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Guideline on clinical investigation of medicinal products for the treatment of gout

Draft

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30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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Executive summary

The main aim of the guideline is to address general guidance on the development of medicinal products for the treatment of gout. This guideline should be read in conjunction with other EMA and ICH guidelines, which may apply to these conditions and patient populations.

Gout is a common disorder, which is caused by hyperuricaemia and the formation of monosodium urate (MSU) crystal deposits. Crystals accumulate preferentially in joints, tendons and the surrounding soft tissues, and may induce an inflammatory reaction. Gout may manifest as intermittent acute gouty arthritis (referred to as "flares" in this document), with symptom-free periods between attacks. During prolonged hyperuricaemia, tophi, i.e. nodular masses of MSU crystals that form within soft tissue, may occur. Tophi can be symptomless, or can trigger an inflammatory reaction. In severe cases, chronic tophaceous gouty arthropathy characterised by inflamed tophi at multiple joints and bone erosions may occur, where patients are not symptom-free in between flares. Renal damage and kidney stone formation may develop in gout.

Standard of care treatment of gout consists of urate-lowering therapy (ULT). Acute flares are treated with analgesics and anti-inflammatory drugs. In addition, prophylactic treatment with NSAIDs or other drugs is frequently given at the start of ULT, as a sudden drop in uric acid levels induced by ULT may precipitate an acute attack of gout.

In this document, guidance is provided on the clinical development of new ULT and anti-inflammatory treatment options. The study design, inclusion criteria, primary endpoints and trial duration largely depend on the treatment goal and mode of action of the new drug.

The aim of ULT is to reduce and maintain the serum uric acid levels to below the saturation level, in order to dissolve and clear the MSU crystal load. Different target levels of serum urate are set for either episodic flaring patients or advanced, treatment resistant patients with visible tophi, requiring a more immediate debulking of the urate load.

For anti-inflammatory drugs, the goals may include the symptomatic treatment of acute flares, the prophylaxis of acute flares (e.g. at the start of ULT), or the reduction of inflammatory symptoms in chronic tophaceous arthropathy.

As co-morbidities such as renal and cardiovascular disorders are common in the target population, which often includes the elderly, safety and optimal dosing in these special populations should be addressed.

1. Introduction (background)

Aetiology & symptoms

Gout is caused by hyperuricaemia and mono-sodium urate (MSU) crystal deposition. Uric acid is a metabolic waste product of purines, constituents of nucleic acids in all cells and widely present in the diet also. Physiologically, above a critical urate serum level of 6.8 mg/dL at 37°C in extracellular fluids, hypersaturation and MSU crystal formation may occur.

Urate crystals are often asymptomatic, but may lead the host to mount an inflammatory defence resulting in acute attacks of painful arthritis and tendo-bursitis, alternating with symptom-free episodes. It has been suggested that the crystals stimulate resident macrophages to produce IL-1 beta via the NALP3 inflammasome complex, resulting in an acute inflammatory response. In more advanced patients, large urate crystal deposits, called tophi, can be formed. Tophi may be symptomless, or

cause chronic inflammation and joint erosions, which can be severe. In addition, chronic renal impairment and acute nephrolithiasis may occur.

The relationship between serum urate levels and gout attacks (flares) is complex. Whereas a prolonged period of hyperuriaemia is a prerequisite to MSU crystal formation causing gout, acute flares are often preceded by a drop in serum urate levels. On the other hand, flares are also reported to be associated with purine-rich meals. *In-vitro* studies indicate that hyperuricaemia facilitates IL-1β production in monocytes after exposure to MSU crystals, and this mechanism might reinforce chronic inflammation in association with tophi.

Epidemiology

The prevalence of gout is estimated as 1-2 % in Europe. Gout is primarily diagnosed in middle-aged males. In male gout patients, co-morbidities like chronic kidney disorders and diabetes, hypertension, obesity , cardiovascular disorders and alcohol dependence are common. Women who develop gout are in general elderly using diuretics. Patients with a genetic predisposition, however, may develop severe gout and chronic tophaceous arthropathy at a young age.

