Study Protocol

Protocol number:	Sobi.ANAKIN-301
NCT number:	03265132
Study title:	A randomized, double-blind, placebo-controlled, multicenter, phase 3 efficacy and safety study of 2 dose levels of subcutaneous anakinra (Kineret®) in patients with Still's disease (SJIA and AOSD)
Version:	Version 4.0, Amended protocol including amendment 3
Date:	03 July 2018

A randomized, double-blind, placebo-controlled, multicenter, phase 3 efficacy and safety study of 2 dose levels of subcutaneous anakinra (Kineret®) in patients with Still's disease (SJIA and AOSD)

The anaSTILLs study

Version 4.0, Amended protocol including amendment 3

Sobi.ANAKIN-301

Type of Study: **Therapeutic Confirmatory**

Canada: CTA Control no. 200300. USA: IND no. 003611.

Investigator statement

I have read the protocol entitled "A randomized, double-blind, placebo-controlled, multicenter, phase 3 efficacy and safety study of 2 dose levels of subcutaneous anakinra (Kineret) in patients with Still's disease (SJIA and AOSD)" and the accompanying current investigator's brochure. I agree to conduct the clinical investigation in compliance with the **Version 4.0, Amended protocol including Amendment 3, Date: 3 July 2018,** the International Council for Harmonisation (ICH) harmonised guideline E6 (R2): Guideline for Good Clinical Practice (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	

Table of contents

Protocol Amendment History and Reasons for Amendment

Version	Date	Reason for Amendment
Version 1.0	05 Sep 2016	Original Protocol
Version 2.0 Non-substantial amendment 1	08 Nov 2016	All changes are administrative and updates are minor. The amendment is considered as non-substantial. • Method of ICF collection updated. • Highlighted that MAS adjudication committee is an independent blinded committee. • Updated exclusion criterion #18 as part of the criterion already stated in exclusion criterion #6. • Updated prior and concomitant therapy section in order to clarify that after the final IMP dose at Week12 the patient can be treated according to standard of care. • Age cut-off updated for the CHAQ/SHAQ assessments including the overall well-being VAS scale. o Updated that CHAQ will be assessed for children <18 years of age. o Updated that SHAQ will be assessed for subject ≥18 years of age. • Updated CHAQ assessment section and appendix to clarify that the interview or self-reporting assessment for children ≥8 years of age will not be used. Only the parent or guardian version of CHAQ will be used. • Vital signs section updated as height will only be measured at the baseline visit. • Physical examination section updated to clarify that presence or absence of signs of joint inflammation such as swelling or tenderness will be captured in joint assessments part of ACR and JADAS27. Other abnormal findings related to the musculoskeletal system should be recorded in the physical examination and reported as medical history or as AEs. • Added section regarding local laboratory assessments in order to clarify which samples are required for assessing patient eligibility. • Clarified for which data variables the CRF will be regarded as source. • Added footnote in the schedule of assessment regarding how to proceed with PK blood draws if exceeding maximum blood volume.
Version 3.0 Amendment 2	12 May 2017	The amendment is considered as substantial. In addition to clarifications, changes to format and wording the following changes have been made to the study design: • Open-label (OL) period removed due to preventing escape to investigational product (anakinra) – all sections related to OL period updated. • Double-blind (DB) period extended to 12 weeks, but primary endpoint at Week 2 remains. • Added Day 4_{Tel} for additional follow-up and for retention reasons. • Updated secondary endpoints supporting primary objective and key secondary endpoints o Added Patient/Parent global assessment of disease activity (key secondary endpoint) o Full ACR at Week 1 (supporting primary objective) o Moved time point from Day 4 to Week 1 • Clarification regarding primary endpoint to be evaluated at Week 2 and sustained efficacy to be evaluated in responders during the remaining study period. • Added objective/endpoint to evaluate time to early termination of anakinra

Version	Date	Reason for Amendment
		versus placebo. • Updated glucocorticoid tapering objective/endpoint. • Escape criteria updated - removed persistent fever from list of criteria • Clarification regarding if not fulfilling the escape criteria, i.e. worsening between Week 1 visit and Week 2 visit, the patient can withdraw. • Highlighted that escape therapy is only standard of care, at the discretion of the investigator. • Added a treatment arm of 4 mg/kg/day, max 200 mg/day. • Applied a concept of "corresponding volume of placebo" in order to minimize number of injections/day. • Removed possibility to dose escalate from 2 mg/kg/day to 4 mg/kg/day as OL period not present. • Removed exclusion criteria #17 (alcohol or substance abuse) as covered in exclusion criteria #18 (inability to cooperate with given instructions or study procedures) and #19 (presence of any medical or psychological condition that can interfere with the patient's ability to comply with the protocol requirements). • Updated exclusion criteria with wash-out periods for prohibited concomitant therapies prior randomization. • Optimized the background therapy with liberalization of background steroids - maximum allowed dose has been increased from 40 mg/day at 60 mg/day. • Clarification regarding the process and evaluation of the interferon- gamma release assay or PPD test results at the Baseline visit, Day 1. • Clarification regarding how fever or rash attributable to the disease should be evaluated by investigator at site visits - patient diary will support the evaluation. • Clarification regarding if patient is on glucocorticoid treatment tapering can start earliest at the week 2 visit • Added rash assessment and description how to collect information regarding rash. • Physical examination section updated to clarify how to handle signs and symptoms related to the disease under study. Also a clarification how to collect information regarding the endpoint Inactive disease was added. • Added in laboratory assessment section that patients with a body weight <15kg, hematology and coagulation samples should not be repeated at visit Week 1, if not clinically indicated, in order to preserve blood volume. • Removed single dose pharmacokinetic in patients <6 years of age (separate group of 6 patients) as OL period not present. Repeated-dose PK sampling (4-5 time points) will be conducted at Week 12 visit at a selected number of sites in approximately 30 patients. • Updated proposed sensitivity analyses and overall statistical analysis - a sensitivity analysis was added for both the primary analysis of ACR30 (+ absence of fever) at Week 2 and the supportive analysis of ACR30 (+ absence of fever) at Week 1. • Updated glucocorticoid tapering steps in appendix 4.
Version 4.0 Amendment 3	03 July 2018	The amendment is considered as substantial. In addition to clarifications, changes to format, and wording, changes have been made to the study design regarding data collection for patients that discontinue study drug early. The possibility to escape from Week 1 visit to the Week 2 visit has been replaced with a Study Drug Discontinuation visit which can take place any time during the study before the Week 12 visit in order to be able to capture data at the timepoint when the study drug is discontinued. Furthermore, changes have been made to comply with ICH GCP addendum: • 3.2 Catalent is changed to Almac for IMP depot and logistics • 4.1 Updated current approval for Kineret i.e. Still's disease, including SJIA

and AOSD, in EU (2018)

- 4.3 Added text: Hepatic events during postmarketing use have been more commonly reported in predisposed patients, including patients with Still's disease, than for patients treated for RA and CAPS.
- Early termination is changed to study drug discontinuation throughout the protocol in order to clarify that early termination is defined as when study drug was discontinued.
- 5.4.1 The objective "To evaluate time to early termination of anakinra versus placebo" is changed to "To evaluate time to study drug discontinuation in anakinra versus placebo treated patients". The corresponding endpoints are changed to "Time to study drug discontinuation for any reason" and "Time to study drug discontinuation due to lack of efficacy or progressive disease".
- 6.1 Escape between Week 1 visit and Week 2 visit is deleted. Added that if a patient discontinues study drug before the Week 12 visit, a Study Drug Discontinuation visit should be performed as soon as possible and before standard of care treatment is initiated if possible. If the study drug is discontinued on a scheduled visit, the Study Drug Discontinuation visit should be performed instead of the scheduled visit unless the study drug is discontinued at the Week 12 visit. For a patient that discontinue study drug before the Week 2 visit, the Week 2 visit should still be performed according to the original schedule of assessments, see 6.3.3. If the Study Drug Discontinuation visit is performed within 3 days prior to the Week 2 visit, the scheduled Week 2 visit should be omitted.
- 6.1 Escape criteria is defined as being a subcategory of patients that has discontinued study drug due to progressive disease
- 6.2 Updated text with: In order to be able to evaluate the primary endpoint at week 2, patients that discontinue study drug before week 2 will be encouraged to do a Study Drug Discontinuation visit as well as the Week 2 visit.
- 6.3.2 Exclusion criteria changed:
    - 6. Wash-out periods for prior medication have been updated based on terminal half-life for non-immunosuppressive agents (4 x t½) and protracted effects on immunocompetent cells and toxicity for immunosuppressant agents
    - 12. Changed to "Presence or suspicion of MAS at baseline"
    - 14. Added "within 5 years"

  6.3.3 Section title has been changed from "Withdrawal of patients from study" to "Study drug discontinuation and withdrawal of patients from the study"**.** Furthermore, the section has been updated to the following: If the patients discontinues study drug, 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 Study Drug Discontinuation visit should be performed instead of the scheduled visit unless the study drug is discontinued at the Week 12 visit. For patients that discontinue study drug before the Week 2 visit, a Week 2 visit should still be performed according to the original schedule of assessments unless consent is withdrawn. However, if the Study Drug Discontinuation visit is performed within 3 days prior to the Week 2 visit, the scheduled Week 2 visit should be omitted. For patients who discontinue study drug and are unable to visit the clinic before initiation of standard of care treatment appropriate assessments should be performed to substantiate the reason for study drug discontinuation, e.g. local lab results.
- 6.4.6 The list of not allowed concomitant treatments has been updated to describe classes of treatments rather then only specific treatments
- 6.5.1 JADAS27 is removed as a separate assessment since the JADAS27 components are collected and derived through other assessments.
- 6.5.1.4 Sentences deleted about that the Investigator should evaluate escape criteria.
- 6.5.1.9 "Unscheduled escape visit" replaced by "Study drug discontinuation

Version	Date	Reason for Amendment
		visit" and the text is rewritten. • 6.5.5. Definition of SUSAR added and how they will be reported. • 6.5.5.6 Added "All laboratory assessments should be performed also for patients <15 kg body weight at the Study Drug Discontinuation visit. If the Week 2 visit is peformed after the Study Drug Discontinuation visit, central lab should also be collected at the Week 2 visit, if not exceeding the maximum allowed blood volume collection according to limitations in relation to the body-weight of the patient. In case any of the safety central lab assessments cannot be analysed from the Week 12 visit the patient should be asked to return for an unscheduled visit to ensure that results are available for all lab assessments." • 6.5.6.2 Added text about Guidelines that are followed regarding validation of immunoassay. • Section 7 is updated to comply with ICH GCP addendum with regards to sponsor's responsibility to monitor quality management of the study. Sentences added: "Sobi will systematically review the study quality management to identify, evaluate and control risks to study critical processes and data which would affect subject 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." • 8.2 Text added: "Patients randomized to anakinra who incorrectly received only placebo will be included in the placebo group." • 8.3.6.2 Text updated regarding how to present results. • 8.3.6.3 Text updated to reflect the change from "early termination" to "study drug discontinuation". • 8.4.2 Text updated how the sensitivity analyses are effected by the change to Study Drug Discontinuation visit from the previous definition of withdrawal • 9.4 Protocol deviations section is added to comply with ICH GCP addendum. • 9.6 Record retention is updated to comply with ICH GCP addendum • Section 12 is updated to comply with the International Committee of Medical Journal Editors. • Appendix 5-Schedule of assessments has been updated to reflect the changes in the protocol.

Synopsis

STUDY IDENTIFIERS

Title of study:	A randomized, double-blind, placebo-controlled, multicenter, phase 3 efficacy and safety study of 2 dose levels of subcutaneous anakinra (Kineret®) in patients with Still's disease (SJIA and AOSD) The anaSTILLs study
Clinical study number:	Sobi.ANAKIN-301
Investigators:	Pediatric and adult rheumatologists in North America.
Study sites:	Approximately 40 study sites
Type of study:	Therapeutic confirmatory, Phase 3

BACKGROUND INFORMATION AND STUDY RATIONALE

Adult-onset Still's disease (AOSD) and systemic juvenile idiopathic arthritis (SJIA) 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, and laboratory manifestations such as high erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), platelet and neutrophil counts. The two diseases also share the increased risk for macrophage activation syndrome (MAS), a severe, potentially fatal, complication. The principal difference between SJIA and AOSD is the patient's age at the time of onset; childhood and young/middle aged adults, respectively. The two groups of patients are typically treated by pediatricians (SJIA) and by adult rheumatologists (AOSD) separately as if they are two separate diagnostic entities.

There is a growing understanding that SJIA and AOSD are one single disease representing an age continuum of a single biologic disease entity. 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 population.

Although the disease manifestations and treatment approach are similar irrespective of age of symptom onset of the disease, there is presently no drug approved for treatment at all ages in USA and Canada. To date, nonsteroidal anti-inflammatory drug, glucocorticoids, methotrexate and IL-1/IL-6 inhibitors are used in the treatment of Still's disease. In USA and Canada the long acting IL-1 inhibitor canakinumab and the IL-6 inhibitor tocilizumab are approved for treatment of SJIA, but no treatments are approved for AOSD. In Europe both anakinra and canakinumab are approved for treatment of Still's disease including SJIA and AOSD.

Existing publications indicate that IL-1 inhibitor treatment early in the disease process is beneficial since it is particularly efficacious in treating the systemic symptoms, which are prominent early during disease progression. Early treatment with an IL-1 inhibitor may also reduce the risk for a later development of arthritis, 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.

There is an unmet medical need for an IL-1 blocking agent with a short half-life which allows quick modification or withdrawal of treatment should untoward effects occur. This is particularly important since there is no diagnostic test for SJIA or AOSD which may mimic other severe diseases, such as infections and malignancy. 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. Anakinra, with a short half-life (approximately 6 hours), could be an alternative treatment to the currently approved therapies.

In both the consensus treatment plans developed by the Childhood Arthritis and Rheumatology Research Alliance and the treatment pathways published by American College of Rheumatology anakinra is presented as an alternative first line treatment for patients with SJIA although it is not approved for the indication. This is a reflection of 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.

Anakinra is a recombinant 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.

There is evidence that IL-1 plays an important role in the systemic features of Still's disease and that inbibition of IL-1 can be an effective treatment strategy for this condition.

The aim of this phase 3 study is to demonstrate the efficacy and to evaluate the safety, pharmacokinetics (PK) and immunogenicity of anakinra in patients with newly diagnosed Still's disease, including SJIA and AOSD.

STUDY OBJECTIVES AND ENDPOINTS

Primary objective

The primary objective of this study is to demonstrate efficacy of anakinra versus placebo in Still's disease as assessed by ACR30 response including absence of fever.

Primary endpoint

- The primary endpoint is ACR30 response at Week 2 with absence of fever attributable to the disease during the 7 days preceding Week 2.

Definition of ACR30 response: An improvement of ≥ 30% from baseline in at least 3 of any 6 variables listed below. Also, no more than 1 of the 6 variables may worsen by > 30% from baseline.

1. Physician global assessment of disease activity (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 (CHAQ/SHAQ)
6. CRP (mg/L)

Definition of fever: Body temperature ≥ 38.0 °C (100.4 °F) attributable to the disease

Secondary endpoints supporting primary objective

- ACR30 response at Week 1 with absence of fever attributable to the disease during 24 hours preceding Week 1.
- ACR50, ACR70 and ACR90 response at Week 1 and Week 2 with absence of fever attributable to the disease during 24 hours before Week 1 and 7 days preceding Week 2.
- Response in the **individual components** of ACR at Week 1 and Week 2. Response is defined as an improvement of ≥ 30%, 50%, 70% and 90% from baseline.
  - 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)
- CRP (mg/L)

- Absence of fever during the 7 days preceding Week 2.

Key secondary objective and endpoints

Objective To demonstrate early onset of efficacy of anakinra versus placebo in Still's disease.

Endpoints

- Absence of fever during the 24 hours preceding Week 1.
- Change from baseline in physician global assessment of disease activity (VAS) at Week 1.
- Change from baseline in patient/parent global assessment of overall well-being (VAS) at Week 1.
- Change from baseline in CRP at Week 1.

Secondary efficacy objectives and endpoints

Objective To evaluate sustained efficacy of anakinra versus placebo in patients that reached at least ACR30 response at Week 2.

Endpoint

- Sustained ACR response at Week 4, Week 8 and Week 12 compared to ACR response at Week 2.

Objective To evaluate efficacy of anakinra versus placebo during 12 weeks treatment.

Endpoints

- ACR30, ACR50, ACR70 or ACR90 response with absence of fever 24 hours before Week 1 or during the 7 days preceding the visit at Week 2, Week 4, Week 8 and Week 12.
- Absence of rash 24 hours before Week 1 or during the 7 days preceding Week 2, Week 4, Week 8 and Week 12.
- Change from baseline in CRP, Hb, platelet count and ferritin at Week 1, Week 2, Week 4, Week 8 and Week 12.
- Change from baseline in patient/parent global assessment of disease related pain (VAS) at Week 1, Week 2, Week 4, Week 8 and Week 12.
- Inactive disease at Week 12.
- Change from baseline in JADAS27 at Week 2 and Week 12.

Objective To evaluate time to study drug discontinuation inanakinra versus placebo treated patients.

Endpoints

- Time to study drug discontinuation for any reason.
- Time to study drug discontinuation due to lack of efficacy or progressive disease.

Objective To evaluate glucocorticoid tapering in anakinra and placebo treated patients.

Endpoints

- Number of patients who have initiated tapering of glucocorticoids at Week 12.

- Number of patients with decreased dose of glucocorticoids by at least 50% at Week 12 compared to baseline.
- Percentage decrease of glucocorticoid dose at Week 12 compared to baseline.

Objective To evaluate the efficacy of anakinra in the 2 separate dose groups.

Endpoint
- Efficacy endpoints as described above.

Safety objective and endpoint

Objective To evaluate the safety of anakinra.

Endpoint
- Adverse events (AEs) (including MAS), vital signs and laboratory safety assessments.

Pharmacokinetic objective and endpoint

Objective To evaluate the PK of anakinra.

Endpoint
- Anakinra trough plasma concentrations and repeated-dose PK parameters at Week 12.

Immunogenicity objectives and endpoints

Objective To evaluate occurrence of ADAs, NAbs and cross-reactivity.

Endpoint
- Occurrence of ADAs, NAbs, and cross-reactivity and titer levels of ADA and NAbs at baseline, Week 1, Week 2, Week 4, Week 8 and Week 12.

Objective To evaluate ADAs in relation to safety.

Endpoint
- Occurrence and titer levels of ADAs in relation to AEs at Week 1, Week 2, Week 4, Week 8 and Week 12.

Objective To evaluate ADAs, and NAbs in relation to efficacy.

