



## **Impact of non-adherence and flare resolution on the cost effectiveness of treatments for gout**

Hill-McManus, Daniel; Marshall, Scott ; Soto, Elena; Lane, Steven; Hughes, Dyfrig

### **Value in Health**

Published: 01/12/2018

Peer reviewed version

[Cyswllt i'r cyhoeddiad / Link to publication](#)

*Dyfyniad o'r fersiwn a gyhoeddwyd / Citation for published version (APA):*

Hill-McManus, D., Marshall, S., Soto, E., Lane, S., & Hughes, D. (2018). Impact of non-adherence and flare resolution on the cost effectiveness of treatments for gout: Application of a linked pharmacometric/pharmacoeconomic model. *Value in Health*, 21(12), 1373-1381.

#### **Hawliau Cyffredinol / General rights**

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal ?

#### **Take down policy**

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

**Title**

Impact of non-adherence and flare resolution on the cost effectiveness of treatments for gout:

Application of a linked pharmacometric/pharmacoeconomic model

**Running Title**

Impact of non-adherence on the cost effectiveness of treatments for gout

**Authors**

Daniel Hill-McManus, BSc; Centre for Health Economic and Medicines Evaluation, Bangor University

Scott Marshall, PhD; Pharmacometrics, Pfizer Ltd, Sandwich

Elena Soto, PhD; Pharmacometrics, Pfizer Ltd, Sandwich

Steven Lane, PhD; Department of Biostatistics, University of Liverpool

Dyfrig Hughes, PhD; Centre for Health Economic and Medicines Evaluation, Bangor University

**Author for correspondence**

Dyfrig Hughes, Centre for Health Economics and Medicines Evaluation, Bangor Institute for Health and Medical Research, Ardudwy Building, Normal Site, Bangor University, Holyhead Road, Bangor, UK. LL57 2PZ. d.a.hughes@bangor.ac.uk. +44(0)1248 382950.

**Funding Statement**

MRC Network of Hubs for Trial Methodological Research (HTMR), reference number MR/L004933/1- Q25, and the MRC North-West HTMR, reference number MR/K025635/1.

**Precis**

Estimation of the impact of varying medication adherence on the cost effectiveness of urate lowering therapies for the treatment of gout.

**Acknowledgements**

We acknowledge the support of the Supercomputing Wales project, which is part-funded by the European Union's Convergence European Regional Development Fund, administered by the Welsh Government.

**Word count:** 3,989

**Number of pages:** 29

**Number of figures:** 3

**Number of tables:** 3

**Supplementary material:** 22 pages, 5 figures and 12 tables

**Title**

Impact of non-adherence and flare resolution on the cost effectiveness of treatments for gout:

Application of a linked pharmacometric/pharmacoeconomic model

**Running Title**

Impact of non-adherence on the cost effectiveness of treatments for gout

**Precis**

Estimation of the impact of varying medication adherence on the cost effectiveness of urate lowering therapies for the treatment of gout.

**Word count:** 3,974

**Number of pages:** 29

**Number of figures:** 3

**Number of tables:** 3

**Supplementary material:** 22 pages, 5 figures and 12 tables

## **Abstract**

### *Background*

Dual urate-lowering therapy (ULT) with lesinurad in combination with either allopurinol or febuxostat is an option for gout patients unsuccessfully treated on either monotherapy. Treatment failure is often a result of poor medication adherence. Imperfect adherence in clinical trials may lead to biased estimates of treatment effect and confound the results of cost effectiveness analyses.

### *Objectives*

This study aims to estimate the impact of varying medication adherence on the cost effectiveness of lesinurad dual therapy; and estimate the value-based price of lesinurad at which the incremental cost effectiveness ratio (ICER) is equal to £20,000 per quality-adjusted life-year (QALY).

### *Methods*

Treatment effect was simulated using published pharmacokinetic-pharmacodynamic (PKPD) models and scenarios representing adherence in clinical trials, routine practice and perfect use. The subsequent cost and health impacts, over the lifetime of a patient cohort, were estimated using a bespoke pharmacoeconomic model.

### *Results*

The base case ICERs comparing lesinurad dual-ULT with monotherapy ranged from £39,184 to £78,350 per QALY gained using allopurinol and £31,901 to £124,212 per QALY using febuxostat, depending on the assumed medication adherence. Results assuming perfect medication adherence imply a per-quarter value-based price of lesinurad of £45.14 when used

in dual-ULT compared with allopurinol alone and £57.75 compared with febuxostat alone, falling to £25.41 and £3.49 respectively in simulations of worsening medication adherence.

### *Conclusions*

The estimated value-based prices of lesinurad only exceeded that which has been proposed in the United Kingdom when assuming both perfect drug adherence and the eradication of gout flares in sustained treatment responders.

### **Highlights**

- Imperfect adherence in clinical trials may lead to biased estimates of treatment effect and confound the results of cost effectiveness analyses
- Use of pharmacokinetic-pharmacodynamic based economic analysis allows for the assessment of the relationship between adherence and cost-effectiveness
- Reduced adherence to urate-lowering therapies for the treatment of gout results in large variations in resulting economic outcomes
- Only by combining perfect drug adherence with an assumed resolution of gout flares in sustained treatment responders did the predicted value-based price exceed that which has been proposed for the UK market

## **Introduction**

Gout is a painful and disabling condition and one that is relatively common in developed countries [1]. When the concentration of uric acid in serum exceeds the saturation point (hyperuricemia) it may crystallise in peripheral joints and surrounding tissues which can lead to gout symptoms. Treatment guidelines recommend that serum uric acid (sUA) be reduced to below a target of either 5 or 6 mg/dL [2], to allow for the dissolution of monosodium urate crystals from affected joints [3]. As well as preventing the progression to more severe disease (e.g. tophaceous gout) and, albeit controversially, reducing the potential of cardiovascular and renal comorbidities, long term treatment reduces and may eventually eliminate the painful flares that characterise gout [4].

The mainstay of therapy is the xanthine oxidase inhibitor (XOi) allopurinol; however, a large proportion of patients are not treated successfully [5]. Treatment failure has been postulated to result from suboptimal dosing or non-adherence, or a combination of both over the long (often symptom-free) treatment period [6]. Medication adherence is known to be especially poor for urate-lowering therapies (ULTs) [7, 8] and, if not recognised and managed appropriately, can result in unnecessary switching to more expensive ULTs such as febuxostat or combined XOi therapy with a uricosuric, such as lesinurad.

Medication adherence can be decomposed into three distinct phases; 1) the initiation of treatment, 2) the degree to which a patient's dose taking matches the prescribed regimen while nominally adhering (implementation) and 3) the discontinuation of treatment (persistence) [9]. Persistence can often be accounted for in the analysis of clinical trials and, while implementation can be recorded using electronic pill dispensers [10], this is seldom done in clinical trials. Imperfect implementation may lead to biased estimates of treatment effect [11] and confound the results of cost effectiveness analyses.

