Research Protocol

ATTACG: Anakinra versus Treatment as usual in the Treatment of ACute Gout

Version 5: 9 February 2016

List of abbreviations

MSU	Monosodium urate
NSAIDs	Non-steroidal anti-inflammatory drugs
SoC	Standard of Care
ULT	Urate lowering therapy
IL	Interleukin
TNF	Tumor necrosis factor
NI	Non-inferiority
NVR	Dutch Society for Rheumatology (in Dutch: Nederlandse Vereniging voor Reumatologie)
SPC	Summary of Product Characteristics (in Dutch: officiële productinfomatie IB1-tekst)
IB	Investigator's Brochure
METC	Medical Ethical Testing Committee (in Dutch: Medisch Ethische Toetsingscommissie)
RA	Rheumatoid arthritis
SC	Subcutaneous
CRP	C-reactive protein
AE	Adverse Event
SAE	Serious Adverse Event
HR-QOL	Health related quality of life
QOL	Quality of life
EDC	Electronic data capture
CRF	Case report form
PROs	Patient Reported Outcomes
NRS	Numeric rating scale
HAQ-DI	Health Assessment Questionnaire Disability Index
SF-36	Short form-36
WPAI 18	Work productivity and activity impairment questionnaire
Sobi	Swedish Orphan Biovitrum Ltd
IMPD	Investigational Medicinal Product Dossier
DSMB	Data Safety Monitoring Board
SUSAR	Suspected Unexpected Serious Adverse Reaction
ITT	Intent-to-treat
PP	Per-protocol
CI	Confidence interval
QALDs	Quality adjusted life days
ICUR	Incremental cost-utility ratio
WMO	Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch Wetenschappeljik Onderzoek)
Wbp	Dutch Personal Data Protection Act (in Dutch: de Wet bescherming persoonsgegevens)

Summary

Background: Gout is a common form of inflammatory arthropathy, with hyperuricemia being the predominant risk factor. The close relationship between gout and hyperuricemia has led to treatment strategies wherein both the acute gout flare and hyperuricemia are targeted simultaneously. Currently available treatment options for gout flares (colchicine, corticosteroids and non-steroidal anti-inflammatory drugs; referred to as standard of care (SoC)) are frequently contra-indicated or poorly tolerated by gout patients due to presence of significant multi-morbidity. Anakinra (Kineret®) is an IL-1 receptor antagonist presently indicated for the treatment of rheumatoid arthritis (RA) and Cryopyrin-Associated Periodic Syndromes. At present, anakinra has been studied in a handful of case series and small open label studies for its clinical efficacy and safety in acute gout.

Objective: To demonstrate non-inferiority (NI) of anakinra compared with the SoC in the treatment of acute gout flares. Also, to compare the safety and cost per quality-adjusted life day between anakinra and SoC and to compare the 3 and 12 months clinical outcome of patients initially treated with anakinra versus SoC and starting ULT.

Study design: A 3 month multi-center randomized, double (dummy)-blinded, placebo controlled NI trial, followed by a 9 month open label follow-up study.

Study population: 200 patients with an acute gout flare.

Intervention: Patients will be randomized to 5 consecutive days of daily a 100mg injection of anakinra + SoC pill placebo or SoC treatment + 5 consecutive days of anakinra injection placebo. SoC treatment dosage and duration is according to standard procedures. Both arms will receive urate lowering therapy according to standard procedures.

Main study endpoints: The main study endpoint is the change in patient-reported pain in the index joint from baseline to the average of pain values at 24, 48 and 72 hours after initiating treatment. Secondary endpoints include (in-) direct costs, quality of life (QOL), physical functioning, treatment side effects, changes in joint swelling & tenderness, C-reactive protein (CRP), uric acid level, patient perceived treatment response and number of recurrent flares.

Burden, risks and benefits: Patients will have to visit the treating rheumatologist at day 1, 7 and at month 3 during the study period. At 6 time points over the course of the study patients will have to fill in a survey questionnaire. During the first 7 days after starting the study (or by onset of a new gout attack), patients will additionally be required to fill in a survey on patient reported outcomes, medication intake and experienced side effects. Main risks associated with using anakinra are the possible physical discomfort of subcutaneous (SC) treatment injections, headache, local (skin) injection site reaction, serious (respiratory or skin) reactions, neutropenia or/and allergic reactions. Relapse of a gout flare might occur sooner in patients receiving anakinra or prednisolone compared to patients receiving prophylactics. The potential risks and concerns associated with this study are managed due to strict inclusion and exclusion criteria and the establishment of a Data Safety Monitoring Board (DSMB) and through active safety monitoring. Any remaining risks are considered acceptable since the risks are not considered severe or life threatening.