Endpoint
- Occurrence and titer levels of ADA, including NAb in relation to ACR response and CRP at Week 1, Week 2, Week 4, Week 8 and Week 12.

Productivity objective and endpoint

Objective To evaluate absenteeism from school or work.

Endpoint
- Number of days off school or work due to Still’s disease.

Exploratory objectives and endpoints

Objective To explore PK/PD relationship between IL-1Ra/anakinra serum concentrations and selected efficacy and safety parameters.

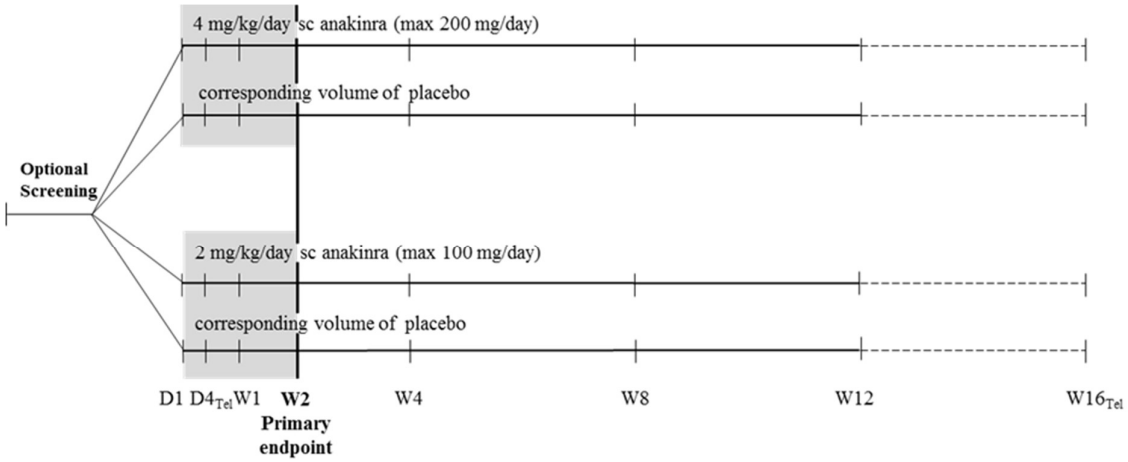
Endpoint
- Population PK/PD parameter estimates and associated covariates describing intra- and inter-individual variability in respective parameter estimate.

Objective To explore the PK properties of anakinra using population analysis.

Endpoint
- Population PK parameter estimates and associated covariates describing intra-and inter-individual variability in respective parameter estimate.

Objective	To explore the effect of anakinra on the exploratory inflammatory biomarkers (IL-6, IL-18, calprotectin and neopterin) in the treatment of patients with Still´s disease.
Endpoint	- Change from baseline in exploratory inflammatory biomarkers at Week 1, Week 2 and Week 12.
Objective	To collect a blood sample for future analysis for genetic factors potentially contributing to the patient's response to anakinra, safety and tolerability. Will be reported separately.

STUDY DESIGN AND METHODS



Study design:

The study consists of a 12-week, randomized, double-blind, placebo controlled period with two dose levels of anakinra and a 4-week safety follow-up after last dose of investigational medicinal product (IMP). The primary endpoint will be evaluated at Week 2. Sustained efficacy and time to study drug discontinuation will be evaluated during the full study period.

A screening visit is optional and may be done to identify patients that could be suitable for the study. During the study 6 visits and 2 telephone contacts are scheduled i.e., Day 1 (baseline visit), Day 4_{Tel}, Week 1, Week 2, Week 4, Week 8, Week 12 and Week 16_{Tel} (End of Study).

Patients will be randomly assigned to study drug, after they meet all of the inclusion criteria and none of the exclusion criteria. Patients will receive treatment for 12 weeks, either anakinra or placebo. Patients will be randomized to anakinra in a dose of either 2 or 4 mg/kg/day, with a maximum dose of 100 or 200 mg once daily, respectively. Patients will be randomized to placebo with corresponding volumes for each of the two anakinra dose levels.

To be able to evaluate the primary objective of the study it is important that the patient remains in the study until the Week 2 visit whenever possible. All patients included in the study will be carefully monitored by the investigator and if there is a need, patients can withdraw from the study drug at any time. If the patients discontinues study drug, a Study Drug Discontinuation visit should be performed before standard of care treatment is initiated if possible.

For patients that discontinue Study drug before the Week 2 visit, the Week 2 visit should be performed according to original schedule of assessements. However, if the Study Drug Discontinuation visit is performed within 3 days prior to the Week 2 visit, the scheduled Week 2 visit should be omitted.

A final follow-up call will be conducted 4 weeks after the last IMP administration according to the assessments described for the Week 16_{Tel} visit.

If the patient is on glucocorticoid treatment the dose can be tapered starting earliest at the Week 2 visit. The patient must have reached at least ACR50 response with no fever in the preceding 7 days at the visit initiating tapering.

If a patient develops MAS, the patient will terminate the study treatment and will be treated according to standard of care. If the MAS event occurs before the Week 2 visit it is preferred, if possible, that the patient returns to conduct the Week 2 visit according to the schedule of assessments. For all patients that are diagnosed with MAS, irrespective of timepoint in the study, a follow-up call should be conducted 4 weeks after the last IMP administration according to the assessments described for the Week 16_{Tel} visit before the patient is withdrawn from the study. MAS is defined as an event of special interest in this study and must be reported as a serious adverse event (SAE).

PK sampling will be conducted in all patients at all study visits. In addition, repeated-dose PK sampling (4-5 time points) will be conducted at Week 12 at a selected number of sites in approximately 30 patients. All patients at these pre-selected sites will be asked to participate in the repeated PK sampling until the target number of patients have completed the repeated PK sampling. If a patient declines to participate in the repeated PK sampling, he/she will still be eligible to participate in the main study. When the overall number of 81 patients has been reached in the study the enrollment will be stopped regardless of whether the target number of repeated-dose PK patients has been reached.

Number of patients:

A total of 81 patients will be randomized, 54 patients to anakinra and 27 patients to placebo treatment. At least a third of the randomized patients should have had a disease onset before the age of 16, and at least a third of the randomized patients in the study should have had a disease onset at the age of 16 or above.

Criteria for inclusion/ exclusion:

Inclusion criteria

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

1. Signed informed consent.
2. Male and female patients with a body weight ≥ 10 kg.
3. Diagnosis of Still's disease:
    a. If < 16 years of age at disease onset, according to adapted ILAR criteria i.e., CARRA-criteria for SJIA.
    b. If ≥16 years of age at disease onset, according to Yamaguchi criteria.
4. If currently on glucocorticoid treatment, a stable dose for at least 1 week prior to randomization. Maximum dose allowed is 1 mg/kg/day, up to a maximum of 60 mg/day.
5. If currently on methotrexate treatment, a stable dose for at least 8 weeks prior to randomization. Maximum dose allowed is 20 mg/m2/week. If prior treatment with methotrexate, discontinuation is required to be at least 4 weeks prior to randomization.
6. 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 randomization.
    (Definition of fever: body temperature ≥38.0°C)

7. Female patients of childbearing potential must use an effective method of contraception during the study (abstinence being a possible option) as well as present a negative pregnancy test prior to randomization.
8. Negative interferon-gamma release assay or PPD test within 2 months prior to randomization. If not available, a test should be performed at day of randomization

Exclusion criteria

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

1. Diagnosis of Still's disease more than 6 months prior to randomization.
2. Previous randomization into this study
3. Participation in another concurrent clinical interventional study within 30 days of randomization.
4. Treatment with an investigational drug within 5 half-lives prior to randomization.
5. Previous or current treatment with anakinra, canakinumab or any other IL-1 inhibitor.
6. Use of the following therapies prior to randomization:
    - Narcotic analgesics within 24 hours prior to randomization
    - Dapsone or etanerceptwithin 3 weeks prior to randomization
    - Intraarticular, intramuscular or intravenous administration of glucocorticoids or intravenous immunoglobulin within 4 weeks prior to randomization
    - Intravenous immunoglobulin with proven Still's disease modifying effect, leflunomide, infliximab or adalimumab within 8 weeks prior to randomization
    - Thalidomide, cyclosporine, mycophenolate mofetil, 6-mercaptopurine, azathioprine, cyclophosphamide,chlorambucil or any other immunosuppressant within 12 weeks prior to randomization
    - Tocilizumab within 12 weeks prior to randomization or any other immunomodulatory medication within 4 half-lives prior to randomization
    - Rituximab within 26 weeks prior to randomization
7. Live vaccines within 1 month prior to randomization.
8. Known presence or suspicion of active, chronic or recurrent bacterial, fungal or viral infections, including tuberculosis, HIV infection or hepatitis B or C infection.
9. Clinical evidence of liver disease or liver injury as indicated by presence of abnormal liver tests
    - AST or ALT >5 x ULN, or
    - AST or ALT >3 x ULN accompanied by elevated bilirubin >2 x ULN.
10. Presence of severe renal function impairment CKD stages 4 and 5 (estimated creatinine clearance < 30 mL/min/1.73m^2).
11. Presence of neutropenia (ANC < 1.5 x 10^9/L).
12. Presence or suspicion of MAS at baseline.
13. A diagnosis of MAS within the last 2 months prior to randomization.
14. History of malignancy within 5 years. 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 Kineret (anakinra).
16. Pregnant or lactating women.
17. Foreseeable inability to cooperate with given instructions or study procedures.
18. Presence of any medical or 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 makes the patient not appropriate for inclusion to the study and treatment with IMP.

Assessments:

Screening visit (optional): Obtain signed informed consent, evaluate eligibility based on the inclusion and exclusion criteria. Local laboratory results are valid for evaluation of eligibility criteria.

Visit 1 (Day 1, baseline): Obtain signed informed consent (if not collected at a screening visit), evaluate eligibility based on the inclusion and exclusion criteria. (Laboratory results are valid for evaluation of eligibility criteria for 36 hours.) Assess medical history, demographics, prior and concomitant medication, vital signs, physical examination and ECG. 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. Additionally evaluate global assessment of the patient disease related pain (VAS). Collect blood for central laboratory assessments, immunogenicity, IL-1Ra/anakinra serum concentration and inflammatory biomarker assessments. Administer IMP and dispense IMP to cover the period until next visit. Record any AE that has occurred. Instruct the patient/patient's caregiver how to complete the diary. Collect sample for exploratory pharmacogenetics markers at any visit after randomization.

Tel f-up (Day 4_{Tel}): Record any AE.

Visit 2 (Week 1): Assess vital signs, physical examination and concomitant medication. Assess all the ACR variables and the global assessment of the patient disease related pain (VAS). Collect blood for central laboratory assessments, immunogenicity, IL-1Ra/anakinra serum concentration and inflammatory biomarker assessments. Record any AE and absenteeism from school or work. Finally dispense IMP.

Visit 3 (Week 2): Assess vital signs, physical examination and concomitant medication. Assess all the ACR variables and the global assessment of the patient disease related pain (VAS). Collect blood for central laboratory assessments, immunogenicity, IL-1Ra/anakinra serum concentration and inflammatory biomarker assessments. Record any AE and absenteeism from school or work. Finally dispense IMP.

Visit 4 and 5 (Week 4 and 8): Assess vital signs, physical examination and concomitant medication. Assess all the ACR variables and the global assessment of the patient disease related pain (VAS). Collect blood for central laboratory assessments, immunogenicity and IL-1Ra/anakinra serum concentration. Record any AE and absenteeism from school or work. Finally dispense IMP.

Visit 6 (Week 12): Assess vital signs, physical examination and concomitant medication. Assess all the ACR variables and the global assessment of the patient disease related pain (VAS). Collect morning stiffness for the evaluation of inactive disease. Collect blood for central laboratory assessments, immunogenicity, IL-1Ra/anakinra serum concentration and inflammatory biomarker assessments. Record any AE and absenteeism from school or work. Finally all IMP should be collected from the patient and accounted for.

For patients enrolled in the repeated-dose PK sampling the visit is scheduled on the day of the last IMP dose and the IMP is administered at site. PK blood samples will be collected at 5 time points between pre-dose and 8 hours after IMP administration.

Tel f-up (Week 16_{Tel}): Record any AE and concomitant medication.

Study Drug Discontinuation visit: Assess vital signs, physical examination and concomitant medication. Assess all the ACR variables and the global assessment of the patient disease related pain (VAS). Collect morning stiffness for the evaluation of

	inactive disease. Collect blood for central laboratory assessments, immunogenicity, IL-1Ra/anakinra serum concentration and inflammatory biomarker assessments. Record any AE and absenteeism from school or work. Finally all IMP should be collected from the patient and accounted for.
Test product; dose and mode of administration:	• anakinra 2 mg/kg/day (max 100 mg/day) sc administration or • anakinra 4 mg/kg/day (max 200 mg/day) sc administration. The dose will be adjusted according to actual body weight (rounded to the nearest kg) and will remain the same throughout the study.
Reference product; dose and mode of administration:	The placebo will be given in a corresponding volume to any of the two different anakinra doses, once daily as sc administration.
Restricted concomitant medication:	Intraarticular, intramuscular and intravenous administration of glucocorticoids are prohibited within 4 weeks prior to randomization and during the study. Other administration of glucocorticoid treatment is allowed as concomitant medication during the study if the patient has had a stable dose for at least 1 week prior to randomization. Maximum dose allowed is 1 mg/kg/day (max 60 mg/day). If the patient is on glucocorticoid treatment, the dose can be tapered starting earliest at the Week 2 visit. The patient must have reached at least ACR50 response with no fever in the preceding 7 days at the visit initiating tapering. All other glucocorticoid treatment is prohibited during the study except topical and inhaled. Methotrexate is allowed as concomitant medication during the study if the patient has had a stable dose for at least 8 weeks prior to randomization. The dose should remain stable throughout the study as long as it is well tolerated. If prior treatment with methotrexate, discontinuation is required to be at least 4 weeks prior to randomization. Initiation of continuous NSAID treatment is prohibited during the study. However on demand treatment is allowed. Narcotic analgesics are not allowed 24 hours prior any study visit. Use of the following treatments are not allowed concomitantly with the IMP (wash-out periods before randomization are stated in the exclusion criteria): • Intraarticular, intramuscular or 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 TNF inhibitor (investigational or marketed) • Dapsone or mycophenolate mofetil • Leflunomide, thalidomide, or cyclosporine • 6-Mercaptopurine, azathioprine, cyclophosphamide, chlorambucil or any other immunosuppressant • Use of any other investigational drug Live vaccines is not allowed within 1 month prior to randomization and until after 1 month following the last study dose. Inactivated vaccines may be permitted according to the investigator's discretion. The investigator should instruct the patient to notify the study site about any new medications he/she takes after the start of the study drug. All medications and significant non-drug therapies administered after the patient starts

	treatment with study drug until Week 16_{Tel} must be listed on the concomitant medication CRF page. Following the 12 week double blind treatment, the patient will be treated at the discretion of the investigator according to standard of care.
Duration of treatment(s):	12 week double-blind, placebo-controlled, anakinra treatment period.
Randomization	The different treatment groups are; • placebo (corresponding volume of anakinra 2 mg/kg/day [max 100 mg/day]), or • placebo (corresponding volume of anakinra 4 mg/kg/day [max 200 mg/day]), or • anakinra 2 mg/kg/day (max 100 mg/day) or • anakinra 4 mg/kg/day (max 200 mg/day) The ratio between the treatment groups is 1:1:2:2, i.e. the ratio placebo:ankinra is 1:2. The randomization numbers will be generated in blocks. Each block will include the four treatment groups per the ratio described above. The randomization will be stratified by age at onset of disease (< 16 years, ≥ 16 years) and glucocorticoid use at inclusion (yes, no) with a requirement to randomize at least a third of the patients with an age at onset of disease < 16 years and a third of the patients with an age at onset ≥ 16 years.
Sample size determination:	Assuming that the ACR30 response rate is 65 % in patients receiving anakinra and 25 % in placebo patients, 81 evaluable patients (54 anakinra and 27 placebo) are required to ensure 90 % power in demonstrating that anakinra improves clinical features of Still's disease using a two-sided test at a 5 % significance level.
Statistical methods:	The comparison of primary interest is between anakinra (2 mg and 4 mg combined) and placebo. The two dose levels of anakinra will be evaluated descriptively. The primary endpoint ACR30 response with absence of fever at Week 2 will be analyzed using a logistic regression model with treatment, age at onset of disease (< 16 years, ≥ 16 years) and glucocorticoid use (yes, no) as explanatory variables. Patients who have discontinued study drug prior to Week 2 will be treated as non-responders in the primary analysis. The estimated probability of ACR30 response in each treatment group, the estimated odds ratio of anakinra to placebo, the corresponding 95 % confidence interval and the p-value from the model will be presented. The binary key secondary endpoint absence of fever at Week 1 will be analyzed using a logistic regression model with treatment, age at onset of disease and glucocorticoid use as explanatory variables. Patients who discontinue study drug prior to Week 1 will be treated as having a presence of fever in the analysis. The estimated probability of absence of fever in each treatment group, the estimated odds ratio of anakinra to placebo, the corresponding 95 % confidence interval and the p-value from the model will be presented. The continuous key secondary endpoints; change from baseline at Week 1 in physician's global assessment of disease activity, patient/parent global assessment of overall well-being and CRP will be analyzed using a mixed model repeated measurement with the measurements on the individual time points as responses and with treatment, age at onset of disease and glucocorticoid use, visit and treatment-visit interaction as fixed effects. For the comparison between treatment groups for each endpoint, the estimated difference, the associated 95 % confidence interval and the p-value from the model will be presented. A multiple testing procedure, combining fixed sequence testing and Hochberg procedure, will be used to ensure an overall significance level of 0.05 for the primary endpoint and key secondary endpoints.

Supportive analyses in sub-groups defined by the stratification variables (< 16 years, ≥ 16 years of age at disease onset) and glucocorticoid use at inclusion (yes, no) will be performed in order to examine the consistency of the treatment effect. For each sub-group, the estimated probability of ACR30 response in each treatment group, the estimated odds ratio of anakinra to placebo and the corresponding 95 % confidence interval will be presented.

