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Title

Impact of non-adherence on the safety and efficacy of uric acid lowering therapies in the treatment of gout

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Structured Summary

AIMS

Dual-urate lowering therapy (ULT) with xanthine oxidase inhibitor and uricosuric medications is a treatment option for severe gout. Uricosurics can cause hyperuricosuria, a risk factor for nephrolithiasis and acute uric acid nephropathy. The aims of this study were to simulate the relation between suboptimal drug adherence and efficacy, and to quantify the risk of hyperuricosuria in gout patients receiving mono and dual-ULTs.

METHODS

The impact of poor medication adherence was studied using 2-compartment PK models based on published evidence and a semi-mechanistic, 4-compartment pharmacodynamic (PD) model. The PKPD model was used to simulate mono and dual-ULT in gout patients with either under-excretion (lowered clearance) or overproduction of uric acid, with suboptimal adherence modelled as either a single drug holiday of increasing duration or doses taken at random.

RESULTS

Simulation results showed a surge in urinary uric acid occurring when dosing is restarted following missed doses. For under-excreters taking a 20 day drug holiday, the addition of 200 mg (or 400 mg) lesinurad to 80 mg febuxostat increased the percentage of patients experiencing hyperuricosuria form 0% to 1.4% (or 3.1%). In overproducers, restarting ULTs following drug holidays of more than 5 days leads to over 60% of patients experiencing hyperuricosuria.

CONCLUSIONS

Sub-optimal medication adherence may compromise safety and efficacy of mono and dual-ULTs, especially in patients with gout resulting from an overproduction of uric acid. Clinicians and pharmacists should consider counselling patients with respect to the risks associated with partial adherence, and offer interventions to improve adherence or tailor treatments, where appropriate.

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Uricosurics, used for the treatment of gout, increase the risk of hyperuricosuria and therefore also acute kidney injury.
- Medication adherence to urate lowering therapies for treating gout is amongst the worst of any chronic disease.

WHAT THIS STUDY ADDS

- Restarting uricosuric treatment following a drug holiday increases the rate of episodic hyperuricosuria.
- Sub-optimal medication adherence may compromise safety and efficacy of mono- and dual-urate lowering therapies, especially in patient groups such as those with gout resulting from an overproduction of uric acid.
- Clinicians and pharmacists should consider counselling patients with respect to the risks associated with partial adherence, and offer interventions to improve adherence or tailor treatments, where appropriate.

Introduction

Gout is a painful and disabling chronic disease which has proven difficult to treat and affects a large and increasing number of people [1]. Long term treatment with urate lowering therapies (ULTs) aims to reduce serum uric acid (sUA) concentrations to below the point of saturation (approximately 6 mg/dL). When treatment with a xanthine oxidase inhibitor (XOI) alone is unsuccessful, a uricosuric can be used in combination [2]. Historically, the use of uricosurics for long-term therapy has been limited due to possible hepatotoxicity (benzbromarone) and drug-drug interactions (probenecid). However, the uric acid transporter-1 (URAT-1) inhibitor lesinurad has recently gained regulatory approved and is intended for long-term therapy in combination with an XOI (such as allopurinol or febuxostat) [3].

As they increase the renal excretion of uric acid, uricosurics such as lesinurad, can cause hyperuricosuria (urinary excretion of uric acid ≥800 mg day^{-1} in men; ≥750 mg day^{-1} in women) [4]. High levels of urinary uric acid (uUA) can cause kidney damage which may be acute, such as stone formation (nephrolithiasis) [5] and intrarenal obstruction (acute urate nephropathy), or chronic as in chronic (or gouty) nephropathy. Acute kidney injury can occur when uric acid concentrations in renal tubules reach supersaturation, which also depends on urine pH [6,7]. Chronic nephropathy is thought to result from long-term hyperuricosuria which may be below supersaturation concentrations. The existence of chronic nephropathy remains controversial [8], but is supported by animal models and some epidemiological studies [9]. The harmful effects of uric acid on the kidney are a possible explanation of the association, in recent clinical trials, between lesinurad and an increase in the rate of raised serum creatinine and, for higher doses, with serious renal adverse events [10].

Adherence to ULT is known to be amongst the lowest of any chronic disease treatment [11,12], with 70% of patients having a drug holiday of at least 60 days over 6 years. Poor adherence to allopurinol

monotherapy is associated with lower treatment success rates [13]. While dual-therapy increased response rates compared with monotherapy in clinical trials [14–16], interruption in dosing (drug holiday) could result in high peaks in uUA concentration when treatment is restarted. Sub-optimal implementation of the dosing regimen (e.g. late doses, skipping a dose, or drug holidays) [17], may therefore increase the risk of renal adverse events caused by uric acid nephropathy.

This study aims to simulate the relation between poor implementation of dosing and efficacy, and to quantify the risk of hyperuricosuria in gout patients receiving mono- and dual-ULT.

Methods

Strategy

A semi-mechanistic pharmacokinetic-pharmacodynamic (PKPD) model, based on previous research on the systems pharmacology of the purine metabolic pathway [18], was developed to capture the pharmacology of ULTs (Figure 1). The system was comprised of four compartments utilising a zero order production rate (k_0) governing the formation of xanthine and first order production rates characterising its biotransformation to uric acid (k_1) and the elimination of xanthine (k_2) and uric acid (k_3) into the urine. These in turn were parameterised in terms of volumes and clearance terms.

The PD model characterises the time course of sUA, uUA, xanthine and urinary xanthine. Two inhibitory indirect response (turnover) models were used to account for the effect of multiple doses of febuxostat on k_0 and k_1 [19]. A stimulatory indirect response [20] equation acting on the k_2 rate parameter was incorporated to model the increased xanthine renal clearance associated with febuxostat [21]. The clearance of uric acid upon multiple doses of lesinurad was modelled using a stimulatory indirect response equation acting on the k_3 rate parameter.

The system and drug PD model parameter estimates were obtained from literature and other publicly available sources. As described below some parameters values were taken directly from the literature while others were estimated using non-linear mixed effects models and clinical trials data**.** The parameters required to characterise the pharmacodynamic model are given in Table 1.

Pharmacokinetics

Two-compartment models with first order absorption for febuxostat and lesinurad obtained from the literature [22,23] were used to simulate typical and individual subject level drug plasma concentration time courses. The PK parameters, covariate effects and associated between subject variability are reproduced in Table 2.

Pharmacodynamics

i) Parameters obtained from literature

The mean rates of renal clearance of uric acid and xanthine (CLUA and CLX) in healthy volunteers, along with the between-subject variability, were obtained using summary data from a phase I dose-escalation study of 154 healthy volunteers receiving febuxostat [24]. The reported average clearance in each group and standard deviations (supplementary material) were used to obtain a weighted average estimate of population typical value and the between subject variability.