Key influences on the decisions not to recommend lesinurad, or febuxostat as first-line treatment in the United Kingdom (UK) were the uncertainties in their effects on acute flares and their lack of cost effectiveness as estimated using economic modelling [12–14]. However, an important limitation of conventional economic models is their limited capacity to account for the impact of poor implementation (i.e. missed or delayed doses) on health outcomes and costs. Pharmacokinetic-pharmacodynamic (PKPD) models together describe the relationship between doses taken and the observed drug effects, via the time course of drug concentration. By specifying variable dose implementation as an input function, this offers a method for predicting the influence of non-adherence on the clinical effectiveness and cost effectiveness of drug treatments [15].

This study aims to estimate the impact of varying dose implementation and persistence on the cost effectiveness of the uricosuric lesinurad as an add-on treatment in patients non-responsive on either allopurinol or febuxostat alone.

## **Methods**

A published PKPD model of lesinurad and febuxostat [16] was extended to include allopurinol and used to simulate the time course of sUA concentration among patients with differing adherence to the dosing regimen. A bespoke pharmacoeconomic (PE) model was developed, with reference to previous economic evaluations of ULTs [17, 18], and linked to the PKPD model to estimate the costs and quality-adjusted life-years (QALYs) accrued over patients' lifetimes for different treatment and adherence scenarios. All PKPD simulations were performed using NONMEM 7.3 [19].

### ***ULT Pharmacokinetic-Pharmacodynamic Model***

The lesinurad and febuxostat PKPD model [16] was used without modification. A separate study presenting PKPD modelling of allopurinol [20] was used to obtain the PK relationships



and associated parameter estimates which were also used without modification. However, since a direct-effect sigmoid  $E_{\max}$  PD model had been used to relate sUA concentrations to oxipurinol (allopurinol's active metabolite) plasma concentrations, a semi-mechanistic indirect-response model [21] was derived from the estimated parameters. This allows for the expected delay between the PK and PD of XOis [16] and is better suited to modelling patterns of imperfect adherence. Details of the necessary steps are described in the Supplementary Material, where tables of all PKPD model parameters are also provided.

### ***Patient Population***

A cohort of 500 gout patients was created for simulations based on the population characteristics of the recently completed CLEAR 1 clinical trial of lesinurad [22]. Individual age and weight, which account for some of the variability in PKPD model parameters, were sampled at random from log-normal distributions using CLEAR 1 mean body weight of 110 kg (SD = 23) and age of 52 (SD = 11). Creatinine clearance (CrCl), a covariate in the PK models, was estimated using the Cockcroft-Gault equation [23]. The resulting distribution was reduced by 15 mL/min and estimates below 30 mL/min were excluded (as per protocol criteria) in order to adjust for the underlying degree of renal impairment and obtain an approximation of the broad CrCl categories available for the CLEAR 1 trial population [24]. In accordance with gout epidemiology, patients were also assigned to have gout resulting from either an overproduction or under-excretion of uric acid in the ratio of 1:9 [25, 26].

### ***PKPD Simulation Modelling***

The PKPD model was used to generate twelve sUA concentration distributions from the patient cohort using four ULT options and three models of medication adherence. These twelve distributions then provide the treatment effectiveness inputs in subsequent pharmacoeconomic modelling. We have considered two scenarios for first-line ULT; these

being gout patients eligible for ULT being either prescribed once daily allopurinol 300 mg or once daily febuxostat 80 mg. This is the recommended dose of febuxostat [12], and 300 mg is the most commonly used dose of allopurinol [27]. If a patient did not achieve a reduction to the 6 mg/dL target on a monotherapy, then dual therapy was used as second-line with lesinurad 200 mg once daily.

The first method of modelling adherence (Adherence model 1) represents the hypothetical best-case scenario in which all patients persist with treatment and implement perfectly. The second and third adherence models are broadly intended to represent a phase 3 clinical trials setting and routine practice, respectively. With the second adherence model (Adherence model 2), treatment persistence was based on discontinuation observed in lesinurad pivotal trials [18], and patients implemented doses randomly according to a probability that was sampled from a beta(2.4,0.6) distribution, such that the population average was 80% of doses with standard deviation of 20%. The third adherence model (Adherence model 3) also used treatment persistence from lesinurad pivotal trials [18] and dose implementation sampled from a beta(2.6,2.6) distribution, such that the population average was 50% of doses with standard deviation of 20%.

For each ULT option and adherence model, treatment in each patient was simulated for 120 days, with the initial 30 days used only to achieve steady-state on first-line monotherapy. On day 30, those patients in the dual-ULT simulation scenarios whose sUA concentration was above 6 mg/dL had lesinurad as second-line added to their daily dosing schedule. Days 30 - 60 were then used to establish those patients newly switched to dual therapy at steady state. The final days from 60 – 120, for all four ULT options, provided the treatment effects that drive the pharmacoeconomic model, including the distribution across sUA concentration categories on day 120 as well as the proportion of days each patient was below 6 mg/dL. The sUA concentrations were collapsed onto four categories: <6, 6 to <8, 8 to <10 and  $\geq$ 10 mg/dL

which provide the distribution across sUA sub-states in the pharmacoeconomic model and are static throughout pharmacoeconomic model simulations (Fig. 1).

### ***Pharmacoeconomic Model***

#### *Overview*

Consistent with previous economic evaluations of gout treatments [18, 28], we used a Markov state-transition model to estimate lifetime costs and QALYs in a cohort of patients eligible for ULT. Whilst treatment was simulated for individual patients in the PKPD model, the economic model used a cohort approach. The model adopts the perspective of the National Health Service in the UK, has a cycle length of 3 months, and a lifetime (50 year) time horizon. Costs and QALYs were both discounted at a rate of 3.5% per annum [29]. The economic model was implemented in R version 3.4.3 [30].

#### *Treatments and Transitions*

The Markov model consisted of 6 main health states which included 4 possible ULT options, no treatment and an absorbing dead state. Within each of the 5 treatment options, patients were distributed between the four sUA concentration sub-states, such that there was a total of 21 model states. The distribution across the sUA concentration sub-states for each treatment depended on the level of dose implementation and was generated using the PKPD model (Fig. 1).

In each pharmacoeconomic simulation, all patients are initially allocated to a single ULT option, where they remain unless they discontinue (non-persistence). A proportion of patients on monotherapy could, therefore, transition to the no-ULT health state and a proportion of those on a dual therapy could transition to either the no-ULT state or to the XO<sub>i</sub> monotherapy health state if only discontinuing the uricosuric component. It was assumed that no patients will discontinue a XO<sub>i</sub> while continuing to take lesinurad as it is not licensed as a

monotherapy [31]. The patients transitioning to either no-ULT or a monotherapy (Fig. 1) were redistributed according to the sUA concentration distribution of this new treatment. Per-cycle treatment discontinuation probabilities were calculated using the results of clinical trials of febuxostat [32] and lesinurad [33]. After every cycle, a proportion of patients transitioned to the death state according to all-cause mortality probabilities derived from life tables for England and Wales in 2015 [34].