Hyperuricaemia is a common finding in the general population. The prevalence of hyperuricaemia has been estimated as high as 21% in the US population, and is possibly similarly prevalent in Europe. Although hyperuricaemia is a prerequisite for the development of gout, it often remains asymptomatic. In an Asian cohort study, only 22% of the subjects with high levels of uric acid above 9 mg/dL, developed gout in a 5 year follow-up period. The reasons why some patients develop a host reaction to urate crystals and others don't, is as yet undetermined.

There is also continuing debate whether asymptomatic hyperuricaemia, i.e. hyperuricaemia in the absence of prior episodes or current clinical manifestations of gout, may an independent risk factor for atherosclerotic disorders, hypertension and chronic kidney disease, as these are common co-morbidities in gout. To date, a causal relationship between asymptomatic hyperuricaemia and cardiovascular and renal disease is unclear.

Current treatment options

Urate lowering therapy

The mainstay of the treatment of gout is urate lowering therapy (ULT). Allopurinol, a xanthine-oxidase inhibitor interfering with the production of uric acid, is considered as a first-line ULT treatment option according to the current EULAR and ACR treatment guidelines. However, allopurinol hypersensitivity syndrome with skin reactions is quite common. Doses of allopurinol must be lowered in patients with impaired renal function, as allopurinol is excreted via the kidneys. Alternatively, febuxostat, another xanthine-oxidase inhibitor is recommended. In patients resistant to or intolerant of xanthine oxidase inhibitors, uricosuric agents such as lesinurad, benzbromarone and probenecid could be considered. Uricosuric agents are not overall available in the European member states.

ULT employs a treat to target approach, the goal of which is to lower serum urate (SUA) below a specified threshold, established to be of clinical benefit. In the EULAR treatment guideline published in 2006, the target for serum urate level is set as < 6 mg/dL, as in several longitudinal studies , the risk of flares was 1.2-2 times higher in patients with SUA levels above a cut-off of 6 mg/dl. Although often used and considered relevant to prevent flares in the long-term, the 6 mg/dl cut-off point may not be sufficient to reduce tophus load in a reasonable time-frame. Several experts and international treatment guidelines therefore recommend a more stringent reduction of SUA to levels below 5 mg/dl to obtain a faster reduction of tophi. The 5 mg/dl target level is based on median SUA levels of the general British male population of 5.1 mg/dl.

Current EU and US clinical practice guidelines are unanimous in failing to endorse drug treatment of asymptomatic hyperuricaemia as the risks at present are perceived to outweigh the benefits.

Other treatment options

For the treatment of acute gout attacks, anti-inflammatory treatments like colchicine, NSAIDs or steroids are commonly prescribed.

As the introduction of a ULT may paradoxically precipitate arthritic flares, treatment guidelines recommend commencement of colchicine and/or NSAIDs as prophylaxis. The optimal treatment period of colchicine prophylaxis remains to be established. Recently, canakinumab, a monoclonal antibody targeting interleukin 1ß, has been registered for the treatment of acute arthritis and prophylaxis of flares.

Pharmacological treatment should be complemented by life-style and dietary advice including weight loss, ensuring adequate hydration and avoiding purine-rich food, sweet beverages, and alcohol.

Many patients suffer from multiple co-morbidities which complicates the treatment of gout. The development of new treatment options in these vulnerable populations is therefore encouraged. There are a considerable number of patients who do not tolerate or who are insufficient responders to the available pharmacological treatment options. New first- and second-line treatment options are therefore in demand.

2. Scope

Guidance is provided on the evaluation of drugs for the treatment of gout, including the prevention and treatment of acute arthritis flares or chronic tophaceous gouty arthropathy. Potential therapies could be urate lowering therapies or anti-inflammatory drugs.

In the circumstance where products are primarily developed for the treatment of acute pain, and where acute gouty arthritis flares are included in the study programme as a model for acute nociceptive pain, reference is made to the EMA guideline on the clinical development of medicinal products intended for the treatment of pain.

No specific guidance is provided in this guideline for the treatment or prophylaxis of acute hyperuricaemia secondary to causes other than gout, such as haemolysis or tumour lysis. It is, however, encouraged that urate lowering therapies are developed for this purpose.

