



1 31 January 2019
2 EMA/CHMP/774470/2018
3 Committee for Medicinal Products for Human Use (CHMP)

4 **Guideline on clinical investigation of medicinal products**
5 **for the treatment of gout**

6 Draft

Draft agreed by Rheumatology Immunology Working Party	December 2018
Adopted by CHMP for release for consultation	31 January 2019
Start of public consultation	08 February 2019
End of consultation (deadline for comments)	31 August 2019

7
8

Comments should be provided using this [template](#). The completed comments form should be sent to R-IWP@ema.europa.eu

9
10
11

Keywords	<i>Gout, urate lowering therapy, tophi, chronic tophaceous arthropathy</i>
-----------------	---

12
13



14 **Table of contents**

15 **Executive summary 3**

16 **1. Introduction (background) 3**

17 **2. Scope..... 5**

18 **3. Legal basis and relevant guidelines 5**

19 **4. Patient selection..... 6**

20 **5. Criteria for assessment of efficacy in confirmatory trials 7**

21 5.1. Efficacy criteria/treatment goals 7

22 5.1.1. Primary efficacy parameters..... 7

23 5.1.2. Secondary efficacy endpoints 8

24 5.2. Methods to assess efficacy criteria 9

25 **6. Strategy and design of clinical trials Study design 10**

26 6.1. Pharmacology studies 10

27 6.1.1. Pharmacokinetics 10

28 6.1.2. Pharmacodynamics..... 10

29 6.1.3. Interactions..... 10

30 6.2. Therapeutic studies 10

31 6.2.1. Exploratory and dose finding studies 10

32 6.2.2. Confirmatory trials..... 11

33 **7. Safety 12**

34 7.1. Specific effects 12

35 7.2. Long-term effects..... 13

36 7.3. Safety endpoints 13

37 **8. Studies in special populations 13**

38 8.1. Studies in elderly patients 13

39 8.2. Studies in paediatric patients 13

40 8.3. Renal impairment..... 13

41 **9. References 14**

42 **Definitions 14**

43

44 **Executive summary**

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

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

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

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

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

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

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

74 **1. Introduction (background)**

75 ***Aetiology & symptoms***

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

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

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

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

93 **Epidemiology**

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

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

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

110 **Current treatment options**

111 *Urate lowering therapy*

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

120 ULT employs a treat to target approach, the goal of which is to lower serum urate (SUA) below a
121 specified threshold, established to be of clinical benefit. In the EULAR treatment guideline published in
122 2006, the target for serum urate level is set as < 6 mg/dL, as in several longitudinal studies, the risk
123 of flares was 1.2-2 times higher in patients with SUA levels above a cut-off of 6 mg/dl. Although often
124 used and considered relevant to prevent flares in the long-term, the 6 mg/dl cut-off point may not be
125 sufficient to reduce tophus load in a reasonable time-frame. Several experts and international
126 treatment guidelines therefore recommend a more stringent reduction of SUA to levels below 5 mg/dl
127 to obtain a faster reduction of tophi. The 5 mg/dl target level is based on median SUA levels of the
128 general British male population of 5.1 mg/dl.

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

131 *Other treatment options*

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

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

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

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

146 **2. Scope**

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

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

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

157 **3. Legal basis and relevant guidelines**

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

- 161 • Guideline on the evaluation of the pharmacokinetics of medicinal products in patients with impaired
162 renal function (CPMP/EWP/225/02)
- 163 • Guideline on the investigation of drug interactions 21 June 2012 CPMP/EWP/560/95/Rev. 1 Corr.
164 2** Committee for Human Medicinal Products (CHMP)
- 165 • Guideline on the clinical development of medicinal products intended for the treatment of pain
166 (EMA/CHMP/970057/2011)

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

181 **4. Patient selection**

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

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

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

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

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

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

201 **5. Criteria for assessment of efficacy in confirmatory trials**

202 **5.1. Efficacy criteria/treatment goals**

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

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

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

220 **5.1.1. Primary efficacy parameters**

221 *Urate lowering therapies (ULT)*

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

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

239 *Anti-inflammatory drugs*

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

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

244 For a claim of the acute treatment of flares, the primary endpoint should reflect a significant and
245 clinically relevant reduction in pain of the index joint(s), in a relatively short time frame of 24 hrs.
246 Other aspects of acute gout flare, such as joint swelling and redness, are to be included as secondary
247 endpoints. If the primary endpoint is the mean change of pain VAS scores from baseline, its clinical
248 relevance should be demonstrated in responder analyses, e.g. defined as an improvement of at least
249 30% from baseline.