This trial also found that the rate of xanthine renal clearance in subjects taking febuxostat, even at doses as low as 10 mg per day, increased 3- to 5-fold from baseline. This may result from saturation of active transport processes responsible for the reabsorption of xanthine from renal tubules [21]. A step function was assumed using a stimulatory E_{max} drug function, eq. 11 in Figure 1, with an $EC_{50,1}$ of 0.001 mg dl^{-1} (a low concentration associated with the 10mg dose) and $E_{max,1}$ of 3.

A previous PD model of lesinurad used a direct effect E_{max} model to relate steady-state average plasma concentration of lesinurad to the individuals' sUA concentration [23]. The parameters of the indirect model ($E_{max,2}$, $EC_{50,2}$) were derived from those given in the published direct model (E^D_{max} and EC^D_{50}) using the steady state equations [19] (supplementary material). The published model includes a covariate effect of creatinine clearance on the maximum reduction in uric acid, E^D_{max}. The stimulatory model drug function $STIM_2$ is given by eq. 12 in Figure 1, while the equations used to derive $E_{max,2}$ and $EC_{50,2}$ are given below.

$$E_{max,2} = \frac{E_0}{E_0 - (E^D_{max}\left(\frac{CrCl}{87}\right)^{b_{crcl}})} - 1$$

$$EC_{50,2} = \frac{E_{max,2}\, EC^D_{50}}{E_0/(E_0 - \left(\frac{E^D_{max}}{2}\right)) - 1} - EC^D_{50}$$

CrCl is the individual's creatinine clearance rate and E_0 is the baseline sUA concentration of trial participants used to derive the direct E_{max} model parameters.

ii) Estimated using statistical modelling

All other parameters were estimated using non-linear mixed effects modelling and febuxostat Phase I trial summary data on daily area under the plasma concentration curve (AUC) and 24-hour urinary excretion of xanthine and uric acid [24] (supplementary material). This was conditional on the clearance estimates and drug PD function parameters obtained directly from the literature in the previous section. A NONMEM dataset was created using the AUC and urinary data and the trial dosing schedule. Each value was an average across all individuals within a dose group and has, therefore, been replicated according to the number of subjects within the group in order to weight by sample size.

The PKPD modelling was conducted using NONMEM 7.3 and the ADVAN6 routine for solving differential equations. The PD model was coded using the differential equations in Figure 1 where equations 3 and 4 correspond directly to published data on 24-hour urinary excretion [24]. However,

additional sUA and serum xanthine accumulation compartments were added to compute the area under the concentration curve at 24 hour intervals. Parameter estimation used the first order algorithm and different initial parameter estimates were tested. No random effects were included on system parameters estimated in NONMEM since the data points do not come from individual subjects. The inhibitory model drug functions INH_1 and INH_2 are given by equations 9 and 10 respectively in Figure 1.

In order to simplify the modelling procedure and make use of all available evidence the statistical modelling was performed in two stages. The first stage used a published PKPD model of febuxostat that used an indirect inhibitory response model applied to a zero order rate of uric acid production [22]. Rewriting uric acid production in the differential equations in our model as zero order the literature parameter estimate of 0.0239 mg dl^{-1} was assumed for $IC_{50,2}$ and the remaining parameters were then estimated. In the second stage, the uric acid production was returned to being first order, such that it is a function of changing xanthine levels, and a new parameter estimate was made of $IC_{50,2}$ with all other parameters fixed.

Gout patient simulation model

We assumed that the febuxostat pharmacodynamic parameters estimated for healthy volunteers could be applied to gout patients with hyperuricemia. However, systems parameters have been adjusted to be representative of a patient population. A typical patient sUA concentration was assumed to be 8.83 mg dl^{-1} (standard deviation of 1.53) as this was the pre-treatment sUA concentration for patients in the CRYSTAL trial which compared febuxostat with lesinurad [25]. We considered two phenotypes, overproducers and under-excreters of uric acid [26,27], and modified the healthy subject system parameters accordingly. For overproducers, the amount of xanthine was scaled up and for under-excreters the clearance of uric acid was scaled down in proportion to the

sUA concentration (Table 3). This assumes the same volumes of distribution of xanthine and uric acid for patients as for healthy subjects.

The model was used to simulate treatment with 120 days ULT in a hypothetical cohort of 1,000 patients with baseline characteristics corresponding to the CRYSTAL trial. The cohort was all male (95% were male in CRYSTAL) and baseline sUA, weight and age were assumed to be lognormally distributed with mean and standard deviations taken from CRYSTAL (study 304) [28]. CrCl, calculated using the Cockcroft-Gault equation [29], overestimated the distribution of the trial participants. All estimates were reduced by 15 ml min^{-1} and estimates below 30 ml min^{-1} were excluded to obtain a better representation of the trial population CrCl. Variability of drug effects in INH_1 and INH_2 could not be estimated and the IC_{50} parameters were assumed to vary according to η_3 with a coefficient of variation of 20%. Steady state was assumed following 30 days of simulated treatment and only the latter 60 days was used to derive results.

The outcomes of interest were the simulated time course of sUA and uUA concentrations, from which we estimated the proportion of patients responding (sUA below ≤5 mg dl^{-1} on day 120) and the proportion of patients experiencing hyperuricosuria (uUA ≥800 mg day^{-1} on any day). The normal range of 24-hour volume of urine is 0.5-1 ml kg^{-1} hr^{-1}, but is likely to be lower in the elderly [30,31]. On this basis a representative daily urine output for a 99 kg male of 15 dl has been assumed for the purpose of estimating uUA concentrations. The soluble limit for uric acid is highly sensitive to urine pH, being much greater in alkaline than in acidic urine. For a given uUA concentration the pH at which saturation would occur was estimated by fitting a linear model to literature data [32] to obtain: saturation pH = 6.36 – 40.96/[uUA].

Modelling adherence

The impact of poor adherence was studied for four different ULT options, namely febuxostat 80 mg monotherapy and lesinurad 400 mg monotherapy, and febuxostat 80mg combined with either lesinurad 200 mg or 400 mg. All are once daily regimens and it was assumed that doses are taken at the same time each day. Two types of poor adherence were considered, the first being a single drug holiday of increasing duration, from 1 to 20 days to assess the impact on uUA burden of restarting treatment following increasing lengths of drug holiday. The second assessed the impact of poor implementation on response rates and peaks in uUA by simulating doses taken completely at random, with a probability ranging from 1 to 0.1. For all dual-ULTs missed doses included both drugs being missed simultaneously. A total of 30 simulations were conducted for each adherence scenario, which used random samples of the model parameter between subject variability, and the results were averaged over the range of simulation results.

Nomenclature of Targets and Ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [33], and are permanently archived in the Concise Guide to PHARMACOLOGY 2015/16 [34].

