's disease can have subclinical MAS, which can cause increases in liver tests.

In the anaSTILL's study (Sobi.ANAKIN-301), all adverse events (AE)s in the anakinra group were considered non-serious and mild in severity. In the placebo group, there was one patient with a serious adverse event (SAE) of severe intensity (lymphoma). No treatment-emergent adverse events (TEAEs) have led to treatment withdrawal in the anakinra group.

A non-interventional, post-authorization safety study (PASS) (Sobi.ANAKIN-302) has evaluated long-term safety of anakinra in 306 patients with SJIA, in real-world setting. Infections/infestations, skin/subcutaneous tissue disorders, and general disorders/administration site conditions were the most frequently reported AEs. There were no malignancies or SAEs leading to death during anakinra treatment. There was one patient who presented a pulmonary SAE (unspecified interstitial lung disease). A causal relationship between anakinra and pulmonary events has not been established. In general, the rate of AEs was higher during the first 6 months of treatment and was significantly lower in the later time periods. The pattern and frequency of AEs, including SAEs, were in line with the established safety profile of anakinra.

In addition, there are more than 20 years of post-marketing use during which the safety profile has remained stable. From the information available, there are no indications of any relevant differences in the safety profile of anakinra in patients with Still's disease compared to patients with other indications for anakinra treatment. However, hepatic events during post-marketing use have been more commonly reported in predisposed patients, including patients with Still's disease, than for patients treated for RA and CAPS. A maximum tolerated dose has not been established for anakinra. In long-term studies, there are no indications of an increasing AE frequency over time.

Injection Site Reactions

The most frequently reported adverse reactions with anakinra in placebo-controlled studies in RA patients were ISRs and they were the most common reason for withdrawal from study in anakinra-treated RA patients. ISRs are typically reported within the first 4 weeks of therapy with a median duration in RA studies of 14 to 28 days and resolve during continued anakinra treatment. ISRs typically appear within the first 2 weeks of therapy and disappear within 4 to 6 weeks. The development of ISRs in patients who have not previously experienced ISRs was uncommon after the first month of therapy.

When the injection is used, it is recommended to warm the injection liquid to room temperature and to use the cold packs to cool the injection site. Alternating the injection site is recommended

to avoid discomfort at the site of injection. After injection, the use of cold packs, topical glucocorticoids and antihistamines can alleviate the discomfort of injection site and injection site reactions.

All healthcare providers treating Still's patients with anakinra should instruct the patients/parents on how to avoid discomfort at the site of the injection and alleviate the signs and symptoms of ISRs, as described in educational materials for healthcare providers and patients/parents.

Serious infections

An increased susceptibility to infections is a potential safety issue with an agent that alters cytokine response. Anakinra has been associated with an increased incidence of serious infections (1.8%) versus placebo (0.7%) (15). These infections were mainly related to the respiratory tract. The safety and efficacy of anakinra in patients with chronic infections have not been evaluated.

Re-use of a syringe may cause infections. It is not possible to estimate the magnitude of the infection risk since it depends on multiple factors, e.g., injection technique, cleaning of injection site, and time of storage at room temperature. Most infections will likely be mild and local at the injection site. There is, however, a risk of serious infections, mainly bacteremia and sepsis.

Allergic reactions

In clinical studies in RA patients, the frequency of allergic reactions was approximately 3% higher for anakinra-treated patients compared to placebo, including all kinds of allergic reactions, e.g., seasonal allergy and hay fever.

DIRA patients may have an increased risk of allergic reactions particularly in the first few weeks due to lack of pre-existing immune tolerance to the protein.

Drug reaction with eosinophilia and systemic symptoms (DRESS)

DRESS is a severe and complex idiosyncratic drug reaction with a long latency period. It is followed by a broad spectrum of clinical manifestations which appear between 2 to 8 weeks after initiating the triggering drug (35, 36). Common features consist of fever, rash, lymphadenopathy, hematological findings (eosinophilia, leukocytosis, etc.), and abnormal liver function tests, which can mimic viral hepatitis. The cutaneous manifestations typically consist of an urticarial, maculopapular eruption and, in some instances, vesicles, bullae, pustules, purpura, target lesions, facial oedema, cheilitis, and erythroderma (37, 38). Visceral involvement (hepatitis, pneumonitis, myocarditis, pericarditis, nephritis, and colitis) is the major cause of morbidity and mortality in this syndrome (39, 40). Many cases are associated with leukocytosis with eosinophilia (90%) and/or mononucleosis (40%) (41). The life-threatening potential of DRESS syndrome is high, and the mortality is estimated to be around 10% in multiple studies (38, 42). Antiepileptic medications, such as phenytoin and phenobarbital, are thought to be the predominant cause of DRESS syndrome with an incidence of 1 per 5000 to 10 000 exposures (43).

DRESS has been reported in patients treated with IL-1 inhibitors, predominantly in pediatric patients with Still's disease (44, 45). Patients with DRESS may require hospitalization, as this condition may be fatal. If signs and symptoms of DRESS are present, typically extensive rash, eosinophilia and involvement of visceral organs, and an alternative etiology cannot be established, anakinra should be discontinued and a different treatment considered.

Pulmonary events

Initial pulmonary symptoms may be mild. However, they progressively become worse. In a published cohort of 25 patients, 17 (68%) died at a mean of 10.2 months from the diagnosis of pulmonary complications (46). These events have mainly been seen in patients with Still's disease, suggesting important relationship to components of the underlying disease.

Pulmonary events (interstitial lung disease, pulmonary hypertension, and alveolar proteinosis) have been reported mainly in SJIA patients treated with IL-6 and IL-1 inhibitors. A causal relationship between anakinra and pulmonary events has not been established. There were no events of interstitial lung disease, pulmonary alveolar proteinosis, or pulmonary hypertension in SJIA patients in study 990758/990779 and in patients with Still's disease in study Sobi.ANAKIN-301. Pulmonary events are not considered a potential risk in either RA, CAPS, or FMF populations.

Malignancies

No overall increased frequency of malignancies in anakinra-treated patients has been observed in clinical studies in RA, including long-term follow-up data. In the anaSTILL's study (Sobi.ANAKIN-301), there were no adverse event reactions denoting malignancies. During the exposure to anakinra in Still's PASS (Sobi.ANAKIN-302), no malignancies were reported. The impact of treatment with anakinra on pre-existing malignancies has not been studied, therefore the use of anakinra in patients with a pre-existing malignancy is not recommended. Due to the immunosuppressive properties of anakinra, there is a theoretical risk that anakinra could increase the frequency of malignancies.

Other risks and overall assessment

In our current proposed study (Sobi.ANAKIN-304), all enrolled patients will be treated with anakinra. All patients included in the study will be carefully monitored and patients that do not respond to IMP can at any time withdraw from study and will receive standard of care treatment according to clinical practices in China, thus minimizing the time patients are exposed to ineffective treatment (non-response to anakinra).

The potential risks associated with anakinra administration will be closely monitored by the sponsor as part of the safety evaluations to be performed during the study.

The overall assessment concludes that the benefit of using anakinra in Still's disease outweighs the known risks associated with the treatment.

4.3.1 Confidentiality of personal data

The following risk mitigations are in place to maintain confidentiality of personal data collected within the study.

Personal data collected and processed in the study will be coded. (The coded personal data can only be directly traced back to a specific patient by using the code key. The code key will never leave the study site and only authorized personnel will have access to it.)

Any reports, publications or presentations resulting from the study will never contain personal data that directly identifies a patient.

As Sobi has it's headquarter in Europe, personal data will be handled in accordance with the European data protection regulation, GDPR. It may be necessary that coded personal data are transferred to, or processed in, countries outside the EU/EEA, where the laws may not protect personal data to the same extent as the laws in the EU/EEA. When personal data are transferred to, or processed in such countries outside the EU/EEA, Sobi is responsible to take all reasonable steps to ensure that the level of protection and confidentiality of personal data is the same as required in the EU/EEA.

5 Study objectives and endpoints

5.1 Primary objective and endpoint

5.1.1 Primary objective

The primary objective is to evaluate the efficacy of anakinra in Chinese patients with Still's disease (SJIA and AOSD) at Week 4.

5.1.2 Primary endpoint

ACR30 response at Week 4 with absence of fever attributable to the disease during the 7 days preceding Week 4 visit.

Definition of ACR30 response in SJIA and AOSD patients:

An improvement of ≥ 30% from baseline to Week 4 visit, in at least 3 of any 6 variables of the ACR core set listed below, with no more than 1 variable worsening by > 30%.

1. Physician global assessment of disease activity (visual analogue scale [VAS]).
2. Patient/parent global assessment of overall well-being (VAS).
3. Number of joints with active arthritis.
4. Number of joints with limitation of motion.
5. Assessment of physical function (Child health assessment questionnaire [CHAQ]/ Stanford health assessment questionnaire [SHAQ]).
6. CRP (mg/L).

Definition of fever: Body temperature ≥ 38.0 °C attributable to the disease.

Definition of active arthritis: Joint with swelling. In absence of swelling, limitation of range of motion accompanied by either pain on motion or tenderness not due to deformity.

5.1.3 Primary estimand

The primary clinical question of interest is the effect of anakinra on the percentage of patients achieving ACR30 (with absence of fever attributable to the disease) at Week 4 in Chinese patients with active Still's disease. A composite estimand strategy will be used whereby patients

who discontinue study drug or receive protocol prohibited concomitant medications prior to week 4 will be imputed as non-responders.

The primary estimand is described by the attributes in Table 1

Table 1 Attributes of the primary endpoint

Population	Patients with active Still's disease, using ILAR for SJIAand Yamaguchi criteria for AOSD, and with a body weight ≥ 10 kg at disease onset.
Treatment	Anakinra, once daily s.c. injection, starting dose of 100 mg/day for patients with body weight ≥ 50 kg and 1-2 mg/kg/day for patients with body weight < 50 kg.
Variable	ACR30 response at Week 4 with absence of fever attributable to the disease during the 7 days preceding Week 4.
Strategy for intercurrent events	A composite estimand strategy will be used. Patients discontinuing study drug prior to Week 4 will be set to ACR30 non-responders. Patients starting to take prohibited concomitant medications prior to Week 4, will be set to ACR30 non-responders.
Summary measure	The proportion of patients who achieve ACR30 response at Week 4 with the absence of fever attributable to the disease during the 7 days preceding Week 4 visit.

5.1.4 Secondary endpoints supporting the primary objective

- Absence of fever during the 7 days preceding Week 4.
- Absence of rash during the 7 days preceding Week 4.
- ACR50, ACR70, and ACR90 response with absence of fever during the 7 days preceding the visit at Week 4.
- Change from baseline in physician global assessment of disease activity (VAS) to Week 4.
- Change from baseline in patient/parent global assessment of overall well-being (VAS) to Week 4.
- Change from baseline in patient/parent global assessment of disease related pain (VAS) to Week 4.

5.2 Secondary objectives and endpoints

To evaluate efficacy of anakinra in Chinese patients with Still's disease (SJIA and AOSD) over time.

- Absence of fever during the 7 days preceding each visit.
- Absence of rash during the 7 days preceding each visit.
- ACR30, ACR50, ACR70, and ACR90 response with absence of fever during the 7 days preceding each visit.
- Change from baseline in physician global assessment of disease activity (VAS).
- Change from baseline in patient/parent global assessment of overall well-being (VAS).

- Change from baseline in patient/parent global assessment of disease related pain (VAS).
- Change from baseline in CRP, ferritin and white blood cells count.

Occurrence of inactive disease.

- Proportion of patients who reach inactive disease at Week 8 and at the following respective visits up to Week 48.

To evaluate the safety of anakinra in patients with Still's disease.

- Occurrence of AEs (SAEs and non-serious AEs, deaths, and AEs leading to study drug discontinuation) at all study visits up to Week 52.
- Vital signs changes over time, including blood pressure, heart rate.
- Changes over time in body weight and height. Height of pediatric patients will be measured at baseline, Weeks 4, 12, 24, 40, and 48.
- Laboratory safety assessment changes over time, and occurrence of abnormal laboratory values at all study visits up to Week 48.

To evaluate the pharmacokinetic of anakinra in patients with Still's disease

- Anakinra serum concentrations at Baseline, Week 2 and Week 4 visits

6 Investigational plan

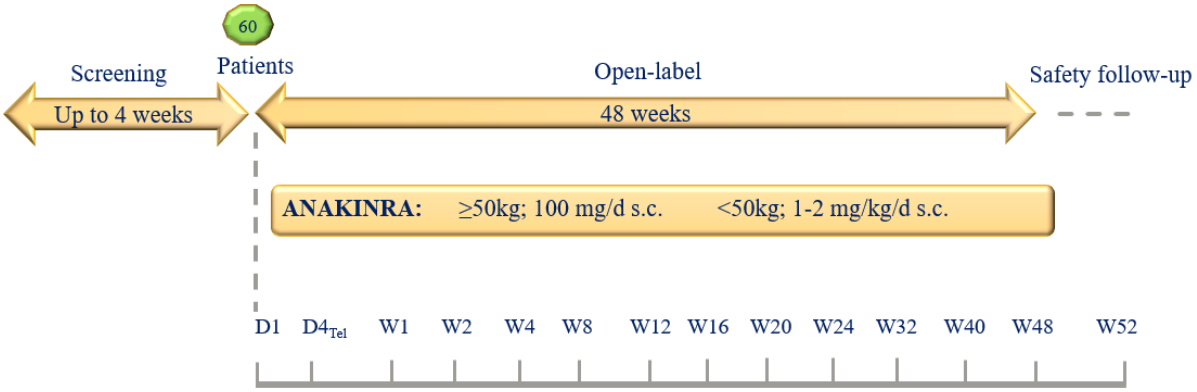
6.1 Overall study design and plan

This is a prospective, open-label, multicenter, efficacy and safety study of anakinra in Chinese patients with Still's disease (SJIA and AOSD). The study consists of a 48-Week treatment period with anakinra followed by a 4-Week period to evaluate safety of anakinra after the last dose of IMP. The study is divided into three parts: screening, treatment period, and safety follow-up, and will be performed in China.

The study will recruit a total of 60 patients (expected allocation is 30 SJIA and 30 AOSD).

The overall study design is described in Figure 1

Figure 1 Overall study design



The patient will enter screening after informed consent is obtained and will undergo screening assessments to confirm eligibility. Duration of the screening period will be kept as short as possible and should not exceed 4 weeks.

Patients will be assigned to study drug after they have met all of the inclusion criteria and none of the exclusion criteria. Patients will receive treatment with anakinra for 48 weeks.

After the last dose of anakinra at Week 48, the safety will continue to be evaluated at a Safety Follow-up visit i.e., at Week 52.

