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The Safety and Efficacy of Lesinurad in Combination with Allopurinol versus Allopurinol Alone in Patients with Gout: A Systematic Review and Meta-Analysis

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Abstract

Background: Lesinurad approved by the US FDA in December 2015. This study assess the efficacy and safety of the combination of lesinurad and allopurinol in gout patients who are non-responsive to allopurinol alone using meta-analysis method.
Method: Search performed in multiple databases from inception to May 2019. Double-blinded RCTs of lesinurad in combination with allopurinol versus allopurinol alone were applied. Three studies, 922 patients met our inclusion criteria. The primary outcome was the number of subjects achieving a serum urate level <6.0 mg/dL at any follow-up point; the secondary endpoints were the number of tophi with complete resolution; any reported gout flares, any serious adverse events, withdrawal, or death.
Results: The relative risk showed a significant reduction in serum urate levels <6 mg/dL in lesinurad 400mg group versus the allopurinol alone group (RR=2.51, 95% CI=2.12- 2.98). Two studies reported reductions in gout flares between the groups (RR=-0.07, 95%CI=-0.08 --0.05). The lesinurad group showed higher serious adverse events when compared with allopurinol alone (RR=1.87, 95%CI=1.09-3.21).
Conclusion: Lesinurad 400mg in combination with allopurinol showed significant reduction in urate levels <6 mg/dL and in number of gout flares. However, there were higher AEs with the combination therapy of lesinurad and allopurinol.

Keywords: Systematic review, Meta-analysis, Lesinurad, Gout, Allopurinol

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1. Introduction

Gout is a clinical condition that encompasses a wide spectrum of pathologic and clinical features and is caused by an accumulation of urate in the body. The main risk factor for gout is hyperuricaemia, defined as an increase in the serum urate level to greater than 6.8 or 7.0 mg/dl[1]. Gout remains the most common form of inflammatory arthritis, with a prevalence of 1.4–2.5% in the UK and 3.9% in the US [2,3]. This phenomenon results in episodes of acute inflammation in both periarticular and articular structures as well as severe pain1. The pain can be reversed by decreasing the concentration of serum urate to less than 6.0 mg/dL[1].

The most recent guidelines for management of gout suggest the use of a combination of pharmacotherapy and lifestyle modifications to target serum urate levels of <6.0 mg/dL in most patients[1,4]. Both the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) guidelines recommend initiating a dose of XO inhibitors, allopurinol or febuxostat as the first-line urate-lowering therapy[1,5]. However, a significant number of patients (greater than 50%) in clinical trials do not achieve the recommended urate levels of less than 6.0 mg/dL. Thus, in cases in which the urate target cannot be achieved with allopurinol alone, treatment guidelines suggest substitution therapy, such as switching from one xanthine oxidase inhibitor to another xanthine oxidase inhibitor [1,3,4].

Lesinurad was recently approved by the Food and Drug Administration in December 2015 following evidence from three phase III studies[6,7,8]. Lesinurad is indicated when combined with a xanthine oxidase inhibitor for the management of hyperuricaemia in gout patients in whom the target serum urate levels cannot be attained with a xanthine oxidase inhibitor alone[9].

Several clinical studies measured both the efficacy and safety of lesinurad combined with allopurinol and demonstrated a reduction in mean urate concentrations as well as an increase in the number of patients who achieved urate targets[6,7,10].

Nonetheless, to our knowledge, there are no systematic reviews or meta-analyses specifically evaluating the efficacy and safety of the combination therapy (lesinurad and allopurinol) compared to allopurinol alone. During the conduct of this work another review was published that had a slightly different aim and will be discussed in further details later on[11]. In line with this, this study was designed to gather evidence from published and unpublished randomized controlled trials to assess both the efficacy and safety of the combination therapy of lesinurad and allopurinol in patients with gout who are non-responsive to allopurinol alone.

2. Research Design and Methods

2.1 Data Sources and Search Strategy

We performed a systematic search of electronic bibliographic databases, including MEDLINE through OVID, EMBASE, cumulative index to nursing and allied health literature (CINAHL), and the Cochrane Central Register of Controlled Trials. In addition, we searched the reference lists of the included articles, and we looked for

unpublished studies in registries of clinical trials, including Clinicaltrials.gov and conference proceedings of the American College of Rheumatology (ACR) and the European League against Rheumatism (EULAR). Our search strategy contained keywords appropriate to the study design, the intervention of interest at any dose and frequency of lesinurad or allopurinol, and the disease of interest. The detailed list of these search strategy keywords is provided in (Appendix 1). The literature search was performed from inception of the databases until May 2019 and was limited to human studies only. No limitations were applied for language, publication date or publication. No protocol registration was completed.

3. Study Selection

We included all randomized controlled trials (RCTs) on patients aged 18 years or older with an inadequate hyperuricemic response (urate level ≥6 mg/dL) to the standard care, allopurinol monotherapy, which compared the combination of lesinurad 400 mg and allopurinol versus allopurinol alone for the treatment of gout at any dose of allopurinol and any duration of follow-up and included at least one of the pre-specified study endpoints. The primary outcome measure was the number of subjects achieving a serum urate level less than 6.0 mg/dL at any follow-up point, while the secondary endpoints were the number of tophi achieving complete resolution, any reported gout flares, any serious adverse events, withdrawal, or death.

Two reviewers, H. Aljohani and H. Almalag, independently reviewed identified abstracts and removed duplicates. The full-text publications of potentially relevant articles were retrieved and rescreened by the same two investigators. Disagreements were resolved by consulting a third reviewer, H. Alkofide.

3.1 Data Extraction and Quality Assessment

Eligible studies were extracted independently by two investigators (H. Aljohani and H. Almalag), and any disagreements were resolved by consulting with a third investigator, (H. Alkofide), We collected data on general study information, study authors, title, source and country, year of publication, and trial characteristics, such as details of the study design, inclusion criteria, and exclusion criteria. Further, information was extracted on patient baseline characteristics, previous and concurrent treatments, intervention details, sample size, outcome measurements, and details regarding duration of follow-up and results.

