National Institute for Health and Care Excellence

Guideline version (Final)

Gout: diagnosis and management

[G] Evidence reviews for urate-lowering therapies for the long-term management of gout

NICE guideline NG219

Evidence reviews underpinning recommendations 1.5.8 to 1.5.10 in the NICE guideline

June 2022

Final

National Institute for Health and Care Excellence

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1.1 Review question: In people with gout (including people with gout and chronic kidney disease), which urate-lowering therapies (either alone or in combination with each other) are the most clinically and cost effective for first-line treatment and second-line treatment if first line is not tolerated or provides inadequate control?

1.1.1 Introduction

Gout is an inflammatory crystal arthritis characterised by hyperuricaemia and deposition of monosodium urate crystals (MSU) into joints and soft tissues. It manifests clinically as acute, intermittent, debilitating joint and soft tissue flares. If hyperuricaemia in people with gout is left untreated over time, flares can increase in frequency with more joints recruited and affected and tophi (nodular masses of MSU crystals) can deposit in joints and soft tissues resulting in irreparable erosive damage and disability.

Urate lowering therapy (ULT) results in suppression of serum uric acid (SUA) and dissolution of deposited MSU crystals and tophi. Long-term ULT prevents acute, painful gouty episodes and formation of tophi with associated disability and can result in cure of gout if used early and effectively in the condition. ULT are usually offered to people who have had 2 or more acute gout flares; people with tophi; people with gout and chronic kidney disease and people with evidence of gouty erosive changes or tophaceous deposition on imaging.

In current UK practice, allopurinol is used as first line ULT and febuxostat as second line when allopurinol is not tolerated or contraindicated. Rasburicase is not specifically licenced for the management of gout, however, it has the potential to reduce serum uric acid levels. Amlodipine, fenofibrate, losartan and Vitamin C have been reported to reduce serum urate levels, but it is unclear if they have a role in gout. This review evaluates which ULT is effective as first-line and second line treatment.

1.1.2 Summary of the protocol

For full details see the review protocol in Appendix A.

Table 1: PICO characteristics of review question – first-line treatment

Population	Inclusion: Adults (18 years and older) with gout using Urate Lowering Therapies (ULT) as first-line treatment Strata: • People with CKD (stage 3) • People with CKD (stages 4-5) • People without CKD or people with CKD stages 1-2 • Mixed population (people with CKD and people without CKD) Exclusion: People with calcium pyrophosphate crystal deposition, including pseudogout.

Intervention(s)	Urate lowering therapies (commonly used in clinical practice in the UK) Xanthine oxidase inhibitors • Allopurinol (dosages separated by severity of gout – mild, moderate and severe) • Febuxostat 80mg and 120mg (analysed separately) Uricosuric therapies • Amlodipine • Fenofibrate • Losartan • Vitamin C Uricase therapies • Rasburicase • Combine all doses (doses much higher or lower than standard doses will be excluded). Dosages used in the UK are detailed in the methodology anything outside of these would be excluded. Febuxostat 80mg and 120mg will be analysed separately. • Combinations of pharmacological interventions This guideline will be updating and replacing the TA on febuxostat (TA164) - evidence included in this review will be relevant for this.
Comparison(s)	• Compared to each other, including within drug classes • Standard care (dietary advice, lifestyle modifications, prophylaxis for flares) • No treatment • Placebo

Outcomes	All outcomes are considered equally important for decision making and therefore have all been rated as critical:
	• health-related quality of life (e.g. as described by SF-36, Gout Assessment Questionnaire (GAQ) and the Gout Impact Scale (GIS) or other validated gout-specific HRQoL measures
	• pain (measured on a visual analogue scale (VAS) or numerical rating scale such as the five-point Likert scale, or reported as pain relief of 50% or greater)
	• joint swelling/joint inflammation
	• joint tenderness
	• frequency of flares
	• patient global assessment of treatment success (response to treatment) (e.g. Likert scales, visual analogue scales (VAS), numerical ratings scales (NRS))
	• adverse events – (1) cardiovascular, (2) renal and (3) gastrointestinal (e.g. diarrhoea) (Total adverse events will be reported if the specific types of adverse events are not reported)
	• adverse events and complications of gout:
	  ○ radiographic joint damage
	  ○ renal stones

	○ tophi • serum urate levels • admissions (hospital and A&E) • GP visits Timepoints: short-term (less than three months), medium-term (three to 12 months) and long-term (more than 12 months) duration
Study design	RCT Systematic reviews of RCTs If insufficient RCT evidence is available (no or little evidence for interventions/comparisons), search for non-randomised studies (prospective and retrospective cohort studies will be considered if they adjust for key confounders: • Age • Gender Published NMAs will be considered for inclusion.

Table 2: PICO characteristics of review question – second-line treatment

Population	Inclusion: Adults (18 years and older) with gout who have used urate-lowering therapies (ULT) as second-line treatment but urate levels are inadequately controlled or first-line treatment is not tolerated Strata: ULT inadequately controlled • People with CKD (stage 3) – inadequately controlled • People with CKD (stages 4-5) – inadequately controlled • People without CKD or people with CKD stages 1-2 – inadequately controlled • Mixed population (people with CKD and people without CKD) – inadequately controlled ULT not tolerated • People with CKD (stages 3) – not tolerated • People with CKD (stage 4-5) – not tolerated • People without CKD or people with CKD stages 1-2 – not tolerated • Mixed population (people with CKD and people without CKD) – not tolerated Exclusion: People with calcium pyrophosphate crystal deposition, including pseudogout.
Intervention(s)	Urate lowering therapies (commonly used in clinical practice in the UK): Xanthine oxidase inhibitors • Allopurinol (dosages separated by severity of gout – mild, moderate and severe) • Febuxostat 80mg and 120mg (analysed separately) Uricosuric therapies • Amlodipine • Fenofibrate • Losartan • Vitamin C

	Uricase therapies • Rasburicase • Combine all doses (doses much higher or lower than standard doses will be excluded). Dosages used in the UK are detailed in the methodology anything outside of these would be excluded. Febuxostat 80mg and 120mg will be analysed separately. • Combinations of pharmacological interventions • Within drug class comparisons will be made
Comparison(s)	• Compared to each other • Standard care (dietary advice, lifestyle modifications, prophylaxis for flares) • No treatment • Placebo

Outcomes	All outcomes are considered equally important for decision making and therefore have all been rated as critical:
	• health-related quality of life (e.g. as described by SF-36, Gout Assessment Questionnaire (GAQ) and the Gout Impact Scale (GIS) or other validated gout-specific HRQoL measures
	• pain (measured on a visual analogue scale (VAS) or numerical rating scale such as the five-point Likert scale, or reported as pain relief of 50% or greater)
	• joint swelling/joint inflammation
	• joint tenderness
	• frequency of flares
	• patient global assessment of treatment success (response to treatment) (e.g. Likert scales, visual analogue scales (VAS), numerical ratings scales (NRS))
	• adverse events – (1) cardiovascular, (2) renal and (3) gastrointestinal (e.g. diarrhoea) (Total adverse events will be reported if the specific types of adverse events are not reported)
	• adverse events and complications of gout:
	  ○ radiographic joint damage
	  ○ renal stones
	  ○ tophi
	• serum urate levels
	• admissions (hospital and A&E)
	• GP visits
	Timepoints: short-term (less than three months), medium-term (three to 12 months) and long-term (more than 12 months) duration

Study design	RCT Systematic reviews of RCTs If insufficient RCT evidence is available (no or little evidence for interventions/comparisons), search for non-randomised studies (prospective and retrospective cohort studies will be considered if they adjust for key confounders: • Age • Gender Published NMAs will be considered for inclusion.

1.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in Appendix A and the methods document.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

1.1.4 Effectiveness evidence

1.1.4.1 Included studies

In total seventeen randomised controlled trials were included in the review[9-11, 28, 42, 48, 53, 65, 78, 91, 96, 100, 119, 122, 129, 136, 137] these are summarised in **Table 3** to **Table 5** below. Evidence from these studies is summarised in the clinical evidence summary below (**Table 6** to **Error! Reference source not found.**).

The studies all evaluated either Allopurinol and/or Febuxostat, no randomised controlled trials were identified for uricosuric or uricase therapies. The committee did not wish to look at cohort studies as a basis for their recommendations where there was more robust evidence (RCTs) for some interventions. The studies are presented by line of treatment. First line included people with gout who had not used urate lowering therapy prior to the study, or where previous ULT was not mentioned (n=5). Second line involved people who had used urate lowering therapy prior to the study (n=2). In addition, there is an unclear or mixed treatment line category with studies that include both first and second line treatments, most had a washout of previous drugs but did not detail the number of patients who had this (n=10). This category was created because most of the studies did not fit into the first line or second line treatment categories and there were few of these to inform the review.

Studies were stratified by CKD status (Stage 3 CKD, No CKD and mixed CKD). As Allopurinol has a very wide range of possible dosages (100mg – 900mg) and these were stratified, according to the BNF definition of gout severity equating to treatment dose provided (mild conditions 100-200mg, moderately severe conditions 300-600mg and 700-900mg for severe conditions). However, most studies included 300mg. Only 80mg and 120mg Febuxostat were included in the review as these are the only dosages available in the United Kingdom.

First-line treatment:

Non-CKD population (n=4)

One study[119] evaluated allopurinol 300mg versus placebo in a non-CKD population. It should be noted that in this study allopurinol was initiated during a flare. Two studies[122,137] evaluated allopurinol 300mg versus febuxostat 80mg in a non-CKD population, one study[54] evaluated febuxostat 80mg versus placebo in a non-CKD population. (Tables 6-8)

Mixed CKD population (n=1)

One study[48] evaluated allopurinol 100 to 200mg versus placebo in a mixed CKD population. The study excluded people with GFR <50mL/min, whereas <60mL/min is considered to be stage 3 CKD. Allopurinol was also initiated during a flare in this study. (Table 9)

Unclear or mixed treatment line:

Stage 3 CKD population (n=1)

One study[42] evaluated febuxostat 80mg versus placebo in a stage 3 CKD population.

Non-CKD population (n=1)

One study included allopurinol 300mg compared to Febuxostat 80mg in a non-CKD population.[129]

Mixed CKD population (n=10)

Two studies[65,100] evaluated allopurinol 300mg versus placebo, but they either did not report the same outcomes or at the same time-points, so were not meta-analysed. Five studies[11, 9, 53, 100,136] evaluated allopurinol 300mg versus febuxostat 80mg in a mixed CKD population, one of these studies[9] evaluated allopurinol at 200mg for those with moderate renal impairment, and 300mg for those without, but as 80% of the population received 300mg this paper was meta-analysed, where appropriate, with the other 300mg allopurinol studies. Three studies[11, Kim, 2014 #555, Schumacher, 2008 #503, evaluated allopurinol 300g versus febuxostat 120mg in a mixed CKD population, and one study[28] included allopurinol 300-600mg versus febuxostat 80 or 120mg using a treat-to-target protocol in a mixed CKD population. Four studies[10, 65, 96, 100] evaluated febuxostat 80mg versus placebo in a mixed CKD population. Three studies[10,Kim, 2014 #555,Schumacher, 2008 #503] evaluated febuxostat 120mg versus placebo in a mixed CKD population.

Second-line treatment:

Non-CKD population (n=1)

One study (Poiley 2016)[91] evaluated allopurinol 300mg versus placebo in a non-CKD population. It should be noted that this study was assessing Arhalofate and was a 5-arm trial but only the relevant comparators, Allopurinol and placebo, were included in this review.

Mixed CKD population (n=1)

One study (Mackenzie 2020)[78] compared allopurinol with a mixed dose (279 mg on average) versus febuxostat mixed dose (81 mg on average) in a mixed CKD population. After randomisation different doses of allopurinol were used: 10% of the patients used 100 mg, 23.3% of the patients used 200 mg, 50.9% used 300 mg, 11.9% used 400 mg, 3.9% of the patients used 500 to 900mg.

1.1.4.2 Excluded studies

Three Cochrane reviews were excluded.[69, 102, 118] Kydd 2014[69] was excluded because the studies included in the review used comparisons not relevant to this review protocol: benzbromarone versus allopurinol; benzbromarone versus probenecid and probenecid versus allopurinol. Seth 2014[102] was excluded as the review included non-randomised controlled studies, which were combined in the analyses with the randomised studies. Furthermore, its analysis was not stratified by CKD status, therefore non-CKD and CKD were combined in the analysis (Taylor 2012[119] and Schumacher 2008)[100]. Tayar 2012[118] was excluded because it included different doses of Febuxostat to that included in our review (because they are not used in clinical practice in the UK). The analyses at the relevant Febuxostat dosage (80mg or 120mg) did not include Saag 2019[96] as it was subsequently published to the Cochrane review. Furthermore, the analyses were not stratified by CKD nor by line of treatment.

See the excluded studies list in Appendix J.

1.1.5 Summary of studies included in the effectiveness evidence

Table 3: Summary of studies for first-line treatment

Study	Intervention and comparison	Population	Outcomes	Comments
Hill 201548	Intervention (n=16) Allopurinol for mild gout 100-200mg. Allopurinol initiated at 100mg daily for the first 14 days, and then increased to 200mg daily for the next 14 days. Duration 28 days. Concurrent medication/care: People were treated for acute gout as deemed appropriate by their referring physician. Each person was treated with prophylactic oral colchicine 0.6mg daily for the first 2 days, then 0.6mg twice daily from days 3-28. Dose reductions to 0.6mg daily were made for concomitant statin use or gastrointestinal intolerance. People unable to take colchicine because of prior adverse reactions received 15mg oral meloxicam daily for prophylaxis during allopurinol initiation. Comparison (n=19) Placebo. Duration 27 days. Concurrent medication/care: People were treated for acute gout as deemed appropriate by their referring physician. Each person was treated with	n=37 People with an acute gout attack were considered if they met at least 1 of the following additional criteria for starting urate-lowering therapy: the presence of gouty tophi; more than 1 acute gout attack per year; a history of nephrolithiasis; urate overproduction (>1000mg in 24-hour urine collection) Age – mean years (range): 56.6 (31-84). Gender (M:F): allopurinol group 14:2; placebo group 16:0 Ethnicity: Not stated Country: USA	Joint tenderness at 28 days Joint inflammation at 28 days Adverse events (withdrawal due to adverse events) at 28 days	CKD - mixed population (people with CKD and people without CKD) – having GFR under 50ml was exclusion criterion. Enrolled people during gout flares: within 72 hours of starting flare treatment

Study	Intervention and comparison	Population	Outcomes	Comments
	prophylactic oral colchicine 0.6mg daily for the first 2 days, then 0.6mg twice daily from days 3-28. Dose reductions to 0.6mg daily were made for concomitant statin use or gastrointestinal intolerance. People unable to take colchicine because of prior adverse reactions received 15mg oral meloxicam daily for prophylaxis during allopurinol initiation.			
Huang 202054	Intervention (n=78) Febuxostat 80mg dissolved in 200 ml water once daily for 24 weeks. Comparison (n=78) Placebo dissolved in 200 ml water once daily for 24 weeks.	n=156 Chinese Han patients with gout and hyperuricaemia (at screening sUA ≥8mg/dl) Age – mean years (SD): Febuxostat group 42.83 (11.65), placebo group 43.33 (10.17) Gender (M:F): not reported Ethnicity: Chinese Han Country: China	Serum urate levels (number of patients achieving sUA <6mg/dL) at 2 months and 6 months Serum urate levels (number of patients achieving sUA <5mg/dL) at 2 months and 6 months	No CKD - People without CKD or people with CKD stages 1-2. People with nephropathy were excluded (25% in the allopurinol and 5% in the placebo group had nephrolithiasis).
Taylor 2012119	Intervention (n=31) Allopurinol 300mg. Duration 10 days. Concurrent medication/care: In addition to the 10-day course of allopurinol or placebo, all patients received	n=57 Patients presenting within 7 days of onset of an acute gout attack were evaluated, and American College of	Frequency of flares at 30 days Gastrointestinal adverse events (colchicine reductions	No CKD - People without CKD or people with CKD stages 1-2 Enrolled people during gout flares: within 7 days of flare onset

Study	Intervention and comparison	Population	Outcomes	Comments
	indomethacin 50 mg 3 times per day for 10 days and colchicine 0.6 mg 2 times per day for 90 days. All patients were started on open-label allopurinol 300 mg daily on day 11 and followed for 30 days Comparison (n=26) Placebo. Duration 10 days. Concurrent medication/care: In addition to the 10-day course of allopurinol or placebo, all patients received indomethacin 50mg 3 times per day for 10 days and colchicine 0.6 mg 2 times per day for 90 days. All patients were started on open-label allopurinol 300 mg daily on day 11 and followed for 30 days	Rheumatology criteria for acute arthritis of gout were met, including the presence of monosodium urate crystals on arthrocentesis of the primary joint on the day of study entry Age – mean years (SD): allopurinol group 57(14), placebo group 61(11) Gender): all male – 51(100%) Ethnicity: not stated Country: USA	due to gastrointestinal symptoms) at 30 days	
Wang 2018122	Intervention (n=80) Febuxostat 80mg once a day. Duration 6 months. Concurrent medication/care: Both groups were given information with health publicity and education, including a diet program, advice on quitting smoking and alcohol, reducing the intake of high purine foods, such as animal organs, seafood and soy products, avoiding excessive exercise, and maintaining good sleep Comparison (n=80)	n=160 people meeting the diagnostic criteria of acute gouty arthritis of the American College of Rheumatology, history of gout attack; in the gout remission period before admission; signed formal informed consent Age – mean years (SD): 61.7 (3.7). Gender (M:F): 88:72	Frequency of flares (acute gout attack rate) at 6 months Gastrointestinal adverse events at 6 months Blood uric acid at 3 and 6 months Serum urate levels (number of patients achieving sUA <6mg/dL) at <3 months and 3-12 months	No CKD - People without CKD or people with CKD stages 1-2

Study	Intervention and comparison	Population	Outcomes	Comments
	Allopurinol 100mg three times a day. Duration 6 months. Concurrent medication/care: Both groups were given information with health publicity and education, including a diet program, advice on quitting smoking and alcohol, reducing the intake of high purine foods, such as animal organs, seafood and soy products, avoiding excessive exercise, and maintaining good sleep.	Ethnicity: not stated Country: China		
Zhang 2019137	Intervention (n=200) Allopurinol for moderate gout 300-600mg. Allopurinol 300mg (up titrated with 100mg/day for weeks 1-2, 200mg/day for weeks 3-4, and 300mg/day from weeks 5-24). Duration 24 weeks (19 weeks at target dose). Concurrent medication/care: Subjects were prohibited from taking any uric acid-reducing medication or any drugs for the prophylaxis of gout flares, such as colchicine, during the study. Subjects who took one or more prohibited medications during the 2 weeks prior to providing informed consent underwent a washout period of at least 2 weeks prior to randomisation Comparison (n=201) Febuxostat 80mg (up titrated from 20mg/day during weeks 1-	n=599 men or women aged between 18 and 85 years, with serum urate levels of >7.0mg/dL with a history of gout, serum urate levels of at least 8.0mg/dL with complications defined as the need for pharmacologic or other treatment for lithangiuria, hypertension, hyperlipidaemia, or abnormal glucose tolerance) or serum urate levels of at least 9.0mg/dL without complications Age – mean years (SD): 47.3 (12.7) Gender (M:F): 546:7 Ethnicity: All subjects were of Asian race	Frequency of flares at 24 weeks Renal adverse events at 24 weeks	No CKD - People without CKD or people with CKD stages 1-2

Study	Intervention and comparison	Population	Outcomes	Comments
	4, 40mg/day weeks 5-8, 60mg/day weeks 9-16 and finally 80mg/day weeks 17-24). Duration 24 weeks (7 weeks at target dose). Concurrent medication/care: Subjects were prohibited from taking any uric acid-reducing medication or any drugs for the prophylaxis of gout flares, such as colchicine, during the study. Subjects who took one or more prohibited medications during the 2 weeks prior to providing informed consent underwent a washout period of at least 2 weeks prior to randomisation.	Country: China		

Table 4: Summary of studies included in the evidence review for mixed treatment line (first and second line)

Study	Intervention and comparison	Population	Outcomes	Comments
Becker 200511	Intervention (n=40) Febuxostat 80mg/day. Duration 28 days. Concurrent medication/care: Colchicine prophylaxis, 0.6mg twice daily, was provided during the washout period and the first 2 weeks of double-blind treatment. Acute flares of gout occurring after the prophylaxis phase were treated at the investigator's discretion.	n=153 People fulfilling the American College of Rheumatology preliminary criteria for the classification of the acute arthritis of primary gout Age – mean years (SD): 54.0 (12.8) Gender (M:F): 136:17 Ethnicity (% Caucasian otherwise not stated):	Frequency of flares at 28 days Gastrointestinal adverse events at 28 days Serum urate levels (number of patients achieving sUA <6mg/dL) at 3-12 months Serum urate levels (number of patients achieving sUA <5mg/dL) at 3-12 months	CKD – mixed population (people with CKD and people without CKD)

Study	Intervention and comparison	Population	Outcomes	Comments
	Intervention (n=38) Febuxostat 120mg/day. Duration 28 days. Concurrent medication/care: Colchicine prophylaxis, 0.6mg twice daily, was provided during the washout period and the first 2 weeks of double-blind treatment. Acute flares of gout occurring after the prophylaxis phase were treated at the investigator's discretion. Comparison (n=38) Placebo. Duration 28 days. Concurrent medication/care: Colchicine prophylaxis, 0.6mg twice daily, was provided during the washout period and the first 2 weeks of double-blind treatment. Acute flares of gout occurring after the prophylaxis phase were treated at the investigator's discretion.	Febuxostat (80mg) group - 88%, febuxostat (120mg) - group 89%, placebo group – 84% Country: USA	Serum urate levels (number of patients achieving sUA <4mg/dL) at 3-12 months	
Becker 200510	Intervention (n=257) Febuxostat 80mg/day. Duration 12 months. Concurrent medication/care: Prophylaxis (250mg of naproxen twice daily or 0.6mg of colchicine once daily) was administered to all	n=762 Adults with gout and a serum urate concentration of at least 8.0mg/dL (480 micromol/L). Age – mean years (SD): 51.8 (12.1)	Frequency of flares at 8 weeks Gastrointestinal adverse events at 12 months Tophus change at 12 months	CKD - mixed population (people with CKD and people without CKD)

Study	Intervention and comparison	Population	Outcomes	Comments
	patients during the washout period and the first eight weeks of double-blind treatment. Subsequent flares of gout were treated at the investigators' discretion. Intervention 2 (n=251) Febuxostat 120mg/day. Duration 12 months. Concurrent medication/care: Prophylaxis (250mg of naproxen twice daily or 0.6mg of colchicine once daily) was administered to all patients during the washout period and the first eight weeks of double-blind treatment. Subsequent flares of gout were treated at the investigators' discretion. Comparison (n=254) Allopurinol 300mg/day. Duration 12 months. Concurrent medication/care: Prophylaxis (250mg of naproxen twice daily or 0.6mg of colchicine once daily) was administered to all patients during the washout period and the first eight weeks of double-blind treatment. Subsequent flares of gout were treated at the investigators' discretion.	Gender (M:F): 729:31 Ethnicity: White = 587 (77%), Black = 62 (8%), Hispanic = 58 (8%, Asian = 25 (3%), Other = 28 (4%) Country: Canada and USA	Serum urate level at 12 months Serum urate levels (number of patients achieving sUA <6mg/dL) at 3-12 months	

Study	Intervention and comparison	Population	Outcomes	Comments
Becker 20109	Intervention (n=756) Allopurinol 200mg-300mg (610 received 300mg, while 145 received 200mg). Duration 6 months. Concurrent medication/care: During a 30-day washout period for subjects receiving prior urate lowering therapy and throughout the subsequent six month treatment period for all subjects, prophylaxis for gout flares was given either as colchicine 0.6mg daily or naproxen 250mg twice daily. All subjects receiving naproxen prophylaxis also received lansoprazole 15mg daily. People with eCLcr <50mL/min were not to receive naproxen Comparison (n=756) Febuxostat 80mg. Duration 6 months. Concurrent medication/care: During a 30-day washout period for subjects receiving prior urate lowering therapy and throughout the subsequent six month treatment period for all subjects, prophylaxis for gout flares was given either as colchicine 0.6mg daily or naproxen 250mg	n=2269 included Age – mean years (SD): 52.8 (11.7). Gender (M:F): 2141:128 Ethnicity: American Indian or Alaska native - 22 (0.97%) Asian – 88 (3.88%) Black or African American – 228 (10.05%) Native Hawaiian or other Pacific islander – 32 (1.4%) White – 1863 (0.82%) Other – 34 (1.49% Missing – 2 (0.09%) Country: USA	Cardiovascular adverse events at 6 months Gastrointestinal adverse events at 6 months Serum urate levels (number of patients achieving sUA <6mg/dL) at 3-12 months	CKD - mixed population (people with CKD and people without CKD)

Study	Intervention and comparison	Population	Outcomes	Comments
	twice daily. All subjects receiving naproxen prophylaxis also received lansoprazole 15mg daily. People with eCLcr <50mL/min were not to receive naproxen			
Desideri, 202128	(n=98) Intervention 1: Xanthine oxidase inhibitor - Allopurinol for moderate gout 300-600mg. Allopurinol 100 up to 600 mg/day Allopurinol 100/300 mg tablets. The initial daily allopurinol dose is 100 mg given orally, to be escalated of 100 mg every 2 weeks in patients with serum urate concentration >6 mg/dl, depending on kidney function and tolerability (permitted between week 2 and week 10 for patients who did not reach the target SUA of <6mg/dL). The maximum dose of allopurinol achievable in the study depended on kidney function and tolerability, but did not exceed 600 mg daily. Comparison (n=99) Intervention 2: Xanthine oxidase inhibitor - Febuxostat 80mg. Febuxostat 80/120 mg/day	n=197 Age - Mean (range): 59.6 (30-83) years. Gender: 82.1% male. Ethnicity: NR Country: Germany, Italy, Netherlands, Poland, Romania, Serbia	Number of people achieving SUA concentrations of ≤6mg/dL at Week 36 (protocol outcome: Serum urate levels at medium (3 to 12 months) Treatment emergent adverse events	Treat to target intervention and comparison. CKD - No CKD - People without CKD or people with CKD stages 1-2 Mixed line- some had used ULT previously. Number of patients achieving SUA concentrations of ≤6mg/dL was reported at 12, 12 and 36 weeks (all medium term timepoint), only the longest timepoint has been reported. Open label study; outcome assessor blinded.