1 Abbreviations and definition of terms

ACR	American College of Rheumatology
ACR30	An improvement of ≥ 30% from baseline in at least 3 of any 6 variables listed below. Also, no more than 1 of the 6 variables may worsen by >30% from baseline. 1. Physician global assessment of disease activity 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 (CHAQ/SHAQ) 6. CRP (mg/L)
ACR50	An improvement of ≥ 50% from baseline in at least 3 of any 6 variables described in ACR30. Also, no more than 1 of the 6 variables may worsen by > 30% from baseline.
ACR70	An improvement of ≥ 70% from baseline in at least 3 of any 6 variables described in ACR30. Also, no more than 1 of the 6 variables may worsen by > 30% from baseline.
ACR90	An improvement of ≥ 90% from baseline in at least 3 of any 6 variables described in ACR30. Also, no more than 1 of the 6 variables may worsen by > 30% from baseline.
ADA	Anti-drug antibodies
ARO	Academic research organization
AE	Adverse event
ANA	Antinuclear antibody
AOSD	Adult-onset Still’s disease
baseline	Before administration of IMP at Day 1
BW	Body weight
CAPS	Cryopyrin-associated periodic syndromes
CARRA	The Childhood Arthritis and Rheumatology Research Alliance
CDASH	Clinical data acquisition standards harmonization
CDISC	Clinical data interchange standards consortium
CHAQ	Childhood health assessment questionnaire

CRP	C-reactive protein
CRF	Case report form
DAS	Disease activity score
DCRI	Duke Clinical Research Institute
DMARD	Disease modifying anti-rheumatic drug
DSMB	Data safety monitoring board
ECG	Electrocardiogram
Escape criteria	• symptomatic serositis, *or* • flare i.e., a worsening of >30% from baseline in at least 3 of any 6 components part of ACR. Patients fulfilling the escape criteria are a subcategory of patients that discontinue study drug due to progressive disease.
ESR	Erythrocyte sedimentation rate
GCP	Good clinical practice
Hb	Hemoglobin
HDL	High-density lipoprotein
ICF	Informed consent form
ICH	International council for harmonization
Ig	Immunoglobulin
IgM	Immunoglobulin M
IL-1	Interleukin 1
IL-1Ra	Interleukin 1 receptor antagonist
IL-6	Interleukin 6
IL-18	Interleukin 18
IMP	Investigational medicinal product
IRB	Institutional review board
IRS	Interactive response system
ISR	Injection site reactions
ITT	Intention-to-treat
JADAS	Juvenile arthritis disease activity score
JIA	Juvenile idiopathic arthritis
k_a	Absorption rate constant
LDL	Low-density lipoprotein

MAS	Macrophage activation syndrome
MedDRA	Medical dictionary for regulatory activities
MCP	Metacarpophalangeal joints
MSD-ECL	Meso Scale Discovery Electrochemiluminescence
NAb	Neutralizing antibodies
NSAID	Nonsteroidal anti-inflammatory drug
NOMID	Neonatal onset multisystem inflammatory disease
PD	Pharmacodynamics
PIP	Proximal interphalangeal joints
PK	Pharmacokinetics
PP	Per-protocol
PPD	Purified protein derivative
PRO	Patient reported outcome
RA	Rheumatoid arthritis
REB	Research ethics board
RF	Rheumatoid factor
SAE	Serious adverse event
SAP	Statistical analysis plan
s.c.	Subcutaneous
SJIA	Systemic juvenile idiopathic arthritis
SHAQ	Stanford Health Assessment Questionnaire
SDTM	Study data tabulation model
Sobi	Swedish Orphan Biovitrum AB (publ)
SOP	Standard operating procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
ULN	Upper limit of normal
VAS	Visual analogue scale

2 Ethics

2.1 Institutional review board and research ethics board

It is the responsibility of the investigator to obtain approval of the study protocol, possible amendments and the written patient information and ICF from the IRB/REB. The investigator should file all correspondence with the IRB/REB. Copies of IRB/REB correspondence and approvals should be forwarded to DCRI, the ARO.

2.2 Ethical conduct of the study

This study will be conducted in compliance with this protocol, the ICH GCP (1), applicable regulatory requirements, and in accordance with the latest revision of the Ethical Principles for Medical Research Involving Human Patients (the Declaration of Helsinki) (2).

2.3 Patient Information and consent

It is the responsibility of the investigator to give each patient, and if applicable the patient's legally authorized representative or parent/guardian, full and adequate verbal and written information regarding the objective and procedures of the study and the possible risks involved prior to any study-related activities. Declining to participate in specific assessments such as genotyping, PK and/or parent's absenteeism from work will in no way affect the patient's ability to participate in the main study. The patient and, if applicable, their legally authorized representative or parent/guardian must be informed about their right to withdraw from the study at any time.

It is the responsibility of the investigator to obtain signed informed consent from all patients and, if applicable, child assent according to local regulations prior to any study-related activities. If required a signed informed consent must also be obtained from the patient's legally authorized representative or parent/guardian. The patient will receive a copy of the patient information and signed ICF.

The patient information and/or consent form must not be changed without prior discussion with DCRI or Sobi. Before any revisions are implemented, the revised written patient information and/or consent form must be approved by the IRB/REB.

3 Study administrative structure

3.1 Sponsor

The sponsor of the study is Sobi, Swedish Orphan Biovitrum AB (publ), Stockholm, Sweden.

3.2 Academic research organization

The conduct of the study will be outsourced to the ARO DCRI, Durham, North Carolina, USA. Site evaluation, monitoring, development of master patient information and ICF, data

management, investigational product management and vendor management are some of the study-related activities and responsibilities that are transferred to DCRI. DCRI has selected Almac Clinical Services, LLC for IMP depot and IMP logistics. DCRI selected Medidata Solutions, Inc. to provide: Rave for the eCRF, Patient Cloud for electronic diaries and Balance for randomization and trial supply management.

Statistical analysis and development of the clinical study report will remain the responsibility of Sobi.

Handling of SAE reporting will be a shared responsibility between Sobi and DCRI.

3.3 Central laboratories

Central laboratories will be used for all study-specific laboratory assessments except those laboratory assessments required to confirm the eligibility of the patient at baseline, evaluate escape criteria (CRP), glucocorticoid tapering or reason for study drug discontinuation. All central laboratories are compliant with Good Laboratory Practice.

ICON Laboratory Services, Inc., 123 Smith Street, Farmingdale, NY 11735, US will be responsible for analyses of clinical chemistry and hematology.

Pacific Biomarkers, 645 Elliott Ave W. Suite 300, Seattle, WA 98119, is responsible for analysis of the exploratory biomarkers in the study.

The analyses of ADA, including validation of the MSD-ECL bridging method to be used, and the analysis of IL-1Ra/anakinra concentrations including validation of the MSD-ECL based method to be used for the purpose are assigned to York Bioanalytical Solutions Limited, Cedar House, Northminster Business Park, Upper Poppleton, York YO26 6QR, United Kingdom.

The analysis of neutralizing ADA including development and validation of the cell-based method to be used will be performed by Euro Diagnostica, Lundavägen 151, 212 24 Malmö Sweden.

3.4 MAS adjudication committee

MAS is the term used to describe a potentially life-threatening complication of systemic inflammatory disorders, which occurs in approximately 10% of patients with SJIA (3) and in similar incidence in AOSD (4). MAS is characterized by an overwhelming inflammatory reaction due to an uncontrolled and dysfunctional immune response involving the continual activation and expansion of T-lymphocytes and macrophages, which results in massive hypersecretion of proinflammatory cytokines.

There will be an independent blinded adjudication committee assigned to enable uniform assessment of MAS cases after all patients have completed the study. The committee will be independent of the sponsor and the investigators, and information from the committee will not be available during the conduct of the study. The adjudication committee will be comprised of clinicians that have experience treating patients with Still´s disease and are familiar with the signs and symptoms of MAS in the pediatric and adult populations.

An adjudication committee charter will describe the process for the adjudication and outline the committee membership, responsibilities, scope of activities and communication plan between committee, sponsor, ARO and study sites.

3.5 Data safety monitoring board

An independent DSMB will be in place during the conduct of the study. Responsibilities of the DSMB will include review of accumulated safety data and assessments to ensure the safety of participating patients and overall integrity of the study, provide recommendations regarding the further conduct of the study and identify any safety issues which may suggest risk to the patients enrolled in the study or prospective patients. A DSMB charter will outline the membership, responsibilities, scope of activities, meeting frequency and communication plan between committee, sponsor, ARO and study sites. The members of the DSMB will collectively have competence and experience with Still's disease (in children and adults), MAS, conduct of randomized clinical studies, interpretation of clinical study data and also have previous DSMB experience.

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 known as SJIA. The diagnosis is based on its typical features and an age at onset of less than 16 years (5).

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 AOSD (6).

AOSD and SJIA 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 IL-1 and IL-6. They share common clinical manifestations such as daily spiking fever, typical transient cutaneous rash, arthritis, lymphadenopathy, hepatosplenomegaly and serositis, and laboratory manifestations such as high ESR, CRP, platelet and neutrophil counts (7). The two diseases also share the increased risk for MAS, a severe, potentially fatal, complication (3, 4). The principal difference between SJIA and AOSD is the patient's age at the time of onset; childhood and young/middle aged adults, respectively. The two groups of patients are typically treated by pediatricians (SJIA) and by adult rheumatologists (AOSD) separately as if they are two separate diagnostic entities.

There is a growing understanding that SJIA and AOSD are one single disease representing an age continuum of a single biologic disease entity (7, 8, 9, 10, 11, 12, 13, 14, 15 and 16). 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 population.

Although the disease manifestations and treatment approach are similar irrespective of age of symptom onset of the disease, there is presently no drug approved for treatment at all ages in USA and Canada. To date, NSAIDs, glucocorticoids, methotrexate and IL-1/IL-6 inhibitors are used in the treatment of Still's disease. In USA and Canada the long acting IL-1 inhibitor canakinumab and the IL-6 inhibitor tocilizumab are approved for treatment of SJIA, but no treatments are approved for AOSD. In Europe both anakinra and canakinumab are approved for treatment of Still's disease including SJIA and AOSD.

Existing publications indicate that IL-1 inhibitor treatment early in the disease process is beneficial since it is particularly efficacious in treating the systemic symptoms, which are prominent early during disease progression (17, 18, 19). Early treatment with an IL-1 inhibitor may also reduce the risk for a later development of arthritis (20), 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 (21, 22).

There is an unmet medical need for an IL-1 blocking agent with a short half-life which allows quick modification or withdrawal of treatment should untoward effects occur. This is particularly important since there is no diagnostic test for SJIA or AOSD which may mimic other severe diseases, such as infections and malignancy. 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. Anakinra, with a short half-life (approximately 6 hours), could be an alternative treatment to the currently approved therapies.

In both the consensus treatment plans developed by CARRA (23, 24) and the treatment pathways published by ACR (25) anakinra is presented as an alternative first line treatment for patients with SJIA although it is not approved for the indication in the US and Canada.This is a reflection of 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 (26, 27).

Anakinra is a recombinant 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 s.c. injection.

Kineret® is currently approved in the US (2001), Canada (2002), and EU/EEA (2002) for the treatment of RA. Kineret is also approved for the most severe form of CAPS, i.e., NOMID, in the US (2012), and for all forms of CAPS in EU/EEA (2013). In addition, Kineret is approved for the treatment of SJIA in Australia (2015) and for Still's disease, including SJIA and AOSD in EU (2018).

In the currently available data 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 of Still's disease and hepatic events occur also in anakinra-treated patients with Still's disease.

Cases of MAS have been described in anakinra-treated patients with Still's disease, both in publications and in spontaneous reports during post marketing use. However, patients with Still's disease, both pediatric and adults, have an increased risk for spontaneous development of MAS. A causal relationship between anakinra and development of MAS has not been established.

There is limited information about the PK of anakinra in SJIA patients, and no information about the PK of anakinra in AOSD patients. The PK of anakinra is however well characterized in healthy volunteers and RA patients. The bioavailability is high (~95%), tmax is about 6 hours and anakinra serum concentrations decline with a half-life of 4-6 hours following 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 (28).

For a detailed description of anakinra characteristics, contraindications, warnings and precautions, adverse reactions and pharmaceutical properties, refer to the product information/monograph and the 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 can be an effective treatment strategy for this condition (29, 30, 31).

The aim of this phase 3 study is to demonstrate the efficacy and to evaluate the safety, PK and immunogenicity of anakinra in patients with newly diagnosed Still's disease, including SJIA and AOSD.

4.3 Potential benefits and risks

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 elevations (19, 32). Another important benefit of anakinra treatment compared to registered biologic treatments 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 (19). Partial response to anakinra has also been reported in some patients with well-established disease at treatment onset (32).

The efficacy of anakinra in adult patients with Still's disease has been evaluated in a meta-analysis conducted by Hong et al. (33). Anakinra was shown to be effective in remitting the manifestations of AOSD, in reducing the doses of glucocorticoid, and was also well tolerated.

The safety profile of anakinra is well established with the known common risks associated predominantly with 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 of >100 mg s.c. were administered to patients with RA. 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. In long-term studies, there are no indications of an increasing AE frequency over time. In addition, there is more than 15 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 postmarketing 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 this study one third of the study population will be randomized to placebo. 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 receive standard of care treatment, thus minimizing the time patients are exposed to ineffective treatment (placebo or non-response to active treatment).

The potential risks associated with anakinra administration will be closely monitored by the sponsor as part of the safety evaluations being performed in the study. To further monitor the safety there will be an independent DSMB.

The overall assessment is that the benefit of using anakinra in Still’s disease outweighs the known risks associated with it.

5 Study objectives and endpoints

5.1 Primary objective and endpoint

Primary objective

The primary objective of this study is to demonstrate efficacy of anakinra versus placebo in Still's disease as assessed by ACR30 response including absence of fever.

Primary endpoint

- The primary endpoint is ACR30 response at Week 2 with absence of fever attributable to the disease during the 7 days preceding Week 2.

Definition of ACR30 response: An improvement of ≥ 30% from baseline in at least 3 of any 6 variables listed below. Also, no more than 1 of the 6 variables may worsen by > 30% from baseline.

1. Physician global assessment of disease activity (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 (CHAQ/SHAQ)
6. CRP (mg/L)

Definition of fever: Body temperature ≥ 38.0 °C (100.4 °F) attributable to the disease

5.2 Secondary endpoints supporting primary objective

Secondary endpoints supporting primary objective

- ACR30 response at Week 1 with absence of fever attributable to the disease during 24 hours preceding Week 1.
- ACR50, ACR70 and ACR90 response at Week 1 and Week 2 with absence of fever attributable to the disease during 24 hours before Week 1 and 7 days preceding Week 2.
- Response in the **individual components** of ACR at Week 1 and Week 2. Response is defined as an improvement of ≥ 30%, 50%, 70% and 90% from baseline.
  - 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)
  - CRP (mg/L)
- Absence of fever during the 7 days preceding Week 2.

5.3 Key secondary objective and endpoints

Objective To demonstrate early onset of efficacy of anakinra versus placebo in Still's disease.

Endpoints

- Absence of fever during the 24 hours preceding Week 1.
- Change from baseline in physician global assessment of disease activity (VAS) at Week 1.
- Change from baseline in patient/parent global assessment of overall well-being (VAS) at Week 1.
- Change from baseline in CRP at Week 1.

5.4 Secondary objectives and endpoints

5.4.1 Secondary efficacy objectives and endpoints

Objective To evaluate sustained efficacy of anakinra versus placebo in patients that reached at least ACR30 response at Week 2.

Endpoint

- Sustained ACR response at Week 4, Week 8 and Week 12 compared to ACR response at Week 2.

Objective To evaluate efficacy of anakinra versus placebo during 12 weeks treatment.

Endpoints

- ACR30, ACR50, ACR70 or ACR90 response with absence of fever 24 hours before Week 1 or during the 7 days preceding the visit at Week 2, Week 4, Week 8 and Week 12.
- Absence of rash 24 hours before Week 1 or during the 7 days preceding Week 2, Week 4, Week 8 and Week 12.
- Change from baseline in CRP, Hb, platelet count and ferritin at Week 1, Week 2, Week 4, Week 8 and Week 12.
- Change from baseline in patient/parent global assessment of disease related pain (VAS) at Week 1, Week 2, Week 4, Week 8 and Week 12.
- Inactive disease at Week 12.
- Change from baseline in JADAS27 at Week 2 and Week 12.

Objective	To evaluate time to study drug discontinuation in anakinra versus placebo.
Endpoint	- Time to study drug discontinuation for any reason. - Time to study drug discontinuation due to lack of efficacy or progressive disease.
Objective	To evaluate glucocorticoid tapering in anakinra and placebo treated patients.
Endpoints	- Number of patients who have initiated tapering of glucocorticoids at Week 12. - Number of patients with decreased dose of glucocorticoids by at least 50% at Week 12 compared to baseline. - Percentage decrease of glucocorticoid dose at Week 12 compared to baseline.
Objective	To evaluate the efficacy of anakinra in the 2 separate dose groups.
Endpoint	- Efficacy endpoints as described above.

5.4.2 Safety objective and endpoint

Objective	To evaluate the safety of anakinra.
Endpoint	AEs (including MAS), vital signs and laboratory safety assessments.

5.4.3 Pharmacokinetic objective and endpoint

Objective	To evaluate the PK of anakinra.
Endpoint	- Anakinra trough plasma concentrations and repeated-dose PK parameters at Week 12.

5.4.4 Immunogenicity objectives and endpoints

Objective	To evaluate occurrence of ADAs, NAbs and cross-reactivity.
Endpoint	- Occurrence of ADAs, NAbs, and cross-reactivity and titer levels of ADA and NAbs at baseline, Week 1, Week 2, Week 4, Week 8 and Week 12.

Objective To evaluate ADAs in relation to safety.

Endpoint
- Occurrence and titer levels of ADAs in relation to AEs at Week 1, Week 2, Week 4, Week 8 and Week 12.

Objective To evaluate ADAs, and NAbs in relation to efficacy.

Endpoint
- Occurrence and titer levels of ADA, including NAb in relation to ACR response and CRP at Week 1, Week 2, Week 4, Week 8 and Week 12.

5.4.5 Productivity objective and endpoint

Objective To evaluate absenteeism from school or work.

Endpoint
- Number of days off school or work due to Still’s disease.

5.5 Exploratory objectives and endpoints

Objective To explore PK/PD relationship between IL-1Ra/anakinra serum concentrations and selected efficacy and safety parameters.

Endpoint
- Population PK/PD parameter estimates and associated covariates describing intra- and inter-individual variability in respective parameter estimate.

Objective To explore the PK properties of anakinra using population analysis.

Endpoint
- Population PK parameter estimates and associated covariates describing intra- and inter-individual variability in respective parameter estimate.

Objective To explore the effect of anakinra on the exploratory inflammatory biomarkers (IL-6, IL-18, calprotectin and neopterin) in the treatment of patients with Still´s disease.