The methodological quality of the included randomized studies was evaluated using the Cochrane Collaboration's risk-of-bias tool for randomized trials[12] . Thirteen risk-of-bias items are included in this tool. An assessment for the first seven items, which are sequence generation, allocation concealment, patients' blinding, caregivers' blinding, outcome assessors' blinding, attrition, and selective outcome reporting were reported as “low,” “high,” or “unclear.” The evaluation of the remaining items, namely, intention-to-treat analysis, baseline balance, co-intervention similarity, compliance, and the presence of other biases, was reported

as “yes” or “no” (Table 1, Table 2).

Table 1: Risk-of-Bias Items Assessed for Randomized, Controlled Trials

1. What is the risk of selection bias (biased allocation to interventions) due to inadequate generation of a randomized sequence? [Low, Unclear, High]
2. What is the risk of selection bias (biased allocation of interventions) due to inadequate concealment of allocations before assignment? [Low, Unclear, High]
3. For each main outcome or class of outcomes, what is the risk of performance bias due to knowledge of the allocated interventions by participants and personnel during the study (lack of study participant and personnel blinding)? [Low, Unclear, High]
4. Was the care provider blinded to the intervention? [Low, Unclear, High]
5. For each main outcome or class of outcomes, what is the risk of detection bias due to knowledge of the allocated interventions by outcome assessment (lack of outcome assessor blinding)? [Low, Unclear, High]
6. For each main outcome or class of outcomes, what is the risk of attrition bias due to amount, nature, or handling of incomplete outcome data? [Low, Unclear, High]
7. What is the risk of reporting bias due to selective outcome reporting? [Low, Unclear, High]
8. Were all randomized participants analyzed in the group to which they were allocated? [Yes, No, Unsure]
9. Were the groups similar at baseline regarding the most important prognostic indicators? [Yes, No, Unsure]
10. Were co-interventions avoided or similar? [Yes, No, Unsure]
11. Was the compliance acceptable in all groups? [Yes, No, Unsure]
12. Was the timing of the outcome assessment similar in all groups? [Yes, No, Unsure]
13. Are there other risks of bias? [Yes, No]

Table 2: Risk-of-Bias Items Assessed for Randomized, Controlled Trials

Study	Sequence generation	Allocation concealment	Blinding Patients	Blinding Caregiver	Blinding Assessors	Attrition bias	Selective outcome reporting	Co-interventions similarity	Other biases	Overall Quality
Bardin et.al. 2016	Unclear	Low	Low	Low	Unclear	No	Low	Yes	No	High
Perez-Ruiz et.al. 2015	Unclear	Low	Low	Low	Unclear	No	Low	Yes	No	High
Saag et.al. 2016	Unclear	Low	Low	Low	Unclear	No	Low	Yes	No	High

After reviewing all risk-of-bias items, we consigned an overall quality grade of good, fair, or poor to each randomized control trial. Studies were considered poor quality if they had one or more of any of the following: absence of blinding, differential loss to follow-up, baseline imbalances. Studies that reported sufficient details about the implementation of blinding (such as double-blinding and use of identical capsules) had low risk of bias for this specific item; whereas studies with insufficient reporting (e.g., reporting of allocation concealment) had unclear risk of bias.

3.2 Data Synthesis and Analysis

The treatment effect of the binary outcomes, number of subjects achieving a urate level less than 6 mg/dl, tophus resolution, and the number of adverse events, withdrawals and deaths, were estimated using the risk ratio (RR) and the corresponding 95% confidence interval (CI). While continuous outcomes, such as occurrence of gout flares, were estimated by difference in mean changes from baseline between the two groups and were calculated for each study included.

We performed meta-analysis by using the random effect models estimated by Mantel-Haenszel. Statistical heterogeneity was measured using I2 statistics, and values of 25%, 50%, and 75% were considered to indicate low, moderate, and high degrees of heterogeneity, respectively. We performed post hoc sensitivity analyses by excluding studies of poor reporting quality. We assessed publication bias by using a funnel plot as shown in (Figure 1). We used RevMan.5 software for statistical analysis.

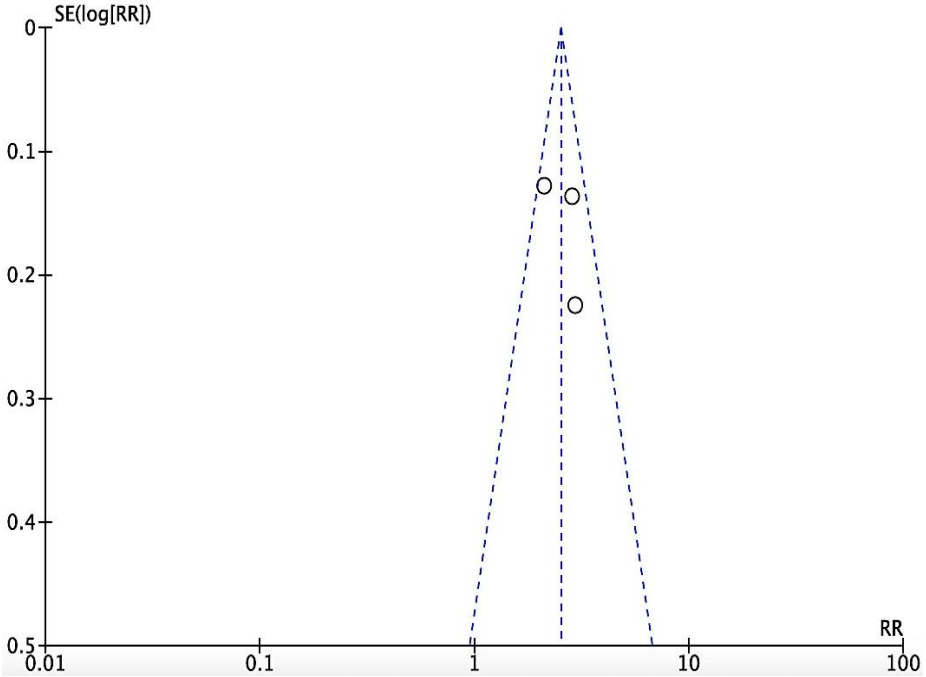


Figure 1: Funnel plot of the included studies.