### *Gout Flares*

Gout sufferers experience acute episodes of intense pain and inflammation known as flares whose frequency is directly proportional to sUA concentration [35]. Clinical trials of newer ULTs have not demonstrated a reduction in the frequency of gout flares when compared with allopurinol; economic evaluations have instead relied on observational data to estimate the reduction in flares resulting from reduced sUA concentrations.

In the base case analysis, we modelled the frequency of gout flares within sUA concentration sub-states using the results of a cross-sectional survey in which 172 out of 620 participants provided both a most recent sUA measurement and a number of flares in the previous 12 months [36]. This was used to derive quarterly flare frequency distributions across five categories (1-2, 3, 4-5 and  $\geq 6$  flares per annum) for each sUA concentration sub-state assuming a constant rate of occurrence. This survey data, however, reporting a single sUA measurement, may not be representative of patients who maintain low sUA concentrations. In order to assess the potential quality of life and cost implications of a trial being able to demonstrate clear benefits in sustained responders and therefore not relying solely of survey data, we developed a second, alternative, model of flare reduction. This assumed that gout patients who sustain a sUA concentration of  $< 6$  mg/dL on  $> 80\%$  of days will become flare-free after 2 years, while the survey data flare rate distributions are applied to all other

patients. This is broadly in line with a study that found 86% of patients whose average sUA concentration was below 6 mg/dL had no recurrent gouty attacks during the 2-year follow-up [37, 38].

The initiation of ULT is known to initially result in an increase in the risk of experiencing gout flares [37] that is proportional to the extent of sUA reduction [28, 39]. This was modelled by fitting a linear model to data on the mean number of flares during the first 3 months of treatment and treatment response rate, for four different ULTs [28]. The predicted number of flares for a zero response rate and for a response rate following treatment was used to calculate a multiplier that is used to increase the baseline number of quarterly flares. This multiplier was applied to every flare frequency category in the first model cycle only; further details are provided in the Supplementary Material.

#### *Costs*

The daily cost of lesinurad 200mg was assumed to be £0.93 [13], allopurinol 300mg £0.03, and febuxostat 80mg £0.87 [40]. We assumed that for all patients, gout flare prophylaxis was provided by 0.5 mg daily colchicine for the full 6 months as recommended [2]. This would require 200 tablets at a cost of £28.56 and it was assumed that unused doses would be discarded.

The average cost of treating a flare was assumed to be £43.78 (2016 prices) and the proportion of flares requiring treatment to be 26.7% [18]. The National Institute for Health and Care Excellence (NICE) recommends quarterly monitoring of sUA concentration and renal function during the first year of ULT and annually thereafter. The estimated average cost of a treatment monitoring visit for lesinurad (£153.07) was assumed for all treatments. Although monitoring may vary between treatments, e.g. liver function tests with febuxostat

and urinary uric acid tests with lesinurad [41], in the absence of data on the frequency of such testing no difference in overall cost was assumed.

### *Health State Utilities*

A literature review and a range of trial derived health state utility values are presented in recent reports submitted to NICE as part of the reappraisal of lesinurad in the UK [42]. As in these published reports, we adopt a base case that uses the mean SF-6D scores in CLEAR 1 and CLEAR 2 clinical trials [43, 44] stratified by flare frequency. These annual health state utilities, stratified according to flare frequency, were used to calculate an average decrement of 0.043 utilities per flare. This was used to reduce the utility of those experiencing flares from the reference health state utility of 0.768 for gout patients experiencing no flares over 12 months. We did not model any impact of sUA concentration on mortality, on the basis of a lack of substantiated evidence of such an association [45].

### *Sensitivity analyses*

A total of 500 iterations of the PKPD model were conducted, each simulating 120 days of treatment in 500 patients. Each iteration produced a sUA concentration distribution that provided inputs to 10 pharmacoeconomic model simulations, resulting in a total of 5,000 simulations. The mean incremental costs and QALYs are presented in later sections and the distribution of these results in the cost effectiveness plane are given in the PSA section of the Supplementary Material.

## **Results**

### *PKPD Model Results*

The results of PKPD simulations (Table 1) suggest that febuxostat 80 mg could be nearly 100% effective in patients who adhere perfectly to their dosing regimen, and only a small

minority of patients would be eligible for dual-ULT with lesinurad. For allopurinol 300 mg, even with perfect adherence, only 57% of patients were estimated to achieve the sUA concentration target of <6 mg/dL, but this is increased to 83% with the addition of lesinurad. As expected, the proportion of patients achieving target concentrations fell with worsening adherence across all treatments, while the proportion eligible for dual-ULT rose. The rank of treatments by response rate remained constant across the three adherence scenarios. Sub-optimal adherence has a larger impact on sustained response (<6 mg/dL on >80% of days) than the single time point response (day 120).

Fig. 2 provides a comparison between the results of pivotal clinical trials and the simulated response rates. Treatment response is defined as sUA <5 mg/dL, as <6 mg/dL was unavailable for all treatments, and the simulated results have been adjusted to account for treatment discontinuation at 6 months in the corresponding trial arm to provide a more appropriate comparison. While our simulated results are broadly in line with the results from pivotal trials, the differences are may be difficult to interpret owing to the many factors relating to trial conduct that have not been accounted for in the PKPD modelling.

### ***Economic Model Results***

Table 2 presents the simulated total costs and QALYs accrued over the lifetime of the patient cohort, with allopurinol 300 mg as first-line and lesinurad add-on as second-line ULT. Under the base case method of calculating flare frequency and with perfect medication adherence (adherence model 1), the incremental cost effectiveness ratio (ICER) of allopurinol with optional lesinurad dual-ULT compared with allopurinol alone was £39,184 per QALY gained. This is considerably higher than the £20,000 per QALY threshold of cost effectiveness used in the UK. The ICER increased to £47,848 and £78,350 per QALY gained in adherence models 2 and 3, in which patients discontinue treatment over time and have

implementation rates of 80% and 50%, respectively. The ICERs were lowered using the alternative flare frequency methodology to £19,019, £31,803 and £77,903 per QALY gained across the three adherence models 1 to 3, respectively.

Patients not eligible for first line treatment with allopurinol may be prescribed febuxostat and, if not adequately controlled, may subsequently be offered dual-ULT with lesinurad. In both perfect adherence scenarios (Table 3), the ICER of febuxostat with optional lesinurad dual-ULT compared with febuxostat alone was £31,901 and £15,376 per QALY gained in the base case and alternative flare frequency models, respectively. The simulations suggest it would be more cost effective to provide lesinurad to non-responders on febuxostat than on allopurinol monotherapy, assuming perfect adherence. However, under adherence models 2 and 3, it appears lesinurad is more cost effective with allopurinol than febuxostat, suggesting febuxostat is less forgiving to missed doses than allopurinol [46].