1. Introduction and Rationale

Gout is a common form of inflammatory arthropathy most frequently seen in men and in women primarily after menopause (1-3). Studies in various geographic locations have shown the prevalence of gout to be increasing over time, which is frequently attributed to the increasing longevity of the population and the accumulation of gout risk factors in older age (1, 4-9). Individuals with gout often present with multiple comorbid conditions, including metabolic syndrome (including hypertension, diabetes mellitus and obesity), cardiovascular disease and kidney disease (3, 4, 10). Hyperuricemia is the predominant risk factor for gout and possibly also for many of its most common comorbidities (1). When left untreated, elevated serum uric acid levels can lead to precipitation of monosodium urate (MSU) crystals in and around the joints, initiating and stimulating a local inflammatory response. Although many individuals with chronic hyperuricemia remain asymptomatic, the risk for gout is greater than when serum uric acid levels are kept within the clinical desired range (0.30 - 0.35 mmol/L). The clinical manifestation of an acute gout flare is recognized for causing excruciating pain. It can have its onset in any joint in the body, however, primarily the lower joints in the legs are affected.

The close relationship between gout and hyperuricemia has led to treatment strategies wherein both the acute gout flare and hyperuricemia are targeted simultaneously (11-13). Three standard options are available to treat pain and inflammation associated with acute gout, including colchicine, non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids[1]. In the Netherlands, allopurinol, febuxostat and benzbromaron are currently available for the treatment of hyperuricemia by normalizing uric acid levels in the body, also referred to as urate lowering therapy (ULT). Reduction of serum uric acid levels following initiation of ULT may induce acute gout flares. To prevent the onset of these flares, NSAIDS and colchicine are, additionally, recommended as prophylactics agents when initiating ULT (14-18). Although gout is a well understood rheumatic disease, currently available treatment options are frequently contra-indicated or poorly tolerated by gout patients, which frequently presents in the presence of significant multi-morbidity.

Since the discovery of the inflammasome, the crucial role of interleukin (IL) - 1 in initiating and maintaining gouty inflammation has become well recognized (3, 19). Precipitated MSU crystals at inflamed joint sites get phagocytized by macrophages or monocytes, leading to intracellular activation of the NALP3 inflammasome. This system subsequently activates caspase-1, promoting the maturation of Pro-IL-1β and extracellular excretion of pro-inflammatory IL-1β (19, 20). Secreted IL-1β then binds to the IL-1 receptor on local endothelial cells and macrophages, signaling them to produce further pro-inflammatory cytokines and chemokines, including tumor necrosis factor (TNF)-α, IL-6, and neutrophil chemo attractants (21). These amplify the inflammatory response, attracting other inflammatory cells, including neutrophils, into the area.

For complex gout patients presenting with multiple comorbidities, IL-1 antagonists may be of great significance. In 2013, the European Medicines Agency approved the medicinal product canakinumab, a fully human monoclonal anti-human IL-1β antibody, for the treatment of acute gout flares. Due to very high costs per treatment, this agent is reimbursed only for patients with frequent gout flares (>2 per year) who cannot tolerate any of the three standard treatments, to a maximum of 2.5 Million euros per year in the Netherlands.

[1] Throughout the entire protocol these standard treatment options, colchicine, NSAIDs and corticosteroids, will be referred to as standard of care (SoC)

Anakinra (Kineret®) is a DNA recombinant IL-1 receptor antagonist currently registered for the treatment of rheumatoid arthritis and Cryopyrin-Associated Periodic Syndromes. It acts by competitively inhibiting the binding of IL-1α and IL-1β to IL-1 type I receptors, causing the biological activity of these interleukins to be neutralized. The clinical efficacy and safety of anakinra in acute gout have been investigated and reported on in a few case series or small open label studies (22-36). Although these studies provide a proof of concept for the plausibility and clinical importance of anakinra as a treatment option for acute gout, no large scale clinical trial has yet been performed. The primary goal of the proposed study is to demonstrate the non-inferiority (NI) of anakinra versus treatment as usual in patients with acute gout. Secondary goals are to compare the cost-effectiveness of anakinra to treatment as usual, to evaluate the safety of anakinra and to compare the 3 and 12 months clinical outcome of gout patients initially treated with anakinra or treatment as usual starting ULT.