4. Result

4.1 Search Results

We retrieved 276 citations from electronic database searches, and after abstract screening, 14 articles met our inclusion criteria[6,7,10,13–16]. The review was guided by Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA), and a PRISMA flow diagram is presented in (Figure 2).

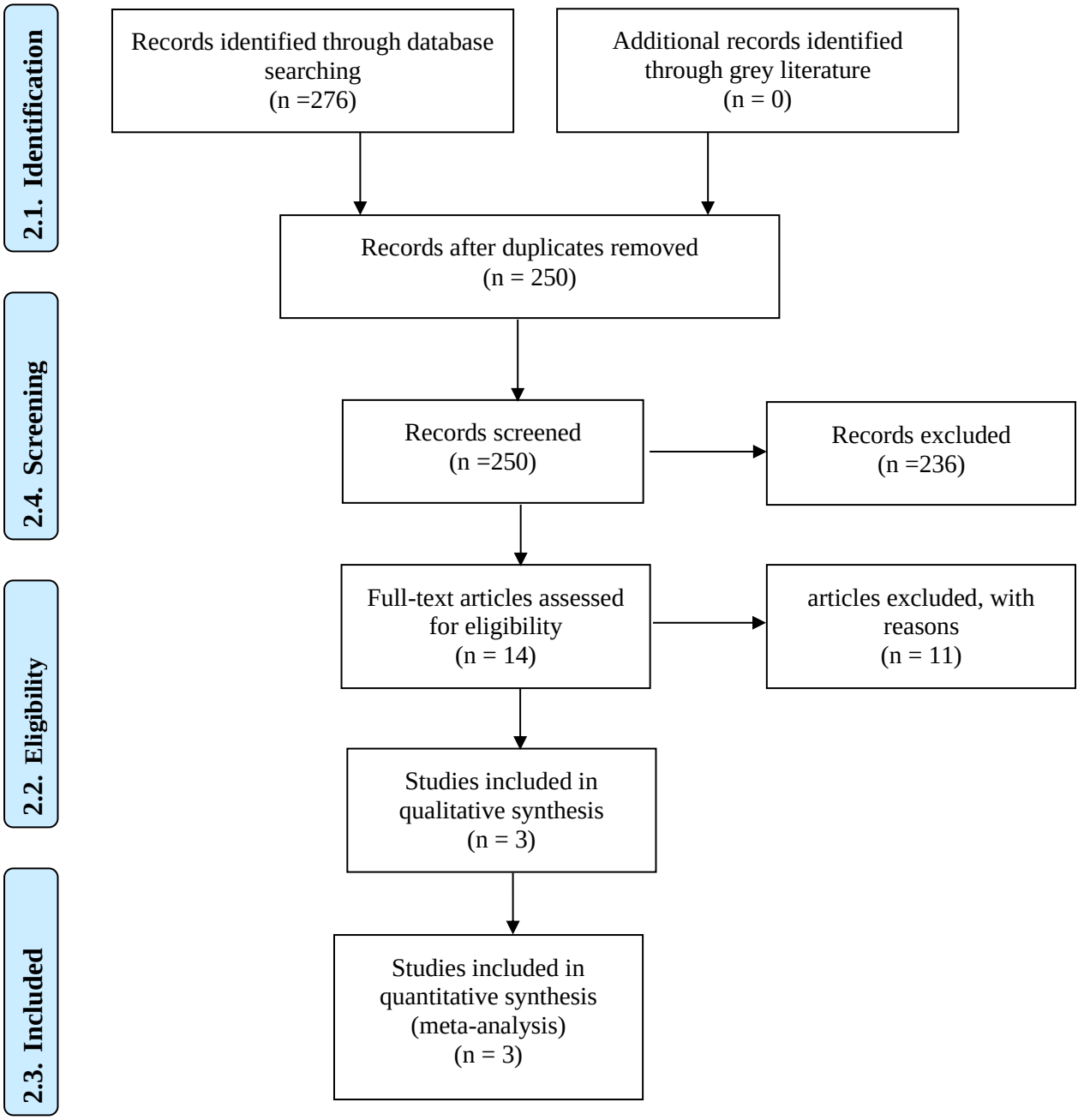


Figure 2: Flow diagram of study selection for the SR of lesinurad versus allopurinol in chronic gout

Another detailed flow diagram is presented in (Figure 3)[17].