Study	Intervention and comparison	Population	Outcomes	Comments
	Febuxostat 80/120 mg film coated tablets. The initial daily dose was 80 mg given orally. In case a patient had a serum urate level 6 mg/dl after 2 weeks of treatment the dose was escalated to 120mg and if tolerated was maintained during the study treatment period.			
Gunawardhana 201842	Intervention (n=37) Febuxostat 80mg immediate release. Duration 3 months. Concurrent medication/care: All people systematically received gout flare prophylaxis for the duration of double-blind treatment from day 1 to the end of treatment, including colchicine 0.6mg every other day. However, if colchicine was contraindicated or not tolerated, naproxen (250mg BID) or other NSAIDs or prednisone were permitted at the investigator's discretion. Comparison (n=38) Placebo. Duration 3 months. Concurrent medication/care: All people systematically received gout flare prophylaxis for the duration of double blind treatment from day 1 to the end of	n=189 Men and women (aged at least 18 years) who: provided informed consent; had a history or presence of gout based on criteria defined by the American Rheumatism Association; had a serum urate level at least 8.0 mg/dL at the day 4 screening visit or at the retest visit; had moderate renal impairment as defined by an eGFR (modification of diet in renal disease) at least 30 and <60mL/min at screening visit on day 21 for patients on urate lowering therapy and on day 4 for people not on urate lowering therapy at the test visit; had a self-reported history of at least 1 gout flare within the 12 months prior to the screening visit	Frequency of flares at 3 months Cardiovascular adverse events, Renal/urinary adverse events at 3 months Gastrointestinal adverse events at 3 months Serum urate levels (number of patients achieving sUA <6mg/dL) at 3 months	CKD – stage 3 CKD. This study explored extended release Febuxostat versus immediate release Febuxostat. There was a 3-week screening/washout period.

Study	Intervention and comparison	Population	Outcomes	Comments
	treatment, including colchicine 0.6mg every other day. However, if colchicine was contraindicated or not tolerated, naproxen (250mg BID) or other NSAIDs or prednisone were permitted at the investigator's discretion.	Age – mean years (SD): 63.1(11.5) Gender (M:F): 134:55 Ethnicity: White = 126 (66.66%), Black or African American = 46 (24.33%) Country: USA		
Huang 201453	Intervention (n=172) Allopurinol 300mg/day. Duration 28 weeks. Concurrent medication/care: People previously on a urate lowering therapy underwent a 2 week washout period before undergoing randomisation Comparison (n=172) Febuxostat 80mg/day. Duration 28 weeks. Concurrent medication/care: People previously on a urate lowering therapy underwent a 2 week washout period before undergoing randomisation	n=516 People aged 18-70 years with a diagnosis of gout fulfilling the American Rheumatology Association's preliminary criteria and with serum urate of at least 8.0mg/dL Age – mean years (SD): 46.7 (11.2). Gender (M:F): 504:12 Ethnicity: Not stated Country: China	Gout flares (subjects requiring treatment for acute gout flares) at 28 weeks Renal adverse events at 28 weeks Gastrointestinal disorders at 28 weeks Change in number of tophi at 28 weeks Serum urate level at 28 weeks	CKD - mixed population (people with CKD and people without CKD)
Kim 201465	Intervention (n=36) Febuxostat 80mg. Febuxostat 80mg/day. Duration 4 weeks. Intervention 2 (n=38)	n=179 Meeting the preliminary criteria for the American College of Rheumatology for gout and had serum urate	Serum urate levels at 4 weeks	CKD – mixed population (people with CKD and people without CKD)

Study	Intervention and comparison	Population	Outcomes	Comments
	Febuxostat 120mg/day. Duration 4 weeks Intervention 2 (n=38) Allopurinol 300mg/day. Duration 4 weeks. Comparison (n=39) Placebo. Duration 4 weeks.	concentration of at least 8.0mg/dL at screening Age – mean years (SD): 50.0 (11.8) Gender (M:F): 179:0 Ethnicity: Not stated Country: South Korea		
Saag 201996	Intervention (n=357) Febuxostat 80mg. Febuxostat 80mg immediate release orally once daily for 3 months. Duration 3 months. Comparison (n=357) Placebo orally once a day for 3 months. Duration 3 months	n=1783 Age at least 18 years; a history or presence of gout; a serum urate level of at least 8.0 mg/dL on the day 4 screening visit; at least 1 gout flare within 12 months prior to screening; eGFR of at least 15mL/min at screening, and at least 30% should have moderate-to-severe renal impairment. Age – mean years (SD): 55.1 (11.7) Gender (M:F): 1577:206 Ethnicity: White = 1147 (64.33%), Black/African American = 474 (26.58%) American Indian or Alaska native – 7 (0.39%),	Frequency of flares at 3 months Cardiovascular adverse events at 3 months Gastrointestinal adverse events at 3 months Serum urate levels (number of patients achieving sUA <6mg/dL) at 3-12 months Serum urate levels (number of patients achieving sUA <5mg/dL) at 3-12 months	CKD - mixed population (people with CKD and people without CKD)

Study	Intervention and comparison	Population	Outcomes	Comments
		Asian – 112 (6.28%) Native Hawaiian or other pacific islander – 20 (1.12%) Other – 23 (1.29%) Country: USA		
Schumacher 2008100	Intervention (n=267) Febuxostat 80mg a day. Duration 28 weeks. Concurrent medication/care: A washout of previous therapy for a period of 2 weeks was achieved with people being offered either colchicine 0.6mg once daily or naproxen 250mg twice daily during the period. They were continued for the first 8 weeks of the study. Intervention 2 (n=269) Febuxostat 120mg a day. Duration 28 weeks. Concurrent medication/care: A washout of previous therapy for a period of 2 weeks was achieved with people being offered either colchicine 0.6mg once daily or naproxen 250mg twice daily during the period. They were continued for the first 8 weeks of the study. Intervention 3 (n=269)	n=1072 People of either sex and 18-85 years of age, inclusive, with gout (defined by the American College of Rheumatology preliminary criteria), hyperuricemia (defined for this study as a serum urate level of at least 8.0mg/dL) and normal (serum creatinine level no more than 1.5mg/dL) or impaired (serum creatinine level >1.5 to no more than 2.0mg/dL) renal function at day -2 Age – mean years (SD): 51.8 (12.2) Gender (M:F): 1005:67 Ethnicity: White = 835 (77.89%), Minority = 237 (22.11%) Country: USA	People requiring treatment for gout flare at 8 weeks Cardiovascular adverse events at 28 weeks Gastrointestinal adverse events at 28 weeks Serum urate levels (number of patients achieving sUA <6mg/dL) at 3-12 months	CKD - mixed population (people with CKD and people without CKD)

Study	Intervention and comparison	Population	Outcomes	Comments
	Allopurinol 300mg a day. Duration 28 weeks. Concurrent medication/care: A washout of previous therapy for a period of 2 weeks was achieved with people being offered either colchicine 0.6mg once daily or naproxen 250mg twice daily during the period. They were continued for the first 8 weeks of the study. Comparison (n=134) Placebo each day. Duration 28 weeks. Concurrent medication/care: A washout of previous therapy for a period of 2 weeks was achieved with people being offered either colchicine 0.6mg once daily or naproxen 250mg twice daily during the period. They were continued for the first 8 weeks of the study.			
Xu 2015129	Intervention (n=168) Allopurinol 300mg/day at a fixed dose for 24 weeks. Duration 24 weeks. Concurrent medication/care: No additional information. Comparison (n=168)	n=504 People of either sex and 18-70 years of age, inclusive, with gout, hyperuricemia (defined for the study as a serum urate level at least 480 micromol/L), normal renal function (serum creatinine concentration no more than 135 micromol/L) and free of gout flare 2	Cardiovascular adverse events at 24 weeks Renal adverse events at 24 weeks Gastrointestinal adverse events at 24 weeks	CKD - No CKD - People without CKD or people with CKD stages 1-2

Study	Intervention and comparison	Population	Outcomes	Comments
	Febuxostat 80mg/day at a fixed dose for 24 weeks. Duration 24 weeks	weeks beforehand and during the 2-week run-in period Age – mean years (SD): 46.8 (11.6) Gender (M:F): 453:24 Ethnicity: not stated Country: China	Serum urate level (change score) at 24 weeks Serum urate levels (number of patients achieving sUA <6mg/dL) at 3-12 months	
Yu 2016136	Intervention (n=54) Febuxostat 80mg once a day for 12 weeks. Duration 12 weeks Comparison (n=55) Allopurinol 300mg once a day. Duration 12 weeks.	n=109 20-65 years old; diagnosed with gout based on the American College of Rheumatology criteria; were not taking urate-lowering agents with serum urate levels of at least 8.0mg/dL Age – mean years (SD): 45.6 (11.5) Gender (M:F): 106:3 Ethnicity: Han Chinese patients Country: Taiwan	Frequency of flares at 3 months Total adverse events at 3 months Serum urate levels (number of patients achieving sUA <6mg/dL) at <3 months and 3-12 months	CKD - mixed population (people with CKD and people without CKD)

Table 5: Summary of studies included in the evidence review second-line treatment

Study	Intervention and comparison	Population	Outcomes	Comments
Mackenzie 202078	Intervention (n=3065) Allopurinol mixed severity dose mean: 279 mg. (100mg -10% of patients, 200mg - 23.3% of patients, 300mg - 50.9%, 400mg - 11.9%, 500-900 mg - 3.9% of patients). If serum urate was not controlled to the European League Against Rheumatism (EULAR)target of less than 0·357 mmol/L (<6 mg/dL)12 on the patient's pre-study allopurinol dose, the patient commenced a lead-in phase in which the dose was increased by 100 mg/day every 2 weeks until the patient's urate concentration was at target or until they reached the maximum licensed dose (900 mg/day) or maximum tolerated dose of allopurinol. Comparison (n=3063) Febuxostat mixed dose, mean 81 mg. (97.5% of patients were on 80 mg, 2.5 % were on 120 mg).Patients in the febuxostat group were given febuxostat orally (80 mg and 120 mg tablets; Patheon France [Bourgoin Jallieu, France] or Menarini [Dresden, Germany]) at 80	n=6128 Eligible patients were aged 60 years or older, had gout, and, in the opinion of the recruiting physician, required urate-lowering therapy. No patients with asymptomatic hyperuricaemia were recruited to the study. Eligible participants also had at least one additional cardiovascular risk factor and were already receiving allopurinol therapy. Age – mean years (SD): 71(6.4) Gender (M:F): 5225:903 Ethnicity: Allopurinol group – white 3036 (99.1%), Asian 14 (0.5%), Afro-Caribbean 8 (0.3%), Oriental 1 (<0.1%), Other 6 (0.2%) Febuxostat group - white 3034 (99.1%), Asian 11 (0.4%), Afro-Caribbean 10 (0.3%), Oriental 2 (0.1%), Other 6 (0.2%) Countries: UK, Denmark, Sweden	Cardiovascular adverse events at >12 months Renal and urinary adverse events at >12 months Gastrointestinal adverse events at >12 months Number of people achieving sUA < 6mg/dL at years (1 – 7) Number of people achieving sUA < 5mg/dL at years (1 – 7) Hospitalisation at >12 months	CKD - mixed population (people with CKD and people without CKD)

Study	Intervention and comparison	Population	Outcomes	Comments
	mg daily for the first 2 weeks after randomisation. After 2 weeks, serum urate concentration was measured and, if not controlled to the EULAR target, the febuxostat dose was increased to 120 mg daily.			
Poiley 201691	Intervention (n=55) Allopurinol 300mg per day. Duration 12 weeks. Concurrent medication/care: People receiving medication known to affect serum urate levels were required to be receiving a stable dose for at least 2 weeks and to continue to receive the same dose during the study. Concomitant use of potent cytochrome 3A4 inhibitors, cytotoxic drugs, or anticoagulants were prohibited as were long term treatments with NSAIDs or systemic corticosteroids. Women of reproductive potential had to use accepted forms of contraception Comparison (n=28) Placebo. Duration 12 weeks. Concurrent medication/care: People receiving medication known to affect serum urate levels were required to be	n=248 People aged 18-75 years diagnosed as having gout according to the American College of Rheumatology criteria and who had experienced at least 3 flares during the 12 months before screening. People had to have a serum urate level of 7.5-12mg/dL and had not received any urate lowering therapy or colchicine for at least 2 weeks at screening. Age – mean years (SD): 52.0 (10.4). Gender (M:F): 229:10 Ethnicity: White = 169 (68.15%), Black = 47 (18.95%), Asian = 13 (5.24%), Other = 10 (4.03%) Country: USA	Joint tenderness (arthralgia) at 12 weeks Cardiovascular adverse events at 12 weeks Change in serum urate level at 12 weeks Serum urate levels (number of patients achieving sUA <6mg/dL) at 3-12 months	No CKD - People without CKD or people with CKD stages 1-2 and people without CKD). It should be noted that this was a 5-arm trial of Arhalofenate 600mg, 800mg, 300mg Allopurinol, 300mg Allopurinol plus Colchicine and placebo, but only the relevant arms were included.

Study	Intervention and comparison	Population	Outcomes	Comments
	receiving a stable dose for at least 2 weeks and to continue to receive the same dose during the study. Concomitant use of potent cytochrome 3A4 inhibitors, cytotoxic drugs, or anticoagulants were prohibited as were long term treatments with NSAIDs or systemic corticosteroids. Women of reproductive potential had to use accepted forms of contraception			

See Appendix D for full evidence tables.

1.1.6 Summary of the effectiveness evidence

First-line treatment:

Non-CKD population (n=4)

Table 6: Clinical evidence summary: non-CKD population – allopurinol 300mg versus placebo

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Allopurinol
Flares (new or recurrent flares) -short-term (<3 months) (30 days)	51 (1 RCT)	LOW[a]	RR 0.64 (0.12 to 3.52)	120 per 1,000	43 fewer per 1,000 (106 fewer to 302 more)
Adverse events (Colchicine reductions due to gastrointestinal symptoms) - short-term (<3 months)	51 (1 RCT)	LOW[a]	RR 0.64 (0.32 to 1.30)	480 per 1,000	173 fewer per 1,000 (326 fewer to 144 more)

a. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. GRADE default MIDs used for all outcomes. For dichotomous outcomes MIDs were taken to be RRs of 0.8 and 1.25.

Table 7: Clinical evidence summary: non-CKD population – allopurinol 300mg versus febuxostat 80mg

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Febuxostat	Risk difference with Allopurinol
Frequency of flares (acute gout attack rate) at 3-12 months (24 weeks)	557 (2 RCTs)	VERY LOW[a,b,c]	RR 1.56 (0.49 to 4.96)	375 per 1,000	210 more per 1,000 (191 fewer to 1,485 more)
Renal adverse events - medium-term (3 to 12 months) (24 weeks)	397 (1 RCT)	MODERATE[a]	RR 0.38 (0.15 to 0.95)	80 per 1,000	50 fewer per 1000 (68 fewer to 4 fewer)
Gastrointestinal adverse events - medium-term (3 to 12 months) (6 months)	160 (1 RCT)	VERY LOW[a,c]	RR 4.00 (0.46 to 35.01)	13 per 1,000	38 more per 1,000 (7 fewer to 425 more)
Serum urate level final value (high is poor) - short-term (<3 months) (1 month post-treatment)	160 (1 RCT)	LOW[a,c]	-	mean 420.57µmol/L	MD 47.32 higher (19.02 higher to 75.62 higher)
Serum urate level, final value (high is poor) - medium-term (3 to 12 months) (1 month post-treatment)	160 (1 RCT)	LOW[a,c]	-	mean 372.06µmol/L	MD 27.97 higher (4.43 higher to 51.51 higher)

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Febuxostat	Risk difference with Allopurinol
Serum urate level number of patients reaching 6mg/dL (<360micromol)/L at <3 months (1 month post-treatment)	160 (1 RCT)	LOW[a,c]	RR 0.75 (0.60 to 0.94)	750 per 1,000	188 fewer per 1,000 (300 fewer to 45 fewer)
Serum urate level number of patients reaching 6mg/dL (<360micromol)/L at 3-12 months (1 month post-treatment)	160 (1 RCT)	VERY LOW[a,c]	RR 0.88 (0.80 to 0.95)	1,000 per 1,000	120 fewer per 1,000 (200 fewer to 50 fewer)

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 or 2 increments because: The point estimate varies widely across studies, I^2=72%, subgroup analysis could not be performed so a random effects model was used.

c. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. GRADE default MIDs used for all outcomes. For dichotomous outcomes MIDs were taken to be RRs of 0.8 and 1.25. For continuous outcomes 0.5 x baseline SD was calculated, serum urate level: 39.

Table 8: Clinical evidence summary: non-CKD population – febuxostat 80 mg vs placebo

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with Febuxostat
Serum urate levels (number of patients achieving sUA 6mg/dL; at <3 months) (8 weeks)	156 (1 RCT)	HIGH[a]	Peto OR 10.11 (4.11 to 24.84)	0 per 1,000	280 more per 1,000 (180 more to 380 more)
Serum urate levels (number of patients achieving sUA 6mg/dL; 3-12 months) (24 weeks)	156 (1 RCT)	HIGH[a]	Peto OR 10.66 (4.54 to 25.01)	0 per 1,000	320 more per 1,000 (220 more to 430 more)
Serum urate levels (number of patients achieving sUA 5mg/dL; at <3 months) (8 weeks)	156 (1 RCT)	HIGH[a]	Peto OR 8.24 (2.15 to 31.52)	0 per 1,000	120 more per 1,000 (40 more to 190 more)
Serum urate levels (number of patients achieving sUA 5mg/dL; 3-12 months) (24 weeks)	156 (1 RCT)	HIGH[a]	Peto OR 8.61 (2.66 to 27.85)	0 per 1,000	150 more per 1,000 (70 more to 240 more)

a. GRADE default MIDs used for all outcomes. For dichotomous outcomes MIDs were taken to be RRs of 0.8 and 1.25.

Mixed CKD population (n=1)

Table 9: Clinical evidence summary: mixed CKD population – allopurinol 100-200mg versus placebo

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with Allopurinol
Joint inflammation (evidence of new joint inflammation) - short-term (<3 months) (28 days)	34 (1 RCT)	LOW[a]	Peto OR 7.39 (0.15 to 372.38)	0 per 1,000	60 more per 1,000 (90 fewer to 210 more)
Joint tenderness (pain in a new joint) -short-term (<3 months) (28 days)	34 (1 RCT)	LOW[a]	RR 2.00 (0.20 to 20.04)	59 per 1,000	59 more per 1,000 (47 fewer to 1,120 more)
Adverse events (withdrawal due to AE) -short-term (<3 months) (28 days)	34 (1 RCT)	LOW[a]	RR 0.50 (0.05 to 5.01)	118 per 1,000	59 fewer per 1,000 (112 fewer to 472 more)

a. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. GRADE default MIDs used for all outcomes. For dichotomous outcomes MIDs were taken to be RRs of 0.8 and 1.25.

Unclear or mixed treatment line:

Stage 3 CKD population

Table 10: Clinical evidence summary: stage 3 CKD population - febuxostat 80 mg versus placebo

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with Febuxostat
Frequency of flares (number of participants with 1 or more flares) - medium-term (3 to 12 months) (3 months)	75 (1 RCT)	HIGH	RR 3.59 (1.30 to 9.92)	105 per 1,000	273 more per 1,000 (32 more to 939 more)
Adverse events -cardiovascular (hypertension) -medium-term (3 to 12 months) (3 months)	76 (1 RCT)	LOW[a]	RR 1.03 (0.07 to 15.82)	26 per 1,000	0 fewer per 1,000 (25 fewer to 379 more)
Adverse events – renal failure- medium-term (3 to 12 months)	76 (1 RCT)	LOW[a]	Peto OR 0.14 (0.01 to 2.20)	53 per 1,000	45 fewer per 1,000 (52 fewer to 54 more)
Adverse events - gastrointestinal -medium-term (3 to 12 months) (3 months)	76 (1 RCT)	MODERATE[b]	RD 0.00 (-0.05 to 0.05)	0 per 1,000	0 fewer per 1,000 (0 fewer to 0 fewer)
Serum urate levels (number of patients achieving sUA 6mg/dL; 3 to 12 months) (3 months)	75 (1 RCT)	HIGH	Peto OR 16.95 (6.31 to 45.50)	0 per 1,000	590 more per 1,000 (430 more to 750 more)

a. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. GRADE default MIDs used for all outcomes. For dichotomous outcomes MIDs were taken to be RRs of 0.8 and 1.25.

b. Zero events in both arms - Imprecision was measured using sample size: no imprecision (sample size>350, serious imprecision (sample size >70 to <350), very serious imprecision (sample size<70).

Non-CKD population

Table 11: Clinical evidence summary: non-CKD population - allopurinol 300mg versus febuxostat 80 mg

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with febuxostat	Risk difference with Allopurinol
Cardiovascular adverse events at 3-12 months (24 weeks)	336 (1 RCT)	VERY LOW[a,b]	Peto OR 7.39 (0.15 to 372.38)	0 per 1,000	10 more per 1,000 (10 fewer to 20 more)
Renal adverse events at 3-12 months (24 weeks)	336 (1 RCT)	VERY LOW[a,b]	RR 0.29 (0.06 to 1.36)	42 per 1,000	30 fewer per 1,000 (39 fewer to 15 more)
Gastrointestinal adverse events at 3-12 months (24 weeks)	336 (1 RCT)	VERY LOW[a,b]	RR 2.00 (0.37 to 10.77)	12 per 1,000	12 more per 1,000 (8 fewer to 116 more)
Serum urate level, change score (high is poor) at 3 – 12 months (24 weeks)	317 (1 RCT)	LOW[a,b]	-	mean (SD) - 216 (137.2) µmol/L	MD 45.6 higher (15.89 higher to 75.31 higher)
Serum urate level number of patients reaching 6mg/dL (<360micromol) at 3 - 12 months (24 weeks)	317 (1 RCT)	MODERATE[a]	RR 0.59 (0.46 to 0.75)	589 per 1,000	241 fewer per 1,000 (318 fewer to 147 fewer)

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. GRADE default MIDs used for all outcomes. For dichotomous outcomes MIDs were taken to be RRs of 0.8 and 1.25. For continuous outcomes 0.5 x baseline SD was calculated, serum urate level 68.6.

Table 12: Clinical evidence summary: non-CKD population – treat-to-target Allopurinol 300mg versus febuxostat 80 mg or 120mg

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Febuxostat	Risk difference with Allopurinol
Number of patients with SUA < or equal to 6mg/dL (SUA) at medium-term (3-12 months) (36 weeks)	182 (1 RCT)	MODERATE[b]	RR 0.78 (0.64 to 0.95)	783 per 1,000	172 fewer per 1,000 (282 fewer to 39 fewer)
Treatment emergent adverse events at medium term (3-12 months) (38 weeks)	197 (1 RCT)	LOW[a,b]	RR 1.25 (0.98 to 1.59)	515 per 1,000	129 more per 1,000 (10 fewer to 304 more)

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. GRADE default MIDs used for all outcomes. For dichotomous outcomes MIDs were taken to be RRs of 0.8 and 1.25.