3. Legal basis and relevant guidelines

This guideline has to be read in conjunction with the introduction and general principles (4) and part of the Annex I to Directive 2001/83 (as amended) and relevant CHMP and ICH guidelines, among them in particular:

- Guideline on the evaluation of the pharmacokinetics of medicinal products in patients with impaired renal function (CPMP/EWP/225/02)
- Guideline on the investigation of drug interactions 21 June 2012 CPMP/EWP/560/95/Rev. 1 Corr. 2** Committee for Human Medicinal Products (CHMP)
- Guideline on the clinical development of medicinal products intended for the treatment of pain (EMA/CHMP/970057/2011)

- Guideline on the clinical investigation of medicinal products to prevent development/slow progression of chronic renal insufficiency (draft EMA/CHMP/500825/2016)
- Reflection paper on assessment of cardiovascular risk of medicinal products for the treatment of cardiovascular and metabolic diseases (draft)
- ICH Topic E 7 Studies in Support of Special Populations: Geriatrics (CPMP/ICH/379/95)
- ICH topic E7 Studies in Support of Special populations: Geriatrics, Questions and Answers (EMA/CHMP/ICH/604661/2009)
- Note for Guidance on Choice of Control Group in Clinical Trials - CPMP/ICH/364/96 (ICH E10);
- Guideline on missing data in confirmatory clinical trials (CPMP/EWP/177/99)
- Statistical principles for clinical trials (ICH E9)
- ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials (draft)
- Note for Guidance on the Extent of Population Exposure to Assess Clinical Safety for Drugs - CPMP/ICH/375/95 (ICH E1A)

4. Patient selection

It is recommended that the diagnosis of gout should be established by a Health Care Professional (HCP). Internationally established diagnostic criteria, e.g. by EULAR–ACR or ESCISIT, could be used.

During acute attacks, serum urate levels may be low. In these cases, it is recommended to confirm the diagnosis of gout by either a history of hyperuricaemia, the presence of MSU crystals in synovial fluid, by imaging –by demonstrating a double contour sign on ultrasound imaging of joints or intra-articular crystals by DECT-, or the presence of tophi.

At inclusion, a distinction may be made between patients with intermittent flaring disease, with symptom free intervals, or advanced patients with chronic arthropathy manifestations. If both patients with or without tophi are included, prior stratification is recommended.

For the selection of subjects in a trial of urate lowering therapy, it is recommended to include gout patients with clear hyperuricaemia, e.g. above 7 mg/dl, at baseline. Naïve or treatment-experienced patients may be eligible. It is recommended to specify the criteria of non-response or intolerance to standard care in the protocol prior to the study, and to stratify patients based on prior treatment.

Patients with other common co-morbidities in gout, such as obesity, diabetes, hypertension, and renal impairment are encouraged be included as well, depending on the safety profile of the drug.

At present, there are no criteria to identify patients with asymptomatic hyperuricaemia who might benefit clinically from urate lowering therapy –with the exception of rare circumstances such as an inherited metabolic or renal defect where the severity of hyperuricaemia might be reasonably anticipated to lead to joint and/or organ damage over time.

5. Criteria for assessment of efficacy in confirmatory trials

5.1. Efficacy criteria/treatment goals

Treatment of gout may have different goals. These may include (a) the reduction of hyperuricaemia and urate crystal load, to ultimately resolve the source of flares and tophi by ULT, or (b) the symptomatic treatment of acute gouty arthritis flares by anti-inflammatory drugs. Anti-inflammatory drugs may also be used in (c) the prophylaxis of flares given that these can be precipitated by the introduction of ULT, or (d) the symptomatic treatment of arthritis symptoms associated with chronic tophaceous arthropathy.

These different treatment goals require specific clinical development plans and clinical trial designs. The development plan and endpoints will mainly be related to the mode of action of the drug. This may either be interventional treatment by means of urate lowering therapy (ULT), or symptomatic treatment by anti-inflammatory/immune-modulating drugs.

There is currently insufficient evidence from trials or epidemiological studies that urate lowering therapy in individuals with asymptomatic hyperuricaemia would be useful to prevent gout, renal impairment or cardiovascular disorders. If drug development in asymptomatic hyperuricaemia is considered, not only an effect on hyperuricaemia, but also the clinical relevance of reduced serum uric acid levels in the prevention of e.g. renal impairment or cardiovascular events should be shown. It is recommended to seek scientific advice at the EMA regarding inclusion criteria, endpoints and study design if asymptomatic hyperuricaemia is considered as an indication.