Results

The combined set of pharmacodynamics (PD) parameters and corresponding between subject variabilities (BSV) which were derived or estimated from the literature are presented in Table 1. Goodness of fit plots and visual predictive checks for the nonlinear mixed effects modelling are provided as supplementary material.

With perfect adherence, uUA concentrations are maintained at low levels under the combined action of febuxostat 80 mg and lesinurad 200 mg (see plots for a typical patient in Figure 2). During a

simulated drug holiday of 8 days, urinary concentrations increase as sUA concentrations return towards baseline. After dosing is restarted, peaks in uUA concentrations occur, for the typical under-excreter the peak reached 39 mg dl^{-1} which exceeds the typical average concentration for a healthy person (30 mg dl^{-1}). For the typical overproducer, the peak uUA concentration was 85 mg dl^{-1} which exceeds the threshold for typical average uUA concentration of an individual with hyperuricosuria (53 mg dl^{-1}). For the typical under-excreter, uUA concentrations after restarting treatment following an 8 day drug holiday could become supersaturated if the urinary pH was towards the acidic end of the normal range (pH <5.3; normal range 4.5-8.0). For the typical overproducer, peak uUA concentrations after restarting treatment are more likely to reach supersaturation at closer to the mid-point of the normal range at approximately 5.9.

Across the population, increasing the length of a drug holiday increases the proportion of patients whose daily amount of uric acid excreted exceeds the threshold for hyperuricosuria upon restarting treatment (Figure 3). The proportion of patients with hyperuricosuria increases with increasing doses of lesinurad and is greatest for lesinurad 400 mg monotherapy. For under-excreters taking a 20 day drug holiday, the addition of 200 mg (or 400 mg) lesinurad to 80 mg febuxostat increased the percentage of patients experiencing hyperuricosuria form 0% to 1.4% (or 3.1%). In overproducers, restarting ULTs following drug holidays of more than 5 days leads to over 60% of patients experiencing hyperuricosuria. In both patient groups, one- or two-day drug holidays are well tolerated compared to longer holidays with only moderate increases in the rates of hyperuricosuria.

With perfect adherence, the proportion of patients treated to target (sUA ≤5 mg dL^{-1} on day 120) is greater than was observed in the CRYSTAL trial (Figure 4). However, success rates fall rapidly as an increasing proportion of doses are missed at random. For daily doses of febuxostat 80 mg, febuxostat 80mg with lesinurad 200 mg, febuxostat 80 mg with lesinurad 400 mg and lesinurad 400 mg monotherapy, the success rates at 100% of doses taken in under-excreters are 87.2%, 94.5%,

96.0% and 15.4%, respectively. At 50% of doses taken at random, these success rates fall to 27.2%, 42.6%, 47.3% and 7.4%, respectively. The corresponding plots for overproducers are provided in the supplementary material.

Increasing the proportion of doses missed at random results in higher rates of hyperuricosuria due to randomly occurring drug holidays, especially in the presence of a uricosuric (Figure 4). The baseline daily uUA excreted in under-excreters is below healthy baseline levels and none of the simulated cohort showed hyperuricosuria in the absence of ULT. For dual-ULT with a uricosuric, however, randomly occurring drug holidays resulted in increasing rates of hyperuricosuria. For example at 30% of doses taken, for febuxostat 80 mg with lesinurad 200 mg, febuxostat 80 mg with lesinurad 400 mg and lesinurad 400 mg monotherapy the rates of hyperuricosuria are 1.3%, 3.2% and 4.9%, respectively.

Discussion

The use of uricosurics, either as monotherapy or in combination with an XOI, results in transient increases in uUA concentrations when dosing is restarted after a drug holiday. As a result, supersaturation of uric acid in urine can occur at pH values within the normal expected range and therefore precipitation of uric acid in the renal tubules is more likely to occur during routine clinical practice. This effect is likely to be greater following a drug holiday from dual-ULTs, than when starting treatment for the first time where, as per the regulatory approval of lesinurad, patients must already have been taking an XOI. Specifically, our simulations indicate that peak uUA concentrations reach the threshold for supersaturation at a urinary pH of 5.3 for under-excreters and of 5.9 for overproducers, so that crystal formation may occur for a urinary pH at or below this level.

Increasing the length of a drug holiday increased the proportion of patients whose daily amount of uric acid excreted exceeded the threshold for hyperuricosuria. The increase was more rapid for patients with over production, suggesting poorer drug forgiveness in this population. Treatment outcomes deteriorated rapidly as an increasing proportion of doses were missed at random. For under-excreters taking febuxostat 80 mg with lesinurad 200 mg, treatment to target rates fell by more than 50% when adherence reduced from 100% to 50%.

Approximately 90% of gout patients have hyperuricemia caused by the renal under-excretion of uric acid [27]. In these cases, unless sUA concentrations are very high, or urinary volume is also lowered, uUA concentrations are likely to be lower than healthy subjects. However, in simulations of drug holidays, after restarting dual-ULT under-excreters had uUA concentrations raised to above the baseline levels for healthy subjects and a small proportion exceeded the threshold for hyperuricosuria. For these patients to be at an increased risk of kidney damage would likely require either a very low urinary output volume or a low urine pH (though still within the typical pH range). Urine pH is itself a primary predictor of nephrolithiasis, since the solubility of uric acid is very sensitive to small changes in pH [35].

Genetic disorders or a high-purine diet can be the cause of an overproduction of uric acid in the remaining 10% of gout patients [36]. Hyperuricosuria is a defining feature of uric acid overproduction [26], putting these patients at an increased risk of kidney injury without treatment. Our simulations suggest that in the case of very good medication adherence (≥80% doses taken), dual-ULT would result in sustained reductions in sUA concentrations and also, therefore, uUA excreted. Regular drug holidays, however, would result in episodes in which uUA output was raised above its already high baseline. For this reason uricosurics may not be appropriate for patients with hyperuricemia due to uric acid overproduction [37], but no cautions are made in the label for lesinurad [38].

To our knowledge this is the first study of the relationship between medication adherence and the efficacy and safety of dual-ULT therapy for the treatment of gout. This is especially timely given the recent approval of lesinurad for use in combination with an XOI in patients who have not responded on an XOI alone [39]. Our analysis benefits from having used a semi-mechanistic PD model which provides a level of complexity capable of capturing the non-steady state system dynamics. The effects of treatments have been investigated in two distinct patient subgroups; the cause of hyperuricemia being either an overproduction or under-excretion of uric acid. When comparing our simulation results with the findings from clinical trials, all of our perfect adherence simulations produced higher treatment success rates than was reported in trials. Mathematical models such as this could be used to anticipate the problems resulting from sub-optimal adherence, and to potentially help identify the properties of more forgiving uricosurics.