Mixed CKD population (n=9)

Table 13: Clinical evidence summary: mixed CKD population – allopurinol 300mg versus placebo

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with Allopurinol
Frequency of flares - medium-term (3 to 12 months) (28 weeks)	402 (1 RCT)	VERY LOW[a,b]	RR 1.13 (0.76 to 1.69)	201 per 1,000	26 more per 1,000 (48 fewer to 139 more)
Cardiovascular adverse events - medium-term (3 to 12 months) (28 weeks)	402 (1 RCT)	VERY LOW[a,b]	RR 0.50 (0.03 to 7.93)	7 per 1,000	4 fewer per 1,000 (7 fewer to 52 more)

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with Allopurinol
Gastrointestinal events (diarrhoea) at 3-12 months (28 weeks)	402 (1 RCT)	VERY LOW[a,b]	RR 0.77 (0.37 to 1.6)	82 per 1000	19 fewer per 1000 (from 52 fewer to 49 more)
Gastrointestinal events (nausea and vomiting) at 3-12 months (28 weeks)	402 (1 RCT)	VERY LOW[a,b]	RR 0.6 (0.19 to 1.93)	37 per 1000	15 fewer per 1000 (from 30 fewer to 34 more)
Gastrointestinal events (gastro and abdominal pain) at 3-12 months (28 weeks)	402 (1 RCT)	VERY LOW[a,b]	RR 1 (0.25 to 3.94)	22 per 1000	0 fewer per 1000 (from 16 fewer to 65 more)
Serum urate level (change from baseline; mg/dL; <3 months) (4 weeks)	73 (1 RCT)	MODERATE[a]	-	mean 0.07 mg/dL	MD 3.83 lower (4.47 lower to 3.19 lower)
Number of people achieving sUA <6.0 mg/dL at 3-12 months (28 weeks)	390 (1 RCT)	LOW[a]	RR 49.25 (6.95 to 349.02)	8 per 1,000	380 more per 1,000 (47 more to 2,740 more)

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. GRADE default MIDs used for all other outcomes. For dichotomous outcomes MIDs were taken to be RRs of 0.8 and 1.25. For continuous outcomes 0.5 x baseline SD for was calculated. For serum urate level this was calculated as 0.55.

Table 14: Clinical evidence summary: mixed CKD population – allopurinol 300mg vs febuxostat 80 mg

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with febuxostat	Risk difference with Allopurinol
Frequency of flares - short-term (<3 months)	1036 (2 RCTs)	VERY LOW[a,b]	RR 0.88 (0.70 to 1.10)	248 per 1,000	30 fewer per 1,000 (74 fewer to 25 more)
Frequency of flares at 3-12 months (3 months)	453 (2 RCTs)	VERY LOW[a,b,c]	RR 1.31 (0.48 to 3.52)	128 per 1,000	40 more per 1,000 (67 fewer to 323 more)

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with febuxostat	Risk difference with Allopurinol
Cardiovascular adverse events - medium-term (3 to 12 months)	2047 (2 RCTs)	VERY LOW[a,b]	RR 0.50 (0.19 to 1.33)	12 per 1,000	6 fewer per 1,000 (10 fewer to 4 more)
Renal adverse events at 3 to 12 months	344 (1 RCT)	LOW[b]	RR 0.50 (0.09 to 2.69)	23 per 1,000	12 fewer per 1,000 (21 fewer to 39 more)
Gastrointestinal adverse events (diahorrea) at 3-12 months)	2556 (3 RCTs)	LOW[a,b]	RR 1.16 (0.85 to 1.57)	60 per 1000	10 more per 1000 (from 9 fewer to 34 more)
Gastrointestinal adverse events (nausea and vomiting) at 3-12 months	1044 (2 RCTs)	VERY LOW[a,b]	RR 0.53 (0.24 to 1.18)	33 per 1000	15 fewer per 1000 (from 24 fewer to 6 more)
Gastrointestinal adverse events (pain/discomfort) at 3-12 months	1044 (2 RCTs)	VERY LOW[a,b]	RR 0.64 (0.25 to 1.63)	21 per 1000	8 fewer per 1000 (from 16 fewer to 13 more)
Gastrointestinal adverse events (disorders) at 3-12 months	853 (2 RCTs)	VERY LOW[a,b]	RR 0.5 (0.17 to 1.46)	24 per 1000	12 fewer per 1000 (from 25 fewer to 6 more)
Total adverse events at medium-term (3-12 months) (3 months)	109 (1 RCT)	LOW[a,b]	RR 0.90 (0.69 to 1.18)	704 per 1,000	70 fewer per 1,000 (218 fewer to 127 more)

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with febuxostat	Risk difference with Allopurinol
Tophi - medium-term (3 to 12 months)	511 (1 RCT)	VERY LOW[a,b]	RR 1.07 (0.69 to 1.67)	128 per 1,000	9 more per 1,000 (40 fewer to 86 more)
Tophi - (change in number of Tophi from baseline) at 3 - 12 months	344 (1 RCT)	HIGH	-	mean -0.28	MD 0.13 higher (0.12 lower to 0.38 higher)
Serum urate levels (change from baseline; <3 months)	71 (1 RCT)	LOW[a,b]	-	mean -4.61 mg/dL	MD 0.85 higher (0.2 higher to 1.5 higher)
Serum urate level, % change - medium-term (3 to 12 months)	509 (1 RCT)	VERY LOW[a,b]	-	mean 44.73%	MD 11.74 higher (8.73 higher to 14.75 higher)
Serum urate level, change score (high is poor) at 3-12 months	344 (1 RCT)	MODERATE[b]	-	mean -4.17 mg/dL	MD 0.92 higher (0.48 higher to 1.36 higher)
Number of patients with sUA <6mg/dL at <3 months	109 (1 RCT)	MODERATE[a]	RR 0.34 (0.20 to 0.56)	704 per 1,000	464 fewer per 1,000 (563 fewer to 310 fewer)
Number of people achieving sUA <6.0 mg/dL at 3-12 months	2625 (4 RCTs)	VERY LOW[a,c]	RR 0.51 (0.41 to 0.64)	693 per 1,000	340 fewer per 1,000 (409 fewer to 249 fewer)

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with febuxostat	Risk difference with Allopurinol

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.; GRADE default MIDs used for all other outcomes. For dichotomous outcomes MIDs were taken to be RRs of 0.8 and 1.25. For continuous outcomes 0.5 x baseline SD was calculated: serum urate level 0.62, tophi 3.29.

c. Downgraded by 1 or 2 increments because: The point estimate varies widely across studies and could not be explained by subgroup analysis and the I^2=0.81 so a random effects model was used.

Table 15: Clinical evidence summary: mixed CKD population – allopurinol 300mg versus febuxostat 120 mg

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with febuxostat	Risk difference with Allopurinol
Frequency of flares - short-term (<3 months)	1038 (2 RCTs)	LOW[a]	RR 0.60 (0.50 to 0.74)	360 per 1,000	144 fewer per 1,000 (180 fewer to 94 fewer)
Cardiovascular adverse events -medium-term (3 to 12 months)	537 (1 RCT)	VERY LOW[a,b]	RR 0.20 (0.02 to 1.71)	19 per 1,000	15 fewer per 1,000 (18 fewer to 13 more)
Gastrointestinal adverse events (diarrhoea) at 3-12 months)	1041 (2 RCTs)	VERY LOW[a,b]	RR 0.96 (0.56 to 1.64)	49 per 1000	2 fewer per 1000 (from 22 fewer to 31 more
Gastrointestinal adverse events (nausea and vomiting) at 3-12 months)	1041 (2 RCTs)	VERY LOW[a,b]	RR 0.69 (0.3 to 1.6)	25 per 1000	8 fewer per 1000 (from 18 fewer to 15 more)
Gastrointestinal adverse events (gastro and abdominal pain) at 3-12 months)	1041 (2 RCTs)	VERY LOW[a,b]	RR 0.88 (0.32 to 2.39)	15 per 1000	2 fewer per 1000 (from 10 fewer to 21 more)
Tophi - medium-term (3 to 12 months)	511 (1 RCT)	VERY LOW[a,b]	RR 0.93 (0.60 to 1.45)	138 per 1,000	10 fewer per 1,000 (55 fewer to 62 more)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with febuxostat	Risk difference with Allopurinol
Serum urate levels (change from baseline; <3 months) (4 weeks)	72 (1 RCT)	MODERATE[a]	-	mean -5.26 mg/dL	MD 1.5 higher (0.72 higher to 2.28 higher)
Serum urate level, % change (high is poor) -medium-term (3 to 12 months) (12 months)	504 (1 RCT)	LOW[a]	-	mean -15.52 %	MD 17.47 lower (20.57 lower to 14.37 lower)
Number of people achieving sUA <6.0 mg/dL at 3-12 months	1012 (2 RCTs)	LOW[a]	RR 0.47 (0.42 to 0.54)	793 per 1,000	420 fewer per 1,000 (460 fewer to 365 fewer)

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. GRADE default MIDs used for all outcomes. For dichotomous outcomes MIDs were taken to be RRs of 0.8 and 1.25. For continuous outcomes 0.5 x baseline SD was calculated, serum urate level:0.56.

Table 16: Clinical evidence summary: mixed CKD population – febuxostat 80 mg versus placebo

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with Febuxostat 80mg
Frequency of flares - short-term (<3 months)	474 (2 RCTs)	VERY LOW[a,b]	RR 1.32 (0.96 to 1.81)	238 per 1,000	76 more per 1,000 (10 fewer to 193 more)
Frequency of flares - medium-term (3 to 12 months)	714 (1 RCT)	MODERATE[a]	RR 1.31 (1.01 to 1.71)	207 per 1,000	64 more per 1,000 (2 more to 147 more)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with Febuxostat 80mg
Cardiovascular adverse events -medium-term (3 to 12 months)	1114 (2 RCTs)	LOW[a]	RR 1.00 (0.44 to 2.28)	22 per 1,000	0 fewer per 1,000 (13 fewer to 29 more)
Gastrointestinal adverse events (abdominal pain)- short-term (<3 months)	78 (1 RCT)	VERY LOW[a,b]	RR 0.47 (0.04 to 5.03	53 per 1,000	28 fewer per 1,000 (51 fewer to 212 more)
Gastrointestinal adverse events (diarrhoea)- short-term (<3 months)	78 (1 RCT)	VERY LOW[a,b]	1.27 (0.30 to 5.29)	79 per 1,000	21 more per 1,000 (55 fewer to 339 more)
Gastrointestinal adverse events (diarrhoea) at 3-12 months	1114 (2 RCTs)	VERY LOW[a,b,c]	RR 1.10 (0.51 to 2.39)	54 per 1000	5 more per 1000 (from 24 fewer to 68 more)
Gastrointestinal adverse events (nausea and vomiting) at 3-12 months	401 (1 RCT)	VERY LOW[a,b]	RR 1.2 (0.43 to 3.35)	37 per 1000	7 more per 1000 (from 21 fewer to 87 more)
Gastrointestinal adverse events (gastro and abdominal pain) at 3-12 months	401 (1 RCT)	VERY LOW[a,b]	RR 1 (0.25 to 3.95)	22 per 1000	0 fewer per 1000 (from 16 fewer to 65 more)
Serum urate levels (change from baseline; mg/dL; <3 months)	72 (1 RCT)	MODERATE[a]	-	mean 0.07 mg/dL	MD 4.68 lower (5.31 lower to 4.05 lower)
Number of people achieving sUA <6.0 mg/dL at 3-12 months	1166 (3 RCTs)	HIGH	RR 92.60 (32.28 to 265.61)	6 per 1,000	529 more per 1,000 (181 more to 1,530 more)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with Febuxostat 80mg
Number of people achieving sUA <5.0 mg/dL at 3-12 months	786 (2 RCTs)	HIGH	RR 112.32 (22.77 to 554.17)	3 per 1,000	284 more per 1,000 (56 more to 1,411 more)
Number of people achieving sUA <4.0 mg/dL at 3-12 months	72 (1 RCT)	MODERATE[a]	Peto OR 8.38 (1.78 to 39.43)	0 per 1,000	190 more per 1,000 (60 fewer to 320 more)

a. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. GRADE default MIDs used for all other outcomes. For dichotomous outcomes MIDs were taken to be RRs of 0.8 and 1.25. For continuous outcomes 0.5 x baseline SD was calculated, serum urate level: 0.65.

b. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

c. The point estimates varied widely and the $I^2 = 58\%$, no subgroup analysis could be carried out so a random effects model was used.

Table 17: Clinical evidence summary: mixed CKD population – febuxostat 120 mg versus placebo

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with Febuxostat
Frequency of flares at <3 months	479 (2 RCTs)	LOW[a]	RR 1.71 (1.26 to 2.32)	238 per 1,000	169 more per 1,000 (62 more to 315 more)
Cardiovascular adverse events at 3-12 months	475 (2 RCTs)	LOW[a,c]	RR 8.21 (0.50 to 135.65)	6 per 1,000	43 more per 1,000 (3 fewer to 797 more)
Gastrointestinal adverse events (abdominal pain) at <3 months	76 (1 RCT)	VERY LOW[a,b]	RR 0.5 (0.05 to 5.28)	53 per 1,000	26 fewer per 1,000 (50 fewer to 225 more)
Gastrointestinal adverse events (diarrhoea) at <3 months	76 (1 RCT)	VERY LOW[a,b]	RR 1.00 (0.22 to 4.65)	79 per 1,000	0 fewer per 1,000 (62 fewer to 288 more)
Gastrointestinal adverse events at 3-12 months	403 (1 RCT)	VERY LOW[a,b]	RR 0.94 (0.56 to 1.58)	142 per 1,000	9 fewer per 1,000 (62 fewer to 82 more)

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with Febuxostat
Serum urate levels (change from baseline mg/dl; <3 months)	73 (1 RCT)	MODERATE[a]	-	mean 0.07 mg/dL	MD 5.33 lower (6.09 lower to 4.57 lower)
Number of people achieving sUA <6.0 mg/dL at 3-12 months	461 (2 RCTs)	LOW[a]	RR 91.26 (17.95 to 464.13)	6 per 1,000	557 more per 1,000 (105 more to 2,859 more)
Number of people achieving sUA <5.0 mg/dL at 3-12 months	69 (1 RCT)	MODERATE[a]	Peto OR 34.41 (13.37 to 88.55)	0 per 1,000	880 fewer per 1,000 (770 fewer to 1000 fewer)
Number of people achieving sUA <4.0 mg/dL at 3-12 months	69 (1 RCT)	MODERATE[a]	Peto OR 15.80 (5.54 to 45.10)	0 per 1,000	560 more per 1,000 (390 more to 730 more)

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. GRADE default MIDs used for all other outcomes. For dichotomous outcomes MIDs were taken to be RRs of 0.8 and 1.25. For continuous outcomes 0.5 x baseline SD for was calculated, serum urate level: 0.58.

c. I^2=61% and subgroup analysis could not be conducted so a random effects model was used.

Second-line treatment

Non-CKD population (n=1)

Table 18: Clinical evidence summary: Non-CKD population – Allopurinol 300mg versus placebo

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with Allopurinol
Joint tenderness (arthralgia) - medium-term (3 to 12 months)	82 (1 RCT)	VERY LOW[a,b]	Peto OR 0.05 (0.00 to 3.34)	36 per 1,000	34 fewer per 1,000 (36 fewer to 74 more)
Adverse events - cardiovascular - medium-term (3 to 12 months)	82 (1 RCT)	VERY LOW[a,b]	RR 0.26 (0.02 to 2.74)	71 per 1,000	53 fewer per 1,000 (70 fewer to 124 more)
Serum urate level (change from baseline; %) -medium-term (3 to 12 months)	82 (1 RCT)	MODERATE[a]	-	mean -0.9 %	MD 27.9 lower (35.6 lower to 20.2 lower) =
Serum urate level (patients with sUA <6mg/dL; (3 to 12months)	82 (1 RCT)	MODERATE[a]	Peto OR 8.99 (3.39 to 23.84)	0 per 1,000	480 more 1,000 (340 more to 620 fewer)

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. GRADE default MIDs used for all other outcomes For dichotomous outcomes MIDs were taken to be RRs of 0.8 and 1.25. For continuous outcomes 0.5 x baseline SD was calculated, serum urate level 0.7.

Mixed CKD population treat-to-target (n=1)

Table 19: Clinical evidence summary: Mixed CKD population – allopurinol (mixed dose, mean 279 mg) versus febuxostat (mixed dose, mean 81 mg)

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with febuxostat	Risk difference Allopurinol
Cardiovascular disorders (number of patients with at least 1 event) at >12 months	6051 (1 RCT)	MODERATE[a]	RR 1.04 (0.94 to 1.15)	190 per 1,000	8 more per 1,000 (11 fewer to 28 more)
Renal and urinary disorders (number of patients with at least 1 event) at >12 months	6051 (1 RCT)	LOW[a,b]	RR 1.03 (0.81 to 1.30)	43 per 1,000	1 more per 1,000 (8 fewer to 13 more)
Gastrointestinal disorders (number of patients with at least 1 event) at >12 months	6051 (1 RCT)	LOW[a,b]	RR 1.10 (0.93 to 1.29)	85 per 1,000	9 more per 1,000 (6 fewer to 25 more)
Number of people achieving sUA <6 mg/dL at 1 year	5057 (1 RCT)	LOW[a,c]	RR 0.89 (0.87 to 0.90)	970 per 1,000	107 fewer per 1,000 (126 fewer to 97 fewer)
Number of people achieving sUA <6 mg/dL at 2 years	4668 (1 RCT)	LOW[a,c]	RR 0.89 (0.87 to 0.90)	971 per 1,000	107 fewer per 1,000 (126 fewer to 97 fewer)

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with febuxostat	Risk difference Allopurinol
Number of people achieving sUA <6 mg/dL at 3 years	3356 (1 RCT)	VERY LOW[a,c]	RR 0.90 (0.88 to 0.92)	973 per 1,000	97 fewer per 1,000 (117 fewer to 78 fewer)
Number of people achieving sUA <6 mg/dL at 4 years	2257 (1 RCT)	VERY LOW[a,c]	RR 0.90 (0.88 to 0.92)	971 per 1,000	97 fewer per 1,000 (117 fewer to 78 fewer)
Number of people achieving sUA <6 mg/dL at 5 years	1494 (1 RCT)	VERY LOW[a,c]	RR 0.89 (0.86 to 0.92)	973 per 1,000	107 fewer per 1,000 (136 fewer to 78 fewer)
Number of people achieving sUA <6 mg/dL at 6 years	753 (1 RCT)	VERY LOW[a,c]	RR 0.92 (0.88 to 0.96)	965 per 1,000	77 fewer per 1,000 (116 fewer to 39 fewer)
Number of people achieving sUA <6 mg/dL at 7 years	168 (1 RCT)	VERY LOW[a,c]	RR 0.92 (0.85 to 0.99)	976 per 1,000	78 fewer per 1,000 (146 fewer to 10 fewer)
Number of people achieving sUA <5mg/dL at 1 year	5057 (1 RCT)	LOW[a,c]	RR 0.52 (0.50 to 0.54)	892 per 1,000	428 fewer per 1,000 (446 fewer to 410 fewer)

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with febuxostat	Risk difference Allopurinol
Number of people achieving sUA <5mg/dL at 2 years	4668 (1 RCT)	LOW[a,c]	RR 0.54 (0.51 to 0.56)	913 per 1,000	420 fewer per 1,000 (447 fewer to 402 fewer)
Number of people achieving sUA <5mg/dL at 3 years	3356 (1 RCT)	VERY LOW[a,c]	RR 0.56 (0.53 to 0.59)	916 per 1,000	403 fewer per 1,000 (430 fewer to 375 fewer)
Number of people achieving sUA <5mg/dL at 4 years	2257 (1 RCT)	VERY LOW[a,c]	RR 0.58 (0.55 to 0.62)	906 per 1,000	381 fewer per 1,000 (408 fewer to 344 fewer)
Number of people achieving sUA <5mg/dL at 5 years	1494 (1 RCT)	VERY LOW[a,c]	RR 0.59 (0.55 to 0.63)	914 per 1,000	375 fewer per 1,000 (411 fewer to 338 fewer)
Number of people achieving sUA <5mg/dL at 6 years	753 (1 RCT)	VERY LOW[a,c]	RR 0.62 (0.56 to 0.68)	914 per 1,000	347 fewer per 1,000 (402 fewer to 292 fewer)
Number of people achieving sUA <5mg/dL at 7 years	168 (1 RCT)	VERY LOW[a,b,c]	RR 0.72 (0.60 to 0.85)	904 per 1,000	253 fewer per 1,000 (361 fewer

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with febuxostat	Risk difference Allopurinol
					to 136 fewer)
Hospitalisation at >12 months	6128 (1 RCT)	MODERATE[a]	RR 1.03 (0.91 to 1.16)	138 per 1,000	4 more per 1,000 (12 fewer to 22 more)

a. Downgraded by 1 or 2 increments because the majority of the evidence included an indirect or very indirect interventions respectively. Mixed dose Allopurinol (279 mg on average) and mixed dose Febuxostat (81 mg on average)

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. Established MIDs for SF-36 physical/mental- 3.75; GAQ - 6.5; GIS: gout concern overall – 7.2, GIS: unmet gout treatment need – 6.9, GIS: gout well-being during attack – 5.2 and GIS: gout concern during attack – 7.6; SF-6D – 0.041; MOS 20 – 20% change in scores; AIMS – 20% change in scores, HAQ-DI – 0.22; GRADE default MIDs used for all other outcomes. For dichotomous outcomes MIDs were taken to be RRs of 0.8 and 1.25.

c. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

See Appendix F for full GRADE tables.

1.1.7 Economic evidence

1.1.7.1 Included studies

Two health economic studies with relevant comparisons were included in this review: one comparing febuxostat (80mg/120mg) versus fixed dose allopurinol (300mg)[56, 80, 111, 112]; and one comparing different treatment sequences including febuxostat (80mg and 120mg), allopurinol (300mg) and no treatment [5].These are summarised in the health economic evidence profiles below (Table 20 and Table 21) and the health economic evidence tables in Appendix G.

No health economic studies were included comparing other drugs included in the review protocol such as: amlodipine, fenofibrate, losartan, vitamin C and rasburicase.

1.1.7.2 Excluded studies

One economic study relating to this review question was identified but was excluded due to the availability of more applicable evidence.[87] This is listed in Appendix J, with reasons for exclusion given.

See also the health economic study selection flow chart in Appendix G.

1.1.8 Summary of included economic evidence

Table 20: Health economic evidence profile: Febuxostat versus allopurinol

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
NICE 2008, Stevenson 2009, Stevenson 2011, Ipsen 2008[56, 80, 111, 112] (UK)	Partially applicable [(a)]	Potentially serious limitations[(b)]	• Probabilistic model based on pooled analysis of RCTs (APEX/FACT[10,100]). Decision tree, split into two time periods: 1. An initial period of 3 months, during which patients may, or may not, suffer from a treatment-initiated flare. 2. A treatment maintenance period from months 4 to 24, during which patients were grouped into four subgroups according to sUA level. • Cost-utility analysis (QALYs) • Population: adults with hyperuricaemia in whom urate deposition has already occurred (including a history or presence of, tophus and/or gouty arthritis) First-line treatment. sUA	£539[(c)]	0.033 QALYs	£16,324 per QALY gained	Probability febuxostat cost effective (£20K threshold): 63% Univariate sensitivity analyses undertaken. The results were most sensitive to the assumed cost of febuxostat, the disutility associated with each incremental level of sUA and the proportion of patients <360 µmol/L in months 4 to 24 for febuxostat. Exploratory modelling done by manufacturer following appraisal consultation document, whereby the model explicitly included a comparison of febuxostat versus placebo in a population contraindicated to allopurinol. The ICER was £3,727 per QALY. This was not reviewed by the ERG.

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
			levels of at least 8 mg/dl (0.48 mmol/l). • Comparators: 1.fixed-dose allopurinol (300 mg once daily) 2.febuxostat (80 mg or 120 mg once daily) Time horizon: 2 years				

Abbreviations: 95% CI= 95% confidence interval; CUA= cost–utility analysis; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ERG = evidence review group; ICER= incremental cost-effectiveness ratio; NR= not reported; pa= probabilistic analysis; PSA = probabilistic sensitivity analysis; QALYs= quality-adjusted life years; SPC = summary of product characteristics; sUA = serum uric acid

(a) No subgrouping for renal impairment. First line comparison only and does not include allopurinol given in a titrated regimen, model uses a fixed dose of 300mg which is not best practice. Does not include other comparators or treatment sequences. ERG had concerns regarding QoL assumptions that lower sUA levels would produce utility gains independently of the incidence of gout flares. In addition, it noted that EQ-5D values from some patients were not plausible, with some without a flare rating their utility as worse than death.

(b) Model structure and comparators do not allow for sequential treatment or treatment discontinuation. Clinical data pooled not meta-analysed. Concern regarding use of sUA concentration as a surrogate outcome for gout flares. The NICE appraisal committee concluded that the relationship was not fully understood, but it was accepted that as sUA concentration levels increased above 6mg/100mL it was likely that symptoms would be more frequent. Model based on bivariate analysis that did not include other confounders rather than multivariate analysis ERG raised concerns with reasons why manufacturer discarded 77% of the UK data set, and 51% of the overall data set from IMSIII observational study, which was used to link sUA levels and number of gout flares expected. Impact of prophylactic colchicine treatment on reduction of incidence of flares overestimated in model due to calculation error. Concerns regarding inputs included (costs of intervention)/excluded (prophylaxis success rate) in PSA, contributing to uncertainty in results presented.

(c) 2006 UK pounds. Cost components incorporated: Cost of flares (hospitalisation, diagnostics and outpatient visits), maintenance cost of gout treatment (outpatient visits, diagnostic laboratory tests, procedures and hospitalisation due to complications of gout) and drug costs (febuxostat 80mg or 120 mg was £0.87 per day and allopurinol 300mg was £0.065 per day).