14 visits and 1 telephone contact are scheduled during the study as follows: Screening visit (Visit 0), Day 1 (Baseline visit), Day 4_{Tel}, Week 1, Week 2, Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 32, Week 40, Week 48 (last dose of anakinra), and Week 52 (end of study).

All patients included in the study will be carefully monitored by the investigator. Patients can withdraw from the study drug at any time for any reason. If a patient permanently discontinues study drug, at any time during the study prior to week 48, a Study Drug Discontinuation visit should be performed, if possible before standard of care treatment is initiated. If clinically not feasible, the Study Drug Discontinuation visit should be performed as soon as possible.

4 weeks after discontinuation of study drug, a subsequent Safety Follow-up visit will be performed, according to the assessments described for the Week 52 visit, after which the patient will be withdrawn from the study.

If the patient is on glucocorticoids treatment the dose can be tapered starting earliest at the Week 4 visit. The patient must have reached at least ACR50 response with no fever in the preceding 7 days at the visit of the initiation of the tapering.

If a patient develops MAS or DRESS, the patient will terminate the study drug and will be treated according to standard of care.

A patient who develops pulmonary events (interstitial lung disease, pulmonary hypertension, or alveolar proteinosis) will be treated according to local standards of care and continuing the study drug will be at the appreciation of the investigator.

DRESS, and pulmonary events (interstitial lung disease, pulmonary hypertension, and alveolar proteinosis) are defined as events of special interest in this study and must be reported as SAEs.

Blood samples for laboratory tests will be collected at the selected study visits.

6.2 Discussion of study design

6.2.1 Rationale for study design

An open-label, single arm design of this prospective study is chosen, considering extreme rarity of the disease under study, its life-threatening nature, and lack of licensed alternative therapeutic approaches for patients with Still's disease.

In orphan diseases and conditions with a risk of fatal issues, or high unmet medical need (such as the case in Still's disease), and where subjects are scarce, the open-label, single arm design is desirable.

The natural history of diseases like Still's is well understood (i.e., chronic progression of the disease, and potentially occurrence of death), the effects of placebo are known to be minimal or non-existent, and as such the inclusion of a placebo control is not necessary to assess efficacy. Moreover, a spontaneous improvement in participants is not expected. In these circumstances, a study structure that consists of an open-label and a single arm is a pertinent alternative to randomized controlled trials (RCTs). For the same reasons, the sample size is primarily driven by feasibility rather than statistical considerations.

6.2.2 Rationale for selection of doses

The PK of anakinra in the Chinese patients with RA were compared with the PK of anakinra in non-Chinese RA patients (0501, 0502, and 990763). When the C_{max} and $AUC_{0-\infty}$ values were dose-normalized to 100 mg, the PK for the Chinese patients were comparable to those for non-Chinese patients with RA. These PK similarities support the usage of comparable dosages of anakinra in China to these used in Caucasian patients.

There are no guidelines available for the treatment of AOSD. The efficacy of anakinra in the treatment of AOSD has been reported in retrospective case series and in one prospective, randomized, open-label trial (47). In a meta-analysis evaluating the evidence for efficacy of anakinra in AOSD (34), all included published studies reported the use of a dosage regimen of 100 mg/day. The overall remission rate with anakinra estimated in the eight studies included in the meta-analysis was more than 80 % (34). The efficacy of higher doses of anakinra in AOSD patients has not been evaluated in a systematic manner. Thus, in the current study, AOSD patients will receive 100 mg/day of anakinra as per the proposed labeling in China.

6.2.3 Rationale for primary endpoint

ACR30 is an established measurement of efficacy in arthritis studies (48, 49, 50, 51). The addition of "absence of fever attributable to the disease in the preceding 7 days" makes the primary endpoint more appropriate to capture improvements in the clinical features of Still's disease (24). ACR30 with the addition of fever is recommended by CARRA for treatment outcome research in SJIA and has been used in pivotal regulatory studies with canakinumab and tocilizumab in SJIA. ACR30 is not age specific and is therefore also well suited to study

treatment outcome in the adult population. As to better reflect the assessment of the health by the patients, CHAQ will be used in the pediatric patients and the SHAQ in the adult patients.

6.3 Selection of study population

The study population comprises a total of 60 male or female Chinese patients 8 months of age or older diagnosed with Still's disease. Approximately half of the patients are expected to have a diagnosis of SJIA (disease onset before the age of 16), and approximately half expected to have been diagnosed with AOSD (disease onset at the age of 16 or above).

In each site, consecutive eligible patients should be invited to participate in the study. Patients will be included in the study if they meet all the inclusion criteria and none of the exclusion criteria.

6.3.1 Inclusion criteria

A patient must fulfill all the following criteria in order to be included in the study:

1. Informed consent form signed by the patient or a legal guardian representative.
2. Male or female patients, 8 months of age or older with a body weight ≥ 10 kg.
3. Diagnosis of Still's disease.
4. Criteria for diagnosis of Still's disease:
   a. If < 16 years of age at disease onset, the diagnosis is made according to ILAR criteria for SJIA (see Appendix 2).
   b. If ≥ 16 years of age at disease onset, the diagnosis is made according to Yamaguchi criteria for AOSD (see Appendix 2).
5. Active disease confirmed by the following three signs and symptoms:
   a. Active arthritis in ≥ 1 joint.
   b. CRP > 30 mg/L.
   c. At least one fever episode attributable to the disease within one week before enrollment.
      Definition of fever: Body temperature ≥ 38.0 °C attributable to the disease
6. Background Treatment with stable dose of ⩽ 1 mg/kg/d (Max 60mg/d) of oral prednisolone or equivalent for at least 3 days prior to enrollment is permitted.
7. If currently on methotrexate (MTX) treatment, the dose must be stable for at least 4 weeks prior to enrollment. Maximum dose allowed is 20 mg/m2/week. If the patient discontinued MTX prior to enrollment, the discontinuation is required to be at least 4 weeks prior to enrollment.
8. Female patients of childbearing potential and male patient with female partner of childbearing potential must use an effective method of contraception during the study (abstinence being a possible option) as well as a negative pregnancy test prior to enrollment.
9. In case of use of oral contraception, women should have been stable on the same brand (or generic equivalent) for a minimum of 3 months before taking study treatment.
10. Negative tuberculosis screening confirmed at screening visit by the Mantoux Tuberculin skin test (TST) using purified protein derivative (PPD), or by Interferon-Gamma-Release Assays (IGRAs) e.g., QuantiFERON® TB Gold Plus (QFT-Plus) or T-Spot® (TB

Test) within 8 weeks prior to enrollment. Negative results must be complemented by the medical history, physical examination, and Chest X-Ray. Patients presenting positive TST or IGRA, with or without active or clinical suspicion of latent tuberculosis, are not eligible to enter the study. Previously vaccinated for Tuberculosis patients: IGRA positive patients are not eligible to enter the Study; TST positive patients with an induration of 15 mm and more are also not eligible to enter the study, TST positive patients (with an induration less than 15 mm) are also not eligible to enter the study, unless an IGRA test is subsequently performed and provides a negative result.

6.3.2 Exclusion criteria

The presence of any of the following will exclude a patient from inclusion in the study:

1. Previous enrollment to this study.
2. Participation in another clinical interventional study 30 days prior to enrollment.
3. Treatment with an investigational drug within 5 half-lives prior to enrollment.
4. Previous or current treatment with anakinra, or any other IL-1 inhibitor except for canakinumab. Previous treatment with canakinumab is allowed if canakinumab was discontinued for reasons other than lack of efficacy and after a washout period of minimum 130 days (Refer to Exclusion Criteria 5). Patients who have discontinued canakinumab because of insufficient effect, refractory disease or toxicities are not allowed to be enrolled in the study.
5. Use of the following therapies prior to enrollment:
   - Narcotic analgesics within 24 hours prior to enrollment.
   - Dapsone within 1 week prior to enrollment or etanercept within 2 weeks prior to enrollment.
   - Intraarticular, intramuscular, or intravenous administration of glucocorticoids within 72h (3 days) prior to enrollment, or intravenous immunoglobulin within 4 weeks prior to enrollment.
   - Leflunomide, infliximab or adalimumab within 8 weeks prior to enrollment.
   - Thalidomide within 72h (3 days) prior to enrollment, cyclosporine within 5 weeks prior to enrollment, tacrolimus hydrate within 2 weeks prior to enrollment, mycophenolate mofetil within 1 week prior to enrollment, 6-mercaptopurine within 48 h (2 days) prior to enrollment, azathioprine within 72 h (3 days) prior to enrollment, cyclophosphamide within 96 h (4 days) prior to enrollment, chlorambucil within 48 h (2 days) prior to enrolment, JAK inhibitors within 5 half-lives prior to enrollment, or any other immunosuppressant within 12 weeks prior to enrollment.
   - Tocilizumab within 4 weeks prior to enrollment or any other immunomodulatory medication within 4 half-lives prior to enrollment.
   - Rituximab within 26 weeks prior to enrollment.
   - Canakinumab within 130 days prior to enrolment.
6. Live vaccines within 4 weeks prior to enrollment.
7. Known presence or suspicion of active, chronic, or recurrent bacterial, fungal, or viral infections, including but not limited to tuberculosis, HIV infection, Covid-19 infection, or

hepatitis B or C infection at baseline. Patients with acute or chronic hepatitis b virus (HBV) (i.e., with positive HBsAg, except if a documented history of vaccination), or at risk of HBV reactivation (i.e., with negative HbsAg AND positive anti-HBc) will be excluded.

8. Clinical evidence of liver disease or liver injury as indicated by presence of abnormal liver tests:
    a. AST or ALT > 5 x ULN, or
    b. AST or ALT > 3 x ULN and elevated bilirubin > 2 x ULN.
9. Presence of severe chronic kidney disease (CKD) stages 4 and 5 (estimated creatinine clearance < 30 mL/min/1.73m^2).
10. Presence of neutropenia (ANC < 1.5 x 10^9/L).
11. Presence of thrombocytopenia (platelets count < 100 x 10^9/L).
12. Presence or suspicion of MAS at baseline.
13. A diagnosis of MAS within the last 2 months prior to enrollment.
14. History of malignancy within 5 years prior to enrollment. Exceptions are basal cell skin cancer, carcinoma-in-situ of the cervix, or low-risk prostate cancer after curative therapy.
15. Known hypersensitivity to E. Coli-derived proteins, or any components of anakinra.
16. Pregnant or lactating women.
17. Foreseeable inability to cooperate with given instructions or study procedures.
18. Presence of any medical, psychological condition, or laboratory result that in the opinion of the investigator can interfere with the patient's ability to comply with the protocol requirements or make the patient not appropriate for inclusion to the study and treatment with IMP.

6.3.3 Withdrawal of patients from treatment or study

A patient should be withdrawn from the study drug if, in the opinion of the investigator, it is medically necessary, or if it is the wish of the patient. The Investigator can decide to permanently discontinue the treatment for his/her patient at any time during the study. Temporary interruptions of study drug are allowed after completion of the Week 4 visit (if interruptions due to safety concern are necessary before completion of Week 4 visit it will lead to permanent discontinuation). The decision to permanently discontinue or interrupt treatment will be based on the Investigators medical judgment taking into account the individual benefit/risk ratio for the patient. A patient who stops the IMP should, whenever possible and irrespective of the reason for withdrawal, be examined as soon as possible. Relevant samples should be obtained, and all relevant assessments should be completed, preferably according to the schedule for the Study Drug Discontinuation visit and the Safety Follow-up visit, after which the patient will be withdrawn from the study (see Sections 6.5.1.8 and 6.5.1.9).

When a patient is withdrawn, the date of the last IMP dose and the date and reason for treatment withdrawal should be clearly described in the relevant sections of the electronic case report form (eCRF). If a patient is removed from treatment because of an AE, the reason for treatment

withdrawal should always be stated as ‘adverse event’ irrespective of whether this was the investigator’s or the patient’s decision.

If the patient withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a patient withdraws from the study, the patient may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

6.3.3.1 Study Drug Discontinuation visit

A patient can discontinue study drug and withdraw from the study at any time and for any reason. If a patient permanently discontinues study drug, a Study Drug Discontinuation visit should be performed before standard of care treatment is initiated, when possible (see Section 6.5.1.8).

6.3.3.2 Final Safety Follow-up visit

Irrespective of when a patient discontinues the study drug, a final Safety Follow-up visit should be conducted at the study site 4 weeks after study drug discontinuation, according to the assessments described for the Week 52 visit (see Table 3). Then the patient will be withdrawn from the study (see Section 6.5.1.9).

6.3.4 Replacement of withdrawn patients

Withdrawn patients who received at least one dose of anakinra will not be replaced.

6.3.5 Screening failures

Screening failures are defined as patients who consent to participate in the clinical study but are not subsequently enrolled into the study. A minimal set of screening failure information is required which includes demographics, reason for screening failure, failed eligibility criteria, and any SAEs.

Patients who do not meet the criteria for participation in this study (screening failures) may be rescreened. Rescreened patients should be assigned a new patient number as set out in the Clinical Data Interchange Standards Consortium (CDISC) standards.

6.3.6 Specific restrictions/requirements

Female patients of childbearing potential must use an effective method of contraception during the study (abstinence being a possible option) as well as a negative pregnancy test prior to enrollment.

Pregnant or lactating women prior to enrollment will not be admitted to the study. If a female patient becomes pregnant during the study, the study treatment will be discontinued. A Study Drug Discontinuation visit and a final Safety Follow-up visit will be performed as described in Section 6.3.3. Then the patient will be withdrawn from the study.

Male patients who are sexually active must use an effective method of contraception during the study (abstinence being a possible option). If the patient's partner becomes pregnant during the study, the investigator must be informed. The study drug must be continued and the visits at study sites must be conducted as per the planned schedule of visits (see Table 3).

6.4 Study intervention(s) and concomitant therapy

Study interventions are all pre-specified, investigational and non-investigational medicinal products, medical devices, and other interventions (e.g., surgical and behavioral) intended to be administered to the study participants during the conduct of the study.

6.4.1 Study intervention(s) administered

During the 48-Week treatment period, all patients will receive anakinra according to their body weight (see Table 2). The anakinra dose that will be evaluated is 100 mg/day for adult patients and pediatric patients with a body weight ≥ 50 kg and 1-2 mg/kg/day (max 100 mg/day) for adult patients and pediatric patients with a body weight < 50 kg. Anakinra will be administered subcutaneously once daily. If patients receiving 1 mg/kg/day are not responding at Week 1, the dose will be escalated to 2 mg/kg/day (max 100 mg/day).

If at the appreciation of the investigator, a patient < 16 years old with a body weight lower than 50 kg, is not responding sufficiently to anakinra treatment at Week 4 visit, the dose will be adjusted according to actual body weight (rounded to the nearest kg), and will be increased up to 4 mg/kg/day with a max of 200 mg/day or the continuation of anakinra will be considered by the investigator. (see dosing instructions in Appendix 3).