The main limitation of this study was our reliance on different sources of data from different populations. This limited our ability to fully quantify the variability and co-dependencies, nonetheless, we consider the model to be representative of existing dual-ULTs. We assumed that non-renal clearance of uric acid, which is responsible for around a third of total excretion [40], was negligible. Nevertheless, the contribution of non-renal clearance relative to renal clearance will be less in scenarios where a uricosuric is taken. Finally, the analysis has focussed on the XOI febuxostat, but allopurinol is by far the most commonly prescribed ULT. However, we have no reason to believe that these findings do not extend to other XOIs (allopurinol) and uricosurics (probenecid and benzbromarone).

With currently available ULTs, a large proportion of patients do not achieve sustained reductions in sUA to below saturation concentrations. The potential reasons for treatment failure include poor implementation (adherence) to treatment, under-dosing, variation in treatment response and the

underlying cause of hyperuricemia [41]. Persistence to ULTs is known to be amongst the lowest of any chronic disease treatment [11,12] and studies provide evidence for both long [42] and short [43] drug holidays. This study shows that renal safety may also be compromised by sub-optimal medication adherence and highlights the need to improve adherence and adapt treatments to poorly adherent populations. This could include instructions on drug labelling [44], indicating a number of doses which can be missed based on the forgiveness of the drug to missed doses [45]. Such measures may improve the safety profile of future uricosurics, which for lesinurad may have influenced reimbursement decisions [46].

If gout patients adhere well to dual-ULT then it appears to offer a means of further reducing sUA concentrations with a negligible increase in urinary uric acid output. However, regular drug holidays, which are commonplace amongst gout patients using ULTs, result in much lower rates of long term treatment success and increased rates of hyperuricosuria when treatment is restarted. This has the potential to increase the risk of kidney damage in all patients, but especially those with hyperuricemia due to overproduction of uric acid. Further research is needed into the impact of adherence patterns on treatment success rates and kidney safety in order to better understand how dual-ULT could be optimally used in the treatment of hyperuricemia in patients with gout. However, at present counselling patients with respect to the risks associated with poor adherence should be advised.

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References

[1] Dalbeth N, Merriman TR, Stamp LK. Gout. Lancet 2016; 6736: 1–14.

[2] Richette P, Doherty M, Pascual E, Barskova V, Becce F, Castaneda-Sanabria J, et al. 2016 updated EULAR evidence-based recommendations for the management of gout. Ann Rheum Dis 2017; 76: 29–42.

[3] Miner J, Tan PK, Hyndman D, Liu S, Iverson C, Nanavati P, et al. Lesinurad, a novel, oral compound for gout, acts to decrease serum uric acid through inhibition of urate transporters in the kidney. Arthritis Res Ther 2016; 18: 214.

[4] Pak CYC, Poindexter JR, Peterson RD, Koska J, Sakhaee K. Biochemical distinction between hyperuricosuric calcium urolithiasis and gouty diathesis. Urology 2002; 60: 789–94.

[5] Bluestone R, Klinenberg J, Lee IK. Benzbromarone as a Long-Term Uricosuric Agent. Adv Exp Med Biol 1980; 122: 283–6.

[6] Maalouf NM, Cameron MA, Moe OW, Sakhaee K. Novel insights into the pathogenesis of uric acid nephrolithiasis. Curr Opin Nephrol Hypertens 2004; 13: 181–9.

[7] Hahn K, Kanbay M, Lanaspa MA, Johnson RJ, Ejaz AA. Serum uric acid and acute kidney injury: A mini review. J Adv Res 2017; In Press.

[8] Moe OW. Posing the question again: does chronic uric acid nephropathy exist? J Am Soc Nephrol 2010; 21: 395–7.

[9] Bellomo G. Uric acid and chronic kidney disease: A time to act? World J Nephrol 2013; 2: 17–25.

[10] EMA. Zurampic Assessment Report. vol. EMA/6459/2. 2015. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/.

[11] Briesacher BA, Ph D, Andrade SE, Sc D, Fouayzi H, Chan A. Comparison of Drug Adherence Rates Among Patients with Seven Different Medical Conditions. Pharmacotherapy 2008; 28: 437–43.

[12] De Vera MA, Marcotte G, Rai S, Galo JS, Bhole V. Medication adherence in gout: A systematic

review. Arthritis Care Res 2014; 66: 1551–9.

[13] Halpern R, Mody RR, Fuldeore MJ, Patel P a, Mikuls T. Impact of noncompliance with urate-lowering drug on serum urate and gout-related healthcare costs: administrative claims analysis. Curr Med Res Opin 2009; 25: 1711–9.

[14] Bardin T, Keenan RT, Khanna PP, Kopicko J, Fung M, Bhakta N, et al. Lesinurad in combination with allopurinol: a randomised, double-blind, placebo-controlled study in patients with gout with inadequate response to standard of care (the multinational CLEAR 2 study). Ann Rheum Dis 2016; 0: 1–10.

[15] Dalbeth N, Jones G, Terkeltaub R, Khanna D, Kopicko J, Bhakta N, et al. SAT0329: Lesinurad, A Novel Selective Uric Acid Reabsorption Inhibitor, in Combination with Febuxostat, in Patients with Tophaceous Gout: The CRYSTAL Phase III Clinical Trial, 2015.

[16] Saag KG, Fitz-Patrick D, Kopicko J, Fung M, Bhakta N, Adler S, et al. Lesinurad Combined With Allopurinol: Randomized, Double-Blind, Placebo-Controlled Study in Gout Subjects With Inadequate Response to Standard of Care Allopurinol (A US-based Study). Arthritis Rheumatol 2017; 69: 203–12.

[17] Vrijens B, De Geest S, Hughes DA, Przemyslaw K, Demonceau J, Ruppar T, et al. A new taxonomy for describing and defining adherence to medications. Br J Clin Pharmacol 2012; 73: 691–705.

[18] Dua P, Demin O, Sokolov V, Yakovleva T, Demin O, Graaf P Van Der. A systems pharmacology model of purine metabolism to explore novel options for the treatment of Gout (Poster). Systems Pharmacology in Drug Discovery & Development. 2014.

[19] Gabrielsson J, Weiner D. Pharmacokinetic and Pharmacodynamic Data Analysis. 5th editio. Apotekarsocieteten; 2016.

[20] Sharma A, Jusko WJ. Characteristics of indirect pharmacodynamic models and applications to clinical drug responses. Br J Clin Pharmacol 1998; 45: 229–39.

[21] Khosravan R, Grabowski BA, Wu J, Joseph-ridge N, Vernillet L. Pharmacokinetics,

Pharmacodynamcis and Safety of Febuxostat , a Non-Purine Selective Inhibitor of Xanthine Oxidase , in a Dose Escalation Study in Healthy Subjects. Clin Pharmacokinet 2006; 45: 821–41.