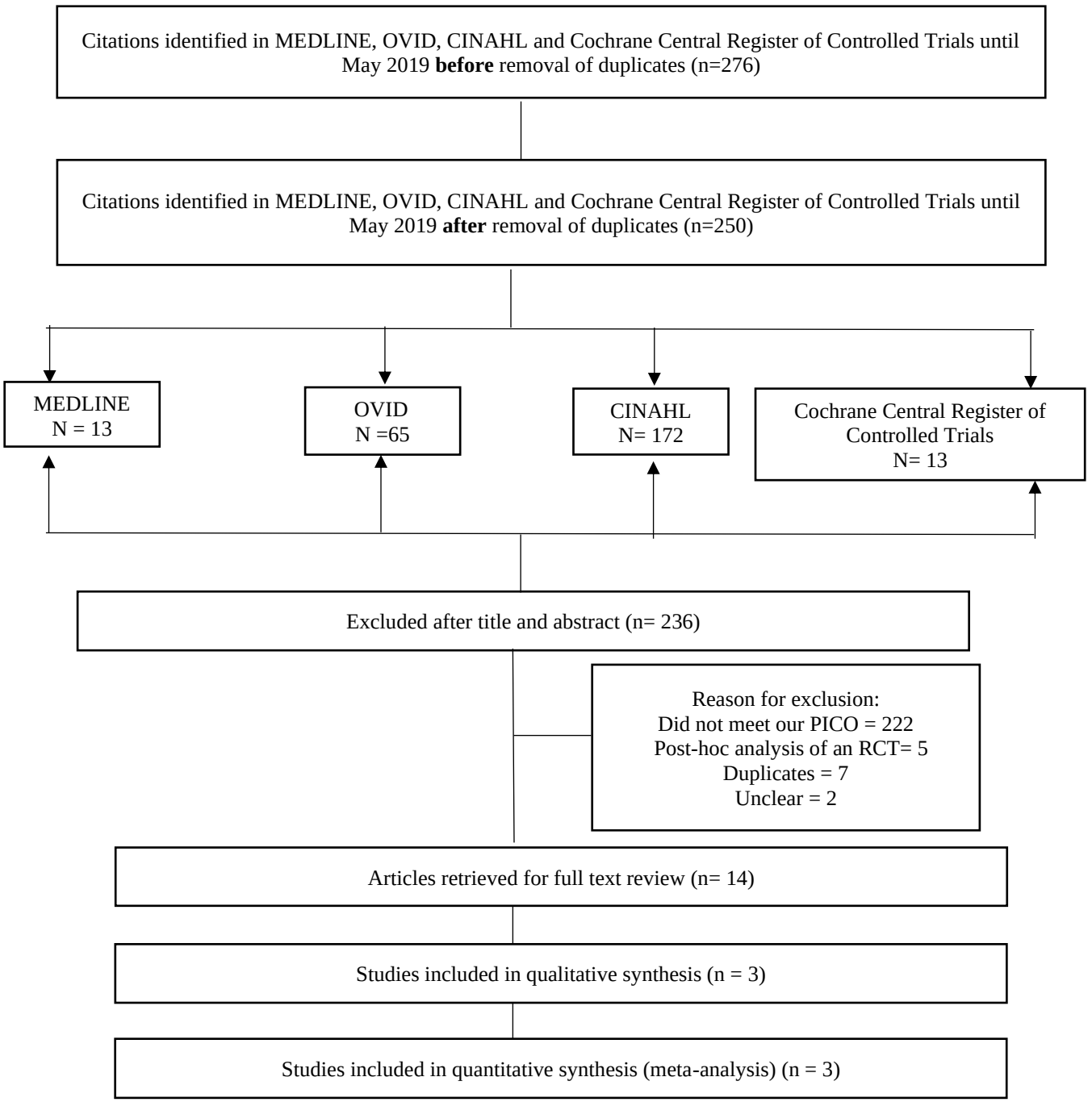


Figure 3: Flow diagram of study selection for the SR of lesinurad versus allopurinol in chronic gout

After full-text review, three randomized trials were included in the systematic review[6,7,10]. Of the remaining 11 studies, three were unavailable in full text (Table 3). The authors were contacted with no response, and no data were requested; the other 8 studies were excluded for being duplicates.

Table 3: Main findings of the articles with abstract only.

Authors	Year	Main findings
Saag K, Bardin T, et al.[1]	2015	In total, 1208 patients were included in the analyses. Demographic characteristics, including age, gender, race, weight, and BMI, were broadly similar between patient groups stratified by baseline renal function. Efficacy, assessed by the proportions of patients with sUA <6.0 mg/dL at 6 and 12 months, was consistently greater (P<0.05) for both lesinurad doses (200 mg and 400 mg) than placebo in all groups assessed. There were no consistent differences in TEAE rates in patients based on baseline renal function. Serum creatinine (sCr) elevations occurred at higher rates in the lesinurad groups (particularly the 400 mg dose) versus placebo, without evident differences when analyzed by baseline renal function.
Sundy J., Perez-Ruiz F., et al.[2]	2011	126 subjects enrolled into the extension study; 113 currently are continuing. Forty-one subjects completed 28 weeks and 8 subjects completed 1 year. Efficacy results are presented for all 41 subjects who completed extension week 28. Combination treated subjects continued to respond with 80% (4/5), 82% (9/11) and 92% (12/13) of ALLO + lesinurad 600 mg, 400 mg, and 200 mg, respectively, maintaining sUA < 6 mg/dL at 28 weeks, compared to 33% (4/12) of ALLO+PBO subjects; 40% (2/5), 64% (7/11) and 46% (6/13) of subjects receiving ALLO + lesinurad 600, 400 and 200 mg, respectively, also achieved sUA<5 mg/dL, compared to 17% (2/12) of ALLO+PBO subjects. 13 subjects (7 PBO/6 lesinurad) withdrew from the study for any reason before or after week 28. Two lesinurad subjects reported SAEs (angina, infected elbow) considered unrelated to lesinurad. CK elevations at baseline were common (24% of all subjects) and post-baseline elevations were also common, but rates were similar between the PBO (29%) and lesinurad (30%) groups. Transient serum creatinine elevations (increase to at least 1.5 x ULN) were observed with long term dosing in the lesinurad group (3.6%), which resolved to within the normal range at the next visit; no such elevations were observed with placebo.
Tausche A., Alten R, et al. [3]	2015	Patients (lesinurad , 107; placebo, 107) were primarily white (81.8%) and male (91.1%) with mean ± SD age of 54.4±12.3 years, 11.2±8.7 years since gout diagnosis, 6.2±7.3 gout flares in past 12 months, tophi (25% of patients), renal impairment (58.9% with estimated creatinine clearance [eCrCL] <90 mL/min), and sUA of 9.3±1.5 mg/dL. Patients had intolerance/ contraindication to allopurinol (91.1%), febuxostat (8.9%) or both (4.2%). Significantly more patients achieved the primary endpoint (sUA <6.0 mg/dL at Month 6) with lesinurad 400mg than placebo (29.9% vs.1.9%). Discontinuation rate was greater with lesinurad 400mg (32.7%) than placebo (15.9%). Overall adverse events (AEs) rate was higher with lesinurad 400mg, mainly due to more renal AEs. Of the 143 patients (placebo, 78; lesinurad, 65) who enrolled in the extension study, 84 (59%) and 35 (24%) completed 6 and 12 months, respectively, prior to early study termination by the Sponsor (mean lesinurad exposure, 223 days). A total of 91 patients (64%) achieved sUA <6.0 mg/dL at some point during the extension study. AEs were similar to the lesinurad 400mg group in the core study.