2. Study Aims

Primary objective

To demonstrate the NI of anakinra compared with the SoC in the treatment of acute gout flares.

Secondary objectives

To compare the cost per quality-adjusted life day between anakinra and SoC.

To evaluate the safety of anakinra in the treatment of acute gout flares.

To compare the 3 and 12 months clinical outcome of patients initially treated with anakinra versus SoC and starting ULT.

3. Study Design

Duration and design

The total study duration is 12 months. The initial 3 month study is a multi-center randomized, double (dummy)-blinded, placebo controlled NI trial, followed by a 9 month open label extension study.

200 patients with crystal proven acute gout will be randomly allocated in the ratio 1:1 to either 1) 5 consecutive days of 100 mg daily anakinra injection and SoC pill placebo or 2) one of the SoC treatment options and 5 consecutive days of 100 mg anakinra injection placebo. SoC treatment allocation, dosage and duration are in line with the national guidelines for gout setup by the Dutch Society of Rheumatology (Dutch: Nederlandse Vereniging voor Reumatologie, NVR) (16). In line with these guidelines, when tolerable, patients will be appointed SoC treatment with colchicine or NSAID which will then be continued prophylactically for 90 days when initiating ULT. Patients in both arms will also receive ULT according to recommendations as stated in the national guidelines for gout by the NVR (16).

Multi-center research

Subjects will be included into the study by rheumatologists working in different medical centers in the Netherlands. Between 4-8 centers will participate in this study. General practitioners in the region of the participating medical centers will be informed and asked to refer patients with suspected gout to the closest study center.

Coordinating pharmacy

The following pharmacy will function as pharmacy for the production, labelling and distribution of study medicines in this study:

Slotervaart Hospital
Department of Pharmacy & Pharmacology
Louwesweg 6
1066 EC Amsterdam, the Netherlands

4. Study Population

Population

The study population will include both male and female patients with an acute gout flare.

Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- At least 18 years of age
- Signed written informed consent
- Identification of intracellular MSU crystals in primary joint through aspiration of joint

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study in case of:

- Absolute contra-indication for all available types of ULT (allopurinol, febuxostat and benzbromaron)

  Contra-indications allopurinol: *Hypersensitivity to the active substance or to any of the excipients (see for the excipients the official SPC for the brand given).*

  Contra-indications febuxostat: *Hypersensitivity to the active substance or to any of the excipients (see for the excipients the official SPC for the brand given).*

  Contra-indications benzbromaron: *Hypersensitivity to the active substance or to any of the excipients (see for the excipients the official SPC for the brand given). Patients with known liver disease. Concomitant use of hepatotoxic drugs, particularly antituberculosis agents. Hepatic porphyia. Severe renal impairment (clearance < 30 ml/min.). Patients with secretion of urate higher than 700 mg/24 hours (= 4.2 mmol/24 hour). Urolithiasis. Acute gout flare*
- Absolute contra-indication for anakinra

  Contra-indications anakinra: *Hypersensitivity to the active substance or to any of the excipients (citric acid anhydrous, sodium chloride, disodium edetate dihydrate, polysorbate 80, sodium hydroxide, water for injections) or to E. coli derived proteins. Kineret must not be used in patients with severe renal impairment (creatinine clearance rate < 30 ml/minute). Kineret treatment must not be initiated in patients with neutropenia (absolute neutrophil count <1.5 x 109 /l).*
- Presence of liver disease that according to the treating physician precludes participation in the study
- Absolute contra-indication for all three of the possible SoC treatments (colchicine, naproxen, prednisolon)

  Contra-indications colchicine: *Hypersensitivity to the active substance or to any of the excipients (microcrystalline cellulose (E460), lactose, sodium carboxy starch, magnesium stearate (E470b)). Women of childbearing age, unless effective contraceptive measures are taken. Colchicine should not be used in patients with severe renal impairment or severe hepatic impairment.*

  Contra-indications naproxen: *Hypersensitivity to the active substance or to any of the excipients (potato starch, lactose, hydroxypropyl cellulose (200 CP), magnesium stearate, colloidal anhydrous silicon dioxide). Naproxen is contra-indicated in patients who have*

previously shown allergic reactions (e.g. asthma, rhinitis or urticaria) in response to acetylsalicylic acid or other prostaglandin-synthesis inhibitors. Severe anaphylactoid reactions have been reported in these patients. In principle, naproxen must not be administered to patients with gastrointestinal ulcerations, congestive gastritis or atrophic gastritis, gastrointestinal bleeding or other bleeding such as cerebrovascular bleeding. Severe renal impairment.