Table 21: Health economic evidence profile: Sequential treatment including febuxostat, allopurinol and no treatment

<table>
<tr><th>Study</th><th>Applicability</th><th>Limitations</th><th>Other comments</th><th>Incremental cost</th><th>Incremental effects</th><th>Cost effectiveness</th><th>Uncertainty</th></tr>
<tr>
<td>Beard 2013[5] (Scotland)</td>
<td>Partially applicable[a]</td>
<td>Potentially serious limitations[b]</td>
<td>• Probabilistic model based on pooled analysis of RCTs (APEX/FACT[10,100]). Decision tree and Markov model:
1. An initial period of 3 months, which included an assessment of sUA response and the flare triggering effect of initiating ULT (decision tree).
2. A treatment maintenance period used to estimate the costs and outcomes over a longer time horizon (represented as a Markov 3-month time cycle health-state structure). Health states included sUA response (defined as achieving an sUA level of 6 mg/dl (0.36 mmol/l) or less), sUA non-response (split into three sUA groups). In each of the sUA categories there was a probability of having an acute flare (1 week duration). When patients failed to gain an adequate sUA response or lost a previously</td>
<td colspan="3">Full incremental analysis (pa):[c] [d]
<table>
<tr><th>Int</th><th>Cost (e)</th><th>QALY</th><th>Inc cost</th><th>Inc QALY</th><th>ICER</th></tr>
<tr><td>1</td><td>£6,821</td><td>3.016</td><td colspan="3">Baseline</td></tr>
<tr><td>4</td><td>£7,043</td><td>3.090</td><td>£222</td><td>0.073</td><td>£3,020</td></tr>
<tr><td>5</td><td>£7,721</td><td>3.198</td><td colspan="3">Dominated by 2</td></tr>
<tr><td>3</td><td>£7,808</td><td>3.238</td><td colspan="3">Dominated by 2</td></tr>
<tr><td>2</td><td>£7,578</td><td>3.239</td><td>£535</td><td>0.149</td><td>£3,591</td></tr>
</table></td>
<td>Probability second line febuxostat cost effective (£20K threshold): ~98%

Subgroup analyses undertaken:
- patients unresponsive to first-line allopurinol (ICER £5,529 compared with no treatment)
- mild to moderate renal impairment using allopurinol 100 or 200mg (ICER £3,613 compared with allopurinol 100mg or 200mg)

Univariate sensitivity analyses undertaken, ICERs for second line treatment with febuxostat following allopurinol compared with allopurinol alone:
- time horizon (lifetime, 1 year)
- Utility drop (50% and 25% at all sUA levels)
- baseline sUA level
- sUA response threshold (<5mg/dL)</td>
</tr>
</table>

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
			attained response because of treatment dropout, the model switched patients to the next treatment in the sequence. • Cost-utility analysis (QALYs) • Population: adults with chronic gout and established hyperuricaemia who are typically treated with allopurinol (300mg once daily). sUA levels of at least 8 mg/dl (0.48 mmol/l). • Comparators: 1.Base case no treatment (NT) 2.Sequence 1: allopurinol 300 mg → febuxostat 80 mg →febuxostat 120 mg →NT 3.Sequence 2: febuxostat 80 mg →febuxostat 120 mg →allopurinol 300 mg →NT 4.Sequence 3: allopurinol 300 mg →NT 5.Sequence 4: febuxostat 80 mg →febuxostat 120 mg →NT				- Allopurinol dose titration (up to 900mg) - extended prophylaxis in first 3 months (CONFIRMS) - long term drop-outs lost to further treatment The conclusion of the model did not change based on these sensitivity analyses.

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
			• Time horizon: 5 years				

Abbreviations: 95% CI= 95% confidence interval; CUA= cost–utility analysis; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ERG = evidence review group; ICER= incremental cost-effectiveness ratio; NR= not reported; pa= probabilistic analysis; PSA = probabilistic sensitivity analysis; QALYs= quality-adjusted life years; SMC = Scottish Medicines Consortium; SPC = summary of product characteristics; sUA = serum uric acid

(a) Model uses a fixed dose of 300mg which is not best practice. Concerns had been raised by NICE TA regarding QoL assumptions that lower sUA levels would produce utility gains independently of the incidence of gout flares and that EQ-5D values from some patients were not plausible, with some without a flare rating their utility as worse than death. In this model extensive sensitivity analyses undertaken to explore these utility weights.

(b) Clinical data pooled not meta-analysed. Concern regarding use of sUA concentration as a surrogate outcome for gout flares. Correlation between sUA and gout flares and QoL data based on unpublished IMS observational study sponsored by manufacturer. Note, ERG for NICE TA raised concerns with reasons why manufacturer discarded 77% of the UK data set, and 51% of the overall data set from this unpublished IMS observational study, unclear if this was addressed in this analysis. Furthermore, concern that the link between sUA gout flares based on bivariate rather than multivariate analysis, unclear if this was addressed in this analysis.

(c) Intervention number in order of least to most effective (in terms of QALYs).

(d) Full incremental analysis of available strategies: first strategies are ruled out that are dominated (another strategy is more effective and has lower costs) or subject to extended dominance (the strategy is more effective and more costly but the incremental cost effectiveness ratio is higher than the next most effective option and so it would never be the most cost effective option); incremental costs, incremental effects and incremental cost effectiveness ratios are calculated for the remaining strategies by comparing each to the next most effective option.

(e) 2009 UK pounds. Cost components incorporated: Cost of flares (hospitalisation, diagnostics and outpatient visits), maintenance cost of gout treatment (outpatient visits, diagnostic laboratory tests, procedures and hospitalisation due to complications of gout) and drug costs (febuxostat 80mg or 120 mg was £0.87 per day and allopurinol 300mg was £0.047 per day).

1.1.9 Economic model

The existing health economic evidence assessing the cost effectiveness of allopurinol and febuxostat compares febuxostat to a fixed dose of allopurinol (300mg). The committee noted that in clinical practice people should be up titrated from 100mg of allopurinol to the required dose needed to achieve target serum urate levels (up to a maximum dose of 900mg) and acknowledged that in clinical practice a number of people would likely require a dose of allopurinol greater than 300mg to achieve target serum urate levels. The committee therefore concluded that the existing evidence base was not a representative comparison of best clinical practice. In addition, the committee also noted the significant price decrease of febuxostat 80mg since the previous TA[56, 80, 111, 112] (£0.87 per day compared to £0.13 per day).

Subsequently this topic was prioritised for original health economic modelling. However, after review of the clinical evidence and discussion with the committee it was concluded an original health economic model would unlikely reduce the uncertainty of the cost effectiveness of allopurinol and febuxostat. This was due to a number of reasons, including the lack of suitable additional clinical evidence published since the FACT and APEX[10,100] trials (the two trials included in the existing HE analyses). Of note, in two additional studies included in the clinical review (the FAST and FORWARD trials) people received higher doses of 300mg allopurinol, however the results for people achieving target serum urate levels were not stratified by dose. Therefore, treatment sequencing emulating a treat-to-target management strategy would not be possible to model and therefore any further modelling would likely be a duplication of the existing economic models and their associated limitations.

Another reason economic modelling was not conducted for this review question is because similar model assumptions would need to be made in terms of linking serum urate levels to the probability of gout flares (based on unpublished data in Beard 2013). In addition, given that the cost of febuxostat 80mg and allopurinol at doses greater than 300mg are so similar, it is likely that the results of any further modelling would be sensitive to any model assumptions made with regard to the effectiveness of allopurinol at doses greater than 300mg. Given these concerns, it was agreed to undertake a costing analysis rather than a cost-utility analysis to aid the committee in their consideration of the cost effectiveness of allopurinol and febuxostat. This analysis determined which ULT (allopurinol and febuxostat) was the least and most costly intervention over a one-year time horizon with a number of different scenarios to account for uncertainty.

A full write-up of the costing analysis can be found in Appendix I but a summary of data inputs and results can be found below.

Overview of the analysis

The costing analysis had a one-year time horizon and assessed the differences in costs between allopurinol and febuxostat using a treat-to-target management strategy. For the proportion of people receiving higher doses of allopurinol and febuxostat than the initial dose (100mg allopurinol and 80mg febuxostat) a treat-to-target management strategy was assumed whereby people were up titrated to higher doses of their ULT monthly. The costing analysis included the costs of:

- ULT
- Prophylaxis
- Initiation of ULT
- Up-titration of ULT

- Flares from initiating ULT (in the first 3 months)
- Flares from up-titrating ULT
- Flares post initiation / up titration for the remainder of the year

The costing analysis had 21 different scenarios.

Data inputs

- Data from the FAST trial[78] was used to obtain the proportion of people receiving different doses of each ULT and the proportion of people achieving target serum urate levels.
- Costs for allopurinol and febuxostat were taken from the British National Formulary[15] and estimated for one year of treatment.
- It was assumed people would receive 1mg of colchicine per day as prophylaxis for one month for each dose of drug they received. For example, someone who was up titrated to 400mg of allopurinol and remained on this dose for the remainder of the year would receive 4 months of prophylaxis.
- Initiation of ULT costs were included for all people. The cost of initiating ULT included the cost of nurse and GP time, the cost of a blood test to measure serum urate levels, and the cost of a renal function test.
- Up titration costs for doses greater than 100mg of allopurinol and 80mg febuxostat included nurse and GP time, and the cost of a blood test to measure serum urate levels. The total cost of up-titration for each drug dosage was dependent on how many times a person up-titrated. For example, someone receiving 300mg of allopurinol incurs the cost of up titrating ULT twice and the cost of initiating ULT once.
- The total cost of a gout flare was estimated by estimating the cost of a hospital treated flare, GP treated flare, the cost of obtaining a repeat prescription, and the cost of a self-managed flare. These costs were multiplied by estimates from the committee for the proportion of people being treated in each setting to estimate the total cost of a gout flare.
- To estimate the cost of gout flares in the first three months of treatment the average number of flares for the first three months of treatment for allopurinol were obtained from Borstad 2004[17] and the average number of flares for the first three months of treatment for febuxostat were taken from the FACT and APEX trials[10,100]. The average number of flares were multiplied by the cost of a gout flare to obtain the cost of gout flares in the first three months of treatment.
- The cost of gout flares for up titration were estimated for doses of allopurinol ≥400mmg of allopurinol. The cost of up titration was calculated based on data from Borstad 2004[17] and assuming a multiplier of 0.8, based on the assumption people experience fewer flares when up titrating compared to initiating ULT.
- The cost of flares for the remainder of the year (excluding the cost of flares from up titration) were estimated based on the proportion of people achieving target serum urate levels from the FAST trial[78], data from the FACT and APEX trials[10,100], and data form the unpublished IMS study.

Scenario analyses

A number of scenario analysis were conducted to account for the uncertainty in data inputs.

- In Scenarios 1 to 8 the proportion of people being treated for a gout flare in each respective setting (hospital treated flare, GP treated flare, the cost of obtaining a

repeat prescription, and the cost of a self-managed flare) were varied and thus the cost of a gout flare was varied.

- In Scenario 9 and 10 data from the FORWARD trial[28] was used for the proportion of people receiving different doses of allopurinol and febuxostat and the proportion of people achieving target serum urate levels. The lowest and highest estimated cost of a gout flare were used respectively.
- Scenarios 11 and 12 were the same as the base case analysis except the average number of flares for allopurinol in the first three months of treatment was taken from the FACT and APEX trials[10,100]. The lowest and highest cost of a gout flare were used respectively.
- In Scenarios 13 and 14 data from the FORWARD trial[28] was used for the proportion of people receiving different doses of allopurinol and febuxostat and the proportion of people achieving target serum urate levels. In addition, the average number of flares for allopurinol in the first three months of treatment was taken from the FACT and APEX trials[10,100]. The estimated lowest and highest cost of a gout flare were used respectively.
- Scenarios 15 and 16 used the pooled data from the FACT and APEX trials[10,100] for the proportion of people receiving each drug dose, the proportion of people achieving target serum urate levels, and the average the number of flares for the first three months of treatment. In this scenario people received a fixed dose of 300mg allopurinol. The lowest and highest cost of a gout flare were used respectively.
- In Scenarios 17 and 18 data from the Doherty trial[29] was used from the proportion of people receiving different doses of allopurinol. Data from the FAST trial[78] was used for the proportion of people receiving different doses of febuxostat and the proportion of people achieving target serum urate levels. The lowest and highest cost of a gout flare were used respectively.
- Scenarios 19 and 20 used data from the Doherty trial[29] for the proportion of people receiving different doses of allopurinol. Data from the FORWARD trial[28] was used for the proportion of people receiving different doses of febuxostat and the proportion of people achieving target serum urate levels. The estimated lowest and highest cost of a gout flare were used respectively.
- In Scenario 21 all data inputs were the same as the base case, except the proportion of people assumed to go to A&E prior a hospital treated flare was 50% as opposed to 100%. All additional settings for the lowest cost of a gout flare were used in this scenario analysis.

Results

The full results for the health economic costing analysis can be found Appendix I. A summary of the results is presented in Table 22. The base case data inputs for Scenario 1 – Scenario 8 include the proportion of people receiving each drug dosage and achieving target serum urate levels from the FAST trial[78], the number of gout flares for the first three months of treatment for allopurinol taken from Borstad[17], and the number of flares from the first three months of treatment for febuxostat taken from the FACT and APEX trials[10,100]. Scenarios 1, 3, 5 and 7 are the base case scenarios when 1% of people receive hospital treatment for a gout flare and scenarios 2, 4, 6 and 8 are the base case scenarios when 5% of people receive hospital treatment for a gout flare (please see Appendix I for more detail).

Table 22: Results summary

Scenario	Scenario description	Total cost allopurinol	Total cost febuxostat	Difference in cost (febuxostat vs allopurinol)	Cheapest intervention
Scenario 1, 3, 5, 7	Base case data inputs and the cost of a gout flare of £27.19 to £30.48	£139.73 to £144.36	£134.16 to £140.49	-£5.57 to -£3.88	Febuxostat
Scenario 2, 4, 6, 8	Base case data inputs and the cost of a gout flare of £52.17 to £55.60	£174.89 to £179.73	£182.17 to £188.77	£7.28 to £9.04	Allopurinol
Scenario 9	FORWARD trial[28] data for the proportion of people receiving each drug dosage and achieving target serum urate levels. Lowest cost of a gout flare (£27.19)	£132.77	£189.89	£57.12	Allopurinol
Scenario 10	FORWARD trial data[28] for the proportion of people receiving each drug dosage and achieving target serum urate levels. Highest cost of a gout flare (£55.60)	£173.64	£247.52	£73.87	Allopurinol
Scenario 11	FAST trial[78] data (base case) for the proportion of people receiving each drug dosage and achieving target serum urate levels. The average number of flares for allopurinol for the first 3 months was obtained from the FACT and APEX trial[10,100]. Lowest cost of a gout flare (£27.19)	£149.72	£134.16	-£15.56	Febuxostat
Scenario 12	FAST trial[78] data (base case) for the proportion of people receiving each drug dosage and achieving target serum urate levels. The average number of flares for allopurinol for the first 3 months was obtained from the FACT and APEX trial[10,100]. Highest cost of a gout flare (£55.60)	£200.16	£188.77	-£11.39	Febuxostat

Scenario	Scenario description	Total cost allopurinol	Total cost febuxostat	Difference in cost (febuxostat vs allopurinol)	Cheapest intervention
Scenario 13	FORWARD trial[28] data for the proportion of people receiving each drug dosage and achieving target serum urate levels. The average number of flares for allopurinol for the first 3 months was obtained from the FACT and APEX trial[10,100]. Lowest cost of a gout flare (£27.19)	£142.76	£189.89	£47.13	Allopurinol
Scenario 14	FORWARD trial[28] data for the proportion of people receiving each drug dosage and achieving target serum urate levels. The average number of flares for allopurinol for the first 3 months was obtained from the FACT and APEX trial[10,100]. Highest cost of a gout flare (£55.60)	£194.08	£247.52	£53.44	Allopurinol
Scenario 15	FACT and APEX trial[10,100] for the proportion of people receiving each drug dosage, achieving target serum urate levels, and the average number of flares for allopurinol for the first 3 months. Lowest cost of a gout flare (£27.19)	£113.85	£271.86	£158.01	Allopurinol
Scenario 16	FACT and APEX trial[10,100] for the proportion of people receiving each drug dosage, achieving target serum urate levels, and the average number of flares for allopurinol for the first 3 months. Highest cost of a gout flare (£55.60)	£164.44	£333.02	£168.58	Allopurinol
Scenario 17	Doherty trial[29] for the proportion of people receiving different doses of allopurinol. FAST trial[78] for the proportion of people receiving different doses of febuxostat and achieving target serum urate levels. Lowest cost of a gout flare (£27.19)	£187.68	£134.16	-£53.52	Febuxostat
Scenario 18	Doherty trial[29] for the proportion of people receiving different doses of allopurinol. FAST trial[78] for the proportion of people receiving different doses of febuxostat and achieving target serum urate levels. Highest cost of a gout flare (£55.60)	£233.88	£188.77	-£45.11	Febuxostat
Scenario 19	Doherty trial[29] for the proportion of people receiving different doses of allopurinol. FORWARD trial[28] for the proportion of people receiving different doses of febuxostat	£188.51	£189.89	£1.38	Allopurinol

Scenario	Scenario description	Total cost allopurinol	Total cost febuxostat	Difference in cost (febuxostat vs allopurinol)	Cheapest intervention
	and achieving target serum urate levels. Lowest cost of a gout flare (£27.19)				
Scenario 20	Doherty trial[29] for the proportion of people receiving different doses of allopurinol. FORWARD trial[28] for the proportion of people receiving different doses febuxostat and achieving target serum urate levels. Highest cost of a gout flare (£55.60)	£235.59	£247.52	£11.93	Allopurinol
Scenario 21	Base case data inputs and 50% of people go to A&E for a hospital treated flare as opposed to 100%. Lowest cost of a gout flare settings for all additional cost of a gout flare inputs.	£140.42	£135.10	-£5.32	Febuxostat

1.1.10 Unit costs

Relevant unit costs are provided below to aid consideration of cost effectiveness.

Table 23: Urate-lowering therapy costs

Resource	Unit costs per day	Unit cost per year[(a)]	Source
Allopurinol tablet 100mg-900mg	£0.04-£0.17	£12.91-£61.57[(b)]	BNF[15], accessed 17/02/2022
Allopurinol tablet 300mg	£0.05	£17.87	
Febuxostat tablet 80mg-120mg	£0.09-£0.87	£31.77-£317.77	

(a) Estimated by the unit cost per day and multiplied by the number of days in the year (assuming 100% adherence).
(b) The highest cost for allopurinol is for 800mg, this consists of two 300mg tablets and two 100mg tablets.

1.1.11 Evidence statements

1.1.11.1 Economic

- One cost-utility analysis found that febuxostat (80mg or 120mg one daily) was cost effective compared to allopurinol (fixed dose 300mg once daily) for first line treatment of adults with hyperuricaemia in whom urate deposition has already occurred (ICER: £16,324 per QALY gained). This analysis was assessed as partially applicable with potentially serious limitations.
- One cost-utility analysis found that a sequential treatment of first line allopurinol (300mg) followed by second line febuxostat (80mg then 120mg) was cost effective compared to no treatment and allopurinol 300 mg (ICER £3,591 per QALY gained compared to allopurinol only). It also found that a sequential treatment of first line allopurinol (300mg) followed by second line febuxostat (80mg then 120mg) dominated (less costly and more effective) a sequential treatment of first line febuxostat (80mg then 120mg) followed by allopurinol (300mg) and a sequence of febuxostat 80mg then 120mg. All comparisons were for treatment of adults with chronic gout and established hyperuricaemia. This analysis was assessed as partially applicable with potentially serious limitations.
- One costing analysis was conducted by the guideline developer comparing the costs of allopurinol and febuxostat for one year of treatment. The results of the costing analysis indicated there were minimal cost differences between the two interventions being compared. This analysis was assessed as partially applicable with potentially serious limitations.

1.1.12 The committee's discussion and interpretation of the evidence

1.1.12.1. The outcomes that matter most

The committee considered the following outcomes important for decision-making: health-related quality of life, pain, joint swelling/joint inflammation, joint tenderness, frequency of flares, patient global assessment of treatment success, adverse events (cardiovascular, renal, and gastrointestinal), adverse events and complications of gout (radiographic joint damage, renal stones, tophi), serum urate levels, admission (hospital and A&E/urgent care) and GP visits.

The committee considered that the impact on day-to-day quality of life was extremely important, as gout can affect many aspects of a person's life including the ability to work. The condition is characterised by severe pain, therefore pain reduction is an important outcome of treatment. People with gout experience most pain when flares occur, and so reducing the frequency of flares along with reduction in joint swelling, inflammation, and joint tenderness can improve a person's discomfort and pain. The committee decided to combine joint swelling and joint inflammation as an outcome as they are synonymous for people with gout. Many of the outcomes may be affected by a person's perception of their gout and therefore patient global assessment of treatment success was important to measure.

The committee noted that cardiovascular, renal, and gastrointestinal events are the most commonly reported adverse events by patients. Total adverse events and complications of gout were also included to ensure that any committee decisions on treatments are informed by all related adverse events. Reduction in complications of gout and admissions to primary and secondary care are beneficial to a person with gout, as well as a potential reduction in NHS costs. The committee agreed that reduction of serum urate level to target is a good indicator that a patients' gout related flare will reduce and stop. The committee recognised this was a surrogate measure to assess the benefit of treatment, but included it as an objective measurement to monitor long-term suppression of serum urate.

Where possible short-term (up to three months), medium-term (three to twelve months) and long-term (more than twelve months) outcomes were reported. The committee noted that although long-term improvement and reduction in pain is the ultimate aim, the short to medium term benefit and improvement in quality of life is important to evaluate, and most of the evidence was in the short or medium-term.

For first line treatment, frequency of flares, adverse events including renal, and GI and serum urate levels were reported. No evidence was reported on health-related quality of life, pain, patient global assessment of treatment success, admissions, and GP visits.

For the unclear/mixed treatment line, frequency of flares, adverse events including cardiovascular, renal, and GI adverse events and tophi were reported. There was no evidence found for health-related quality of life, pain, joint swelling/joint inflammation, joint tenderness, patient global assessment of treatment success, admissions, and GP visits.

Second line outcomes included joint tenderness, CV renal and GI adverse events, serum urate levels and hospital admissions. No evidence was reported for health-related quality of life, pain, joint swelling/inflammation, frequency of flares, patient global assessment of treatment success, complications of gout and GP visits.

1.1.12.2 The quality of the evidence

Evidence from 17 randomised controlled trials (RCTs) were included in the review. The review aimed to evaluate long term urate lowering therapies (ULT) for the management of gout, however very little evidence was in the long-term. The number of strata (line of therapy, CKD status) and different methods of reporting outcomes meant that little data could be combined and meta-analysed, and the studies were relatively small so there was limited evidence available. The committee wished to establish first line and second line treatment options, however the studies did not always clearly report, or had mixed, treatment lines. In order to provide enough evidence, the category of unclear/mixed treatment line was created, to ensure all evidence in the area was included, however they did not strictly answer the question. Similarly, CKD status was often not stated or was a mix of CKD and non-CKD populations within the studies which was not useful in informing recommendations for different CKD populations.

The committee noted no studies had been identified for uricosuric or uricase therapies, but as they are not used as a primary ULT they agreed further research is unlikely to impact on clinical practice and not a priority area for a research recommendation. The committee did not want to search for cohort studies, as RCTs are more robust, and therefore preferential for a question about the effectiveness of drug treatments.

First-line treatment:

Only five studies were included, two of which were very small. The quality of evidence ranged from very low to high, the lower ratings were mostly due to risk of bias and imprecision. The main reasons for high or very high risk of selection bias were due to a lack of allocation concealment and attrition bias due to a high rate of missing data. Febuxostat compared to allopurinol (in a non-CKD population was the only comparison that was able to be meta-analysed for frequency of flares and number of patients achieving sUA. There was inconsistency for frequency of flares at 24 weeks in the non-CKD population when comparing allopurinol (300mg) to febuxostat (80 mg), but subgroup analysis to investigate heterogeneity could not be performed because there were only two studies. For mixed CKD there was only one small study (n=34), of allopurinol, at 100-200mg which is a lower dose than is thought beneficial. The lack of data, and variability of quality for first line-treatment, meant the committee had lower confidence in the results.

Unclear/mixed treatment line:

Most of the outcomes were serum urate level change or target achievement, which were considered as surrogate outcomes for gout flares. The quality of the evidence varied from very low to high, with outcomes being downgraded mainly due to selection bias, attrition bias and imprecision. Inconsistency was found for frequency of flares at 3 months in a mixed CKD population, but it was not possible to conduct subgroup analysis to investigate heterogeneity as there were only 2 studies. The committee acknowledged the variability in quality of evidence and the lack of clarity of treatment line.

Second line treatment:

For second line treatment there was limited evidence from two studies. One study included allopurinol 300mg compared to placebo in a non-CKD population with the quality of the evidence ranging from low to moderate, lowered by selection bias due to insufficient information allocation concealment and imprecision. Another study for allopurinol (mixed dose, mean 279mg) compared to febuxostat (mixed dos e, mean 81mg) in a mixed CKD population, the quality of the evidence ranged from low to moderate rating. This was due to imprecision where the wide confidence intervals of effect estimates crossed the minimum clinically important difference (MID) thresholds resulting in uncertainty in the effect. The lack of evidence and uncertainty in the effect was noted by the committee.