### ***Value-Based Price***

For each probabilistic economic simulation we calculated the price of lesinurad at which the ICER comparing dual-ULT to allopurinol or febuxostat monotherapy is equal to the £20,000 per QALY threshold (value-based price). The resulting distributions of prices are plotted in Fig. 3 along with a line indicating the price of lesinurad originally proposed for the UK market [18]. Using the base case methodology for flare frequency, very few value-based prices of lesinurad are more than, or equal to, the price originally proposed for the UK market, regardless of the adherence model which was assumed. The simulations resulting in the highest proportion of value-based prices greater than, or equal, to the proposed price used the alternative flare frequency methodology and required adherence models 1 (53% versus allopurinol and 61% versus febuxostat). In scenarios of imperfect adherence the value-based prices of lesinurad often fall below zero. This is primarily due to dual-ULT being associated



with lower rates of treatment discontinuation in clinical trials and, therefore, accruing higher costs from the XO<sub>i</sub> component of dual-therapy.

## **Discussion**

This was a study of the effectiveness and cost effectiveness of lesinurad as a second-line ULT following first-line treatment with either allopurinol 300mg or febuxostat 80mg, adopting an approach to cost effectiveness that is consistent with a UK NICE appraisal [47]. A population PKPD model used to simulate mono and dual-ULTs showed that while treatment could be highly effective at reducing sUA concentrations to below target, response rates rapidly fell as adherence was reduced by allowing treatment discontinuation and reducing dose implementation from an average of 100% down to 50%. Using the price of lesinurad originally proposed for the UK market, there was only one scenario in which the ICER of dual therapy with lesinurad compared with allopurinol or febuxostat monotherapies was below the higher end of the cost effectiveness threshold of £30,000 per QALY. This was using treatment effectiveness simulated using perfect drug adherence and a pharmacoeconomic model which used the alternative flare frequency methodology in which sustained responders become flare-free. By calculating the value-based price at a threshold of £20,000 per QALY, we have shown the extent to which the pricing of a uricosuric for second-line ULT depends on drug adherence.

Our results broadly agree with the results of previous economic evaluations of lesinurad. Based on the manufacturer's evidence and independent review, a NICE appraisal committee considered the most plausible ICER for lesinurad plus allopurinol compared with allopurinol alone to be at least £62,298 per QALY gained [14]. Our base-case estimates range from £39,184 to £78,350 depending on the level of medication adherence assumed.

Linked PKPD and pharmacoeconomic modelling provide a means of studying the implications of drug pharmacology and adherence on the economic potential of new medicines [48]. These methods can reveal the best-case economic value of new treatments in the case of perfect drug adherence and estimate the rate at which this changes with worsening persistence or dose implementation. The linkage of these two disciplines is increasingly being implemented in order to study a variety of issues in drug development [48–53]. However, we are not aware of any studies that have estimated the impact of changing levels of drug adherence on modelled economic outcomes. Since treatment discontinuation and imperfect dose implementation are both a feature of latter stage clinical trials and routine practice use of medicines, understanding how this may affect cost effectiveness could be of use to both manufacturers and health care providers.

While PKPD simulation allows rapid analysis of previously untested treatment scenarios, it may not always provide a substitute for clinical trials. The mixture of data sources informing the models, possible model misspecification, simplifying assumptions and differences in time or in the patient population can all result in predictions that differ from what would be observed in a trial setting [54]. Furthermore, we have assumed that within the data from which the PKPD models were constructed patients adhered to their dosing regimen. This may not be the case and could result in biased model results [55]. The adherence patterns we assumed were not based on real-world evidence of adherence to ULTs due to an absence of studies that disentangle persistence from implementation. The possible treatment strategies for gout are more nuanced than was considered in this study. Guidelines recommend that allopurinol is used as first line but that it should be initiated at a low dose (e.g. 100 mg) before being titrated up to 900 mg per day or until response is achieved. Similarly, febuxostat could also be initiated at 40mg and titrated up to a possible 120 mg. The economic evaluation did not consider the potential adverse drug reactions; allopurinol is known to cause rare

hypersensitivity reactions, there are possible cardiovascular complications associated with febuxostat, and lesinurad is associated with renal complications that may be exacerbated by poor medication adherence [16].

Gout remains a condition that is typically poorly managed, even in a clinical trials setting with newer ULTs. For health care payers our results provide an indication of the extent to which poor adherence to ULTs erodes the cost effectiveness of these medicines when translating from clinical trials to routine practice. Development of ULTs with greater drug forgiveness [46] would to some extent mitigate the effects of poor implementation and result in greater effectiveness relative to existing treatments. Pharmaceutical companies conducting future clinical trials of novel ULTs should be mindful that achieving sUA endpoints alone, without also showing reductions in gout flares, is not likely to provide an attractive value-based price. This is due, in part, to uncertainty in the rate and scale of reductions in gout flares following a reduction in sUA and the weak evidence base linking sUA to other potential health outcomes, such as cardiovascular diseases. Designing clinical trials to demonstrate the eradication of gout in sustained responders, which is expected in most patients [3], is likely to increase the potential value-based price of new ULTs. An alternative approach could be a sub-study designed to bridge the evidence gap between sUA concentration and flares. For example, Jutkowitz et al. [56] have estimated the potential value of conducting various 1-year studies.

This study has found that medication adherence has a significant influence on the potential cost effectiveness of second-line dual-ULT with lesinurad compared with either allopurinol or febuxostat alone. However, although treatment effect is enhanced under perfect medication adherence, dual-ULT is not expected to be cost effective relative to either monotherapies at a threshold of £20,000 per QALY. The estimated value-based prices of lesinurad only

exceeded that which has been proposed in the UK when assuming both perfect drug adherence and the eradication of gout flares in sustained treatment responders

## References

1. Kuo C-F, Grainge MJ, Zhang W, Doherty M. Global epidemiology of gout: prevalence, incidence and risk factors. *Nat Rev Rheumatol*. 2015;11:649.
2. Hui M, Carr A, Cameron S, Davenport G, Doherty M, Forrester H, et al. The British Society for Rheumatology Guideline for the Management of Gout. *Rheumatology*. 2017;56(7):1056-1059.
3. Shoji A, Yamanaka H, Kamatani N. A Retrospective Study of the Relationship Between Serum Urate Level and Recurrent Attacks of Gouty Arthritis: Evidence for Reduction of Recurrent Gouty Arthritis With. *Arthritis Rheum (Arthritis Care Res)*. 2004;51(3):321-325.
4. Pascual E, Sivera F. Time required for disappearance of urate crystals from synovial fluid after successful hypouricaemic treatment relates to the duration of gout. *Ann Rheum Dis*. 2007;66:1056-1058.
5. Seth R, Kydd A, Buchbinder R, Bombardier C, Edwards C. Allopurinol for chronic gout. *Cochrane Database Syst Rev*. 2014;(10).
6. 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 Arthritis Rheum*. 2014;44(2):170-174.
7. Yin R, Li L, Zhang G, Cui Y, Zhang L, Zhang Q, et al. Rate of adherence to urate-lowering therapy among patients with gout: a systematic review and meta-analysis.