Contra-indications prednisolon: *Hypersensitivity to the active substance or to any of the excipients (lactose, magnesium stearate (E470b), silicon dioxide (E551), potato starch, pregelatinized potato starch, sodium (potato) starch glycolate, magnesium stearate (E572), erythrosine (E127)). Gastric and duodenal ulcers. Acute infectious processes, particularly viral infections and systemic fungal infections. Tropical worm infections. Administration after vaccination with a live attenuated virus. Ocular herpes simplex.*

- Known history of allergy or sensitivity to latex
- Current use of any ULT (ULT therapies are allopurinol, febuxostat and benzbromaron)
- Concurrent use of other IL-1 agents (to this category belong: canakinumab and rilonacept)
- Patient reports no to mild gout related pain
- Pregnancy or lactation
- Women who are planning on becoming pregnant within the study period (12 months)
- Patients with active or recurrent bacterial, fungal or viral infection
- Patients using TNF inhibitors (to this category belong: Certolizumab, Golimumab, Adalimumab, Etanercept, Infliximab)
- Patient has insufficient knowledge of the Dutch language for completing questionnaires independently

5. Treatment of subjects

Investigational treatment

Patients allocated to the investigational treatment group will receive Kineret® (active substance anakinra). For specific information regarding the product characteristics, safety, therapeutic indications, dosage and duration, etcetera, please see *Chapter 6: Investigational treatment* of this protocol.

Comparator treatment

Subjects allocated to the active comparator group will receive colchicine, naproxen (NSAIDS) or prednisolon (systemic corticosteroids). These treatments are standard medicinal products currently registered for treating acute gouty arthritis. Per specific case, the treating rheumatologist will decide on the SoC treatment the patient may receive, according to their medical history, contraindications, intolerances, etcetera. This is in line with the guidelines for gout treatment as setup by the NVR (16). All the participating centers will receive medication for all three of the SoC treatments, making the rheumatologists free to choose the best tolerable SoC treatment for the patient. For specific information (e.g. dosage and duration) on the standard treatments, please see *Chapter 7: Non-investigational treatment* of this research protocol.

Non-active placebos

To ensure blinding, patients will receive non-active placebos. Subjects in the investigational anakinra treatment group will receive a non-active placebo resembling the SoC treatments. Subjects in the comparator group will receive a non-active anakinra injection placebo (NaCl 0.9%, 0.67 ml) resembling the anakinra treatment injection. For details on the blinding of study medication see *Chapter 8: Methods*, *section Randomization, Blinding and treatment allocation* of this research protocol.

Urate lowering therapy (ULT)

All subjects included in either treatment arm will start ULT at baseline. ULT is part of standard prophylaxis in the treatment of recurrent acute gout flares according to the NVR treatment guidelines for gout (16). When tolerable, Patients will be appointed ULT with allopurinol When allopurinol cannot be tolerated, alternatively benzbromaron or febuxostat will be appointed. Please see *Chapter 7: Non-investigational treatment* of this research protocol for further details.

Rescue Medication

No rescue medication will be prescribed during the first 7 days after starting the study (baseline – day 7). Patients may use over the counter medicines as NSAIDs and acetaminophen during this time. Patients will be asked to report the use of any over the counter medicines, as well as other medication in the patient flare diary. During the rest of the study period, patients can use over the counter medication and will be asked to rapport the use in the flare diary during the occurrence of refractory gout attacks.

Refractory gout attack

Patients will return to their treating rheumatologist 7 days after starting the study medication for their initial acute gout flare. In case of an ongoing or new gout flare between day 7 until the end of the study, the treating rheumatologist will decide on the gout treatment to give the patient. Treatment options will be according to standard clinical care. Anakinra treatment will not be available as treatment option for refractory gout attacks. Patients will be instructed to contact their treating rheumatologist in case a new gout flare arises during the study period. The treating rheumatologist can, together with the sponsor, decide if breaking the treatment randomization code is needed in order to provide the best optimal care for the patient.

6. Investigational treatment

For a detailed description of the investigational product characteristics, therapeutic indications, dosages, pharmaceutical properties, side effects, etcetera, please see the Summary of Product Characteristics (SPC) and Investigator's Brochure (IB) submitted as part of the dossier for the Medical Ethical Testing Committee (in Dutch: Medisch Ethische Toetsingscommissie, METC). A short summary of general information regarding anakinra and studies with anakinra for gout is given below.