5.1.1. Primary efficacy parameters

Urate lowering therapies (ULT)

The aim of ULT is to lower uric acid levels and to clear the body of the MSU crystal load, which is the cause of inflammatory reactions, manifest as acute gout attacks (flares) or chronic bursitis or arthritis. If ULT is successful, ultimately, tophi and flares will disappear or be significantly reduced. Serum uric acid (SUA) may serve as a surrogate endpoint, as it has been shown that when the SUA is continuously kept below the hyper-saturation level, the crystal deposits and associated symptoms like tophi and flares, eventually decrease. As it takes time for the body to be cleared of uric acid crystals, and as uric acid levels fluctuate over time depending on food and fluid intake, the primary endpoint should not consist of SUA levels at a single time-point, but should reflect a sustained SUA response below a critical target level. SUA should, therefore, be frequently monitored in the trials (at least every 4 weeks).

For confirmatory trials, the primary endpoint should be defined as sustained SUA levels below a target level of 6 mg/dl, for a period of 3 consecutive months, which starts once the treatment is optimised and stable. An additional treatment aim is the reduction of tophi. For patients with tophaceous gout, the 6 mg/dl target may not be sufficiently stringent to achieve a relevant reduction of the tophus load in a reasonable time frame. For tophaceous gout patients a target level < 5 mg/dl is considered more appropriate. The primary endpoint for tophaceous gout should then be the percentage that achieves stable levels of SUA < 5 mg/dl for a period of at least three consecutive months.

Anti-inflammatory drugs

The treatment goal of anti-inflammatory drugs could be the acute treatment of flares, or in the case of more chronic disease, the reduction of chronic arthritic symptoms by a sustained anti-inflammatory

effect. Another specific goal may be the prophylaxis of flares upon initiation of an ULT in a former ULT naïve population.

For a claim of the acute treatment of flares, the primary endpoint should reflect a significant and clinically relevant reduction in pain of the index joint(s), in a relatively short time frame of 24 hrs. Other aspects of acute gout flare, such as joint swelling an redness, are to be included as secondary endpoints. If the primary endpoint is the mean change of pain VAS scores from baseline, its clinical relevance should be demonstrated in responder analyses, e.g. defined as an improvement of at least 30% from baseline.

For a prophylaxis indication at start of ULT, the primary endpoint should be the mean number of flares in a specific time frame, e.g. 3-6 months after the start of ULT in ULT-naïve patients.

Patients refractory to ULT who developed chronic gouty arthropathy, with tophi at multiple joints and without symptom-free intervals, are considered a suitable target population for long-acting or chronic anti-inflammatory treatments. Validated scales that include the multiple domains of gouty arthritis are currently lacking. The primary endpoint should include a reduction of arthropathic pain, with Patient's Global Assessment as key secondary or co-primary endpoint after 3 months. Function should be included as well, as key secondary endpoint. A later time-point for primary analyses may also be considered if adequately justified, e.g. for treatments with a more gradual onset of effect.

5.1.2. Secondary efficacy endpoints

Urate lowering therapies

- **Serum Urate:**

  Mean and median change from baseline to 3, 6 and 12 months, and AUC

  Responders with a target level < 5 mg/dl for 3 consecutive months (if not already chosen as primary endpoint in tophaceous gout)

- **Tophus regression:**

  Responder rates: Complete resolution (e.g. measured by visual inspection using callipers).

- **Imaging (Optional):**

  Tophi mass: Ultrasound or Dual Energy Computer Tomography (DECT).

Anti-inflammatory treatment modalities

Swollen and tender joint counts

C-reactive protein

Optional: X-ray of the feet and/or hand (erosions, Sharp-van der Heijden scores).

All therapies

- Gout flares requiring treatment: Number of flares *(if not already chosen as primary endpoint in the context of flare prophylaxis)*, time to flare;
- The use of analgesic rescue drugs;
- Functional scores: e.g. HAQ-DI;
- Quality of life: e.g. SF-36 (physical component score, including Arthritis Specific Health Index);

- Patient's Global Assessment (if not already chosen as primary endpoint in chronic tophaceous arthopathy);
- Physician Global Assessment.

