Study Protocol

Protocol number:	Sobi.ANAKIN-401
NCT number:	03002974
Study title:	A randomized, double-blind, active-control, multicenter, efficacy and safety study of 2 dose levels of subcutaneous anakinra compared to intramuscular triamcinolone in the treatment of acute gouty arthritis, followed by an extension period of up to 2 years. The anaGO study.
Version:	Version 6.0, Amended protocol including amendment 4
Date:	24 January 2018

A randomized, double-blind, active-control, multicenter, efficacy and safety study of 2 dose levels of subcutaneous anakinra compared to intramuscular triamcinolone in the treatment of acute gouty arthritis, followed by an extension period of up to 2 years

The anaGO study

Amended Protocol of the Study Sobi.ANAKIN-401

IND No: 003611

Type of Study: Therapeutic exploratory Phase 2

Original protocol date: 9 September 2016

Amendment no 1: 13 December 2016

Amendment no 2: 5 May 2017

Amendment no 3: 8 September 2017

Amendment no 4: 24 January 2018

Investigator statement

I have read the protocol entitled "A randomized, double-blind, active-control, multicenter, efficacy and safety study of 2 dose levels of subcutaneous anakinra compared to intramuscular triamcinolone in the treatment of acute gouty arthritis followed by an extension period of up to 2 years" and the accompanying current investigator's brochure and summary of product characteristics. I agree to conduct the clinical investigation in compliance with the Protocol, Version 6.0, 24 January 2018, the International Council for Harmonisation (ICH) harmonised guideline E6(R2): Guideline for Good Clinical Practice, applicable regulatory/government regulations, and in accordance with the latest revision of the Ethical Principles for Medical Research Involving Human Subjects (the Declaration of Helsinki). I will not implement any changes to study procedures or conduct without prior approval from the sponsor and, when applicable, the Institutional Review Board and Regulatory Authority.

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

Signature of Principal Investigator	Date

Printed name of Principal Investigator

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1 Synopsis

STUDY IDENTIFIERS

Title of study:	A randomized, double-blind, active-control, multicenter, efficacy and safety study of 2 dose levels of subcutaneous anakinra compared to intramuscular triamcinolone in the treatment of acute gouty arthritis, followed by an extension period of up to 2 years
Clinical study number:	Sobi.anakin-401
Investigators:	Kenneth G. Saag, MD, MSc, Principal Coordinating Investigator University of Alabama 2000 6th Ave S FL 3 Birmingham, AL 35233, USA Approximately 35 additional investigators
Study center(s):	Approximately 35 centers in US
Type of study:	Therapeutic Exploratory Phase 2

STUDY OBJECTIVES

Primary objective:	To evaluate the efficacy of anakinra compared to triamcinolone acetonide with respect to patient-assessed pain intensity in the treatment of a gouty arthritis flare (based on patients' first flare treated in the study).
Secondary objective(s):	To evaluate the primary and the secondary endpoints supporting primary objective for the 2 different anakinra dose groups (100 and 200 mg) compared to triamcinolone (40 mg) in the treatment of the first gouty arthritis flare. To evaluate the time to onset of effect, time to response, time to pain resolution, time to rescue medication, physician's assessment of global response and clinical signs, patient´s assessment of global response, inflammatory biomarkers and safety of anakinra compared to triamcinolone in the treatment of the first gouty arthritis flare both for the combined anakinra group (100 and 200 mg) and the 2 different anakinra dose groups. To evaluate the primary and secondary endpoints and safety of the combined anakinra group (100 and 200 mg), the 2 different anakinra dose groups and triamcinolone in the treatment of subsequent flares. Subsequent flares are flares occurring after the first flare in the study and within 52 weeks of randomization of the last randomized patient in the study. However the extension will be a maximum of two years (104 weeks) for the individual patient in the study.
Exploratory objective(s):	To explore the effect of anakinra on health related quality of life (HRQL) and health care resource utilization in the treatment of gouty arthritis.

	To explore the effect of anakinra on exploratory inflammatory biomarkers in serum in the treatment of gouty arthritis flares. To analyze for genetic factors potentially contributing to the patient's response to anakinra, safety and tolerability.
STUDY ENDPOINTS	
Primary endpoint:	Change in patient-assessed pain intensity from baseline to 24-72 hours (average of the assessments performed at 24, 48 and 72 hours). Patient will score their pain intensity in the joint most affected at baseline (i.e., the index joint) on a 0-100 mm visual analogue scale (VAS), ranging from no pain (0) to unbearable pain (100).
Secondary endpoint(s) supporting primary objective	Change from baseline in patient-assessed pain intensity in the index joint as measured by VAS and a 5-point Likert scale at 6, 12, 18, 24, 36, 48, 72 hours and Days 5, 6, 7 and 8.
Secondary endpoint(s):	The following endpoints will be assessed for the first flare and subsequent flares. All comparisons versus baseline (pre-dose measurement at Visit 1) will be made against the baseline of the first and subsequent flares, respectively. • Time to onset of effect (≥20% change from baseline pain intensity on VAS). • Time to response (≥50% change from baseline pain intensity on VAS). • Response (≥50% change from baseline on VAS) at 24, 48 and 72 hours, Day 8 and Day 15 (Yes/No). • Resolution of pain (defined as <10 mm on VAS) at 72 hours, Day 8 and Day 15 (Yes/No). • Time to resolution of pain (defined as <10 mm on VAS). • Time to intake of rescue medication from first IMP administration. • Type and number of occasions of intake of rescue medication from first IMP administration to Day 8. • Physician's assessment of global response to treatment (5-point Likert scale) at 72 hours, Day 8 and Day 15. • Physician's assessment of clinical signs (index joint tenderness, swelling and erythema) at 72 hours, Day 8 and Day 15. • Patient´s assessment of global response to treatment (5-point Likert scale) at 72 hours, Day 8 and Day 15. • Change from baseline in the inflammatory biomarkers CRP and SAA at 72 hours, Day 8 and Day 15. • Safety variables (AEs, vital signs, laboratory safety assessments).

- Serum concentration of IL-1Ra/anakinra at baseline, 72 hours (just before IMP administration) and at Day 8, Day 15, Day 28 and Week 12 (the assessment at Day 28 and Week 12 will only be performed if no subsequent flare has occurred at the specific timepoint).
- Occurrence of ADA against anakinra at Visit 1 (before IMP administration) and at Day 8, Day 15, Day 28 and Week 12 (the assessment at Day 28 and Week 12 will only be performed if no subsequent flare has occurred at the specific timepoint).

Additional assessment for the subsequent flares:

- Change in patient-assessed pain intensity from baseline to 24-72 hours (average of the assessments performed at 24, 48 and 72 hours).
- Change from baseline in patient-assessed pain intensity in the index joint as measured by VAS score and 5-point Likert scale at 6, 12, 18, 24, 36, 48, 72 hours and Days 5, 6, 7 and 8.

Exploratory endpoint(s):

- Change from baseline in health related quality of life (Short Form (36) Health Survey (SF-36®)) at Day 8 and Day 15.
- Work productivity and activity impairment due to a gouty arthritis flare (WPAI:SHP) and health care resource utilization: number of days of unscheduled outpatient visits during the last week recorded at Day 8 and Day 15 with hospitalization and number.
- Change from baseline in exploratory inflammatory biomarkers in serum at 72 hours, Day 15 and Week 12.
- Change from baseline in health related quality of life (EQ-5D-5L) at Day 8 and Day 15.

STUDY DESIGN AND METHODS

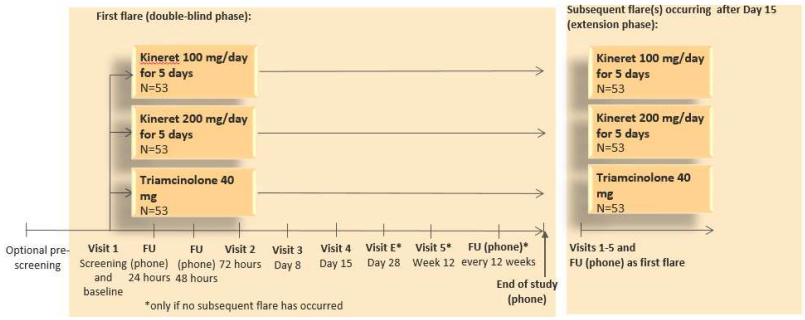
Study design:

This is a randomized, double-blind, active-control, multicenter study to investigate the efficacy and safety of 2 doses of anakinra in the treatment of a gouty arthritis flare followed by an extension period to investigate the safety and efficacy of anakinra when treating subsequent flares.

The study consists of three periods: an optional pre-screening period, a double-blind treatment period and an extension period.

The treatment period of the first flare is double-blind, and the patients will be randomized to treatment with 100 mg anakinra, 200 mg anakinra or 40 mg triamcinolone acetonide in a 1:1:1 ratio. Anakinra is administered as once daily s.c. doses for 5 days and the reference product (Triamcinolone acetonide 40 mg) as one i.m. injection. The treatment period will be followed by an extension period during which the patients will receive the

same treatment for any subsequent flares after Day 15 of the latest flare, see figure below. Each new flare treated with IMP will initiate a new serie of study visits and assessments according to the schedule of events. The extension period will continue for all patients until 52 weeks after randomization of the last randomized patient in the study. However an individual patient's treatment will not start later than two years (104 weeks) after randomization. Thus the study will not exceed 104+12 weeks for any patient.



When all patients have conducted the Day 15 visit of the first flare (Visit 4), the database will be locked and a primary analysis will be conducted. A second database lock will be conducted when all patients have completed the study.

The treatment period for each flare will consist of 4 to 6 visits to the study center. The visits are the screening/baseline visit (Visit 1/Day 1), the 72-hour visit (Visit 2/Day 4), the one-week visit (Visit 3/Day 8), the two-week visit (Visit 4/Day 15), the four-week visit (Visit E/Day 28) and the 3-month visit (Visit 5/Week 12). If a subsequent flare has been treated with IMP beforeDay 28 and/or Week 12 visit, the Day 28 and/or Week 12 visit will be cancelled.

A follow-up by phone will be performed at 24 and 48 hours post first IMP administration to remind the patients to complete the assessments and recordings in the eDiary. A follow-up by phone will also be performed every 12 weeks following Visit 5 of the latest flare.

The patient's participation in the study will be completed by an End-of-study follow-up by phone at the end of the extension period or at the Week 12 visit of the last flare treated with IMP in the study, whichever occurs latest.

All patients will be followed throughout the study, irrespective of treatment withdrawal or use of rescue medication.

At each baseline visit (first and subsequent flares), the joint that is most affected i.e., most painful will be defined as the index joint.

	Rescue medication: Patients who have difficulty in tolerating their pain are allowed to take rescue medication after the 24-hour post-dose pain assessment but not within 6 hours before the 48- and 72-hour post-dose pain assessments. Permitted rescue medication includes topical ice/cold packs, paracetamol and/or codeine or short-acting tramadol. Patients still having insufficient relief with the rescue medication listed above after the 72-hour post-dose pain assessment are allowed to take oral prednisone or prednisolone at a starting dose up to 0.5 mg/kg per day for a maximum of 5 days.
Number of patients planned:	A maximum of 169 patients can be randomized in this study. Initially159 patients will be randomized, 53 to triamcinolone and 106 to anakinra (53 to 100 mg and 53 to 200 mg). For each randomized patient that have not contributed with any value for analysis of the primary endpoint (e.g. no value collected for patient-assessed pain intensity from baseline to 72 hours), one extra patient can be randomized in the study. A maximum of 10 extra patients can randomized under this protocol.
Diagnosis and main criteria for inclusion:	Main inclusion criteria: 1. Signed informed consent to participate in this study. 2. Male and female patients, aged ≥18 years. 3. Patient meeting the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) 2015 gout classification criteria. 4. History of ≥1 self-reported flares of gouty arthritis within 12 months prior to randomization. 5. Patient-reported current ongoing flare of gouty arthritis characterized by baseline pain intensity in the index joint of ≥50 mm on a 0-100 mm VAS. 6. Currently tender (≥1 on a 0-4-point Likert scale) and swollen (≥1 on a 0-4-point Likert scale) index joint. 7. Onset of current ongoing flare within 4 days prior to randomization. 8. The patient meets at least one of the following criteria for both treatment options NSAIDs and colchicine a. At least one episode of being intolerant, or unresponsive to the treatment, see Appendices 4-6. b. The investigator judges that the patient is either contraindicated or not appropriate for the treatment. Inappropriateness may be due to anticipated changes in patient status such as worsening of comorbidities or use of concomitant medication, see Appendices 4-6.

9. Criterion omitted
10. If on urate-lowering therapy, a stable dose and regimen for at least 2 weeks prior to randomization and expectance to remain on a stable dose and regimen for ≥ 2 weeks after administration of the first dose of study treatment.
11. Women of childbearing potential willing to use adequate contraception
12. If applicable, willingness and capability to make s.c. injections at home.
13. Patient is willing and able to use an electronic device for e.g. recording of pain.

Inclusion criteria for IMP treatment of subsequent flare(s):

14. Patient-reported, current flare of gouty arthritis characterized by pain intensity in the index joint of ≥30 mm on a 0–100 mm VAS.
15. Tender (≥1 on a 0-4-point Likert scale) and swollen (≥1 on a 0-4-point Likert scale) index joint.
16. Women of childbearing potential willing to use adequate contraception

Main exclusion criteria:

1. Use of specified pain relief medications or biologics (including glucocorticoids, narcotics, paracetamol/acetaminophen, NSAIDs, colchicine, IL-blockers and tumor necrosis factor [TNF] inhibitors) within specified periods (see Appendix 1) prior to randomization.
2. Contra-indication to triamcinolone acetonide.
3. Polyarticular gouty arthritis involving more than 4 joints.
4. Rheumatoid arthritis, evidence/suspicion of infectious/septic arthritis, or other acute inflammatory arthritis.
5. History of malignancy within the past 5 years. Exceptions are basal cell skin cancer, carcinoma-in-situ of the cervix or low-risk prostate cancer after curative therapy.
6. Known hypersensitivity to *Escherichia coli*-derived proteins, Kineret® (anakinra), Kenalog® (triamcinolone acetonide) or any components of the products.
7. Participation in another concurrent investigational study within 30 days of randomization or intake of an investigational drug within five times the half-life of that investigational drug has passed.
8. Previous inclusion in this study.
9. Known presence or suspicion of active or recurrent bacterial, fungal or viral infections at the time of randomization, including tuberculosis, or HIV infection or hepatitis B or C infection.

10. Presence of severe renal function impairment chronic kidney disease (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. Uncontrolled clinically significant hematologic, pulmonary, endocrine, metabolic, gastrointestinal, CNS or hepatic disease as judged by the investigator.
13. History of myocardial infarction, unstable angina, cerebrovascular events, or coronary artery bypass grafting, New York Heart Association (NYHA) class III or IV heart failure within the previous 3 months prior to randomization.
14. ECG with clinically relevant finding making the patient not appropriate for inclusion in the study, as judged by the investigator.
15. Patients with a documented history of alcohol or substance abuse within 12 months prior to randomization (consumption of > 21 units of alcohol/week is considered alcohol abuse)
16. Patients who have undergone major surgery within 2 weeks, or have an unhealed operation wound/s.
17. Presence of any medical or psychological condition or laboratory result that in the opinion of the investigator might create risk to the patients (or interfere with the subject´s ability to comply with the protocol requirements, or to complete the study).
18. Earlier or current treatment with anakinra
19. Pregnant and lactating women
20. History of >12 flares overall in the 6 months prior to randomization.

Exclusion criteria for IMP re-treatment of subsequent flare(s):

21. IMP treatment of latest flare initiated within the last 14 days.
22. Known presence or suspicion of active or recurrent bacterial, fungal or viral infections, including tuberculosis, or HIV infection or hepatitis B or C infection.
23. Presence of severe renal function impairment CKD stages 4 and 5 (estimated creatinine clearance <30 mL/min/1.73m2).
24. Presence of neutropenia (ANC < 1.5 x 109/L).
25. History of myocardial infarction, unstable angina, cerebrovascular events, or coronary artery bypass grafting, NYHA class III or IV heart failure within the previous 3 months prior to Visit 1.
26. ECG with clinically relevant finding making the patient not appropriate for IMP treatment, as judged by the investigator.
27. Patients who have undergone major surgery within 2 weeks prior to Visit 1, or have an unhealed operation wound/s.
28. Pregnant or lactating women

29. Presence of any condition or laboratory result that in the opinion of the investigator makes the patient not appropriate for treatment with IMP.

Visit schedule and assessments:

The schedule of events is presented in Appendix 2.

Pre-screening (optional): Eligibility based on the inclusion and exclusion criteria.

Visit 1 (Screening and baseline): Obtain signed informed consent, eligibility based on the inclusion and exclusion criteria, medical and surgical history, prior and concomitant medication, demographics, medical examination of current flare (including identification of index joint), local screening laboratory safety assessments, physical examination, vital signs and ECG, and patient's assessment of pain intensity. The patient´s assessment of health related quality of life (SF-36®, EQ-5D-5L®), the physician´s assessment of clinical signs will be performed. Blood will be collected for central laboratory safety assessments, immunogenicity, inflammatory biomarker and IL1ra/anakinra serum concentration assessments. Randomization, IMP administration patient/caregiver IMP injection training and patient diary training.

Follow-up by phone at 24 and 48 hours (reminder calls): A follow-up telephone call will be made to remind the patient to record pain intensity, IMP-administration and any use of rescue medication in the eDiary.

Visit 2 (72 hours): Patient´s assessment of pain intensity, the patient´s and physician´s global assessment of response to treatment, the physician´s assessment of clinical signs, blood sampling for central laboratory safety, inflammatory biomarkers and IL1ra/anakinra serum concentration assessments, vital signs, AEs and concomitant and rescue medication. IMP administration.

Visit 3 (Day 8): Blood sampling for central laboratory safety. Patient's assessment of pain intensity, patient´s and physician's global assessment of response, physician´s assessment of clinical signs, the patient´s assessment of health related quality of life and health care resource utilization, assessments, immunogenicity assessments, inflammatory biomarkers and anakinra serum concentration assessments, vital signs, AEs and concomitant and rescue medication.

Visit 4 (Day 15): Patient´s assessment of pain intensity, the patient´s and physician's global assessment of response, the physician´s assessment of clinical signs, the patient´s assessment of health related quality of life and health care resource utilization.