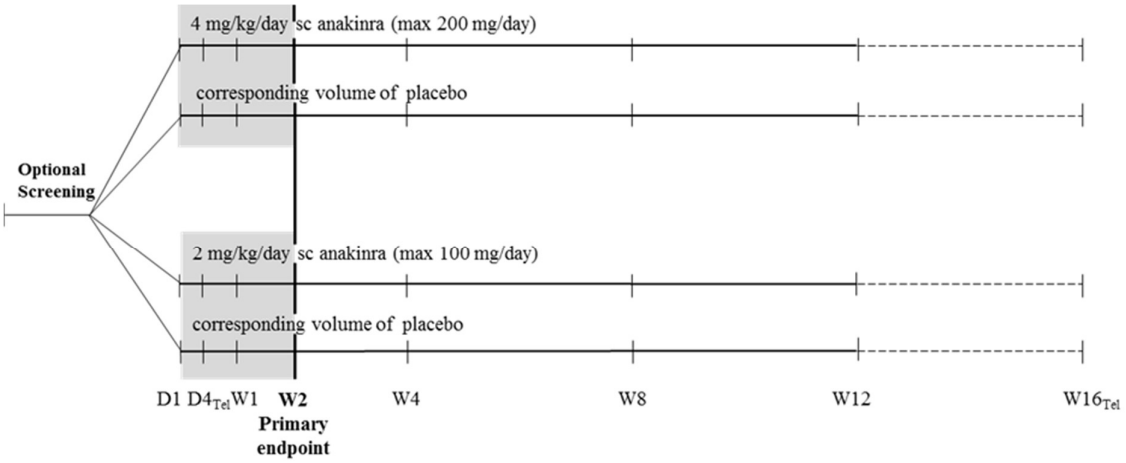
Endpoint
- Change from baseline in exploratory inflammatory biomarkers at Week 1, Week 2 and Week 12.

Objective To collect a blood sample for future analysis for genetic factors potentially contributing to the patient's response to anakinra, safety and tolerability. Will be reported separately.

6 Investigational plan

6.1 Overall study design and plan

Figure 1 Study design



The study consists of a 12-week, randomized, double-blind, placebo controlled period with two dose levels of anakinra and a 4-week safety follow-up after last dose of IMP. The primary endpoint will be evaluated at Week 2. Sustained efficacy and time to study drug discontinuation will be evaluated during the full study period.

A screening visit is optional and may be done to identify patients that could be suitable for the study. See Figure 1. During the study 6 visits and 2 telephone contacts are scheduled i.e., Day 1 (baseline visit), Day 4_{Tel}, Week 1, Week 2, Week 4, Week 8, Week 12 and Week 16_{Tel} (End of Study).

Patients will be randomly assigned to study drug, after they meet all of the inclusion criteria and none of the exclusion criteria. Patients will receive treatment for 12 weeks, either anakinra or placebo. Patients will be randomized to anakinra in a dose of either 2 or 4 mg/kg/day, with a maximum dose of 100 or 200 mg once daily, respectively. Patients will be randomized to placebo with corresponding volumes for each of the two anakinra dose levels.

To be able to evaluate the primary objective of the study it is important that patients remain in the study until the Week 2 visit whenever possible. However, patients can discontinue study drug at any time during the study e.g. due to lack of efficacy or progressive disease. Patients fulfilling the escape criteria are a subcategory of patients that discontinue study drug due to progressive disease (see Table 1).

Table 1 Escape criteria

• symptomatic serositis, *or* • flare i.e., a worsening of >30% from baseline in at least 3 of any 6 components part of ACR.

If the investigator judges that a patient must discontinue study drug before the Week 12 visit, a Study Drug Discontinuation visit should be performed before standard of care treatment is initiated, if possible. If the study drug is discontinued on a scheduled visit, the Study Drug Discontinuation visit should be performed instead of the scheduled visit unless the study drug is discontinued at the Week 12 visit. For a patient that discontinues study drug before the Week 2 visit, the Week 2 visit should still be performed according to the original schedule of assessments, see 6.3.3. However, if the Study Drug Discontinuation visit is performed within 3 days prior to the Week 2 visit, the scheduled Week 2 visit should be omitted. A final follow-up call will be conducted 4 weeks after the last IMP administration according to the assessments described for the Week 16_{Tel} visit (see 6.5.1.8).

All patients included in the study will be carefully monitored by the investigator and if there is a need patients can withdraw from the study at any time, see 6.3.3.

If a patient is on glucocorticoid treatment the dose can be tapered starting earliest at the Week 2 visit. The patient must have reached at least ACR50 response with no fever in the preceding 7 days at the visit initiating tapering.

If a patient develops MAS, the patient will terminate the study treatment and will be treated according to standard of care. If the MAS event occurs before the Week 2 visit it is preferred, if possible, that the patient returns to conduct the Week 2 visit according to the schedule of assessments. For all patients that are diagnosed with MAS, irrespective of timepoint in the study, a follow-up call should be conducted 4 weeks after the last IMP administration according to the assessments described for the Week 16_{Tel} visit (see 6.5.1.8) before the patient is withdrawn from the study. MAS is defined as an event of special interest in this study and must be reported as a serious adverse event.

PK sampling will be conducted in all patients at all study visits. In addition, repeated PK sampling (4-5 time points) will be conducted at Week 12 at a selected number of sites in approximately 30 patients (see 6.5.6.1.1). All patients at these pre-selected sites will be asked to participate in the repeated PK sampling until the target number of patients have completed the repeated PK sampling. If a patient declines to participate in the repeated PK sampling, he/she will still be eligible to participate in the main study. When the overall number of 81 patients has been reached in the study the enrollment will be stopped regardless of whether the target number of repeated PK patients has been reached.

6.2 Discussion of study design

A randomized placebo controlled double-blind study is the optimal way to document safety and efficacy of an investigational product. In this study the number of patients receiving

placebo has been kept to a minimum, which means that only one third of the patients will be randomized to placebo and two thirds will be randomized to active treatment in two dose levels.

The main comparison will be between anakinra (combined dose groups) and placebo at week 2. In order to be able to evaluate the primary endpoint at week 2, patients that discontinue study drug before week 2 will be encouraged to do a Study Drug Discontinuation visit as well as the Week 2 visit (if the Study Drug Discontinuation visit is performed within 3 days prior to the Week 2 visit, the scheduled Week 2 visit should be omitted). Patients who discontinue study drug will receive standard of care. Options for standard of care will be determined at the discretion of the investigator in dialogue with the patient/caregiver. As patients may already have been administered anakinra in the study this should be taken into consideration when switching to standard of care.

Since IL-1 inhibition has a rapid onset of effect, supported by the published data showing that approximately 90% of patients became afebrile after three days of anakinra treatment and the fact that ACR response rates were similar at day 15 and day 29 in the study with the IL-1 inhibitor canakinumab, it is appropriate to evaluate the primary endpoint after two weeks treatment with anakinra (19, 20, 34). Sustained efficacy of anakinra treatment will be evaluated during the 12 week period for patients who are responders at week 2. In addition, time to study drug discontinuation will be an endpoint for evaluation of efficacy in the study as well as the possibility to taper glucocorticoid treatment.

Trough and repeated PK assessments will be included in this study in order to characterize the pharmacokinetics of anakinra in this patient population.

6.2.1 Rationale for selection of doses

The selection of doses is based on published studies, clinical practice and treatment guidelines.

Anakinra is recommended for treatment of SJIA in the Consensus Treatment Plans for New-Onset SJIA by the CARRA (23). Based on clinical experience, CARRA recommends a starting dose of 2 mg/kg/day (max 100 mg) and a maximum dose of 4 mg/kg/day (max 200 mg).

The proposed doses of 2 and 4 mg/kg/day are also supported by previous published experiences and the maximum dose of 4 mg/kg/day was used in a number of the supporting publications (19, 20, 32, 35). In a few cases, 4 mg/kg/day has been used as the starting dose (37).

In a published study by Vastert et al 2014, anakinra was used as first-line therapy in patients with new-onset SJIA (19). Patients fulfilled the ILAR criteria for SJIA. Anakinra 2 mg/kg/day was used as a starting dose, with a maximum dosage of 100 mg/day, in all 20 included patients. The 2 mg/kg/day dose was maintained in 18 of the patients and increased to 4 mg/kg/day in 2 patients. Treatment was stopped if patients met at least adapted ACR Pedi 90 improvement (i.e., 90% improvement of ACR with absence of fever) after 3 months treatment. The authors concluded that an excellent response was observed in nearly all patients within 3 months, and that more than 80% of the patients achieved persistent disease remission, either on or off medication, during a mean follow-up of 2 years and 8 months.

Population PK parameter estimates of anakinra based on an analysis of sparse sampling concentration data from children and adolescents was published by Urien et al 2013 (28). The study included data from 87 patients of which 22 were SJIA patients with a median age of 7.6 years (range 2.26 to 16.8 years) and a median body weight of 21 kg (range 10 to 83 kg). From a PK point of view, higher dose levels are needed in small children due to higher clearance in children with lower body weight (see Table 2). As an example, based on this population PK analysis, a patient with a body weight of 20 kg is predicted to require a dose of 4 mg/kg/day to achieve similar anakinra exposure ($AUC_{0\text{-}24h,\ ss}$ and $C_{min,\ ss}$) as a dose of 2mg/kg/day in a 50 kg patient.

Table 2 Predicted exposure of anakinra in three hypothetical patients

	Anakinra 2 mg/kg/day (max 100 mg)		**Anakinra 4 mg/kg/day (max 200 mg)**	
BW	**AUC0-24h,ss[1] (ng·h/mL)**	**Cmin,ss[1] (ng/mL)**	**AUC0-24h,ss[1] (ng·h/mL)**	**Cmin,ss[1] (ng/mL)**
20 kg	11561	95	23121	191
50 kg	18776	236	37552	472
100 kg	13556	212	27111	424

[1] Predicted steady-state exposure based on the following published population PK parameters for anakinra (28): $k_a = 0.38\ (h^{-1})$; $CL/F = 0.847 \times (BW/70)^{0.47}$ (L/h); $V/F = 2.581 \times (BW/70)^{0.76}$ (L)

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 (36). In a meta-analysis evaluating the evidence for efficacy of anakinra in AOSD, 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% (33). The efficacy of higher doses of anakinra in AOSD patients has not previously been evaluated in a systematic manner. Thus, in the current study, including also the higher dose level 4 mg/kg with a maximum dose of 200 mg anakinra, we will evaluate if higher dose levels would give further benefit for AOSD patients.

6.2.2 Rationale for primary endpoint

ACR30 is an established measurement of efficacy in arthritis studies (38, 39, 40, 41). 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 (42). 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.

6.3 Selection of study population

A total of 81 patients will be randomized, 54 patients to anakinra and 27 patients to placebo treatment. At least a third of the randomized patients should have had a disease onset before the age of 16, and at least a third of the randomized patients in the study should have had a disease onset at the age of 16 or above.

6.3.1 Inclusion criteria

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

1. Signed informed consent.
2. Male and female patients with a body weight ≥ 10 kg.
3. Diagnosis of Still's disease:
    a. If < 16 years of age at disease onset, according to adapted ILAR criteria i.e., CARRA-criteria for SJIA. See Appendix 1.
    b. If ≥16 years of age at disease onset, according to Yamaguchi criteria. See Appendix 1.
4. If currently on glucocorticoid treatment, a stable dose for at least 1 week prior to randomization. Maximum dose allowed is 1 mg/kg/day, up to a maximum of 60 mg/day.
5. If currently on methotrexate treatment, a stable dose for at least 8 weeks prior to randomization. Maximum dose allowed is 20 mg/m^2/week. If prior treatment with methotrexate, discontinuation is required to be at least 4 weeks prior to randomization.
6. 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 randomization.
    (Definition of fever: body temperature ≥38.0°C)
7. Female patients of childbearing potential must use an effective method of contraception during the study (abstinence being a possible option) as well as present a negative pregnancy test prior to randomization.
8. Negative interferon-gamma release assay or PPD test within 2 months prior to randomization. If not available, a test should be performed at day of randomization (see 6.5.5.6.1).

6.3.2 Exclusion criteria

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

1. Diagnosis of Still's disease more than 6 months prior to randomization.
2. Previous randomization into this study
3. Participation in another concurrent clinical interventional study within 30 days of randomization.
4. Treatment with an investigational drug within 5 half-lives prior to randomization.
5. Previous or current treatment with anakinra, canakinumab or any other IL-1 inhibitor.
6. Use of the following therapies prior to randomization:
    - Narcotic analgesics within 24 hours prior to randomization
    - Dapsone or etanercept within 3 weeks prior to randomization
    - Intraarticular, intramuscular or intravenous administration of glucocorticoids or intravenous Ig within 4 weeks prior to randomization
    - Intravenous Ig with proven Still's disease modifying effect, leflunomide, infliximab, or adalimumab within 8 weeks prior to randomization

- Thalidomide, cyclosporine, mycophenolate mofetil, 6-mercaptopurine, azathioprine, cyclophosphamide, chlorambucil, or any other immunosuppressant within 12 weeks prior to randomization
- Tocilizumab within 12 weeks prior to randomization or any other immunomodulatory medication within 4 half-lives prior to randomization
- Rituximab within 26 weeks prior to randomization

7. Live vaccines within 1 month prior to randomization.
8. Known presence or suspicion of active, chronic or recurrent bacterial, fungal or viral infections, including tuberculosis, HIV infection or hepatitis B or C infection.
9. Clinical evidence of liver disease or liver injury as indicated by presence of abnormal liver tests
    - AST or ALT >5 x ULN, ***or***
    - AST or ALT >3 x ULN accompanied by elevated bilirubin >2 x ULN.
10. Presence of severe renal function impairment CKD stages 4 and 5 (estimated creatinine clearance < 30 mL/min/1.73m^2).
11. Presence of neutropenia (ANC < 1.5 x 10^9/L).
12. Presence or suspicion of MAS at baseline. (See Appendix 2 for guidance).
13. A diagnosis of MAS within 2 months prior to randomization.
14. History of malignancy within 5 years. 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 Kineret (anakinra).
16. Pregnant or lactating women.
17. Foreseeable inability to cooperate with given instructions or study procedures.
18. Presence of any medical or 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 makes the patient not appropriate for inclusion to the study and treatment with IMP.

6.3.3 Study drug discontinuation and withdrawal of patients from the study

A patient can discontinue study drug and withdraw from the study at any time. If a patient discontinues study drug, 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 Study Drug Discontinuation visit should be performed instead of the scheduled visit unless the study drug is discontinued at the Week 12 visit.

For patients that discontinue study drug before the Week 2 visit, a Week 2 visit should still be performed according to the original schedule of assessments unless consent is withdrawn. However, if the Study Drug Discontinuation visit is performed within 3 days prior to the Week 2 visit, the scheduled Week 2 visit should be omitted.

For patients who discontinue study drug and are unable to visit the clinic before initiation of standard of care treatment appropriate assessments should be performed to substantiate the reason for study drug discontinuation, e.g. local lab results.

A final follow-up call will be conducted 4 weeks after the last IMP administration according to the assessments described for the Week 16_{Tel} visit.

If a patient discontinues study drug because of an AE, the reason should always be stated as 'adverse event' irrespective of whether the study drug discontinuation was decided by the investigator or due to patient's withdrawal of consent.

Patients who fail to return to the clinic or cannot be reached by telephone for follow-up assessments will be contacted by the study site personnel (2 documented phone calls followed by 1 registered letter) in an attempt to have them comply with the protocol and to document the reason for withdrawal.

Irrespective of when a patient is withdrawn a follow-up call should be conducted 4 weeks after the last IMP dose, according to Week 16_{Tel} (see 6.5.1.8).

6.3.4 Replacement of withdrawn patients

A randomized patient that is withdrawn will not be replaced.

6.3.5 Screening failures

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

Individuals who do not meet the criteria for participation in this study (screening failure) may be rescreened. Rescreened participants should be assigned the same enrolment number as for the initial screening.

6.4 Treatments

6.4.1 Treatments administered

Patients will receive treatment for 12 weeks, either anakinra or placebo depending on the randomization schedule, see Table 3. The anakinra doses that will be evaluated are 2 mg/kg/day (max 100 mg/day) and 4 mg/kg/day (max 200 mg/day). The dose will be adjusted according to actual body weight (rounded to the nearest kg) and will remain the same throughout the study. See dosing instructions in Appendix 3.

The placebo will be given in a corresponding volume of the anakinra dose. These means that:

- Patients randomized to 2 mg/kg/day (max 100 mg/day) and patients with a body weight < 29 kg and randomized to 4 mg/kg/day (max 200 mg/day) or placebo will only require one injection per day.
- Patients randomized to 4 mg/kg/day (max 200 mg/day), or placebo, with a body weight ≥ 29 kg will require two injections per day.

Table 3 Investigational medicinal products

Investigational product	Daily dose	Dosage form	Route	Dosage regimen
anakinra	**2** mg/kg (max **100** mg)	Solution for injection in pre-filled syringe	Subcutaneous	Once daily
corresponding volume of placebo	Solution volume equivalent to **2** mg/kg (max **100** mg [0.67 mL])	Solution for injection in pre-filled syringe	Subcutaneous	Once daily
anakinra	**4** mg/kg (max **200** mg)	Solution for injection in pre-filled syringe	Subcutaneous	Once daily
corresponding volume of placebo	Solution volume equivalent to **4** mg/kg (max **200** mg [1.33 mL])	Solution for injection in pre-filled syringe	Subcutaneous	Once daily

6.4.2 Identity of investigational medicinal products

The investigational product anakinra is delivered as a sterile solution for injection, pre-filled in a single-use graduated 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. The pre-filled graduated syringe has a pre-attached 29 Gauge thin wall half inch needle, a butyl rubber plunger and a latex free rigid needle shield.

The placebo is also delivered as a sterile solution for injection, in an identical single-use pre-filled graduated syringe. The placebo consists of the active product vehicle (0.67 mL) but without the active ingredient, anakinra.

The anakinra drug substance is manufactured by [redacted] product and placebo are manufactured by [redacted]

The IMP is packaged and labeled by [redacted] Each kit consists of 7 syringes.

Labeling of IMP complies with national regulatory requirements.

6.4.3 Storage, preparation and administration of IMP

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

Possible deficiencies related to the handling, quality or identity of the IMP should be reported both to the study monitor and also directly to 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.

6.4.3.1 Preparation and administration of IMP

The IMP is intended to be injected by the patient or the caregiver. Each IMP syringe contains 0.67 mL equivalent to 100 mg anakinra or placebo. Depending on the patient weight and randomized dose, the full content of a syringe or part of the content of a syringe will be injected to match the prescribed dose.

The prefilled graduated syringe(s) should be taken out from cold storage and be placed in 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 2-inch area around the belly button)
- front of the middle thighs
- upper outer areas of the buttocks

The IMP administration will be supervised by the investigator or investigational site staff at the Day 1 visit and the exact time point for the administration will be recorded. At all other occasions when the IMP is self-administered the patient will record the exact time point of the administration in the diary.

The graduated syringes are for single use and must be discarded after use.

See detailed instructions regarding preparation and administration of IMP in the pharmacy manual.