1.1.12.3 Benefits and harms

First-line treatment:

The committee noted that allopurinol and febuxostat are the only two available licensed choice of drugs where evidence was identified for urate-lowering treatment of gout. For first line treatment, Febuxostat showed a clinical benefit for reduction in the frequency of flares when compared to allopurinol and for reaching serum urate target levels compared to allopurinol and placebo in a non-CKD population, but there was uncertainty around the effect sizes. The committee noted that serum urate levels is a proxy outcome but is useful in clinical practice as long-term reduction of serum urate can stop gout flares. More informative

clinical outcomes for clinical decision-making such as the frequency of flares, was rarely reported, and cardiovascular adverse events which were not reported. In contrast Allopurinol showed benefits for adverse events such as fewer withdrawals and gastrointestinal issues when compared with placebo. When febuxostat was compared to allopurinol in a non-CKD population there were fewer renal adverse events in the allopurinol arm but no difference in gastrointestinal adverse events. Renal adverse events were thought more serious than gastrointestinal, so the benefit was weighted towards allopurinol. In a mixed CKD study, allopurinol had higher joint inflammation and joint tenderness than the placebo group but had fewer adverse events. However, there was uncertainty in these results as the study was very small and the event rate was low. Overall, Febuxostat was more effective, but Allopurinol had lower adverse events. The findings were based on limited data (few studies, drugs compared to placebo had very small numbers of participants and studies had a variable GRADE ratings) which made it difficult for the committee to conclude on balance the best ULT for first line treatment of gout, therefore both were recommended. Most of the evidence was in a non-CKD population, and one small study included a mixed CKD population, no evidence was found for stage 3 or 4-5 CKD. The committee did not think the evidence was strong enough to make separate recommendations based on CKD status.

Unclear/mixed treatment line

The mixed first-line/second-line data mainly showed clinical benefits for achievement of the target serum urate level for Febuxostat, or Allopurinol compared with placebo in mixed CKD populations. Febuxostat 80mg was more likely to achieve a target serum urate level than allopurinol 300mg in a mixed CKD population, whereas allopurinol 300mg was more beneficial in a non-CKD population for the same outcome. There were clinical benefits of Allopurinol for total adverse events when compared to Febuxostat 80mg and for frequency of flares compared to Febuxostat 120mg in a mixed CKD population. This dosage (120mg) of Febuxostat not only had a clinical harm for frequency of flares, there was no difference for GI events, cardiovascular events and tophi in a mixed CKD population. There was a clinical harm for febuxostat compared to placebo for frequency of flares in a stage 3 CKD population. One treat-to-target study of Allopurinol 300-600mg compared to Febuxostat 80mg/120mg in a non-CKD population (unclear or mixed line treatment) found a clinical benefit of Febuxostat for achieving serum urate level <6mg/dL and reducing adverse events in the long-term. Overall, the results were mixed for effectiveness of Allopurinol and Febuxostat at the lower dose, more who were taking Febuxostat achieved the serum urate level target than Allopurinol but those on Allopurinol had lower frequency of flares. There was no clinical difference for Febuxostat at the higher dosage of 120mg, except for higher frequency of flares. This category was a mix of first and second line (or it was unclear) so it was difficult for the committee to distinguish what the evidence was showing, with regards to first or second line treatment. There was no evidence found for stage 4-5 CKD population and the evidence was mainly mixed CKD so no specific recommendations were made for people with CKD.

Second line treatment:

For second line ULT, there was clinical benefit for cardiovascular adverse events and attaining the target serum urate level for allopurinol compared with placebo in a non-CKD population. This was evidence was from a small RCT. There was a clinical benefit of Febuxostat for achieving the target serum urate level compared with allopurinol in a mixed CKD population. There was no difference between the drugs for adverse events

(cardiovascular, renal or urinary or GI) or hospitalisations in a mixed CKD population. The evidence was based on one very large trial. There was no evidence found for CKD stage 3 or 4-5. The committee did not make recommendations on these CKD status.

Overall

The committee discussed the evidence and concluded there was not enough evidence between allopurinol and febuxostat to justify recommending one over the other for first line treatment of gout, or by CKD status. Currently, febuxostat is not frequently prescribed because clinicians are used to prescribing allopurinol and febuxostat is associated with an increase in flare rate when it is initiated. The committee noted that febuxostat is easier to titrate than allopurinol as there are only two available doses and once daily dosing may result in greater adherence than with allopurinol. The evidence showed that achievement of target serum urate level is more frequently achieved with febuxostat, however, it also causes more flares and therefore more people would need prophylaxis with colchicine, NSAIDs or corticosteroids.

Most studies included in the evidence review compared febuxostat to sub-optimal doses of allopurinol (up to 300 mg) and many patients would need higher doses of allopurinol to achieve a target serum urate level. Based on the lack of conclusive evidence in support of one drug over another and their clinical experience, the committee agreed that allopurinol and febuxostat should both be offered as a first line treatment dependent on comorbidities and patient preference. For second-line treatment there was less evidence available and similarly to first line not enough for the committee to support one drug over another. They therefore made a weaker recommendation to consider either drug if the target serum urate level has not been reached or not tolerated by the first-line treatment. For further details on how to reach target dose see recommendation 1.5.5, which details that monthly serum levels should guide dose increases.

The committee were aware of the MHRA guidance that Febuxostat should be used with caution in people with cardiovascular disease. On this basis the committee made a second recommendation to offer allopurinol for people with major cardiovascular disease as first line treatment, however they noted that this may change in due course in light of new evidence considered by the MHRA.

1.1.12.4 Cost effectiveness and resource use

Two cost utility analyses were identified and presented to the committee for this review. The first was a cost-utility analyses that formed part of a NICE technology appraisal (TA) submission for febuxostat (NICE 2008). This analysis found that febuxostat (80mg or 120mg one daily) was cost effective compared to allopurinol (fixed dose 300mg once daily) for first line treatment of adults with hyperuricaemia in whom urate deposition has already occurred (ICER: £16,324 per QALY gained). The analysis was from a UK NHS perspective and had a 2-year time horizon.

This analysis was assessed as partially applicable with potentially serious limitations. The main applicability concerns were that this analysis was for first line treatment only and did not include allopurinol given in a titrated regimen and that it did not include other comparators or treatment sequences. In addition, no subgrouping for renal impairment was included. The NICE TA evidence review group (ERG) had concerns regarding the QoL assumption: that lower sUA levels would produce utility gains independently of the incidence of gout flares. In

addition, it noted that EQ-5D values from some patients were not plausible, with some without a flare rating their utility as worse than death.

There were also several methodological limitations with the model. Firstly, the model structure and comparators did not allow for sequential treatment or treatment discontinuation and the clinical data used in the model was pooled and not meta-analysed. There were also concerns regarding the use of sUA concentration as a surrogate outcome for gout flares. In addition, the ERG also raised concerns as to why the manufacturer discarded 77% of the UK data set, and 51% of the overall data set from IMSIII observational study, which was used to link sUA levels and number of gout flares expected.

Although the analysis found that first line febuxostat was cost effective compared to a fixed dose of allopurinol. The analysis did not demonstrate that febuxostat was more clinically or cost effective compared to the more appropriate comparator of allopurinol up titrated in accordance with established best clinical practice.

A second cost-utility analysis formed part of the Scottish Medicines Consortium (SMC) appraisal of febuxostat (Beard 2013). This analysis found that a sequential treatment of first line allopurinol (300mg) followed by second line febuxostat (80mg then 120mg) was cost effective compared to no treatment and allopurinol 300mg (ICER £3,591 per QALY gained compared to allopurinol only). It also found that a sequential treatment of first line allopurinol (300mg) followed by second line febuxostat (80mg then 120mg) dominated (less costly and more effective) a sequential treatment of first line febuxostat (80mg then 120mg) followed by allopurinol (300mg) and a sequence of febuxostat 80mg then 120mg. All comparisons were for treatment of adults with chronic gout and established hyperuricaemia. The analysis was from a Scottish NHS perspective and had a 5-year time horizon.

This analysis was assessed as partially applicable with potentially serious limitations. The limitations were similar to those highlighted in the NICE TA as the data sources were primarily the same. Additional limitations highlighted by the SMC were that the base case time horizon was short, there was a lack of data to estimate the impact of potential dose titration above 300mg/day for allopurinol, uncertainty over the impact of prophylaxis on short term flare rates, and uncertainty over the quality-of-life impact (and disutility) associated with sUA level.

Beard 2013 improved on a number of the concerns highlighted in the NICE TA submission such as inclusion of treatment sequences and up-titration of allopurinol beyond 300mg (although this is only done in a sensitivity analysis and was based on assumptions rather than clinical data). Concerns remain as to the data source used to link sUA to probability of gout flares and EQ5D data (by sUA level and for flares) which come from an unpublished observational study. As a result of this economic analysis the SMC recommended febuxostat when treatment with allopurinol was inadequate, not tolerated or contraindicated.

The committee noted that in current practice people will typically be initiated on ULT (100mg allopurinol), and then little to no follow-up is provided to ensure people have achieved target serum urate levels. People may receive or obtain a follow-up appointment and be up titrated to 200mg or 300mg allopurinol if they have persistent flares or they seek additional treatment for their gout. This however, is at odds with best clinical practice, which is for people to be initiated on 100mg of allopurinol and up titrated monthly until target serum urate levels have been achieved. In general, people with gout who achieve target serum urate levels will experience less frequent and severe flares thus resulting in improved quality of life and lower gout flare management costs.

Unit costs for allopurinol and febuxostat were presented to the committee. Of note, the cost of febuxostat 80mg has reduced substantially since Beard 2013 (from £0.87 to £0.09 per unit) and the cost of allopurinol 300mg has marginally increased (£0.047 to £0.049) A

committee member noted that the cost febuxostat 120mg is likely to reduce in the next year as it is now off patent. This may therefore impact the conclusions of Beard 2013 because the differences in QALYs were very small. The incremental QALY reported in Beard was 0.001 more for a sequence of first line allopurinol followed by febuxostat versus a sequence of first line febuxostat followed by allopurinol. The total costs were £230 more for febuxostat first line versus allopurinol first line (of which £150 is attributed to drug-related costs). It is not possible to adjust these for current prices as the proportion of patients receiving each drug and for what duration in each sequence were not reported.

The need to conduct a de novo model was discussed with the committee. However, concerns were raised regarding the feasibility of modelling allopurinol at doses greater than 300mg as there is no clinical evidence for this dose. After review of the clinical evidence and discussion with the committee it was concluded original health economic modelling would unlikely reduce the uncertainty of the cost effectiveness of allopurinol and febuxostat due to a lack of appropriate clinical evidence published since the FACT and APEX trials (the two trials included in the existing HE analyses). Although the FAST and FORWARD trials included in the clinical were published after the FACT and APEX trials, these trials did not present results for people achieving target serum urate levels by dose. Therefore, any further modelling would likely be a duplication of the existing economic models and their associated limitations, such as the lack of evidence for the use of allopurinol at doses greater than 300mg, or that similar model assumptions would need to be made in terms of linking sUA to probability of gout flares (based on unpublished data in Beard 2013). In addition, given that the cost of febuxostat 80mg and allopurinol at doses greater than 300mg are so similar, it is likely that the results of any further modelling would be sensitive to any model assumptions made with regard to the effectiveness of allopurinol at doses greater than 300mg. Given these concerns, it was agreed to undertake a costing analysis rather than a cost-utility analysis to aid the committee in their consideration of the cost effectiveness of allopurinol and febuxostat. This analysis determined which ULT (allopurinol & febuxostat) was the least and most costly intervention over a one-year time horizon with a number of different scenarios conducted to account for uncertainty.

The results indicated allopurinol was the cheapest intervention in 12 out of the 21 scenarios. The results of the costing analysis were most sensitive to the proportion of people receiving 120mg of febuxostat due to the higher price of 120mg febuxostat. In addition, in the base case scenarios the results of the costing analysis were sensitive to whether 1% or 5% of people received treatment for a gout flare in hospital. When 1% of people received treatment for a gout flare in hospital febuxostat was cheaper (range £4.05 to £5.82). However, when 5% of people received treatment in hospital for a gout flare allopurinol was cheaper (range £7.10 to £8.80).

As mentioned above, the committee anticipate the cost of febuxostat 120mg to decrease within the year, although they could not provide an exact price estimate. When the price of 120mg febuxostat falls this will likely have an impact on the results for the scenarios where the FORWARD trial data was used (21.7% of people received 120mg febuxostat). This price decrease would unlikely result in febuxostat being cheaper but would decrease the price difference between allopurinol and febuxostat.

A significant limitation of our analysis is that a number of assumptions were required for various data inputs. In addition, data for the mean number of flares for the remainder of the year were obtained from the previous TA which used the IMS unpublished data. This was heavily criticised by the ERG, but no additional data was available for the purpose of our analysis.

The committee qualitatively discussed how the results of the analysis may be impacted if the costs were calculated for a longer duration or if quality of life had been incorporated into the costing analysis. Of note, a longer time horizon and inclusion of quality-of-life data was not

included in our analysis due to the reliance on the IMS observational data for calculating the average number of flares people experience in the long run and quality-of-life.

Over time, the committee concluded febuxostat may be more expensive than allopurinol but noted this would be highly dependent on the proportion of people receiving lower doses of allopurinol and 120mg febuxostat. The committee acknowledged that the proportion of people receiving different dosages of allopurinol to achieve target serum urate levels probably lies within the range of the proportions observed in the FAST and Doherty trials (i.e., the proportion of people receiving higher doses of allopurinol would probably be marginally higher than those observed in the FAST trial). Most people achieve target serum urate levels on 80mg of febuxostat (as in line with the proportions observed in the FAST trial – 97.5%). 80mg of febuxostat costs £0.10 per unit resulting in a yearly cost of £36.50. For the cost of allopurinol, once people receive 400mg or more, the yearly ULT cost is the same or higher than the cost for 80mg of febuxostat. However, once people require 120mg of febuxostat the yearly cost of this is much higher (£317.77) compared to the yearly cost of the most expensive dose of allopurinol (£67.83 – 800mg allopurinol). Overall, in terms of ULT costs, ≥500mg allopurinol is more expensive than 80mg of febuxostat, ≤300mg allopurinol is cheaper than 80mg febuxostat, and 400mg allopurinol and 80mg febuxostat costs the same. The committee acknowledged that these costs do not include the costs of up titration and prophylaxis and noted it was difficult to accurately estimate what doses of allopurinol people would require to achieve target serum urate levels. However, because of the higher costs associated with 120mg of febuxostat the committee concluded febuxostat may be slightly more expensive in the long run. Although, once again, this highly dependent on the proportion of people receiving different doses of allopurinol. In addition, if as expected, the price of 120mg febuxostat decreases the long-term cost difference between allopurinol and febuxostat will be negligible, or febuxostat may become the cheaper treatment option.

The incremental QALYs in Beard 2013 were 0.001 more for a sequence of first line allopurinol followed by febuxostat versus a sequence of first line febuxostat followed by allopurinol. Although this study compared a fixed dose of 300mg allopurinol the committee concluded the QALY differences may not be dissimilar if people received either ULT with a treat-to-target management strategy. People receiving febuxostat experience a greater number of flares upon initiation of ULT. However, more people achieve target serum urate levels with febuxostat (97% compared to 86%), and subsequently fewer flares are observed in the long run. Once again, because the data used to estimate the quality of life was based on the IMS data the committee accepted the uncertainty surrounding the QALY differences but concluded the differences in utility would likely be minimal between the two treatment options, although the direction of change may be different.

The committee also noted that in current practice adherence to allopurinol is poorer compared to febuxostat over time. Poor adherence to medication will likely result in increased flares and therefore people receiving febuxostat may have better long-term outcomes. However, incorporating adherence into the costing analysis would have required a number of assumptions to be made thus limiting the interpretive value of the results. The proportion of people achieving target serum urate levels in the FAST trial was relatively constant for both allopurinol and febuxostat over the 7 year follow up period, but the committee discussed that in trial settings people are generally more compliant with their medication. In addition, a large number of people were lost to follow-up over the follow up period of the FAST trial. Median follow-up was 1,467 days and at the beginning of the trial there were 5,057 participants. However, at year four and seven there were 2,257 and 168 participants respectively. Therefore, the high levels of discontinuation in the trial may explain why the proportion of people achieving target serum urate levels was relatively constant over time.

The committee noted there are a number of reasons adherence to allopurinol may be worse in clinical practice, noting the higher pill burden associated with allopurinol (for all doses except 100mg and 300mg allopurinol). In addition, the committee noted one of the reasons adherence to febuxostat may be better is because febuxostat is currently prescribed as a second-line treatment. Therefore, people may be more compliant with their medication because failure with second-line treatment would result in no additional treatment being available.

In all scenarios of the costing analysis the difference in long-terms costs were very small where the difference in costs ranged from £0.37 to £2.53. Because the long-term cost of flares were calculated based on the IMS data and the proportion of people achieving target serum urate levels, additional research on the relationship between target serum urate levels and the number of flares people experience receiving allopurinol and febuxostat using a treat-to-target management strategy would be required for these cost differences to be sufficiently assessed. The committee noted this may be addressed in the research recommendation on which target serum urate level is best using a treat to target strategy to treat gout (see evidence review K).

Overall, the committee made a recommendation for either allopurinol or febuxostat as a first-line therapy when initiating treat-to-target ULT unless people have major cardiovascular disease, in which case allopurinol should be prescribed as first-line treatment. This is a change in clinical practice as currently people are offered allopurinol as a first-line treatment.

The committee acknowledged that there was uncertainty in the results of the costing analysis due to a lack of data being available to estimate the cost of a gout flare and lack of additional data being available to estimate the mean number of flares. However, the committee were confident there were minimal cost differences between allopurinol and febuxostat when using a treat-to-target management strategy for treatment with ULT.

The committee discussed the change in current practice to offer either ULT as first-line treatment could result in less time being spent with patients because the majority of people receiving febuxostat only require 80mg to achieve target serum urate levels and therefore are not up titrated further. In addition, for the small proportion of people requiring 120mg febuxostat these people are only up-titrated once compared to people on higher doses of allopurinol.

A sub-group analysis was not conduced for a CKD population due to a lack of evidence available, but the committee noted people with gout and CKD would be prescribed lower doses of allopurinol. In the scenario analyses where lower doses of allopurinol were prescribed allopurinol was cheaper than febuxostat and therefore may be more cost effective to prescribe for people with CKD. The committee did however note the most cost effective ULT would be person dependent.

This recommendation is not expected to directly lead to a substantial resource impact because the differences in costs between allopurinol and febuxostat are minimal. However, of note, if more people are offered ULT as a result of the recommendations made as part of this guideline there will likely be a significant resource impact associated with the increased uptake of ULT.

1.1.12.5 Other factors the committee took into account

The committee recognised that unlicensed uricosuric drugs such as benzbromarone and probenecid are used to treat gout in rheumatology clinics when patients are unresponsive to, intolerant of, or have contraindications to allopurinol and febuxostat. These treatments were not included within the question protocol because they do not have a licence for use in the UK and would not be recommended by NICE guidelines for use within the NHS.

1.1.13 Recommendations supported by this evidence review

This evidence review supports recommendations 1.5.8 to 1.5.10.

1.1.14 References

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Appendices

Appendix A – Review protocols

Review protocol for first-line urate lowering therapies

ID	Field	Content
0.	PROSPERO registration number	CRD42021230893
1.	Review title	Which urate-lowering therapies (either alone or in combination with each other) are the most clinically and cost effective as second line treatment if first line is not tolerated or provides inadequate control
2.	Review question	In people with gout (including people with gout and chronic kidney disease), which urate-lowering therapies (either alone or in combination with each other) are the most clinically and cost effective as second line treatment if first line is not tolerated or provides inadequate control?
3.	Objective	To determine which urate-lowering therapy or combinations of urate-lowering therapies are most clinically and cost-effective as second line treatment if first line is not tolerated or provides inadequate control.
4.	Searches	The following databases (from inception) will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE Medline search strategy to be quality assured using the PRESS evidence-based checklist (see methods chapter for full details) Searches will be restricted by: • English language studies • Human studies

		The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review.
5.	Condition or domain being studied	Gout (including people with gout and chronic kidney disease)
6.	Population	Inclusion: Adults (18 years and older) with gout who have used urate-lowering therapies (ULT) as first-line treatment but are inadequately controlled or first-line treatment is not tolerated Strata: **ULT inadequately controlled** • People with CKD (stage 3) – inadequately controlled • People with CKD (stages 4-5) – inadequately controlled • People without CKD or people with CKD stages 1-2 – inadequately controlled • Mixed population (people with CKD and people without CKD) – inadequately controlled **ULT not tolerated** • People with CKD (stages 3) – not tolerated • People with CKD (stage 4-5) – not tolerated • People without CKD or people with CKD stages 1-2 – not tolerated • Mixed population (people with CKD and people without CKD) – not tolerated Exclusion: People with calcium pyrophosphate crystal deposition, including pseudogout.
7.	Intervention/Exposure/Test	Urate lowering therapies (commonly used in clinical practice in the UK) Xanthine oxidase inhibitor • Allopurinol (dosages separated by severity of gout – mild, moderate, and severe) • Febuxostat 80mg and 120mg (analysed separately)

		Uricosuric • Amlodipine • Fenofibrate • Losartan • Vitamin C • Uricase • Rasburicase • Combine all doses (doses much higher or lower than standard doses will be excluded). Dosages used in the UK are detailed in the methodology anything outside of these would be excluded. Febuxostat 80mg and 120mg will be analysed separately. • Combinations of pharmacological interventions • Within drug class comparisons will be made
8.	Comparator/Reference standard/Confounding factors	• Compared to each other • Standard care (dietary advice, lifestyle modifications, prophylaxis for flares) • No treatment • Placebo
9.	Types of study to be included	RCT Systematic reviews of RCTs If insufficient RCT evidence is available (no or little evidence for interventions/comparisons), search for non-randomised studies (prospective and retrospective cohort studies will be considered if they adjust for key confounders: • Age • Gender Published NMAs will be considered for inclusion.
10.	Other exclusion criteria	Non-English language studies. Conference abstracts will be excluded as it is expected there will be sufficient full text published studies available

11.	Context	There are a range of ULT which can be used in adults with gout who do not respond to first-line ULT in various healthcare settings including primary care and secondary care.
12.	Primary outcomes (critical outcomes)	All outcomes are considered equally important for decision making and therefore have all been rated as critical: • health-related quality of life (e.g., as described by SF-36, Gout Assessment Questionnaire (GAQ) and the Gout Impact Scale (GIS) or other validated gout-specific HRQoL measures • pain (measured on a visual analogue scale (VAS) or numerical rating scale such as the five-point Likert scale, or reported as pain relief of 50% or greater) • joint swelling/joint inflammation • joint tenderness • frequency of flares • patient global assessment of treatment success (response to treatment) (e.g., Likert scales, visual analogue scales (VAS), numerical ratings scales (NRS)) • adverse events – (1) cardiovascular, (2) renal and (3) gastrointestinal (e.g., diarrhoea) (total adverse events will be reported if the specific types of adverse events are not reported) • adverse events and complications of gout: o radiographic joint damage o renal stones o tophi • serum urate levels • admissions (hospital and A&E/urgent care) • GP visits Timepoints: short-term (less than three months), medium-term (three to 12 months) and long-term (more than 12 months) duration.
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations, and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if

		necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary. Study investigators may be contacted for missing data where time and resources allow.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual For Intervention reviews • Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) • Randomised Controlled Trial: Cochrane RoB (2.0) • Non-randomised study, including cohort studies: Cochrane ROBINS-I
16.	Strategy for data synthesis	• Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). Fixed-effects (Mantel-Haenszel) techniques will be used to calculate risk ratios for the binary outcomes where possible. Continuous outcomes will be analysed using an inverse variance method for pooling weighted mean differences. Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. An I^2 value greater than 50% will be considered indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented pooled using random-effects.

		If sufficient data is available and it is methodologically appropriate, network meta-analysis (NMA) will be conducted. NMA will be prioritised for the following outcomes, based on the importance of the outcomes for decision-making and the committee's knowledge about the availability of evidence: • Serum urate levels • Frequency of flares • GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/ • Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome. • WinBUGS will be used for network meta-analysis, if possible given the data identified.	
17.	Analysis of sub-groups	Subgroups that will be investigated if heterogeneity is present: • Setting (primary and secondary) • Choice of drug (drugs within the class, based on the intervention arm only) Age (over 65 years vs under 65 years)	
18.	Type and method of review	☒	Intervention
		☐	Diagnostic
		☐	Prognostic
		☐	Qualitative
		☐	Epidemiologic
		☐	Service Delivery
		☐	Other (please specify)

19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date	18th September 2020		
22.	Anticipated completion date	13th June 2022		
23.	Stage of review at time of this submission	Review stage	Started	Completed
		Preliminary searches	☑	☑
		Piloting of the study selection process	☑	☑
		Formal screening of search results against eligibility criteria	☑	☑
		Data extraction	☐	☐
		Risk of bias (quality) assessment	☐	☐
		Data analysis	☐	☐
24.	Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail managementofgout@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and National Guideline Centre		
25.	Review team members	From the National Guideline Centre: Gill Ritchie [Guideline lead] Sedina Lewis [Senior systematic reviewer] Audrius Stonkus [Systematic reviewer] Alexandra Bonnon [Health economist] Amber Hernaman [Project manager] Joseph Runicles [Information specialist]		
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.		