Blood sampling for central laboratory safety assessments, immunogenicity assessments, inflammatory biomarkers and IL1ra/anakinra serum concentration assessments, physical examination and vital signs, AEs and concomitant and rescue medication.

Visit E (Day 28): Visit E will only be performed if no subsequent flare has occurred. Data will be collected on concomitant medication and adverse events. Blood will be collected for immunogenicity assessments and IL-1Ra/anakinra serum concentration assessments.

Visit 5 (Week 12): Visit 5 will only be performed if no subsequent flare has occurred. SAEs and outcomes of previously recorded AEs will be recorded and blood will be collected for immunogenicity assessments, inflammatory biomarkers and IL-1Ra/anakinra serum concentration assessments.

Follow up by telephone at every 12 weeks after Visit 5 of the latest flare (retention calls): A follow-up telephone call will be made to record outcomes of previously reported AEs and to encourage patient to remain in the study.

Subsequent flare(s):

Visits 1 to 5 (six visits; baseline, 72 hours, Day 8, Day 15, Day 28 and Week 12 after first IMP dose for subsequent flare): Assessments as described for Visits 1 to 5 above with the exception of informed consent, demographics (excluding weight) and randomization. Type of AEs to be collected will depend on time since last administration of IMP.

Follow-up by phone at 24 and 48 hours after first IMP dose for subsequent flare and at every 12 weeks after Visit 5 : Assessments as described for the first flare.

End of study:

End-of-study follow-up by phone will be performed either;

1. 52 weeks after randomization of the last patient in the study
   or
2. 104 weeks after randomization of the individual patient

whichever occurs first.

If the IMP treatment started week 40 or later in case 1), or week 92 in case 2), the Week 12 visit will replace the End-of-study follow-up by phone.

Outcomes of previously reported AEs will then be recorded.

Test product; dose and mode of administration:	Arm A: anakinra, 100 mg, s.c. injection, once daily for 5 days. Arm B: anakinra, 200 mg, s.c. injection, once daily for 5 days. Arm C: matching anakinra placebo, s.c. injection, once daily for 5 days. During the extension period the patients will continue to receive the same treatment for subsequent flares occurring after Day 15 of the last flare.
Reference product; dose and mode of administration:	Arms A and B: Matching Triamcinolone placebo, single i.m. injection. Arm C: Triamcinolone, 40 mg single i.m. injection.

Duration of treatment(s):	For each flare, IMP will be administered for 5 days.
Randomization:	Patients will be randomized to treatment with anakinra 100 mg, anakinra 200 mg or triamcinolone 40 mg in a 1:1:1 ratio. The randomization will be stratified by ULT use (yes/no) and BMI (<30.0 or ≥30.0 kg/m^2) at inclusion. For subsequent flares in the extension period, patients will continue to receive treatment with anakinra 100 mg, anakinra 200 mg or triamcinolone 40 mg in a 1:1:1 ratio. The randomized groups will be as follows: Arm A: anakinra 100 mg Arm B: anakinra 200 mg Arm C: triamcinolone 40 mg
Statistical methods:	At least 159 patients will be randomized, 53 to triamcinolone and 106 to anakinra (53 to 100 mg and 53 to 200 mg). The sample size calculation is based on the change in pain intensity on a visual analog scale (VAS) 0-100 mm from baseline to the average over 24-72 hours. A sample size of 106 randomized patients receiving anakinra and 53 randomized patients receiving triamcinolone is required to ensure a power of 80% to reject the null hypothesis of no difference between anakinra and triamcinolone assuming a true difference of 12 mm on VAS mean change and a standard deviation of 25 mm when using a two-sided test with a significance level of 5%. The comparison of primary interest is between anakinra (100 mg and 200 mg combined) and triamcinolone. The primary endpoint will be estimated using a mixed model repeated measures analysis with the measurements on the individual time points as responses (baseline, 6, 12, 18, 24, 48 and 72 hours), and with treatment (anakinra 100 mg, anakinra 200 mg and triamcinolone), ULT use (yes/no), BMI (<30.0 and ≥30.0 kg/m2), visit and treatment-visit-interaction as fixed effects and center as random effect. An unstructured covariance matrix will be used to account for within-subject correlation. The estimated mean change from baseline to 24-72 hours for each treatment group (anakinra and triamcinolone), the estimated difference between the groups and the associated 95 % confidence interval and p-value based on this model will be presented. Further, each of the two doses of anakinra, 100 mg and 200 mg, will be compared to triamcinolone using the same model as for the primary comparison. The secondary time-to-event endpoints will be analyzed using a stratified log-rank test, with ULT use (yes/no) and BMI (<30.0 or ≥30.0 kg/m^2) as stratification factors. The secondary continuous endpoints will be analyzed using an analysis of covariance including factors for treatment, ULT use (yes/no) and BMI (<30.0 or ≥30.0 kg/m^2) and baseline value as covariate.

The secondary binary endpoints will be analyzed using a logistic regression model with treatment, ULT use (yes/no) and BMI (<30.0 or ≥30.0 kg/m^2) as explanatory variables. Safety tabulations of adverse event data and laboratory data will be performed.

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

2 Abbreviations and definition of terms

ACR	American College of Rheumatology
ADA	Anti-drug antibodies
AE	Adverse event
Anakinra	Recombinant interleukin 1 receptor antagonist
ANC	Absolute neutrophil count
BMI	Body mass index
CAPS	Cryopyrin-associated periodic syndrome
CDASH	Clinical data acquisition standards harmonization
CDISC	Clinical data interchange standards consortium

CKD	Chronic kidney disease
CLIA	Clinical laboratory improvement amendments
CRO	Contract research organization
CRP	C-reactive protein
ECG	Electrocardiogram
eCRF	Electronic case report form
EEA	European economic area
ED	Emergency department
eGFR	Estimated glomerular filtration rate
EQ-5D-5L®	EuroQol 5 dimensions 5 levels
EULAR	European League Against Rheumatism
GCP	Good clinical practice
GLP	Good laboratory practice
HRQL	Health related quality of life
IB	Investigator brochure
ICF	Informed consent form
ICH	International conference on harmonisation
IEC	Independent Ethics Committee
IL	Interleukin
IL-1Ra	Endogenous Interleukin 1 receptor antagonist
i.m.	Intramuscular
IMP	Investigational medicinal product
IRB	Institutional review board
ISR	Injection-site reaction
ITT	Intention-to-treat
IWRS	Interactive web response system
MAR	Missing at random
MCS	Mental component summary
MedDRA	Medical dictionary for regulatory activities
MNAR	Missing not at random
MPO	Myeloperoxidase

MSD-ECL	Meso Scale Discovery Electrochemiluminescence
MSU	Monosodium urate
NAb	Neutralizing antibodies
NOMID	Neonatal onset multisystem inflammatory disease
NSAID	Non steroidal anti-inflammatory drugs
NYHA	New York Heart Association
OMERACT	Outcome measures in rheumatology
PCS	Physical component summary
PK	Pharmacokinetic
PP	Per-protocol
QoL	Quality of life
RA	Rheumatoid arthritis
SAA	Serum amyloid A
SAE	Serious adverse event
SAP	Statistical analysis plan
s.c.	Subcutaneous
SDTM	Study data tabulation model
SF-36	Short Form (36) Health Survey (acute v. 2)
SJIA	Systemic juvenile idiopathic arthritis
Sobi	Swedish Orphan Biovitrum AB (publ)
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reaction
TIA	Transient ischemic attack
TNF	Tumour necrosis factor
ULT	Urate lowering therapy
VAS	Visual analogue scale
WHODRUG	World health organisation drug dictionary
WPAI:SHP	Work productivity and activity impairment:specific health problems

3 Ethics

3.1 Independent ethics committee

It is the responsibility of the investigator to obtain independent ethics committee (IEC)/ institutional review board (IRB) approval of the study protocol, possible amendments and the written patient information and informed consent form (ICF). The investigator should file all correspondence with the IRB. Copies of IRB correspondence and approvals should be forwarded to the contract research organization (CRO).

3.2 Ethical conduct of the study

This study will be conducted in compliance with this protocol, the International council of harmonisation (ICH) Guideline for good clinical practice (GCP) (1), applicable regulatory requirements, and in accordance with the latest revision of the ethical principles for medical research involving human subjects (the declaration of Helsinki) (2).

3.3 Patient information and consent

It is the responsibility of the investigator to give each patient prior to any study-related activities, full and adequate verbal and written information regarding the objective and procedures of the study and the possible risks involved. The patients must be informed about their right to withdraw from the study at any time. The written patient information and/or consent form must not be changed without prior discussion with Swedish Orphan Biovitrum AB (publ) (Sobi). Before any revisions are implemented, the revised written patient information and/or consent form must be approved by the IRB/IEC.

It is the responsibility of the investigator to obtain signed informed consent from all patients prior to any study related activities. The patients should receive a copy of the written information and signed ICF.

Once the ICF has been signed, the patient will be assigned an enrollment number.

4 Study administrative structure

4.1 Sponsor

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

4.2 Contract research organization

The conduct of the study is fully outsourced to Pharmaceutical Research Associates, Inc., Raleigh, North Carolina, USA (PRA). Site evaluation, monitoring, development of master written patient information and ICF, data management, investigational product management, safety reporting and vendor management are some of the related activities and responsibilities that are transferred to PRA.

PRA has assigned Almac, for investigational medicinal product (IMP) depot and IMP logistics, ERT, Philadelphia, Pennsylvania, USA to provide and manage electronic diaries and Perceptive, a division of Parexel International Corp, Waltham, Massachusetts, USA for handling of the interactive web response system (IWRS).

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

4.3 Central Laboratories

Central laboratories will be used for all study specific laboratory assessments. All central laboratories are compliant with good laboratory practice (GLP).

The analysis of anti-drug antibodies (ADA), including validation of the bridging method to be used, and the analysis of endogenous interleukin 1 receptor antagonist (IL-1Ra)/anakinra concentrations, including validation of the Meso Scale Discovery electrochemiluminescence (MSD-ECL)based method to be used for the purpose will be performed by York Bioanalytical Solutions Limited, Cedar House, Northminster Business Park, Upper Poppleton, York, United Kingdom.

The analysis of neutralizing ADA (NAb) including development and validation of the cell-based method to be used will be performed by Euro Diagnostica, Malmö, Sweden.

PRA has assigned the central laboratory sample shipments, intermediate depot storage and analysis of laboratory safety variables, C-reactive protein (CRP) and serum amyloid A (SAA), to Eurofins Central Laboratory, Lancaster, Pennsylvania, USA which has accreditation for the purpose.

Analysis of inflammatory biomarkers will be performed by Eurofins Global Central Laboratory, Breda, the Netherlands under clinical laboratory improvement amendments (CLIA) accreditation (IL-6, IL-8, calprotectin, neopterin and myeloperoxidase).

5 Background

5.1.1 Gouty arthritis

Gouty arthritis is a chronic, progressive inflammatory arthritis characterized by the deposition of monosodium urate (MSU) crystals primarily in and around joints, as a result of persistent hyperuricemia. Development of gouty arthritis is typically observed in patients with serum urate

concentrations above the level at which MSU crystals form at physiological pH and temperature (6.8 mg/dL, 0.41 mmol/L) (12). It is one of the most common inflammatory arthritis in adults (22).

The long-term goal in the treatment of gouty arthritis is to reduce serum uric acid concentrations (12), and urate-lowering therapy (ULT) has been shown to be effective in preventing gouty arthritis flares (18). However, many patients fail to achieve adequate uric acid control and some patients experience flares of gouty arthritis at normal serum uric acid levels.

A gouty arthritis flare is an acute and severely painful condition caused by the inflammatory response triggered by the MSU crystals. The flares are characterized by rapid onset and build-up of severe pain, warmth, swelling, decreased range of motion, and redness of the involved joints. Early during the disease, flares tend to last from a few hours up to a week. Later during the course of the disease, the flares tend to last longer. The frequency of flares also often increases over time in patients who are inadequately treated (9).

5.1.2 Current therapy for gouty arthritis flare and medical need

A gouty arthritis flare causes extreme pain and significant disability, and the goal of acute pharmacologic therapy is to provide a prompt, effective and safe pain relief. There are several anti-inflammatory pharmacological options approved for the treatment of acute gouty arthritis, including non steroidal anti-inflammatory drugs (NSAIDs), colchicine, and glucocorticoids. Recently, both the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) published guidelines and recommendations for the management of gout (12, 17). However, in daily practice, many patients continue to experience poor clinical outcome of therapy. Conventional therapy is not always suitable or effective, and many patients with gouty arthritis have underlying comorbidities, including hypertension, chronic kidney disease, coronary artery disease, hyperlipidemia, chronic hepatitis, osteoporosis, gastroesophageal disease and diabetes (11). There is, thus, a need for effective treatment for patients who have either contraindications to, or are not appropriate for, are intolerant of, or have disease that is refractory to existing therapies.

5.1.3 Rationale for IL-1 blocking therapy

The central pathogenic cause of gout is MSU crystal deposition. MSU crystals induce secretion of interleukin-1β (IL-1β) via activation of the NALP3 inflammasome (14). IL-1β is a pivotal cytokine that mediates inflammation and joint damage. Several lines of evidence suggest that the initiation of inflammation in gouty arthritis is similar to that occurring in hereditary autoinflammatory syndromes such as e.g. cryopyrin-associated periodic syndromes (CAPS), for which IL-1 blockade is highly effective (31). Therefore, IL-1 blockade may be an appropriate therapeutic intervention for gouty arthritis flares. This is supported by clinical data for canakinumab (20, 5) and by published case studies, retrospective reviews and case reports on anakinra in gouty arthritis (19, 7, 10, 16, 21).

5.1.4 Anakinra

Anakinra is a recombinant IL-1 receptor antagonist 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 controls active inflammation. Anakinra has a short half-life (4-6 hours) and is administered as a subcutaneous (s.c.) injection daily at home.

Anakinra is currently approved in the US (2001), Canada (2002), and EU/EEA (2002) for the treatment of rheumatoid arthritis (RA). Anakinra is also approved for the most severe form of CAPS, i.e. neonatal onset multisystem inflammatory disease (NOMID), in the US (2012), and for all forms of CAPS in EU/EEA (2013). In addition, anakinra is approved for the treatment of systemic juvenile idiopathic arthritis (SJIA) in Australia (2015).

For a detailed description of anakinra characteristics, contraindications, warnings and precautions, adverse reactions and pharmaceutical properties, refer to the product information/monograph and the investigator brochure (IB).

5.1.4.1 Reports on clinical benefit in gouty arthritis flares

Published clinical case series have evaluated the clinical efficacy of anakinra in gouty arthritis in various clinical situations (19, 7, 10, 16, 21). Different dose regimens have been used, but most patients have been treated with once-daily s.c. injections of 100 mg for 3 to 5 days. The characteristics of the treated patients have varied, including different clinical manifestations of gouty arthritis, intolerance to, or inadequate response to conventional therapies, such as NSAIDs, colchicine, or glucocorticoids.

The published case series have provided supportive evidence for the efficacy of IL-1 inhibition with anakinra in the treatment of gouty arthritis flares. No new or unexpected adverse events have occurred and the safety profile is consistent between these reports and the known safety profile for anakinra in other indications.

5.1.4.2 Safety

The safety profile of anakinra is well established. Since its approval in the US 2001 for the treatment of RA, it is calculated that, up to 01 May 2016, the total post-marketing exposure is 84 408 patient-years.

In placebo-controlled studies in RA patients, the most frequently reported adverse reactions were injection-site reactions (ISRs), which were mild to moderate in most patients. From studies in RA there are indications that ISRs are more frequent when daily doses of >100 mg s.c. are administered. In RA studies, the vast majority of ISRs occurred within the first 4 weeks of therapy. Less than 20% of the ISRs occurred during the first 5 days, also when daily doses of >100 mg were administered.
The incidence of serious adverse events (SAEs) at the recommended dose in RA (100 mg/day) was comparable with placebo. The incidence of serious infections was higher in anakinra-treated patients with RA compared to patients receiving placebo (2 % vs. < 1 %). In clinical studies and during post-marketing use, rare cases of opportunistic infections have been observed including fungal, mycobacterial, bacterial, and viral pathogens. In clinical studies of RA, neutropenia (absolute neutrophil count (ANC) <1 x 109/L) occurred in 0.4 % of patients receiving anakinra.

Repeated short-term administration of anakinra has not been previously studied. This type of administration could possibly result in an increased risk for development of ADA, which may result in an increased risk for allergic/anaphylactic reactions, ISRs or reduced efficacy. The occurrence of ADA against anakinra has been evaluated in clinical studies in RA, and no correlation between ADA development and AEs has been observed.

In an open-label study in NOMID (the most severe form of CAPS), patients were treated with anakinra up to 5 years. The safety profile was similar to the safety profile observed in studies of patients with RA, with the exception of the ISR frequency which was comparable to the ISR frequency of placebo-treated patients in RA studies.

In previous clinical studies of sepsis, more than 1000 patients received anakinra i.v. at doses up to 2 mg/kg/hour over a 72-hour treatment period. The safety profile in these studies was similar to that seen in other indications (33, 34, 35). The maximum tolerated dose of anakinra has not been established in humans.

The safety profile of anakinra is similar across indications and dose levels studied. In long-term studies, there are no indications of increasing AE rates over time. The safety profile is also comparable between adults below 65 years of age and elderly.

5.2 Study rationale

The main aim of this study is to evaluate the efficacy and safety of anakinra in patients for whom NSAIDs and colchicine are either contraindicated or not appropriate, not tolerated or do not provide an adequate response, and to select the appropriate dose in order to reduce the pain and inflammation of a gouty arthritis flare. The study will also evaluate the safety and immunogenicity of anakinra when treating subsequent flares during a 1-2 years study extension.

5.3 Potential risks and benefits

Published case series have provided supportive evidence for the efficacy of IL-1 inhibition with anakinra in the treatment of gouty arthritis flares (19, 7, 10, 16, 21). No new or unexpected adverse events have occurred, and the safety profile is consistent between the reports and the known safety profile of anakinra.

The use of anakinra for the treatment of gouty arthritis flares is supported by the described central pathogenic role of IL-1 in acute gouty arthritis (14) as well as by clinical data for the IL-1β inhibitor canakinumab (20, 5).

The safety profile of anakinra is well established and has been similar across indications and dose levels (see 5.1.4.2), with the exception of ISRs that were more frequent when doses of >100mg s.c. were administered to patients with RA. However, less than 20% of ISRs occurred during the first 5 days of anakinra treatment. From the limited information available, there are no

indications of any relevant differences in the safety profile of anakinra in patients with gouty arthritis compared to patients with other indications for anakinra treatment.