- BMJ Open*. 2018;8(4):e017542.
8. Scheepers LEJM, van Onna M, Stehouwer CDA, Singh JA, Arts ICW, Boonen A. Medication adherence among patients with gout: A systematic review and meta-analysis. *Semin Arthritis Rheum*. 2018;47(5):689-702.
  9. Vrijens B, De Geest S, Hughes DA, Przemyslaw K, Demonceau J, Ruppert T, et al. A new taxonomy for describing and defining adherence to medications. *Br J Clin Pharmacol*. 2012;73(5):691-705.
  10. El Alili M, Vrijens B, Demonceau J, Evers SM, Hiligsmann M. A scoping review of studies comparing the medication event monitoring system (MEMS) with alternative methods for measuring medication adherence. *Br J Clin Pharmacol*. 2016:268-279.
  11. Breckenridge A, Aronson JK, Blaschke TF, Hartman D, Peck CC, Vrijens B. Poor medication adherence in clinical trials: consequences and solutions. *Nat Rev Drug Discov*. 2017;16(3):149-150.
  12. National Institute for Health and Care Excellence. *Febuxostat for the Management of Hyperuricaemia in People with Gout: Technology Appraisal Guidance*.; 2008.
  13. National Institute for Health and Care Excellence. *Lesinurad for Treating Chronic Hyperuricaemia in People with Gout: First Appraisal Consultation Document*.; 2016.
  14. National Institute for Health and Care Excellence. *Final Appraisal Determination: Lesinurad for Treating Chronic Hyperuricaemia in People with Gout*.; 2017.
  15. Hughes D, Cowell W, Koncz T, Cramer J. Methods for Integrating Medication Compliance and Persistence in Pharmacoeconomic Evaluations. *Value Heal*. 2007;10(6):498-509.
  16. Hill-McManus D, Soto E, Marshall S, Lane S, Hughes. Impact of non-adherence on

- the safety and efficacy of uric acid-lowering therapies in the treatment of gout. *Br J Clin Pharmacol*. 2018;84(1):142-152.
17. Beard SM, Scheele BG Von, Nuki G, Pearson I V. Cost-effectiveness of febuxostat in chronic gout. *Eur J Heal Econ*. 2014;15:453-463.
  18. National Institute for Health and Care Excellence. Single Technology Appraisal [ID761]: Lesinurad for treating chronic hyperuricaemia in people with gout, Committee Papers. 2016.
  19. Beal S, Sheiner L, Boeckmann A, Bauer R. NONMEM 7.3.0 Users Guides (1989-2013). 2013.
  20. Wright DFB, Duffull SB, Merriman TR, Dalbeth N, Barclay ML, Stamp LK. Predicting allopurinol response in patients with gout. *Br J Clin Pharmacol*. 2015;81(2):277-289.
  21. Gabrielsson J, Weiner D. *Pharmacokinetic and Pharmacodynamic Data Analysis*. 5th ed. Apotekarsocieteten; 2016.
  22. Food and Drug Administration. *Lesinurad for the Proposed Indication of Treatment of Hyperuricemia Associated with Gout in Combination with a Xanthine Oxidase Inhibitor (FDA Briefing Package)*.; 2015.
  23. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16(1):31-41.
  24. 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(1):203-212.

25. Pittman J, Bross M. Diagnosis and management of gout. *Am Fam Physician*. 1999;59(7):1799-1806.
26. Choi HK, Mount DB, Reginato AM. Pathogenesis of gout. *Ann Intern Med*. 2005;143(7):499-516.
27. Sarawate CA, Patel PA, Schumacher HR, Yang W, Brewer KK, Bakst AW. Serum urate levels and gout flares: analysis from managed care data. *J Clin Rheumatol*. 2006;12(2):61-65.
28. Beard SM, Scheele BG Von, Nuki G, Pearson I V. Cost-effectiveness of febuxostat in chronic gout. 2014:453-463.
29. National Institute for Health and Care Excellence. *Guide to the Methods of Technology Appraisal 2013*.; 2013.
30. R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing. 2017.
31. Food and Drug Administration. *Zurampic Label (Reference ID: 3864748)*.; 2015.
32. Becker MA, Schumacher HR, Macdonald PA, Lademacher C, Becker MA, Schumacher HR, et al. Clinical Efficacy and Safety of Successful Longterm Urate Lowering with Febuxostat or Allopurinol in Subjects with Gout Clinical Efficacy and Safety of Successful Longterm Urate Lowering with Febuxostat or Allopurinol in Subjects with Gout. *J Rheumatol*. 2009;36(6):1273-1282.
33. National Institute for Health and Care Excellence. *ACD2: Lesinurad for Treating Chronic Hyperuricaemia in People with Gout*.; 2017.
34. The Office for National Statistics. England and Wales 2015. *Natl Life Tables*. 2015.

35. Halpern R, Fuldeore MJ, Mody RR, Patel PA, Mikuls TR. The effect of serum urate on gout flares and their associated costs: An administrative claims analysis. *J Clin Rheumatol*. 2009;15(1):3-7.
36. Khanna PP, Nuki G, Bardin T, Tausche A, Forsythe A, Goren A, et al. Tophi and frequent gout flares are associated with impairments to quality of life , productivity , and increased healthcare resource use : Results from a cross-sectional survey. 2012:1-11.
37. Shoji A, Yamanaka H, Kamatani N. A Retrospective Study of the Relationship Between Serum Urate Level and Recurrent Attacks of Gouty Arthritis : Evidence for Reduction of Recurrent Gouty Arthritis With. *Arthritis Rheum (Arthritis Care Res*. 2004;51(3):321-325.
38. Shiozawa A, Szabo SM, Bolzani A, Cheung A, Choi HK. Review Serum Uric Acid and the Risk of Incident and Recurrent Gout: A Systematic Review. *J Rheumatol*. 2017;44(3):388-396.
39. Becker MA, Macdonald PA, Hunt BJ, Lademacher C, Joseph-ridge N. Determinants of the Clinical Outcomes of Gout During the First Year of Urate-Lowering Therapy. *Nucleosides, Nucleotides and Nucleic Acids*. 2008;27(6):585-591.
40. Joint Formulary Committee. British National Formulary (online) London: BMJ Group and Pharmaceutical Press. <<http://www.medicinescomplete.com>>.
41. 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(10):1431-1446.