1. Analysis of Gout Subjects Receiving Lesinurad and Allopurinol Combination Therapy By Baseline Renal Function - ACR Meeting Abstracts.http://acrabstracts.org/abstract/analysis-of-gout-subjects-receiving-lesinurad-and-allopurinol-combination-therapy-by-baseline-renal-function/. Accessed March 17, 2018.
2. Talk: Efficacy and SAFETY of Lesinurad (RDEA594), A NOVEL Uricosuric Agent, Given In COMBINATION with ALLOPURINOL In ALLOPURINOL-REFRACTORY Gout PATIENTS: PRELIMINARY RESULTS FROM the RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE 2B Extension STUDY (2011 ACR/ARHP Annual Scientific Meeting). https://acr.confex.com/acr/2011/webprogram/Paper23977.html. Accessed March 16, 2018.
3. Tausche A-K, Alten R, Dalbeth N, et al. SAT0307 Lesinurad Monotherapy in Gout Patients Intolerant to Xanthine Oxidase Inhibitors (Light): A Randomized, Double-Blind, Placebo-Controlled, 6-Month Phase III Clinical Trial. Ann Rheum Dis. 2015;74(Suppl 2):769.1-769. doi:10.1136/annrheumdis-2015-eular.2090.

4.2 Descriptive summary of included studies

All three included studies compared lesinurad in combination with allopurinol to allopurinol alone for the management of chronic gout patients, although the studies differed in terms of study settings and duration of follow-up (Table 4).

Table 4: Description of study characteristics

Study	Year of study	No. of participant	Mean age	Mean urate level	Male (%)	Country	Intervention	Comparison	Follow up period	Mean Gout flares	Chronic gout (Years)
Perez-Ruiz et. al.	2015	208	50.9	6.9	98.1	Multinational*	Les 400 mg+	Allopurinol	1 month	3.8	7.0
Bardin et. al.	2016	611	51.3	6.9	96.0	Multinational*	Les 400 mg+	Allopurinol	6 months	5.9	11.1
Saag et. al.	2016	603	52.0	6.9	93.2	USA	Les 400 mg+	Allopurinol	6 months	4.8	11.3

*Multinational: Canada, Georgia, Poland, Spain, Ukraine, the UK, South Africa, Australia, New Zealand and the USA
+Les: Lesinurad

Two of the included studies had a 6-month follow-up period, while the other had a one-month follow-up period. Therefore, we used these periods of follow-up to assess the efficacy and safety endpoints in this study. The total number of patients recruited in the three trials was 1422, with 479 in the placebo group and the remaining 943 divided into groups based on administered lesinurad dose. The mean age of participants in these trials ranged from 51.1 years to 51.7 years, and mean baseline serum urate level was 6.9 mg/dl. The mean proportion of patients who had gout flares in the 12 months prior to study inclusion was 4.9 months across the trials.

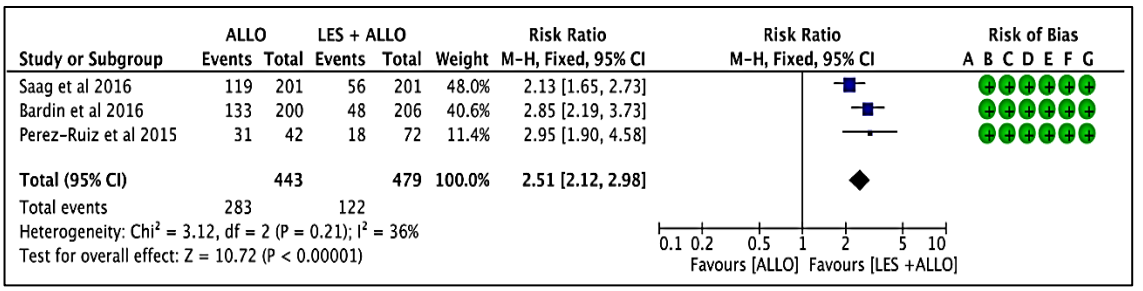
5. Risk of bias assessment

Overall, all three trials had a low risk of bias. However, all included studies had an unclear sequence generation and blinding of assessors. The discontinuation rates were higher in the lesinurad in combination with allopurinol group than in the allopurinol alone group.

5.1 Pooled results for efficacy outcomes

Achieving urate levels less than 6 mg/dl:

All trials (n= 922) reported reduction in the serum urate level to less than 6 mg/dL at the last follow-up period. Pooled analysis from these three studies showed a greater significant reduction in the serum urate level in the lesinurad 400 mg in combination with allopurinol group than in the allopurinol group (RR = 2.51, 95% CI = 2.12- 2.98, I2= 36%; Figure 4).



-Risk of bias legend: (A) random sequence generation (selection bias), (B) Allocation concealment (selection bias), (C) blinding of participant and personnel (performance bias), (D) Blinding of outcome assessment (detection bias), (E) incomplete outcome data (attrition bias), (F) selective reporting (reporting bias), (G) other bias

Figure 4: Reduction in serum uric acid less than 6 mg/dL in lesinurad group versus allopurinol group during the follow-up

Gout flares:

Two of the trials reported gout flares, and an overall pooled estimate of these two trials showed a smaller likelihood of having gout flares in the lesinurad 400 mg in combination with allopurinol group than in the allopurinol group (MD=-0.07, 95% CI= -0.08 - -0.05, I2= 0%; Figure 5).

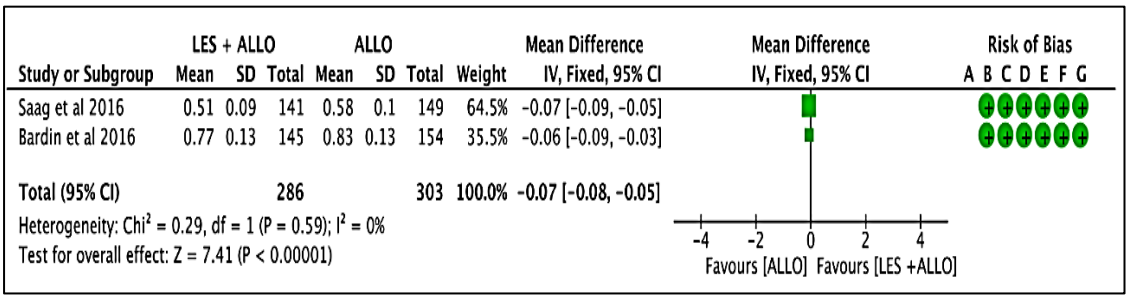


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Figure 5: Presence of gout flares at follow-up in lesinurad group versus allopurinol group

Tophi resolution:

Two of the trials reported tophi resolution; pooled analysis showed that the lesinurad 400 mg in combination with allopurinol group had greater tophus resolution than the allopurinol group, though this result was statistically non-significant (RR=0.79, 95% CI= 0.42-1.49, I2=0%; Figure 6).