There is limited experience of the intermittent, short-term treatment with anakinra that is planned for patients with repeated flares of gouty arthritis in this study. This type of administration may result in an increased development of ADA, which could possibly result in an increased risk for allergic/anaphylactic reactions, injection-site reactions or reduced efficacy.

The proposed indication for anakinra treatment of acute gouty arthritis includes patients that are refractory to, or do not tolerate standard therapy, i.e., patients eligible for anakinra treatment are expected to have several comorbidities. Patients with coronary artery disease (29, 25), type 1 diabetes (28), type 2 diabetes (27), and hepatic failure (45) have all been studied in separate studies with anakinra. There are no indications from these studies that the studied populations have a different safety profile than other patient groups treated with anakinra. In addition, patients with stroke have been treated with anakinra bolus doses up to 500 mg i.v. followed by up to 10 mg/kg/hour i.v. for 24 hours (36) with a similar safety profile and no dose-limiting toxicities (30, 26). Since anakinra elimination is dependent on renal function, a study with administration of single 100 mg s.c. doses in patients with various degrees of renal failure has been performed. The results show that both systemic exposure and plasma clearance were significantly correlated with the degree of renal impairment but there were no relevant differences in the safety profile of anakinra between subjects with normal renal function and those with different degrees of renal impairment (47).

The potential risks associated with anakinra administration (including development of ADA) will be closely monitored as part of the safety evaluations being performed in the study.

The suggested class effect of IL-1 blocking therapy, the well-established safety profile of anakinra, and its short half-life makes anakinra a candidate for treatment of patients with gouty arthritis flares. Based on the information available, the proposed treatment with anakinra is not expected to present any major additional risks for the patient population.

In this study, all patients will receive active treatment (100 mg anakinra, 200 mg anakinra or 40 mg triamcinolone) and are expected to get pain relief when treated for their gouty arthritis flares. Patients are also allowed to add on treatment with rescue medication. To be included in the study, the patients cannot have taken pain medication during the last 1 to 24 hours (dependent on the half-life of the medicines). It is therefore important that the patients are included as soon as possible after the onset of the flare to minimize the patient's time without pain relief treatment.

The benefits for the patients to participate in the study are the possibility to access an investigational drug potentially more effective than conventional treatment and to get a thorough medical follow-up of each flare occurring during one year. To strive for normalized serum urate levels the patient will be allowed to continue or initiate ULT treatment during the course of the study (40).

6 Study objectives and endpoints

6.1 Primary objective

To evaluate the efficacy of anakinra compared to triamcinolone acetonide 40 mg intramuscular (i.m) injection, hereafter referred to as triamcinolone, with respect to patient-assessed pain intensity in the treatment of a gouty arthritis flare (based on patients' first flare treated in the study).

6.1.1 Primary endpoint

Change in patient-assessed pain intensity from baseline to 24-72 hours (average of the assessments performed at 24, 48 and 72 hours).

Patients will score their pain intensity in the joint most affected at baseline (i.e., the index joint) on a 0-100 mm visual analogue scale (VAS), ranging from no pain (0) to unbearable pain (100).

6.1.2 Secondary endpoints supporting primary objective

Change from baseline in patient-assessed pain intensity in the index joint as measured by VAS and a 5-point Likert scale at 6, 12, 18, 24, 36, 48, 72 hours and Days 5, 6, 7 and 8.

6.2 Secondary objectives

To evaluate the primary endpoint and the secondary endpoints supporting primary objective for the 2 different anakinra dose groups compared to triamcinolone in the treatment of the first gouty arthritis flare.

To evaluate the time to onset of effect, time to response, time to pain resolution, time to rescue medication, physician's assessment of global response and clinical signs, patient´s assessment of global response, inflammatory biomarkers and safety of anakinra compared to triamcinolone in the treatment of the first gouty arthritis flare both for the combined anakinra group (100 and 200 mg) and the 2 different anakinra dose groups.

To evaluate the primary and secondary endpoints and safety of the combined anakinra group (100 and 200 mg), the 2 different anakinra dose groups and triamcinolone in the treatment of subsequent flares. Subsequent flares are flares occurring after the first flare in the study and within 52 weeks of randomization of the last randomized patient in the study.However the extension will be a maximum of two years (104 weeks) after randomization for the individual patient in the study.

6.2.1 Secondary endpoints

The following endpoints will be assessed for the first flare and subsequent flares. All comparisons versus baseline (pre-dose measurement at Visit 1) will be made against the baseline of the first and subsequent flares, respectively.

- Time to onset of effect (defined as ≥20% change from baseline pain intensity on VAS).
- Time to response (defined as ≥50% change from baseline pain intensity on VAS).
- Response (defined as ≥50% change from baseline pain intensity on VAS) at 24, 48 and 72 hours, Day 8 and Day 15 (Yes/No).
- Resolution of pain (defined as <10 mm on VAS) at 72 hours, Day 8 and Day 15 (Yes/No).
- Time to resolution of pain (defined as <10 mm on VAS).
- Time to intake of rescue medication from first IMP administration.
- Type and number of occasions of intake of rescue medication from first IMP administration to Day 8.
- Physician's assessment of global response to treatment (5-point Likert scale) at 72 hours Day 8 and Day 15.
- Physician's assessment of clinical signs at 72 hours, Day 8 and Day 15 in index joint tenderness, swelling and erythema.
- Patient´s assessment of global response to treatment (5-point Likert scale) at 72 hours, Day 8 and Day 15.
- Change from baseline in the inflammatory biomarkers CRP and SAA at 72 hours, Day 8 and Day 15.
- Safety variables (AEs, vital signs, laboratory safety assessments).
- Serum concentration of IL-1Ra/anakinra at baseline, 72 hours (just before IMP administration) and at Day 8, Day 15, Day 28 and Week 12 (the assessment at Week 12 will only be performed if no subsequent flare has occurred).
- Occurrence of ADA against anakinra at Visit 1 (before IMP administration) and at Day 8, Day 15, Day 28 and Week 12 (the assessment at Day 28 and Week 12 will only be performed if no subsequent flare has occurred).

Additional assessment for the subsequent flares:

- Change in patient-assessed pain intensity from baseline to 24-72 hours (average of the assessments performed at 24, 48 and 72 hours).
- Change from baseline in patient-assessed pain intensity in the index joint as measured by VAS score and 5-point Likert scale at 6, 12, 18, 24, 36, 48, 72 hours and Days 5, 6, 7 and 8.

6.3 Exploratory objectives

To evaluate the effect of anakinra compared to triamcinolone on health related quality of life (HRQL) and health care resource utilization in the treatment of gouty arthritis flares.

To evaluate the effect of anakinra compared to triamcinolone on exploratory inflammatory biomarkers in serum in the treatment of gouty arthritis flares. The results will be reported separately.

To analyze for genetic factors potentially 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. The results will be reported separately.

6.3.1 Exploratory endpoints

The following exploratory endpoints will be assessed for both the first and subsequent gouty arthritis flares. All comparisons versus baseline (pre-dose measurement at Visit 1) will be made against the baseline of the first and subsequent flares, respectively.

- Change from baseline in health related quality of life (Short Form (36) Health Survey, acute version 2 (SF-36®)) at Day 8 and Day 15.
- Work productivity and activity impairment due to a gouty arthritis flare (WPAI:SHP v.2.0) and health care resource utilization: number of days with hospitalization and number of unscheduled outpatient visits during the last week recorded at Day 8 and Day 15.
- Change from baseline in exploratory inflammatory biomarkers in serum at 72 hours, Day 15 and Week 12.
- Change from baseline in health related quality of life (EQ-5D-5L) at Day 8 and Day 15.

7 Investigational plan

7.1 Overall study design and plan

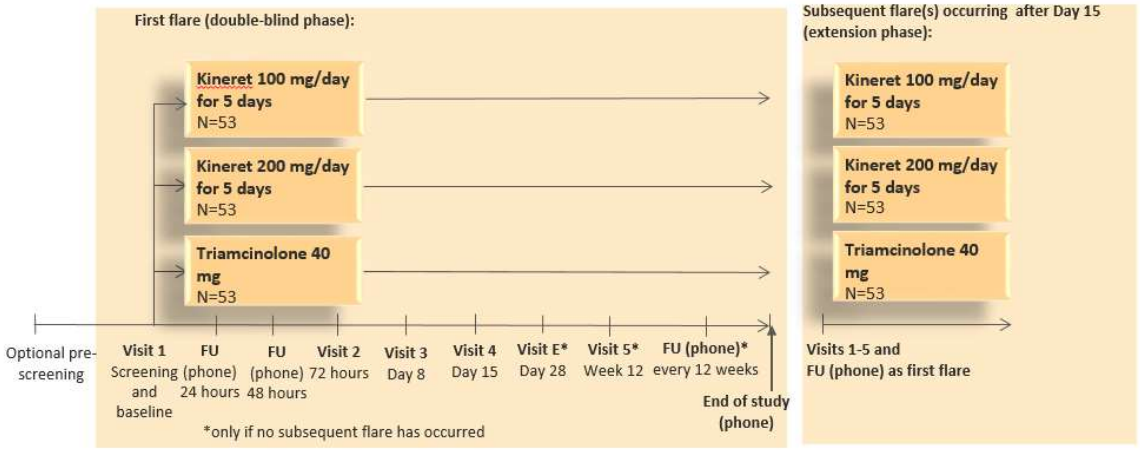
This is a randomized, double-blind, active-control, multicenter study to investigate the efficacy and safety of 2 doses of anakinra in the treatment of a gouty arthritis flare followed by an extension period to investigate the safety and efficacy of anakinra when treating subsequent flares.

The study consists of three periods: an optional pre-screening period, a double-blind treatment period and an extension period.

The treatment period of the first flare is double-blind, and the patients will be randomized to treatment with 100 mg anakinra, 200 mg anakinra or 40 mg triamcinolone in a 1:1:1 ratio. Anakinra will be administered as once daily s.c. injections for 5 days (Days 1 to 5) and triamcinolone as one i.m. injection (Day 1). The treatment period will be followed by an extension period. During this period the patients will receive the same treatment for subsequent flares occurring after Day 15 of the latest flare. The extension period will continue for all patients until 52 weeks after randomization of the last randomized patient in the study. However

the study treatment of an individual patient's flare will not start later than 2 years (104 weeks) after randomization of that patient. Thus the study will not exceed 104 + 12 weeks for any patient. Figure 1.

Figure 1 **Study flow chart**



When all patients have conducted the Day 15 visit of the first flare (Visit 4), the database will be locked and the primary analysis will be conducted. A second database lock will be conducted when all patients have completed the extension period.

The assessment period for each flare will consist of 4 to 6 visits to the study center. The visits are the screening/baseline visit (Visit 1/Day 1), the 72-hour visit (Visit 2/Day 4), the one-week visit (Visit 3/Day 8), the two-week visit (Visit 4/Day 15), the four week visit (Visit E/Day 28) and the 3-month visit (Visit 5/Week 12). If a subsequent flare has been treated before the Day 28 visit, the Day 28 and Week 12 visits will be cancelled. If a subsequent flare has been treated before the Week 12 visits that visit will be cancelled.

A follow-up by phone will be performed at 24 and 48 hours post first IMP administration to remind the patient to complete the assessments and recordings in the eDiary. A follow-up by phone will also be performed every 12 weeks following Visit 5 of the latest flare.

An end-of-study follow-up will be performed either;

1. 52 weeks after randomization of the last patient in the study

or

2. 104 weeks after randomization of the individual patient

whichever occurs first.

If the IMP treatment started week 40 or later in case 1), or week 92 weeks in case 2), the Week 12 visit will replace the End-of-study follow-up by phone.

All patients will have their follow-up visits/phone calls, irrespective of treatment withdrawal or use of rescue medication.

Subsequent flares occurring before the Day 15 visit of the latest flare (Visit 4) will be treated with permitted rescue medication i.e., no IMP will be administered.

7.2 Discussion of study design

7.2.1 Study population

This study is designed to evaluate the efficacy and safety of anakinra in the treatment of gouty arthritis flares in patients for whom NSAIDs and colchicine are either contraindicated or not appropriate due to anticipated changes in patient status, not tolerated or do not provide an adequate response. Both in- and out-patients can be included in the study.

The appropriateness for treatment with NSAIDs and colchicine will depend on several factors, for example:

- Presence, severity and number of controlled and/or uncontrolled co-morbidities
- Number and type of concomitant medications
- Age of the patient
- Previous experience of therapy i.e., individual efficacy and safety outcomes

Due to the complexity of the numerous combinations of above-mentioned factors, the suitability for treatment will be assessed at the discretion of the investigator. To increase consistency, the investigators' assessment will be supported by checklists (see Appendices 4-6).

To ensure a reliable diagnosis of gouty arthritis, patients to be included in the study must meet the ACR/EULAR 2015 gout classification criteria (15).

At least one self-reported flare of gouty arthritis during the previous 12 months is required for inclusion in the study to ensure that the patients have an active gouty arthritis.

To ensure that a significant number of subsequent flares are treated in the study, the extension period will continue for all patients until 52 weeks after randomization of the last randomized patient in the study or a maximum of 104 weeks after randomization of the individual patient in the study.

The first flare of gouty arthritis to be treated in the study will be characterized by a baseline pain intensity in the index joint of ≥50 mm on a 0 to 100 mm VAS. This VAS cut-off ensures restriction of the study population to patients with moderate to severe pain.

For subsequent flares to be treated with IMP, a cut-off level of ≥30 mm on a 0 to 100 mm VAS will be used. This cut-off is based on a proposed definition for a flare based on self-reported items in patients previously diagnosed as having gouty arthritis (32). Patient-reported flare, joint pain at rest (>3 (0-10 scale)), warm joints, and swollen joints were the most strongly associated with presence of a gouty arthritis flare. The rationale behind including and, thus, giving IMP treatment to patients with lower VAS scores at subsequent flares compared to the initial flare (≥50 mm on a 0 to 100 mm VAS), is that the aim of the extension phase is primarily to study safety and immunogenicity, not efficacy. If gouty arthritis flares of mild pain intensity (30-50 mm on the VAS scale) were to be treated outside the study i.e. with a mix of acute gout therapies, the safety assessment of the IMP treatments would be confounded.

The required time from flare onset to treatment initiation (≤4 days) was selected to minimize the likelihood that a treatment effect coincide with the natural resolution of the flare (usually within 7 to 10 days).

7.2.2 Efficacy evaluation

7.2.2.1 Definition of primary endpoint

The primary endpoint is the change in patient-assessed pain intensity from baseline to 24-72 hours (average of the assessments performed at 24, 48 and 72 hours). Patients will score their pain intensity in the joint most affected at baseline (i.e. the index joint) on a 0 to 100 mm VAS.

The maximum severity of pain during a gouty arthritis flare is usually reached within 12 to 24 hours and complete resolution usually occurs within 7 to 10 days in patients with moderate to severe gouty arthritis (17). Therefore, an average of the assessments performed at 24, 48 and 72 hours over a critical period of 24 to 72 hours is proposed. The likelihood of spontaneous recovery is also lower during the early phase of a flare.

The proposed primary endpoint is in line with the FDA Guidance for Industry, Analgesic Indications: Developing Drug and Biological Products (24):

- "Efficacy endpoints in an analgesic trial should reflect direct rating of pain intensity by the patient… We recommend the use of a well-defined and reliable patient-reported outcome measure of the patient's pain intensity" (IV.A.3 page 10)
- "…visual or numerical rating of pain intensity, or a categorical rating with several categories. It may be a single rating at a given point in time, or an average or other summary or several ratings over a period of time." (IV.B.11.a page 25)

Patient-reported outcome is also endorsed by the Outcome Measures in Rheumatology (OMERACT) gout special interest group (8), and has been used as primary endpoint when the effect on the pain of a gouty arthritis flare has been studied with conventional, US-approved therapy such as etoricoxib and colchicine, as well as with investigational therapy such as canakinumab and rilonacept.

The comparison of primary interest is between anakinra (100 mg and 200 mg combined) and 40 mg triamcinolone. As a secondary objective, the 2 different doses of anakinra will be compared to 40 mg triamcinolone in respect to the primary endpoint, i.e. change in pain intensity from baseline to 24-72 hours.

7.2.2.2 Definitions of secondary efficacy endpoints

<u>Response (≥50% change from baseline on VAS)</u>

According to the FDA Guidance mentioned above, a responder analysis, in which the outcome for each patient is summarized as a success or a failure based on a single cut-off point can be used (24).

In this study, response is defined as a VAS pain relief of 50% or greater from baseline. In the ACR guidelines, an adequate response is defined as ≥50 % improvement in pain score at ≥24

hours (12). This definition has also been used in previous acute gouty arthritis studies with colchicine and canakinumab (43, 5).

Onset of effect (≥20% change from baseline on VAS)

Two studies in patients admitted to emergency departments with heterogeneous causes of pain have indicated that a difference of 13 mm on a VAS represents, on average, the minimum change in acute pain that is clinically significant (3, 4). In the canakinumab gouty arthritis studies, the patients had mean VAS score of approximately 70 mm at baseline. 13 mm/70 mm is less than a 20% change from baseline (5). This would justify a cut-off of ≥20% change from baseline on VAS as clinically meaningful. In the ACR guidelines an adequate response was defined as ≥20 % improvement in pain score within 24 hours (12).

Resolution of pain in patient-assessed pain intensity (VAS<10)

In this study, resolution of pain is defined as <10 mm in pain intensity on the VAS scale.

To fully assess time to onset of effect, time to response and time to resolution of pain, the patients will record their pain assessment daily up until Day 15.

7.2.3 Comparator

According to the FDA Guidance for Industry, Analgesic Indications: Developing Drug and Biological Products“ trials intended to support a finding of efficacy for an analgesic should be designed as superiority trials. The comparator can be a lower dose of the investigational drug, a placebo or an active comparator” (24).

A gouty arthritis flare is an acute and severely painful condition, and using placebo as a comparator is not considered ethical (8).

A single i.m. dose of 40 mg triamcinolone has been selected as comparator in this study since good pain reduction has been shown when compared to canakinumab (5, 20). Furthermore, one injection of a systemic glucocorticoid eliminates the need for a glucocorticoid tapering regimen.