6.4.4 Method of assigning patients to a treatment group

A total of 81 patients will be randomized, 54 patients are planned to be randomized to anakinra treatment and 27 patients are planned to be randomized to placebo. The different treatment groups are;

- placebo (corresponding volume of anakinra 2 mg/kg/day [max 100 mg/day]), or
- placebo (corresponding volume of anakinra 4 mg/kg/day [max 200 mg/day]), or
- anakinra 2 mg/kg/day (max 100 mg/day) or
- anakinra 4 mg/kg/day (max 200 mg/day)

The ratio between the treatment groups is 1:1:2:2, i.e. the ratio placebo:ankinra is 1:2.

The randomization numbers will be generated in blocks. Each block will include the four treatment groups per the ratio described above. The block size will not be revealed before breaking of the blind.

The randomization will be stratified by age at onset of disease (< 16 years, ≥ 16 years) and glucocorticoid use at inclusion (yes, no) with a requirement to randomize at least a third of the patients with an age at onset of disease < 16 years and a third of the patients with an age at onset ≥ 16 years. Medidata Balance Randomization and Trial Supply System will be used for IRS and Biostatistics at DCRI will be responsible for generating the randomization scheme, which will link sequential patient randomization numbers to treatment codes.

6.4.5 Blinding and unblinding

6.4.5.1 Blinded treatment assignment

The treatment assignment will be blinded (placebo and active treatment) for the patients, the investigators and any personnel involved with the study conduct or evaluation at the investigational sites, ARO and sponsor. In order to avoid the need to give all patients two injections daily the placebo will be given in a corresponding volume of the anakinra dose (see 6.4.4).

Unblinding, i.e., breaking the code for an individual patient during the study, is restricted to emergency situations and should only be used under circumstances where knowledge of the treatment is necessary for the proper handling of the patient. The decision to break the code must be made by the investigator. The study monitor and sponsor must as soon as possible be informed about the code break.

Unblinding should be documented according to instructions in the Medidata Balance Randomization and Trial Supply System.

6.4.5.2 Blinded independent joint assessor

To minimize bias from observed efficacy or laboratory changes a blinded independent and trained assessor will perform the joint examination. To improve consistency between evaluations, it is strongly recommended that the assessments are conducted by the same assessor at a site.

6.4.6 Prior and concomitant therapy

Intraarticular, intramuscular and intravenous administration of glucocorticoids are prohibited within 4 weeks prior to randomization and during the study. Other administration of glucocorticoid treatment is allowed as concomitant medication during the study if the patient has had a stable dose for at least 1 week prior to randomization. Maximum dose allowed is 1 mg/kg/day (max 60 mg/day). If the patient is on glucocorticoid treatment, the dose can be tapered starting earliest at the Week 2 visit. The patient must have reached at least ACR50 response with no fever in the preceding 7 days at the visit initiating tapering. A suggested glucocorticoid tapering schedule is provided in Appendix 4. All other glucocorticoid treatment is prohibited during the study except topical and inhaled.

Methotrexate is allowed as concomitant medication during the study if the patient has had a stable dose for at least 8 weeks prior to randomization. The dose should remain stable throughout the study as long as it is well tolerated. If prior treatment with methotrexate, discontinuation is required to be at least 4 weeks prior to randomization.

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

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

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

- Intraarticular, intramuscular or 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 TNF inhibitor (investigational or marketed)
- Dapsone or mycophenolate mofetil,Leflunomide, thalidomide or cyclosporine, 6-Mercaptopurine, azathioprine, cyclophosphamide, chlorambucil, or any other immunosuppressant
- Use of any other investigational drug

Live vaccines is not allowed within 1 month prior to randomization and until after 1 month following the last study dose. Inactivated vaccines may be permitted according to the investigator's discretion. The investigator should instruct the patient to notify the study site about any new medications he/she takes after the start of the study drug. All medications and significant non-drug therapies administered after the patient starts treatment with study drug until Week 16_{Tel} must be listed on the concomitant medication CRF page.

Following the 12 week double blind treatment, the patient will be treated at the discretion of the investigator according to standard of care.

6.4.7 Treatment compliance

IMP accountability records will be kept. The pharmacy and the investigator must maintain accurate records demonstrating date and amount of IMP(s) received, to whom and by whom administered or dispensed (patient-by-patient accounting), and accounts of returned IMP(s) and any IMP accidentally or deliberately destroyed. At the end of the study, any remaining IMP(s) will be returned to identified drug depot for destruction, or destroyed locally. In either case, a certificate of destruction must be issued.

6.4.8 Overdose management

For this study, any dose of IMP greater than 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 CRF, and any untoward medical occurrence associated with an overdose will be recorded the same way as any adverse event (see 6.5.5.1).

6.5 Efficacy, safety, pharmacokinetic, and exploratory assessments

6.5.1 Study schedule

See the schedule of assessments in Appendix 5

6.5.1.1 Screening visit (optional)

The screening may be done at a separate visit before the baseline visit to identify patients that could be suitable for the study and/or to ensure that required lab results are available before randomization (see 6.5.5.6.1). Applicable ICFs must be obtained prior to any screening

activities (see 2.3). Once the ICF has been signed, the patient will be assigned an enrolment number.

Any SAE that occur after the informed consent has been signed must be reported (see 6.5.5.1.4).

6.5.1.2 Baseline visit, Day 1

If a screening visit has not been performed applicable ICFs must be obtained prior to any study related activities. Once the ICF has been signed, the patient will be assigned an enrolment number.

Any SAE that occur after the informed consent has been signed must be reported.

All inclusion and exclusion criteria should be reviewed (see 6.3) to assess patient's eligibility. The laboratory tests that are needed for evaluation of inclusion and exclusion criteria should be performed before randomization (see 6.5.5.6.1). If it is expected that any of the lab results are not available within reasonable time a screening visit should be performed the day before (the eligibility laboratory results are valid for 36 hours). See 6.5.1.1. However, a patient can be randomized before results from a interferon-gamma release assay or a PPD test has been confirmed. If the results from this test is positive, that is not due to vaccination (PPD), the patient must be withdrawn from the study (see 6.3.3).

Data will be collected on medical history (see 6.5.2), demographics (see 6.5.3) and prior and concomitant medication (see 6.4.6). Vital signs (see 6.5.5.2) and physical examination (see 6.5.5.3) will be performed.

If the patient has been found eligible, the patient will be randomized .

As part of ACR the physician global assessment of disease activity, patient or parent global assessment of overall well-being, the patient or parent assessment of physical function, assessment of number of joints with active arthritis and number of joints with limited range of motion will be assessed (see 6.5.4.1). Global assessment of the patient disease related pain (see 6.5.4.2), and a 12-lead ECG (see 6.5.5.4) will be assessed.

Prior to the first IMP administration, blood samples will be collected for central laboratory assessments (see 6.5.5.6.2) immunogenicity assessments (see 6.5.5.5), IL-1Ra/anakinra serum concentration assessments (see 6.5.6) and exploratory inflammatory biomarkers (see 6.5.7). For patients consenting to pharmacogenetic assessment an additional blood sample will be collected at a suitable visit after randomization (see 6.5.7.2).

Finally, the first dose of IMP is to be administered and the time point of administration will be recorded. The patient or patient's caregiver will be instructed how to administer the IMP dose on a daily basis and how to complete the diary (see 9.2) and IMP covering the period until next visit will be dispensed.

Adverse events, will be recorded from the time of the first IMP administration (see 6.5.5.1).

6.5.1.3 Day 4_{Tel} telephone follow-up

A telephone contact will be performed at Day 4 for retention reasons, to follow-up on compliance of study procedures and to answer any additional questions from patients or parents/caregivers. Data will be collected on adverse events. If not possible to reach patient or parent/caregiver this should be documented in the CRF.

6.5.1.4 Week 1 visit

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

Assessments conducted at the visits are the ACR variables, physical examination including complete joint exam, vital signs, concomitant medication and global assessment of the patient disease related pain. If any fever or rash attributable to the disease has occurred during the last 24 hours, this will be recorded. Data from the patient diary will support the evaluation.

Blood will be collected for central laboratory assessments, immunogenicity assessments, IL-1Ra/anakinra serum concentration assessments and exploratory inflammatory biomarkers. Adverse events as well as number of days of absenteeism from school or work since the baseline visit (also recorded for guardians where appropriate) will be recorded. The patient diary will be reviewed to confirm that instructions are followed and IMP covering the period until next visit will be dispensed. After all assessments have been performed, the daily IMP administration can occur.

6.5.1.5 Week 2 visit

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 joint count, vital signs, concomitant medication, and global assessment of the patient disease related pain. If any fever or rash attributable to the disease has occurred during the 7 days preceding the Week 2 visit, this will be recorded. Data from the patient diary will support the evaluation.

Blood samples will be collected for central laboratory assessments, immunogenicity assessments, IL-1Ra/anakinra serum concentration assessments and exploratory inflammatory biomarkers. Adverse events as well as number of days of absenteeism from school or work since previous visit (also recorded for guardians where appropriate) will be recorded. The patient diary will be reviewed to confirm that instructions are followed and IMP covering the period until next visit will be dispensed. After all assessments have been performed, the daily IMP administration can occur.

If the patient is on glucocorticoid treatment the possibility to start tapering can be commenced earliest at the Week 2 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 suggested glucocorticoid tapering instructions.

6.5.1.6 Week 4 and Week 8 visits

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 including complete joint exam, global assessment of the patient disease related pain, vital signs, and concomitant medication. If any fever or rash attributable to the disease has occurred during the 7 days preceding the visit, this will be recorded. Data from the patient diary will support the evaluation.

Blood samples will be collected for central laboratory assessments, immunogenicity assessments and IL-1Ra/anakinra serum concentration assessments. Adverse events as well as number of days of absenteeism from school or work since previous visit (also recorded for guardians where appropriate) will be recorded. The patient diary will be reviewed to confirm

that instructions are followed and IMP covering the period until next visit will be dispensed. After all assessments have been performed at the visit the daily IMP administration can occur.

If the patient is on glucocorticoid treatment consider the possibility to taper if the patient has reached at least ACR50 response with no fever in the preceding 7 days. See Appendix 4 for suggested glucocorticoid tapering instructions.

6.5.1.7 Week 12 visit

The visit will 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, global assessment of the patient disease related pain, vital signs, and concomitant medication. If any fever or rash attributable to the disease has occurred during the 7 days preceding the Week 12 visit, this will be recorded. Data from the patient diary will support the evaluation.

Blood samples will be collected for central laboratory assessments, immunogenicity assessments, IL-1Ra/anakinra serum concentration assessments and exploratory inflammatory biomarkers. Inactive disease (see 6.5.4.5) will be evaluated. Adverse events as well as number of days of absenteeism from school or work since previous visit (also recorded for guardians where appropriate) will be recorded. The patient's diary will be reviewed. Finally all IMP should be collected from the patient and accounted for.

For patients enrolled in the repeated-dose PK sampling, this visit should be scheduled on the same day as the last dose of IMP administration is planned. For details regarding the blood sampling procedure and IMP administration see 6.5.6.1.

6.5.1.8 Week 16_{Tel} telephone follow-up

A follow-up telephone call will be made at Week 16_{Tel} (End of study). Data will be collected on concomitant medications and adverse events.

6.5.1.9 Study Drug Discontinuation visit

The visit is performed if the investigator judges that a patient must discontinue study drug before the Week 12 visit. 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 of the assessments of the scheduled visit, unless the study drug is discontinued at the Week 12 visit.

Assessments conducted at the visit are the ACR variables, physical examination including complete joint exam, global assessment of the patient disease related pain, vital signs, and concomitant medication. If any fever or rash attributable to the disease has occurred during the 7 days preceding the Study Drug Discontinuation visit, this will be recorded. If this visit is performed before the Week 1 visit, fever and rash attributable to the disease during the 24-hours preceding the Study Drug Discontinuation visit will be recorded. Data from the patient diary will support the evaluation.

Blood samples will be collected for central laboratory assessments, immunogenicity assessments, IL-1Ra/anakinra serum concentration assessments and exploratory

inflammatory biomarkers. Inactive disease (see 6.5.4.5) will be evaluated. Adverse events, number of days of absenteeism from school or work since previous visit (for guardians where appropriate) as well as morning stiffness will be recorded. The reason for study drug discontinuation is recorded in the CRF. "Escape criteria" can be evaluated in the CRF. Finally, all IMP should be returned and accounted for.

Patients that discontinue study drug before the Week 2 visit should still return for a Week 2 visit according to original schedule of assessments. If the Study Drug Discontinuation visit is performed within 3 days prior to the Week 2 visit, the scheduled Week 2 visit should be omitted.

A final follow-up call will be conducted 4 weeks after the last IMP administration according to the assessments described for the Week 16_{Tel}.

6.5.2 Medical history

The details of the patient's relevant medical history as judged by the investigator will be recorded in the CRF at visit Day 1 (baseline).

6.5.3 Demographics

The patient´s date of birth, gender, race and ethnicity will be recorded in the CRF at the first visit, either the optional screening visit or Day 1 (baseline).

6.5.4 Efficacy assessments

6.5.4.1 ACR with absence of fever

The ACR30 criteria will be used to determine efficacy defined as improvement from baseline of at least 30% in at least 3 of response variables 1 to 6, with no more than one variable 1 to 6 worsening by more than 30% and no intermittent fever attributable to the disease during the preceding 7 days.

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 (100.4 °F) attributable to the disease.

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 treating physician and is conducted at the following visits: Day1, Week 1, Week 2, Week 4, Week 8, Week 12 and, if applicable, the Study Drug Discontinuation visit. See Appendix 7.

6.5.4.1.2 Patient/parent global assessment of overall well-being

For patients ≥18 years 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 randomization this VAS will be assessed by the CHAQ health status index which will be completed by parent or guardian. To ensure consistency, the form should be completed throughout the study by the same parent or guardian who completed the baseline global assessment.

The assessment is conducted at the following visits: Day 1, Week 1, Week 2, Week 4, Week 8, Week 12 and, if applicable, the Study Drug Discontinuation visit. See Appendix 8 and Appendix 9.

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 joint with swelling, or in the absence of swelling, limitation of motion accompanied by either pain on motion or tenderness not due to deformity.

A blinded independent trained assessor will conduct the joint evaluation at the following visits: Day 1, Week 1, Week 2 Week 4, Week 8, Week 12 and, if applicable, the Study Drug Discontinuation visit.

6.5.4.1.4 Number of joints with limitation of motion

The number of joints with limitation of motion will be assessed using the ACR definition. A blinded independent trained assessor will conduct the joint evaluation at the following visits: Day 1, Week 1, Week 2, Week 4, Week 8, Week 12, and, if applicable, the Study Drug Discontinuation visit.

6.5.4.1.5 Assessment of physical function

6.5.4.1.5.1 Childhood Health Assessment Questionnaire

The CHAQ© is validated to assess physical ability and functional status for children (43, 44). Hence, CHAQ will be administered throughout the study for patients that are <18 years of age at the time of randomization and will be completed by the parent or guardian as a proxy for the child. 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 0-3, 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 0-3). The discomfort and health status index will be presented separately, see section 6.5.4.2 and 6.5.4.1.2.
The assessment is conducted at the following visits: Day 1, Week 1, Week 2, Week 4, Week 8, Week 12 and, if applicable, the Study Drug Discontinuation visit. See Appendix 9.

6.5.4.1.5.2 Stanford Health Assessment Questionnaire

The SHAQ© is a PRO instrument designed to represent a model of patient-oriented outcome assessment for patients ≥18 years (45, 46). The SHAQ assesses the patient's level of functional ability and 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 eight 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 are made on a scale from zero (no disability) to three (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 is conducted at the following visits: Day 1, Week 1, Week 2, Week 4, Week 8, Week 12 and, if applicable, the Study Drug Discontinuation visit. See Appendix 9.

6.5.4.1.6 C-reactive protein

CRP will be determined in serum in order to identify the presence and severity of inflammation, and to monitor response to treatment. The assessment is conducted at the following visits: Day 1, Week 1, Week 2, Week 4, Week 8, Week 12 and, if applicable, the Study Drug Discontinuation visit.

6.5.4.1.7 Fever

For endpoint evaluation in this study the definition of fever is ≥38.0°C (100.4 °F) and should be attributable to the disease as judged by the investigator.

Fever will be measured orally, under the tongue and using the same thermometer (provided for the study) throughout the study. The measurement and time point will be recorded in the patient's diary. Fever will be measured during the treatment period whenever there is a fever episode. In addition the patient will get a question daily in the diary asking if he/she experienced any fever episode that day.

6.5.4.2 Global assessment of the patient disease related pain

For patients ≥18 years the global assessment of disease related pain will be assessed on a VAS scale ranging from 0 – 100 mm, from no pain (0 mm) to very severe pain (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 randomization this VAS will be assessed by the CHAQ discomfort index which will be completed by the parent or guardian as a proxy. To ensure consistency, the VAS should be completed throughout the study by the same parent or guardian who completed the baseline global assessment.

The assessment is conducted at the following visits: Day 1, Week 1, Week 2, Week 4, Week 8,Week 12 and, if applicable, the Study Drug Discontinuation visit. See Appendix 9 and Appendix 10.

6.5.4.3 JADAS27

JADAS is a tool that will be assessed for scoring actual disease activity (47, 48, 49). The JADAS27 includes 4 measures: physician global assessment of disease activity, patient or parent global assessment of overall well-being, 27 active joint count, and CRP. The JADAS variables are part of the ACR response criteria with the joint evaluation performed to count the number of joints with active disease. The JADAS27 includes the following 27 joints: cervical spine, elbows, wrists, metacarpophalangeal joints (from first to third), proximal interphalangeal joints, hips, knees, and ankles.

JADAS27 is calculated as the sum of its four components, physician global assessment of disease activity converted to cm from the VAS (0=no activity, 10=maximum activity); patient global assessment of well-being converted to cm from the VAS (0=very well, 10=very poor); active joint count (0-27); and CRP. Prior to calculation CRP is truncated to a 0 – 10 scale according to the following formula: (CRP (mg/l) −10)/10. Before calculation, CRP values <10 mg/l are converted to 10 and CRP values >110 mg/l are converted to 110. The JADAS27 tool yields a global score of 0–57.

The JADAS27 components are collected and evaluated at the Day 1, Week 2,Week 12 and, if applicable, at the Study Drug Discontinuation visit. See Appendix 11.

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 on a daily basis by the patient in the diary. If present and attributable to the disease, rash will also be recorded as part of the physical examination performed at every visit. In addition, at Week 12 and, if applicable, at the Study Drug Discontinuation visit the presence or absence of rash will be recorded to assess "inactive disease".

6.5.4.5 Inactive disease

In the absence of a biologic marker for active or inactive disease, 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 splenomegaly, 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 (50).