[22] Centre for Drug Evaluation and Research. Clinical Pharmacology and Biopharmaceutics Review (NDA 21-856). 2008. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/021856s000_ClinPharmR_P1.pdf.

[23] Centre for Drug Evaluation and Research. Clinical Pharmacology and Biopharmaceutics Review (Application Number: 207988Orig1s000). 2014. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/207988Orig1s000SumR.pdf.

[24] TAP Pharmaceutical Products Inc. TMX-99-001 Study Report 2004: Obtained via the EMA on 16/06/16.

[25] Ardea Biosciences. Lesinurad in Combination With a Xanthine Oxidase Inhibitor for Treatment of Hyperuricemia Associated With Gout. Briefing Document for the Arthritis Advisory Committee. 2015. Available at: http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/arthritisadvisorycommittee/ucm467951.pdf.

[26] Pittman J, Bross M. Diagnosis and management of gout. Am Fam Physician 1999; 59: 1799–806.

[27] Choi HK, Mount DB, Reginato AM. Pathogenesis of gout. Ann Intern Med 2005; 143: 499–516.

[28] FDA. Lesinurad for the proposed indication of treatment of hyperuricemia associated with gout in combination with a xanthine oxidase inhibitor (FDA Briefing Package) (NDA 207988). 2015. Available at: https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM467942.pdf.

[29] Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron

1976; 16: 31–41.

[30] Tissot W, Amundsen CL, Diokno AC, Webster GD, Coats AC. Bladder Diary Measurements in Asymptomatic Males: Frequency, Volume per Void, and 24-hour Volume. Neurourol Urodyn 2008; 27: 198–204.

[31] Parsons M, Tissot W, Cardozo L, Diokno A, Anundsen CL, Coats AC. Normative Bladder Diary Measurements: Night Versus Day. Neurourol Urodyn 2007; 26: 465–76.

[32] Mehta TH, Goldfarb DS. Uric Acid Stones and Hyperuricosuria. Adv Chronic Kidney Dis 2012; 19: 413–8.

[33] Southan C, Sharman JL, Benson HE, Faccenda E, Pawson AJ, Alexander SPH, et al. The IUPHAR / BPS Guide to PHARMACOLOGY in 2016 : towards curated quantitative interactions between 1300 protein targets and 6000 ligands. Nucleic Acids Res 2016; 44: 1054–68.

[34] Alexander SPH, Kelly E, Marrion N, Peters JA, Benson HE, Faccenda E, et al. THE CONCISE GUIDE TO PHARMACOLOGY 2015 / 16 : Overview. Br J Pharmacol 2015; 172: 5729–43.

[35] Mehta TH, Goldfarb DS. Uric Acid Stones and Hyperuricosuria. Adv Chronic Kidney Dis 2012; 19: 413–8.

[36] Doherty M. New insights into the epidemiology of gout. Rheumatology 2009; 49: 613–4.

[37] Khanna D, Fitzgerald JD, Khanna PP, Bae S, Singh MK, Neogi T, et al. 2012 American college of rheumatology guidelines for management of gout. part 1: Systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. Arthritis Care Res 2012; 64: 1431–46.

[38] FDA. Zurampic label. 2015. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/%0A207988lbl.pdd.

[39] Center for Drug Evaluation and Research. Lesinurad Approval Package. Application Number: 207988Orig1s000. 2015. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/207988Orig1s000Approv.pdf.

[40] Ichida K, Matsuo H, Takada T, Nakayama A, Murakami K, Shimizu T, et al. Decreased extra-

renal urate excretion is a common cause of hyperuricemia. Nat Commun 2012; 3: 764.

[41] Stamp LK, Merriman TR, Barclay ML, Singh JA, Roberts RL, Wright DF, et al. Impaired response or insufficient dosage? - examining the potential causes of “inadequate response” to allopurinol in the treatment of gout. Semin Arthitis Rheum 2014; 44: 170–4.

[42] Harrold LR, Andrade SE, Briesacher B, Raebel MA, Fouayzi H, Yood RA, et al. The Dynamics of Chronic Gout Treatment: medication gaps and return to therapy. Am J Med 2010; 123: 1–11.

[43] de Klerk E, van der Heijde D, Landewe R, van der Tempel H, Urquhart J, van der Linden S. Patient compliance in rheumatoid arthritis, polymyalgia rheumatica, and gout. J Rheumatol 2003; 30: 44–54.

[44] Levy G, Zamacona MK, Jusko WJ. Developing compliance instructions for drug labeling. Clin Pharmacol Ther 2000; 68: 586–91.

[45] Assawasuwannakit P, Braund R, Duffull SB. Quantification of the Forgiveness of Drugs to Imperfect Adherence. CPT Pharmacometrics Syst Pharmacol 2015; 4: 204–11.

[46] National Institute for Health and Care Excellence. Single Technology Appraisal: Lesinurad for treating chronic hyperuricaemia in people with gout, Committee Papers 2016; [ID761].

Tables

Model	Name*	Source	Parameter estimates		BSV (SD^2)#	
System PD Parameter	BX (mg)	Estimated	θ_1	8.94	-	NE
	VX (dl)	Estimated	θ_2	333	-	NE
	CLX (dl/h)	Literature	θ_3	10.57	-	NE
	BUA (mg)	Estimated	θ_4	703	-	NE
	VUA (dl)	Estimated	θ_5	154	-	NE
	CLUA (dl/h)	Literature	θ_6	4.11	-	NE
Febuxostat PD Parameter	$E_{max,1}$	Assumed	θ_7	3	-	NE
	$EC_{50,1}$	Assumed	θ_8	0.001	-	NE
	$I_{max,1}$	Assumed	θ_9	1	-	NE
	$IC_{50,1}$	Estimated	θ_{10}	0.1320	η_3	0.2
	$I_{max,2}$	Assumed	θ_{11}	1	-	NE
	$IC_{50,2}$	Estimated	θ_{12}	0.00113	η_3	0.2
Lesinurad PD Parameter[a]	E_0	Literature	θ_{13}	6.77	-	NE
	E_{max}^D	Literature	θ_{14}	-2.55	η_4	0.346
	b_{crcl}	Literature	θ_{15}	0.564	-	NE
	EC_{50}^D	Literature	θ_{16}	0.0974	-	NE

Table 1. PD parameters for febuxostat and lesinurad - literature and statistical estimates combined

*BX: Baseline amount of xanthine; VX: Volume of xanthine distribution; CLX: Renal clearance of xanthine; BUA: Baseline amount of uric acid; VUA: Volume of uric acid distribution; CLUA: Renal clearance of uric acid; $E_{max,1}$ and $EC_{50,1}$: parameters of $STIM_1$ acting on k_2; $I_{max,1}$ and $IC_{50,1}$: parameters of INH_1 acting on k_0; $I_{max,2}$ and $IC_{50,2}$: parameters of INH_2 acting on k_1; E_0, $E_{max}{}^D$, b_{crcl} and $EC_{50}{}^D$: literature values used to derive parameters of $STIM_2$ acting on k_3