7.2.4 Dose and treatment duration

7.2.4.1 Dosage regimen

The pharmacokinetic (PK) profile of anakinra in adult RA patients supports once-daily s.c. administration also to patients with a gouty arthritis flare. With once daily administration, steady state serum concentrations of anakinra will almost be reached already after the first dose. As reflected in the approved label for anakinra, sufficient anakinra exposure has been maintained during a once-daily dosage interval.

7.2.4.2 Dose levels

In published case series of anakinra (see Section 10.2.1), different dose levels have been used. The majority of patients have been treated with once-daily s.c. injections of 100 mg anakinra with generally positive outcome. In the case series where patients were treated with 100 mg for 3 days, patient-assessed improvement of pain varied between 50 and 100 % (19).

In the 2 anakinra dose-response studies in patients with RA (30, 75, 150 mg (44) and 0.04, 0.1, 0.4, 1, 2 mg/kg (46)), the change from baseline in patient-reported pain intensity (a component of the primary efficacy endpoint) tended to increase with increasing doses, and the largest differences versus placebo were achieved at daily s.c. doses of 150 mg and 2 mg/kg, respectively.

Based on the results of the RA studies and the case series in acute gouty arthritis, 100 mg was selected as the lowest daily dose to be tested in this study.

The gouty arthritis population proposed to be indicated for treatment with anakinra is assumed to have a higher mean body weight than the RA patients. For reference, the mean (SD) body weight was 98 (18) kg in the canakinumab clinical studies in patients with acute gouty arthritis (N=368) (6), as compared to 77 (19) kg in the anakinra clinical study safety pool in RA patients (N=3330). As the anakinra clearance increases with increasing body weight, once-daily s.c. doses of both 100 and 200 mg will be evaluated in this study.

The safety profile of anakinra is well established and has been similar across indications and dose levels during long-term treatment (see section 5.1.4.2). Thus, a once-daily s.c. administration of 200 mg anakinra is not expected to result in an increased incidence of adverse events compared with 100 mg, the only exception being ISRs that, in studies of RA, were more frequent with s.c. doses above 100 mg.

The dose range chosen for this study may not allow discrimination based on statistically significant differences. The study will allow descriptive comparisons of efficacy and safety at 2 relevant dose levels.

7.2.4.3 Treatment duration

The treatment duration of 5 days is chosen to cover the most severe part of the flare and to minimize IMP exposure.

7.3 Selection of study population

7.3.1 Inclusion criteria

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

1. Signed informed consent to participate in this study.
2. Male and female patients, aged ≥18 years
3. Patient meeting the ACR/EULAR 2015 gout classification criteria (Appendix 7 (15)).
4. History of ≥1 self-reported flares of gouty arthritis within 12 months prior to randomization.
5. Patient-reported, current ongoing flare of gouty arthritis characterized by baseline pain intensity in the index joint of ≥50 mm on a 0-100 mm VAS.
6. Currently tender (≥1 on a 0-4-point Likert scale) and swollen (≥1 on a 0-4-point Likert scale) index joint.

7. Onset of currently ongoing flare within 4 days prior to randomization.
8. The patient meets at least one of the following criteria for both treatment options NSAIDs and colchicine
    a. At least one episode of being intolerant, or unresponsive to the treatment, see Appendices 4-6.
    b. The investigator judges that the patient is either contraindicated or not appropriate for the treatment. Inappropriateness may be due to anticipated changes in patient status such as worsening of comorbidities or use of concomitant medication, see Appendices 4-6.
9. Criterion omitted
10. If on urate-lowering therapy, a stable dose and regimen for at least 2 weeks prior to randomization and expectance to remain on a stable dose and regimen for ≥ 2 weeks after administration of the first dose of study treatment.
11. Women of childbearing potential willing to use adequate contraception.
12. If applicable, willingness and capability to make s.c. injections at home.
13. Willingness and capability to use an electronic device for e.g. recording of pain.

Inclusion criteria for IMP treatment of *subsequent* flare(s):

14. Patient-reported, current flare of gouty arthritis characterized by pain intensity in the index joint of ≥30 mm on a 0–100 mm VAS, see section 7.2.1.
15. Tender (≥1 on a 0-4-point Likert scale) and swollen (≥1 on a 0-4-point Likert scale) index joint.
16. Women of childbearing potential willing to use adequate contraception.

7.3.2 Exclusion criteria

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

1. Use of specified pain relief medications or biologics (including glucocorticoids, narcotics, paracetamol/acetaminophen, NSAIDs, colchicine, IL-blockers and tumor necrosis factor [TNF] inhibitors) within specified periods (see Appendix 1) prior to randomization.
2. Contraindication to triamcinolone.
3. Polyarticular gouty arthritis involving more than 4 joints.
4. Rheumatoid arthritis, evidence/suspicion of infectious/septic arthritis, or other acute inflammatory arthritis.
5. History of malignancy within the past 5 years. Exceptions are basal cell skin cancer, carcinoma-in-situ of the cervix or low-risk prostate cancer after curative therapy.
6. Known hypersensitivity to *Escherichia coli*-derived proteins, Kineret® (anakinra), Kenalog® (triamcinolone acetonide) or any components of the products.

7. Participation in another concurrent investigational study within 30 days of randomization or intake of an investigational drug within five times the half-life of that investigational drug has passed.
8. Previous inclusion in this study.
9. Known presence or suspicion of active or recurrent bacterial, fungal or viral infections, including tuberculosis, or HIV infection or hepatitis B or C infection.
10. Presence of severe renal function impairment chronic kidney disease (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. Uncontrolled clinically significant hematologic, pulmonary, endocrine, metabolic, gastrointestinal, CNS or hepatic disease as judged by the investigator.
13. History of myocardial infarction, unstable angina, cerebrovascular events, or coronary artery bypass grafting, New York Heart Association (NYHA) class III or IV heart failure within the previous 3 months prior to Visit 1.
14. ECG with clinically relevant finding making the patient not appropriate for IMP treatment, as judged by the investigator.
15. Patients with a documented history of alcohol or substance abuse within 12 months prior to randomization (consumption of > 21 units of alcohol/week is considered alcohol abuse).
16. Patients who have undergone major surgery within 2 weeks prior to randomization, or have an unhealed operation wound/s.
17. Presence of any medical or psychological condition or laboratory result that in the opinion of the investigator might create risk to the patients (or interfere with the patient´s ability to comply with the protocol requirements, or to complete the study).
18. Earlier or current treatment with anakinra.
19. Pregnant or lactating women.
20. History of >12 flares overall in the 6 months prior to randomization.

Exclusion criteria for IMP re-treatment of *subsequent* flare(s):

21. IMP treatment of latest flare initiated within the last 14 days.
22. Known presence or suspicion of active or recurrent bacterial, fungal or viral infections, including tuberculosis, or HIV infection or hepatitis B or C infection.
23. Presence of severe renal function impairment CKD stages 4 and 5 (estimated creatinine clearance <30 mL/min/1.73m^2).
24. Presence of neutropenia (ANC < 1.5 x 10^9/L).
25. History of myocardial infarction, unstable angina, cerebrovascular events, or coronary artery bypass grafting, NYHA class III or IV heart failure within the previous 3 months prior to Visit 1.
26. ECG with clinically relevant finding making the patient not appropriate for IMP treatment, as judged by the investigator.
27. Patients who have undergone major surgery within 2 weeks prior to Visit 1, or have an unhealed operation wound/s.
28. Pregnant or lactating women.

29. Presence of any condition or laboratory result that in the opinion of the investigator makes the patient not appropriate for treatment with IMP.

7.3.3 Withdrawal of patients from treatment or study

7.3.3.1 Withdrawal from study treatment

A patient should be withdrawn from the study treatment if, in the opinion of the investigator, it is medically necessary, or if it is the wish of the patient.

When a patient is withdrawn from treatment, the date of the last IMP administration and the date and reason for treatment withdrawal should be clearly described in the relevant sections of the electronic case report form (eCRF). If a patient is removed from treatment because of an adverse event (AE), the reason for treatment withdrawal should always be stated as 'adverse event' irrespective of whether this was the investigator's or the patient's decision.

If a patient has been withdrawn from study treatment of one flare but fulfils the eligibility criteria for a subsequent flare, study treatment can be re-initiated. However, this is not applicable if the withdrawal from study treatment was due to a safety concern related to the IMP treatment, as judged by the investigator, see below (7.3.3.2).

All patients will continue to participate in the study and should be followed and assessed according to the protocol until the End of study follow-up call even if study treatment is discontinued unless consent is withdrawn or the patient is lost to follow-up.

7.3.3.2 Withdrawal from study

A patient can withdraw from the study at any time but should be encouraged to complete all study assessment up to Visit E, Day 28, following the last treated flare. If this is not possible an attempt should be made to examine the patient and collect relevant samples and make all relevant assessments according to the next scheduled visit.

The eCRF should be completed as far as possible .If a patient has been withdrawn from study treatment due to safety concerns as judged by the investigator to be related to IMP treatment the patient should be withdrawn from the study after Visit E.

If a patient's treatment allocation is unblinded at the request of the investigator, IMP treatment should be stopped and the patient should be withdrawn from the study after Visit E.

7.3.4 Replacement of withdrawn patients

Patients withdrawn from the study will not be replaced.

7.3.5 Screen failures

Screen failures are defined as patients who consent to participate in the clinical study but are not subsequently randomized into the study. A minimal set of screen failure information is required which includes demography, reason/s for screen failure, eligibility criteria, and any SAE.

Patients who do not meet the criteria for participation in this study (screen failure) may be rescreened for a later flare. Rescreened patients should keep the same study specific patient ID as for the initial screening.

7.3.6 Patients with data collection failure for primary endpoint

Patients with data collection failure for primary endpoint are defined as patients who are randomized in the clinical study but have no values collected for patient-assessed pain intensity from baseline to 72 hours for the first flare. These patients will however continue in the study and be included in the ITT and safety populations.

For each primary endpoint collection failures, one extra patient can be randomized in the study.

Maximum 10 extra patients can be randomized under this protocol.

7.4 Treatments

7.4.1 Treatments administered

The patients will receive IMPs according to the randomization schedule, Table 1.

Table 1 Investigational medicinal products

Arm	Investigational product	Dosage form	Route	Daily dose	Dosage regimen
A	Anakinra	Solution	s.c. injection	100 mg	Once daily for 5 days
	Anakinra placebo	Solution	s.c. injection	-	Once daily for 5 days
	Triamcinolone placebo	Solution	i.m. injection	-	Single injection
B	Anakinra	Solution	s.c. injection	100 mg	Once daily for 5 days
	Anakinra	Solution	s.c. injection	100 mg	Once daily for 5 days
	Triamcinolone placebo	Solution	i.m. injection	-	Single injection
C	Anakinra placebo	Solution	s.c. injection	-	Once daily for 5 days
	Anakinra placebo	Solution	s.c. injection	-	Once daily for 5 days
	Triamcinolone	Solution	i.m. injection	40 mg	Single injection

7.4.2 Identity of investigational medicinal products

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

The matching placebo for anakinra is delivered as a sterile solution for injection in a single-use prefilled syringe identical to the anakinra 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] and drug product and matching placebo for anakinra are manufactured [redacted]

The registered triamcinolone (Kenalog®) will be used as reference product and a matching placebo triamcinolone will be prepared for this study. The triamcinolone acetonide placebo is manufactured by [redacted]

The reference product, triamcinolone acetonide (Kenalog®), is delivered in vials containing a 40 mg/mL solution, 1 mL for i.m. injection.

The matching placebo for triamcinolone acetonide injectable suspension is manufactured as an emulsion to have the same appearance as the reference product. The triamcinolone acetonide placebo will be prepared by diluting commercially available lipid emulsion with physiological saline to obtain a white emulsion with appropriate tonicity for i.m. injection. The obtained emulsion is identical in appearance as the comparator suspension. The triamcinolone acetonide placebo is delivered in a vial and stopper identical to the triamcinolone acetonide vial and stopper. However, the colour of the caps on the Kenalog vials and the corresponding placebo vials might not be identical during the whole study duration (see section 7.4.6.2 regarding the role of the unblinded pharmacist/nurse).

Labeling will comply with national regulatory requirements.

Possible deficiencies related to the quality or identity of the investigational products should be reported both to the CRO study monitor and also directly to complaints@sobi.com.

7.4.3 Storage of IMP

The IMP (anakinra or placebo prefilled 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. The IMP should not be frozen or shaken.

Possible deficiencies related to site distribution or storage of IMP should be reported in accordance with instructions provided in the IMP handling manual.

For more details, see also 7.4.6.

7.4.4 Method of assigning patients to a treatment group

The patients will be randomized to treatment with 100 mg anakinra, 200 mg anakinra or 40 mg triamcinolone in a 1:1:1 ratio.

The randomized groups will be as follows:

Arm A: anakinra 100 mg,

Arm B: anakinra 200 mg

Arm C: triamcinolone 40 mg

An IWRS will be used for the randomization. Biostatistics at Perceptive will generate the randomization scheme for the IWRS, which will link sequential patient randomization numbers to treatment codes.

The randomization will be stratified by ULT use (yes/no) and BMI (<30.0 or ≥30.0 kg/m^2) at inclusion.

The randomization numbers will be generated in blocks. Within each block, equal numbers of patients will be allocated to each treatment group. The block size will not be revealed before breaking of the blind.

A separate IWRS manual will be provided to the investigators.

7.4.5 Selection of doses

Refer to Section 7.2.4.1, 7.2.4.2 and 7.2.4.3 for the rationale for the selected dosage regimen, dose levels and treatment duration. The rationale for the choice of reference product is presented in Section 7.2.3.

7.4.6 Selection and timing of doses for each patient

7.4.6.1 Home storage and transportation

The Day 1 IMP injections will be administered at the hospital/clinic. Patients who are then discharged from the hospital or clinic, will get IMP for the next two days (Day 2 and 3) to be injected at home. The patients will return to the hospital/clinical Day 4 and the fourth dose of IMPs will be administered at site. When the patients return home they will get the IMP for the next day (Day 5) to be injected at home. The IMP will be transported by the patients to their homes in provided cold packs. The IMPs should be kept refrigerated at home in its original cartons and protected from light. The IMPs should not be frozen or shakened during storage.

7.4.6.2 Preparation and dosage

Anakinra and matching placebo

At each day of IMP administration period (Days 1 to 5), the anakinra and/or matching placebo will be given as two (2) s.c. injections of 0.67 mL solution in single-use prefilled syringes for s.c. injection.

30 minutes before injection, the prefilled syringes should be taken out from cold storage to equilibrate the injection solution with room temperature.

Triamcinolone and matching placebo

At Visit 1 of each flare, the triamcinolone or matching placebo will be given as one (1) i.m. 1 mL injection withdrawn with a syringe from a vial containing a 40 mg/mL solution. The vial should be shaken before use to ensure a uniform suspension. Prior to withdrawal, the suspension should be inspected for clumping or granular appearance (agglomeration). An agglomerated product results from exposure to freezing temperatures and should not be used.

In addition to the above instructions, a separate study drug handling manual will be provided. The manual will include working instructions for unblinded pharmacist/nurse responsible for removal of the triamcinolone/placebo vial caps if the caps differ in colour. The unblinded pharmacist/nurse must not be involved in the conduct of the study. The study monitor will inform the Investigator/Study Coordinator if an unblinded procedure is needed.

7.4.6.3 Administration

The IMP administration will be initiated on the day of randomization (Visit 1) and the administrations scheduled for the first day of each flare will be supervised or given by the investigator (or delegated study staff) at the out-patient clinic, emergency department (ED) or hospital. If the patient is treated by an out-patient clinic or is discharged from ED/hospital before the end of 5-day IMP administration period, the daily s.c. injections at 24, 48 hours and Day 5 will be administered at home by the patient themselves or a caregiver.

At the 72-hour visit (Day 4, Visit 2), the IMP administration will be supervised or given by the investigator.

Instructions on appropriate use should be given by the investigator to the patient or caregiver. Patients or caregivers should not be allowed to administer any IMP until the patient or caregiver has demonstrated a thorough understanding of procedures and an ability to inject the IMP correctly. A patient leaflet with detailed instructions on the handling, injection and disposal of IMP will be handed out.

Anakinra and matching placebo

The IMP should be administered using subcutaneous injections into fat tissue.

The used syringes should be disposed of and the patients will receive disposal boxes for at home use.

Triamcinolone and matching placebo

For systemic therapy, injection should be made deeply into the gluteal muscle. For adults, a minimum needle length of 1½ inches is recommended. In obese patients, a longer needle may be required.

Throughout each treatment period, the actual number of IMP administrations and timepoint of each administration will be recorded in the eCRF or the patient diary.

7.4.7 Blinding

The first part of the study, i.e. treatment and follow-up of the patients' first flare, is double-blind. Treatment assignment will be blinded for the patients, the investigators and any personnel involved with the study conduct or evaluation at the investigational sites, CRO and sponsor.

Until all patients have completed the Day 15 visit of the first flare (Visit 4), the randomization scheme will only be disclosed to selected CRO personnel to ensure correct packaging of the IMP and correct set-up of the IWRS. The disclosure of the randomization scheme and any individual patient's treatment assignment will be protected by standard operating procedures (SOPs) of the CRO.

When all patients have completed the Day 15 visit of the first flare, collected data up to this date will be analysed by the Sponsor. Blinding will be maintained for patients, investigators, site staff, CRO and applicable vendors throughout the extension phase to prevent any bias in data handling. The Sponsor will take no part in the operational conduct of the study during the extension phase. Details of this process will be outlined in the "Process guideline data integrity document"

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 IWRS manual.

7.4.8 Prior and concomitant therapy

For a list of medication restricted or prohibited (including timeframe) before randomization, see Appendix 1. Other therapy considered necessary for the patient's welfare may be given at the discretion of the investigator.

All therapy taken within specified timelines (see below) prior to and up to 30 days after first IMP administration of each treated flare will be recorded in the eCRF:

- 3 months: treatment with amiodarone, digitoxin, leflunomide, and amphotericin
- 1 month: all other prescription drugs
- 1 week: herbal products, vitamins, minerals, and over-the-counter medications

No other medicinal product under investigation may be used during the study.

Live vaccines should not be given concurrently with anakinra.

Patients are allowed to take urate lowering therapy (ULT) during the study. To be eligible for study participation, the patients should be on a stable dose and regimen for ≥ 2 weeks prior to randomization and expected to remain on a stable dose and regimen for ≥ 2 weeks after study start. During the study, initiation or change of dose and regimen of ULT treatment are allowed after the pain assessment at Day 15 of each flare. The treatment should follow ACR guidelines for ULT (13).