Name and descriptive

Kineret® contains the active substance anakinra. It is a recombinant, nonglycosylated form of the human IL-1 receptor antagonist (r-metHuIL-1ra). Besides the inclusion of a single methionine residue at its amino terminus, it is identical to the naturally present human IL-1 receptor antagonist. Anakinra is produced by means of recombinant DNA technology in *Escherichia coli* cells. Currently, Kineret® is registered for treating adults with signs and symptoms of rheumatoid arthritis (RA) and for cryopyrin-associated periodic syndromes.

Summary of findings from pre-clinical studies

Pre-clinical information regarding anakinra is listed in the SPC. One animal study has been done with anakinra and gout by So et al. 2007 (34). The effectiveness of IL-1 inhibition in relieving inflammatory manifestations associated with gout was studied in *in-vivo* MSU crystal-induced inflammation BALB/c mice. The mice were given anakinra injections, anti-IL-1R1 monoclonal antibodies or anti-TNF monoclonal antibodies and the level of neutrophil recruitment was determined. Both anakinra and the anti-IL-1R1 monoclonal antibody showed comparable inhibitory effects on neutrophil recruitment. The results were statistically significant compared to a positive MSU control.

Summary of findings from clinical studies

In total, the clinical effectiveness of anakinra in gout has been documented in 15 case reports and/or series and 1 small open-label study (updated 20 March 2015) (22-37). The patients included in these studies were all complex gouty arthritis patients with severe comorbidities and/or intolerance to conventional therapies. Treatment with anakinra was, therefore, used as an alternative agent. In the 15 case reports and/or series, anakinra demonstrated to rapidly and effectively alleviate the pain associated with gout in the majority of the patients. Dosage regimes differed between patients, with some taking 100 mg anakinra daily for three consecutive days, whilst others took anakinra daily or every other day for up to six months. In this population, observed side effects included one injection site reaction, neutropenia in another patient, one case of leukopenia, seven infectious complications and twice the occurrence of a H1N1 Influenza infection after initiating anakinra therapy. One critically ill case developed an infectious complication (herpes zoster) one day after completing a 6-day anakinra treatment, possibly related to the anakinra treatment. One patient developed a postoperative wound infection, whereby the site was possibly already infected before anakinra treatment was initiated. Four patients could not discontinue anakinra treatment without getting an acute flare within several days after stopping. One open-label clinical trial has been documented, including 10 patients taking 100 mg subcutaneous (SC) anakinra for 3 consecutive days (34). Patients responded rapidly to anakinra, with the most rapid onset observed within 24 hours. The subjective symptoms of gout were greatly relieved 48 hours after the first injection in all patients. No side effects were observed during the study period,

and there were no infectious complications. Only one patient had a minor flare at one month follow-up. For anakinra in gout, no randomized-controlled clinical trials have been reported. In general, the documented studies show the possible efficacy of anakinra for the treatment and rapid relief of acute gout flares in severe and complex comorbid gout patients, not able to take or tolerate conventional therapies.

Summary of known and potential risks and benefits

The potential risks associated with using anakinra for the treatment of acute gouty arthritis are:

- Physical discomfort of SC treatment injection
- Local (skin) injection site reaction (pain, inflammation, erythema, or ecchymoses)
- Serious infections (respiratory and skin infections, Influenza infections)
- Allergic reaction and anaphylaxis (angioedema, urticarial and pruritus) to anakinra or other constituents, including latex
- Decreased neutrophil count, leading to neutropenia
- Drug interaction between ULT and anakinra
- Elevated levels of liver enzymes
- Gastrointestinal disturbances related to liver disorders (yellow skin and eyes, nausea, loss of appetite, dark-colored urine, light-colored stools)
- Headaches

The potential benefits associated with the use of anakinra for the treatment of acute gout arthritis are alleviation of inflammation, pain and disease burden.

Description and justification of route of administration and Dosage

Active and placebo Kineret® will be administered by SC injection once daily. Each syringe contains 100mg anakinra or non-active anakinra (NaCL 0.9%, 0.67 ml) placebo. The route of administration will be identical to current standard procedures applied for RA patients. To prevent and avoid discomfort at the site of injection, it is recommended to change the injection site location regularly. Current recommendations as listed in the SPC for the method of administration for anakinra, will also be applicable and followed in this study.