Dose adjustment to lower dose is not allowed.

Table 2 Investigational medicinal product

Investigational product	Daily dose	Dosage form	Route	Dosage regimen
Anakinra	≥ 50 kg: 100 mg/day < 50 kg: **1**-**2** mg/kg/day (max **100** mg/day)	Solution for injection in pre-filled glass syringe	Subcutaneous	Once daily
Anakinra dose adjustments (only allowed for patients weighing less than 50 kg)	Patients > 16 y. old and < 50 kg receiving 1 mg/kg/day with no response at week 1: **2** mg/kg/day (max **100** mg/day)	Solution for injection in pre-filled glass syringe	Subcutaneous	Once daily
	Patients < 16 y.old and < 50 kg not responding sufficiently at Week 4: **4** mg/kg/day (max **200** mg/day)	Solution for injection in pre-filled glass syringe	Subcutaneous	Once daily

6.4.2 Identity of investigational medicinal products

The investigational medicinal product anakinra is delivered as a sterile solution for injection, pre-filled in a single-use glass syringe with the total amount 100 mg. The total volume of injection is 0.67 mL and the concentration of anakinra in the solution is 150 mg/mL. The pre-filled glass syringe has attached a 29 gauge thin wall half inch needle, a butyl rubber plunger, and a latex free rigid integrated needle shield.

The commercial anakinra drug substance is manufactured by Pfizer Health AB (Strängnäs, Sweden). Drug product is manufactured by Hospira Zagreb (a Pfizer company, Zagreb, Croatia).

All IMP will be packaged and labeled in accordance with all applicable regulatory requirements and Good Manufacturing Practice guidelines.

Possible deficiencies related to the handling and quality of the IMP should be reported to the study monitor and also directly to complaints@sobi.com.

6.4.3 Storage, preparation, and administration of IMP

6.4.3.1 The investigational medicinal product

The anakinra pre-filled glass syringes must be stored at refrigerated conditions at 2-8 °C (36°-46°F) in a secure area at the study site. The investigational product should be kept in its original carton and away from light both at the study site and when stored by the patient at home. The IMP should not be frozen or shaken. After the first dose, anakinra will be transported by the patients to their homes in sponsor-approved cooler bags.

Possible deficiencies related to the handling, quality, or identity of the IMP occurring at home, at the study sites, and during the transportation until destruction should be reported to the sponsor at complaints@sobi.com. Possible deficiencies related to site distribution or storage of investigational products should be reported in accordance with instructions provided in the pharmacy manual.

6.4.3.2 Preparation and administration of IMP

The IMP is intended to be injected by the patient or the parent. Each IMP syringe contains 0.67 mL equivalent to 100 mg anakinra. Depending on the patient weight, the full content of a syringe or part of the content of a syringe will be injected to match the prescribed dose. If the dose of anakinra is above 100 mg (see Table 2), the content of a 2nd syringe will be fully or partly injected according to the prescribed dose.

The pre-filled glass syringe should be taken out from cold storage and be placed at room temperature 30 minutes before injection.

The IMP should be administered at the same time each day, preferably in the morning, by a s.c. injection into fat tissue in one of the following areas:

- Outer area of the upper arms.
- Abdomen (except the 5 cm area around the belly button).
- Front of the middle thighs.
- Upper outer areas of the buttocks.

The patient will record the exact time point of the self-administered anakinra injection and the injection site in the Diary. For the self-administration of anakinra, patients/parents will be educated by study staff members. An educational material for handling self-injections of anakinra will be distributed to the patients. Patients are advised to rotate the injection site.

The prefilled syringes are for single use and must be discarded after use. All used syringes must be returned in their original package to the study site at the next visit. The number of returned syringes must be recorded and thereafter discarded by the study site according to the department or the hospital policies for destroying and recycling of single use medicinal products (destruction certificate not mandatory for discarding used syringes). Unused syringes should also be returned to the study site and then shipped back to the depot site for destruction or destructed locally if regional regulations allow.

At each study visit a new pack of syringes, corresponding to the number of injections until the next study visit, will be dispensed to the patients.

Detailed instructions regarding preparation and administration of IMP are described in the pharmacy manual.

6.4.4 Method of assigning patients

A total of 60 patients (expected allocation is 30 SJIA and 30 AOSD) will be treated with open label anakinra; 100 mg/day for patients with a body weight ≥ 50 kg and anakinra 1-2 mg/kg/day (max 100 mg/day) for patients with a lower body weight i.e., < 50 kg.

In each site, consecutive male or female Chinese patients 8 months of age or older diagnosed with Still's disease should be invited to participate in the study. Enrollment into the study will be competitive and will continue until 60 patients have received their first dose of IMP.

6.4.5 Selection of doses

In this study, anakinra will be used in accordance with the terms of the marketing authorization in China.

6.4.6 Selection and timing of doses for each patient

The dose of anakinra to be used is 100 mg/day for adult and pediatric patients weighing ≥ 50 kg and anakinra 1-2 mg/kg/day (max 100 mg/day) for adult and pediatric patients with a body weight < 50 kg. If patients receiving 1 mg/kg/d are not responding at Week 1, the dose will be escalated to 2 mg/kg/day. Anakinra will be administered by subcutaneous injection once daily for 48 weeks. The lowest possible dose is 20 mg.

If at the appreciation of the investigator, a patient < 16 years old with a body weight below 50 kg, is not responding sufficiently to anakinra treatment at Week 4 visit, the dose will be adjusted according to actual body weight (rounded to the nearest kg), and will be increased up to 4 mg/kg/day with a max of 200 mg/day or the continuation of anakinra will be considered by the investigator.

6.4.7 Overdose management

For this study, any dose of IMP greater than the dose prescribed will be considered an overdose. No dose-limiting toxicities have been observed during clinical studies and a maximum tolerated dose for anakinra has not been established. No specific treatment is indicated for IMP overdose. If an overdose of IMP is administered, the actual dose taken will be recorded in the eCRF, and any untoward medical occurrence associated with an overdose will be recorded the same way as for any AEs (see Section 6.5.5.1).

6.4.8 Prior and concomitant therapy

Other therapy considered necessary for the patient's welfare may be given at the discretion of the investigator. All such therapy must be recorded in the eCRF (type of medication, time to administration during the study, the duration of treatment, and the reason for administration of such treatment). No other medicinal product under investigation may be used concomitantly with the IMP in this study or within 5 half-lives prior to enrollment.

Intraarticular, intramuscular, and intravenous administration of glucocorticoids are prohibited within 72 h (3 days) prior to enrollment and during the study. Oral glucocorticoids treatment is allowed as concomitant medication during the study if the patient has had a stable dose for at least 3 days prior to enrollment. The dose of oral glucocorticoids should not exceed 1 mg/kg/day (max 60 mg/day) of prednisolone or equivalent. All other glucocorticoids treatments are prohibited during the study except topical and inhaled.

MTX is allowed as concomitant medication during the study if the patient has had a stable dose for at least 4 weeks prior to enrollment. Maximum dose allowed is 20 mg/m^2/week. The dose should remain stable throughout the study at the discretion of the investigator. If the patient discontinued MTX prior to enrollment, the discontinuation is required to be at least 4 weeks prior to first dose of IMP.

Initiation of continuous NSAIDs treatment is prohibited during the study. However, on demand treatment is allowed.

Narcotic analgesics are not allowed 24 hours prior to any study visit.

Use of the following treatments is not allowed concomitantly with IMP (wash-out periods before enrollment are stated in the exclusion criteria (see Section 6.3.2):

- Intraarticular, intramuscular, and intravenous administration of glucocorticoids.
- Intravenous immunoglobulins.
- Canakinumab or any other IL-1 inhibitor.
- Tocilizumab, rituximab, or any other immunomodulatory medication.
- Etanercept, adalimumab, infliximab, or any other tumor necrosis factor (TNF) inhibitor (investigational or marketed).
- Dapsone or mycophenolate mofetil.
- Leflunomide, thalidomide, or cyclosporine.
- 6-Mercaptopurine, azathioprine, cyclophosphamide, chlorambucil, JAK inhibitors, or any other immunosuppressant.
- Use of any other investigational drug.
- Live vaccines are not allowed within 4 weeks prior to enrollment and until after 4 weeks following the last study dose. Inactivated vaccines may be permitted according to the investigator's discretion.

The investigator should instruct the patients to notify the study site about any new medications they take after the start of the IMP. All medications and significant non-drug therapies administered after the patient starts treatment with IMP until Week 52 visit must be entered to the concomitant medication or procedures eCRF pages respectively. Following Week 48, the patient will be treated at the discretion of the investigator according to standard of care in China.

6.4.9 Treatment compliance

Accountability records will be kept for the IMP. The pharmacy and investigator/head of site must maintain accurate records demonstrating date and amount of IMP received, to whom and by whom administered or dispensed (patient-by-patient accounting), and accounts of returned (used or unused) IMP and any IMP accidentally or deliberately destroyed. All unused IMP will be counted. At the end of the study, any remaining IMP will be destroyed locally or returned to the depot for destruction depending on local regulations. After destruction a certificate of destruction will be issued.

6.4.10 Continued access to study treatment after End of Study

After the patient has completed Week 48, Study Drug Discontinuation Visit they should be treated and followed-up according to investigator judgment and local practice. No further investigational medicinal product will be provided.

6.5 Efficacy and safety assessments

6.5.1 Study schedule

6.5.1.1 Schedule of events

All visits should take place as close to planned dates as possible. Detailed information on assessments and timing could be found in Sections 6.5.1.2-6.5.5.5 and Table 3.

Table 3 Schedule of events

Assessments	Screening visit (V0) (up to 4 weeks before visit 1)	**Baseline**	**Day 4** (+/-2 days)	**Week 1** (+/-2 days)	**Week 2** (+/- 2 days)	**Week 4** (+/-2 days)	**Week 8** (+/-5 days)	**Week 12** (+/-5 days)	**Weeks 16, 20, 24, 32, and 40** (+/-5 days)	**Week 48** (Study Drug Discontinuation visit) (+/-5 days)	**Week 52 Safety follow-up** (+5 days)
	Visit 1	Tel follow up	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7-11	Visit 12	Visit 13
	D-28 to D0	Day 1	Day 4	Day 8	Day 15	Day 29	Day 57	Day 85	D 113-281	Day 337	Day 365
Informed consent	X										
Eligibility criteria	X	X									
Medical history & Demographics	X										
Vital Signs											
Blood pressure	X	X		X	X	X	X	X	X	X	X
Heart rate	X	X		X	X	X	X	X	X	X	X
Body Temperature	X	X		X	X	X	X	X	X	X	X
Physical examination	X[1]	X		X	X	X	X[2]	X[2]	X[2]	X[2]	X
Body weight	X	X		X	X	X	X	X	X	X	X
Height of pediatric patients		X				X		X	X[3]	X	
ECG	X										
Prior and concomitant medications and procedures	X	X	X	X	X	X	X	X	X	X	X
Laboratory assessments											
Blood and urine sampling[a]	X[4]	X		X[5]	X	X[6]	X	X	X	X[6]	
Anakinra serum concentration (PK)		X[7]			X[7]	X[7]					
Efficacy Assessments											
ACR30 Response		X		X	X	X	X	X	X	X	
ACR50 Response		X		X	X	X	X	X	X	X	
ACR70 Response		X		X	X	X	X	X	X	X	
ACR90 Response		X		X	X	X	X	X	X	X	
Physician global assessment of disease activity (VAS)		X		X	X	X	X	X	X	X	

Assessments	Screening visit (V0) (up to 4 weeks before visit 1)	**Baseline**	**Day 4** (+/-2 days)	**Week 1** (+/-2 days)	**Week 2** (+/- 2 days)	**Week 4** (+/-2 days)	**Week 8** (+/-5 days)	**Week 12** (+/-5 days)	**Weeks 16, 20, 24, 32, and 40** (+/-5 days)	**Week 48** (Study Drug Discontinuation visit) (+/-5 days)	**Week 52 Safety follow-up** (+5 days)
		Visit 1	Tel follow up	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7-11	Visit 12	Visit 13
	D-28 to D0	Day 1	Day 4	Day 8	Day 15	Day 29	Day 57	Day 85	D 113-281	Day 337	Day 365
Patient/parent global assessment of overall well-being (VAS)		X		X	X	X	X	X	X	X	
Number of joints with active arthritis		X		X	X	X	X	X	X	X	
Number of joints with limitation of motion		X		X	X	X	X	X	X	X	
Physical function (CHAQ/SHAQ)		X		X	X	X	X	X	X	X	
Global assessment of the patient disease related pain (VAS)		X		X	X	X	X	X	X	X	
Morning stiffness		X					X	X	X	X	
Inactive Disease Status[b]							X	X	X	X	
Completion of Diary[c]		Recording by the patient/parent during the study									
Safety Assessments											
Adverse events recording	X[8]	X	X	X	X	X	X	X	X	X	X
IMP administration (at study site)		X		X	X	X	X	X	X	X	
IMP dispensing		X		X	X	X	X	X	X		

[1] Includes chest X ray.
[2] For evaluating inactive disease (to be done from Week 8 and onwards) the following signs will specifically be recorded: body temperature, rash, serositis, hepatosplenomegaly, and generalized lymphadenopathy.
[3] Height measurements of SJIA patients at Weeks 24 and 40.
[4] Includes HIV test, HbsAg, anti-HBc, HCV test and COVID-19 test.
[5] For patients with a body weight ≤ 15 kg hematology and coagulation samples should not be repeated at Week 1 visit, if not clinically indicated, in order to preserve blood volume.
[6]All laboratory assessments should be performed including for patients with a body weight ≤ 15 kg.
[7] At Baseline, Week 2 and Week 4 visits, PK samples will be taken pre-dose, 15min (±5 min) post-dose for all patients with a body weight > 15 kg.
[8] SAEs occurring during the screening phase will be recorded and reported.
[a] Full list of laboratory assessments is shown in Table 4 and Table 5.
[b] For evaluating inactive disease from Week 8 and onwards, the following signs will specifically be recorded: body temperature, rash, serositis, hepatosplenomegaly, and generalized lymphadenopathy. Inactive disease status will be captured in the EDC system
[c] A diary will be used for recordings of fever episodes and patient´s assessment of rash from baseline up to Week 48 visit. Site of injection and time point of IMP administrations will be recorded daily during the first 4 weeks of treatment.

6.5.1.2 Screening visit, Visit 0 (Day -28 to 0)

The screening visit will take place during the 4 weeks preceding the entry to the study. Obtain signed informed consent prior to any screening activities (see Section 3.3). Assign a patient number to the patient after the ICF is signed, evaluate eligibility based on the inclusion and exclusion criteria. Local laboratory results are valid for evaluation of eligibility criteria (see Section 6.5.5.2). Record the medical history and demographics of the patient, and perform vital signs check (blood pressure, heart rate and body temperature), physical examination (including body weight), and ECG. Record prior and concomitant medications and procedures. Any SAEs that occur after the ICF has been signed must be reported (see Section 6.5.5.1.4).