Concomitant pain medication will be restricted and only rescue medication will be allowed, see 7.5.5.4.

7.4.9 Treatment compliance

The date and time of the IMP administrations on Day 1 (Visit 1) and Day 4 (Visit 2) will be recorded in the eCRF. The date and time of the IMP administrations on Days 2, 3 and 5 will be recorded in the patient diary.

7.4.10 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 trials. No specific treatment is indicated for IMP overdose. If an overdose of IMP is administered, the actual dose taken should be recorded in the eCRF, and any untoward medical occurrence associated with an overdose should be recorded the same way as any adverse event (see section 7.5.6.1).

7.5 Efficacy and safety assessments

7.5.1 Study schedule

7.5.1.1 Schedule of events

See appendix 2.

7.5.1.2 Pre-screening (optional)

Pre-screening is optional and may be done to identify patients that fulfil the study eligibility criteria with the exception of having a current flare of gouty arthritis.

When a pre-screened patient reports a flare of gouty arthritis, the procedures for the baseline visit (Visit 1) will be followed.

7.5.1.3 Baseline, Visit 1

A signed informed consent form must be obtained from the patient prior to any study-related activities. Once the ICF has been signed, the patient will be assigned an enrollment number.

Any SAE that occur after informed consent has been signed must be reported (see Section 7.5.6.1.4).

Data will be collected on medical and surgical history (see Section 7.5.2), prior and concomitant medication (see Section 7.4.8) and demographics (see Section 7.5.4).

Medical examination of current flare (see 7.5.3), local screening laboratory safety assessments (see Section 7.5.6.2), vital signs and physical examination (see Section 7.5.6.3) and a 12-lead ECG (see Section 7.5.6.4) will be performed.

The joint that is most affected, i.e. most painful, will be defined as the index joint and the patient will assess the pain intensity in the index joint on a VAS and Likert scale. These pain assessments will be done as close as possible to randomization and will serve as baseline values.

Once all inclusion and exclusion criteria have been reviewed and recorded (see Section 7.3) and the patient has been found eligible, the patient will be randomized and assigned a randomization number.

Prior to the first IMP administration, blood will be collected for central laboratory safety assessments (see 7.5.6.2), CRP and SAA(see 7.5.5.6), immunogenicity assessments (see 7.5.6.5), exploratory inflammatory biomarkers (see 7.5.8), exploratory pharmacogenetic markers (see 7.5.8.3) and IL-1Ra/anakinra serum concentration assessments (see 7.5.7). The patient assessment of health related quality of life (SF-36® and EQ-5D-5L), the physician´s assessment of clinical signs will be performed (see 7.5.5).

Once all predose assessments have been completed, the IMP (i.m. and s.c. injections) will be supervised or administered by the investigator. If the patient or a caregiver is to administer subsequent s.c. injections at home, detailed instructions will be given before discharge (not applicable if patient is hospitalized) (see 7.4.6.3) and IMP for Days 2 and 3 will be provided to the patient.

The patient will be given detailed instructions on how to use the patient diary to record pain intensity (VAS and Likert scale), IMP administration and intake of rescue medication. The patient will also be instructed on the use of permitted rescue medication.

Adverse events, both serious and non-serious, will be recorded from the time point of the first IMP administration (see 7.5.6.1).

For subsequent flares, Visit 1 will not include the informed consent procedure, randomization and recording of demographic data (except body weight).

7.5.1.4 Follow up by telephone at 24 and 48 hours (reminder calls)

Follow up telephone calls to remind the patient to complete the pain intensity assessements and to record the IMP-adminstration and intake of any rescue medication will be made at 24±2 hours and at 48±2 hours after the first IMP administration.

7.5.1.5 72-hour, Visit 2

Visit 2 will occur 72±4 hours after the first IMP administration of each flare (Day 4).

Vital signs will be recorded and data will be collected on concomitant medication including rescue medication. Adverse events will be recorded.

The compliance with the instructions for how to use the patient diary will be reviewed.

Prior to the IMP administration, blood will be collected for central laboratory safety assessments, CRP and SAA, exploratory inflammatory biomarkers and IL-1Ra/anakinra serum concentration assessments. The patient´s assessment of pain intensity, the patient´s global assessment of response to treatment, the physician´s global assessment of response to treatment, the physician´s assessment of clinical signs will be performed

Once all predose assessments have been completed, the IMP (s.c. injections) will be supervised or administered by the investigator.

If the patients is to take the remaining s.c. injection at home, IMP for Day 5 will be provided to the patient.

7.5.1.6 Day 8, Visit 3

Visit 3 will occur 1 week after the first IMP administration of each flare (Day 8±1 day).

The patient´s assessment of pain intensity, the patient´s global assessment of response to treatment, physician´s global assessment of response to treatment, the physician´s assessment of clinical signs will be performed.

The patient´s assessment of health related quality of life (SF-36® and EQ-5D-5L), will be performed and the health care resource utilization including WPAI:SHP will be recorded.

Vital signs will be recorded and data will be collected on concomitant medication including rescue medication. Adverse events will be recorded.

The compliance with the instructions for how to use the patient diary will be reviewed.

Blood will be collected for central laboratory safety assessments, CRP and SAA, immunogenicity assessments, and IL-1Ra/anakinra serum concentration assessments.

7.5.1.7 Day 15, Visit 4

Visit 4 will occur 2 weeks after the first IMP administration of each flare (Day 15±1 day).

The patient´s assessment of pain intensity, the patient´s global assessment of response to treatment, physician´s global assessment of response to treatment, the physician´s assessment of clinical signs will be performed.

The patient´s assessment of health related quality of life (SF-36® and EQ-5D-5L), will be performed and the health care resource utilization including WPAI:SHP will be recorded.

Blood will be collected for central laboratory safety assessments, CRP and SAA, immunogenicity assessments, exploratory inflammatory biomarkers and IL-1Ra/anakinra serum concentration assessments.

Vital signs, physical examination and concomitant medication including rescue medication will be recorded. Adverse events will be recorded.

The compliance with the instructions for how to use the patient diary will be reviewed.

7.5.1.8 Day 28, Visit E

Visit E will only be performed at Day 28±2 days if no subsequent flare has occurred.

Adverse events and concomitant medication will be recorded. Blood will be collected for, immunogenicity assessments and IL-1Ra/anakinra serum concentration assessments.

7.5.1.9 Week 12, Visit 5

Visit 5 will only be performed at Week 12±5 days if no subsequent flare has occurred.

SAEs and outcomes of previously recorded AEs will be recorded and blood will be collected for CRP and SAA, immunogenicity assessments, exploratory inflammatory biomarkers and IL-1Ra/anakinra serum concentration assessments.

7.5.1.10 Follow up by telephone every 12 weeks (retention calls)

A follow-up telephone call to record outcomes of previously reported AEs and encourage patient to remain in the study will be done every 12 weeks ± 5 days after Visit 5 of last flare. These calls will be performed until study end.

7.5.1.11 End of study call

An end-of-study phone call will be performed either;

1. 52 weeks after randomization of the last patient in the study

or

2. 104 weeks after randomization of the individual patient

whichever occurs first.

If the IMP treatment started week 40 or later in case 1), or week 92 weeks in case 2), the Week 12 visit will replace the End-of-study follow-up by phone.

Outcomes of previously reported AEs will be recorded.

7.5.2 Medical and surgical history

The patient's medical and surgical history will be recorded in the eCRF at Visit 1 at first flare and will be updated at Visit 1 of subsequent flares.

The patient´s gouty arthritis, the disease duration, the number of gouty arthritis flares during the past 12 months, presence of tophi and presence of gout-related joint damage will be recorded at the first flare.

Detailed information on the presence of the following selected comorbidities will be collected: CKD, current or previous symptoms of heart failure, diabetes, hypertension, obesity, coronary artery disease, hypercholesterolemia, osteoporosis and presence of severe infections. For definitions, see Appendix 3.

Intolerance, unresponsiveness, contraindication or other inappropriateness for treatment with NSAIDs and colchicine will be recorded.

The source of information may be medical records, referral letters, interviews and/or clinical assessments.

7.5.3 Medical examination of current flare

Time of pain onset, the number and distribution of joints involved and index joint will be determined and recorded in the eCRF at Visit 1 of each flare.

The medical examination of subsequent flares will be recorded even if the patient is not eligible for IMP treatment of the current flare.

7.5.4 Demography

The patient's date of birth, gender, race, ethnicity, body weight, body length and waist circumference will be recorded in the eCRF at Visit 1 of the first flare. The body weight recording will be repeated at Visit 1 of subsequent flares.

7.5.5 Efficacy assessments

7.5.5.1 Patient-assessed pain intensity, VAS scale

The patients will score their current pain intensity in the joint most affected (i.e., the index joint) on a continuous 0-100 mm visual analogue scale (VAS), ranging from no pain (0) to unbearable pain (100).

For each flare, the pain intensity will be assessed in the index joint and recorded in the patient diary prior to the first IMP administration. Subsequent pain assessment will be recorded in the patient diary at 6, 12, 18, 24, 36, 48, 72 hours and Day 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 and 15. At 24, 48, 72 hours and Day 5, the assessments will take place just before IMP administration. If the time point for assessment occurs during sleep, pain intensity will be recorded just before and after sleep, and the assessment closest to the scheduled timepoint will be used in the analysis.

7.5.5.2 Patient assessed pain intensity, Likert scale

In addition to the VAS scale, the patients will score their current pain intensity in the index joint on a 5-point Likert scale (0-4 point scale: "none", "mild", "moderate", "severe", "extreme").

For each flare, the pain intensity will be assessed in the index joint and recorded in the patient diary prior to the first IMP administration. Subsequent pain assessment will be recorded in the patient diary at 6, 12, 18, 24, 36, 48, 72 hours and Day 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 and 15. At 24, 48, 72 hours and Day 5 the assessments will take place before IMP administration. If the time point for assessment occurs during sleep, pain intensity will be recorded just before and after sleep.

7.5.5.3 Global response to treatment, Likert scale

Both the patient and the investigator will assess the global response to treatment on a 5-point Likert scale (0-4 point scale: 0=excellent, 1=very good, 2=good, 3=fair, 4=poor response to treatment).

For each flare, the global response to treatment will be assessed in the eCRF at 72 hours, Day 8 and Day 15.

7.5.5.4 Use of rescue medication

Patients who have difficulty in tolerating their pain are allowed to take rescue medication as needed after the 24-hour post-dose pain assessment but not within 6 hours before the 48- and 72-hour post-dose pain assessments.

Rescue medication can be used at the discretion of the investigator and should be prescribed according to the product label; contraindications, interactions and precautions.

Permitted rescue medication includes paracetamol/acetaminophen (up to 1000 mg 4 times daily) and/or codeine (up to 50 mg 4 times daily) or short acting tramadol (up to 100 mg 4 times daily).

Topical ice/cold packs may also be used as rescue therapy.

However, patients will be permitted to continue thrombosis prophylaxis with low dose acetyl salicylic acid (≤ 325 mg/day).

At the discretion of the investigator, patients still having insufficient relief with above drugs after the 72-hour post-dose pain assessment are allowed to take oral prednisone, prednisolone or equivalent at a dose up to 0.5 mg/kg per day for a maximum of 5 days.

Subsequent flares occurring before Day 15 of the latest flare will be treated with permitted rescue medication.

The name, dose, date and time of all rescue medication taken at site will be recorded in the eCRF at Visit 1 to 4 of each flare. Rescue medication taken at home between Visit 1 and 4 of each flare will be recorded in the patient diary.

7.5.5.5 Clinical signs of the most affected joint (index joint tenderness, swelling and erythema)

The investigator will assess the tenderness (on the basis of palpation or passive motion) of the index joint on a 4-point Likert scale (0=no pain, 1=mild/patient states there is pain when touched, 2=moderate/patient states there is pain and winces, 3=severe/patient states there is pain, winces and withdraws).

The investigator will assess the swelling of the index joint on a 4-point Likert scale (0=no swelling, 1=mild swelling, 2=moderate swelling, 3=severe swelling or bulging beyond joint margins).

The investigator will assess erythema of the index joint as either “present” or “absent”.

For each flare, assessments of joint tenderness, swelling and erythema will be performed and recorded in the eCRF at baseline, 72 hours, Day 8 and Day 15.

7.5.5.6 Inflammatory biomarkers

Blood samples will be collected for assessment of CRP and SAA at baseline, 72 hours, Day 8, Day 15 and Week 12 of each flare. The date and time of blood collection will be recorded in the eCRF.

7.5.6 Safety assessments

7.5.6.1 Adverse events

7.5.6.1.1 Definitions

Adverse event

An adverse event is any untoward medical occurrence in a patient or trial subject 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 adverse event.
- The test result leads to a medical/surgical intervention including withdrawal of IMP(s) 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.

Gouty arthritis flare

A flare of gouty arthritis 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 eCRF.

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 patient or may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse.

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

Hospitalization

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

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

Hospitalization or prolongation of 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.

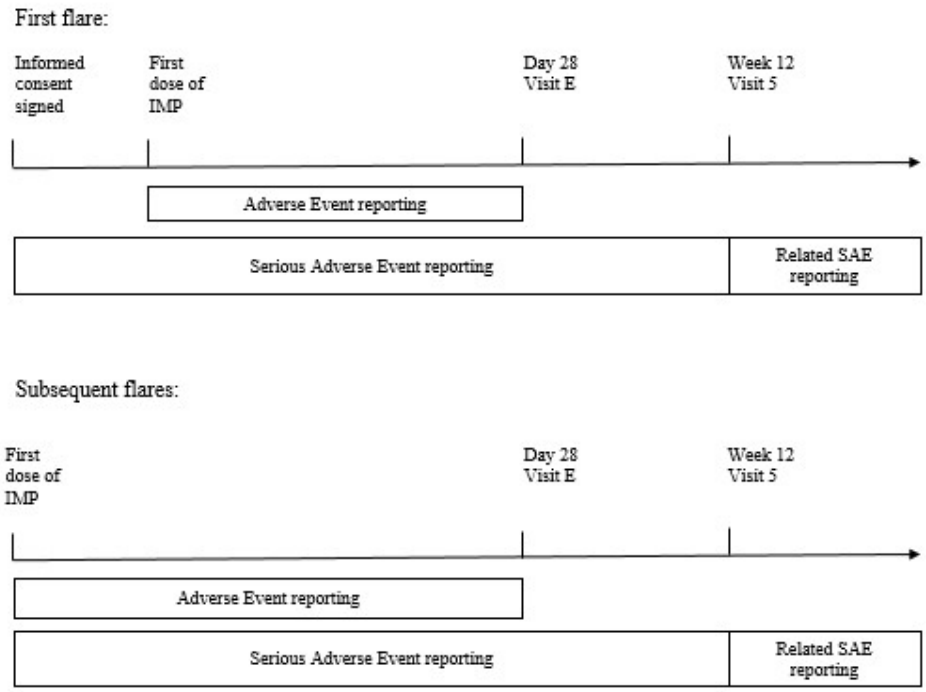
7.5.6.1.2 Adverse event reporting period

The period for recording all adverse events, including SAEs, on the eCRF begins upon receiving the first dose of IMP and ends at visit E, 28 days after the first dose of IMP. SAEs will also be collected from signing of the ICF until the Week 12 visit (Visit 5). Furthermore, any SAE should be reported irrespective of the time of occurrence if a causal relationship between the event and the IMP(s) is suspected, Figure **2**.

If the patient is treated with IMP for a subsequent flare, the adverse event (including SAE) reporting period starts again when the first dose is administered.

Refer to section 7.5.6.1.4 for information how unresolved adverse events and SAEs should be followed up.

Figure 2 **AE reporting**



7.5.6.1.3 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 eCRF using concise medical terminology. In addition, each patient will be questioned about adverse events at each clinic visit and follow up during the AE-reporting period (see Figure 2). At visit 2 of each flare the question asked will be "Since you started treatment of this flare have you had any health problems". At subsequent visits 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).

7.5.6.1.4 Serious adverse event reporting

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

If an SAE occurs, Drug Safety at PRA is to be notified by entering required information about the SAE into the appropriate module of the eCRF using the designated Serious Adverse Event Form within 24 hours of awareness of the event by the investigator.

The form for collection of SAE information is not the same as the general adverse event eCRF page. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same adverse event term should be used on both forms.

All new information obtained, relevant to an SAE report, should be forwarded to Drug Safety at PRA within the same timeframe as the initial information.

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

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

Fax information to Drug Safety at PRA. For the attention of:

PRA Drug Safety associate

Toll Free Fax: 1.888.772.6619

Toll Free Phone: 1.800.772.2215

Email: SAOSafety@prahs.com

7.5.6.1.5 Exposure during pregnancy

All events of exposure to the IMP during pregnancy (female patient or male patient's partner) shall be reported to Drug Safety at PRA Health sciences (see section above 7.5.6.1.4) 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).

In all reported situations of exposure during pregnancy, PRA Health sciences will provide the investigator with a Pregnancy Report Form which shall be completed and returned by the investigator. The investigator is responsible for monitoring the outcome of the pregnancy and to inform PRA (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 or delivery should be recorded in the eCRF and as applicable be reported to PRA Health sciences as described previously in this section.

7.5.6.1.6 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 follow-up by telephone, as applicable. How to report changes in an ongoing adverse event during a patient's participation in the study is described in the eCRF 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.

7.5.6.2 Laboratory safety assessments

Clinically significant abnormal laboratory values should be reported as adverse events (see 7.5.6.1.1 for details).

Blood and urine samples for determination of hematology, biochemistry and coagulation variables will be collected before the first IMP administration, at 72 hours (before IMP administration), Day 8 and Day 15 of each flare, see Table 2. The date and time of blood and urine collection will be recorded in the eCRF.

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. The procedures and materials used, e.g. collection and storage tubes, will be described in the laboratory manual.

Laboratory safety assessments performed to assess a patient´s eligibility for study inclusion will be conducted by the local laboratories according to each clinic´s standard procedures. All other laboratory safety analyses will be performed by the central safety laboratory using routine methods. The sampling handling procedures for laboratory tests run at the local laboratory will be described in the laboratory manual.