5.2. Methods to assess efficacy criteria

If specific diet or hydration recommendations are given to reduce the uric acid load, these should be standardised across the participating treatment centres and study arms.

Measurement of urate levels

It is recommended to standardise the bio-analytical method of measuring serum or plasma urate acid levels across study centres, or to use a central laboratory, in order to avoid bias when different analytical methods are used (e.g. colorimetric methods tend to give higher values than uricase assays).

Tophi assessments

Several methods are available for the measurement of tophi. It is recommended to select 1-2 anatomically separated "marker" tophi at baseline for further assessments.

Visible sub-dermal tophi could be assessed by digital callipers, which have been shown to be sensitive to changes in randomised trials of urate lowering therapies. It is recommended to predefine criteria in the protocol of complete or partial response.

Several imaging methods have been evaluated to diagnose subdermal and articular tophaceous mass, including ultrasound or DECT scans. A correlation to SUA levels and DECT outcomes has been demonstrated in prospective case series. At present, no ultrasound assessment data are available from randomised trials on ULT products. If appropriately validated, ultrasound or DECT outcomes could serve as supportive evidence.

Tophi assessment should be conducted in a blinded manner. Inter-rater reliability should be assessed. For tophi assessment based on imaging, a central blinded reader is recommended.

Flares

A gout flare is an intensely painful and disabling inflammatory arthritis, usually involving a single joint but occasionally involving two or more joints. At present, no validated scales are available for the assessment of flares. The definition of flares should be specified in the study protocol.

During trials, flares may be self-diagnosed, as gout flares are often distinctive and recognisable for patients. Patients should be uniformly instructed how to recognise a flare. Symptoms of interest that are often recognised as a gout flare by patients are the specific joints that were affected at the acute flare (e.g. involvement of the first metatarsophalangeal joint and ankle), swollen and warm joint(s), and acute onset of pain. Patient-assessed flares should be established based on pain scales, the need of analgesics, patient reported number and severity of swollen and warm joint(s), and functional impairment. Iinstructional materials illustrating the severity of flare scores should be provided for patients, e.g. unable to walk because of pain, or not tolerating the light touch of e.g. a blanket.

Other important factors that need to be recorded at baseline -and throughout the study if variable in time- are gender, age, body-weight and BMI, renal function, co-morbidity and co-medications (e.g. thiazide diuretics).

6. Strategy and design of clinical trials Study design

6.1. Pharmacology studies

6.1.1. Pharmacokinetics

Considering the general target population, pharmacokinetics (PK) in elderly and renally impaired patients should be established. As obesity is common in the target population, it needs to be reviewed whether dose adjustments are required for obese subjects, from both a pharmacokinetic and clinical point of view.

Gout is relatively rare in women, particularly at younger and middle age groups. PK and pharmacodynamic data from females of different age groups might be helpful in bridging efficacy and safety from predominantly male study populations.

Reference is made to the PK guidelines mentioned under Section 3 of this document.

6.1.2. Pharmacodynamics

For new immune-modulating-treatment options, the pharmacodynamic effects on the native and adaptive immune system should be explored. The "pharmacodynamic half-life" and potential carry-over effects of the anti-inflammatory effect needs to be estimated.

6.1.3. Interactions

Possible PK interactions with drugs commonly used in gout patients (e.g. xanthine-oxidase inhibitors, NSAIDs, colchicine, diuretics, oral anti-diabetic treatment options and lipid lowering drugs) should be considered.

Pharmacodynamic interactions with co-medication that has a secondary effect on uric acid levels, such as e.g. thiazide diuretics, fenofibrate, losartan, should be controlled for, as these drugs may interfere with the study outcomes of target UA levels. The use of concurrent immune-modulating drugs or NSAIDs may interfere with outcomes of flares.

6.2. Therapeutic studies

6.2.1. Exploratory and dose finding studies

The proof of concept and dose of ULT may be explored in short-term trials. Depending on the onset and mode of action of the drug, a period of 6-12 weeks may be sufficient for exploratory trials. For urate lowering therapies, change from baseline of SUA levels is a suitable endpoint for exploring the dose.