6.5.1.3 Baseline visit, Day 1 (Visit 1)

Re-evaluate patient's eligibility based on the inclusion and exclusion criteria. Local laboratory results obtained prior to dosing are valid for evaluation of eligibility criteria for 72 hours. If the patient meets the eligibility criteria, he/she will be assigned to anakinra treatment. However, a patient can be assigned before IGRA or a PPD test results are obtained. In case of a positive result for mycobacterium tuberculosis that is not due to vaccination (PPD), the patient must be withdrawn from the study.

Prior to the first injection of IMP, the investigator must:

- Record vital signs (see Section 6.5.5.3) and perform physical examination (height of pediatric patients, weight, chest, abdomen, skin, joints examination, other as applicable judged by the investigator) (see Section 6.5.5.4).
- Record any SAEs and prior and concomitant medications and procedures since the screening visit.
- Assess the ACR variables which include physician global assessment of disease activity (VAS), patient/parent global assessment of overall well-being (VAS), number of joints with active arthritis, number of joints with limitation of motion, assessment of physical function (CHAQ/SHAQ), and CRP.
- Evaluate global assessment of the patient disease related pain (VAS).
- Provide instructions for the completion of the diary to the patient/parent.
- Blood and urine samples will be collected for laboratory assessments.
- Blood sample for pre-dose PK analysis for patients with a body weight > 15 kg.

Then, the first injection of IMP will be administered at study site and the time point for administration will be recorded. Post-dose PK blood sample will be collected 15 (±5 min) after IMP injection for patients with a body weight > 15 kg. Any AE occurring from this point will be recorded. Anakinra covering the period until next visit will be dispensed.

The patient or patient's parent will be instructed on how to inject or self-inject the IMP.

6.5.1.4 Telephone Follow-up visit (Day 4_{Tel})

A telephone contact will be performed at Day 4 for retention reasons, to follow up on compliance with study procedures, and to answer any additional questions from the patient or the parent. Data on adverse events from study treatment initiation will be collected. If not possible to reach the patient or the parent this should be documented in the eCRF. Concomitant medications/procedures will be recorded.

6.5.1.5 Week 1 (Visit 2)

The visit should be scheduled as close as possible to 24 hours after last IMP dose.

Assessments conducted at the visit are the ACR variables, physical examination, including complete joint exam, vital signs, global assessment of the patient disease related pain. Concomitant medications/procedures will be recorded. If any fever or rash have occurred during the last 24 hours, they will be recorded. Data from the patient Diary will support the evaluation.

Blood samples will be collected for laboratory assessments. Adverse events will be recorded. The patient's Diary will be reviewed. After all assessments have been performed, the daily IMP injection will be administered and IMP covering the period until next visit will be dispensed.

6.5.1.6 Week 2 (Visit 3)

The visit should be scheduled as close as possible to 24 hours after last IMP dose.

Assessments conducted at the visit are the ACR variables, physical examination, including a complete joints exam, vital signs, and global assessment of the patient disease related pain. Concomitant medications/procedures will be recorded. If any fever or rash have occurred during the 7 days preceding the Week 2 visit, they will be recorded. Data from the patient diary will support the evaluation.

Blood samples will be collected for laboratory assessments and the pre-dose PK analysis for patients with a body weight > 15 kg. Adverse events will be recorded. The patient's Diary will be reviewed. After all assessments have been performed, the daily IMP injection will be administered, and IMP covering the period until next visit will be dispensed. Post-dose PK blood sample will be collected 15 (±5 min) after IMP injection for patients with a body weight > 15 kg.

6.5.1.7 Week 4 to Week 40 (Visit 4 to Visit 11)

The visits will be scheduled as close as possible to 24 hours after last IMP dose.

Assessments conducted at the visits are the ACR variables, physical examination (includes height of pediatric patients at Weeks 4, 12, 24, and 40), complete joints exam, vital signs, global assessment of the patient disease related pain, and morning stiffness (starting from Week 8 visit). Concomitant medications/procedures will be recorded. If any fever or rash have occurred during the 7 days preceding the visit, they will be recorded.

Blood samples will be collected for laboratory assessments at each study visit (at Week 4 this includes blood samples for pre-dose PK analysis for patients with a body weight > 15 kg). Inactive disease will be evaluated from Week 8 to Week 48 visits (see Section 6.5.4.5). Adverse events will be recorded. The patient's diary will be reviewed. After all assessments have been performed, the daily IMP injection will be administered, and IMP treatment covering the period until next visit will be dispensed. At Week 4 a post-dose PK blood sample will be collected 15 (±5 min) after IMP injection for patients with a body weight > 15 kg.

If the patient is on glucocorticoids treatment, the glucocorticoids tapering can be started earliest at the Week 4 visit. The patient should have reached at least ACR50 response with no fever in the preceding 7 days at the visit initiating tapering. See Appendix 4 for glucocorticoids tapering instructions.

6.5.1.8 Week 48, Study drug discontinuation visit (Visit 12)

The visit will be scheduled as close as possible to 24 hours after last anakinra dose.

Assessments conducted at the visit are the ACR variables, physical examination (includes height of pediatric patients and complete joints exam), vital signs, global assessment of the patient disease related pain, and morning stiffness. Concomitant medications/procedures will be recorded. If any fever or rash have occurred during the 7 days preceding Week 48 visit, they will be recorded. Data from the patient Diary will support the evaluation.

Blood samples will be collected for laboratory assessments. Inactive disease will be evaluated (see Section 6.5.4.5). Adverse events will be recorded. The patient's Diary will be reviewed. After all assessments have been performed, the last dose of anakinra injection will be administered. Finally, all IMP syringes (used and unused) should be collected from the patient in their original package and accounted for. Depending on local regulations the used and unused syringes will be destroyed at study site or shipped back to the depot site for destruction.

6.5.1.9 Week 52, Safety Follow-up visit (Visit 13)

A Follow-up Safety visit (End of Study) will be conducted at study site to collect data on concomitant medications/procedures and adverse events.

6.5.1.10 Study Drug Discontinuation visit

If a patient discontinues IMP at any time during the study prior to Week 48, a Study Drug Discontinuation visit should be performed before standard of care treatment is initiated, when possible. If the study drug is discontinued on a scheduled visit, the assessments for the Study Drug Discontinuation visit should be performed instead, unless the study drug is discontinued at the Week 48 visit. For patients who discontinue study drug and are unable to visit the study site before initiation of standard of care treatment, appropriate assessments should be performed to substantiate the reason for study drug discontinuation, e.g., local laboratory results.

Assessments conducted at the Study Drug Discontinuation visit are the ACR variables, physical examination (includes height of pediatric patients and complete joints exam), vital signs, global assessment of the patient disease related pain, and morning stiffness. Concomitant medications/procedures will be recorded. Inactive disease will be evaluated. If any fever or rash have occurred during the 7 days preceding the Study Drug Discontinuation visit, they will be recorded. If this visit is performed before the Week 1 visit, fever and rash during the 24-hours preceding the Study Drug Discontinuation visit will be recorded.

Blood samples will be collected for laboratory assessments. Adverse events will be recorded. The reason for study drug discontinuation will be recorded in the eCRF. Finally, all IMP (used and unused) should be collected from the patient in their original package and accounted for. Depending on local regulations the used and unused syringes will be destroyed at study site or shipped back to the depot site for destruction.

6.5.1.11 Safety Follow-up visit after study drug discontinuation

Four weeks after the study drug discontinuation i.e., after the last IMP injection, a subsequent Safety Follow-up visit will be performed, according to the assessments described for the Week 52 visit (see Table 3). Upon completion of the visit, the patient will be withdrawn from the study.

If a patient discontinues study drug because of an AE, the reason should always be stated as "adverse event" regardless of whether the study drug discontinuation was the investigator's or the patient's decision.

Patients who fail to return to the study site, will be contacted by the study site personnel (three documented phone calls) in an attempt to have them comply with the protocol and to document the reason for withdrawal.

6.5.2 Medical history

Medical history will be collected during the screening period up until the day of the first dose.

Relevant medical history events as judged by the investigator with onset date at any time prior to ICF signature date will be recorded in the eCRF.

The date of patient's SJIA or AOSD diagnosis should be recorded in the eCRF.

6.5.3 Demography

The patient´s date of birth (month and year), gender, race, and ethnicity will be recorded in the eCRF at the Screening visit (Visit 0).

6.5.4 Efficacy assessments

6.5.4.1 ACR30/50/70/90 response with absence of fever

The ACR30/50/70/90 criteria will be used to determine efficacy and are defined respectively as improvement of ≥ 30%, ≥ 50%, ≥ 70% and ≥ 90% in at least 3 of any 6 variables of the ACR core set listed below, with no more than 1 variable worsening by > 30%, and no intermittent fever attributable to the disease during the preceding 7 days.
In clinical practice, ACR30/50/70/90 criteria are used independently of the age of the patients.
The assessment of the health quality will use the CHAQ and the SHAQ for the pediatric and the adult patients with Still's disease, respectively.
The variables listed below are included in ACR:

1. Physician global assessment of disease activity (on a 0-100 mm VAS).
2. Patient/parent global assessment of overall well-being (on a 0-100 mm VAS).
3. Number of joints with active arthritis.
4. Number of joints with limitation of motion.
5. Assessment of physical function (CHAQ/SHAQ).
6. CRP (mg/L).

Definition of fever: Body temperature ≥ 38.0 °C attributable to the disease.

Definition of active arthritis: Joint with swelling. In absence of swelling, limitation of range of motion accompanied by either pain on motion or tenderness not due to deformity.

6.5.4.1.1 Physician global assessment of disease activity

The physician will rate the patient's current condition on a 0-100 mm VAS, ranging from no disease activity (0 mm) to very severe disease activity (100 mm). Scores on the 100-mm

linear scale will be measured to the nearest millimeter from the left. To enhance objectivity, the physician must not be aware of the patient or parent global assessment of patient's overall well-being, when performing his own assessment on that patient. The assessment should be completed by the study physician at the following visits: Baseline, Week 1, Week 2, Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 32, Week 40, Week 48, and at the Study Drug Discontinuation visit (if applicable).

6.5.4.1.2 Patient/parent global assessment of overall well-being

The global assessment of overall well-being will be assessed on a VAS scale ranging from 0-100 mm, from very well (0 mm) to very poor (100 mm). Scores on the 100-mm linear scale will be measured to the nearest millimeter from the left. For patients < 18 years of age at enrollment VAS will be collected as part of the CHAQ. For patients ≥ 18 years of age at enrollment, VAS will be collected as a part of the SHAQ (see Appendix 8).

The assessment will be conducted at the following visits: Baseline, Week 1, Week 2, Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 32, Week 40, Week 48, and at the Study Drug Discontinuation visit (if applicable) (see Appendix 7 and Appendix 8).

6.5.4.1.3 Number of joints with active arthritis

The number of joints with active arthritis will be assessed using the ACR definition. The ACR definition of active arthritis is any joints with swelling, or in the absence of swelling, limitation of range of motion accompanied by either pain on motion or tenderness not due to deformity.

The joints assessment will be conducted by a trained study staff or by the study physician at the following visits: Baseline, Week 1, Week 2, Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 32, Week 40, Week 48, and at the Study Drug Discontinuation visit (if applicable).

6.5.4.1.4 Number of joints with limitation of motion

The number of joints with limitation of motion will be determined by a trained study staff or by the study physician at the following visits: Baseline, Week 1, Week 2, Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 32, Week 40, Week 48, and at the Study Drug Discontinuation visit (if applicable).

6.5.4.2 Assessment of physical function

6.5.4.2.1 Childhood Health Assessment Questionnaire (CHAQ©)

The CHAQ (see Appendix 8) is a validated patient reported outcome measure (PROM) to assess physical ability and functional status for children (52, 53). CHAQ will be administered throughout the study for patients who are < 18 years of age at the time of enrollment and will be completed by the parent or guardian as a proxy for the child up to 14 years of age, and by the patients themselves if they are above 15 years old. To ensure consistency, the CHAQ should be completed throughout the study by the same parent or guardian who completed the baseline CHAQ assessment, if possible.
The CHAQ has three indices: disability, discomfort, and health status. The disability index assesses the physical function in 8 domains: dressing and grooming, arising, eating, walking, reaching, personal hygiene, gripping, and activities. The score range is 0 to 3 (0 = without any

difficulty; 1 = with some difficulty; 2 = with much difficulty; 3 = unable to do). The highest scoring item in each domain determines the score for that domain. The mean score for the 8 domains is the disability index (range 0 to 3). The discomfort index is determined by the presence of pain and its severity (see Section 6.5.4.3). The health status index is defined by the global assessment of the overall well-being (see Section 6.5.4.1.2). The discomfort and health status indices will also be presented and analyzed separately.
The assessment will be conducted at the following visits: Baseline, Week 1, Week 2, Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 32, Week 40, Week 48, and at the unscheduled Study Drug Discontinuation visit (if applicable).

6.5.4.2.2 Stanford Health Assessment Questionnaire (SHAQ©)

The SHAQ (see Appendix 8) is a validated PROM designed to assess physical ability and functional status for patients ≥ 18 years (54, 55). The SHAQ includes questions of fine movements of the upper extremity, locomotor activities of the lower extremity, and activities that involve both upper and lower extremities. There are 20 questions in 8 categories of functioning which represent a comprehensive set of functional activities: dressing, rising, eating, walking, hygiene, reach, grip, and usual activities. The stem of each item asks over the past week "are you able to…" perform a particular task. The patient's response is made on a scale from 0 (no disability) to 3 (completely disabled). The score for each category is the single response within the category with the highest score (greatest difficulty). The score for the disability index is the mean of the eight category scores.

The assessment will be conducted at the following visits: Baseline, Week 1, Week 2, Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 32, Week 40, Week 48, and if applicable, at the Study Drug Discontinuation visit (if applicable).

6.5.4.2.3 C-reactive protein

CRP levels will be determined in serum in order to identify the presence and severity of inflammation, and to monitor response to treatment. The measurement of CRP will be conducted at the following visits: Screening visit, Baseline, Week 1, Week 2, Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 32, Week 40, Week 48, and at the Study Drug Discontinuation visit (if applicable).

6.5.4.2.4 Fever

For endpoint evaluation in this study, the fever is defined as a body temperature which is ≥ 38.0 °C and should be attributable to the disease as judged by the investigator.

Temperature will be measured in the ear on daily basis (tympanic temperature) using the same thermometer throughout the study. When body temperature is ≥ 38.0 °C the temperature values and time points for the measurements will be recorded in the Diary.