Table 2 The laboratory safety variables

Biochemistry Aspartate aminotransferase (AST)* Alanine aminotransferase (ALT)* Total bilirubin* (if >upper limit of normal also conjugated and non-conjugated bilirubin) Alkaline phosphatase (ALP) Prothrombin Time/International Normalized Ratio (PT-INR)* Albumin* Cholesterol (total, LDL and HDL) Triglycerides Creatinine* Sodium (Na)* Potassium (K)* Ferritin Erythrocyte sedimentation rate* Uric acid Glucose* HbA1c Troponin T C-reactive protein (CRP) Serum amyloid A (SAA) Calcium Magnesium	**Hematology** Hemoglobin* Hematocrit White blood cells* Differential blood count* Thrombocytes* **Bacteriology** Tuberculosis§ **Urine analysis** Albumin U-erythrocytes Human chorionic gonadotropin (hCG) test (for women of child-bearing age)*

*At Visit 1 of each flare, these laboratory safety variables will also be assessed at the local laboratory to assess a patient´s eligibility before inclusion. Baseline safety laboratory tests can be taken up to 72 hours before randomization, provided that the patient does not show signs and/or symptoms of new ailments or increasing signs and/or symptoms of known concomitant diseases.

§To be taken at Visit 1 or 2 (if Visit 1 occurs on a Friday or Saturday) of first flare to have result available before treatment of subsequent flares.

7.5.6.3 Vital signs and physical examination

Vital signs (blood pressure, heart rate and body temperature) will be recorded in the eCRF before the first IMP administration, at 72 hours (before IMP administration), Day 8 and Day 15 of each flare.

Blood pressure and heart rate will be measured in sitting position after the patient has rested comfortably for at least 5 minutes.

Body temperature will be measured using a tympanic thermometer according to each clinic´s standard procedures.

Clinically significant abnormal vital signs values should be reported as adverse events (see 7.5.6.1.1 for details).

A general physical examination will be assessed and recorded as “normal” or “abnormal” at Day 1 and Day 15. Abnormalities should be specified. Any persisting abnormalities should be stated each time the examination is performed. New abnormalities should be recorded as adverse events.

7.5.6.4 Electrocardiograms

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

All recorded ECGs will be reviewed by the investigator and the review will be documented in the eCRF. If a patient shows an abnormal ECG, additional safety recordings may be made and the abnormality followed to resolution if required. If any 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 7.5.6.1 for details).

7.5.6.5 Anti-drug antibodies

Blood samples for determination of ADA will be collected before the first IMP administration, at Day 8, Day 15, Day 28 and Week 12 of each flare (at Day 28 and/or Week 12 only if no subsequent flare has occurred at an earlier time point). The date and time of blood collection will be recorded in the eCRF.

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 analytical site 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.

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 an antibody positive result and a confirmatory assay with a statistically pre-defined confirmatory cut-point. Confirmed positive samples will be further analysed for antibody titers and for potential cross-reactivity with IL-1Ra that has been 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 analysed for the presence of neutralizing antibodies (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 NAb in the sample.

7.5.7 Anakinra serum concentrations

7.5.7.1 Sampling procedure

Blood samples for determination of endogenous IL-1Ra/anakinra serum concentrations will be collected before the first IMP administration, pre-dose at 72 hours (as close to 24 hours after

previous IMP administration as possible), Day 8, Day 15, Day 28 and Week 12 of each flare (at Day 28 and/or Week 12 only if no subsequent flare has occurred at an earlier time point). The date and time of blood collection will be recorded in the eCRF.

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 bioanalytical laboratory 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.

7.5.7.2 Bioanalytical method

The current available bioanalytical method will not differentiate between endogenous IL-1Ra and anakinra concentrations in serum. Serum samples to determine the combined level of endogenous IL-1Ra concentrations/anakinra concentrations will be analyzed by York Bioanalytical Solutions Limited using a validated MSD-ECL method in which endogenous IL-1Ra/anakinra are captured between a solid phase bound monoclonal antibody and polyclonal antibodies to anakinra.

7.5.8 Exploratory assessments

7.5.8.1 Health related quality of life and health care resource utilization

Health related quality of life will be assessed by the patients using the Short Form (36) Health Survey (SF-36®, acute v. 2) and the EuroQol 5 dimension 5 levels (EQ-5D-5L) at baseline and at Day 8 and 15 at first and subsequent flares.
SF-36® measures the impact of disease on overall quality of life. It consists of eight individual domains that can be grouped into two domains; a physical component summary (PCS), composed of physical functioning, role-physical, bodily pain and general health, and a mental component summary (MCS) composed of vitality, social functioning, role-emotional and mental health (37). Scores range from 0 to 100, where 0 represents the worst possible health and 100 is perfect health (38). SF-36® has been validated for use in patients with gouty arthritis (39, 40). In this study the acute (one-week) recall version of SF-36® version 2 will be used (41). It was created by changing the recall period for six of the eight scales (Role-Physical, Bodily Pain, Vitality, Social Functioning, Role-Emotional and Mental Health) from “the past four weeks” to “the past week”. The other two scales, Physical Functioning and General Health, do not have a recall period and the items and instructions for these scales are accordingly identical in the acute and standard forms.

The EQ-5D-5L, a self-report questionnaire, is a descriptive system of health-related quality of life states consisting of five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) each of which can take one of five responses. The responses record five levels of severity (no problems/slight problems/moderate problems/severe problems/extreme problems) within a particular EQ-5D dimension.

Health care resource utilization due to acute gouty arthritis will be collected for the period between Day 1 and Day 15. Number of days with hospitalization and number of unscheduled

outpatient visits during the last week will be recorded at Day 8 and Day 15. In addition, the Work Productivity and Activity Impairment Questionnaire V2.0 (WPAI:SHP) will be completed by the patient at the same timepoints. The WPAI is a patient-reported quantitative assessment of the amount of absenteeism, presenteeism and daily activity impairment attributable to general health (WPAI:GH) or a specific health problem (WPAI:SHP). The 6 questions in the WPAI:SHP questionnaire for gout are; employment status (yes/no), work hours missed due to gout, work hours missed due to any other reason, hours of actual working, productivity while were working (0-10 scale; gout had no effect on my work/gout completely prevented me from working) and a global measure of activity impairment (1-10, gout had no effect on my daily activities/gout completely prevented me from doing my daily activities) (42). WPAI:SHP has a recall period defined as “past 7 days not including today”.

7.5.8.2 Exploratory inflammatory biomarkers

Blood samples for determination of the exploratory inflammatory biomarkers IL-6, IL-8, calprotectin, neopterin and myeloperoxidase (MPO) will be collected before the first IMP administration, at 72 hours (before IMP administration), Day 15 and Week 12 of each flare. The date and time of blood collection will be recorded in the eCRF.

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 also be described in the laboratory manual.

Samples collected for IL-8, calprotectin and neopterin will be analyzed by Eurofins Global Central Laboratory, Bergschot 71, 4817 PA Breda, the Netherlands. Full details of the methods used will be described in a separate bioanalytical report(s). Blood samples collected for later analysis of IL-6, MPO and possibly other exploratory biomarkers will be stored at the Eurofins laboratory in case of a need to further evaluate proinflammatory responses/lack of response to treatment.

7.5.8.3 Exploratory pharmacogenetic assessment

A pharmacogenetics sample will be collected at Day 1 of the first flare from all patients randomized in the study. 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 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 examined

prior to any analytical measurements as part of the analytical method validation, to rule out any possible interference with the analyte.

8 Quality control and quality assurance

This study will be conducted in compliance with this protocol, study specific procedures, CRO 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.

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 eCRFs. All patient informed consent forms 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.

9 Statistical plan

9.1 Determination of sample size

Up to totally 169 patients can be randomized in the study. Initially 159 patients will be randomized, 53 to triamcinolone and 106 to anakinra (53 to 100 mg and 53 to 200 mg). As described in protocol section 7.3.6, up to a maximum of 10 extra patients can be randomized.

The sample size calculation is based on the change in pain intensity on a VAS 0-100 mm from baseline to the average over 24-72 hours. A sample size of 106 randomized patients receiving anakinra and 53 randomized patients receiving triamcinolone is required to ensure a power of 80% to reject the null hypothesis of no difference between anakinra and triamcinolone assuming a true difference of 12 mm on VAS mean change and a standard deviation of 25 mm when using a two-sided test with a significance level of 5%.

9.2 Definition of study populations

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

Intention-to-treat (ITT) population: This population is the primary analysis population and will comprise all randomized patients, grouped according to randomized treatment.

Per-protocol (PP) population: This population will comprise all ITT patients who have no major protocol violations potentially affecting efficacy. Patients will be grouped according to treatment

actually received and the actual stratification information. Patient assignment to the PP population will be performed prior to breaking the blind.

Safety population: This population will comprise all patients who received at least one dose of investigational product. Patients will be grouped according to actual treatment during the first gouty arthritis flare.

The ITT is the primary analysis population for the primary and secondary efficacy endpoints. Presentations of efficacy endpoints for subsequent flares will also be based on the ITT population. The PP population will be used for sensitivity analyses of efficacy endpoints for the first flare. The safety population will be used for analyses of safety endpoints for the whole study period.

9.3 Overall statistical and analytical plan

All details of the statistical analyses of primary and secondary variables will be described in a separate study specific statistical analysis plan (SAP) which will be finalized before the clinical database is locked for the study period containing the first gouty arthritis flare and the treatment code unblinded.

Statistical analysis will be performed using SAS software Version 9.4 or later (SAS Institute, Inc, Cary, North Carolina, United States).

9.3.1 General statistical issues

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 mean value for each treatment group, the estimated difference between groups, the associated 95% two-sided confidence interval and p-value.

9.3.2 Demographics and baseline characteristics

Demographic data and baseline characteristics including physical examination and medical examination of current flare will be presented using summary statistics. Continuous variables will be summarized using the number of patients, the mean, the standard deviation, the median, the minimum value, and the maximum value. Categorical variables will be summarized using frequency counts and percentages.

9.3.3 Analysis related to primary objective

9.3.3.1 Primary endpoint

The primary endpoint is the change in patient-assessed pain intensity from baseline to 24-72 hours (average of the assessments performed at 24, 48 and 72 hours) for the patients' first flare.

The comparison of primary interest is between anakinra (100 mg and 200 mg combined) and triamcinolone, and the null and alternative hypotheses with regard to this are defined as:

H_0: $\mu_{anakinra} = \mu_{triamcinolone}$

H_A: $\mu_{anakinra} \neq \mu_{triamcinolone}$

The primary endpoint will be estimated using a mixed model repeated measures analysis with the measurements on the individual time points as responses (baseline, 6, 12, 18, 24, 48 and 72 hours), and with treatment (anakinra 100 mg, anakinra 200 mg and triamcinolone), ULT use (yes/no), BMI (<30.0 and ≥30.0 kg/m^2), visit and treatment-visit-interaction as fixed effects and center as random effect. An unstructured covariance matrix will be used to account for within-subject correlation.. The estimated mean change from baseline to 24-72 hours for each treatment group (anakinra and triamcinolone), the estimated difference between the groups and the associated 95 % confidence interval and p-value based on this model will be presented.

The assumptions of normality and homogeneity of variance will be assessed by inspection of normal probability plots and residual plots.

The primary efficacy analysis mixed model repeated measures approach assumes that the underlying missing data mechanism is missing at random (MAR). Since the MAR assumption may not hold, a tipping point analysis will be used for performing sensitivity analysis under the missing not at random (MNAR) assumption. For data that is missing, a shift parameter (with a range of values) will be added to imputed values. This will assess the value of the shift parameters, for anakinra and triamcinolone, which would overturn the conclusions of the primary analysis. The tipping point analysis will assume that the missing outcomes on anakinra and triamcinolone will vary independently including scenarios where the dropouts on anakinra have worse outcomes than triamcinolone.

The full details of the sensitivity analyses to assess the robustness of the primary analysis will be pre-specified in the SAP.

9.3.3.2 Secondary endpoints supporting the primary objective

To further evaluate the effect of anakinra, the change from baseline in pain intensity at 6, 12, 18, 24, 36, 48, 72 hours and at Days 5, 6, 7 and 8 for the first flare will be evaluated using the following two patient-assessed scales:

- Patient-assessed pain intensity in the index joint on a VAS scale
- Patient-assessed pain intensity in the index joint on a 5-point Likert scale

The VAS pain intensity will be evaluated using a similar mixed model repeated measures analysis as for the primary endpoint. For each time point, the estimated change from baseline for each treatment group (anakinra and triamcinolone), the estimated difference between the groups and the associated 95 % confidence interval and p-value based on this model will be presented.

The Likert pain intensity will be evaluated using a mixed model repeated measures analysis with the measurements on the individual time points as responses, and with treatment (anakinra 100 mg, anakinra 200 mg and triamcinolone), ULT use (yes/no), BMI (<30.0 and ≥30.0 kg/m^2), visit and treatment-visit-interaction as fixed effects. For each time point, the estimated mean change from baseline for each treatment group (anakinra and triamcinolone), the estimated difference

between the groups and the associated 95 % confidence interval and p-value based on this model will be presented.

9.3.4 Analysis related to secondary objectives

9.3.4.1 Pain intensity for anakinra dose groups, 100 and 200 mg

The primary endpoint, change in patient-assessed pain intensity as measured by VAS from baseline to 24-72 hour for the first flare, will be evaluated for the two different anakinra doses (100 mg and 200 mg) in comparison to triamcinolone.

The effect of the two different anakinra doses will be evaluated using the same mixed model repeated measures model analysis as for the primary endpoint. The estimated mean change from baseline to 24-72 hours for each of the two anakinra doses (100 mg and 200 mg) and triamcinolone, the estimated differences anakinra 100 mg – triamcinolone and anakinra 200 mg – triamcinolone and the associated 95% confidence intervals and p-values from the model will be presented.

The estimated mean change from baseline for the secondary endpoints supporting the primary endpoint for each of the two anakinra doses (100 mg and 200 mg) and triamcinolone, the estimated differences anakinra 100 mg – triamcinolone and anakinra 200 mg – triamcinolone and the associated 95% confidence intervals and p-values from the model will also be presented.

9.3.4.2 Response

Response is defined as at least 50% change from baseline pain intensity on VAS, and the time to response for the first flare will be analyzed using a stratified log-rank test, with ULT use (yes/no) and BMI (<30.0 or ≥30.0 kg/m^2) as stratification factors. Based on this model, the estimated hazard ratio (anakinra vs. triamcinolone), 95% confidence interval and p-value will be presented. Further, the hazard ratios for the comparisons of the two different anakinra treatment groups versus triamcinolone will also be estimated, with corresponding 95% confidence intervals and p-values.

In addition, the number and proportion of responders in the different treatment groups at 24, 48 and 72 hours, Day 8 and Day 15 will be presented.

The change in pain intensity will also be visualized by graphically presenting the percent of patients who improved in each category of percent improvement on the VAS scale at 72 hours.

9.3.4.3 Onset of effect

Onset of effect is defined as at least 20% change from baseline pain intensity on VAS, and the time to onset of effect for the first flare will be analyzed using a stratified log-rank test, with ULT use (yes/no) and BMI (<30.0 or ≥30.0 kg/m^2) as stratification factors. Based on this model, the estimated hazard ratio (anakinra vs. triamcinolone), 95% confidence interval and p-value will be presented. Further, the hazard ratios for the comparisons of the two different anakinra

treatment groups versus triamcinolone will also be estimated, with corresponding 95% confidence intervals and p-values.

In addition, the number and proportion of patients with onset of effect in the different treatment groups at 6, 12, 24, 48 and 72 hours will be presented.

9.3.4.4 Resolution of pain

Resolution of pain is defined as <10 mm in patient-assessed pain intensity on VAS, and the time to resolution for the first flare will be analyzed using a stratified log-rank test, with ULT use (yes/no) and BMI (<30.0 or ≥30.0 kg/m^2) as stratification factors. Based on this model, the estimated hazard ratio (anakinra vs. triamcinolone), 95% confidence interval and p-value will be presented. Further, the hazard ratios for the comparisons of the two different anakinra treatment groups versus triamcinolone will also be estimated, with corresponding 95% confidence intervals and p-values.

In addition, the number and proportion of patients with resolution of pain in the different treatment groups at 72 hours, Day 8 and Day 15 will be presented.

9.3.4.5 Rescue medication

Time to first intake of rescue medication during the first flare will be analyzed using a stratified log-rank test, with ULT use (yes/no) and BMI (<30.0 or ≥30.0 kg/m^2) as stratification factors. Based on this model, the estimated hazard ratio (anakinra vs. triamcinolone), 95% confidence interval and p-value will be presented. Further, the hazard ratios for the comparisons of the two different anakinra treatment groups versus triamcinolone will also be estimated, with corresponding 95% confidence intervals and p-values.

In addition, the proportion of patients who took rescue medication from the first IMP administration at Visit 1 up to and including Day 8 and Day 15 in the different treatment groups will be presented. The type and number of occasions of intake of rescue medication will also be presented by descriptive statistics.

9.3.4.6 Physician's assessment of global response to treatment

Physician's assessment of global response to treatment at 72 hours, Day 8 and Day 15 for the first flare will be evaluated using an analysis of variance model including factors for treatment (anakinra 100 mg, anakinra 200 mg and triamcinolone), ULT use (yes/no) and BMI (<30.0 or ≥30.0 kg/m^2). The estimated mean global response to treatment for each treatment group (anakinra and triamcinolone), the estimated difference between the groups and the associated 95% confidence interval and p-value from the model will be presented.

Further, the difference of the two different anakinra treatment groups versus triamcinolone will also be estimated, with corresponding 95% confidence intervals and p-values.

9.3.4.7 Physician's assessment of clinical signs

The investigator will assess the tenderness, swelling and presence of erythema in the index joint.

Physician's assessment of tenderness at 72 hours, Day 8 and Day 15 for the first flare will be evaluated using an analysis of covariance model including factors for treatment (anakinra 100

mg, anakinra 200 mg and triamcinolone), ULT use (yes/no) and BMI (<30.0 or ≥30.0 kg/m^2), and baseline tenderness as covariate. The estimated mean tenderness for each treatment group (anakinra and triamcinolone), the estimated difference between the groups and the associated 95% confidence interval and p-value from the model will be presented. Further, the estimated mean tenderness for each of the two anakinra doses (100 mg and 200 mg), the difference of the two different anakinra treatment groups versus triamcinolone will also be estimated, with corresponding 95% confidence intervals and p-values.