42. National Institute for Health and Care Excellence. *Single Technology Appraisal: Lesinurad for Treating Chronic Hyperuricaemia in People with Gout. Committee Papers 2*. Vol [ID761].; 2016.
43. 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;76(5):811-820.
44. 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(1):203-212.
45. Li X, Meng X, Timofeeva M, Tzoulaki I, Tsilidis KK, Ioannidis JPA, et al. Serum uric acid levels and multiple health outcomes: umbrella review of evidence from observational studies, randomised controlled trials, and Mendelian randomisation studies. *BMJ*. 2017;357:j2376.
46. Assawasuwannakit P, Braund R, Duffull SB. Quantification of the Forgiveness of Drugs to Imperfect Adherence. *CPT Pharmacometrics Syst Pharmacol*. 2015;4(3):204-211.
47. National Institute for Health and Care Excellence. *Guide to the Single Technology Appraisal Process*.; 2009.
48. Pink J, Lane S, Hughes DA. Mechanism-based approach to the economic evaluation of pharmaceuticals: Pharmacokinetic/pharmacodynamic/pharmacoeconomic analysis of rituximab for follicular lymphoma. *Pharmacoeconomics*. 2012;30(5):413-429.

49. Pink J, Pirmohamed M, Lane S, Hughes DA. Cost-effectiveness of pharmacogenetics-guided warfarin therapy vs. alternative anticoagulation in atrial fibrillation. *Clin Pharmacol Ther.* 2014;95(2):199-207.
50. van Hasselt JGC, Gupta A, Hussein Z, Beijnen JH, Schellens JHM, Huitema ADR. Integrated Simulation Framework for Toxicity, Dose Intensity, Disease Progression, and Cost Effectiveness for Castration-Resistant Prostate Cancer Treatment With Eribulin. *CPT Pharmacometrics Syst Pharmacol.* 2015;4(7):374-385.
51. Slejko JF, Willke RJ, Ribbing J, Milligan P. Translating Pharmacometrics to a Pharmacoeconomic Model of COPD. *Value Heal.* 2016;19(8):1026-1032.
52. Kamal MA, Smith PF, Chaiyakunapruk N, Wu DBC, Pratoomsot C, Lee KKC, et al. Interdisciplinary pharmacometrics linking oseltamivir pharmacology, influenza epidemiology and health economics to inform antiviral use in pandemics. *Br J Clin Pharmacol.* 2017;83(7):1580–1594.
53. Hoogendoorn M, Feenstra TL, Asukai Y, Borg S, Hansen RN, Jansson S-A, et al. Cost-effectiveness models for chronic obstructive pulmonary disease: cross-model comparison of hypothetical treatment scenarios. *Value Heal J Int Soc Pharmacoeconomics Outcomes Res.* 2014;17(5):525-536.
54. Holford N, Ma SC, Ploeger BA. Clinical Trial Simulation: A Review. *Clin Pharmacol Ther.* 2010;88(2):166-182.
55. Vrijens B, Gross R, Urquhart J. The odds that clinically unrecognized poor or partial adherence confuses population pharmacokinetic/pharmacodynamic analyses. *Basic Clin Pharmacol Toxicol.* 2005;96(3):225-227.
56. Jutkowitz E, Alarid-Escudero F, Choi HK, Kuntz KM, Jalal H. Prioritizing Future

Research on Allopurinol and Febuxostat for the Management of Gout: Value of Information Analysis. *Pharmacoeconomics*. 2017;35(10):1073-1085.

**Table 1 Distribution of patients across sUA concentration categories following ULT with varying levels of dose implementation using 500 PKPD simulations**

Urate lowering therapy option*	Percentage of subjects in sUA category (mg/dl) at day 120				% < 6 mg/dl on ≥80% of days	% Receiving lesinurad
	<6	6 to <8	8 to <10	≥10		
<i>100% dose implementation</i>						
Allopurinol 300mg (ALL)	57	40	3	0	56.6	NA
ALL + optional lesinurad 200mg	83	17	0	0	83.0	43.7
Febuxostat 80mg (FBX)	97	3	0	0	97.3	NA
FBX + optional lesinurad 200mg	99	1	0	0	99.3	2.6
<i>80% dose implementation</i>						
Allopurinol 300mg (ALL)	41	49	10	0	35.7	NA
ALL + optional lesinurad 200mg	63	33	5	0	52.5	59.6
Febuxostat 80mg (FBX)	81	15	4	0	71.3	NA
FBX + optional lesinurad 200mg	84	14	3	0	74.6	18.4
<i>50% dose implementation</i>						
Allopurinol 300mg (ALL)	19	53	24	3	12.7	NA
ALL + optional lesinurad 200mg	36	46	16	2	21.0	80.1
Febuxostat 80mg (FBX)	49	36	14	1	25.1	NA
FBX + optional lesinurad 200mg	53	34	12	1	30.2	49.5
<i>No Treatment</i>	0	21	57	22	0	NA

\* Allopurinol 300 mg once daily; febuxostat 80 mg once daily; lesinurad 200 mg once daily

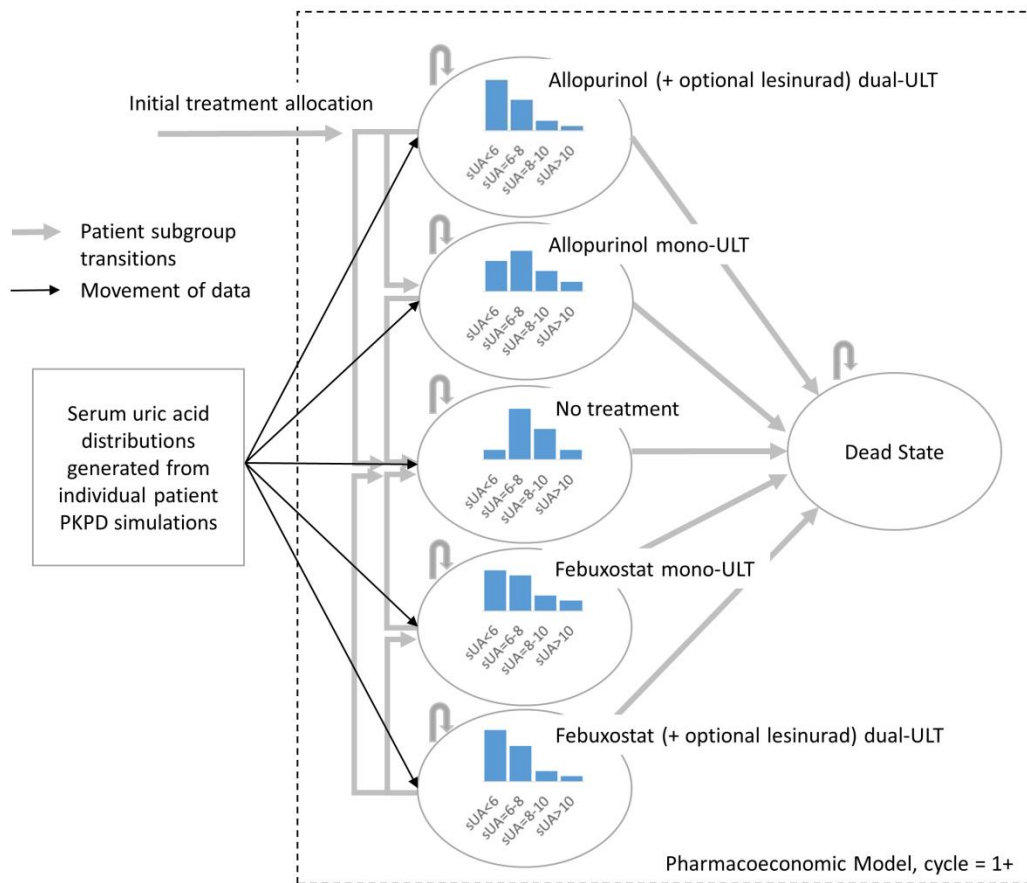
**Table 2** Economic model results in patients with allopurinol 300 mg monotherapy as first line treatment and add-on lesinurad 200 mg in non-responders as second line treatment. The ICER was calculated as the difference in lifetime costs divided by the difference in lifetime QALYs. Costs and effects were discounted at 3.5%; ICER: incremental cost effectiveness ratio; QALYs: quality-adjusted life-years; adherence model 1: perfect adherence to dosing regimen; adherence model 2: treatment discontinuation and 80% average implementation; adherence model 3: treatment discontinuation and 50% average implementation