6.5.4.2.5 Systemic manifestations

Systemic manifestations are defined by the following symptoms: fever, rash, arthritis and/or arthralgia, and elevated levels of CRP. Systemic manifestations will be evaluated at each study visit. In case of persistence of the systemic symptoms at Week 1, the dose for patients receiving 1 mg/kg/day of anakinra should be increased to 2 mg/kg/day (max of 100 mg/day). If the systemic symptoms persist at Week 4 visit, the investigator should consider a dose

adjustment for patients below the age of 16 years and with a body weight < 50 kg (up to 4 mg/kg/day with a max dose of 200 mg/day) (see Appendix 2).

6.5.4.3 Global assessment of the patient disease related pain

For patients ≥ 18 years of age at enrollment, the global assessment of disease related pain will be assessed on a VAS ranging from 0 to 100 mm, from no pain (0 mm) to very severe pain (100 mm) by the patients themselves. Scores on the 100-mm linear scale will be measured to the nearest millimeter from the left. For patients < 18 years of age at enrollment, this VAS will be assessed by the CHAQ discomfort index (see Section 6.5.4.2.1).

The assessment will be conducted at the following visits: Baseline, Week 1, Week2, Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 32, Week 40, Week 48, and at the Study Drug Discontinuation visit (if applicable).

6.5.4.4 Rash

A typical sign of Still's disease is the characteristic evanescent salmon-colored rash. Rash is an endpoint and will be evaluated throughout the study.

Any occurrence of rash will be recorded by the patient in the Diary. If present and attributable to the Still's disease, rash will not be recorded as an AE, but as related to the disease by the study physician during the study visits, and at the Study Drug Discontinuation visit (if applicable). The presence or absence of rash will also be recorded to assess "inactive disease" from Week 8 up to Week 48.

6.5.4.5 Inactive disease

In the absence of a biologic marker for the disease activity, clinical signs and symptoms become necessary to determine the state of the disease. Inactive disease is a composite of the following parameters: no joints with active arthritis, no fever, no rash, no serositis, no hepatosplenomegaly, no generalized lymphadenopathy attributable to Still's disease, CRP level within normal limits, physician's global assessment of disease activity score below 10 mm on a 100-mm VAS, and a documented morning stiffness ≤ 15 minutes (56).

The assessment of the disease activity will be conducted at Baseline, Week 8 and at the following respective visits up to Week 48, and at the Study Drug Discontinuation visit (if applicable).

6.5.5 Safety assessments and procedures

6.5.5.1 Adverse events

6.5.5.1.1 Definitions

Adverse event (AE)

An AE is any untoward medical occurrence in a study patient to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment.

AEs include the following:

- Abnormal test findings, as specified below.

- Clinically significant signs and symptoms.
- Changes in physical examination findings.
- Progression/worsening of underlying disease.

The following situations should also be handled according to the same principles as AEs:

- Medication errors[1].
- Misuse[2].
- Abuse[3].

In addition, signs and symptoms resulting from the following should also be handled according to the same principles as AEs:

- Overdose.
- Withdrawal of treatment.
- Interactions.

[1] Medication error; An unintended failure in the IMP treatment process that leads to, or has the potential to lead to, harm to the patient.

[2] Misuse; Situations where the IMP is intentionally and inappropriately used not in accordance with the terms of the clinical study protocol.

[3] Abuse; Persistent or sporadic, intentional excessive use of IMP by a study subject accompanied by harmful physical and/or psychological effects.

Abnormal test findings

An abnormal test finding, e.g., abnormal laboratory analysis results, vital signs, or ECG, should be recorded as an AE in any of the following situations:

- The investigator considers the abnormal test finding to be clinically significant.
- The abnormal test finding is associated with accompanying symptoms. Note, that the symptom, not the test result, should be recorded as an AE.
- The abnormal test finding leads to a medical/surgical intervention including withdrawal of IMP or discontinuation from the study. Repeat/confirmatory testing is not considered a medical intervention.

Preexisting conditions

A preexisting condition (i.e., a disorder present before the AE reporting period started and noted on the pretreatment medical history/physical examination form) should not be reported as an AE unless the condition worsens, or episodes increase in frequency during the AE reporting period.

Procedures

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins

during the AE reporting period should be reported as the AE and the resulting appendectomy entered in the concomitant procedures section of the eCRF.

Lack of efficacy

Failure of the anticipated pharmacologic action or therapeutic benefit (as detailed in the approved product label) shall be recorded as an AE when the observed lack of efficacy is associated with an SAE or a serious outcome for the patient.

Serious adverse event (SAE)

An AE that meets one or more of the following criteria/outcomes is classified as serious:

- Results in death.
- Is life-threatening (i.e., at immediate risk of death).
- Requires in-patient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect (i.e., in an offspring to the study patient).
- Is a medically important AE.

Medically important AEs are events that may not result in death, be life threatening, or require hospitalization but may be considered serious when, based upon appropriate medical judgment, may jeopardize the patient, or may require medical or surgical intervention to prevent one of the 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.

Serious also includes any other event that the investigator or company judges to be serious. Any suspected transmission of an infectious agent via IMP shall also be considered serious.

Hospitalization

Hospitalization includes transfers within a hospital (e.g., from the psychiatric unit to the intensive care unit) and also includes admissions less than 24 hours. The following situations are not considered hospitalizations (although other SAE criteria may still apply):

- Outpatient procedures / ambulatory care.
- Emergency department visits.

Hospitalization in the absence of an AE occurring during the study should not be considered an SAE. This includes:

- Hospitalization due to a pre-existing condition not associated with a worsening of the pre-existing condition.
- Protocol specified admission.
- Elective admission, e.g., due to cosmetic surgery.
- Pre-planned admission for a condition specified at baseline for the patient.

Suspected Unexpected Serious Adverse Reaction (SUSAR)

A SUSAR is an unexpected serious adverse event, suspected to be related to the study drug, which is not consistent with the reference safety information in the Investigator's Brochure (IB).

Medical events of special interest for safety surveillance

a. Drug reaction with eosinophilia and systemic symptoms

DRESS is defined as an event of special interest in this study, for rationale see Section 4.3. The diagnosis of DRESS will be made by the investigator based on the RegiSCAR scoring system (see Appendix 5) (62). If a diagnosis of DRESS is made at any point after the patient signed informed consent, the event must be reported as a SAE (see Section 6.5.5.1.4). A Study Drug Discontinuation visit should be scheduled and the patient will be withdrawn from the study and will be treated according to standard of care in China. For all patients that are diagnosed with DRESS, irrespective of timepoint in the study, a Safety Follow-up visit should be conducted 4 weeks after the last IMP administration (according to the assessments that are described for the Week 52 visit) before the patient is withdrawn from the study.

b. Pulmonary events (interstitial lung disease, pulmonary hypertension, and alveolar proteinosis)

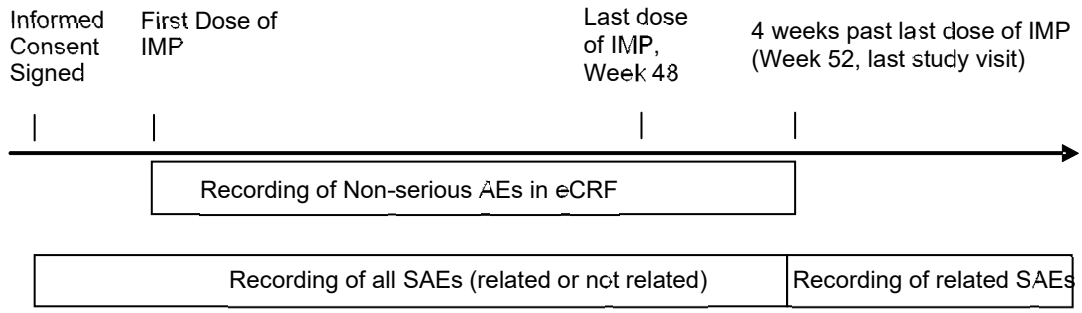
Pulmonary events (interstitial lung disease, pulmonary hypertension, and alveolar proteinosis) are defined as events of special interest in this study, for rationale see Section 4.3. The diagnosis of pulmonary events will be made by the investigator based on the patients overall clinical signs and symptoms, radiological findings, and laboratory findings. If a diagnosis of a pulmonary event is made at any point after the patient signed informed consent, the event must be reported as a SAE (see Section 6.5.5.1.4). Patients who develop pulmonary events will be treated according to local standards of care in China and will continue the IMP at the discretion of the investigator.

6.5.5.1.2 Adverse event reporting period

The period for recording AEs in the eCRF, begins upon receiving the first dose of investigational medication and ends at the last study visit, 4 weeks past the last dose of IMP. All AEs must be collected and recorded in the specific AE form of the eCRF irrespective whether they are caused or not by the IMP, and regardless of seriousness of the AE.

SAEs should be recorded in the eCRF from the time the patient has signed the informed consent until 4 weeks past the last dose of IMP. Furthermore, any SAE, if a causal relationship between the event and the IMP is suspected, which occurs after last study visit (i.e., after Week 52), should be reported (see Figure 2).

Figure 2 Overview of Non-serious AE and SAE reporting period



6.5.5.1.3 Obtaining and recording of adverse event information

The investigator has to record all observed AEs (directly observed, spontaneously reported by the patient, or solicited), in the eCRF using concise medical terminology. In addition, each patient will be questioned about AEs at each study visit following initiation of treatment. At the first study visit, the question to patients will be "Since the Screening visit have you had any health problems?". At subsequent visits/telephone call, the question will be: "Since the last study visit, have you had any health problems?"

When possible and appropriate, a diagnosis rather than individual signs and symptoms shall be recorded. The investigator is responsible for obtaining sufficient information to determine seriousness, causality, and outcome of each AE.

Severity assessment

The investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum severity of the AE. If the severity of an AE worsens during study treatment administration, only the worst severity should be reported on the AE page. If the AE lessens in severity, no change in the severity is required. For the purpose of consistency, these severity grades are defined as follows:

MILD	Does not interfere with patient's usual function
MODERATE	Interferes to some extent with patient's usual function
SEVERE	Interferes significantly with patient's usual function

Severity versus seriousness

A mild, moderate, or severe AE may or may not be serious (see section 6.5.5.1.1). These terms are used to describe the severity of a specific event. Medical judgment should be used on a case-by-case basis.

For example, a headache may be severe in severity, but would not be classified as serious unless it met one of the criteria for serious events listed above.

Causality assessment

Each AE must be assessed by the investigator as to whether or not there is a reasonable possibility of causal relationship to the study treatment and reported as either related or

unrelated. The determination of the likelihood that the study treatment caused the AE will be provided by an investigator who is a qualified physician.

6.5.5.1.4 SAE and non-serious related AE reporting

Both serious and non-serious AEs are to be reported on the AE page of the eCRF as specified in the eCRF instructions, and the investigator must assess the causal relationship of the event to study drug.

The Sobi Global Pharmacovigilance & Patient Safety (GPV) department is to be notified by e-mail to adverseevent@sobi.com, using the designated Serious Adverse Event/Non-serious related AE form, within 24 hours of the investigator's first knowledge of the following events:

- All SAEs (whether or not considered by the investigator to be related to study drug)
- All non-serious related AEs (all non-serious AEs considered by the investigator to be related to study drug)

The SAE reporting form/non-serious related AE reporting form is not always the same as the adverse event eCRF form. The forms must be completed in a consistent manner. For example, the same AE term should be used both in the reporting form and in the eCRF form. If the patient is hospitalized in a hospital other than the study site, it is the investigator's responsibility to contact this hospital to obtain all SAE relevant information and documentation.

All new information obtained, relevant to an SAE and a non-serious related AE report, should be forwarded to Sobi GPV within the same timeframe as the initial information.

The investigator shall provide Sobi with sufficient information to enable a complete medical assessment of the reported event. Best efforts shall be made by the investigator to provide Sobi GPV with additional information regarding any SAE and non-serious related AE as requested, and completing AE questionnaires if applicable.

Prompt notification by the Investigator to Sobi GPV of a SAE and non-serious related AE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

- An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor, will review it and will notify the IECs/IRBs, if appropriate according to local requirements.
- Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.
- The reference safety document to assess expectedness of a suspected serious adverse reaction and reported by the sponsor to Health Authorities, IECs/IRBs, and investigators is the reference safety information section of the current version of the Investigator's Brochure.

6.5.5.1.5 Follow-up of unresolved adverse events

All AEs should be followed until they are resolved, or the investigator assesses them as "chronic" or "stable", or the patient's participation in the study ends, i.e., until the last Follow-up visit 4 weeks after the last dose of IMP. How to report changes in an ongoing AE during a patient's participation in the study is described in the eCRF instructions.

In addition, all SAEs and non-serious AEs assessed by the investigator as related to the IMP should continue to be followed until they resolve or until the investigator assesses them as "chronic" or "stable", even after the patient's participation in the study is over, but without further recordings into the eCRF.

6.5.5.1.6 Exposure during pregnancy and breastfeeding

Female patients with childbearing potential, defined as all women physiologically capable of becoming pregnant are expected to use highly effective methods of contraception during dosing and for 1 month after last dose of study drug.

Highly effective contraception methods include:

- Total abstinence (when this is in line with the preferred and usual lifestyle of the patient). Periodic abstinence (e.g., calendar, ovulation, symptom-thermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- Use of oral, (estrogen and progesterone), injected or implanted hormonal methods of contraception or placement of an intra-uterine device or intra-uterine system, or other forms of hormonal contraception that have comparable efficacy (failure rate < 1 %), for example hormone vaginal ring or transdermal hormone contraception.
- In case of use of oral contraception, women should have been stable on the same brand (or generic equivalent) for a minimum of 3 months before taking study treatment.

Reporting of pregnancy

All events of exposure to the IMP during pregnancy (female patient or male patient's partner) or breastfeeding, shall be reported to Sobi GPV by e-mail to **adverseevent@sobi.com** within 24 hours of awareness by any study personnel, using the pregnancy notification form, whether the exposure is associated with an AE or not. This includes all situations where a female is or has been found to be pregnant after being exposed to IMP; directly, indirectly or via her partner (paternal exposure).

In all reported situations of exposure during pregnancy, Sobi will provide the investigator with a Pregnancy report form which shall be completed and returned by the investigator.

Follow-up of pregnancy

Any pregnancy must be followed to its conclusion, and its outcome must be reported to the Sobi GPV. The investigator is responsible for monitoring the outcome of the pregnancy and to inform Sobi of relevant information and any information requested related to the outcome of the pregnancy. Before collecting any details on the pregnancy, its outcome, the birth, and health of the baby, a separate consent form should be collected from the mother and/or the father of the child, as required by Chinese regulations.

Any AEs and SAEs occurring in female patients participating to the study, and observed during and in relation to pregnancy, delivery, or breastfeeding should be recorded in the eCRF and as applicable be reported to Sobi GPV as described previously in this section.