For anti-inflammatory treatment options developed for the treatment of acute flares, a single flare episode could be sufficient to explore efficacy and safety. Another suitable model may be patients that initiate ULT. It is recommended to evaluate the duration of PD effect in the exploratory trials, to provide guidance for a safe re-treatment interval before the start of the confirmatory trial.

6.2.2. Confirmatory trials

6.2.2.1. Urate lowering therapies

In general, parallel, randomised, double-blind, placebo-controlled trials should be performed for a minimum of 6 months. The pivotal trials should be sufficiently long to establish a sustained effect of urate lowering for at least 3 months, once the treatment is optimised at a stable dose level.

For first line treatment options, at least one of the pivotal trials should include standard care allopurinol as an active control. If demonstration of superiority compared with a standard urate-lowering treatment option like allopurinol is intended, a two-arm active-controlled study without placebo-control is also appropriate. For non-inferiority trials, a placebo control should be ~~included~~ considered as well for a period of 3 months at the minimum, to establish assay sensitivity, unless otherwise justified –i.e. that a considerable treatment effect could be reasonably expected for the active control in the study population sample-.

For second line treatment options, combination therapy with an XOI maybe appropriate in specific cases –e.g. to prevent high urinary uric acid load and acute nephrotoxicity of a uricosuric drug. A placebo-controlled add-on study is required. The same study duration -6 months at the minimum- should be considered as aforementioned in monotherapy studies. Inclusion of an additional study arm with active control + XOI background therapy can be considered as well in this setting.

For second line monotherapy treatment options, where XOI-combination is not appropriate, it could still be considered to continue former XOI in the placebo arm only –provided that these patients are tolerant to XOI-, as prior XOI may still have some efficacy in incomplete responders.

The primary endpoint should reflect a sustained effect of SUA levels below the critical SUA level of 6 mg/dl (see section 5.1.1 for details of the definition of the primary endpoint). Gout flares should be recorded, and these could serve as secondary endpoint.

Urate lowering therapies may induce and worsen gout flares after the start of the treatment at first instance, as a sudden drop in SUA levels may trigger a host defence to dissolving crystals. Standardised prophylactic measures should be considered to prevent flares at the short term (e.g 3 months). In the statistical analyses of flare incidence, the use of prophylaxis should be taken into account. This should be predefined in the statistical analyses plan.

For trials targeting tophaceous gout patients, the target level should be below 5 mg/dl (see section 5.1.1). Tophi and flares should be assessed as well in these trials as secondary endpoints.

To demonstrate maintenance of efficacy, data should be provided for a minimum study duration of 12 months in one of the trials, with an active control, that could be standard of care. A formal demonstration of non-inferiority is not required. The strategy for analysing intercurrent events, such as the drop-out due to flares shortly after the introduction of ULT or after the withdrawal of concurrent flare prophylaxis treatment, or differential adherence to the study drug, needs to be addressed a priori in the statistical analyses plan.

6.2.2.2. Anti-inflammatory therapies

Symptomatic treatment of acute flares

For an indication of acute treatment of flares, patients currently suffering from a moderate-severe gouty arthritis flare should be included, as diagnosed by a physician.

The primary endpoint should be clinically relevant pain relief within 24 hrs (see section 5.1.1 for details). Outcomes reflective of arthritis symptoms like swelling and redness, and the amount of rescue analgesic drugs are suitable secondary endpoints.

Parallel, randomised, double-blind, placebo- -controlled trials should be performed. Rescue analgesics should be readily available and pre-defined in the protocol. The treatment effect could also be established by showing superiority towards an active comparator in a two-arm trial. No placebo-control is needed if the study objective is demonstrating superiority towards an active control. NSAIDs, colchicine or steroids are considered as relevant comparators in an active controlled trial. If non-inferiority is aimed for, this should, in principle, be established in a three arm study, which includes placebo to establish assay sensitivity –unless it has been demonstrated before that the active control has a clear effect.

The blinded phase of the study should be continued for at least 2 weeks, depending on the mode of action of the drug, for the evaluation of the effects of the drug in the phase after the acute gout attack, when inflammation may still be present.

In the clinical development plan, it should be established what is a safe interval between recurrent treatments. Efficacy and safety data should also be obtained from patients who receive repeat courses –of multiple gout attacks-.