The inactive disease assessment is conducted at Week 12 and at the Study Drug Discontinuation visit.

6.5.4.6 Absenteeism from school or work

The number of days a patient is away from formal education, or work, due to Still's disease since last visit will be recorded in the CRF at all visits after baseline including a possible

Study Drug Discontinuation visit. The same is valid for the patient caregiver when the patient requires their attendance.

6.5.5 Safety assessments

6.5.5.1 Adverse events

6.5.5.1.1 Definitions

Adverse event

An AE is any untoward medical occurrence in a patient or trial patient administered a pharmaceutical product; the event does not necessarily have a causal relationship with the treatment or usage.

Adverse events include the following:

- Abnormal test findings, as specified below.
- Clinically significant signs and symptoms.
- Changes in physical examination findings.
- Progression/worsening of underlying disease.

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

- Overdose.
- Withdrawal of treatment.
- Interactions.
- Abuse.
- Misuse.

Abnormal test findings

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

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

Preexisting conditions

A preexisting condition (i.e., a disorder present before the adverse event reporting period started and noted on the pretreatment medical history/physical examination form) should not

be reported as an adverse event unless the condition worsens or episodes increase in frequency during the adverse event reporting period.

Worsening of Still's disease

A worsening of the disease under study should not be reported as an adverse event unless it leads to hospitalization or fulfills any other seriousness criterion.

Procedures

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as adverse events. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an adverse event. For example, an acute appendicitis that begins during the adverse event reporting period should be reported as the adverse event and the resulting appendectomy entered in the comments section of the CRF.

Serious adverse event (SAE)

An adverse event 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).

Other medically important adverse events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or the patient 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.

SAEs also include any other event that the investigator or sponsor judges to meet SAE reporting criteria. Any suspected transmission of an infectious agent via IMP shall also be considered an SAE.

Medical events of special interest for safety surveillance

MAS is defined as an event of special interest in this study, for rationale see 4.1. The diagnosis of MAS will be made by the investigator based on the patients overall clinical signs and symptoms, including laboratory changes over time. The 2016 Classification Criteria for Macrophage Activation Syndrome Complicating Systemic Juvenile Idiopathic Arthritis for patients < 16 years of age may be used to guide this assessment for all patients in the study. See Appendix 2. If a MAS diagnosis is made at any point after patient signed informed

consent, the event must be reported as a serious adverse event and the patient will be withdrawn from the study and will be treated according to standard of care, see 6.3.3.

Hospitalization

Hospitalization or prolongation of 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 adverse event 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.
- Admission or prolongation for administrative reasons, such as technical, practical, or social reasons.

Suspected Unexpected Serious Adverse Reaction (SUSAR)

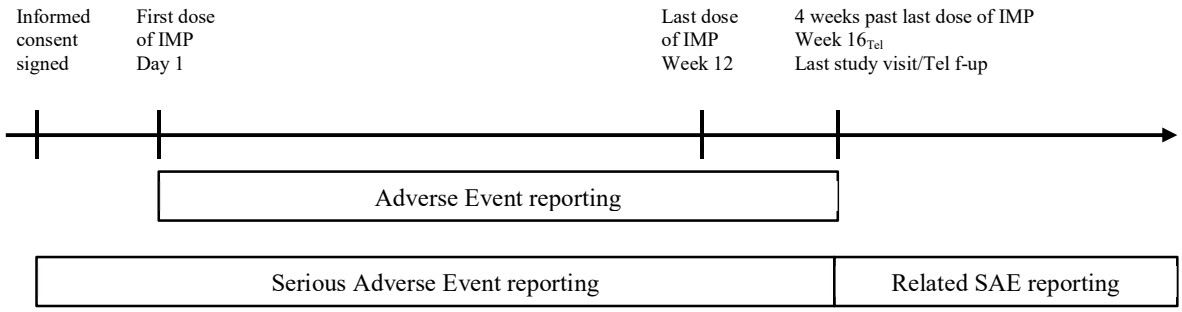
A SUSAR is a serious adverse event which is not consistent with the Investigator's Brochure and that the investigator and or Sobi identifies as related to IMP.

6.5.5.1.2 Adverse event reporting period

SAEs should be recorded within the CRF, from the time the patient has signed the informed consent until 4 weeks past the last dose of IMP. See Figure 2. Non-serious AEs will be recorded within the CRF from the first administration of IMP until 4 weeks past the last dose of IMP. Furthermore any SAE, if a causal relationship between the event and the IMP(s) is suspected, which occurs after last study visit/telephone follow-up, should be reported (see 6.5.5.1.4).

Refer to section 6.5.5.1.6 for information how unresolved adverse events and SAEs should be followed up.

Figure 2 Adverse event report period



6.5.5.1.3 Eliciting and recording adverse event information

The investigator is to record all directly observed adverse events, and all adverse events spontaneously reported by the patient, in the CRF using concise medical terminology. In addition, each patient will be questioned about adverse events at each clinic visit and follow up telephone contact following initiation of treatment as described in schedule of assessments (see Appendix 5). At the first study visit the question asked will be "Since you started treatment have you had any health problems?". At subsequent visits/telephone calls the question asked will be: "Since last asked, 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 adverse event.

Severity assessment

The investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the adverse event. For the purpose of consistency, these intensity 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

Note the distinction between the gravity (seriousness) and the intensity (severity) of an adverse event. **Severe** is a measure of intensity; thus, a **severe** reaction is not necessarily a **serious** reaction. For example, a headache may be severe in intensity, but would not be classified as serious unless it met one of the criteria for serious events listed above.

Causality assessment

For each adverse event, the investigator must make a causality assessment to determine if there is a reasonable possibility that the IMP(s) caused the adverse event. The adverse event is assessed as **related or not related** to the IMP(s).

6.5.5.1.4 Serious adverse event reporting

Both serious and non-serious adverse events are to be reported on the adverse event page of the CRF as specified in the CRF instructions.

If an SAE occurs, it must be recorded in the CRF within 24 hours of awareness of the event by the investigator.

All new information obtained, relevant to an SAE report, should be reported within the same timeframe as the initial information.

The investigator shall provide sufficient information to enable a complete medical assessment of the reported event. Best efforts shall be made by the investigator to provide additional information related to any SAE as requested.

If the CRF is not functioning, the SAE can be reported by faxing/emailing a completed paper SAE report form or by direct telephone communication with DCRI Safety Surveillance at the numbers provided below. The event must be updated electronically in the CRF by the clinical site once CRF function resumes.

Fax information to DCRI Safety Surveillance:

Toll Free Fax: 1-866-668-7138

Toll Free Phone: 1-866-668-7799

Email: dcrisafetysurveillance@dm.duke.edu

Any SAE, if a causal relationship between the event and the IMP(s) is suspected, which occurs after the last study visit/telephone follow-up, should be reported to Sobi by e-mail to drugsafety@sobi.com or fax to + 46 8 697 32 30 and according to local regulations as applicable.

Sobi will report SUSARs to the relevant competent health authorities in all concerned countries according to local regulations. DCRI will notify Duke IRB, central IRBs and investigators. Investigators will then report SUSARs to their local IRB/REB as per individual IRB/REB guidelines.

6.5.5.1.5 Exposure during pregnancy and breastfeeding

Pregnancy occurring during a clinical investigation, although not considered a serious adverse event, must be reported within the same timelines as a serious adverse event. All events of exposure to the IMP during pregnancy (female patient or male patient's partner) or breastfeeding shall be recorded within 24 hours of awareness by any study personnel, whether the exposure is associated with an adverse event 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).

The pregnancy will be reported on the appropriate pregnancy form. The investigator is responsible for monitoring the outcome of the pregnancy and to inform DCRI (or, if the study has been completed, inform Sobi by e-mail to drugsafety@sobi.com or fax to + 46 8 697 32 30) of relevant information and any information requested related to the outcome of the pregnancy.

Any adverse events and SAEs observed during and in relation to pregnancy, delivery or breastfeeding should be recorded in the CRF and as applicable be reported to DCRI as described previously in this section.

6.5.5.1.6 Follow-up of unresolved adverse events

All adverse events 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 or at the follow-up by telephone Week 16_{Tel}, as applicable. How to report changes in an ongoing adverse event during a patient's participation in the study is described in the CRF instructions.

In addition, all serious and non-serious adverse events 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 CRF.

6.5.5.2 Vital signs

Vital signs (blood pressure, heart rate and body weight) will be assessed at the Day 1 visit before the first IMP administration and at all visits until the Week 12. It will also be assessed if the Study Drug Discontinuation visit is performed. Height will only be measured at the Day 1 visit. Blood pressure and heart rate will be measured in sitting position after the patient has rested comfortably for at least 5 minutes.

New clinically significant abnormal vital signs values should be reported as adverse events (see 6.5.5.1.1 for details).

6.5.5.3 Physical examination

A general physical examination will be assessed at Day 1 and at all visits until the Week 12 visit. 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.

At the Week 12 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 rash, serositis, splenomegaly and generalized lymphadenopathy will be recorded to assess "inactive disease" (see 6.5.4.5).

Any persisting abnormalities should be stated each time the examination is performed. If any abnormalities are reported at baseline they should be recorded as medical history. New abnormalities reported after first dose of IMP should be recorded as AEs (see 6.5.5.1.1 for details).

The presence or absence of signs of joint inflammation will not be reported as AEs (see 6.5.5.1.1 Preexisting conditions/Worsening of Still's disease) but will be captured in joint assessment as part of ACR.

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 visits (see 6.5.4.4). If not judged to be attributable to the disease it should be recorded as an AE.

6.5.5.4 Electrocardiogram

A baseline 12-lead ECG will be recorded before the first IMP administration, at the Day 1 visit. The 12-lead ECG recordings will be measured in supine position after the patient has rested comfortably for at least 5 minutes.

The ECGs will be reviewed and documented in the CRF. 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 baseline they should be recorded as medical history. However, if findings are judged serious it should be reported as a SAE (see 6.5.5.1.1 for details).

6.5.5.5 Anti-drug antibodies

Blood samples for determination of ADA will be collected before the first IMP administration at the Day 1 visit and at all visits until the Week 12. It will also be collected if the Study Drug Discontinuation visit is performed. Once dosing with IMP has started, the ADA samples should preferably be taken 24 hours after a previous dose of anakinra or as close to the next IMP administration as possible in order to improve detection of ADA.

The sampling handling procedures, including the time of each blood collection, the time of placement of sera into frozen storage (at the end of the sample workup) and the date of transfer or shipment of the samples to the responsible analyst will be documented in detail in the laboratory manual. 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 lab assessments at any visit exceeds the maximum allowed blood volume collection the assessments for the study should be prioritized according to the specification in the laboratory manual.

Serum samples to determine ADA will be analyzed by York Bioanalytical Solutions Limited using validated methods. This includes a bridging format immunoassay for screening of samples using a statistically defined cut-point for determination of a positive result and a confirmatory assay with a statistically pre-defined confirmatory cut-point. Confirmed positive samples will be further analyzed for antibody titers and for potential cross-reactivity with IL-1Ra produced by a human cell line to achieve an endogenous-like glycosylation pattern to mimic natural human IL-1Ra.

Confirmed ADA positive samples will also be further analyzed for the presence of NAb at Euro Diagnostica with a validated method using an IL-1 responsive reporter gene cell line. Inhibition of the antagonistic effect of IL-1Ra on IL-1 mediated cell activation in the presence of an ADA positive serum sample will indicate the presence of NAbs in the sample.

6.5.5.6 Laboratory assessments

Clinically significant abnormal laboratory values should be reported as adverse events, except at baseline when they should be recorded as part of the medical history.

The laboratory lab manual will define which labs to prioritize to ensure that the maximum allowed blood volume is never exceeded in pediatric patients according to NIH guidelines or any local guidelines (54, 55). Blood sampling for the care of the patients should always have the priority over blood samples collected specifically for this study. For patients with a body

weight <15 kg, central laboratory hematology and coagulation samples should not be repeated at Week 1 visit, if not clinically indicated, in order to preserve blood volume.

All laboratory assessments should be performed also for patients <15 kg body weight at the Study Drug Discontinuation visit. If the Week 2 visit is peformed after the Study Drug Discontinuation visit, central lab should also be collected at the Week 2 visit, if not exceeding the maximum allowed blood volume collection according to limitations in relation to the body-weight of the patient.

In case any of the safety central lab assessments cannot be analysed from the Week 12 visit the patient should be asked to return for an unscheduled visit to ensure that results are available for all lab assessments..

6.5.5.6.1 Local laboratory assessments

Laboratory tests needed for evaluation of inclusion and exclusion criteria can be performed at the local laboratory before randomization. See Table 4. However, a patient can be randomized before results from an interferon-gamma release assay or a PPD test has been confirmed. If the results from this test is positive, that is not due to vaccination (PPD), the patient must be withdrawn from the study. If available, and if there are no concerns regarding blood volume for sampling, it is preferable to use the interferon-gamma release assay. Local laboratory results are valid for 36 hours before randomization, provided that the patient does not show signs and/or symptoms of new ailments or increasing signs and/or symptoms that makes the patient non-eligible for the study in the opinion of the investigator. The local laboratory results are valid for inclusion regardless of central laboratory results, however any clinically significant findings in central laboratory results should be followed up.

To guide the investigator for decision making to determine start of glucocorticoid tapering and to evaluate if the patient is fulfilling the escape criterion, a local lab CRP assessment can be done, if not possible to await central lab results.

Table 4 Test conducted at local laboratory to confirm patient eligibility

Clinical chemistry	**Hematology**
Aspartate aminotransferase (AST)	White blood cells
Alanine aminotransferase (ALT)	Differential blood count
Total bilirubin (if >upper limit of normal also conjugated and non-conjugated bilirubin)	Thrombocytes (platelet count)
Alkaline phosphatase (ALP)	**Coagulation**
Triglycerides	Fibrinogen
Creatinine	
Ferritin	**Urine analysis**
C-reactive protein (CRP)	Human chorionic gonadotropin (hCG) test (for women of childbearing potential)
	Interferon-gamma release assay or PPD test*

*Only required if no interferon-gamma release assay or PPD test is present within 2 months prior randomization. Interferon-gamma release assay can be analysed by central lab.

6.5.5.6.2 Central laboratory, clinical chemistry hematology and coagulation

Blood and urine samples for determination of hematology, coagulation and clinical chemistry variables will be collected at all visits and will be performed by the central safety laboratory using routine methods. The date and time of collection will be recorded on the appropriate CRF. See Table 5.

The sampling handling procedures, including the time of each blood/urine 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 analyst, 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.

Table 5 Laboratory assessments

Clinical chemistry	**Hematology**
C-reactive protein (CRP)	Hemoglobin
Ferritin	Hematocrit
Aspartate aminotransferase (AST)	White blood cells
Alanine aminotransferase (ALT)	Differential blood count
Total bilirubin (if >upper limit of normal also conjugated and non-conjugated bilirubin)	Thrombocytes (platelet count)
Alkaline phosphatase (ALP)	**Coagulation**
Gamma-Glutamyl Transferase (γ GT)	Fibrinogen
Albumin	D-dimer
Cholesterol (total, LDL and HDL)	Prothrombin
Triglycerides	
Blood Urea nitrogen	
Creatinine	
Sodium (Na)	
Potassium (K)	
Calcium (Ca)	
Phosphorous (P)	
Magnesium (Mg)	
Glucose	
Lactate dehydrogenase (LDH)	

6.5.6 Pharmacokinetic assessments

A pre-selected number of sites will be involved to evaluate the repeated-dose PK of anakinra. The specific sites will include patients into the PK assessments until the required number of patients has been reached.

In addition to the patients enrolled at the PK sites, serum concentrations of IL-1Ra/anakinra will be determined at every study visit for all patients randomized into the study.

For all PK assessment, the exact date and time of blood sampling as well as the date and time of the IMP administrations before the PK sampling should be recorded in the CRF.

6.5.6.1 Sampling procedure

If the blood volume required for the planned lab assessments at any visit exceeds the maximum allowed blood volume collection according to limitations in relation to the body-weight of the patient the assessments for the study should be prioritized according to the specification in the laboratory manual.

6.5.6.1.1 Repeated-dose pharmacokinetics (pre-selected PK sites)

The repeated-dose PK of anakinra will be evaluated at 2 mg/kg/day (max 100 mg/day) and 4 mg/kg/day (max 200 mg/day). The planned target per dose level is 5 patients with disease onset <6 years, 5 patients with disease onset ≥6 to <16 years and 5 patients with a disease onset ≥16 years.

At the Week 12 visit, the IMP dose will be administered at the site and blood samples will be collected before the IMP administration and at 2, 4, 6 and 8 hours after IMP administration. The visit will be scheduled so that the IMP dose will be administered 24 hours (acceptance range 22-30 hours) after previous IMP dose the day before.

If exceeding maximum allowed blood volume for any patient, the samples at 4 and 6 hours may be replaced by a sample at 5 hours.

See Appendix 6 for a detailed description of the PK sampling procedure.

6.5.6.1.2 Anakinra serum concentrations (all sites)

Blood samples for determination of IL-1Ra/anakinra serum concentrations will be collected from all patients before IMP administration at all visits.

6.5.6.2 Bioanalytical method

Serum samples to determine the combination of endogenous IL-1Ra concentrations and anakinra (IL-1Ra/anakinra) will be analyzed by York Bioanalytical Solutions Limited using an immunoassay validated following the FDA Guidance for Industry on Bioanalytical Method Validation (May 2001), the EMA Guideline on bioanalytical method validation (2012) and Viswanathan CT et al Workshop/Conference Report AAPS Journal. 2007;9(1):E30-E42 in which IL-1Ra/anakinra is captured between a solid phase bound monoclonal antibody and polyclonal antibodies to anakinra.

6.5.6.3 Pharmacokinetic evaluation

6.5.6.3.1 Non-compartmental analysis

The serum anakinra concentration data from full PK sampling will be analyzed by non-compartmental analysis (NCA) using Phoenix WinNonlin. The following PK variables will be derived where applicable:

C_{max}	Observed maximum serum concentration of anakinra
t_{max}	Time to reach C_{max} following dose injection
AUC_{last}	Area under the serum concentration-time curve from time zero to the last quantifiable concentration (C_{last}), calculated by the linear up-log down trapezoidal method
AUC_{0-24h}	Area under the serum concentration-time curve during a dosage interval
V_d/F	Apparent volume of distribution following subcutaneous administration
$t_{½}$	Apparent terminal half-life, calculated by $0.693/\lambda_z$
CL/F	Apparent total clearance of drug from serum after subcutaneous administration

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

Samples with serum concentrations below the lower limit of quantitation (LLOQ) at early time-points will be treated as zero. Serum concentrations below the LLOQ appearing in the terminal samples will be omitted from the analysis.