6.5.5.2 Laboratory safety assessments

Due to the low blood volume in patients with a body weight ≤ 15 kg, it may be necessary to reduce sampling. Therefore, local laboratory sampling will be used and also, patients with a body

weight ≤ 15 kg will not participate and provide blood samples for the PK analysis. WHO recommendations regarding blood sampling are to be followed and if patient care or normal disease monitoring requires prioritization of sampling, this should be adhered to. For patients with a body weight ≤ 15 kg, laboratory hematology and coagulation samples should not be repeated at Week 1 visit, if not clinically indicated, in order to preserve blood volume.

Samples will be analyzed at the local laboratory using the local laboratory's standardized analytical procedures and local procedures for blood collection and processing will be followed. The local laboratory should be accredited or participate in an external quality assurance scheme, e.g. China National Accreditation Service for Conformity Assessment (CNAS). The results from the local laboratory will constitute the primary data of the study to be used for statistical analysis.

In the event a study site is unable to analyze any of the protocol required laboratory tests at the local hospital laboratory, such samples can be sent to an external laboratory for analysis, and the results will be accepted in this study. Similarly, test results of the patients performed in other hospitals can be accepted in this study. The test content, test time window, and test result time window and requirements should be consistent with the study protocol.

Clinically significant laboratory values should be reported as AEs (see Section 6.5.5.1.1 for details), except at Baseline visit when they should be recorded as part of the medical history.

Local laboratory will also be used for patient care and treatment decisions in between study visits.

If a sample cannot be performed on the day of the scheduled visit, assessments within ±1 day window from scheduled visit date will be accepted.

All laboratory assessments should be performed also for patients ≤15 kg body weight at the Week 48 visit and at Study Drug Discontinuation visit.

In case any of the safety laboratory assessments cannot be analyzed at the Week 48 visit, the patient should be asked to return for an unscheduled visit to ensure that results are available for all laboratory assessments.

6.5.5.2.1 Assessments to confirm eligibility

Tests needed for evaluation of inclusion and exclusion criteria should be performed before enrollment (see Table 4). However, a patient can be enrolled before results from IGRA or a TST have been confirmed. If the results from these tests are positive the patient must be withdrawn from the study. [Interferon-Gamma-Release Assays (IGRAs) e.g., QuantiFERON® TB Gold Plus (QFT-Plus) or T-Spot® (TB Test) can be performed within 8 weeks prior to enrollment. Previously vaccinated for Tuberculosis patients: IGRA positive patients are not eligible to enter the Study; TST positive patients with an induration of 15 mm and more are also not eligible to enter the study, TST positive patients (with an induration less than15 mm) are also not eligible to enter the study, unless an IGRA test is subsequently performed and provides a negative result.

Test results are valid for 72 hours before enrollment, provided that the patient does not show signs and/or symptoms of new ailments, or increasing signs and/or symptoms that make the patient ineligible for the study in the opinion of the investigator. Any clinically significant findings in laboratory results should be followed up.

Table 4 Tests to confirm the patient eligibility

Clinical chemistry Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Total bilirubin (including, conjugated and unconjugated bilirubin) Alkaline phosphatase (ALP) Triglycerides Creatinine Creatinine clearance Ferritin C-reactive protein (CRP) **Urine analysis** Human chorionic gonadotropin (Beta hCG) test (for women of childbearing potential)[1]	**Hematology** Hemoglobin Hematocrit White blood cells count Red blood cells count Differential blood count (neutrophils, lymphocytes, monocytes, eosinophils, basophils) Thrombocytes (platelets count) **Coagulation** Fibrinogen D-dimer Prothrombin **Tuberculosis testing** IGRA or TST test[2] **Viral infection testing** HIV HBsAg, anti-HBc, hepatitis c virus (HCV) Covid-19 **Still's diagnosis** IgM-RF and ANAs **Imaging** Chest X-ray[3]

[1] Blood sample is also accepted
[2] Only required if no IGRA or PPD test is present within 8 weeks prior enrollment.
Abbreviations: IGRA, Interferon-gamma release assay; TST, Tuberculin skin test; PPD, Purified protein derivative; IgM-RF, Immunoglobulin M-Rheumatoid factor; ANAs, Antinuclear antibodies.
[3] Chest X-Ray for tuberculous testing at screening visit. Negative results must be complemented by the medical history, physical examination, and Chest X-Ray.

6.5.5.2.2 Laboratory assessments during the study

Blood samples for determination of hematology, coagulation, and clinical chemistry variables will be collected at all visits and will be performed by the local laboratory using routine methods. The date and time of collection will be recorded on the appropriate eCRF (see Table 5).

To guide the investigator for decision making to determine start of glucocorticoids tapering and to evaluate if the patient is fulfilling the escape criteria, a CRP assessment can be done.

Table 5 Laboratory assessments during the study

Clinical chemistry C-reactive protein (CRP) Ferritin Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Total bilirubin (including, conjugated and unconjugated bilirubin) Alkaline phosphatase (ALP) Gamma-Glutamyl Transferase (γ GT) Albumin Cholesterol (total, LDL and HDL) Triglycerides Blood Urea nitrogen Creatinine clearance Sodium (Na) Potassium (K) Calcium (Ca) Phosphorous (P) Magnesium (Mg) Glucose Lactate dehydrogenase (LDH)	**Hematology** Hemoglobin Hematocrit White blood cells count Red blood cells count Differential blood count (neutrophils, lymphocytes, monocytes, eosinophils, basophils) Thrombocytes (platelets count) Erythrocyte Sedimentation Rate **Coagulation** Fibrinogen D-dimer Prothrombin

6.5.5.3 Vital signs

Clinically significant abnormal vital signs values should be reported as AEs (see Section 6.5.5.1.1 for details), except at Screening and Baseline visits when they should be recorded as part of the medical history.

Vital signs (blood pressure, heart rate, and body temperature) will be assessed at the Screening visit (Visit 0), the Day 1 visit before the first IMP administration and at all visits until Week 48. It will also be assessed if the Study Drug Discontinuation visit is performed. Blood pressure and heart rate will be measured in sitting position after the patient has rested comfortably for at least 5 minutes. If a patient changes their posture during the measurement process, the measurement will be repeated since this might affect the accuracy of the readings.

6.5.5.4 Physical examination

If any abnormalities are reported at baseline they should be recorded as medical history. New abnormalities reported after the first dose of IMP or worsening of abnormalities should be reported as AEs (see Section 6.5.5.1.1 for details).

A general physical examination (including body weight) will be assessed at Screening visit (Visit 0), at Baseline, and at all study visits until Week 48. Height of pediatric patients will be measured at Baseline visit and Weeks 4, 12, 24, 40, and 48, (see Table 3). It will also be assessed if the Study Drug Discontinuation visit is performed. The assessment will be recorded as "normal" or "abnormal". Abnormalities should be specified.

From Week 8 visit up to Week 48 visit and at the Study Drug Discontinuation visit, if applicable, the presence or absence of specific physical examination findings which are associated with

Still's disease such as body temperature, rash, serositis, splenomegaly, hepatomegaly, and generalized lymphadenopathy will be recorded to assess "inactive disease" (see Section 6.5.4.5).

Any persisting abnormalities should be stated each time the examination is performed.

Any occurrence of rash will be recorded on a daily basis by the patient in the Diary and as part of the physical examination assessment performed at the study visits (see Section 6.5.4.4). If not judged to be attributable to the disease it should be recorded as an AE.

6.5.5.5 Electrocardiograms

Clinically significant abnormal ECG findings should be reported as AEs (see Section 6.5.5.1.1 for details).

A 12-lead ECG will be recorded at the Screening visit (Visit 0), unless performed per routine care within 4 weeks prior to first dose of IMP. The 12-lead ECG recordings will be measured in supine position after the patient has rested comfortably for at least 5 minutes. Heart rate will not be captured from the ECG but should be captured from the blood pressure measurement.

The ECGs will be reviewed and documented in the eCRF. If a patient shows an abnormal ECG, additional safety recordings may be made, and the abnormality followed to resolution if required. If any clinically significant abnormalities are found at screening, they should be recorded as medical history. However, if findings are judged serious, they should be reported as SAEs (see Section 6.5.5.1.1 for details).

6.5.6 Pharmacokinetic assessments

6.5.6.1 Sampling procedures

Serum concentrations of anakinra will be determined at Baseline, Week 2, and Week 4 visits in all patients, with a bodyweight > 15 kg, enrolled into the study. Pharmacokinetic assessments are an integral part of the study however if a patient is not able to provide blood samples for pharmacokinetic assessments for any justifiable reason it will not hinder participation in the study. Samples will be collected before the IMP administration and at 15 minutes (±5 min) after IMP administration.

The sampling handling procedures for the PK samplings, including the date and time of each sample collection, the time of placement of sera/plasma into frozen storage (at the end of the sample workup), and the date of transfer or shipment of the samples to the responsible laboratory will be described in detail in the laboratory manual. Additionally, the procedures and materials used, e.g., collection and storage tubes will be described in the laboratory manual.

If the blood volume required for the planned laboratory assessments at any visit exceeds the maximum allowed blood volume collection according to limitations in relation to the body weight of the patient, blood sampling for the care of the patients should always have the priority over blood samples collected specifically for this study.

6.5.6.2 Bioanalytical method

Serum samples to determine anakinra serum concentration will be analyzed using an ECL-MSD immunoassay validated following the FDA Guidance for Industry on Bioanalytical Method Validation (64), the EMA Guideline on bioanalytical method validation (65), and Viswanathan

CT et al. Workshop /Conference Report (66) in which anakinra is captured by a biotinylated anti human IL-1Ra goat polyclonal antibody and detected a sulfo-tag goat polyclonal antibody.

All the details regarding PK analysis will be described in a sample analysis plan which will be agreed and signed before any biological serum sample is measured by the respective laboratory.

6.5.6.3 Pharmacokinetic evaluation

The individual serum concentration data, and the actual time for anakinra administration and blood sampling will be used throughout the analyses.

Samples with serum concentrations below the lower limit of quantitation (LLOQ) at early time-points will be treated as zero.

7 Quality control and quality assurance

This study will be conducted in compliance with this protocol, study specific procedures, the CRO standard operating procedures (SOPs), applicable Sobi SOPs, the ICH Guideline for GCP (1), and applicable regulatory requirements.

Sobi will systematically review the study quality management to identify, evaluate and control risks to study critical processes and data which would affect patient safety and reliability of study data.

Sobi will establish a systematic, prioritized, risk-based approach to monitoring and has chosen a combination of on-site and centralized monitoring.

Monitoring visits to the study sites will be performed periodically during the study, to help ensure compliance with the protocol, study specific procedures, and applicable regulatory requirements. Virtual site monitoring will be considered where local travel is restricted. Source documents will be reviewed for verification of agreement with data in eCRFs. All patient's ICFs will be reviewed. The investigator or institution guarantees access to source documents by Sobi, its representatives, and appropriate regulatory agencies.

The study site may be subject to quality assurance audits by Sobi or its representatives, as well as inspections by appropriate regulatory agencies.

It is important that the investigators and their relevant personnel are available during the monitoring visits and possible audits, and that sufficient time is devoted to these processes.

8 Statistical plan

A formal statistical analysis plan (SAP) will be written and will provide details of all analyses to be conducted.

8.1 Determination of sample size

Sample size: 60 patients with Still's disease (expected allocation is 30 SJIA and 30 AOSD) will be enrolled. The sample size is based on feasibility and practical considerations rather than

statistical. However, assuming an expected ACR30 response rate of at least 75%, the planned sample size ensures at least 80% probability that the observed response rate in each patient population is ≥ 70%.

8.2 Definition of study populations

8.2.1 All treated Analysis Set

All safety and efficacy summaries will be conducted on the "All treated Analysis Set" which will comprise all patients who received at least one dose of IMP.

8.2.2 Pharmacokinetic Analysis Set

The Pharmacokinetic (PK) Analysis Set includes all patients who received at least one dose of IMP and who had at least one serum concentration data above the lower limit of the calibration range. Pharmacokinetic Analysis Set will be used in the analysis of all pharmacokinetic variables.

8.3 Overall statistical and analytical plan

All details of the statistical analyses will be described in a separate study specific statistical analysis plan (SAP). Statistical analysis will be performed using SAS software Version 9.4 or later (SAS Institute, Inc, Cary, North Carolina, United States).

8.3.1 General statistical issues

The statistical analysis will be described in more detail in the SAP.

All endpoints will be summarized with descriptive statistics. For binary data (e.g. proportions of patients achieving a defined variable) the counts and percentages with corresponding 95% confidence intervals will be presented.

For measurements of continuous endpoints, summary statistics will include n, mean, median, standard deviation, 95% confidence intervals, minimum and maximum values.

Suitable tabular and graphical summaries will be prepared for individual data and for appropriate summary statistics, and all data will be listed.

No formal statistical hypothesis testing will be performed.

8.3.2 Demographics and baseline characteristics

All demographics and baseline characteristics will be summarized with descriptive statistics.

8.3.3 Analysis of the primary estimand/primary endpoint

The primary estimand is defined in Section 5.1.3. The primary endpoint is ACR30 response at Week 4 with absence of fever attributable to the disease during the 7 days preceding Week 4 as defined in Section 5.1.2 and will be summarized as proportion of patients who achieve ACR30 response, with corresponding 95% confidence interval. In the derivation of the primary endpoint, patients with intercurrent events (treatment discontinuation, and prohibited concomitant medications) prior to Week 4 will be set to non-responders in the analysis (see Table 1). Missing data are handled as described in Section 8.3.10.

8.3.4 Analysis of secondary endpoints

For binary secondary endpoints data will be presented as proportion of patients achieving the endpoint with corresponding 95% confidence intervals.

For continuous secondary endpoints, summary statistics will be presented including mean, median, standard deviation, 95% confidence intervals, minimum and maximum values.

For all secondary endpoints, data will be summarized as observed at each timepoint with no imputation for missing data or intercurrent events.

8.3.5 Analysis of safety and tolerability data

8.3.5.1 Adverse events

Reported AEs during the study will be coded using MedDRA. The incidence of AEs will be summarized in frequency tables by treatment, system organ class (SOC), preferred term (PT), and maximum severity. Separate tabulations will be performed for serious and non-serious AEs.

A TEAE is defined as an AE with a start date/time after the first administration of IMP and within 28 days after stopping therapy.

The number and percentage of patients with at least one TEAE, at least one severe TEAE, at least one serious TEAE, including death, at least one non-serious TEAE, any related TEAEs, any fatal TEAEs and any TEAEs leading to study drug withdrawn, will be summarized in frequency tables by SOC, and PT.

The number of patients with DRESS, and pulmonary events (interstitial lung disease, pulmonary hypertension, and alveolar proteinosis) will be reported.