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

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

259 **5.1.2. Secondary efficacy endpoints**

260 ***Urate lowering therapies***

261 - **Serum Urate:**

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

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

265 - **Tophus regression:**

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

267 - **Imaging (Optional):**

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

269 ***Anti-inflammatory treatment modalities***

270 Swollen and tender joint counts

271 C-reactive protein

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

273 ***All therapies***

274 - Gout flares requiring treatment: Number of flares (*if not already chosen as primary endpoint in the*
275 *context of flare prophylaxis*), time to flare;

276 - The use of analgesic rescue drugs;

277 - Functional scores: e.g. HAQ-DI;

278 - Quality of life: e.g. SF-36 (physical component score, including Arthritis Specific Health Index);

- 279 – Patient’s Global Assessment (if not already chosen as primary endpoint in chronic tophaceous
280 arthropathy);
- 281 – Physician Global Assessment.

282 **5.2. Methods to assess efficacy criteria**

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

285 *Measurement of urate levels*

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

290 *Tophi assessments*

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

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

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

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

303 *Flares*

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

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

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

318 **6. Strategy and design of clinical trials Study design**

319 **6.1. Pharmacology studies**

320 **6.1.1. Pharmacokinetics**

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

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

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

329 **6.1.2. Pharmacodynamics**

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

333 **6.1.3. Interactions**

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

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

341 **6.2. Therapeutic studies**

342 **6.2.1. Exploratory and dose finding studies**

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

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

351 **6.2.2. Confirmatory trials**

352 **6.2.2.1. Urate lowering therapies**

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

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

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

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

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

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

379 For trials targeting tophaceous gout patients, the target level should be below 5 mg/dl (see section
380 5.1.1). Tophi and flares should be assessed as well in these trials as secondary endpoints.

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

387 **6.2.2.2. Anti-inflammatory therapies**

388 *Symptomatic treatment of acute flares*

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

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

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

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

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

408 *Prophylaxis of flares upon initiation of ULT treatment*

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

415 *Symptomatic treatment of chronic tophaceous arthropathy*

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

423 **7. Safety**

424 **7.1. Specific effects**

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

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

432 **7.2. Long-term effects**

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

434 **7.3. Safety endpoints**

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

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

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

444 **8. Studies in special populations**

445 **8.1. Studies in elderly patients**

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

448 **Efficacy in elderly patients**

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

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

453 **Safety in elderly patients**

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

458 **8.2. Studies in paediatric patients**

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

463 **8.3. Renal impairment**

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

468

469 **9. References**

470 Khanna et al., 2012 American College of Rheumatology Guidelines for Management of Gout. Part 1:
471 Systematic Nonpharmacologic and Pharmacologic Therapeutic Approaches to Hyperuricemia, Arthritis
472 Care & Research Vol. 64, No. 10, October 2012, pp 1431–1446

473 Khanna et al., 2012 American College of Rheumatology Guidelines for Management of Gout. Part 2:
474 Therapy and Antiinflammatory Prophylaxis of Acute Gouty Arthritis, Arthritis Care & Research Vol. 64,
475 No. 10, October 2012, pp 1447–1461

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

478 Sing J.A. et al., Patient-reported Outcomes in Chronic Gout: A Report from OMERACT 10, J Rheumatol.
479 2011; 38(7): 1452-7.

480 Wallace S.L., et al., Preliminary criteria for the classification of the acute arthritis of primary gout.
481 Arthritis Rheum 1977; 20: 895-900

482 Zhang W. et al., EULAR evidence based recommendations for gout. Part I: Diagnosis. Report of a task
483 force of the Standing Committee for International. Clinical Studies Including Therapeutics (ESCISIT),
484 Ann Rheum Dis 2006;65:1301–1311.

485 Zhang W.et al., EULAR evidence based recommendations for gout. Part II: Management. Report of a
486 task force of the EULAR Standing Committee for International. Clinical Studies Including Therapeutics
487 (ESCISIT) Ann Rheum Dis 2006;65:1312–1324.

488 **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

489