6.5.6.3.2 Exploratory population PK analysis

All anakinra serum concentration data will be included in the population PK analysis. The objective is to explore the PK and the impact of covariates (e.g. body weight, age and dose level) on the PK of anakinra. The outcome may facilitate simulations of PK within the patient population(s).The population PK analysis may be reported separately.

6.5.6.3.3 Exploratory population PK/PD analysis

All anakinra serum concentration data will be included in the population PK/PD analysis. The objective of this analysis is to explore the relationship between anakinra exposure and selected efficacy endpoints e.g. CRP and safety endpoints. The outcome may facilitate simulations of concentration-effect relationships within the patient population(s). The population PK/PD analysis may be reported separately.

6.5.7 Exploratory laboratory assessments

If the blood volume required for the planned lab assessments at any visit exceeds the maximum allowed blood volume collection the assessments for the study should be prioritized according to the specification in the laboratory manual.

6.5.7.1 Exploratory inflammatory biomarkers

Several biomarkers of inflammation have been described to be indicative of the severity of rheumatic disease including JIA, SJIA, AOSD and RA and with potential value in the evaluation of response to treatment. Blood samples for determination of the exploratory inflammatory biomarkers IL-6, IL-18, calprotectin and neopterin will be collected before the first IMP administration at Day 1 and thereafter at following visits: Week 1, Week 2, Week 12 and, if applicable, at the Study Drug Discontinuation visit. The date and time of collection will be recorded in the CRF.

The sampling handling procedures, including the time of each blood 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 analyst, will be described in detail in the laboratory manual. The procedures and materials used, e.g., collection and storage tubes, will be described in the central manual.

6.5.7.2 Exploratory pharmacogenetic assessment

For patients consenting to pharmacogenetic assessment an additional blood sample will be collected at a suitable time point after randomization. This sample may be stored for up to 10 years and analyzed for genetic factors contributing to the patient's response to anakinra, safety and tolerability. Such genetic factors may include genes within the target pathway, or other genes believed to be related to the response to anakinra. Some genes currently insufficiently characterized or unknown may be understood to be important at the time of analysis. The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to anakinra.

The sample handling procedures, including the time of each blood sample collection, the time of placement into frozen storage (at the end of the sample workup) and the date of transfer or shipment of the samples will be documented in detail in the laboratory manual. The procedures and materials used, e.g., collection and storage tubes, as described in the laboratory manual.

7 Quality control and quality assurance

This study will be conducted in compliance with this protocol, study specific procedures, ARO SOPs, Sobi SOPs (for unblinding of suspected unexpected serious adverse reaction [SUSARs], statistical analysis and study reporting), the ICH GCP guideline, 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 subject 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 site will be performed periodically during the study, to help ensure compliance with the protocol, study specific procedures and applicable regulatory requirements. Source documents will be reviewed for verification of agreement with data in CRFs. All patient 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 a quality assurance audit by Sobi or its representatives, as well as inspection by appropriate regulatory agencies.

It is important that the investigator(s) and the(ir) relevant personnel are available during the monitoring visits and possible audits and that sufficient time is devoted to these processes.

8 Statistical plan

8.1 Determination of sample size

Assuming that the ACR30 response rate is 65 % in patients receiving anakinra and 25 % in placebo patients, 81 evaluable patients (54 anakinra and 27 placebo) are required to ensure 90 % power in demonstrating that anakinra improves clinical features of Still’s disease using a two-sided test at a 5 % significance level. These assumptions are based on the canakinumab and tocilizumab phase III clinical studies in SJIA where 65-85 % of active patients and 10-25 % of placebo patients responded at two weeks, as well as the Nordstrom study in AOSD where 50 % of anakinra treated patients were in remission after 4 weeks of treatment.

While the study is powered to demonstrate efficacy in the overall population, it will also be possible to estimate the treatment effect with reasonable precision in the sub-groups (< 16 years, ≥ 16 years of age at disease onset). With at least 30 patients in one of the sub-populations, the lower 95 % confidence limit for the odds ratio will exceed 1.0 when the

ACR30 (+ absence of fever) response rate is 65 % in patients receiving anakinra and 25 % in the placebo patients.

8.2 Definition of study populations

The following analysis sets/populations will be used for the statistical analyses:

ITT population: This population is the primary analysis population and will comprise all randomized patients, grouped according to randomization.

PP population: This population will comprise ITT patients that do not have any major protocol violations potentially influencing efficacy variables up to the Week 2 visit. Patients will be grouped according to treatment actually received and the correct stratification information.

Safety population: This population will comprise all patients who received at least one kit of investigational product and patients will be grouped according to the actual treatment received. Patients randomized to placebo that incorrectly received one kit of anakinra or more will be included in the corresponding anakinra group. Patients randomized to anakinra who incorrectly received only placebo kits will be included in the placebo group.

PK population: This population will comprise patients who received anakinra without any major protocol deviations with respect to administration of investigational product. All patients with at least one PK measurement will be included in the population to present anakinra plasma concentrations. Patients in the repeated dose PK population should not have any major protocol deviations with respect to the repeated dose PK measurements.

The ITT is the primary analysis population for the primary and secondary efficacy endpoints. The PP population will be used as a sensitivity analysis for the primary endpoint, the endpoints supporting the primary objective and the key secondary endpoints. The Safety population will be used for the safety analyses. The PK population will be used for evaluating the PK of anakinra.

8.3 Overall statistical and analytical plan

All details of the statistical analyses will be described in a separate study specific SAP which will be finalized before the clinical database is locked and the treatment code is unblinded. 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 comparison of primary interest is between anakinra (2 mg/kg and 4 mg/kg combined) and placebo. The two dose groups of anakinra will be evaluated descriptively.

All statistical tests will be two-sided and performed using a 5 % significance level if not stated otherwise. Results will be presented as the estimated value for each treatment group, anakinra (2 mg/kg and 4 mg/kg combined) and placebo, the estimated difference between groups, the associated two-sided 95 % confidence interval and p-value. The estimated value for each dose group of anakinra and the associated two-sided 95 % confidence interval will

also be presented. For continuous secondary endpoints, if assumption of normal distribution seems to be violated for a specific endpoint, corresponding non-parametric methods will be used to check the robustness of the results.

Continuous variables will be summarized using the number of patients, the mean, the standard deviation, the median, the minimum and the maximum value. Categorical variables will be summarized using frequency counts and percentages.

The laboratory data evaluation will be based on the results from the central laboratory.

8.3.2 Demographics and baseline characteristics

Demographic data and baseline characteristics will be presented using descriptive statistics.

8.3.3 Analysis related to primary objective

The primary endpoint is ACR30 response at Week 2 with absence of fever attributable to the disease during the 7 days preceding Week 2.

In order to evaluate the ACR30 response, the relative change from baseline to Week 2 will be calculated for the following variables:

1. Physician global assessment of disease activity (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 CHAQ/SHAQ
6. CRP (mg/L) results from central laboratory

If the change from baseline in at least 3 out of these 6 variables is an improvement of ≥ 30 % and no more than 1 of the 6 variables has a worsening of > 30 %, and absence of fever during the 7 days preceding Week 2 the patient will be deemed a responder. Patients who have discontinued study drug prior to Week 2 will be treated as non-responders in the analysis.

The null and alternative hypotheses with respect to the primary efficacy endpoint are defined as:

H_0: OR = 1

H_A: OR ≠ 1

ACR30 response will be analyzed using a logistic regression model with treatment, age at onset of disease (< 16 years, ≥ 16 years) and glucocorticoid use (yes, no) as explanatory variables. The estimated probability of ACR30 response in each treatment group and 95 % confidence interval will be presented. The estimated odds ratio of anakinra (combined dose groups) to placebo, the corresponding 95 % confidence interval and the p-value from the model will be presented.

8.3.4 Analysis related to secondary endpoints supporting the primary objective

To further support the primary endpoint, the following secondary endpoints will be analyzed:

- ACR30 response at Week 1 with absence of fever during 24 hours preceding Week 1.
- ACR50, ACR70 and ACR90 response at Week 1 and Week 2 with absence of fever attributable to the disease during 24 hours before Week 1 and 7 days preceding Week 2.
- Response in the **individual components** of ACR at Week 1 and Week 2. Response is defined as an improvement of ≥ 30%, 50%, 70% and 90% from baseline.
    - 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)
    - CRP (mg/L)
- Absence of fever during the 7 days preceding Week 2.

ACR30, ACR50, ACR70 and ACR90, with absence of fever in the preceding 24 hours at Week 1 and ACR50, ACR70 and ACR90, with absence of fever in the preceding 7 days, at Week 2 will be analyzed using logistic regression models with treatment, age at onset of disease (< 16 years, ≥ 16 years) and glucocorticoid use (yes, no) as explanatory variables. Patients who have discontinued study drug will be treated as non-responders in the analyses.

The response in the individual components of ACR at Week 1 and Week 2 will be analyzed using logistic regression models with treatment, age at onset of disease (< 16 years, ≥ 16 years) and glucocorticoid use (yes, no) as explanatory variables. Patients who have discontinued study drug prior to Week 1 will be treated as non-responders in the analyses of the individual components of ACR at Week 1 and patients who have discontinued study drug prior to Week 2 will be treated as non-responders in the analyses of the individual components of ACR at Week 2.

The absence of fever at Week 2 will be analyzed using a logistic regression model with treatment, age at onset of disease (< 16 years, ≥ 16 years) and glucocorticoid use (yes, no) as explanatory variables. Patients who have discontinued study drug prior to Week 2 will be treated as having a presence of fever in the analysis.

The response in the individual components of ACR at Week 1 and Week 2 will also be presented descriptively by using the number of responders/non responders/non responders due study drug discontinuation. In this presentation non responders who have remained on study drug in the study to the week of interest will be further classified into two categories: no response defined as < 30% improvement to < 30% worsening and worsening of response defined as at least 30% worsening from baseline.

8.3.5 Analysis related to key secondary objective

To evaluate the key secondary objective, the following endpoints will be analyzed:

- Absence of fever during the 24 hours preceding Week 1.

- Change from baseline in physician global assessment of disease activity (VAS) at Week 1.
- Change from baseline in patient/parent global assessment of overall well-being (VAS) at Week 1.
- Change from baseline in CRP at Week 1.

The absence of fever at Week 1 will be analyzed using a logistic regression model with treatment, age at onset of disease (< 16 years, ≥ 16 years) and glucocorticoid use (yes, no) as explanatory variables. Patients who discontinued study drug prior to Week 1 will be treated as having a presence of fever in the analysis. The estimated probability of absence of fever in each treatment group, the estimated odds ratio of anakinra to placebo, the corresponding 95 % confidence interval and the p-value from the model will be presented.

The three continuous endpoints; change in CRP, change in physician's global assessment of disease activity and change in patient/parent global assessment of overall well-being, will be analyzed using a mixed model repeated measurement with the measurements on the individual timepoints (i.e. Baseline and Week 1 or if the Week 1 visit is not performed due to Study drug discontinuation before Week 1 the Study drug Discontinuation visit will be used) as responses and with treatment, age at onset of disease (< 16 years, ≥ 16 years) and glucocorticoid use (yes, no), visit and treatment-visit interaction as fixed effects. For the comparison between anakinra (combined dose groups) and placebo for each endpoint, the estimated difference, the associated 95 % confidence interval and the p-value from the model will be presented.

8.3.6 Analysis related to secondary objectives

8.3.6.1 Sustained efficacy in ACR- responders

To evaluate sustained efficacy in patients that initially responded to treatment at Week 2, the ACR responses at Week 4, Week 8 and Week 12 will be compared to the response at Week 2. For patients that met the ACR30, ACR50, ACR70 or ACR90 response criteria, with absence of fever in the preceding 7 days at Week 2, the number and percentage that still meet the corresponding ACR response criteria at Week 4, Week 8 and Week 12 will be presented.

In addition, sustained efficacy will be presented in relationship to glucocorticoid tapering.

8.3.6.2 Efficacy of anakinra during 12 weeks treatment

The number and percentage of patients with ACR30, ACR50, ACR70 or ACR90 response with absence of fever (during 24 hours before Week 1 or 7 days preceding Week 2, Week 4, Week 8 and Week 12) at Week 1, Week 2, Week 4, Week 8 and Week 12 will be presented.

Each ACR (+ absence of fever) response will also be tabulated and presented graphically in a stacked bar plot, reflecting the proportions of patients in each treatment group that:

- Remain in the study on study drug at the applicable timepoint and are ACR (+ absence of fever) responders.
- Remain in the study on study drug at the applicable timepoint and are non-responders.
- Discontinued study drug before the applicable timepoint and did fulfill the escape criteria.

- Discontinued study drug before the applicable timepoint due to progressive disease (except those that did fulfill the escape criteria).
- Discontinued study drug before the applicable timepoint due to lack of efficacy.
- Discontinued study before the applicable timepoint due to other reasons than lack of efficacy and progressive disease.

The number and percentage of patients with absence of rash (during 24 hours before Week 1 or 7 days preceding Week 2, Week 4, Week 8 and Week 12) at Week 1, Week 2, Week 4, Week 8 and Week 12 will be presented.

The absolute values and the changes from baseline in CRP, Hb, platelet count and ferritin at Week 1, Week 2, Week 4, Week 8 and Week 12 will be presented by descriptive statistics.

The absolute values and the changes from baseline in patient/parent global assessment of disease related pain (VAS) at Week 1, Week 2, Week 4, Week 8 and Week 12 will be presented by descriptive statistics.

8.3.6.3 Time to study drug discontinuation

The time to study drug discontinuation will be analyzed using a stratified log-rank test, with age at onset of disease (< 16 years, ≥ 16 years) and glucocorticoid use (yes, no) as stratification factors. Based on this model, the estimated hazard ratio of anakinra (combined dose groups) versus placebo and the 95% confidence interval will be presented.

The time to study drug discontinuation due to lack of efficacy or progressive disease will be analyzed using a stratified log-rank test, with age at onset of disease (< 16 years, ≥ 16 years) and glucocorticoid use (yes, no) as stratification factors. Study drug discontinuation for other reasons than lack of efficacy or progressive disease will be censored at the time of study drug discontinuation in the analysis. Based on this model, the estimated hazard ratio of anakinra (combined dose groups) versus placebo and the 95% confidence interval will be presented.

Kaplan Meier curves will be generated for anakinra (combined dose groups), anakinra 2 mg/kg, anakinra 4 mg/kg and placebo.

8.3.6.4 Glucocorticoid tapering

The number and percentage of patients who have initiated tapering of glucocorticoids at Week 12 will be presented.

The number and percentage of patients that have been able to decrease the glucocorticoid dose with at least 50 % from baseline to Week 12 will be presented.

For patients that initiated tapering the percentage decrease of glucocorticoid dose at Week 12 compared to baseline will be presented by descriptive statistics.

8.3.7 Analysis of safety and tolerability data

8.3.7.1 Adverse events

All adverse events will be coded using MedDRA.The number and percentage of patients with at least one adverse event recorded at each level of summarization will be summarized in

frequency tables by treatment, system organ class, preferred term, relation to investigational product and maximum severity. Percentages will be based on the number of patients in the safety population for the specific treatment group.

The number and percentage of patients with at least one SAE, including death, at least one non-SAE, and adverse events leading to investigational product discontinuation will also be tabulated by system organ class and preferred term.

The number and percentage of patients with MAS will be tabulated.

8.3.7.2 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.

8.3.7.3 Vital signs

Weight, blood pressure and heart rate will be presented over time by descriptive statistics.

8.3.7.4 Physical examination

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

8.3.7.5 Anti-drug antibodies

The number and percentage of patients with ADA and NAb and cross-reactivity at baseline, Week 1, Week 2, Week 4, Week 8 and Week 12 will be presented. ADA titers at baseline, Week 2, Week 4, Week 8 and Week 12 will be summarized by descriptive statistics.

Occurrence and titer levels of ADA in relation to AEs will be presented.

Occurrence and titer levels of ADA, including Nab in relation to ACR response and CRP will be presented.

8.3.8 Analysis of pharmacokinetics

The PK variables will be presented by descriptive statistics by dose and age group.

8.3.9 Analysis related to productivity objective

The number of days off school or work due to Still’s disease during the study will be presented for each visit by descriptive statistics.

8.3.10 Analysis related to exploratory objectives

8.3.10.1 Inactive disease

The number and percentage of patients with inactive disease at Week 12 will be presented.

8.3.10.2 JADAS27

The change from baseline in JADAS27 at Week 2, and Week 12 will be presented by descriptive statistics.

8.3.10.3 Population PK/PD analysis

See section 6.5.6.3.

8.3.10.4 Population PK analysis

See section 6.5.6.3.

8.3.10.5 Inflammatory biomarkers

The change from baseline in IL-6, IL-18, calprotectin and neopterin at Week 1, Week 2 and Week 12 will be presented by descriptive statistics.

8.3.11 Interim analysis

No interim analysis of efficacy data is planned. An independent DSMB will review safety data on an ongoing basis (details will be specified in a separate DSMB charter).

8.3.12 Multiple comparison/multiplicity

A multiple testing procedure, combining fixed sequence testing and Hochberg procedure, will be used to ensure an overall significance level of 0.05.

A fixed sequential testing will apply for the primary and the key secondary endpoints, i.e., the key secondary endpoints will only be tested if the null hypothesis related to the primary endpoint is rejected. The Hochberg procedure will then be applied for the three key secondary endpoints.

8.3.13 Exploratory subgroup analyses

Supportive analyses of the primary endpoint in each subgroup defined by the stratification variables age at onset of disease (< 16 years, ≥ 16 years of) and glucocorticoid use at inclusion (yes, no) , as well as body weight (≤50 kg, > 50 kg), sex and race will be performed in order to examine the consistency of the treatment effect. For each subgroup, the estimated probability of ACR30 (+ absence of fever) response in each treatment group, the estimated odds ratio of anakinra to placebo, and the corresponding 95 % confidence interval will be presented.

Exploratory subgroup analyses of the key secondary endpoints will also be performed for subgroups, including those defined by the stratification variables age at onset of disease (< 16 years, ≥ 16 years) and glucocorticoid use at inclusion (yes, no), as well as body weight (≤50 kg, > 50 kg), sex and race.

Further subgroup analyses may be defined in the statistical analysis plan.

No formal hypothesis tests will be performed.

8.4 Data standards

Collection of data should be performed in the 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 SDTM format.

8.4.1 Handling of missing data

For the primary endpoint ACR30 the following imputation will be used:

- Patients that discontinue study drug prior to Week 2 will be set to non-responders.
- For patients with missing information in any of the ACR30 components, that specific component will be set to no change. For patients with missing information on fever, the patients will be treated as having a presence of fever.