27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/
29.	Other registration details	[Give the name of any organisation where the systematic review title or protocol is registered (such as with The Campbell Collaboration, or The Joanna Briggs Institute) together with any unique identification number assigned. If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here. If none, leave blank.]
30.	Reference/URL for published protocol	[Give the citation and link for the published protocol, if there is one.]
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE. [
32.	Keywords	[Give words or phrases that best describe the review.]

33.	Details of existing review of same topic by same authors	[Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible. NOTE: most NICE reviews will not constitute an update in PROSPERO language. To be an update it needs to be the same review question/search/methodology. If anything has changed it is a new review]	
34.	Current review status	☐	Ongoing
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35..	Additional information	[Provide any other information the review team feel is relevant to the registration of the review.]	
36.	Details of final publication	www.nice.org.uk	

Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2005 abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[83] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies. *Setting:* • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden).

	• OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2005 or later but that depend on unit costs and resource data entirely or predominantly from before 2005 will be rated as 'Not applicable'. • Studies published before 2005 will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B – Literature search strategies

- In people with gout (including people with gout and chronic kidney disease), which urate-lowering therapies (either alone or in combination with each other) are the most clinically and cost effective for first-line treatment?

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[82]

For more information, please see the Methodology review published as part of the accompanying documents for this guideline.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 24: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 06 July 2021	Randomised controlled trials Systematic review studies Observational studies Exclusions (animal studies, letters, comments)
Embase (OVID)	1974 – 06 July 2021	Randomised controlled trials Systematic review studies Observational studies Exclusions (animal studies, letters, comments)
The Cochrane Library (Wiley)	Cochrane Reviews to 2021 Issue 7 of 12 CENTRAL to 2021 Issue 7 of 12	None

Medline (Ovid) search terms

1.	exp Gout/
2.	gout*.ti,ab.
3.	toph*.ti,ab.
4.	podagra.ti,ab.
5.	pseudogout.ti,ab.
6.	or/1-5
7.	letter/
8.	editorial/

9.	news/
10.	exp historical article/
11.	Anecdotes as Topic/
12.	comment/
13.	case report/
14.	(letter or comment*).ti.
15.	or/7-14
16.	randomized controlled trial/ or random*.ti,ab.
17.	15 not 16
18.	animals/ not humans/
19.	exp Animals, Laboratory/
20.	exp Animal Experimentation/
21.	exp Models, Animal/
22.	exp Rodentia/
23.	(rat or rats or mouse or mice).ti.
24.	or/17-23
25.	6 not 24
26.	Limit 25 to English language
27.	randomized controlled trial.pt.
28.	controlled clinical trial.pt.
29.	randomi#ed.ti,ab.
30.	placebo.ab.
31.	randomly.ti,ab.
32.	Clinical Trials as topic.sh.
33.	trial.ti.
34.	or/27-33
35.	Meta-Analysis/
36.	exp Meta-Analysis as Topic/
37.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
38.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
39.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
40.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
41.	(search* adj4 literature).ab.
42.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
43.	cochrane.jw.
44.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
45.	or/35-44
46.	Epidemiologic studies/
47.	Observational study/
48.	exp Cohort studies/

49.	(cohort adj (study or studies or analys* or data)).ti,ab.
50.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
51.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
52.	Controlled Before-After Studies/
53.	Historically Controlled Study/
54.	Interrupted Time Series Analysis/
55.	(before adj2 after adj2 (study or studies or data)).ti,ab.
56.	exp case control studies/
57.	case control*.ti,ab.
58.	Cross-sectional studies/
59.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
60.	or/46-59
61.	26 and (34 or 45 or 60)

Embase (Ovid) search terms

1.	exp Gout/
2.	gout*.ti,ab.
3.	toph*.ti,ab.
4.	podagra.ti,ab.
5.	pseudogout.ti,ab.
6.	or/1-5
7.	letter.pt. or letter/
8.	note.pt.
9.	editorial.pt.
10.	case report/ or case study/
11.	(letter or comment*).ti.
12.	or/7-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animal/ not human/
16.	nonhuman/
17.	exp Animal Experiment/
18.	exp Experimental Animal/
19.	animal model/
20.	exp Rodent/
21.	(rat or rats or mouse or mice).ti.
22.	or/14-21
23.	6 not 22
24.	Limit 23 to English language
25.	random*.ti,ab.
26.	factorial*.ti,ab.
27.	(crossover* or cross over*).ti,ab.

28.	((doubl* or singl*) adj blind*).ti,ab.
29.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
30.	crossover procedure/
31.	single blind procedure/
32.	randomized controlled trial/
33.	double blind procedure/
34.	or/25-33
35.	systematic review/
36.	meta-analysis/
37.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
38.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
39.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
40.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
41.	(search* adj4 literature).ab.
42.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
43.	cochrane.jw.
44.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
45.	or/35-44
46.	Clinical study/
47.	Observational study/
48.	family study/
49.	longitudinal study/
50.	retrospective study/
51.	prospective study/
52.	cohort analysis/
53.	follow-up/
54.	cohort*.ti,ab.
55.	53 and 54
56.	(cohort adj (study or studies or analys* or data)).ti,ab.
57.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
58.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
59.	(before adj2 after adj2 (study or studies or data)).ti,ab.
60.	exp case control study/
61.	case control*.ti,ab.
62.	cross-sectional study/
63.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
64.	or/46-52,55-63
65.	24 and (34 or 45 or 64)

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Gout] explode all trees
#2.	gout*:ti,ab
#3.	toph*:ti,ab
#4.	podagra:ti,ab
#5.	pseudogout:ti,ab
#6.	(or #1-#5)

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to a Gout population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA – this ceased to be updated after March 2018). NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional searches were run on Medline and Embase for health economics studies and quality of life studies.

Table 25: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	Health Economics 1 January 2014 – 14 June 2021 Quality of Life 1946 – 14 June 2021 Modelling 1946 – 14 June 2021	Health economics studies Quality of life studies Modelling Studies Exclusions (animal studies, letters, comments)
Embase	Health Economics 1 January 2014 – 14 June 2021 Quality of Life 1974 – 14 June 2021 Modelling 1974 – 14 June 2021	Health economics studies Quality of life studies Modelling Studies Exclusions (animal studies, letters, comments)
Centre for Research and Dissemination (CRD)	HTA - Inception – 31 March 2018 NHSEED - Inception to March 2015	None

Medline (Ovid) search terms

1.	exp Gout/
2.	gout*.ti,ab.
3.	toph*.ti,ab.
4.	Uric Acid/
5.	uric acids*.ti,ab.
6.	(urate adj (crystal* or sodium or mono sodium)).ti,ab.
7.	hyperuricemia/
8.	(hyperuric* or hyper uric*).ti,ab.

9.	podagra.ti,ab.
10.	or/1-9
11.	letter/
12.	editorial/
13.	news/
14.	exp historical article/
15.	Anecdotes as Topic/
16.	comment/
17.	case report/
18.	(letter or comment*).ti.
19.	or/11-18
20.	randomized controlled trial/ or random*.ti,ab.
21.	19 not 20
22.	animals/ not humans/
23.	exp Animals, Laboratory/
24.	exp Animal Experimentation/
25.	exp Models, Animal/
26.	exp Rodentia/
27.	(rat or rats or mouse or mice).ti.
28.	or/21-27
29.	10 not 28
30.	limit 29 to English language
31.	Economics/
32.	Value of life/
33.	exp "Costs and Cost Analysis"/
34.	exp Economics, Hospital/
35.	exp Economics, Medical/
36.	Economics, Nursing/
37.	Economics, Pharmaceutical/
38.	exp "Fees and Charges"/
39.	exp Budgets/
40.	budget*.ti,ab.
41.	cost*.ti.
42.	(economic* or pharmaco?economic*).ti.
43.	(price* or pricing*).ti,ab.
44.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
45.	(financ* or fee or fees).ti,ab.

46.	(value adj2 (money or monetary)).ti,ab.
47.	or/31-46
48.	quality-adjusted life years/
49.	sickness impact profile/
50.	(quality adj2 (wellbeing or well being)).ti,ab.
51.	sickness impact profile.ti,ab.
52.	disability adjusted life.ti,ab.
53.	(qal* or qtime* or qwb* or daly*).ti,ab.
54.	(euroqol* or eq5d* or eq 5*).ti,ab.
55.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
56.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
57.	(hui or hui1 or hui2 or hui3).ti,ab.
58.	(health* year* equivalent* or hye or hyes).ti,ab.
59.	discrete choice*.ti,ab.
60.	rosser.ti,ab.
61.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
62.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
63.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
64.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
65.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
66.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
67.	or/48-66
68.	exp models, economic/
69.	*Models, Theoretical/
70.	*Models, Organizational/
71.	markov chains/
72.	monte carlo method/
73.	exp Decision Theory/
74.	(markov* or monte carlo).ti,ab.
75.	econom* model*.ti,ab.
76.	(decision* adj2 (tree* or analy* or model*)).ti,ab.
77.	or/68-76
78.	30 and (47 or 67 or 77)

Embase (Ovid) search terms

1.	exp gout/
2.	gout*.ti,ab.
3.	toph*.ti,ab.
4.	exp uric acid/

5.	uric acid*.ti,ab.
6.	(urate adj (crystal* or sodium or mono sodium)).ti,ab.
7.	exp hyperuricemia/
8.	(hyperuric* or hyper uric*).ti,ab.
9.	podagra.ti,ab.
10.	or/1-9
11.	letter.pt. or letter/
12.	note.pt.
13.	editorial.pt.
14.	Case report/ or Case study/
15.	(letter or comment*).ti.
16.	or/11-15
17.	randomized controlled trial/ or random*.ti,ab.
18.	16 not 17
19.	animal/ not human/
20.	Nonhuman/
21.	exp Animal Experiment/
22.	exp Experimental animal/
23.	Animal model/
24.	exp Rodent/
25.	(rat or rats or mouse or mice).ti.
26.	or/18-25
27.	10 not 26
28.	limit 27 to English language
29.	health economics/
30.	exp economic evaluation/
31.	exp health care cost/
32.	exp fee/
33.	budget/
34.	funding/
35.	budget*.ti,ab.
36.	cost*.ti.
37.	(economic* or pharmaco?economic*).ti.
38.	(price* or pricing*).ti,ab.
39.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
40.	(financ* or fee or fees).ti,ab.
41.	(value adj2 (money or monetary)).ti,ab.
42.	or/29-41
43.	quality adjusted life year/
44.	"quality of life index"/
45.	short form 12/ or short form 20/ or short form 36/ or short form 8/

46.	sickness impact profile/
47.	(quality adj2 (wellbeing or well being)).ti,ab.
48.	sickness impact profile.ti,ab.
49.	disability adjusted life.ti,ab.
50.	(qal* or qtime* or qwb* or daly*).ti,ab.
51.	(euroqol* or eq5d* or eq 5*).ti,ab.
52.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
53.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
54.	(hui or hui1 or hui2 or hui3).ti,ab.
55.	(health* year* equivalent* or hye or hyes).ti,ab.
56.	discrete choice*.ti,ab.
57.	rosser.ti,ab.
58.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
59.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
60.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
61.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
62.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
63.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
64.	or/43-63
65.	statistical model/
66.	exp economic aspect/
67.	65 and 66
68.	*theoretical model/
69.	*nonbiological model/
70.	stochastic model/
71.	decision theory/
72.	decision tree/
73.	monte carlo method/
74.	(markov* or monte carlo).ti,ab.
75.	econom* model*.ti,ab.
76.	(decision* adj2 (tree* or analy* or model*)).ti,ab.
77.	or/67-76
78.	28 and (42 or 64 or 77)

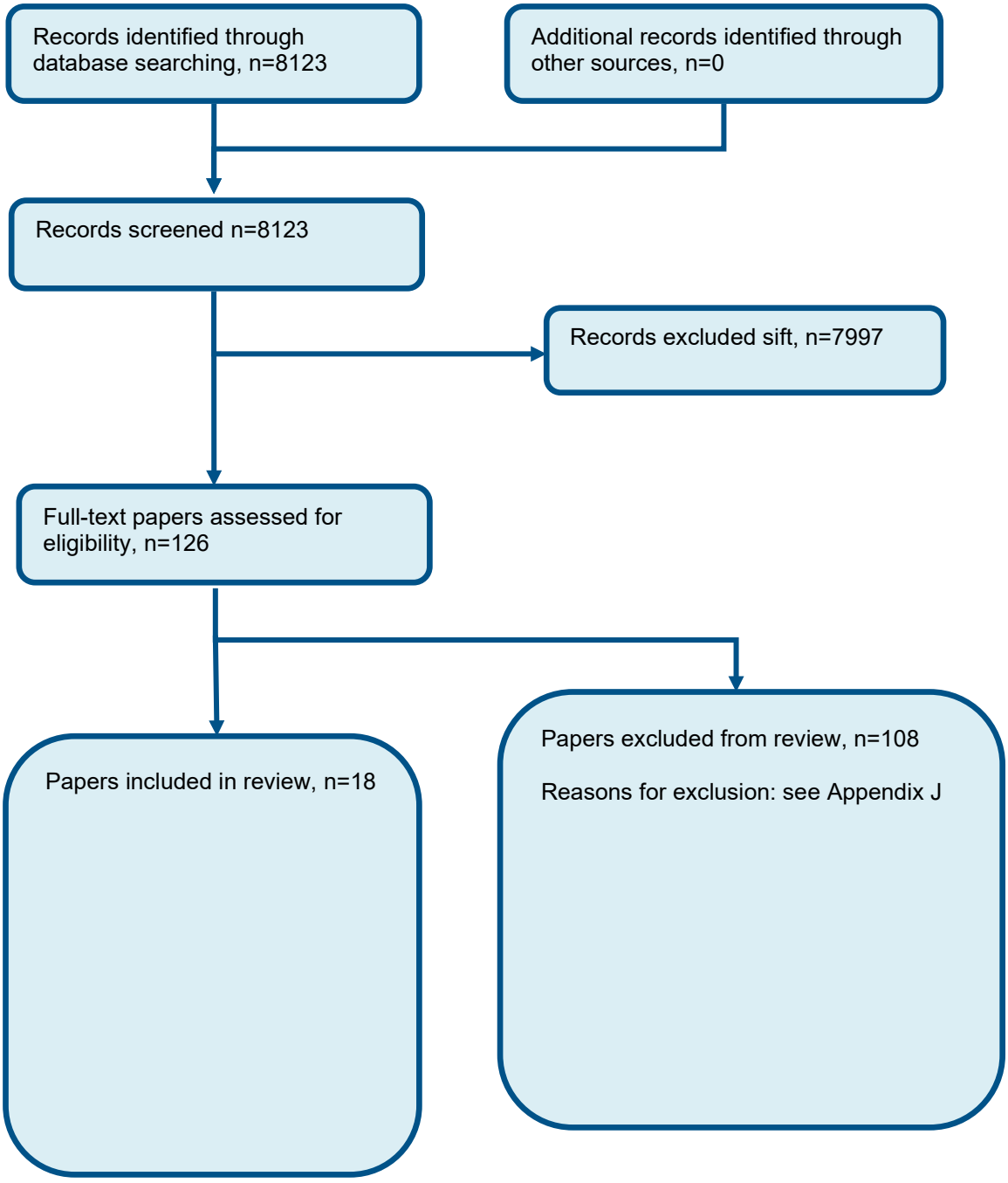
NHS EED and HTA (CRD) search terms

#1.	MeSH DESCRIPTOR Gout EXPLODE ALL TREES
#2.	(gout*)
#3.	(toph*)
#4.	MeSH DESCRIPTOR Uric Acid EXPLODE ALL TREES
#5.	(uric acid*)
#6.	((urate near (crystal* or sodium or mono sodium)))
#7.	MeSH DESCRIPTOR Hyperuricemia EXPLODE ALL TREES
#8.	((hyperuric* or hyper uric*))

#9.	(podagra)
#10.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9

Appendix C – Effectiveness evidence study selection

Figure 1: Flow chart of clinical study selection for the review of urate lowering therapies for the long-term management of gout



Appendix D – Effectiveness evidence

Study	Poiley 2016[91]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=248)
Countries and setting	Conducted in USA; Setting: Outpatient follow up
Line of therapy	2nd line
Duration of study	Intervention + follow up: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: People with gout according to the American College of Rheumatology criteria
Stratum	People without chronic kidney disease or people with CKD stages 1-2
Subgroup analysis within study	Not applicable
Inclusion criteria	People aged 18-75 years diagnosed as having gout according to the American College of Rheumatology criteria and who had experienced at least 3 flares during the 12 months before screening. People had to have a serum urate level of 7.5-12mg/dL and had not received any urate lowering therapy or colchicine for at least 2 weeks at screening.
Exclusion criteria	People with an estimated creatinine clearance of <60mL/min/1.73 m^2, a fractional excretion of urate >10%, or a history of kidney stones; liver function test results and creatine kinase levels at least 3x the upper limit of normal; people with secondary hyperuricaemia or xanthinuria; uncontrolled blood pressure; abnormal electrocardiograph; people with a body mass index of >42 kg/m^2; people with a medical condition that could interfere with the conduct of the study
Recruitment/selection of patients	No additional information
Age, gender and ethnicity	Age - Mean (SD): 52.0 (10.4). Gender (M:F): 229:10. Ethnicity: White = 169, Black = 47, Asian = 13, Other = 10
Further population details	1. Age: < 65 years 2. Setting: Not stated / Unclear
Extra comments	Baseline serum urate (mean [SD]): 9.1 (1.50 mg/dL
Indirectness of population	No indirectness
Interventions	(n=55) Intervention 1: Xanthine oxidase inhibitor - Allopurinol for moderate gout 300-600mg. Allopurinol 300mg per day. Duration 12 weeks. Concurrent medication/care: People receiving medication known to affect serum urate levels were required to be receiving a stable dose for at least 2 weeks and to continue to receive the same dose during the study.

	Concomitant use of potent cytochrome 3A4 inhibitors, cytotoxic drugs, or anticoagulants were prohibited as were long term treatments with NSAIDs or systemic corticosteroids. Women of reproductive potential had to use accepted forms of contraception. Indirectness: No indirectness Further details: 1. Choice of drug (drugs within the class, based on the intervention arm only): Allopurinol 300mg (n=28) Intervention 2: Placebo. Duration 12 weeks. Concurrent medication/care: People receiving medication known to affect serum urate levels were required to be receiving a stable dose for at least 2 weeks and to continue to receive the same dose during the study. Concomitant use of potent cytochrome 3A4 inhibitors, cytotoxic drugs, or anticoagulants were prohibited as were long term treatments with NSAIDs or systemic corticosteroids. Women of reproductive potential had to use accepted forms of contraception. Indirectness: No indirectness Further details: 1. Choice of drug (drugs within the class, based on the intervention arm only): Placebo This study was a five arm trial, with participants randomised to 600mg Arhalofenate, 800mg Arhalofenate, 300mg Allopurinol, 300mg Allopurinol 300mg plus Colchicine and placebo. Only the Allopurinol 300mg and placebo arms were analysed for this review.
Funding	Supported by CymaBay Therapeutics. Drs Steinberg, Choi, Martin, McWherter and Boudes own stock or stock options in CymaBay Therapeutics; Dr. McWherter, and Boudes own stock or stock options in CymaBay Therapeutics, Dr McWherter also is listed as an inventor on the CymaBay Therapeutics arhalofenate patents. Dr Davis received consulting fees from CymaBay Therapeutics for work on the current study (less than $10,000).

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ALLOPURINOL FOR MODERATE GOUT 300-600MG versus PLACEBO

Protocol outcome 1: Joint tenderness at medium-term (3 to 12 months)
- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Joint tenderness (Arthralgia) at 12 weeks; Group 1: 0/54, Group 2: 1/28
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, men, ethnicity, weight, BMI, serum urate, gout flares and patients with tophi; Group 1 Number missing: 7, Reason: 3 adverse event, 1 noncompliance, 1 lost to follow-up, 2 other; Group 2 Number missing: 5, Reason: 1 adverse event, 1 prohibited medication, 2 lost to follow-up, 1 patient decision

Protocol outcome 2: Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at medium-term (3 to 12 months)
- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Cardiovascular (hypertension) adverse events at 12 weeks; Group 1: 1/54, Group 2: 2/28
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups

- Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, men, ethnicity, weight, BMI, serum urate, gout flares and patients with tophi; Group 1 Number missing: 7, Reason: 3 adverse event, 1 noncompliance, 1 lost to follow-up, 2 other; Group 2 Number missing: 5, Reason: 1 adverse event, 1 prohibited medication, 2 lost to follow-up, 1 patient decision Protocol outcome 3: Serum urate levels at medium-term (3 to 12 months) - Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Change in serum urate level from baseline at 12 weeks; Group 1: mean -28.8 % (SD 20.3); n=54, Group 2: mean -0.9 % (SD 14.8); n=28; Comments: Baseline allopurinol: 9.0 (1.4). Baseline placebo: 9.1 (1.4). Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, men, ethnicity, weight, BMI, serum urate, gout flares and patients with tophi; Group 1 Number missing: 7, Reason: 3 adverse event, 1 noncompliance, 1 lost to follow-up, 2 other; Group 2 Number missing: 5, Reason: 1 adverse event, 1 prohibited medication, 2 lost to follow-up, 1 patient decision - Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): number of people achieving sUA <6mg/dL at 12 weeks; Group 1: 26/54, Group 2: 0/28 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, men, ethnicity, weight, BMI, serum urate, gout flares and patients with tophi; Group 1 Number missing: 7, Reason: 3 adverse event, 1 noncompliance, 1 lost to follow-up, 2 other; Group 2 Number missing: 5, Reason: 1 adverse event, 1 prohibited medication, 2 lost to follow-up, 1 patient decision	
Protocol outcomes not reported by the study	Health-related quality of life at short-term (< 3 months); Health-related quality of life at medium-term (3 to 12 months); Health-related quality of life at long-term (>12 months); Pain at short-term (< 3 months); Pain at medium-term (3 to 12 months); Pain at long-term (>12 months); Joint swelling/joint inflammation at short-term (< 3 months); Joint swelling/joint inflammation at medium-term (3 to 12 months); Joint swelling/joint inflammation at long-term (> 12 months); Joint tenderness at short (< 3 months); Joint tenderness at long-term (> 12 months); Patient global assessment of treatment success (response to treatment) at short-term (< 3 months); Patient global assessment of treatment success (response to treatment) at medium-term (3 to 12 months); Patient global assessment of treatment success (response to treatment) at long-term (> 12 months); Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at short-term (< 3 months); Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at long-term (> 12 months); Admissions (hospital & A&E) at short-term (< 3 months); Admissions (hospital & A&E) at medium-term 3 to 12 months); Admissions (hospital & A&E) at long-term (> 12 months); Discontinuation of ULT at short-term (< 3 months); Discontinuation of ULT at medium-term (3 to 12 months); Discontinuation of ULT at long-term (> 12 months); Frequency of flares at short-term (< 3 months); Frequency of flares at medium-term (3 to 12 months); Frequency of flares at long-term (> 12 months); Serum urate levels at short-term (< 3 months); Serum urate levels at long-term (> 12 months); Adverse events and complications of gout (radiographic joint damage, renal stones, tophi) at short-term (< 3 months); Adverse events and complications of gout

	(radiographic joint damage, renal stones, tophi) at medium-term (3 to 12 months); Adverse events and complications of gout (radiographic joint damage, renal stones, tophi) at long-term (> 12 months)

Study	**Becker 2005A[11]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=153)
Countries and setting	Conducted in USA; Setting: Outpatient follow up
Line of therapy	Mixed line
Duration of study	Intervention + follow up: 28 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Fulfilling the American College of Rheumatology preliminary criteria for the classification of the acute arthritis of primary gout
Stratum	Mixed population (people with chronic kidney disease and people without chronic kidney disease)
Subgroup analysis within study	Not applicable:
Inclusion criteria	People fulfilling the American College of Rheumatology preliminary criteria for the classification of the acute arthritis of primary gout
Exclusion criteria	Serum creatinine level >1.5mg/dL (calculated creatinine clearance <50mL/minute); pregnancy or lactation; concurrent therapy with urate-lowering agents, azathioprine, 6-mercaptopurine, or medications containing aspirin (>325mg) or other salicylates; a body mass index >50kg/m²; a history of xanthinuria, active liver disease, or hepatic dysfunction; changes in thiazide or steroid therapy (within 1 month of study) or in hormone replacement/oral contraceptive therapy (within 3 months of study); or a history of alcohol abuse or intake of at least 14 alcohol containing drinks per week
Recruitment/selection of patients	This study was conducted at 24 centres in the US
Age, gender and ethnicity	Age - Mean (SD): 54.0 (12.8). Gender (M:F): 136:17. Ethnicity: Caucasian = 133, Otherwise not stated
Further population details	1. Age: < 65 years 2. Setting: Not stated / Unclear
Extra comments	Baseline serum urate (mean [SD]): 9.7 (1.2) mg/dL
Indirectness of population	No indirectness