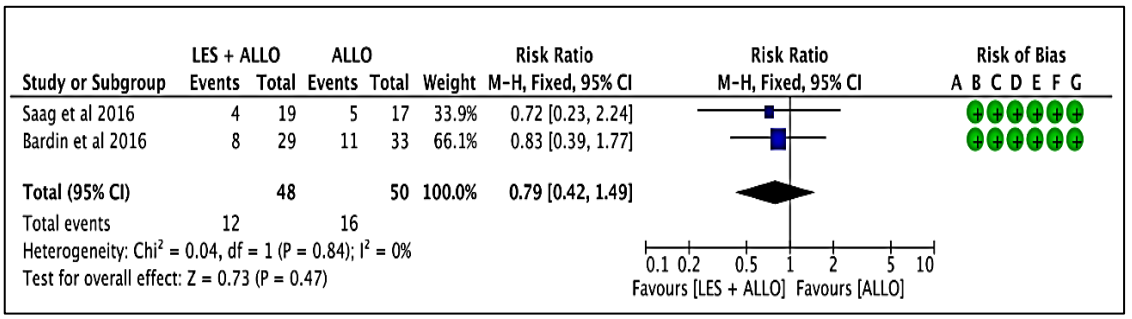

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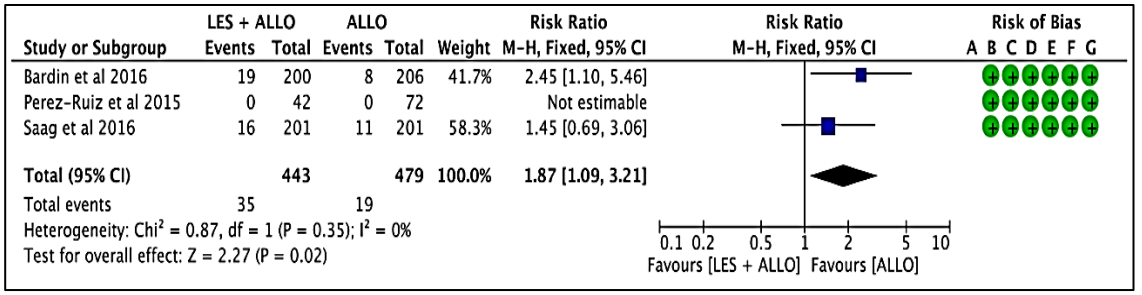
Figure 6: Number of tophus resolution at follow-up in lesinurad group versus allopurinol group

5.2 Pooled results for safety outcomes

Adverse events:

All trials reported any serious treatment emergent adverse event (TEAE), which was defined as any major or non-major adverse cardiovascular (CV) event and any renal and kidney stones adverse event (Appendix 2). Serious TEAE was defined as serious CV events, including non-fatal myocardial infarction, CV deaths, and nonfatal stroke. Overall pooled analysis showed that subjects in the lesinurad 400 mg in combination with allopurinol group had a higher percentage of any serious TEAE than subjects in the allopurinol group (RR=1.87,95% CI= 1.09- 3.21, I2= 0%; Figure 7).



-Risk of bias legend: (A) random sequence generation (selection bias), (B) Allocation concealment (selection bias), (C) blinding of participant and personnel (performance bias), (D) Blinding of outcome assessment (detection bias), (E) incomplete outcome data (attrition bias), (F) selective reporting (reporting bias), (G) other bias

Figure 7: Any serious Treatment Emergent Adverse Events (TEAEs) occur in lesinurad group versus allopurinol group during follow-up period

Withdrawals:

All trials reported the number of subjects who withdrew from the study, but none reported the reasons for withdrawal. Pooled analysis showed a greater percentage of withdrawal in the lesinurad 400 mg in combination with allopurinol group than in the allopurinol group (RR=1.45, 95%= 0.74- 2.83, I2=0%; Figure 8).

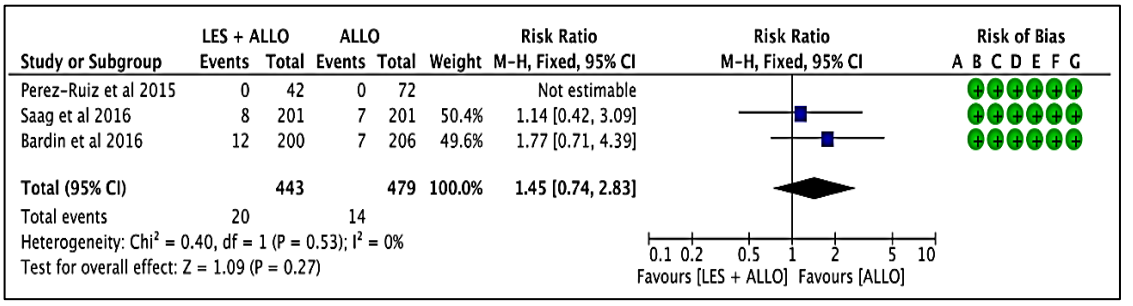


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Figure 8: Number of withdrawal in lesinurad group versus allopurinol group during follow-up period

Deaths:

All trials reported the number of deaths. Pooled analysis showed a significant number of deaths in the lesinurad 400 mg in combination with allopurinol group compared with the allopurinol group (RR=5.15, 95%= 0.25- 106.59; Figure 9).