#BSV: Between subject variability; SD: Standard deviation; NE: Not estimated; Error model used: $\theta_i = \theta_u \exp(\eta_i)$

[a]Lesinurad: Parameters of the direct Emax model used to derive the corresponding parameters of the indirect response model in Figure 1

Parameter	*Febuxostat*		*Lesinurad*	
	Estimate	BSV (CV%)	Estimate	BSV (CV%)
CL/F_0 (dl h^{-1})[a]	49.3	18.3	69.9	63.4
b_CRCL	0.142	NA	0.322	NA
b_WT	0.155	NA	-	NA
Vc/F_0 (dl)[b]	322	NE	241	12.2
b_WT	-	NA	0.511	NA
Vp/F (dl)	222	NE	83	20.5
Q/F (dl h^{-1})	55.7	NE	4.48	NE
Ka (h^{-1})	13.7	176	0.69	121.7
Tlag (h)	0.23	NE	0.233	38.9

Table 2. PK parameters for lesinurad and febuxostat

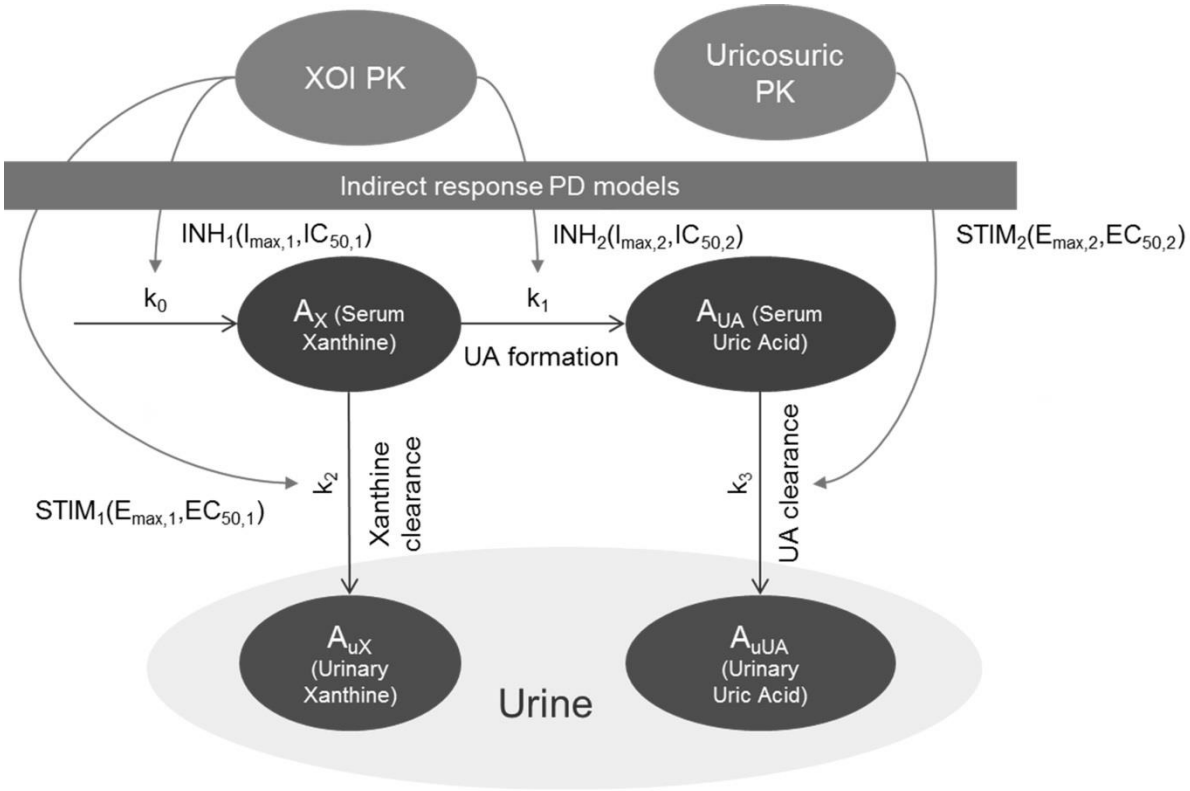
[a]Febuxostat: CL/F = CL/F_0 + b_CRCL*CRCL + b_WT*WT; Lesinurad: CL/F = CL/F_0 * (CRCL/87)^b_CRCL

[b]Lesinurad: VC/F = VC/F_0 * (WT/70)^b_WT

CL/F: Apparent clearance; Vc/F: Volume of the central compartment; Vp/F: Volume of the peripheral compartment; Q/F: Inter-compartmental clearance rate; Ka: First-order absorption; Tlag: Absorption time-lag; BSV: between-subject variability; CV%: Percentage coefficient of variation; NE: Not estimated; NA: Not applicable

Parameter	Healthy subject	Gout patient	
		Under-excreter	Overproducer
sUA (mg dl^{-1})	-	LN(8.83,1.53)	LN(8.83,1.53)
BX (mg)	θ_1	θ_1	$\theta_1*(BUA/\theta_4)$
VX (dl)	θ_2	θ_2	θ_2
CLX (dl h^{-1})	θ_3	θ_3	θ_3
BUA (mg)	θ_4	θ_5*sUA	θ_5*sUA
VUA (dl)	θ_5	θ_5	θ_5
CLUA (dl h^{-1})	θ_6	$\theta_6*(\theta_4/BUA)$	θ_6

Table 3. Individual system parameters for healthy subject and gout patients



System dynamics equations:

$$\frac{dA_X}{dt} = k_0 * INH_1 - k_1 * INH_2 * A_X - k_2 * STIM_1 * A_X \quad \text{(eq. 1)}$$

$$\frac{dA_{UA}}{dt} = k_1 * INH_2 * A_X - k_3 * STIM_2 * A_{UA} \quad \text{(eq. 2)}$$

$$\frac{dA_{uX}}{dt} = k_2 * STIM_1 * A_X \quad \text{(eq. 3)}$$

$$\frac{dA_{uUA}}{dt} = k_3 * STIM_2 * A_{UA} \quad \text{(eq. 4)}$$

No treatment steady-state:

$$k_2 = \frac{CLX}{VX} \quad \text{(eq. 5)} \qquad k_3 = \frac{CLUA}{VUA} \quad \text{(eq. 6)}$$

$$k_1 = \frac{k_3 * BUA}{BX * (M_{UA}/M_X)} \quad \text{(eq. 7)} \qquad k_0 = \frac{k_1 * BX}{k_2 * BX} \quad \text{(eq. 8)}$$