8.3.5.2 Clinical laboratory results

Clinical laboratory safety data will be presented over time by descriptive statistics. In addition, the number of patients with abnormal laboratory values will be presented using shift tables.

8.3.5.3 Vital signs

Vital signs data will be presented over time using descriptive statistics.

8.3.5.4 Physical examination

The number and percentage of patients with presence of physical examination findings will be presented over time.

8.3.6 Analysis of pharmacokinetic and pharmacodynamic

The concentration data of anakinra will be presented using descriptive statistics.

8.3.7 Interim analysis

An interim analysis may be performed for Interim Clinical study reports which can be authored during the study for regulatory purposes.

Due to the administrative aim, this interim analysis will not have an impact on the ongoing study conduct.

8.3.8 Analysis and reporting

The final data will be analyzed and reported when all patients have completed all visits of the study.

8.3.9 Exploratory subgroup analyses

Due to the small sample size, subgroup analyses may not add any value, however all key endpoints will be reported by SJIA and AOSD separately.

Further subgroup analyses may be defined in the SAP.

8.3.10 Handling of missing data

No imputation will be used for missing data in the statistical analyses. As such, patients with missing data at each timepoint will be presented as missing from the endpoint.

9 Data collection, handling and record keeping

9.1 Data standards

Collection of data should be performed in the clinical data acquisition standards harmonization (CDASH) format, according to the CDISC. The standards should be used to the extent possible and/or required for the specific study/project. The minimum requirement of the CDISC standard is to collect all core variables specified as “Required” in the Study Data Tabulation Model format.

9.2 Case report form

A CRF is required and should be completed for each enrolled patient. In this study a web based, validated electronic data capture (EDC) software tool will be used to collect and process the study data. The management of the EDC system will be based on the model of outsourcing.

The data should be entered by site users into the EDC system on an ongoing basis. In principle, it is recommended to perform data entry within 5 working days from the visit date unless otherwise specified by the site Clinical Trial Agreement. To ensure data quality within EDC, automated edit checks will be built into the EDC system and triggered to correct or verify the input data. Any data changes or modifications within EDC will be automatically tracked by an audit trail detailing date, time and name of the user performing corrections. All patient or parent reported outcomes (CHAQ/SHAQ) will be completed on paper and entered in the eCRF.

Clinical data management will be conducted in accordance with regulatory standards. This applies to data recorded directly in eCRF and to data from other sources stored at secure servers (e.g. IXRS, Laboratory). Additional details regarding data collection and validation procedures will be detailed in a Data Management Plan.

Access to the EDC system is granted and revoked in accordance with regulatory requirements. Only authorized personnel will have access to the electronic data capture system upon completion of the user training.

The investigator will review and approve the eCRF entries for each patient with an electronic signature. The signatures serve to attest that the information contained on the eCRFs is correct. At all times, the investigator has final responsibility for the accuracy and authenticity of all data entered on the eCRFs.

The completed original eCRFs are the sole property of Sobi and should not be made available in any form to third parties, except for authorized representatives of appropriate regulatory authorities, without written permission from Sobi.

At the end of the study, a final copy of the database will be stored at the Sponsor. Sobi will ensure that an eCRF copy of trial's final and locked data is provided to the Investigator in a form of a write protected PDF files and that the eCRF copies are an exact copy of the data maintained in the database.

9.3 Patient Diary

A patient diary will be used by the patient during the treatment period. The patient Diary is intended to collect variables used for the assessment of the primary endpoints and to monitor the treatment with the IMP during the study. Signs and symptoms recorded in the diary will only be reported as AEs if not judged to be attributable to the disease. The occurrence of adverse event will be assessed in parallel during the visits. In the Diary, the patient will record the sites and timepoints of all IMP administrations during the first 4 weeks after first dose. The time point of any fever episode together with the actual body temperature, and the occurrence of rash should be recorded in the Diary throughout the full study participation. The patient or patient's parent will be instructed on how to complete the diary at their first visit. The diary will be reviewed by the site at each visit for completeness.

9.4 Source data

Patient source documents are the physician's patient records maintained at the study site. In most cases, the source documents will be the hospital's or the physician's chart. In those cases, the information collected on the eCRFs must match those charts. In some cases, a portion of the source documents for a given patient may be the eCRF or Diary.

For some data, the patient records will not be considered source documents. For collected patient reported outcome data e.g., the actual/original forms completed by the patients are considered as source documents.

A separate source document location agreement will be completed and signed by the principal investigator and the monitor before study start.

Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g. via an audit trial).

The investigator(s)/institution(s) will permit direct access to source data/documents for study related monitoring, audits, IECs/IRBs review, and regulatory inspection(s).

9.5 Protocol Deviations

A protocol deviation is generally an unplanned excursion from the protocol that is not implemented or intended as a systematic change. The investigator is responsible for ensuring that the study is conducted in accordance with the procedures and evaluations described in this protocol and must protect the rights, safety, and welfare of patients. The investigator should not implement any deviation from, or changes of, the protocol, unless it is necessary to eliminate an immediate hazard to study patients.

A protocol waiver is a documented prospective approval of a request from an investigator to deviate from the protocol. Protocol waivers are strictly prohibited.

When a deviation from the protocol is identified, the investigator or designee must ensure the CRO is notified. The CRO will follow up with the investigator, as applicable, to assess the deviation and the possible impact on the safety of the patient and/or efficacy of the IMP to be able to determine patient's continuation in the study.

The investigator and the CRO must contact Sobi immediately if a deviation is discovered that significantly affects or has the potential to significantly affect human patient protection or the reliability of study results.

For the purpose of this study, deviations requiring notification to Sobi and the CRO are defined in the Monitoring Plan. For example, any patient who:

- Entered into the study even though they did not meet eligibility criteria.
- Developed withdrawal criteria during the study and were not withdrawn.
- Received incorrect dose.
- Received excluded concomitant treatment.

The investigator will also assure that deviations are reported and documented in accordance with IECs/IRBs and applicable regulatory requirements.

9.6 Database closure

Prior to database closure, all tasks or criteria defined in the data management plan must be completed and documented. The study database must be locked (hard or soft lock) before generation of any results. The database lock will be approved by relevant study personnel and all edit accesses will be removed. The study database can only be unlocked in case critical errors affecting the main conclusions of the study are discovered.

9.7 Record retention

The investigator should maintain a record of the location(s) of investigator's essential documents as defined in the ICH GCP Guideline (1) including source documents and should have control of and continuous access to all essential documents and records generated by the investigator/institution before, during, and after the study.

All documents and data relating to the study will be kept securely by the investigator in a secure file and/or electronically. The storage system used during the study and for archiving (irrespective of the type of media used) should provide for document identification, version history, search, and retrieval. The data will be available for evaluation and/or audits from Health Authorities, Sobi or Sobi's representatives.

When a copy is used to replace an original document (e.g. source documents, CRF), the copy should fulfill the requirements for certified copy as defined in ICH GCP Guideline (1).

The records should be retained by the Investigator as specified in the Clinical Trial Agreement and in accordance with local regulations.

If the investigator relocates, retires, or for any reason withdraws from the study, the study records may be transferred to an acceptable designee, such as another investigator or another institution. Archiving on behalf of the investigator can also be delegated to Sobi.

9.8 Data Protection

Study patients will be assigned a unique identifier by the sponsor. Any patient records or datasets that are transferred to the sponsor will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.

The patient must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient who will be required to give consent for their data to be used as described in the informed consent

The patient must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IEC/IRB members, and by inspectors from regulatory authorities

The contract between sponsor and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties.

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

10 End of study

The end of study at a patient level is either the Safety Follow up Visit after the Week 48 visit (Week 52 visit) or the Safety Follow up visit after an early Study Drug Discontinuation Visit.

The end of this study at the study level is defined as date of the last patient out, i.e. the last patient's last visit.

11 Sponsor's discontinuation criteria

Sobi reserves the right to discontinue the study prior to inclusion of the intended number of patients, but intends only to exercise this right for valid scientific or administrative reasons. After such a decision, the investigator must contact all participating patients. All study materials must be collected and all the eCRFs completed to the greatest extent possible.

12 Dissemination and publication of results

Sobi will register the study by posting study information and post study results regardless of outcome on a publicly accessible website in accordance with applicable laws and regulations, e.g., on http://www.chictr.org.cn/, http://www.chinadrugtrials.org.cn/ and www.clinicaltrials.gov (posting only study information, no study results). The results of this study will be published within 12 months of the end of study.

Sobi is committed to publishing study results in a complete, accurate, balanced, transparent, and timely manner. Sobi follows the principles of the International Committee of Medical Journal Editors (ICMJE) recommendations for the conduct, reporting, editing, and publication of scholarly work in medical journals including criteria for authorship (60).

The data from this study will be considered for reporting at a scientific meeting or for publication in a scientific journal. The sponsor will be responsible for these activities and will work with the investigators to determine how the publication is written, the number and order of authors, the journal or scientific meeting to which it will be submitted, and other related issues. The results of the study, or any part thereof, shall not be published without the prior written consent and approval of Sobi, such consent and approval not to be unreasonably withheld.

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14 Appendices

Appendix 1 Additional Protocol Signatures

Sponsor's Statistician

Helena Ahlin,
Senior Statistical Scientist
E-mail helena.ahlin@sobi.com

Signature

Date

Appendix 2 Diagnosis criteria

SJIA: Onset of the disease < 16 years of age

ILAR criteria (61)
• Arthritis in one or more joints with, or preceded by • Daily fever for at least 2 weeks, that at some point is documented to be quotidian for at least 3 days, and accompanied by one or more of the following: 1. Evanescent (non-fixed) erythematous rash 2. Generalized lymph node enlargement 3. Hepatomegaly and/or splenomegaly 4. Serositis **Exclusions** 1. Psoriasis or a history of psoriasis in the patient or first degree relative 2. Arthritis in an HLA-B27 positive male beginning after the 6th birthday 3. Ankylosing spondylitis, enthesitis related arthritis, sacroilitis with inflammatory bowel disease, Reiter's syndrome, or acute anterior uveitis, or a history of one of these disorders in a first degree relative 4. The presence of IgM rheumatoid factor on at least 2 occasions at least 3 months apart

AOSD: Onset of the disease ≥ 16 years of age

Yamaguchi criteria (62)
Classification of AOSD requires 5 or more criteria including 2 or more major criteria[1]. Any disease listed under "exclusions" should be excluded. **Major criteria** 1. Fever of 39˚C or higher, lasting 1 week or longer 2. Arthralgia lasting 2 weeks or longer 3. Typical rash[2] 4. Leukocytosis (10 000/mm^3 or greater) including 80% more of granulocytes **Minor criteria** 1. Sore throat 2. Lymphadenopathy and/or splenomegaly[3] 3. Liver dysfunction[4] 4. Negative RF and negative ANAs[5] **Exclusions** 1. Infections (especially, sepsis and infectious mononucleosis) 2. Malignancies (especially, malignant lymphoma) 3. Rheumatic diseases (especially, polyarteritis nodosa and rheumatoid vasculitis with extraarticular features)

Abbreviations: RF, Rheumatoid factor; ANAs, Antinuclear antibodies.

[1] All criteria are applicable only in absence of other clinical explanations.
[2] Macular or maculopapular nonpruritic salmon-pink eruption usually appearing during fever.
[3] Lymphadenopathy is defined as recent development of significant lymph node swelling, and splenomegaly is confirmed on palpation or by an echogram.
[4] Liver dysfunction is defined as an abnormally elevated level of AST, ALT and/or LDH, which is attributed to liver damage associated with this disease but not with drug allergy/toxicity or other causes. For the differentiation, it is

recommended to see if liver function returns to normal upon discontinuation of hepatotoxic drug or not, before applying this criterion.
[5] RF in serum must be negative by routine test for the detection of IgM RF, and serum ANA must be negative by routine immunofluorescence test.

Appendix 3 Dosing instructions

Dose 1 mg/kg/day (max 50 mg/day)

Body weight (kg)	IMP dose administered (mg)	Range of dose received (mg/kg)
10-23.9	20	0.8-2.0
24.0-34.9	30	0.9-1.3
35.0-43.9	40	0.9-1.1
44.0-50	50	1.0-1.1

Dose 2 mg/kg/day (max 100 mg/day)

Body weight (kg)	IMP dose administered (mg)	Range of dose received (mg/kg)
10-12	20	1.7-2.0
13-17	30	1.8-2.3
18-22	40	1.8-2.2
23-27	50	1.9-2.2
28-32	60	1.9-2.1
33-37	70	1.9-2.1
38-42	80	1.9-2.1
43-49	90	1.9-2.1
≥ 50	100	≤ 2.0

Dose 4 mg/kg/day (max 200 mg/day); in case of dose adjustment

Body weight (kg)	IMP dose administered (mg)	Range of dose received (mg/kg)
10-11	40	3.6-4.0
12-13	50	3.8-4.2
14-16	60	3.8-4.3
17-18	70	3.9-4.1
19-21	80	3.8-4.2
22-23	90	3.9-4.1
24-28	100	3.6-4.2
29-31	120	3.9-4.1
32-33	130	3.9-4.1
34-36	140	3.9-4.1
37-38	150	3.9-4.1
39-41	160	3.9-4.1
42-43	170	4.0
44-46	180	3.9-4.1
47-49	190	3.9-4.0
≥ 50	200	≤ 4.0

Appendix 4 Guidance for glucocorticoids tapering

Tapering of the glucocorticoids dose is suggested at an interval of every second week. The table below describes **an example** of tapering steps if the start dose is = 1 mg/kg.

The tapering can be commenced earliest at the Week 4 visit and if the patient has reached at least ACR50 response with no fever in the preceding 7 days.