Prophylaxis of flares upon initiation of ULT treatment

Prophylaxis of gout flares could be established in patients starting with ULT. A randomised non-inferiority trial with an active control is considered appropriate to confirm efficacy. Colchicine or NSAIDs are appropriate comparators in this setting. The optimal treatment duration of prophylaxis needs to be established, e.g. by comparing different treatment episodes. To establish assay sensitivity, a placebo control with rescue medication can be applied, for a short-term period (e.g. 6 weeks). Alternatively, superiority to a low-dose arm can be sufficient to establish assay sensitivity.

Symptomatic treatment of chronic tophaceous arthropathy

Some patients will develop severe tophi associated with chronic arthritis symptoms, despite adequate treatment with ULT. For such patients, treatment with long-acting anti-inflammatory drugs or long-term use of anti-inflammatory drugs may be indicated. In support of this chronic indication, a double-blinded placebo controlled study is required. The placebo may be as short as three months. It is recommended that blinding is further maintained for 6 months. Background therapy with ULT should remain stable, as this may interfere with the outcomes. For further establishment of the maintenance of efficacy, a randomised withdrawal trial is recommended.

7. Safety

7.1. Specific effects

Urate lowering therapies have the capacity to induce flares in the initial treatment phase, which should be recorded as adverse events.

For biologicals including monoclonal antibodies or innovative synthetic molecules that are given parenterally, infusion reactions and drug-antibody forming should be monitored. For uricase enzym products, monitoring SUA outcomes maybe helpful as an indirect indicator of neutralising antibody formation. For immune-modulatory drugs particularly, possible effects on the immune system and the risk of infections should be monitored.

7.2. Long-term effects

Safety data should become available for a period of minimal 12 months of follow-up.

7.3. Safety endpoints

Renal function (serum creatinine, urine protein, estimated creatinine clearance) need to be routinely monitored for all gout treatments.

Laboratory outcomes should include liver function tests, lipids, full blood count, in addition to other parameters relevant to the product.

Obesity, hyperlipidaemia and hypertension, diabetes type II and renal impairment are common co-morbidities in gout. Gout patients are also deemed to be at risk of cardiovascular disorders although a causal link with elevated urate levels has not been definitively established. Lipids, blood pressure and cardiac events should be carefully monitored during the studies. MACE (Major Adverse Cardiovascular Events) should be pre-defined in the protocol.

8. Studies in special populations

8.1. Studies in elderly patients

Although middle-aged males are mostly affected, gout may persist in old age. In women, gout typically emerges due to diuretics use at elder age.

Efficacy in elderly patients

Renal function declines with age. This may impact the efficacy of uricosuric drugs in particular, where response is related to remaining renal capacity. Data should be presented for various

age groups (for example <65, 65-74, 75-84 and > 85) to assess the consistency of the treatment, and the need for age specified dose recommendations need to be discussed.

Safety in elderly patients

The background risk of common co-morbidities, such as cardiovascular disorders and renal impairment may increase with age. Elderly may be more at risk of infections for immune-modulating drugs. Sufficient numbers of elderly patients should be included, preferably of gout patients over 70 years of age as the aforementioned risk factors are often more prominent in this age group.

8.2. Studies in paediatric patients

Gout is extremely rare in children, and children are therefore not considered as a target population. Acute hyperuricaemia secondary to cell-lysis, however , may occur in children e.g. in the treatment of leukaemia. If ULTs are developed for this condition, it is encouraged to include children as well in drug-development.

8.3. Renal impairment

As renal impairment is common in gout patients, the efficacy and safety in gout patients with renal impairment should be addressed in the drug-development programme of a new treatment option. The dose needs to be established for all gradations of renal impairment (mild/moderate/severe), unless this is not possible for safety reasons.

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Definitions

BMI	Body Mass Index
ESCISIT	EULAR Standing Committee for International Clinical Studies Including Therapeutics
EULAR–ACR	European League Against Rheumatism/ American College of Rheumatology
DECT	Dual Energy Computer Tomography
MACE	Major Acute Cardiovascular Events
MSU	Monosodium urate
PK	Pharmacokinetics
SUA	Serum Uric Acid/Serum urate
UA	Uric Acid/Serum urate
ULT	Urate Lowering therapy