Preparation and labelling of investigational medicinal product

Finished products of anakinra and anakinra placebo injections will be delivered by Swedish Orphan Biovitrum AB (Sobi) to the coordinating pharmacy before the start of the study. The coordinating pharmacy is responsible for preparing and re-labeling these medicinal products. During preparation and labeling of anakinra and anakinra placebos, the coordinating pharmacy will comply with the GMP guidelines.

Drug accountability

The allocation of anakinra and anakinra placebo to the local pharmacy of each participating sites will be done under strict supervision of the central coordinating pharmacy and the proper environmental settings. The study medication will be delivered to, accepted by and stored at the local pharmacy of each participating site. The nurse/treating rheumatologist is responsible for retrieving these packages

and handing these over to the patient or the patient can retrieve the medication package and return to the treating rheumatologist/nurse who will further guide the patient. If during the trial any of the products are not fit for use or are not being used, these will be retoured to the central coordinating pharmacy and replaced if needed and possible. The treating rheumatologist/nurse should together with the local pharmacy ensure proper sending of the unusable medication to the coordinating pharmacy in case of retouring products.

7. Non-investigational treatment

Name and description of available SoC treatments

Colchicine

Colchicine is indicated for treating acute gouty arthritis in patients who cannot tolerate, or who have contra-indications for, NSAIDs. It is also used as a prophylaxis for gout flares when initiating ULT in patients who cannot tolerate, or who have contra-indications for, NSAIDs.

NSAID, naproxen

Therapeutic indications for naproxen include many inflammatory musculoskeletal diseases, including gouty arthritis. Naproxen is a prostaglandin synthetase inhibitor and belongs to the group of NSAIDs, which are used to control pain and inflammation.

Systemic corticosteroid, prednisolon

Prednisolon is used to treat rheumatic conditions and other bodily disorders. Prednisolon is a corticosteroid which primarily acts as a glucocorticosteroid. The therapeutic effect of glucocorticosteroids is mostly through two mechanisms; an anti-inflammatory or immunosuppressive (anti-allergic) mechanism.

Urate Lowering Therapy

Different ULT treatments are available; allopurinol, febuxostat and benzbromaron. All are aimed at lowering the urate/uric acid levels in the blood serum, however, the mechanism of action differs between the three. Allopurinol and febuxostat work by inhibiting the action of the enzyme xanthine oxidase, which plays a role by the conversion from hypoxanthine into uric acid. Benzbromaron acts as a uricosuric agent, which causes the excretion of uric acid in the urine to be increased.

Non-active SoC placebos

Oral SoC placebo medication will be provided in capsules, identical in size, shape color and appearance to the active SoC treatment. For details about the blinding of study medication, see *Chapter 8: Methods*, *section Randomization, Blinding and treatment allocation*.

Dosage and method of administration

For all SoC treatments and placebos and ULT treatments, the dosage, duration and method of administration will be in line with the Gout Guidelines of the NVR and standard care procedures (16). For colchicine (placebo) this is 3 daily dosages of 0.5 mg for 90 days, for naproxen (placebo) twice a day 500 mg for 90 days and for prednisolone (placebo) 35 mg daily dosage for 5 days. Colchicine and naproxen will be continued for 90 days as these are given as prophylaxes when initiating ULT. Patients receiving naproxen will be prescribed antacids in line with the standard procedure when receiving NSAID for longer periods of time. For ULT treatment the first choice will be allopurinol 100 mg daily for 1 week followed by 300 mg. Alternatively benzbromaron or febuxostat will be used. Dosage will be adjusted according to treating to target of urate serum concentration below 0.30 mmol/L. ULT will be initiated at baseline.

Preparation and labelling of non-investigational medicinal product

The central coordinating pharmacy will ensure the proper number of SoC treatments and placebos will be acquired before the start of the study. During the preparation and labeling of SoC treatment and SoC placebos the coordinating pharmacy will comply with the GMP guidelines.

Drug accountability

The allocation of SoC and SoC placebo to the local pharmacy of each participating sites will be done under strict supervision of the central coordinating pharmacy and the proper environmental settings. The study medication will be delivered to, accepted by and stored at the local pharmacy of each participating site. The nurse/treating rheumatologist is responsible for retrieving these packages and handing these over to the patient or the patient can retrieve the medication package and return to the treating rheumatologist/nurse who will further guide the patient. If during the trial any of the products are not fit for use or are not being used, these will be retoured to the central coordinating pharmacy and replaced if needed and possible. The treating rheumatologist/nurse should together with the local pharmacy ensure proper sending of the unusable medication to the coordinating pharmacy in case of retouring products.