For the key secondary endpoints the following imputation will be used:

- Patients who have missing information on fever during 24 hours preceding Week 1 will be treated as having a presence of fever in the analysis.
- For the continuous key secondary endpoints repeated measures models will be used to handle missing data.

For the other secondary endpoints no imputation will be performed, i.e., all presentations will be based on observed cases.

8.4.2 Sensitivity analyses

The primary efficacy endpoint and the key secondary endpoints will be analysed using the PP population as described in Section 8.3.4 and 8.3.5.

For patients who discontinue study drug before Week 2, a Study Drug Discontinuation visit should be performed before standard of care treatment is initiated and a Week 2 visit should preferably also be performed (if the Study Drug Discontinuation visit is performed within 3 days prior to the Week 2 visit, the scheduled Week 2 visit should be omitted). As a sensitivity analysis, for both the primary analysis of ACR30 (+ absence of fever) at Week 2 and the supportive analysis of ACR30 (+ absence of fever) at Week 1 a comparison of treatment groups including patients who have discontinued study drug will be performed using the ACR assessment closest to Week 2 or Week 1 respectively. However, study drug discontinuation due to progressive disease will be treated as non-responders.

A tipping point analysis will also be performed for the primary efficacy endpoint. For patients where no plausible assumption can be made depending on the reason for the missing outcome (e.g. patients that discontinue study drug due to lack of efficacy and progressive disease), the number of responders that can potentially be observed among patients with a missing ACR30 outcome at Week 2 in the anakinra group versus the placebo group will be presented in a basic tipping point display. Pairs of number of responders in the anakinra and placebo group that lead to statistical significance will be marked and pairs that lead to non-significance will not be marked. The tipping point boundary is the staircase region between marked and unmarked rectangles (51). This analysis will be repeated allowing the assumptions to vary for all patients with a missing ACR30 outcome at Week 2, except those

patients who have discontinued study drug and fulfilled the escape criteria who will still be treated as non-responders.

9 Data collection, handling and record keeping

9.1 Case report form

A CRF is required and should be completed for each included patient. In this study electronic CRF will be used. The completed original CRFs 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.

It is the responsibility of the investigator to ensure completion and to review and approve all CRFs. CRFs must be signed electronically by the investigator. These signatures serve to attest that the information contained on these CRFs is correct. At all times, the investigator has final responsibility for the accuracy and authenticity of all clinical and laboratory data entered on the CRFs.

9.2 Patient diary

A patient diary will be used by the patient during the treatment period to record any occurrence of rash, time point of any fever episode together with the actual body temperature and timepoint of all IMP administrations. The patient or patient caregiver will be instructed on how to complete the diary at their first visit. The diary will be reviewed at each visit for completeness.

9.3 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 CRFs must match those charts. In some cases, a portion of the source documents for a given patient may be the CRF or patient diary.

In this study, the following could be recorded as source data directly in the CRFs:

- Number of joints with active arthritis
- Number of joints of limitation of motion
- Joint count for JADAS27
- Morning stiffness
- Absenteeism from school or work

In this study, the following are recorded as source data directly in a patient diary:

- Fever
- Rash
- IMP administration

9.4 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 the study is conducted in accordance with the procedures and evaluations described in this protocol and must protect the rights, safety, and welfare of subjects. The investigator should not implement any deviation from, or changes of, the protocol, unless it is necessary to eliminate an immediate hazard to study subjects.

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 that DCRI is notified. DCRI will follow up with the investigator, as applicable, to assess the deviation and the possible impact to the safety and/or efficacy of the subject to determine subject continuation in the study.

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

The investigator will also assure that deviations are reported and documented in accordance with IRB/REB requirements. Any applicable regulatory requirements will be the responsibility of Sobi.

9.5 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 before breaking of the blind and 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. Medical coding will be performed by DCRI and approved by Sobi before database lock. AEs, diagnoses from Medical History and procedures will be classified according to MedDRA. Previous and Concomitant Medications will be coded using the latest version of the World Health Organisation Drug Dictionary (WHODRUG).

A reconciliation of the clinical and safety database will be performed prior to database lock.

9.6 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 according to local regulations or as specified in the Clinical Trial Agreement.

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.

10 End of study

The end of this study is defined as the date of 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 within 30 days. All study materials must be collected at sites and all the CRFs completed to the greatest extent possible.

12 Dissemination and publication of results

Sobi will register the study and post study results regardless of outcome on a publicly accessible website in accordance with applicable laws and regulations, e.g., www.clinicaltrials.gov.

The results of this study will be published within 1 year after the product has received marketing approval. If drug development is discontinued before approval, the results will be published within 1 year after such discontinuation.

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 (57).

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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Appendix 1 Diagnose criteria

Onset of the disease <16 years of age

Adapted ILAR criteria (52**)**
• 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:
a. Psoriasis or a history of psoriasis in the patient or first degree relative
b. Arthritis in an HLA-B27 positive male beginning after the 6th birthday
c. 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
d. The presence of IgM rheumatoid factor on at least 2 occasions at least 3 months apart

Onset of the disease ≥16 years of age

Yamaguchi criteria (53**)**
Classification of AOSD requires 5 or more criteria including 2 or more major criteria.[$] 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* 4. Leukocytosis (10,000/mm^3 or greater) including 80% more of granulocytes **Minor criteria:** 1. Sore throat 2. Lymphadenopathy and/or splenomegaly[a] 3. Liver dysfunction[b] 4. Negative RF and negative ANA[c] **Exclusions:** I. Infections (especially, sepsis and infectious mononucleosis). II. Malignancies (especially, malignant lymphoma) III. Rheumatic diseases (especially, polyarteritis nodosa and rheumatoid vasculitis with extraarticular features)

* Macular or maculopapular nonpruritic salmon-pink eruption usually appearing during fever.

[a] Lymphadenopathy is defined as recent development of significant lymph node swelling, and splenomegaly is confirmed on palpation or by an echogram.

[b] Liver dysfunction is defined as an abnormally elevated level of transaminases and/or lactate dehydrogenase, 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.

[c] 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.

[$] All criteria are applicable only in absence of other clinical explanations.

Appendix 2 Guidance for MAS diagnosis

Characteristic clinical features of macrophage activation syndrome (MAS) are high non-remitting fever, hepatosplenomegaly, generalized lymphadenopathy, central nervous system dysfunction, and hemorrhagic manifestations. Typical laboratory abnormalities include pancytopenia, increased levels of ferritin, liver enzymes, lactate dehydrogenase, triglycerides, D-dimers, and soluble CD25 (sCD25), and decreased fibrinogen level. A typical histopathologic feature of MAS is the accumulation of well-differentiated macrophages exhibiting hemophagocytic activity in bone marrow biopsy specimen or aspirates (3, 56).

In patients <16 years old with systemic juvenile idiopathic arthritis the following laboratory classification criteria have been proposed (3), which can be used as a guidance, but the diagnosis of MAS will be made by the investigator based on the patients overall clinical signs and symptoms, including laboratory changes over time.

2016 Classification of macrophage activation syndrome in systemic juvenile idiopathic arthritis (3)

A febrile patient with known or suspected systemic juvenile idiopathic arthritis is classified as having macrophage activation syndrome if the following criteria is met:

- Ferritin >684 ng/ml

and any 2 of the following:

- Platelet count ≤181 x 10^9/liter
- Aspartate aminotransferase >48 units/liter
- Triglycerides >156 mg/dl
- Fibrinogen ≤360 mg/dl

Laboratory abnormalities *should not be otherwise explained by the patient's condition*, such as, for example, concomitant immune-mediated thrombocytopenia, infectious hepatitis, visceral leishmaniasis, or familial hyperlipidemia.

Appendix 3 Dosing instructions

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
43-47	90	1.9-2.1
≥48	100	≤2.1

Dose 4 mg/kg/day (max 200 mg/day)

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
47-48	190	4.0
≥49	200	≤4.1

Appendix 4 Guidance for glucocorticoid tapering

Tapering of the glucocorticoid 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 2 visit and if the patient has reached at least ACR50 response with no fever in the preceding 7 days.

	Body weight						
	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 2)	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 Schedule of assessments

Assessments - page 1(2)	Screening visit (optional)	**Visit 1**	**Tel f-up**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Tel f-up**	Study Drug Discontinuation visit
		Day 1	Day 4_{Tel} (+/-2 days)	Week 1 (+2 days)	Week 2 (+2 days)	Week 4 (+/-2 days)	Week 8 (+/-2 days)	Week 12 (+/-2 days)	Week 16_{Tel} (+5 days)	
				Day 8	Day 15	Day 29	Day 57	Day 85	Day 113	
Informed consent	X	X								
Eligibility criteria	X	X								
Randomization		X								
Medical history & Demographics		X								
Vital signs										
Blood pressure		X		X	X	X	X	X		X
Heart rate		X		X	X	X	X	X		X
Body weight		X		X	X	X	X	X		X
Height		X								
Physical examination		X		X	X	X	X	X[5]		X[5]
ECG		X								
Prior and/or concomitant medication		X		X	X	X	X	X	X	X
Blood Collection										
Laboratory assessments (incl. CRP)		X		X[3]	X[7]	X	X	X		X[6]
Immunogenicity assessments		X		X	X	X	X	X		X
IL-1Ra/anakinra serum concentration		X		X	X	X	X	X		X
Inflammatory biomarkers (IL-6, IL-18, calprotectin, neopterin)		X		X	X			X		X
Exploratory pharmacogenetics markers		X[4]								

[1] Assessment performed by blinded, trained and independent joint assessor.
[2] A diary will be used for daily recordings of fever episodes, patient´s assessment of rash and time point of IMP administrations.
[3] For patients with a body weight <15 kg hematology and coagulation samples should not be repeated at visit Week 1, if not clinically indicated, in order to preserve blood volume.
[4] Any time after randomization.
[5] For evaluating inactive disease, the following signs will specifically be recorded: rash, serositis, splenomegaly, hepatomegaly and generalized lymphadenopathy.
[6] All laboratory assessments should be performed also for patients <15 kg body weight .
[7] If the Week 2 visit is peformed after the Study Drug Discontinuation visit, central lab should also be collected at the Week 2 visit, if not exceeding the maximum allowed blood volume collection according to limitations in relation to the body-weight of the patient.

Assessments - page 2(2)	Screening visit (optional)	**Visit 1**	**Tel f-up**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Tel f-up**	Study Drug Discontinuation visit
		Day 1	Day 4_{Tel} (±2 days)	Week 1 (+2 days)	Week 2 (+2 days)	Week 4 (+/-2 days)	Week 8 (+/-2 days)	Week 12 (+/-2 days)	Week 16_{Tel} (+ 5 days)	
				Day 8	Day 15	Day 29	Day 57	Day 85	Day 113	
Efficacy Assessments										
Physician global assessment of disease activity (VAS)		X		X	X	X	X	X		X
Patient/parent global assessment of overall well-being (VAS)		X		X	X	X	X	X		X
Number of joints with active arthritis[1]		X		X	X	X	X	X		X
Number of joints with limitation of motion[1]		X		X	X	X	X	X		X
Physical function (CHAQ or SHAQ)		X		X	X	X	X	X		X
Global assessment of the patient disease related pain (VAS)		X		X	X	X	X	X		X
Morning stiffness								X		X
Completion of diary[2]					X					
Recording of absenteeism from school or work				X	X	X	X	X		X
Adverse events		X	X	X	X	X	X	X	X	X
IMP administration (at site)		X								
IMP dispensing		X		X	X	X	X			

[1] Assessment performed by blinded, trained and independent joint assessor.
[2] A diary will be used for daily recordings of fever episodes, patient´s assessment of rash and time point of IMP administrations.
[3] For patients with a body weight <15 kg hematology and coagulation samples should not be repeated at visit Week 1, if not clinically indicated, in order to preserve blood volume.
[4] Any time after randomization.
[5] For evaluating inactive disease, the following signs will specifically be recorded: rash, serositis, splenomegaly, hepatomegaly and generalized lymphadenopathy.
[6] All laboratory assessments should be performed also for patients <15 kg body weight.
[7] If the Week 2 visit is peformed after the Study Drug Discontinuation visit, central lab should also be collected at the Week 2 visit, if not exceeding the maximum allowed blood volume collection according to limitations in relation to the body-weight of the patient.

Appendix 6 Schedule of repeated PK assessments Week 12

The assessments described below are **additional** assessments for patient enrolled to the repeated-dose PK sampling. All patients that do the repeated-dose PK assessments are also assessed according to schedule of assessments in Appendix 5.

	Visit 1	Tel f-up	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Tel f-up
	Day 1	Day 4_{Tel} (+/-2 days)	Week 1 (+2 days)	Week 2 (+2 days)	Week 4 (+/- 2 days)	Week 8 (+/- 2 days)	Week 12 (+/- 2 days)	Week 16_{Tel} (+/- 2 days)
			Day 8	Day 15	Day 29	Day 57	Day 85	Day 113
Blood collection - repeated-dose pharmacokinetics								
Pre-dose							X	
2h after dose							X	
4h after dose							X[1]	
6h after dose							X[1]	
8h after dose							X	
IMP administration (at site)							a, X	

[1]If exceeding maximum allowed blood volume for any patient, the samples at 4 and 6 hours may be replaced by a sample at 5 hours
a No administration of IMP at home before the visit

Appendix 7 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 8 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 randomization, this question will be collected as a part of the CHAQ (see Appendix 9).

For patients ≥18 years of age at randomization, this question will be collected as a part of the SHAQ (see Appendix 9).

Appendix 9 Physical function (CHAQ/SHAQ)

Parent proxy reporting CHAQ for children <18 years old:

anaSTILLs Sobi SUBJECT ID:_____ DATE COMPLETED:_____ 1–2

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	☐

*I **confirm** that the information on this module is accurate.*	Patient's initials:	Date:
Investigator's name:	Staff's initials:	Date:

anaSTILLs Sobi SUBJECT ID:_____ DATE COMPLETED:_____ 2–2

	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

*I **confirm** that the information on this module is accurate.*	Patient's initials:	Date:
Investigator's name:	Staff's initials:	Date:

SHAQ for patients ≥18 years old:

anaSTILLs sobi SUBJECT ID:_____ **HAQ 1–6**

HEALTH ASSESSMENT QUESTIONNAIRE

Was assessment completed? **No** ❑ *(If **no**, give reason in comments)*
Yes ❑

Date completed: _____
day/month/year

In this section we are interested in learning how your illness affects your ability to function in daily life.

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

DRESSING & GROOMING **Are you able to:**	**Without ANY Difficulty**	**With SOME Difficulty**	**With MUCH Difficulty**	**UNABLE To Do**
- 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?	❑	❑	❑	❑

Comments:

*I **confirm** that the information on this module is accurate.*	Patient's initials:	Date:
Investigator's name:	Staff's initials:	Date:

English for USA - V11

anaSTILLs sobi SUBJECT ID:_____ HAQ 2-6

HEALTH ASSESSMENT QUESTIONNAIRE

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

WALKING Are you able to:	Without ANY Difficulty	With SOME Difficulty	With MUCH Difficulty	UNABLE To Do
- Walk outdoors on flat ground?	❑	❑	❑	❑
- Climb up five steps?	❑	❑	❑	❑

Please check any AIDS or DEVICES that you usually use for any of the activities on pages 1 and 2:

❑ Cane ❑ Crutches ❑ Built up or special utensils

❑ Walker ❑ Wheelchair ❑ Special or built up chair

❑ Devices used for dressing

❑ Other *(specify)* _____

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

❑ Dressing and Grooming ❑ Arising ❑ Eating ❑ Walking

*I **confirm** that the information on this module is accurate.*	Patient's initials:	Date:
Investigator's name:	Staff's initials:	Date:

English for USA - V11

anaSTILLs sobi SUBJECT ID:_____ HAQ 3-6

HEALTH ASSESSMENT QUESTIONNAIRE

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

HYGIENE **Are you able to:**	**Without ANY Difficulty**	**With SOME Difficulty**	**With MUCH Difficulty**	**UNABLE To Do**
- 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 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?	❑	❑	❑	❑

*I **confirm** that the information on this module is accurate.*	Patient's initials:	Date:
Investigator's name:	Staff's initials:	Date:

English for USA - V11

anaSTILLs sobi SUBJECT ID:_____ HAQ 4-6

HEALTH ASSESSMENT QUESTIONNAIRE

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

ACTIVITIES Are you able to:	Without ANY Difficulty	With SOME Difficulty	With MUCH Difficulty	UNABLE To Do
- 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 the activities (hygiene, reach, gripping & opening things, errands & chores):

❑ Raised toilet seat
❑ Bathtub bar
❑ Bathtub seat
❑ Long-handled appliances for reach
❑ Jar opener *(for jars previously opened)*
❑ 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

*I **confirm** that the information on this module is accurate.*	Patient's initials:	Date:
Investigator's name:	Staff's initials:	Date:

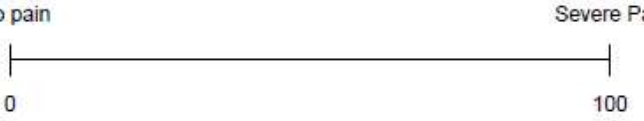
English for USA - V11

anaSTILLs sobi SUBJECT ID:_____ HAQ 5-6

HEALTH ASSESSMENT QUESTIONNAIRE

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

Place a vertical (|) mark through the line to indicate the severity of the pain.



*I **confirm** that the information on this module is accurate.*	Patient's initials:	Date:
Investigator's name:	Staff's initials:	Date:

English for USA - V11

anaSTILLs sobi SUBJECT ID:_____ HAQ 6-6

HEALTH ASSESSMENT QUESTIONNAIRE

Considering all the ways your illness affects you, place a vertical (|) mark through the line to indicate how well you are doing.

*I **confirm** that the information on this module is accurate.*	Patient's initials:	Date:
Investigator's name:	Staff's initials:	Date:

English for USA - V11

Appendix 10 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 randomization, this question will be collected as a part of the CHAQ (see Appendix 9).

For patients ≥18 years of age at randomization, this question will be collected as a part of the SHAQ (see Appendix 9).

Appendix 11 Joint count JADAS27

The JADAS included the following 4 measures: physician global assessment of disease activity, patient/parent global assessment of well-being, active joint count and CRP.

Joint count

The JADAS27 includes the following joints: cervical spine, elbows, wrists, metacarpophalangeal joints (from first to third), proximal interphalangeal joints, hips, knees, and ankles (48).

Joint count		**Left**	**Right**
Elbow			
Wrist			
MCP	1		
	2		
	3		
PIP	1		
	2		
	3		
	4		
	5		
Knee			
Hips			
Ankles			
Cervical spine			NA
Total			

Appendix 12 Additional Protocol Signatures

Sponsor's Clinical Program Leader

Sponsor's Statistician