Pharmacodynamic models:

$$INH_1 = \frac{IC_{50,1}}{IC_{50,1} + C_F(t)} \quad \text{(eq. 9)} \qquad INH_2 = \frac{IC_{50,2}}{IC_{50,2} + C_F(t)} \quad \text{(eq. 10)}$$

$$STIM_1 = 1 + \frac{E_{max,1} * C_F(t)}{EC_{50,1} + C_F(t)} \quad \text{(eq. 11)} \qquad STIM_2 = 1 + \frac{E_{max,2} * C_L(t)}{EC_{50,2} + C_L(t)} \quad \text{(eq. 12)}$$

Figure 1. Diagrammatic and mathematical representations of the pharmacodynamics of dual-urate lowering therapies. k_0, k_1, k_2 and k_3 are the rate parameters for the production of xanthine, xanthine to uric acid conversion, removal of xanthine to urine and removal of uric acid to urine, respectively. INH_1, INH_2, $STIM_1$ and $STIM_2$ are the pharmacodynamic model drug functions. A_X and A_{UA} are the

total time-varying amounts of xanthine and uric acid in serum, respectively. $C_F(t)$ and $C_L(t)$ are the plasma concentrations of febuxostat of lesinurad, respectively. BX: Baseline amount of xanthine; VX: Volume of xanthine distribution; CLX: Renal clearance of xanthine; BUA: Baseline amount of uric acid; VUA: Volume of uric acid distribution; CLUA: Renal clearance of uric acid.

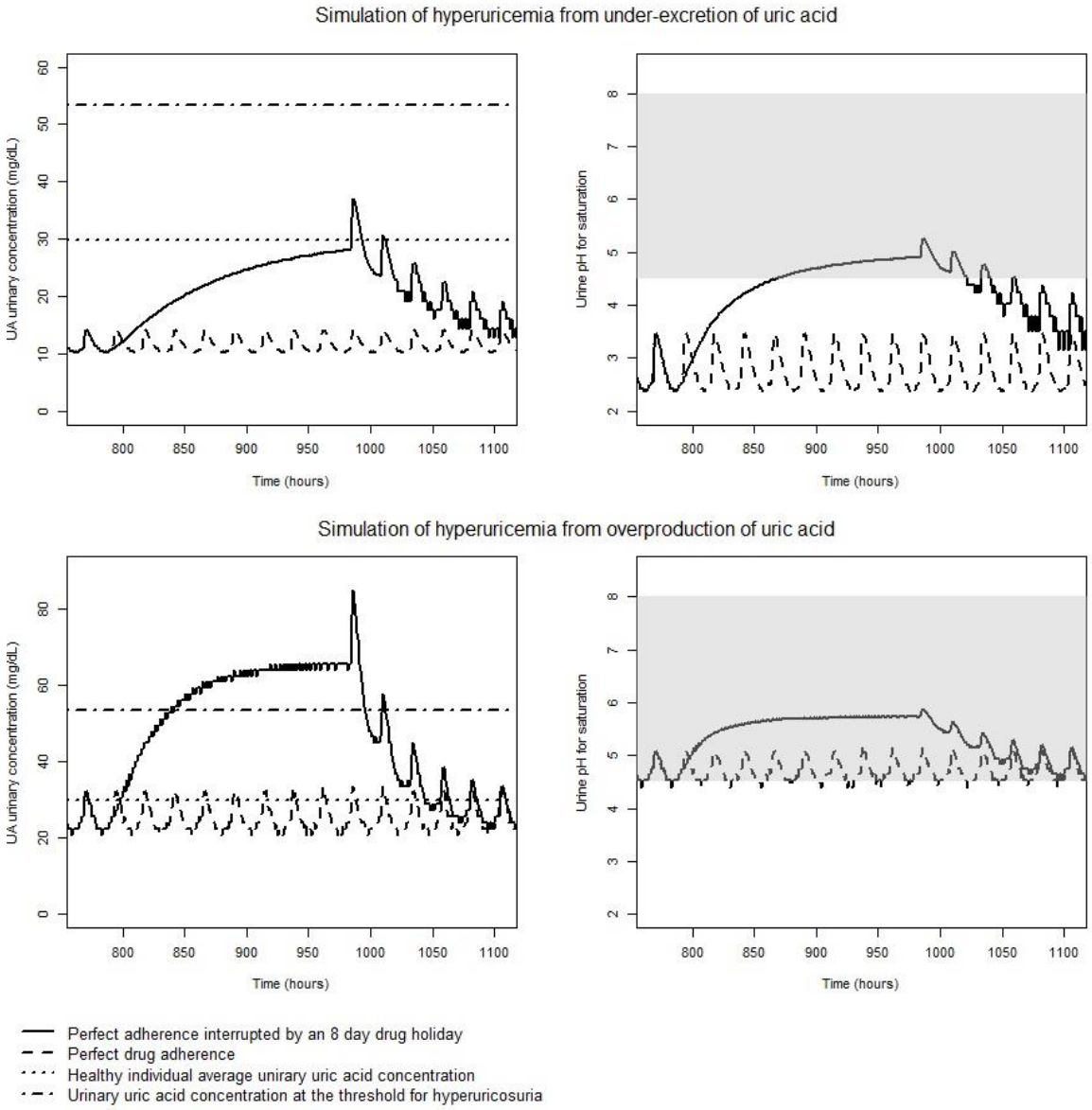


Figure 2. Simulated urinary uric acid (uUA) concentration and estimated pH for uric acid supersaturation assuming a daily volume of urine of 15 dl. The simulated uUA concentration over time (left-hand panel) and the estimated pH at which this concentration would become supersaturated (right-hand panel). Imperfect adherence is modelled as an 8-day drug holiday (beginning on day 33). The shaded area represents the normal range for urine pH. The upper plots are the central estimates from the PKPD model for a gout patient with hyperuricemia from a reduced rate of uric acid clearance, and the lower plots for hyperuricemia due to overproduction xanthine. ULTs used in these simulations were febuxostat 80 mg and lesinurad 200 mg, both once daily.