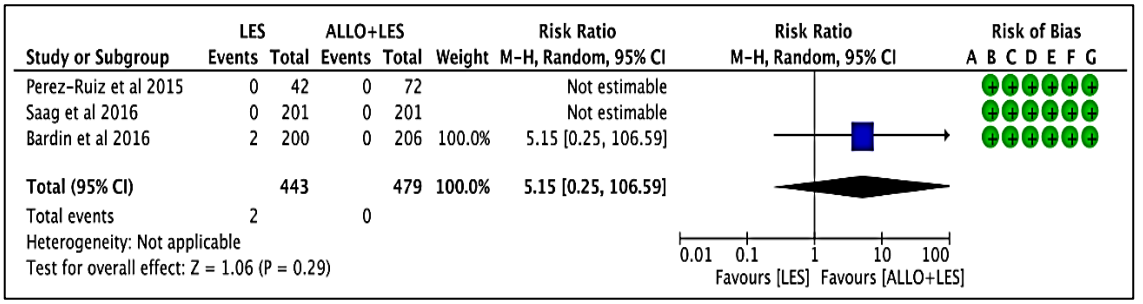

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Figure 9: Number of deaths in lesinurad group versus allopurinol group during follow-up period

6. Discussion

Our systematic review showed a significant reduction in serum urate in the lesinurad 400 mg in combination with allopurinol group compared with that in the allopurinol group. Further, our findings demonstrated a significant reduction in gout flares in the combination group versus allopurinol alone. However, the risk of emergent adverse events was higher in the lesinurad and allopurinol group than in the allopurinol alone group.

Recently new systematic review and meta-analysis was done by Ying Wu.J et al. published in September 2018, the objectives of this study was to assess the efficacy and safety of lesinurad for the treatment of hyperuricemia in patients with gout[11]. Our systematic review evaluates more safety outcomes though it was specifically done in patients taking allopurinol alone versus allopurinol in combination with lesinurad. Ying Wu.J et al, had similar findings as our work with more safety concerns from our part.

Previously published randomized control trials were found, including three randomized control trials that measured the efficacy and safety of lesinurad in combination with allopurinol. The CLEAR 1 study showed a significant increase in the proportion of patients achieving urate targets at six months, with adverse effects similar to those in the allopurinol alone group [6]. Second, the 12-month, randomized, phase III trial drew similar conclusions, demonstrating a considerable increase in the number of patients attaining serum urate targets by six months compared with allopurinol only therapy [7]. Last, the recent randomized, double-blind Phase II study indicated that lesinurad showed clinically and statistically

significant decreases in urate levels in combination with allopurinol compared to allopurinol alone [10]. These data from previous individual studies showed consistent results with our systematic review and meta-analysis and provide evidence that lesinurad in combination with allopurinol has significant efficacy endpoints compared with allopurinol alone.

There are a limited number of medications used as prophylaxis in gout patients compared to the number of medications used to treat gout attacks. Therefore, this systematic and the previously published one by Ying Wu.J et al provides the best available evidence for the efficacy and safety of combining lesinurad with allopurinol as prophylaxis in treating gout patient with inadequate control with xanthine oxidase inhibitor alone. Lesinurad is not yet recommended in recent guidelines; although both systematic reviews and meta-analysis could change the practice of gout management based on the observed efficacy of this medication when combined with allopurinol in reduction of urate level, gout flares and tophus resolution.

This review had several limitations. First, although we recognized a small to moderate heterogeneity in some of the pooled analysis, unfortunately, we could not identify the reasons for this due to the limited number of RCTs published, preventing us from exploring the heterogeneity through either subgroup analyses or meta-regression. Lesinurad was only recently approved for treatment of gout, which explains the low number of available RCTs. One possible explanation for the heterogeneity is the difference in follow-up period duration, which in one of the studies was too short to assess and address the other clinically relevant outcomes, such as gout flares and tophus resolution, although it was able to demonstrate the difference in serum urate level between the lesinurad combined with allopurinol group and the allopurinol group. Nonetheless, it is important to note that we only observed low to moderate heterogeneity in our primary efficacy endpoints, which strengthened the results of this analysis. Second, we were unable to confirm the optimal dose strategy and duration for either lesinurad or allopurinol in cases of renal disease. In addition, our systematic review did not measure the efficacy of lesinurad in combination with allopurinol after six months, as individual studies only included a maximum six months follow-up period. Third, although we tried to identify unpublished studies, we were unable to exclude the possibility of publication bias.

7. Conclusion

This systematic review investigated the use of lesinurad in combination with allopurinol versus allopurinol alone in the treatment of chronic gout with inadequate response to standard therapy. Our findings suggest that the combination therapy of lesinurad with allopurinol results in significant improvement in efficacy outcomes compared with allopurinol alone. However, combination therapy had more adverse events than allopurinol alone. Given the limited number of medications used as prophylaxis in gout patients, this combination therapy could be used to treat adults

with gout with an inadequate response to standard care with emphasis on safety issues and treatment should only be used when necessary. Future trials are needed to demonstrate the efficacy and safety of this combination therapy, specifically for renal disease patients, as recent studies omit renal disease patients. In addition, longer follow-up durations are required to confirm long-term safety and efficacy.

References

[1] Khanna D, Fitzgerald JD, Khanna PP, et al. 2012 American College of Rheumatology Guidelines for Management of Gout. Part 1: Systematic Nonpharmacologic and Pharmacologic Therapeutic Approaches to Hyperuricemia. The American College of Rheumatology; 2012. doi:10.1002/acr.21772

[2] Kuo C-F, Grainge MJ, Zhang W, Doherty M. Global epidemiology of gout: prevalence, incidence and risk factors. Nat Rev Rheumatol. 2015;11(11):649-662. doi:10.1038/nrrheum.2015.91

[3] Neogi T, Th A Jansen TL, Dalbeth N, et al. 2015 Gout Classification Criteria An American College of Rheumatology/European League Against Rheumatism Collaborative Initiative. Vol 67.; 2015. doi:10.1002/art.39254

[4] Arthritis Types | Arthritis | CDC. Centers for Disease Control and Prevention. .

[5] EULAR RECOMMENDATIONS FOR THE MANGMENT OF HYPERURICEMIA IN PATIENTS WITH GOUT. EULAR. 2016. doi:10.20452/pamw.4001

[6] Saag KG, Fitz-Patrick D, Kopicko J, et al. Lesinurad Combined With Allopurinol: A Randomized, Double-Blind, Placebo-Controlled Study in Gout Patients With an Inadequate Response to Standard-of-Care Allopurinol (a US-Based Study). Arthritis Rheumatol. 2017;69(1):203-212. doi:10.1002/art.39840

[7] Bardin T, Keenan RT, Khanna PP, 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. November 2016:annrheumdis-2016-209213. doi:10.1136/annrheumdis-2016-209213

[8] Dalbeth N, Jones G, Terkeltaub R, 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. Ann Rheum Dis. 2015;74(Suppl 2):778.1-778. doi:10.1136/annrheumdis-2015-eular.2182

[9] Zurampic New FDA Drug Approval | CenterWatch. FDA CenterWatch.