Physician's assessment of swelling at 72 hours, Day 8 and Day 15 for the first flare will be evaluated using an analysis of covariance model including factors for treatment (anakinra 100 mg, anakinra 200 mg and triamcinolone), ULT use (yes/no) and BMI (<30.0 or ≥30.0 kg/m^2), and baseline swelling as covariate. The estimated mean swelling for each treatment group (anakinra and triamcinolone), the estimated difference between the groups and the associated 95% confidence interval and p-value from the model will be presented. Further, the estimated mean swelling for each of the two anakinra doses (100 mg and 200 mg), the difference of the two different anakinra treatment groups versus triamcinolone will also be estimated, with corresponding 95% confidence intervals and p-values.

The presence of erythema at 72 hours, Day 8 and Day 15 for the first flare will be analyzed using a logistic regression model with treatment, ULT use (yes/no) and BMI (<30.0 or ≥30.0 kg/m^2) as explanatory variables. The estimated risk of erythema in each treatment group, the estimated odds ratio of anakinra to triamcinolone, the corresponding 95% confidence interval and the p-value from the model will be presented. Further, the odds ratios for the comparisons of the two different anakinra treatment groups versus triamcinolone will also be estimated, with corresponding 95% confidence intervals and p-values.

9.3.4.8 Patient´s assessment of global response to treatment

Patient's assessment of global response to treatment at 72 hours, Day 8 and Day 15 for the first flare will be evaluated using an analysis of variance including factors for treatment (anakinra 100 mg, anakinra 200 mg and triamcinolone), ULT use (yes/no) and BMI (<30.0 and ≥30.0 kg/m^2). The estimated mean global response to treatment for each treatment group (anakinra and triamcinolone), the estimated difference between the groups and the associated 95% confidence interval and p-value from the model will be presented. Further, the estimated mean global response for each of the two anakinra doses (100 mg and 200 mg), the difference of the two different anakinra treatment groups versus triamcinolone will also be estimated, with corresponding 95% confidence intervals and p-values.

9.3.4.9 Inflammatory biomarkers

The change from baseline in CRP at 72 hours, Day 8 and Day 15 will be evaluated using an analysis of covariance model including factors for treatment, ULT use (yes/no) and BMI (<30.0 or ≥30.0 kg/m^2), and baseline CRP as covariate. The estimated mean change in CRP for each treatment group (anakinra and triamcinolone), the estimated difference between the groups and the associated 95% confidence interval and p-value from the model will be presented. Further, the estimated mean change in CRP for each of the two anakinra doses (100 mg and 200 mg), the estimated differences anakinra 100 mg – triamcinolone and anakinra 200 mg – triamcinolone and the associated 95% confidence intervals and p-values from the model will be presented.

The change from baseline in SAA at 72 hours, Day 8 and Day 15 will be evaluated using an analysis of covariance model including factors for treatment, ULT use (yes/no) and BMI (<30.0 or ≥30.0 kg/m^2), and baseline SAA as covariate. The estimated mean change in SAA for each treatment group (anakinra and triamcinolone), the estimated difference between the groups and the associated 95% confidence interval and p-value from the model will be presented. Further, the estimated mean change in SAA for each of the two anakinra doses (100 mg and 200 mg), the estimated differences anakinra 100 mg – triamcinolone and anakinra 200 mg – triamcinolone and the associated 95% confidence intervals and p-values from the model will be presented.

The evaluation of CRP and SAA at Week 12 will be presented by descriptive statistics.

9.3.4.10 Subsequent flares

The evaluation of efficacy at subsequent flares will be presented by the combined anakinra group, the 2 different anakinra doses (100 mg and 200 mg) and triamcinolone, and by flare, i.e. patient's 2nd flare, 3rd flare etc.

Patient-assessed pain intensity on VAS and Likert will be summarized by descriptive statistics for each time point, i.e. baseline, 6, 12, 18, 24, 36, 48, 72 hours and Days 5, 6, 7 and 8 as well as the change from baseline at these time points.

The number and proportion of responders in the treatment groups at 24, 48 and 72 hours, Day 8 and Day 15 will be summarized by descriptive statistics.

The number and proportion of patients with onset of effect in the different treatment groups at 6, 12, 24, 48 and 72 hours will be summarized by descriptive statistics.

The number and proportion of patients with resolution of pain in the treatment groups at 72 hours, Day 8 and Day 15, respectively, will be summarized by descriptive statistics.

The number and proportion of patients that took rescue medication from the first IMP administration at Visit 1 up to and including the Day 8 visit in the treatment groups will be summarized by descriptive statistics. The type and amount of rescue medication will also be presented.

Physician's assessment of global response to treatment, physician's assessment of clinical signs and patient's assessment of global response to treatment at 72 hours, Day 8 and 15, respectively, will be summarized by descriptive statistics.

The change from baseline in CRP and SAA at 72 hours, Day 8 and Day 15, respectively, will be summarized by descriptive statistics.

9.3.4.11 Anti-drug antibodies

The number and proportion of patients with ADA and NAb at baseline, Day 8, Day 15, Day 28 and Week 12 will be summarized by descriptive statistics. ADA titers at baseline, Day 8, Day 15, Day 28 and Week 12 will be summarized by descriptive statistics. For baseline, Day 8 and Day 15, pain intensity on VAS will be presented by ADA presence and by NAb presence. The presentations will be repeated for each subsequent flare.

AEs and SAEs will be presented by ADA presence for the whole study period. AEs and SAEs will be classified as occurring during ADA presence when the starting date for the AE is within

the time period after the latest negative assessment until next negative assessment with a positive assessment of ADA in between.

9.3.4.12 Serum concentration of IL-1Ra/anakinra

The serum concentration of endogenous IL-1Ra/anakinra at baseline, 72 hours, Day 8, Day 15, Day 28 and Week 12 for the first flare and subsequent flare will be presented by descriptive statistics.

9.3.5 Analysis related to exploratory objectives

9.3.5.1 SF-36

Based on the SF-36 questionnaire, the patient's score for each of the individual eight domains as well as the PCS and the MCS will be calculated.

The change from baseline in SF-36 physical functioning domain score at Day 8 for the first flare will be evaluated using an analysis of covariance model including factors for treatment, ULT use (yes/no) and BMI (<30.0 or ≥30.0 kg/m^2), and baseline SF-36 physical functioning score as covariate. The estimated mean change in SF-36 physical functioning domain score for each treatment group (anakinra and triamcinolone), the estimated difference between the groups and the associated 95% confidence interval and p-value from the model will be presented.

The change from baseline in the patient's score for the other 7 domains as well as the PCS and the MCS will be presented by descriptive statistics.

For subsequent flares the 8 domains from SF-36 as well as the PCS and the MCS will be presented by descriptive statistics.

9.3.5.2 EQ-5D-5L

The change from baseline in the five domains in EQ-5D, the EQ-5D Index and the EQ-5D-VAS at baseline, Day 8 and Day 15 for each flare will be presented by descriptive statistics.

9.3.5.3 WPAI:SHP

Based on the WPAI:SHP the following scores will be calculated for Day 8 and Day 15; percent work time missed due to gout, percent impairment while working due to gout, percent overall work impairment due to gout and percent activity impairment due to gout.

The WPAI:SHP scores at Day 8 and Day 15 for the first flare and subsequent flares will be presented by descriptive statistics.

9.3.5.4 Health care resource utilization

The number of days with hospitalization and the number of un-scheduled outpatient visits from Day 1 to Day 15 for the first flare and subsequent flares will be presented by descriptive statistics.

9.3.5.5 Exploratory inflammatory biomarkers

The change from baseline in exploratory inflammatory biomarkers in serum (primarily IL-8, calprotectin and neopterin) at 72 hours, Day 15 and Week 12 (in case of no subsequent flare prior to the Week 12 time point) for the first flare and subsequent flares will be presented by descriptive statistics. The same presentations will be made if samples are analyzed for IL-6 and MPO.

9.3.6 Analysis of safety and tolerability data

Safety tabulations will be performed with respect to adverse event data, clinical laboratory results and vital sign data. Continuous variables will be summarized using the number of patients, the mean, the standard deviation, the median, the minimum value, and the maximum value. Categorical variables will be summarized using frequency counts and percentages. No statistical hypothesis tests will be performed.

All data will be displayed in individual patient data listings.

9.3.6.1 Adverse events

All adverse events will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA).

The number and percent 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 percent 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. Separate presentations will be made for the double-blind period (first flare) and the extension period.

9.3.6.2 Clinical laboratory results

Clinical laboratory safety data will be presented using summary statistics. In addition, the number of patients with abnormal laboratory values will be presented using shift tables. The presentations will be based on the results from the central laboratory safety data.

9.3.7 Interim analysis

No interim analysis of efficacy data is planned. The main efficacy analyses will be performed when all patients have completed the Day 15 visit of the first flare (Visit 4).

9.3.8 Multiple comparison/multiplicity

No adjustment for multiplicity will been performed.

9.3.9 Exploratory subgroup analyses

In order to examine the consistency of the treatment effect, the primary analysis will be repeated within predefined subgroups using the ITT population. These subgroups will include the randomization strata, ULT usage (yes/no) and BMI (<30.0 and ≥30.0 kg/m^2), as well as age (<65 years and ≥65 years), sex, race, renal function (CKD stage 1, 2 and 3*)* and usage of rescue medication during the first flare (yes/no). For each subgroup, the estimated change in pain intensity in each treatment group (anakinra and triamcinolone), the estimated difference in change in pain intensity between treatments and the corresponding 95% confidence intervals will be presented. P-values will not be presented. Further, the change in pain intensity will also be evaluated for the two anakinra doses for each subgroup.

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

9.3.10 Handling of missing data

Patients should continue in the study even if study treatment is withdrawn and every effort should be made to complete the assessments according to the protocol. The evaluation of patient-assessed pain using VAS and Likert scales have repeated assessment time points and repeated measures models will be used to handle missing data, i.e. no imputation is needed. To evaluate the robustness of this model for the primary endpoint, a tipping point analysis will be used for performing sensitivity analysis under the MNAR assumption (see 9.3.3.1 for details). For the secondary time-to-event analyses, patients who do not have an event at the time for analysis will be censored at the last time point with recorded information. For other secondary endpoints the analyses will be based on observed data. Details will be fully described in the SAP.

10 Data collection, handling and record keeping

10.1 Data standards

Collection of data should be performed in the Clinical Data Acquisition Standards Harmonization (CDASH) format, according to the Clinical Data Interchange Standards Consortium (CDISC). The standards should be used to the extent possible and/or required for the specific study/project. The minimum requirement of the CDISC standard is to collect all core variables specified as ‘Required’ in the Study Data Tabulation Model (SDTM) format.

10.2 Case report form

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

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

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

10.3 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 eCRFs must match those charts. In some cases, a portion of the source documents for a given patient may be the eCRF or the patient diary.

- In this study, the following are recorded as source data directly in the eCRFs: the index joint of current flare, time of pain onset, physician's assessment of global response to treatment
- In this study, the following are recorded as source data directly in the patient diary: IMP administration (date and time), rescue medication recorded by the patients between visits (name, dose, date and time), patient's assessment of pain intensity (VAS), patient's assessment of global response to treatment, SF-36, EQ-5D-5L, WPAI:SHP.

10.4 Database closure

The database will be locked twice, first for the primary analysis when all patients have conducted the Day 15 visit of the first flare in the study and then after study closure.

Prior to the first database closure, all tasks or criteria defined in the data management plan must be completed and documented. For the primary analysis, the study database will 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. After the data transfer for primary analysis has occurred, the database will be unlocked to continue with data entry activities. However, records pertaining to the primary analysis will stay locked. The database will be locked a second time following the same procedure after the study is considered completed.

Before each of the database locks medical coding will be performed by the CRO and approved by Sobi. AEs, diagnoses from Medical History and procedures will be classified according to the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). Previous and Concomitant Medications will be coded using the latest version of the World Health Organisation Drug Dictionary (WHODRUG) and a reconciliation of AEs in the clinical and safety database will be performed.

10.5 Record retention

To enable evaluations and/or audits from Health Authorities or Sobi, the investigator agrees to keep records in accordance with the essential documents defined in the ICH GCP Guidelines (1), including the identity of all participating patients (sufficient information to link records, e.g., eCRFs and hospital records), an archival copy on compact disc of the eCRFs provided by PRA and detailed records of IMP accountability. 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, another institution, or to Sobi. The investigator must obtain Sobi's written permission before disposing of any records.

11 End of study

The end of this study is defined as the date of the last patient's last visit/end of study call.

12 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 the primary analysis, when all patients have conducted the Day 15 visit of the first flare, Sobi reserves the right to discontinue the study if the data would indicate that the continuation of the study would not be appropriate.

After such a decision, the investigator must contact all participating patients within 30 days. The investigator shall return to the CRO all unused investigational product and other study materials, and complete all the eCRFs to the greatest extent possible.

13 Dissemination and publication of results

Sobi will publicly disclose this study by posting the protocol and study results on www.clinicaltrials.gov according to FDA requirements for trials studying a new use of an FDA-approved drug,.

After completion of the study, the data 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.

14 References

1 ICH Harmonised Guideline: Integrated addendum to ICH E6 (R1), Guideline for Good Clinical Practice E6 (R2). Current *Step 4* version dated 9 November 2016. Available from: http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html

2 World Medical Association Declaration of Helsinki; Ethical Principles for Medical Research Involving Human Subjects. Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, latest amendment at the to 64th WMA General Assembly, Fortaleza, Brazil, October 2013. Available from: http://www.wma.net/en/30publications/10policies/b3/

3 Todd KH et al. Clinical significance of reported changes in pain severity. Ann Emerg Med. April 1996;27:485-489.

4 Gallagher EJ et al. Prospective validation of clinically important changes in pain severity measured on a visual analog scale. Ann Emerg Med. December 2001;38:633-638.

5 Schlesinger N, at al. Canakinumab for acute gouty arthritis in patients with limited treatment options: results from two randomised, multicentre, active-controlled, double-blind trials and their initial extensions. Ann Rheum Dis, 2012;71:1839–1848.

6 Chakraborty A, et al. Pharmacokinetic and Pharmacodynamic Properties of Canakinumab in Patients With Gouty Arthritis. The Journal of Clinical Pharmacology 2013, 53(12) 1240–1251.

7 Chen K et al. Anakinra's efficacy is variable in refractory gout: Report of ten cases. Semin Arthritis Rheum, 2010;40:210-214.

8 Dalbeth N, et al. Outcome measures in acute gout: a systematic literature review. J Rheumatol. 2014a;41:558–568.

9 Dalbeth N, et al, Hyperuricaemia and gout: time for a new staging system? Ann Rheum Dis 2014b;73:1598-1600.

10 Ghosh P, et al. Treatment of acute gouty arthritis in complex hospitalized patients with anakinra. Arthritis Care Res 2013;65(8):1381–1384.

11 Keenan R, et al. Prevalence of contraindications and prescription of pharmacologic therapies for gout. Am J Med, 2011a;124:155-163.

12 Khanna D, et al. 2012 American college of rheumatology guidelines for management of gout. Part 2: Therapy and antiinflammatory prophylaxis of acute gouty arthritis. Arthritis Care Res, 2012b;64(10):1447–1461.

13 Khanna D et al. 2012 American College of RheumatologyGuidelines for Management of Gout. Part 1: Systematic Nonpharmacologic and Pharmacologic Therapeutic Approaches to Hyperuricemia. Arhritis Care & Research Vol. 64, No. 10, Oct 2012, pp 1431-1446

14 Martinon F, et al. Gout-associated uric acid crystals activate the NALP3 inflammasome. Nature, 2006;440:237-241.

15 Neogi T, et al. 2015 Gout Classification Criteria. An American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 2015;67(10):2557–2568.

16 Ottaviani S, et al. Efficacy of anakinra in gouty arthritis: a retrospective study of 40 cases. Arthritis Res Ther 2013:15:R123.

17 Richette P, et al. Updated EULAR evidence-based recommendations for the management of gout. Ann Rheum Dis 2014:73 (suppl 2:783)

18 Shoji A, et al. A retrospective study of the relationship between serum urate level and recurrent attacks of gouty arthritis: Evidence for reduction of recurrent gouty arthritis with antihyperuricemic therapy. Arthritis Rheum, 2004;51(3):321-325.

19 So A, et al. A pilot study of IL-1 inhibition by anakinra in acute gout. Arthritis Res Ther, 2007;9:R28.

20 So A, et al. Canakinumab for the Treatment of Acute Flares in Difficult-to-Treat Gouty Arthritis. Arthritis Rheum, 2010;62(10): 3064–3076.

21 Thueringer J, et al. Anakinra for the treatment of acute severe gout in critically ill patients. Semin Arthritis Rheum, 2015;45:81-85.

22 Kuo CF, et al. Global epidemiology of gout: prevalence, incidence and risk factors. Nat Rev Rheumatol 11, 649-662 Pages:, 2015.

23 US prescribing information for Kineret (anakinra) http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails

24 FDA Guidance for Industry, Analgesic Indications: Developing Drug and Biological Products.http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

25 Abbate Aet al. Interleukin-1 Blockade With Anakinra to Prevent Adverse Cardiac Remodeling After Acute Myocardial Infarction (Virginia Commonwealth University Anakinra Remodeling Trial [VCU-ART] Pilot Study). Am J Cardiol 2010;105:1371–1377.

26 Emsley H, et al. A randomised phase II study of interleukin-1 receptor antagonist in acute stroke patients. J Neurol Neurosurg Psychiatry 2005;76:1366–1372

27 Larsen C et al. Interleukin-1–Receptor Antagonist in Type 2 Diabetes Mellitus. N Engl J Med 2007;356:1517-26.

28 Moran A, et al. Interleukin-1 antagonism in type 1 diabetes of recent onset: two multicentre, randomised, double-blind, placebo-controlled trials. Lancet, 2013; 381: 1905–15.

29 Morton A, et al. The effect of interleukin-1 receptor antagonist therapy onmarkers of inflammation in non-ST elevationacute coronarysyndromes: the MRC-ILA Heart Study. European Heart Journal, 2015;36: 377–384.

30 Singh N, et al. The effect of intravenous interleukin-1 receptor antagonist on inflammatory mediators in cerebrospinal fluid after subarachnoid haemorrhage: a phase II randomised controlled trial. Journal of Neuroinflammation 2014, 11:1.

31 Jesus A et al. IL-1 Blockade in Autoinflammatory Syndromes. Annu Rev Med. 2014; 65: 223–244.

32 Gaffo AL et al. Arthritis Developing a provisional definition of flare in patients with established gout. Arthritis Rheum 2012; May;64(5):1508-17.