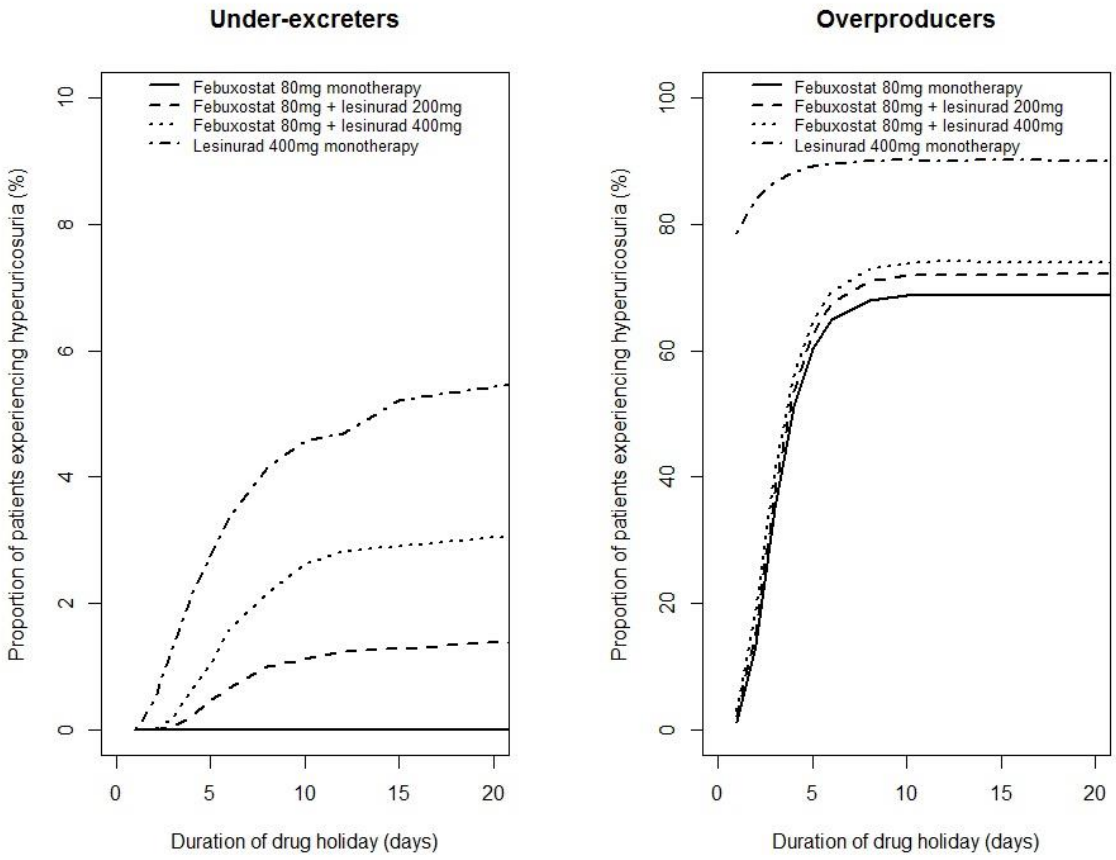


Figure 3. Proportion of simulated patients with one-day hyperuricosuria following a single drug holiday taking place after one month of perfect adherence.

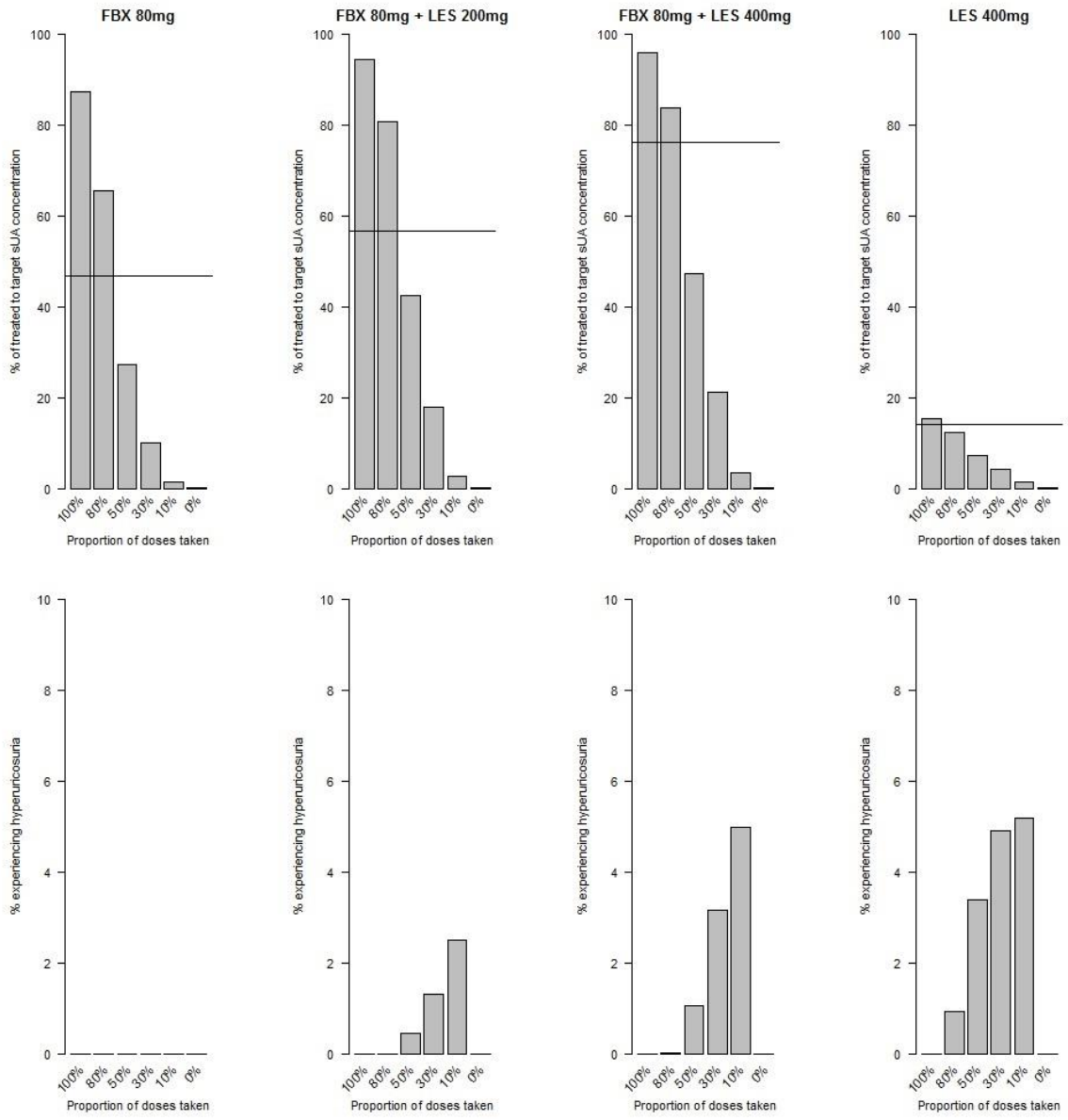


Figure 4. Treatment success rates (top row) and the proportion of patients experiencing one-day hyperuricosuria during two months of urate lowering therapy (ULT) (bottom row). Horizontal lines provide the reference response rates for this treatment arm from the CRYSTAL trial comparing febuxostat and lesinurad and study 303 for lesinurad 400 mg monotherapy. Results are for under-excreters of uric acid only, for overproducers see the supplementary material. FBX: Febuxostat; LES: Lesinurad.