[10] Perez-Ruiz F, Sundy JS, Miner JN, et al. Lesinurad in combination with allopurinol: results of a phase 2, randomised, double-blind study in patients with gout with an inadequate response to allopurinol. Ann Rheum Dis. 2016;75(6):1074-1080. doi:10.1136/annrheumdis-2015-207919

[11] Jie-Ying Wu YC. Efficacy and Safety of Lesinurad in Patients with Hyperuricemia Associated with Gout: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Am Coll Clin Pharm. 2018. doi:0.1002/phar.2183
[12] Higgins JPT, Altman DG SJ (Editors). Chapter 8: Assessing Risk of Bias in Included Studies.; 2011. doi:10.1001/jama.2013.109501.Conflict
[13] Talk: Pharmacokinetics, Efficacy and SAFETY of Lesinurad, A NOVEL URAT1 Inhibitor, In Individuals with Mild to Moderate Renal IMPAIRMENT (2011 ACR/ARHP Annual Scientific Meeting).
[14] Talk: Efficacy and SAFETY of Lesinurad (RDEA594), A NOVEL Uricosuric Agent, Given In COMBINATION with ALLOPURINOL In ALLOPURINOL-REFRACTORY Gout PATIENTS: PRELIMINARY RESULTS FROM the RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE 2B Extension STUDY (2011 ACR/ARHP Annual Scientific Meeting).
[15] Tausche A-K, Alten R, Dalbeth N, et al. SAT0307 Lesinurad Monotherapy in Gout Patients Intolerant to Xanthine Oxidase Inhibitors (Light): A Randomized, Double-Blind, Placebo-Controlled, 6-Month Phase III Clinical Trial. Ann Rheum Dis. 2015;74 (Suppl2): 769.1-769. doi:10.1136/annrheumdis-2015-eular.2090
[16] Analysis of Gout Subjects Receiving Lesinurad and Allopurinol Combination Therapy By Baseline Renal Function - ACR Meeting Abstracts.
[17] PRISMA.

List of abbreviations

RCT: Randomized Control Trails
ACR: American College of Rheumatology
EULAR: European League Against Rheumatism
TEAEs: Treatment Emergent Adverse Events
CV: Cardiovascular
RR: Relative Risk
CI: Confidence Intervals

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Conflict of interest*:* *all authors* declare no competing interests.
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APPENDIX 1

EMBASE	
1	Clinical trial
2	Randomized controlled trial
3	Randomization
4	Single blind procedure
5	Double blind procedure
6	Crossover procedure
7	Placebo
8	Randomi?ed controlled trial$
9	Rct
10	Random allocation
11	Randomly allocated
12	Allocated randomly
13	(allocated adj2 random)
14	Single blind$
15	Double blind$
16	Placebo$
17	Prospective study
18	1-18
29	Case study
20	Case report
21	Abstract report or letter
22	20-22
23	19 not 23
24	RDEA 594

25	RDEA-594
26	RDEA594
27	Lesinida
28	Lesinurad
29	ZURAMPIC
30	ZINC84757007
31	AKOS027327368
32	AK323774
33	GTPL7673
34	878672-00-5
35	UNII-09ERP08I3W
36	09ERP08I3W
37	Zurampicreg
38	C17H14BrN3O2S
39	SCHEMBL842962
40	W-5949
41	D09921
42	SC-94287
43	KB-78121
44	GTPL7673
45	HE067018
46	MFCD22572730
47	3777AH
48	MolPort-039-138-666
49	FGQFOYHRJSUHMR-UHFFFAOYSA-N
50	CS-1389
51	CHEMBL2105720
52	CHEBI:90929
53	HY-15258
54	Zyloprim
55	Uripurinol
56	adenock
57	4-HPP
58	HPP
59	BW-56-158
60	AL-100
61	Allopurinol
62	Allopurinolum
63	Alopurinol
64	NSC 1390
65	NSC 101655
66	Cellidrin
67	Lopurin
68	Allopur

69	Adenock
70	Zyloric
71	Milurit
72	Embarin
73	Urosin

APPENDIX 2

Renal-related Treatment Emergent Adverse Events (TEAEs)

Acute prerenal failure
Anuria
Azotemia
Blood creatinine abnormal
Blood creatinine increased
Blood urea abnormal
Blood urea increased
Blood urea nitrogen/creatinine ratio increased
Creatinine renal clearance abnormal
Creatinine renal clearance decreased
Cystatin C abnormal
Cystatin C increased
Glomerular filtration rate abnormal
Glomerular filtration rate decreased
Hypercreatininemia
Inulin renal clearance abnormal
Inulin renal clearance decreased
Nephropathy
Nephropathy toxic
Obstructive uropathy
Oliguria
Postrenal failure
Renal cortical necrosis
Renal failure
Renal failure acute
Renal failure chronic
Renal function test abnormal
Renal impairment
Renal injury
Renal papillary necrosis
Renal tubular atrophy
Renal tubular disorder
Renal tubular necrosis
Urate nephropathy
Urea renal clearance decreased
Urine output decreased

Kidney Stone TEAEs

Calculus bladder
Calculus ureteric
Calculus urethral
Calculus urinary
Nephrolithiasis
Renal stone removal
Stag horn calculus
Ureteric calculus removal
Ureterolithotomy
Urinary calculus removal
Urinary stone analysis

Major adverse cardiovascular events (MACE)

All deaths (both CV and non-CV deaths)
Nonfatal myocardial infarction
Nonfatal stroke

Non-major adverse cardiovascular events (non-MACE)

Unstable angina with urgent coronary revascularization
Cerebral revascularization (elective and non-elective)
Hospitalized congestive heart failure
Arrhythmias not associated with ischemia
Venous and peripheral arterial vascular thrombotic events (e.g. pulmonary embolism, deep venous thrombosis, arterial dissection, thrombosis and peripheral arterial ischemia)
Transient ischemic attack