ULT Treatment Option	Lifetime Cost	Lifetime QALYs	Δ Cost vs ALL	Δ QALYs vs ALL	ICER vs ALL
<i>Base case flare frequency methodology</i>					
<i>Adherence model 1</i>					
Allopurinol 300mg (ALL)	£3,757	13.36	-	-	-
ALL + optional lesinurad 200mg	£6,352	13.42	£2,594	0.066	<b>£39,184</b>
<i>Adherence Model 2</i>					
Allopurinol 300mg (ALL)	£2,246	13.22	-	-	-
ALL + optional lesinurad 200mg	£4,068	13.26	£1,822	0.038	<b>£47,848</b>
<i>Adherence Model 3</i>					
Allopurinol 300mg (ALL)	£2,277	13.19	-	-	-
ALL + optional lesinurad 200mg	£4,796	13.22	£2,519	0.032	<b>£78,350</b>
<i>Alternative flare frequency methodology</i>					
<i>Adherence model 1</i>					
Allopurinol 300mg (ALL)	£3,614	13.49	-	-	-
ALL + optional lesinurad 200mg	£6,139	13.63	£2,525	0.133	<b>£19,019</b>
<i>Adherence Model 2</i>					
Allopurinol 300mg (ALL)	£2,221	13.24	-	-	-
ALL + optional lesinurad 200mg	£4,024	13.30	£1,804	0.057	<b>£31,803</b>
<i>Adherence Model 3</i>					
Allopurinol 300mg (ALL)	£2,277	13.19	-	-	-
ALL + optional lesinurad 200mg	£4,784	13.23	£2,507	0.032	<b>£77,903</b>

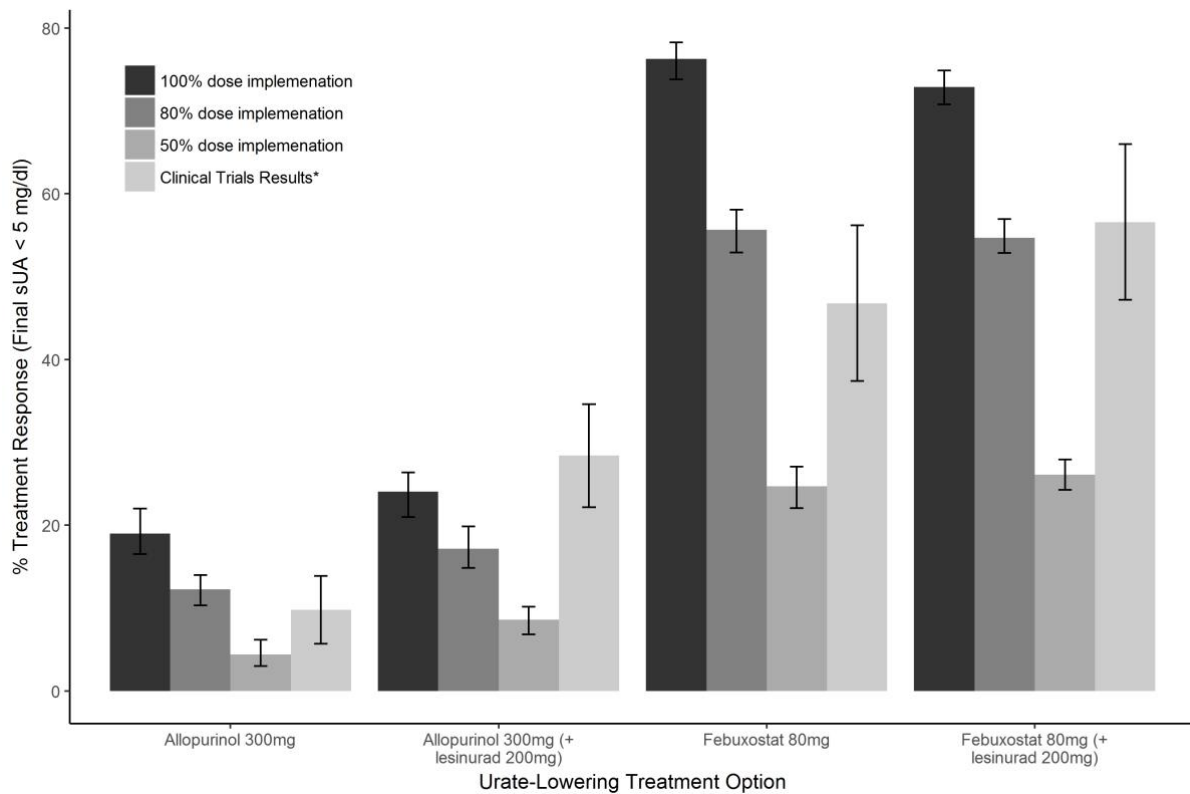
**Table 3** Economic model results in patients with febuxostat 80 mg monotherapy as first line treatment and add-on lesinurad 200 mg in non-responders as second line treatment. The ICER was calculated as the difference in lifetime costs divided by the difference in lifetime QALYs. Costs and effects were discounted at 3.5%; ICER: incremental cost effectiveness ratio; QALYs: quality-adjusted life-years; adherence model 1: perfect adherence to dosing regimen; adherence model 2: treatment discontinuation and 80% average implementation; adherence model 3: treatment discontinuation and 50% average implementation