33 Opal, S et al. Confirmatory interleukin-1 receptor antagonist trial in severe sepsis:A phase III, randomized, doubleblind, placebo-controlled, multicenter trial. Critical Care Medicine Issue: Volume 25(7), July 1997: 1115-1124

34 Fisher, CJ. et al. Recombinant Human Interleukin 1 Receptor Antagonist in the Treatment of Patients With Sepsis Syndrome Results From a Randomized, Double-blind, Placebo-Controlled Trial. JAMA; June 1994; pp 1836-1843

35 Fisher, CJ. et al Initial evaluation of human recombinant interleukin-1 receptor antagonist in the treatment of sepsis syndrome: A randomized, open-label, placebo-controlled multicenter trial. Critical Care Medicine 1994; Vol 22(1): pp 12-21

36 Navneet Singh et al. The effect of intravenous interleukin-1 receptor antagonist on inflammatory mediators in cerebrospinal fluid after subarachnoid haemorrhage: a phase II randomised controlled trial. Journal of Neuroinflammation 2014; 11:1

37 Ware JE Jr et al. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992;30:473–483.

38 http://www.rand.org/health/surveys_tools/mos/36-item-short-form.html

39 Singh JA et al. Gout is associated with more comorbidities, poorer health-related quality of life and higher healthcare utilisation in US veterans. Ann Rheum Dis. 2008;67:1310–1316.

40 Khanna D, Ahmed M, Yontz D, Ginsburg SS, Park GS, Leonard A, Tsevat J. The disutility of chronic gout. Qual Life Res. 2008;17:815–822.

41 SF-36® Health Survey Update. http://www.sf-36.org/tools/sf36.shtml.

42 Reilly MC et al. The validity and reproducibility of a work productivity and activity impairment instrument. PharmacoEconomics 1993; 4(5):353-65

43 Terkeltaub RA et al. High versus low dosing of oral colchicine for early acute gout flare: Twenty-four-hour outcome of the first multicenter, randomized, double-blind, placebo controlled, parallel-group, dose-comparison colchicine study. Arthritis Rheum. 10 Apr;62(4):1060-8

Clinical study reports submitted with the original MA-BLA:

44 Study 0560 A Randomized, Double-blind, Placebo-controlled, Multicentre, Dose-ranging Study of the Efficacy and Safety of Recombinant-Methionyl Human Interleukin-1 Receptor Antagonist (Anakinra) in Patients With Active Rheumatoid Arthritis. Oct 1999. Data on file.

45 Study 0563: An Open-label, Single-dose Study of the Safety, Pharmacokinetics, and Tolerability of Recombinant-methionyl Human Interleukin-1 Receptor Antagonist (r-metHuIL-1Ra) in Patients with Hepatic Dysfunction. Dec 1999. Data on file.

46 Study 960180: A 24-Week Study to Evaluate the Safety and Efficacy of Anakinra Therapy in the Presence of Background Methotrexate in Subjects With Active Rheumatoid Arthritis. Nov 1999. Data on file.

47 Study 20000268: Open-label, Single-dose Study of the Pharmacokinetics of Anakinra (r-metHuIL-1Ra) in Subjects With Various Degrees of Renal Function. Mar 2004. Data on file.

15 Appendices

Appendix 1
List of medication restricted or prohibited before randomization

Glucocorticoids	• Oral prednisolone ≥10 mg or equivalent within 24 hours of randomization. • Chronic glucocorticoid treatment, defined as ≥5 mg/day prednisolone or equivalent taken for >28 days of randomization. • Intra-articular glucocorticoids within 14 days of randomization. • Intramuscular glucocorticoids within 21 days of randomization.
Narcotics	• Opiates including tramadol within 6 hours of randomization. • Opiates with sustained release formulation within 5 days of randomization. • Chronic opiate treatment within 14 days of randomization.
Acetaminophen/ Paracetamol/	• Any acetaminophen (paracetamol) within 1 hour or >1 g within 4 hours of randomization.
NSAIDs and Coxibs	• Any ibuprofen within 4 hours or >400 mg within 8 hours of randomization. • Any diclofenac within 8 hours or >50 mg within 24 hours of randomization. • Any naproxen within 12 hours or >500 mg within 24 hours of randomization. • Any other NSAID within 24 hours of randomization. • Any cyclooxygenase-2 inhibitors within 24 hours of randomization. • Any acetyl salicylic acid within 4 hours or >600 mg within 24 hours of randomization.[1]
Colchicine	• Colchicine >1.2 mg within 7 days of randomization.
IL-1 or IL-6 blocker	• Any IL-1 or IL-6 blocker within 30 days or 5 half-lives before randomization, whichever is longest.
TNF inhibitor	• TNF inhibitor within 30 days or 5 half-lives before randomization, whichever is longest.
Combinations and others	• Over-the-counter analgesic acetyl salicylic acid - or paracetamol/acetaminophen -based combination medication, any tablet within 4 hours of randomization or more than 2 tablets within 24 hours of randomization. • Other biologic drug within 30 days or 5 half-lives before randomization, whichever is longest. • Topical ice/cold packs within 2 hours of randomization.

[1] Patients will be permitted to continue thrombosis prophylaxis with low dose acetyl salicylic acid (≤ 325 mg/day).

Appendix 2 Schedule of events

Assessment	**Optional pre-screening**	**Baseline and subsequent flare(s)**									**End of study**
		Visit 1[1]	**FU (by phone)**	**FU (by phone)**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit E[2]**	**Visit 5[2]**	**FU (by phone)[2]**	**FU (by phone)[12]**
		Baseline (Day 1)	24±2 hrs (Day 2)	48±2 hrs (Day 3)	72 hours±4 hrs (Day 4)	Day 8± 1day	Day 15±1 day	Day 28±2 days	Week 12±5 days	Every 12 weeks ±5 days	Week 104 ±5 days or 52 weeks ±5 days after last randomized patient
Informed consent		x[1]									
Eligibility criteria	x[6]	x									
Medical and surgical history, and demographics		x[1]									
Randomization		x[1]									
IMP administration at study site		x			x						
Patient/care giver IMP injection training		x									
Patient diary training		x									
Prior and concomitant medication		x			x	x	x	x			
Recording of rescue medication[11]		x			x	x	x				
Medical examination of current flare		x									
ECG		x									
Vital sign assessments		x			x	x	x				
Physical examination		x					x				
Laboratory safety assessments, local		x									
Laboratory safety assessments, central		x			x	x	x				
Adverse events		x[8]			x[8]	x[8]	X[8]	x	x[3]		
Immunogenicity assessment		x				x	x	x	x		
Patient´s assessment of pain intensity (VAS and Likert)[5]		x			x	x	x				
Patient´s assessment of global response to treatment					x	x	x				
Physician´s assessment of global response to treatment					x	x	x				

Assessment	Optional pre-screening	Baseline and subsequent flare(s)									End of study
		Visit 1[1]	FU (by phone)	FU (by phone)	Visit 2	Visit 3	Visit 4	Visit E[2]	Visit 5[2]	FU (by phone)[2]	FU (by phone)[12]
		Baseline (Day 1)	24±2 hrs (Day 2)	48±2 hrs (Day 3)	72 hours±4 hrs (Day 4)	Day 8± 1day	Day 15±1 day	Day 28±2 days	Week 12±5 days	Every 12 weeks ±5 days	Week 104 ±5 days or 52 weeks ±5 days after last randomized patient
Physician´s assessment of clinical signs (joint tenderness, swelling and erythema)		x			x	x	x				
Health related QoL, SF-36 (acute v. 2)		x				x	x				
Health related QoL, EQ-5D-5L		x				x	x				
Health care resource utilization incl WPAI:SHP						x	x				
Inflammatory biomarkers (CRP and SAA)		x			x	x	x		x		
IL-1Ra/anakinra serum concentration assessment		x[10]			x[10]	x	x	x	x		
Exploratory inflammatory biomarkers		x			x		x		x		
Exploratory pharmacogenetic markers		x[9]									
Reminder calls			x	x							
Retention/end of study call/Follow up of ongoing AEs										x	x

[1]For subsequent flares, Visit 1 will not include informed consent, demographics (excluding weight) and randomization
[2]The Visit E and 5 and the follow-up by phone every 12 weeks after last flare has occurred and been treated with IMP.
[3]SAEs and outcomes of previously recorded AEs will be collected.
[4]Only SAEs considered related to the IMP will be collected.
[5]A patient diary will be used for patient assessment of pain intensity predose and at 6, 12, 18, 24, 36, 48, 72 (Day 4) hours and Day 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 and 15.
[6]Pre-screening is optional and may be done to identify patients that fulfil the study eligibility criteria with the exception of having a current flare of gouty arthritis.
[7] Baseline safety laboratory tests can be taken up to 72 hours before randomization, provided that the patient does not show signs and/or symptoms of new ailments or increasing signs and/or symptoms of known concomitant diseases.
[8] Physician's assessments should be performed before recording of adverse events
[9] Only assessed at first flare
[10] Pre-dose
[11] Patients should record any intake of rescue medication between visits in the patients diary.
[12] A Visit 5/Week 12 visit may replace the End of study FU by phone if the IMP treatment started week 40 or later in case 1) or week 92 weeks in case 2). See section 7.5.1.11

Appendix 3

Detailed information on the presence of selected comorbidities will be collected at Visit 1 of the first flare.

Disease	Definition
Chronic kidney disease (CKD)	Estimated glomerular filtration rate (eGFR) <90 mL/min
Current or previous symptoms of heart failure	Stage according to the New York Heart Association (NYHA) guidelines
Diabetes mellitus	Plasma glucose >126 mg/dL after an overnight fast or taking antidiabetic medication*
Hypertension	Blood pressure >140/90 mmHg (at repeated measurements) or taking antihypertensive treatment
Obesity	Body mass index (BMI) ≥30 kg/m^2
Cardiovascular disease	History of angina pectoris and myocardial infarction
Hyperlipidemia	Cholesterol >240 mg/dL or taking stable cholesterol-lowering treatments, increased low-density lipoprotein levels(>160 mg/dL) , hypertriglyceridaemia (triglycerides >150 mg/dL), decreased high-density lipoprotein levels (<40 mg/dL in men or <50 mg/dL in women)
Cerebrovascular disease	Previous ischemic or hemorrhagic stroke, previous TIA, carotid or vertebral stenosis/occlusion
Osteoporosis	Osteoporosis (T-score ≤ −2.5)

*A subject with a consistent range between ~100 and ~126 mg/dl (~5.6 and ~7 mmol/l) (American Diabetes Association guidelines) is considered hyperglycemic.

Appendix 4

Evidence of intolerance after treatment of gouty arthritis flares with NSAIDs and colchicine. The list includes examples and are not limited to the conditions listed below.

	NSAIDs	**Colchicine**
Examples of intolerance after treatment with NSAID and colchicine	• Uncontrolled hypertension (w/wo anti-HTN medications and SBP≥140 mm Hg or DBP≥90 mm Hg) • Decreased renal function (eGFR <60mL/min/1.73m^2) • Fluid retention (edema) • Hepatic toxicity with increased level of liver tests • Nausea, dyspepsia, diarrhea • Central nervous system effects (eg, headache, dizziness)	• Vomiting, abdominal pain, nausea • Diarrhea • Thrombocytopenia • Agranulocytosis • Myopathy • Myelotoxicity • Peripheral neuropathy • Severe cutaneous eruption

HTN=hypertension SBP=systolic blood pressure DBP=diastolic blood pressure

Appendix 5

List of conditions that make the patient either contraindicated or not appropriate (safety concerns) to treatment with NSAIDs or colchicine in treatment of gouty arthritis flares. The list includes examples and are not limited to the conditions listed below.

	NSAIDs	**Colchicine**
Unsuitable for or contraindicated or not appropriate for treatment with	• Uncontrolled hypertension (w/wo anti-HTN medications and SBP≥140 mm Hg or DBP≥90 mm Hg) [1] • Cardiovascular disease; history of angina, ischemia, positive stress test or MI • Heart failure • Impaired renal function (eGFR <60mL/min/1.73m^2) • Concurrent use of thiazide diuretics and/or an ACE inhibitor or angiotensin receptor II antagonists, especially in CKD • Current treatment with anticoagulants • Gastroesophageal disease (GERD with prescribed h2 receptor antagonist or PPI or documented PUD or history of upper GI bleed) • Active or latent peptic ulcer/GI bleed (specifically in elderly patients) • Hypersensitivity (should not be given to patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin (acetyl salicylic acid) or NSAIDs) • Conditions with increased risk for bleedings including hematological disease • Inflammatory bowel disease (IBS)	• Patients with renal or hepatic impairment should not be given colchicine in conjunction with P-gp or strong CYP3A4 inhibitors • Potential toxicity due to PK/PD drug interactions especially in conjunction with p-gp or CYP3A4 inhibitors (e.g., diltiazem, verapamil, clarithromycin and cyclosporin), concurrent use of simva-, atorva-, and fluva-, and pravastatin • Gout attack onset ≥36 hours prior to treatment initiation • Patients on prophylactic colchicine treatment already and have received acute gout treatment regimen with colchicine within 14 days

HTN=hypertension SBP=systolic blood pressure DBP=diastolic blood pressure MI=myocardial infarction eGFR= estimated glomerular filtration rate ACE=angiotensin converting enzyme CKD=chronic kidney disease GERD=gastresophageal reflux disease PPI=proton pump inhibitor PUD=peptic ulcer disease GI=gastro-intestinal P-gp=P-glycoprotein CYP=Cytochrome P-450 PK=pharmacokinetic PD=pharmacodynamics IBS=irritable bowel syndrome

Appendix 6

Signs of unresponsiveness to NSAIDs and colchicine treatment of gouty arthritis flares. The list includes examples and are not limited to the conditions listed below.

	NSAIDs	**Colchicine**
Unresponsiveness to therapy	Evidence of lack of efficacy for NSAIDs (one of the following criteria must have been met): • losing efficacy over time; • at least 1 NSAID tested but failed; • inadequate/unsatisfactory pain relief	Evidence of lack of efficacy for colchicine (one of the following criteria must have been met): • losing efficacy over time; • failed in treating acute gout pain; • inadequate/unsatisfactory pain relief; • incapacity to achieve/maintain adequate dose regimen

Appendix 7

ACR/EULAR 2015 gout classification criteria (15).

The ACR/EULAR gout classification criteria*		
	Categories	Score
Step 1: Entry criterion (only apply criteria below to those meeting this entry criterion)	At least 1 episode of swelling, pain, or tenderness in a peripheral joint or bursa	
Step 2: Sufficient criterion (if met, can classify as gout without applying criteria below)	Presence of MSU crystals in a symptomatic joint or bursa (i.e., in synovial fluid) or tophus	
Step 3: Criteria (to be used if sufficient criterion not met)		
Clinical		
Pattern of joint/bursa involvement during symptomatic episode(s) ever†	Ankle or midfoot (as part of monoarticular or oligoarticular episode without involvement of the first metatarsophalangeal joint	1
	Involvement of the first metatarsophalangeal joint (as part of monoarticular or oligoarticular episode)	2
Characteristics of symptomatic episode(s) ever		
Erythema overlying affected joint (patient- reported or physician-observed)	One characteristic	1
Can't bear touch or pressure to affected joint	Two characteristics	2
Great difficulty with walking or inability to use affected joint	Three characteristics	3
Time course of episode(s) ever		
Presence (ever) of ≥2, irrespective of anti-inflammatory treatment:		
Time to maximal pain <24 hours	One typical episode	1
Resolution of symptoms in ≤14 days	Recurrent typical episodes	2
Complete resolution (to baseline level) between symptomatic episodes		
Clinical evidence of tophus (Figure 2)		
Draining or chalk-like subcutaneous nodule under transparent skin, often with overlying vascularity, located in typical locations: joints, ears, olecranon bursae, finger pads, tendons (e.g., Achilles)	Present	4
Laboratory		
Serum urate: Measured by uricase method. Ideally should be scored at a time when the patient was not receiving urate-lowering treatment and it was >4 weeks from the start of an episode (i.e., during intercritical period); if practicable, retest under those conditions. The highest value irrespective of timing should be scored.	<4 mg/dl (<0.24 mmoles/liter)	-4
	6–<8 mg/dl (0.36–<0.48 mmoles/liter)	2
	8–<10 mg/dl (0.48–<0.60 mmoles/liter)	3
	≥10 mg/dl (≥0.60 mmoles/liter)	4
Synovial fluid analysis of a symptomatic (ever) joint or bursa (should be assessed by a trained observer)d	MSU negative	-2
Imaging (Figure 3)e		
Imaging evidence of urate deposition in symptomatic (ever) joint or bursa: ultrasound evidence of double-contour sign or DECT demonstrating urate deposition	Present (either modality)	4
Imaging evidence of gout-related joint damage: conventional radiography of the hands and/or feet demonstrates at least 1 erosion	Present	4

* A web-based calculator can be accessed at: http://goutclassificationcalculator.auckland.ac.nz, and through the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) web sites.
† Symptomatic episodes are periods of symptoms that include any swelling, pain, and/or tenderness in a peripheral joint or bursa.

‡ If serum urate level is <4 mg/dl (<024 mmoles/liter), subtract 4 points; if serum urate level is ≥4-<6 mg/dl (≥0.242, 0.36 mmoles/liter), score this item as 0.
§ If polarizing microscopy of synovial fluid from a symptomatic (ever) joint or bursa by a trained examiner fails to show monosodium urate monohydrate (MSU) crystals, subtract 2 points. If synovial fluid was not assessed, score this item as 0.
¶ If imaging is not available, score these items as 0.
# Hyperechoic irregular enhancement over the surface of the hyaline cartilage that is independent of the insonation angle of the ultrasound beam (note: false-positive double-contour sign [artifact] may appear at the cartilage surface but should disappear with a change in the insonation angle of the probe) (31, 32)
** Presence of color-coded urate at articular or periarticular sites. Images should be acquired using a dual-energy computed tomography (DECT) scanner, with data acquired at 80 kV and 140 kV and analyzed using gout-specific software with a 2-material decomposition algorithm that color-codes urate (33). A positive scan is defined as the presence of color-coded urate at articular or periarticular sites. Nailbed, submillimeter, skin, motion, beam hardening, and vascular artifacts should not be interpreted as DECT evidence of urate deposition (33).
†† Erosion is defined as a cortical break with sclerotic margin and overhanging edge, excluding distal interphalangeal joints and gull wing appearance.