	10-20 kg	**20-30 kg**	**30-40 kg**	**40-50 kg**	**50-60 kg**	**≥ 60 kg**	**Weight-based dose**
Stable dose at baseline	10 mg	20 mg	30 mg	40 mg	50 mg	60 mg	1 mg/kg (max 60mg)
Dose prescribed at first tapering step (earliest at Week 4)	7.5 mg	15 mg	22.5 mg	30 mg	37.5 mg	45 mg	0.75 mg/kg
Dose prescribed at second tapering step (2 weeks after tapering commences)	5 mg	10 mg	15 mg	20 mg	25 mg	30 mg	0.5 mg/kg
Dose prescribed at third tapering step (4 weeks after tapering commences)	2.5 mg	5 mg	7.5 mg	10 mg	12.5 mg	15 mg	0.25 mg/kg
Dose prescribed at fourth tapering step (6 weeks after tapering commences)	1 mg	2.5 mg	2.5 mg	5 mg	5 mg	7,5 mg	0,12 mg/kg
Dose prescribed at fifth tapering step (8 weeks after tapering commences)	off	off	off	off	off	off	off

Appendix 5 Guidance for DRESS diagnosis; RegiSCAR Scoring System (63)

SCORE	-1	0	1	2	min	max
Fever ≥ 38.5 ^{0} C	No/U	Yes			-1	0
Enlarged lymph nodes		No/U	Yes		0	1
Eosinophilia Eosinophils Eosinophils, if leukocytes <4000		No/U	 700-1499/µl 10-19.9%	 ≥1500/µl ≥20%	0	2
Atypical lymphocytes		No/U	Yes		0	1
Skin involvement Skin rash extent (% BSA) Skin rash suggesting DRESS Biopsy suggesting DRESS	 No No	 No/U U Yes/U	 >50% Yes		-2	2
Organ involvement * Liver Kidney Lung Muscle/heart Pancreas Other organ(s)		 No/U No/U No/U No/U No/U No/U	 Yes Yes Yes Yes Yes Yes		0	2
Resolution ≥ 15 days	No/U	Yes			-1	0
Evaluation other potential causes: ANA Blood culture Serology for HVA/ HVB/ HVC Chlamydia-/ Mycoplasma pneumoniae Other serology/PCR If none positive and ≥ 3 of above negative			 Yes		0	1
TOTAL SCORE					-4	9

Abbreviations: U, unknown/unclassifiable; BSA, body surface area; DRESS, Drug reaction with eosinophilia and systemic symptom; ANA, Antinuclear antibody; HVA, Hepatitis A; HVB, Hepatitis B; HVC, Hepatitis C; PCR, Polymerase chain reaction.
* After exclusion of other explanations: 1 = 1 organ, 2 = ≥ 2 organs

- Final score < 2: No case.
- Final score 2-3: Possible case.
- Final score 4-5: Probable case.
- Final score > 5: Definite case.

1/ Fever (-1, 0)
If core temperature is < 38.5 °C: deduction of 1 point.

2/ Lymphadenopathy (0, +1)
Tender enlarged lymph nodes at least at two different anatomic locations: 1 point.

3/ Peripheral blood
a/ Eosinophilia (0, +1,+2):
- Absolute eosinophilia of 700-14991499 10^9E/L:1 point, if ≥ 1500 10^9E/L: 2 points.
- If leukocyte count is < 4000 10^9E/L: % eosinophils ≥ 10%-19.9%: 1 point, eosinophils ≥ 20%: 2 points.

b/ Atypical lymphocytes (0, +1): If present: 1 point.

4/ Skin reaction (morphology, extent) (-2, -1, 0, +1, +2)
a/ Morphology (-1, 0, +1): If morphology is suggestive for DRESS: 1 point; if suggestive for a different type of reaction: deduction of 1 point, otherwise 0 points.
Morphology is considered suggestive for DRESS at presence of ≥ 2 of following criteria:
- Scaling/desquamation e.g., exfoliative dermatitis.
- Oedema, especially facial oedema (excluding lower leg oedema).
- Purpura (excluding lower leg).
- Infiltration.

b/ Extent rash (0, +1): If morphology is compatible with DRESS and extent rash > 50% of BSA: 1 point.
c/ Histology (-1, 0): 3
When histology is compatible with DRESS: 0 points, when suggestive for another diagnosis: deduction 1 point.

5/ Involvement of internal organs (0, 1, 2):
For acute involvement of each organ, 1 point is given, with a maximum of 2 points. Organ involvement is based on history, clinical investigation, medical imaging, biopsy, or other tissue/fluid investigation. Organ involvement is also calculated at presence of the following abnormal laboratory values:
a/ Liver (0, 1)
- ALT > 2 times upper normal limit (x UNL) on at least 2 successive dates or
- Conjugated bilirubin > 2 x UNL on at least 2 successive dates, or
- AST, total bilirubin, and ALP; all > 2 x UNL at least.

b/ Kidney (0, 1)
Serum creatinine more than 1.5 times above the base value for the patient on at least 2 successive dates, and/or proteinuria above 1g/day, haematuria, decreased creatinine clearance, decreased GFR.
c/ Lung (0, 1)
Cough and/or dyspnea in conjunction with:
- Evidence of interstitial involvement on imaging and/or
- Abnormal broncho-alveolar lavage fluid, or biopsy and/or
- Abnormal blood gasses.

d/ Muscle, Heart (0, 1): 4
Muscle pain and/or weakness, myocarditis (often non-specific symptoms: hypotension, fatigue, chest pain, dyspnea, malaise, palpitations, tachycardia, cardiac dysfunction, cardiomegaly, sudden cardiac death), with:
- Raised serum creatine phosphokinase (CPK) > 2 x UNL.
- Raised isoenzymes: CPK-3/ CPK-MM (indicative for skeletal muscle), raised CPK-2/MB fraction (indicative for heart muscle involvement).
- Serum troponin (T) > 0.01 µg/L.
- Abnormal imaging: chest X-ray/ ECHO/ CT scan/ MRI scan/ EMG including ECG: ST-T electrocardiogram abnormalities or conduction defects (ST-segment depression, T-wave inversions, or non-diagnostic ECG changes [paced or bundle branch block]).
- Endomyocardial biopsy.

e/ Pancreas (0, 1): Amylase and/or lipase ≥ 2 x UNL.
f/ Other organs: spleen, thyroid gland, central nervous system, gastro-intestinal tract
- Clinical symptoms and additional investigations: enlargement/imaging, including EEG.
- Abnormal laboratory values: TSH, FT4, FT3.
- Biopsy.

6/ Duration (-1, 0): If the total duration of the reaction is ≤ 15 days or unknown: deduction 1 point.
7/ Exclusion of other causes, e.g., infections, virus (re)activation (0, 1) o Hepatitis A, B or C. o Mycoplasma /Chlamydia pneumoniae. o Blood cultures ≤ 3 days of index date. o Other (infections): serology, PCR, microbiological cultures. o ANAs. In case of a positive result for any of these, organ involvement is re-evaluated for a possible alternative cause. If ≥ 3 mentioned groups are investigated and no positive result is found, an extra point is given to express thorough investigation for alternative causes. o EBV, CMV, and HHV6/7 are also recorded; results however do not influence the score.

Abbreviations: BSA, Body surface area; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; ALP, Alkaline phosphatase; UNL, Upper normal limit; GFR, Glomerular Filtration Rate; CPK, Creatinine phosphokinase; CPK-MM, Creatinine phosphokinase-MM; CPK-MB, Creatinine phosphokinase-MB; T, Troponin; CT scan, Computed tomography scan; ECHO, Echocardiogram; MRI scan, Magnetic resonance imaging scan; EMG, Electromyography; ECG, Electrocardiogram; EEG, Electroencephalogram; TSH: Thyroid-stimulating hormone; FT4, Free Thyroxine; FT3, Free tri-iodothyronine; PCR, Polymerase chain reaction; ANAs, Antinuclear antibodies; EBV, Epstein-Barr virus; CMV, Cytomegalovirus; HHV, Human Herpesvirus.

Appendix 6 Physician global assessment of disease activity

The physician will rate the patient's current condition on a 0-100 mm VAS, ranging from no disease activity (0 mm) to very severe disease activity (100 mm).

The below question will be answered by the investigator.

"Considering all the ways that Still's disease affects your patient, how would you rate his or her condition today?"

Please place a single mark on the line below.

Note: The VAS above is not presented in accurate length

The result of the investigator's assessment of the patient's disease activity should be withheld from the patient to minimize influencing his/her own assessment.

Appendix 7 Patient/parent global assessment of overall well-being

The patient or parent global assessment of overall well-being will be assessed on a 0-100 mm VAS, from very well (0 mm) to very poor (100 mm).

For patients < 18 years of age at enrollment, this question will be collected as a part of the CHAQ (see Appendix 8.

For patients ≥ 18 years of age at enrollment, this question will be collected as a part of the SHAQ (see Appendix 8).

Appendix 8 Physical function questionnaires (CHAQ/SHAQ) (52)

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 check the one response which best describes your child's usual activities (averaged over an entire day) **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 & GROOMING					
Is your child able to:					
- Dress, including tying shoelaces and doing buttons?	☐	☐	☐	☐	☐
- Shampoo his/her hair?	☐	☐	☐	☐	☐
- Remove socks?	☐	☐	☐	☐	☐
- Cut fingernails?	☐	☐	☐	☐	☐
ARISING					
Is your child able to:					
- Stand up from a low chair or floor?	☐	☐	☐	☐	☐
- Get in and out of bed or stand up in a crib?	☐	☐	☐	☐	☐
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 outdoors on flat ground?	☐	☐	☐	☐	☐
- Climb up five steps?	☐	☐	☐	☐	☐

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

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

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

- Dressing and Grooming	☐	- Eating	☐
- Arising	☐	- Walking	☐

	Without ANY Difficulty	With SOME Difficulty	With MUCH Difficulty	UNABLE To do	Not Applicable
HYGIENE					
Is your child able to:					
- Wash and dry entire body?	☐	☐	☐	☐	☐
- Take a tub bath (get in and out of tub)?	☐	☐	☐	☐	☐
- Get on and off the toilet or potty chair?	☐	☐	☐	☐	☐
- Brush teeth?	☐	☐	☐	☐	☐
- Comb/brush hair?	☐	☐	☐	☐	☐
REACH					
Is your child able to:					
- Reach and get down a heavy object such as a large game or books from just above his/her head?	☐	☐	☐	☐	☐
- Bend down to pick up clothing or a piece of paper from the floor?	☐	☐	☐	☐	☐
- Pull on a sweater over his/her head?	☐	☐	☐	☐	☐
- Turn neck to look back over shoulder?	☐	☐	☐	☐	☐
GRIP					
Is your child able to:					
- Write or scribble with pen or pencil?	☐	☐	☐	☐	☐
- Open car doors?	☐	☐	☐	☐	☐
- Open jars which have been previously opened?	☐	☐	☐	☐	☐
- Turn faucets on and off?	☐	☐	☐	☐	☐
- Push open a door when he/she has to turn a door knob?	☐	☐	☐	☐	☐
ACTIVITIES					
Is your child able to:					
- Run errands and shop?	☐	☐	☐	☐	☐
- Get in and out of a car or toy car or school bus?	☐	☐	☐	☐	☐
- Ride bike or tricycle?	☐	☐	☐	☐	☐
- Do household chores (e.g. wash dishes, take out trash, vacuuming, yardwork, make bed, clean room)?	☐	☐	☐	☐	☐
- Run and play?	☐	☐	☐	☐	☐

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

☐ - Raised toilet seat	☐ - Bathtub bar
☐ - Bathtub seat	☐ - Long-handled appliances for reach
☐ - Jar opener (for jars previously opened)	☐ - Long-handled appliances in bathroom

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

☐ - Hygiene	☐ - Gripping and opening things
☐ - 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. 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

No pain 0 ├──┤ 100 Very severe pain

GLOBAL 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.

Very well 0 ├──┤ 100 Very poor

The STANFORD HEALTH ASSESSMENT QUESTIONNAIRE©
Stanford University School of Medicine, Division of Immunology & Rheumatology

HAQ Disability Index:
In this section we are interested in learning how your illness affects your ability to function in daily life. Please feel free to add any comments on the back of this page.

Please check the response which best describes your usual abilities OVER THE PAST WEEK:

	Without ANY difficulty [0]	With SOME difficulty [1]	With MUCH difficulty [2]	UNABLE to do [3]
DRESSING & GROOMING				
Are you able to:				
-Dress yourself, including tying shoelaces and doing buttons?	☐	☐	☐	☐
-Shampoo your hair?	☐	☐	☐	☐
ARISING				
Are you able to:				
-Stand up from a straight chair?	☐	☐	☐	☐
-Get in and out of bed?	☐	☐	☐	☐
EATING				
Are you able to:				
-Cut your meat?	☐	☐	☐	☐
-Lift a full cup or glass to your mouth?	☐	☐	☐	☐
-Open a new milk carton?	☐	☐	☐	☐
WALKING				
Are you able to:				
-Walk outdoors on flat ground?	☐	☐	☐	☐
-Climb up five steps?	☐	☐	☐	☐

Please check any AIDS OR DEVICES that you usually use for any of these activities:

- ☐ Cane
- ☐ Walker
- ☐ Crutches
- ☐ Wheelchair
- ☐ Devices used for dressing (button hook, zipper pul long-handled shoe horn, etc.)
- ☐ Built up or special utensils
- ☐ Special or built up chair
- ☐ Other (Specify:_____)

Please check any categories for which you usually need HELP FROM ANOTHER PERSON:

- ☐ Dressing and Grooming
- ☐ Arising
- ☐ Eating
- ☐ Walking

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Please check the response which best describes your usual abilities **OVER THE PAST WEEK:**

	Without ANY difficulty [0]	With SOME difficulty [1]	With MUCH difficulty [2]	UNABLE to do [3]
HYGIENE				
Are you able to:				
-Wash and dry your body?	☐	☐	☐	☐
-Take a tub bath?	☐	☐	☐	☐
-Get on and off the toilet?	☐	☐	☐	☐
REACH				
Are you able to:				
-Reach and get down a 5-pound object (such as a bag of sugar) from just above your head?	☐	☐	☐	☐
-Bend down to pick up clothing from the floor?	☐	☐	☐	☐
GRIP				
Are you able to:				
-Open car doors?	☐	☐	☐	☐
-Open jars which have been previously opened?	☐	☐	☐	☐
-Turn faucets on and off?	☐	☐	☐	☐
ACTIVITIES				
Are you able to:				
-Run errands and shop?	☐	☐	☐	☐
-Get in and out of a car?	☐	☐	☐	☐
-Do chores such as vacuuming or yardwork	☐	☐	☐	☐

Please check any AIDS OR DEVICES that you usually use for any of these activities:

☐ Raised toilet seat
☐ Bathtub seat
☐ Jar opener (for jars previously opened)
☐ Bathtub bar
☐ Long-handled appliances for reach
☐ Long-handled appliances in bathroom
☐ Other (Specify:_____)

Please check any categories for which you usually need HELP FROM ANOTHER PERSON:

☐ Hygiene
☐ Reach
☐ Gripping and opening things
☐ Errands and chores

We are also interested in learning whether or not you are affected by pain because of your illness.

How much pain have you had because of your illness IN THE PAST WEEK:

PLACE A VERTICAL (|) MARK ON THE LINE TO INDICATE THE SEVERITY OF THE PAIN

No Pain — **Severe Pain**

0 — **100**

Considering all the ways that your arthritis affects you, rate how you are doing on the following scale by placing a vertical mark on the line.

Very Well — **Very Poor**

0 — **100**

Appendix 9 Global assessment of the patient disease related pain

The patient's global assessment of disease related pain will be assessed on a 0-100 mm VAS, from no pain (0 mm) to very severe pain (100 mm).

For patients < 18 years of age at enrollment, this question will be collected as a part of the CHAQ (see Appendix 8).

For patients ≥ 18 years of age at enrollment, this question will be collected as a part of the SHAQ (see Appendix 8).