ULT Treatment Option	Lifetime Cost	Lifetime QALYs	Δ Cost vs FBX	Δ QALYs vs FBX	ICER vs FBX
<i>Base case flare frequency methodology</i>					
<i>Adherence model 1</i>					
Febuxostat 80mg (FBX)	£9,157	13.46	-	-	-
FBX + optional lesinurad 200mg	£9,311	13.46	£154	0.005	<b>£31,901</b>
<i>Adherence Model 2</i>					
Febuxostat 80mg (FBX)	£5,094	13.28	-	-	-
FBX + optional lesinurad 200mg	£5,803	13.29	£709	0.010	<b>£74,136</b>
<i>Adherence Model 3</i>					
Febuxostat 80mg (FBX)	£5,122	13.23	-	-	-
FBX + optional lesinurad 200mg	£7,015	13.25	£1,893	0.015	<b>£124,212</b>
<i>Alternative flare frequency methodology</i>					
<i>Adherence model 1</i>					
Febuxostat 80mg (FBX)	£8,884	13.70	-	-	-
FBX + optional lesinurad 200mg	£9,034	13.71	£149	0.010	<b>£15,376</b>
<i>Adherence Model 2</i>					
Febuxostat 80mg (FBX)	£5,024	13.34	-	-	-
FBX + optional lesinurad 200mg	£5,724	13.36	£700	0.017	<b>£40,078</b>
<i>Adherence Model 3</i>					
Febuxostat 80mg (FBX)	£5,151	13.23	-	-	-
FBX + optional lesinurad 200mg	£7,031	13.25	£1,880	0.022	<b>£86,870</b>

## Figures



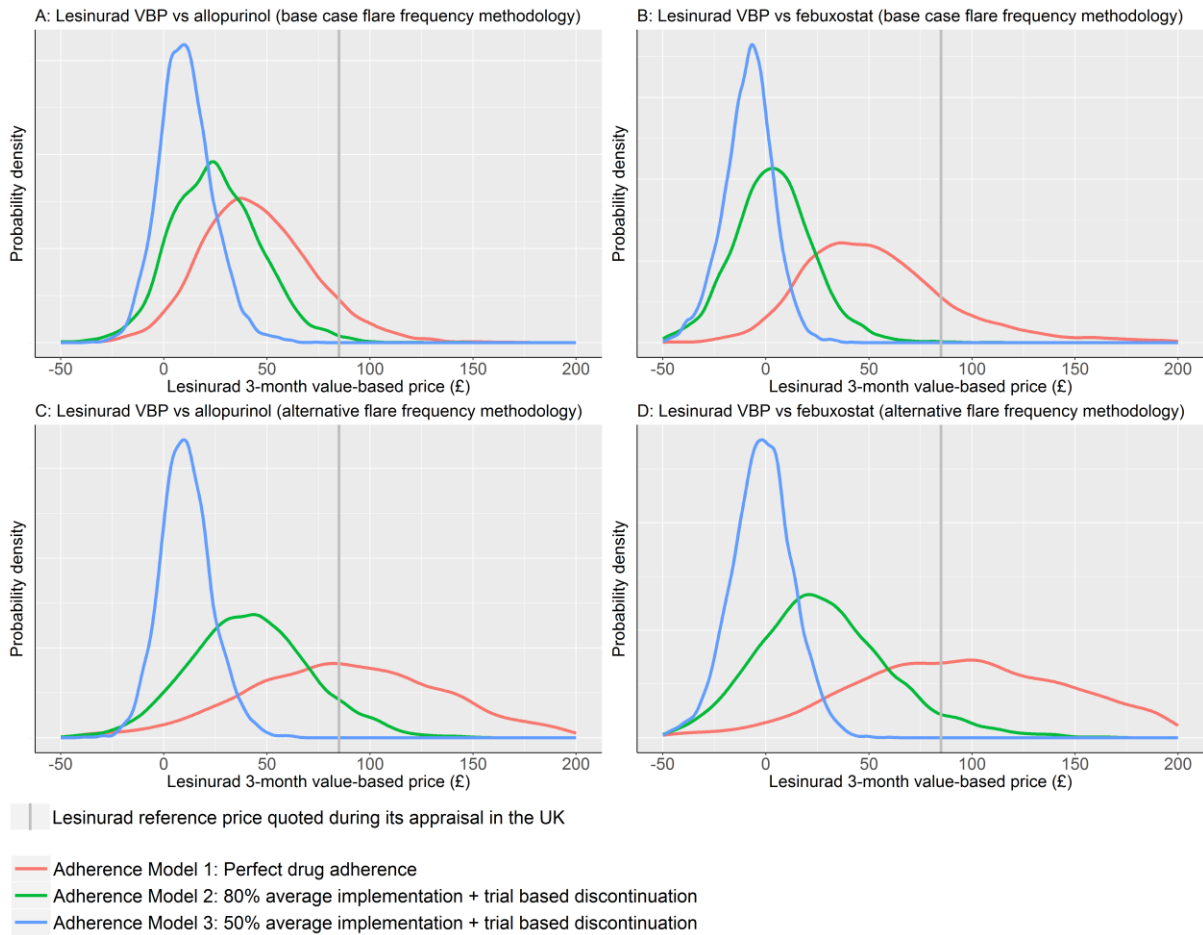
**Fig. 1** Illustration of the structure of the pharmacoeconomic model showing patient subgroup transitions and the sUA distributions set by PKPD simulations. In this example, the model estimates the lifetime costs and QALY gains resulting from all patients being initially allocated to allopurinol with optional lesinurad dual-ULT. This process is repeated using three adherence models and four initial ULT allocations in order to compare treatments options.



**Fig. 2** Simulated treatment response rates for three adherence models and the treatment response in the corresponding treatment arm in clinical trials. The threshold for treatment response has been defined as 5 mg/dl. Clinical trials results are at 6 months and assume non-responder imputation for patients who discontinued. Discontinuation rates were also applied to simulated results assuming equal probability of discontinuation amongst responders and non-responders. Confidence intervals on PKPD simulations account for patient heterogeneity and parameter random effects, but not uncertainty in parameters estimates or within individual residual variability.

\* Allopurinol 300mg and allopurinol 300mg + lesinurad 200mg response rate is 9.8% and 28.4% respectively from CLEAR 1 and CLEAR 2 trials; Febuxostat 80mg and febuxostat 80mg + lesinurad 200mg response rate is 46.8% and 56.6% respectively from the CRYSTAL trial.





**Fig. 3** The value-based price of lesinurad as part of dual-ULT in combination with either febuxostat or allopurinol in patients not responding to either monotherapy alone. The value-based price distributions are obtained using the results of 5,000 probabilistic economic model simulations. Value-based price is defined as the price of lesinurad at which the modelled incremental cost per QALY comparing dual-ULT to mono-ULT is equal to the £20,000 threshold. The vertical line indicates the price of lesinurad quoted during its appraisal in the UK.