Interventions	(n=40) Intervention 1: Xanthine oxidase inhibitor - Febuxostat 80mg. Febuxostat 80mg/day. Duration 28 days. Concurrent medication/care: Colchicine prophylaxis, 0.6mg twice daily, was provided during the washout period and the first 2 weeks of double-blind treatment. Acute flares of gout occurring after the prophylaxis phase were treated at the investigator's discretion. Indirectness: No indirectness Further details: 1. Choice of drug (drugs within the class, based on the intervention arm only): Febuxostat 80mg (n=38) Intervention 2: Xanthine oxidase inhibitor - Febuxostat 120mg. Febuxostat 120mg/day. Duration 28 days. Concurrent medication/care: Colchicine prophylaxis, 0.6mg twice daily, was provided during the washout period and the first 2 weeks of double-blind treatment. Acute flares of gout occurring after the prophylaxis phase were treated at the investigator's discretion. Indirectness: No indirectness Further details: 1. Choice of drug (drugs within the class, based on the intervention arm only): Febuxostat 120mg (n=38) Intervention 3: Placebo. Duration 28 days. Concurrent medication/care: Colchicine prophylaxis, 0.6mg twice daily, was provided during the washout period and the first 2 weeks of double-blind treatment. Acute flares of gout occurring after the prophylaxis phase were treated at the investigator's discretion. Indirectness: No indirectness Further details: 1. Choice of drug (drugs within the class, based on the intervention arm only): Placebo
Funding	Principal author funded by industry (Drs Becker, Schumacher and Wortmann have received consulting fees from TAP Pharmaceutical Products)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FEBUXOSTAT 80MG versus PLACEBO

Protocol outcome 1: Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at short-term (< 3 months)
- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Gastrointestinal adverse events at 28 days; Group 1: 13/40, Group 2: 13/38; Comments: Febuxostat 80mg: Abdominal pain = 3%, diarrhoea = 10%. Placebo: Abdominal pain = 5%, diarrhoea = 8%. Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Baseline details: Reported age, gender, ethnicity, uric acid production, tophus present, comorbidities and baseline serum urate in the intention to treat population; Group 1 Number missing: 3, Reason: 2 adverse events, 1 noncompliance; Group 2 Number missing: 2, Reason: 1 adverse events, 1 gout flare
- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Gastrointestinal adverse events (abdominal pain) at 28 days; Group 1: 1/40, Group 2: 2/38; Comments: Febuxostat 80mg: Abdominal pain = 3%, diarrhoea = 10%. Placebo: Abdominal pain = 5%, diarrhoea = 8%. Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Baseline details: Reported age, gender, ethnicity, uric acid production, tophus present, comorbidities and baseline serum urate in the intention to treat population; Group 1 Number missing: 3, Reason: 2 adverse events, 1 noncompliance; Group 2 Number missing: 2, Reason: 1 adverse events, 1 gout flare

- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Gastrointestinal adverse events (diarrhoea) at 28 days; Group 1: 4/40, Group 2: 3/38; Comments: Febuxostat 80mg: Abdominal pain = 3%, diarrhoea = 10%. Placebo: Abdominal pain = 5%, diarrhoea = 8%. Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Baseline details: Reported age, gender, ethnicity, uric acid production, tophus present, comorbidities and baseline serum urate in the intention to treat population; Group 1 Number missing: 3, Reason: 2 adverse events, 1 noncompliance; Group 2 Number missing: 2, Reason: 1 adverse events, 1 gout flare

Protocol outcome 2: Frequency of flares at short-term (< 3 months)
- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Frequency of flares at 28 days; Group 1: 17/40, Group 2: 14/38; Comments: Reports percentages of the population who had events. Taken from 'Entire study period' group. Reported febuxostat 80mg: 43% (of 40) = 17. Reported placebo: 37% (of 38) = 14.
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, gender, ethnicity, uric acid production, tophus present, comorbidities and baseline serum urate in the intention to treat population; Group 1 Number missing: 3, Reason: 2 adverse events, 1 noncompliance; Group 2 Number missing: 2, Reason: 1 adverse events, 1 gout flare

Protocol outcome 3: Serum urate levels at medium-term (3 to 12 months)
- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): number of people achieving sUA <6mg/dL at 28 days; Group 1: 28/37, Group 2: 0/35
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, gender, ethnicity, uric acid production, tophus present, comorbidities and baseline serum urate in the intention to treat population; Group 1 Number missing: 3, Reason: 2 adverse events, 1 noncompliance; Group 2 Number missing: 2, Reason: 1 adverse events, 1 gout flare
- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): number of people achieving sUA <4mg/dL at 28 days; Group 1: 7/37, Group 2: 0/35
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, gender, ethnicity, uric acid production, tophus present, comorbidities and baseline serum urate in the intention to treat population; Group 1 Number missing: 3, Reason: 2 adverse events, 1 noncompliance; Group 2 Number missing: 2, Reason: 1 adverse events, 1 gout flare
- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): number of people achieving sUA <5mg/dL at 28 days; Group 1: 18/37, Group 2: 0/35
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, gender, ethnicity, uric acid production, tophus present, comorbidities and baseline serum urate in the intention to treat population; Group 1 Number missing: 3, Reason: 2 adverse events, 1 noncompliance; Group 2 Number missing: 2, Reason: 1 adverse events, 1 gout flare

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FEBUXOSTAT 120MG versus FEBUXOSTAT 80MG

Protocol outcome 1: Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at short-term (< 3 months)
- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Gastrointestinal adverse events at 28 days; Group 1: 11/38, Group 2: 13/40; Comments: Febuxostat 120mg: Abdominal pain = 3, diarrhoea = 8. Total = 11. Febuxostat 80mg: Abdominal pain = 3, diarrhoea = 10. Total = 13. Combined from individual events so unsure about denominator, be careful during analysis.
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, gender, ethnicity, uric acid production, tophus present, comorbidities and baseline serum urate in the intention to treat population; Group 1 Number missing: 2, Reason: 2 adverse events; Group 2 Number missing: 3, Reason: 2 adverse events, 1 noncompliance

Protocol outcome 2: Frequency of flares at short-term (< 3 months)
- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Frequency of flares at 28 days; Group 1: 21/38, Group 2: 17/40; Comments: Reports percentages of the population who had events. Taken from 'Entire study period' group. Reported febuxostat 120mg: 55% (of 38) = 21. Reported febuxostat 80mg: 43% (of 40) = 17.
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, gender, ethnicity, uric acid production, tophus present, comorbidities and baseline serum urate in the intention to treat population; Group 1 Number missing: 2, Reason: 2 adverse events; Group 2 Number missing: 3, Reason: 2 adverse events, 1 noncompliance

Protocol outcome 3: Serum urate levels at medium-term (3 to 12 months)
- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): number of people achieving sUA <6mg/dL at 28 days; Group 1: 32/34, Group 2: 28/37
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, gender, ethnicity, uric acid production, tophus present, comorbidities and baseline serum urate in the intention to treat population; Group 1 Number missing: 2, Reason: 2 adverse events; Group 2 Number missing: 3, Reason: 2 adverse events, 1 noncompliance
- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): number of people achieving sUA <4mg/dL at 28 days; Group 1: 19/34, Group 2: 7/37
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Baseline details: Reported age, gender, ethnicity, uric acid production, tophus present, comorbidities and baseline serum urate in the intention to treat population; Group 1 Number missing: 2, Reason: 2 adverse events; Group 2 Number missing: 3, Reason: 2 adverse events, 1 noncompliance
- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): number of people achieving sUA <5mg/dL at 28

days; Group 1: 30/34, Group 2: 18/37
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, gender, ethnicity, uric acid production, tophus present, comorbidities and baseline serum urate in the intention to treat population; Group 1 Number missing: 2, Reason: 2 adverse events; Group 2 Number missing: 3, Reason: 2 adverse events, 1 noncompliance

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FEBUXOSTAT 120MG versus PLACEBO

Protocol outcome 1: Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at short-term (< 3 months)
- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Gastrointestinal adverse events at 28 days; Group 1: 11/38, Group 2: 13/38; Comments: Febuxostat 120mg: Abdominal pain = 3, diarrhoea = 8. Total = 11. Placebo: Abdominal pain = 5, diarrhoea = 8. Total = 13. Combined from individual events so unsure about denominator, be careful during analysis.
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, gender, ethnicity, uric acid production, tophus present, comorbidities and baseline serum urate in the intention to treat population; Group 1 Number missing: 2, Reason: 2 adverse events; Group 2 Number missing: 2, Reason: 1 adverse events, 1 gout flare

Protocol outcome 2: Frequency of flares at short-term (< 3 months)
- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Frequency of flares at 28 days; Group 1: 21/38, Group 2: 14/38; Comments: Reports percentages of the population who had events. Taken from 'Entire study period' group. Reported febuxostat 120mg: 55% (of 38) = 21. Reported placebo: 37% (of 38) = 14.
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, gender, ethnicity, uric acid production, tophus present, comorbidities and baseline serum urate in the intention to treat population; Group 1 Number missing: 2, Reason: 2 adverse events; Group 2 Number missing: 2, Reason: 1 adverse events, 1 gout flare

Protocol outcome 3: Serum urate levels at medium-term (3 to 12 months)
- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): number of people achieving sUA <6mg/dL at 28 days; Group 1: 32/34, Group 2: 0/35
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, gender, ethnicity, uric acid production, tophus present, comorbidities and baseline serum urate in the intention to treat population; Group 1 Number missing: 2, Reason: 2 adverse events; Group 2 Number missing: 2, Reason: 1 adverse events, 1 gout flare
- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): number of people achieving sUA <4mg/dL at 28 days; Group 1: 19/34, Group 2: 0/35

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, gender, ethnicity, uric acid production, tophus present, comorbidities and baseline serum urate in the intention to treat population; Group 1 Number missing: 2, Reason: 2 adverse events; Group 2 Number missing: 2, Reason: 1 adverse events, 1 gout flare - Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): number of people achieving sUA <5mg/dL at 28 days; Group 1: 30/34, Group 2: 0/35 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, gender, ethnicity, uric acid production, tophus present, comorbidities and baseline serum urate in the intention to treat population; Group 1 Number missing: 2, Reason: 2 adverse events; Group 2 Number missing: 2, Reason: 1 adverse events, 1 gout flare	
Protocol outcomes not reported by the study	Health-related quality of life at short-term (< 3 months); Health-related quality of life at medium-term (3 to 12 months); Health-related quality of life at long-term (>12 months); Pain at short-term (< 3 months); Pain at medium-term (3 to 12 months); Pain at long-term (>12 months); Joint swelling/joint inflammation at short-term (< 3 months); Joint swelling/joint inflammation at medium-term (3 to 12 months); Joint swelling/joint inflammation at long-term (> 12 months); Joint tenderness at short-term (< 3 months); Joint tenderness at medium-term (3 to 12 months); Joint tenderness at long-term (> 12 months); Patient global assessment of treatment success (response to treatment) at short-term (< 3 months); Patient global assessment of treatment success (response to treatment) at medium-term (3 to 12 months); Patient global assessment of treatment success (response to treatment) at long-term (> 12 months); Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at medium-term (3 to 12 months); Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at long-term (> 12 months); Admissions (hospital & A&E) at short-term (< 3 months); Admissions (hospital & A&E) at medium-term 3 to 12 months); Admissions (hospital & A&E) at long-term (> 12 months); Discontinuation of ULT at short-term (< 3 months); Discontinuation of ULT at medium-term (3 to 12 months); Discontinuation of ULT at long-term (> 12 months); Frequency of flares at medium-term (3 to 12 months); Frequency of flares at long-term (> 12 months); Serum urate levels at short-term (< 3 months); Serum urate levels at long-term (> 12 months); Adverse events and complications of gout (radiographic joint damage, renal stones, tophi) at short-term (< 3 months); Adverse events and complications of gout (radiographic joint damage, renal stones, tophi) at medium-term (3 to 12 months); Adverse events and complications of gout (radiographic joint damage, renal stones, tophi) at long-term (> 12 months)

Study	**CONFIRMS trial: Becker 2010[9]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=2269)

Countries and setting	Conducted in USA; Setting: Outpatient follow up
Line of therapy	Mixed line
Duration of study	Intervention + follow up: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diagnosis of gout fulfilling the American Rheumatology Association preliminary criteria and serum urate of at least 8.0mg/dL
Stratum	Mixed population (people with chronic kidney disease and people without chronic kidney disease)
Subgroup analysis within study	Not applicable
Inclusion criteria	Subjects aged 18 to 85 years with a diagnosis of gout fulfilling American Rheumatology Association preliminary criteria and sUA ≥ 8.0 mg/dL.
Exclusion criteria	Secondary hyperuricemia (for example, due to myeloproliferative disorder); xanthinuria; severe renal impairment (eCLcr <30 ml/minutes; alanine aminotransferase and aspartate aminotransferase values >1.5 times the upper limit of normal; consumption of more than 14 alcoholic drinks per week or a history of alcoholism or drug abuse within five years; or a medical condition that, in the investigator's opinion, would interfere with treatment, safety, or adherence to the protocol.
Recruitment/selection of patients	People were enrolled at 324 sites in the United States
Age, gender and ethnicity	Age - Mean (SD): 52.8 (11.7). Gender (M:F): Gender (M:F): 2141:128. Ethnicity: American Indian or Alaska Native = 22, Asian = 88, Black or African American = 228, Native Hawaiian or Other Pacific Islander = 32, White = 1863, Other = 34, Missing = 2
Further population details	1. Age: < 65 years 2. Setting: Secondary care
Extra comments	Serum urate level (mean [SD]): 9.6 (1.2)
Indirectness of population	No indirectness
Interventions	(n=756) Intervention 1: Xanthine oxidase inhibitor - Febuxostat 80mg. Febuxostat 80mg. Duration 6 months. Concurrent medication/care: During a 30-day washout period for subjects receiving prior urate lowering therapy and throughout the subsequent six month treatment period for all subjects, prophylaxis for gout flares was given either as colchicine 0.6mg daily or naproxen 250mg twice daily. All subjects receiving naproxen prophylaxis also received lansoprazole 15mg daily. People with eCLcr <50mL/min were not to receive naproxen. Indirectness: No indirectness Further details: 1. Choice of drug (drugs within the class, based on the intervention arm only): Febuxostat 80mg (n=756) Intervention 2: Xanthine oxidase inhibitor – Allopurinol mixed dose allopurinol 200-300 mg. Allopurinol 200mg-300mg (610 received 300mg, while 145 received 200mg). Duration 6 months. Concurrent medication/care: During a 30-day washout period for subjects receiving prior urate lowering therapy and throughout the subsequent six-month treatment period for all

	subjects, prophylaxis for gout flares was given either as colchicine 0.6mg daily or naproxen 250mg twice daily. All subjects receiving naproxen prophylaxis also received lansoprazole 15mg daily. People with eCLcr <50mL/min were not to receive naproxen. Indirectness: Serious indirectness; Indirectness comment: <20% of participants received allopurinol 200mg Further details: 1. Choice of drug (drugs within the class, based on the intervention arm only): Allopurinol 200-300 mg
Funding	Study funded by industry (This trial was completely funded by TAP Pharmaceutical Products, Inc., which is now a part of Takeda Global Research & Development Center, Inc., Deerfield, IL, USA. It is registered as NCT00430248 on clinicaltrials.gov. Assistance in manuscript preparation was provided by Meryl Gersh, PhD, of AlphabioCom, LLC., in Radnor, PA, USA, and was funded by Takeda Global Research & Development Center, Inc.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FEBUXOSTAT 80MG versus ALLOPURINOL FOR MODERATE GOUT 300-600MG

Protocol outcome 1: Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at medium-term (3 to 12 months)
- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Gastrointestinal adverse events (diarrhoea) at 6 months; Group 1: 47/756, Group 2: 57/756
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported gender, race, ethnicity, age, BMI, alcohol use, serum urate, years with gout, completed previous febuxostat study, renal function and medical history; Group 1 Number missing: 158, Reason: 61 adverse events, 2 protocol violation, 24 personal reasons, 33 loss to follow up, 1 therapeutic failure, 20 withdrew consent, 2 did not meet inclusion/exclusion criteria, 7 gout flare, 8 other; Group 2 Number missing: 135, Reason: 64 adverse events, 4 protocol violation, 9 personal reasons, 28 loss to follow up, 1 therapeutic failure, 16 withdrew consent, 0 did not meet inclusion/exclusion criteria, 2 gout flare, 11 other
- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Cardiovascular adverse events at 6 months; Group 1: 7/756, Group 2: 5/756; Comments: Have combined non-fatal MI (1, 1), coronary revascularisation (1, 0), TIA (1, 0), venous and peripheral arterial vascular thrombotic event (0, 2), congestive heart failure (1, 0), and arrhythmia (1, 4). Not including non-fatal stroke (0, 2) or CV death (2, 0).
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported gender, race, ethnicity, age, BMI, alcohol use, serum urate, years with gout, completed previous febuxostat study, renal function and medical history; Group 1 Number missing: 158, Reason: 61 adverse events, 2 protocol violation, 24 personal reasons, 33 loss to follow up, 1 therapeutic failure, 20 withdrew consent, 2 did not meet inclusion/exclusion criteria, 7 gout flare, 8 other; Group 2 Number missing: 135, Reason: 64 adverse events, 4 protocol violation, 9 personal reasons, 28 loss to follow up, 1 therapeutic failure, 16 withdrew consent, 0 did not meet inclusion/exclusion criteria, 2 gout flare, 11 other

Protocol outcome 2: Serum urate levels at medium (3 to 12 months)
- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Number of people achieving sUA <6mg/dL at 6 months; Group 1: 507/756, Group 2: 318/756

Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Baseline details: Reported gender, race, ethnicity, age, BMI, alcohol use, serum urate, years with gout, completed previous febuxostat study, renal function and medical history; Group 1 Number missing: 158, Reason: 61 adverse events, 2 protocol violation, 24 personal reasons, 33 loss to follow up, 1 therapeutic failure, 20 withdrew consent, 2 did not meet inclusion/exclusion criteria, 7 gout flare, 8 other; Group 2 Number missing: 135, Reason: 64 adverse events, 4 protocol violation, 9 personal reasons, 28 loss to follow up, 1 therapeutic failure, 16 withdrew consent, 0 did not meet inclusion/exclusion criteria, 2 gout flare, 11 other	
Protocol outcomes not reported by the study	Health-related quality of life at short (< 3 months); Health-related quality of life at medium (3 to 12 months); Health-related quality of life at long (>12 months); Pain at short (< 3 months); Pain at medium (3 to 12 months); Pain at long (>12 months); Joint swelling/joint inflammation at short (< 3 months); Joint swelling/joint inflammation at medium (3 to 12 months); Joint swelling/joint inflammation at long (> 12 months); Joint tenderness at short (< 3 months); Joint tenderness at medium (3 to 12 months); Joint tenderness at long (> 12 months); Patient global assessment of treatment success (response to treatment) at short (< 3 months); Patient global assessment of treatment success (response to treatment) at medium (3 to 12 months); Patient global assessment of treatment success (response to treatment) at long (> 12 months); Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at short (< 3 months); Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at long (> 12 months); Admissions (hospital & A&E) at short (< 3 months); Admissions (hospital & A&E) at medium 3 to 12 months); Admissions (hospital & A&E) at long (> 12 months); Discontinuation of ULT at short (< 3 months); Discontinuation of ULT at medium (3 to 12 months); Discontinuation of ULT at long (> 12 months); Frequency of flares at short (< 3 months); Frequency of flares at medium (3 to 12 months); Frequency of flares at long (> 12 months); Serum urate levels at short (< 3 months); Serum urate levels at long (> 12 months); Adverse events and complications of gout (radiographic joint damage, renal stones, tophi) at short (< 3 months); Adverse events and complications of gout (radiographic joint damage, renal stones, tophi) at medium (3 to 12 months); Adverse events and complications of gout (radiographic joint damage, renal stones, tophi) at long (> 12 months)

Study	**FACT trial: Becker 2005B[10]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=762)
Countries and setting	Conducted in Canada, USA; Setting: Outpatient follow up
Line of therapy	Mixed line
Duration of study	Intervention + follow up: 12 months

Method of assessment of guideline condition	Adequate method of assessment/diagnosis: People meeting the American College of Rheumatology for acute arthritis of gout
Stratum	Mixed population (people with chronic kidney disease and people without chronic kidney disease)
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults with gout and a serum urate concentration of at least 8.0mg/dL (480 micromol/L).
Exclusion criteria	A serum creatinine concentration of more than 1.5mg/dL (133 micromol/L) or an estimated creatinine clearance rate of less than 50mL/min/1.73m^2; pregnancy or lactation; use of urate-lowering agents, azathioprine, 6-mercaptopurine, thiazide diuretics, or medications containing aspirin (more than 325mg daily) or other salicylates); a body mass index of more than 50; a history of xanthinuria, active liver disease or hepatic dysfunction; use of prednisone at more than 10mg per day; a change in hormone replacement therapy or oral-contraceptive therapy within the previous 3 months; a history of alcohol abuse or an alcohol intake of more than 14 drinks per week
Recruitment/selection of patients	This study was conducted at 112 centres in the United States and Canada
Age, gender and ethnicity	Age - Mean (SD): 51.8 (12.1). Gender (M:F): 729:31. Ethnicity: White = 587, Black = 62, Hispanic = 58, Asian = 25, Other = 28
Further population details	1. Age: < 65 years 2. Setting: Secondary care
Extra comments	Baseline serum urate (mean [SD]): 9.84 (1.25) mg/dL
Indirectness of population	No indirectness
Interventions	(n=257) Intervention 1: Xanthine oxidase inhibitor - Febuxostat 80mg. Febuxostat 80mg/day. Duration 12 months. Concurrent medication/care: Prophylaxis (250mg of naproxen twice daily or 0.6mg of colchicine once daily) was administered to all patients during the washout period and the first eight weeks of double-blind treatment. Subsequent flares of gout were treated at the investigators' discretion. Indirectness: No indirectness Further details: 1. Choice of drug (drugs within the class, based on the intervention arm only): Febuxostat 80mg (n=251) Intervention 2: Xanthine oxidase inhibitor - Febuxostat 120mg. Febuxostat 120mg/day. Duration 12 months. Concurrent medication/care: Prophylaxis (250mg of naproxen twice daily or 0.6mg of colchicine once daily) was administered to all patients during the washout period and the first eight weeks of double-blind treatment. Subsequent flares of gout were treated at the investigators' discretion. Indirectness: No indirectness Further details: 1. Choice of drug (drugs within the class, based on the intervention arm only): Febuxostat 120mg (n=254) Intervention 3: Xanthine oxidase inhibitor - Allopurinol for moderate gout 300-600mg. Allopurinol 300mg/day. Duration 12 months. Concurrent medication/care: Prophylaxis (250mg of naproxen twice daily or 0.6mg of colchicine once daily) was administered to all patients during the washout period and the first eight weeks of double-blind treatment.

	Subsequent flares of gout were treated at the investigators' discretion. Indirectness: No indirectness Further details: 1. Choice of drug (drugs within the class, based on the intervention arm only): Allopurinol 300mg
Funding	Study funded by industry (The study was designed by the academic investigators and the corporate sponsor (TAP Pharmaceutical Products).)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FEBUXOSTAT 80MG versus ALLOPURINOL FOR MODERATE GOUT 300-600MG

Protocol outcome 1: Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at medium (3 to 12 months)

- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Gastrointestinal adverse events (diarrhoea) at 12 months; Group 1: 8/257, Group 2: 8/254; Comments: Values are combined so the denominator is unclear, be careful while analysing this data.
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, sex, race, baseline serum urate, years with gout, history or presence of tophi, previous urate-lowering therapy and coexisting conditions; Group 1 Number missing: 89, Reason: 1 withdrew without receiving drug. 25 lost to follow up. 16 adverse events. 10 gout flare. 19 personal reasons. 7 protocol violation. 11 other reasons.; Group 2 Number missing: 67, Reason: 1 withdrew without receiving study drug. 21 lost to follow up, 8 adverse event, 9 gout flare, 13 personal reasons, 1 protocol violation, 14 other reasons
- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Gastrointestinal adverse events (Gastrointestinal atonic and hypomotility disorders) at 12 months; Group 1: 5/257, Group 2: 4/254; Comments: Values are combined so the denominator is unclear, be careful while analysing this data.
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, sex, race, baseline serum urate, years with gout, history or presence of tophi, previous urate-lowering therapy and coexisting conditions; Group 1 Number missing: 89, Reason: 1 withdrew without receiving drug. 25 lost to follow up. 16 adverse events. 10 gout flare. 19 personal reasons. 7 protocol violation. 11 other reasons.; Group 2 Number missing: 67, Reason: 1 withdrew without receiving study drug. 21 lost to follow up, 8 adverse event, 9 gout flare, 13 personal reasons, 1 protocol violation, 14 other reasons
- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Gastrointestinal adverse events (nausea and vomiting symptoms) at 12 months; Group 1: 5/257, Group 2: 3/254; Comments: Values are combined so the denominator is unclear, be careful while analysing this data.
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, sex, race, baseline serum urate, years with gout, history or presence of tophi, previous urate-lowering therapy and coexisting conditions; Group 1 Number missing: 89, Reason: 1 withdrew without receiving drug. 25 lost to follow up. 16 adverse events. 10 gout flare. 19 personal reasons. 7 protocol violation. 11 other reasons.; Group 2 Number missing: 67, Reason: 1 withdrew without receiving study drug. 21 lost to follow up, 8 adverse event, 9 gout flare, 13 personal reasons, 1 protocol violation, 14 other reasons
- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Gastrointestinal adverse events (Gastrointestinal signs and symptoms) at 12 months; Group 1: 5/257, Group 2: 1/254; Comments: Values are combined so the denominator is unclear, be careful while analysing this data.

Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, sex, race, baseline serum urate, years with gout, history or presence of tophi, previous urate-lowering therapy and coexisting conditions; Group 1 Number missing: 89, Reason: 1 withdrew without receiving drug. 25 lost to follow up. 16 adverse events. 10 gout flare. 19 personal reasons. 7 protocol violation. 11 other reasons.; Group 2 Number missing: 67, Reason: 1 withdrew without receiving study drug. 21 lost to follow up, 8 adverse event, 9 gout flare, 13 personal reasons, 1 protocol violation, 14 other reasons

- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): number of people achieving sUA <6mg/dL at 12 months; Group 1: 185/253, Group 2: 88/242
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, sex, race, baseline serum urate, years with gout, history or presence of tophi, previous urate-lowering therapy and coexisting conditions; Group 1 Number missing: 89, Reason: 1 withdrew without receiving drug. 25 lost to follow up. 16 adverse events. 10 gout flare. 19 personal reasons. 7 protocol violation. 11 other reasons.; Group 2 Number missing: 67, Reason: 1 withdrew without receiving study drug. 21 lost to follow up, 8 adverse event, 9 gout flare, 13 personal reasons, 1 protocol violation, 14 other reasons

Protocol outcome 2: Frequency of flares at medium (3 to 12 months)
- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Frequency of flares at 8 weeks; Group 1: 55/255, Group 2: 52/251; Comments: Day 1- week 8. I haven't extracted the other timepoints as they don't start from baseline
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, sex, race, baseline serum urate, years with gout, history or presence of tophi, previous urate-lowering therapy and coexisting conditions; Group 1 Number missing: 89, Reason: 1 withdrew without receiving drug. 25 lost to follow up. 16 adverse events. 10 gout flare. 19 personal reasons. 7 protocol violation. 11 other reasons.; Group 2 Number missing: 67, Reason: 1 withdrew without receiving study drug. 21 lost to follow up, 8 adverse event, 9 gout flare, 13 personal reasons, 1 protocol violation, 14 other reasons

Protocol outcome 3: Serum urate levels at medium (3 to 12 months)
- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Serum urate level at 12 months; Group 1: mean -44.73 % (SD 19.1); n=256, Group 2: mean -32.99 % (SD 15.33); n=253; Comments: Baseline febuxostat 80mg: 9.80 (1.24). Baseline allopurinol: 9.90 (1.23).
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, sex, race, baseline serum urate, years with gout, history or presence of tophi, previous urate-lowering therapy and coexisting conditions; Group 1 Number missing: 89, Reason: 1 withdrew without receiving drug. 25 lost to follow up. 16 adverse events. 10 gout flare. 19 personal reasons. 7 protocol violation. 11 other reasons.; Group 2 Number missing: 67, Reason: 1 withdrew without receiving study drug. 21 lost to follow up, 8 adverse event, 9 gout flare, 13 personal reasons, 1 protocol violation, 14 other reasons

Protocol outcome 4: Adverse events and complications of gout (radiographic joint damage, renal stones, tophi) at medium (3 to 12 months)
- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Tophus change at 12 months; Group 1: 33/257, Group 2: 35/254

Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, sex, race, baseline serum urate, years with gout, history or presence of tophi, previous urate-lowering therapy and coexisting conditions; Group 1 Number missing: 89, Reason: 1 withdrew without receiving drug. 25 lost to follow up. 16 adverse events. 10 gout flare. 19 personal reasons. 7 protocol violation. 11 other reasons.; Group 2 Number missing: 67, Reason: 1 withdrew without receiving study drug. 21 lost to follow up, 8 adverse event, 9 gout flare, 13 personal reasons, 1 protocol violation, 14 other reasons

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FEBUXOSTAT 120MG versus FEBUXOSTAT 80MG

Protocol outcome 1: Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at medium (3 to 12 months)

- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Gastrointestinal adverse events (diarrhoea) at 12 months; Group 1: 7/257, Group 2: 8/254; Comments: Values are combined so the denominator is unclear, be careful while analysing this data.
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, sex, race, baseline serum urate, years with gout, history or presence of tophi, previous urate-lowering therapy and coexisting conditions; Group 1 Number missing: 89, Reason: 1 withdrew without receiving drug. 25 lost to follow up. 16 adverse events. 10 gout flare. 19 personal reasons. 7 protocol violation. 11 other reasons.; Group 2 Number missing: 67, Reason: 1 withdrew without receiving study drug. 21 lost to follow up, 8 adverse event, 9 gout flare, 13 personal reasons, 1 protocol violation, 14 other reasons
- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Gastrointestinal adverse events (Gastrointestinal atonic and hypomotility disorders) at 12 months; Group 1: 2/257, Group 2: 5/254; Comments: Values are combined so the denominator is unclear, be careful while analysing this data.
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, sex, race, baseline serum urate, years with gout, history or presence of tophi, previous urate-lowering therapy and coexisting conditions; Group 1 Number missing: 89, Reason: 1 withdrew without receiving drug. 25 lost to follow up. 16 adverse events. 10 gout flare. 19 personal reasons. 7 protocol violation. 11 other reasons.; Group 2 Number missing: 67, Reason: 1 withdrew without receiving study drug. 21 lost to follow up, 8 adverse event, 9 gout flare, 13 personal reasons, 1 protocol violation, 14 other reasons
- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Gastrointestinal adverse events (nausea and vomiting symptoms) at 12 months; Group 1: 3/257, Group 2: 5/254; Comments: Values are combined so the denominator is unclear, be careful while analysing this data.
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, sex, race, baseline serum urate, years with gout, history or presence of tophi, previous urate-lowering therapy and coexisting conditions; Group 1 Number missing: 89, Reason: 1 withdrew without receiving drug. 25 lost to follow up. 16 adverse events. 10 gout flare. 19 personal reasons. 7 protocol violation. 11 other reasons.; Group 2 Number missing: 67, Reason: 1 withdrew without receiving study drug. 21 lost to follow up, 8 adverse event, 9 gout flare, 13 personal reasons, 1 protocol violation, 14 other reasons
- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Gastrointestinal adverse events (Gastrointestinal signs and symptoms) at 12 months; Group 1: 1/257, Group 2: 5/254; Comments: Values are combined so the denominator is unclear, be careful while analysing this data.
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low,

Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, sex, race, baseline serum urate, years with gout, history or presence of tophi, previous urate-lowering therapy and coexisting conditions; Group 1 Number missing: 89, Reason: 1 withdrew without receiving drug. 25 lost to follow up. 16 adverse events. 10 gout flare. 19 personal reasons. 7 protocol violation. 11 other reasons.; Group 2 Number missing: 67, Reason: 1 withdrew without receiving study drug. 21 lost to follow up, 8 adverse event, 9 gout flare, 13 personal reasons, 1 protocol violation, 14 other reasons

- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): number of people achieving sUA <6mg/dL at 12 months; Group 1: 193/242, Group 2: 185/249
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, sex, race, baseline serum urate, years with gout, history or presence of tophi, previous urate-lowering therapy and coexisting conditions; Group 1 Number missing: 98, Reason: 18 lost to follow up, 23 adverse event, 28 gout flare, 13 personal reasons, 2 protocol violation, 14 other reasons; Group 2 Number missing: 89, Reason: 1 withdrew without receiving drug. 25 lost to follow up. 16 adverse events. 10 gout flare. 19 personal reasons. 7 protocol violation. 11 other reasons.

Protocol outcome 2: Frequency of flares at medium (3 to 12 months)
- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Frequency of flares at 8 weeks; Group 1: 90/250, Group 2: 55/255; Comments: Day 1- week 8. I haven't extracted the other timepoints as they don't start from baseline
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, sex, race, baseline serum urate, years with gout, history or presence of tophi, previous urate-lowering therapy and coexisting conditions; Group 1 Number missing: 98, Reason: 18 lost to follow up, 23 adverse event, 28 gout flare, 13 personal reasons, 2 protocol violation, 14 other reasons; Group 2 Number missing: 89, Reason: 1 withdrew without receiving drug. 25 lost to follow up. 16 adverse events. 10 gout flare. 19 personal reasons. 7 protocol violation. 11 other reasons.

Protocol outcome 3: Serum urate levels at medium (3 to 12 months)
- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Serum urate level at 12 months; Group 1: mean -51.52 % (SD 19.91); n=251, Group 2: mean -44.73 % (SD 19.1); n=256; Comments: Baseline febuxostat 120mg: 9.84 (1.26). Baseline febuxostat 80mg: 9.80 (1.24).
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, sex, race, baseline serum urate, years with gout, history or presence of tophi, previous urate-lowering therapy and coexisting conditions; Group 1 Number missing: 98, Reason: 18 lost to follow up, 23 adverse event, 28 gout flare, 13 personal reasons, 2 protocol violation, 14 other reasons; Group 2 Number missing: 89, Reason: 1 withdrew without receiving drug. 25 lost to follow up. 16 adverse events. 10 gout flare. 19 personal reasons. 7 protocol violation. 11 other reasons.

Protocol outcome 4: Adverse events and complications of gout (radiographic joint damage, renal stones, tophi) at medium (3 to 12 months)
- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Tophus change at 12 months; Group 1: 28/251,

Group 2: 33/257
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, sex, race, baseline serum urate, years with gout, history or presence of tophi, previous urate-lowering therapy and coexisting conditions; Group 1 Number missing: 98, Reason: 18 lost to follow up, 23 adverse event, 28 gout flare, 13 personal reasons, 2 protocol violation, 14 other reasons; Group 2 Number missing: 89, Reason: 1 withdrew without receiving drug. 25 lost to follow up. 16 adverse events. 10 gout flare. 19 personal reasons. 7 protocol violation. 11 other reasons.

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FEBUXOSTAT 120MG versus ALLOPURINOL FOR MODERATE GOUT 300-600MG

Protocol outcome 1: Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at medium (3 to 12 months)

- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Gastrointestinal adverse events (diarrhoea) at 12 months; Group 1: 7/257, Group 2: 8/254; Comments: Values are combined so the denominator is unclear, be careful while analysing this data.
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, sex, race, baseline serum urate, years with gout, history or presence of tophi, previous urate-lowering therapy and coexisting conditions; Group 1 Number missing: 89, Reason: 1 withdrew without receiving drug. 25 lost to follow up. 16 adverse events. 10 gout flare. 19 personal reasons. 7 protocol violation. 11 other reasons.; Group 2 Number missing: 67, Reason: 1 withdrew without receiving study drug. 21 lost to follow up, 8 adverse event, 9 gout flare, 13 personal reasons, 1 protocol violation, 14 other reasons
- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Gastrointestinal adverse events (Gastrointestinal atonic and hypomotility disorders) at 12 months; Group 1: 2/257, Group 2: 4/254; Comments: Values are combined so the denominator is unclear, be careful while analysing this data.
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, sex, race, baseline serum urate, years with gout, history or presence of tophi, previous urate-lowering therapy and coexisting conditions; Group 1 Number missing: 89, Reason: 1 withdrew without receiving drug. 25 lost to follow up. 16 adverse events. 10 gout flare. 19 personal reasons. 7 protocol violation. 11 other reasons.; Group 2 Number missing: 67, Reason: 1 withdrew without receiving study drug. 21 lost to follow up, 8 adverse event, 9 gout flare, 13 personal reasons, 1 protocol violation, 14 other reasons
- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Gastrointestinal adverse events (nausea and vomiting symptoms) at 12 months; Group 1: 3/257, Group 2: 3/254; Comments: Values are combined so the denominator is unclear, be careful while analysing this data.
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, sex, race, baseline serum urate, years with gout, history or presence of tophi, previous urate-lowering therapy and coexisting conditions; Group 1 Number missing: 89, Reason: 1 withdrew without receiving drug. 25 lost to follow up. 16 adverse events. 10 gout flare. 19 personal reasons. 7 protocol violation. 11 other reasons.; Group 2 Number missing: 67, Reason: 1 withdrew without receiving study drug. 21 lost to follow up, 8 adverse event, 9 gout flare, 13 personal reasons, 1 protocol violation, 14 other reasons
- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Gastrointestinal adverse events (Gastrointestinal signs and symptoms) at 12 months; Group 1: 1/257, Group 2: 1/254; Comments: Values are combined so the denominator is unclear, be careful while analysing this data.

Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, sex, race, baseline serum urate, years with gout, history or presence of tophi, previous urate-lowering therapy and coexisting conditions; Group 1 Number missing: 89, Reason: 1 withdrew without receiving drug. 25 lost to follow up. 16 adverse events. 10 gout flare. 19 personal reasons. 7 protocol violation. 11 other reasons.; Group 2 Number missing: 67, Reason: 1 withdrew without receiving study drug. 21 lost to follow up, 8 adverse event, 9 gout flare, 13 personal reasons, 1 protocol violation, 14 other reasons

- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): number of people achieving sUA <6mg/dL at 12 months; Group 1: 193/242, Group 2: 88/242
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, sex, race, baseline serum urate, years with gout, history or presence of tophi, previous urate-lowering therapy and coexisting conditions; Group 1 Number missing: 98, Reason: 18 lost to follow up, 23 adverse event, 28 gout flare, 13 personal reasons, 2 protocol violation, 14 other reasons; Group 2 Number missing: 67, Reason: 1 withdrew without receiving study drug. 21 lost to follow up, 8 adverse event, 9 gout flare, 13 personal reasons, 1 protocol violation, 14 other reasons

Protocol outcome 2: Frequency of flares at short (< 3 months)
- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Frequency of flares at 8 weeks; Group 1: 90/250, Group 2: 52/251; Comments: Day 1- week 8. I haven't extracted the other timepoints as they don't start from baseline
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, sex, race, baseline serum urate, years with gout, history or presence of tophi, previous urate-lowering therapy and coexisting conditions; Group 1 Number missing: 98, Reason: 18 lost to follow up, 23 adverse event, 28 gout flare, 13 personal reasons, 2 protocol violation, 14 other reasons; Group 2 Number missing: 67, Reason: 1 withdrew without receiving study drug. 21 lost to follow up, 8 adverse event, 9 gout flare, 13 personal reasons, 1 protocol violation, 14 other reasons

Protocol outcome 3: Serum urate levels at medium (3 to 12 months)
- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Serum urate level at 12 months; Group 1: mean -51.52 % (SD 19.91); n=251, Group 2: mean -32.99 % (SD 15.33); n=253; Comments: Baseline febuxostat 120mg: 9.84 (1.26). Baseline allopurinol: 9.90 (1.23).
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, sex, race, baseline serum urate, years with gout, history or presence of tophi, previous urate-lowering therapy and coexisting conditions; Group 1 Number missing: 98, Reason: 18 lost to follow up, 23 adverse event, 28 gout flare, 13 personal reasons, 2 protocol violation, 14 other reasons; Group 2 Number missing: 67, Reason: 1 withdrew without receiving study drug. 21 lost to follow up, 8 adverse event, 9 gout flare, 13 personal reasons, 1 protocol violation, 14 other reasons

Protocol outcome 4: Adverse events and complications of gout (radiographic joint damage, renal stones, tophi) at medium (3 to 12 months)
- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Tophus change at 12 months; Group 1: 28/251,

Group 2: 35/254 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, sex, race, baseline serum urate, years with gout, history or presence of tophi, previous urate-lowering therapy and coexisting conditions; Group 1 Number missing: 98, Reason: 18 lost to follow up, 23 adverse event, 28 gout flare, 13 personal reasons, 2 protocol violation, 14 other reasons; Group 2 Number missing: 67, Reason: 1 withdrew without receiving study drug. 21 lost to follow up, 8 adverse event, 9 gout flare, 13 personal reasons, 1 protocol violation, 14 other reasons	
Protocol outcomes not reported by the study	Health-related quality of life at short (< 3 months); Health-related quality of life at medium (3 to 12 months); Health-related quality of life at long (>12 months); Pain at short (< 3 months); Pain at medium (3 to 12 months); Pain at long (>12 months); Joint swelling/joint inflammation at short (< 3 months); Joint swelling/joint inflammation at medium (3 to 12 months); Joint swelling/joint inflammation at long (> 12 months); Joint tenderness at short (< 3 months); Joint tenderness at medium (3 to 12 months); Joint tenderness at long (> 12 months); Patient global assessment of treatment success (response to treatment) at short (< 3 months); Patient global assessment of treatment success (response to treatment) at medium (3 to 12 months); Patient global assessment of treatment success (response to treatment) at long (> 12 months); Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at short (< 3 months); Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at long (> 12 months); Admissions (hospital & A&E) at short (< 3 months); Admissions (hospital & A&E) at medium 3 to 12 months); Admissions (hospital & A&E) at long (> 12 months); Discontinuation of ULT at short (< 3 months); Discontinuation of ULT at medium (3 to 12 months); Discontinuation of ULT at long (> 12 months); Frequency of flares at long (> 12 months); Serum urate levels at short (< 3 months); Serum urate levels at long (> 12 months); Adverse events and complications of gout (radiographic joint damage, renal stones, tophi) at short (< 3 months); Adverse events and complications of gout (radiographic joint damage, renal stones, tophi) at long (> 12 months)

Study	**FORWARD- Intensive urate lowering therapy of febuxostat compared to allopurinol (EudraCT NUMBER 2914-005567-33) trial: Desideri 2021[28]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=197)
Countries and setting	Conducted in Germany, Italy, Netherlands, Poland, Romania, Serbia; Setting: Not stated

Line of therapy	Mixed line
Duration of study	Intervention + follow up: The study duration was 39 weeks, which included the: Run-in/screening period: 1 week (extendable up to a maximum of 30 days according to variability of SUA levels); Treatment period: 36 weeks; Safety follow-up period: 2 weeks.
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ? crystal proven diagnosis or anamnestic diagnosis according to Wallace et al.
Stratum	People without chronic kidney disease or people with CKD stages 1-2
Subgroup analysis within study	Not applicable
Inclusion criteria	Male or female patients 18 years and older, history of gout flare in the 4 weeks prior to study entry, history of crystal proven diagnosis or anamnestic diagnosis of gout according to Wallace et al. To be eligible, a patient had to present at least 6 of the following 12 clinical, laboratory and x-ray phenomena: 1. Maximum inflammation developed within 1 day, 2. More than one attack of acute arthritis, 3. Monoarticular arthritis attack, 4. Redness observed over joints, 5. First metatarsophalangeal (MTP) pain or swelling, 6. Unilateral first MTP joint attack, 7. Unilateral tarsal joint attack, 8. Suspected or proven tophus, 9. Hyperuricemia, 10. Asymmetric swelling within a joint on a X ray, 11. Subcortical cysts without erosions on X ray, 12. Negative organisms on culture of joint fluid; 4. Naive to ULT or previously treated with ULT, but with no ULT treatment in the last 1 month prior to study entry and only if reason for ULT interruption was not due to safety concerns. 5. Patients at study entry have elevated serum urate level >8 mg/dl. 6. Overall Cardiovascular (CV) risk based on the scoring proposed by the Joint Task Force of the European Society of Cardiology and other European Societies on cardiovascular disease prevention in clinical practice between 5 and 15-% (inclusive). Patients with diabetes mellitus type 2 could be included in the study if their CV risk score is calculated as ≤7%. 7. Allowed concomitant medications should be maintained stable during the last 2 weeks before randomisation. All patients had to be flare free at study entry. Patients had to be either naive to ULT or previously treated with ULT more than one month prior to study entry and only if the ULT discontinuation was not due to safety concerns. Additional criteria for inclusion were an SUA level of at least 8.0mg/dL at study entry.
Exclusion criteria	Severe chronic renal failure (creatinine clearance < 30 ml/min), Hepatic failure, active liver disease or hepatic dysfunction, defined as both alanine aminotransferase (ALT) and aspartate aminotransferase (AST) >2 times the upper limit of normal, diabetes mellitus type1, life-threatening co-morbidity or with a significant medical condition and/or

	conditions that would interfere with the treatment, the safety or the compliance with the protocol, diagnosis of, or receiving treatment for malignancy (excluding basiloma skin cancer) in the previous 5 years, patients who have experienced either myocardial infarction or stroke, patients with inflammatory based arthritis (e.g.: rheumatoid arthritis, etc.), patients with congestive heart failure, New York Heart Association (NYHA) Class III or IV, patients with untreated/uncontrolled thyroid function, patients with clinically severe peripheral arterial disease Concomitant administration of any of the following: azathioprine, mercaptopurine, theophylline, meclofenamate, sulfinpyrazone, trimethoprim-sulfamethoxazole, cyclophosphamide, benzbromarone, pyrazinamide, captopril and enalapril (for Allopurinol), tegafur, pegloticase and tacrolimus. Hypersensitivity to any one of the active substances or to any of the excipients Any contraindication to febuxostat or allopurinol (with reference to the summary of product characteristics). Subject is unable to take either of the protocol-required gout flare prophylactic medications (NSAID or colchicine) due to contraindications or intolerance, e.g. hypersensitivity, active gastric ulcer disease, renal impairment and/or changes in liver enzymes Participation in another trial of an investigational drug or device within 30 days prior to screening, or prior treatment with investigational product(s) Women of childbearing potential (WOCBP), including peri-menopausal women who have had a menstrual period within 1 year, not willing to use highly effective method of birth control throughout the study period and for 4 weeks after study completion defined as a method which results in a failure rate of less than 1% per year such as: combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable), intrauterine device (IUD), intrauterine hormone-releasing system (IUS), bilateral tubal occlusion, vasectomised partner (provided that partner is the sole sexual partner of the trial participant and that the vasectomised partner has received medical assessment of the surgical success), sexual abstinence; Severe psychiatric disorders/neurological disorders Severe concurrent pathology, including terminal illness (cancer, AIDS, etc) Abuse of alcohol, analgesics, or psychotropic drugs Inability or unwillingness, in the investigator's opinion, to follow study procedures including, but not limited to the ability to obtain adequate PWV/Pulse Wave Analysis (PWA) recordings. Special attention was made to any physical abnormalities which could affect quality of PWV/PWA measurement: Neck region- neck flexibility and accessibility of carotid artery,

	Upper arm and thigh region- exclude any abnormalities which would prevent adequate placement of the cuff; Inability or unwillingness to issue informed consent
Recruitment/selection of patients	Not reported
Age, gender, and ethnicity	Age - Mean (range): 59.6 (30-83) years. Gender (M:F): 82.1% male. Ethnicity: NR
Further population details	1. Age: Not applicable 2. Setting: Not stated / Unclear
Extra comments	Population was naive to ULT or previously treated with ULT. Crystal proven diagnoses Febuxostat: 3, Allopurinol: 1 Amnestic diagnosis Febuxostat: 92, Allopurinol: 93 Other Febuxostat: 3, Allopurinol: 4
Indirectness of population	No indirectness
Interventions	(n=98) Intervention 1: Xanthine oxidase inhibitor - Allopurinol for moderate gout 300-600mg. Allopurinol 100 up to 600 mg/day Allopurinol 100/300 mg tablets. The initial daily allopurinol dose is 100 mg given orally, to be escalated of 100 mg every 2 weeks in patients with serum urate concentration >6 mg/dl, depending on kidney function and tolerability (permitted between week 2 and week 10 for patients who did not reach the target SUA of <6mg/dL). The maximum dose of allopurinol achievable in the study depended on kidney function and tolerability, but did not exceed 600 mg daily. Duration 36 weeks. Concurrent medication/care: To prevent flares in the initial stages of treatment, patients were treated with colchicine 0.5 - 1 mg QD or in case of colchicine intolerance, Naproxen 550 mg BID with Omeprazole (20-40 mg once daily), if indicated to be used, according to EULAR guidelines... Indirectness: No indirectness Further details: 1. Choice of drug (drugs within the class, based on the intervention arm only): (n=99) Intervention 2: Xanthine oxidase inhibitor - Febuxostat 80mg. Febuxostat 80/120 mg/day Febuxostat 80/120 mg film coated tablets. The initial daily dose was 80 mg given orally. In case a patient had a serum urate level 6 mg/dl after 2 weeks of treatment the dose was escalated to 120 mg and if tolerated was maintained during

	the study treatment period. Duration 36 weeks. Concurrent medication/care: To prevent flares in the initial stages of treatment, patients were treated with colchicine 0.5 - 1 mg QD or in case of colchicine intolerance, Naproxen 550 mg BID with Omeprazole (20-40 mg once daily), if indicated to be used, according to EULAR guidelines... Indirectness: No indirectness Further details: 1. Choice of drug (drugs within the class, based on the intervention arm only):
Funding	Study funded by industry (Menarini International Operations Luxembourg)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ALLOPURINOL 100-600MG versus FEBUXOSTAT 80-120MG

Protocol outcome 1: Serum urate levels at medium-term (3 to 12 months)
- Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Number of people achieving SUA concentrations of ≤6mg/dL at Week 36; Group 1: 55/90, Group 2: 72/92
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Difference in cardiovascular risk score:
Allopurinol group: 6.81 (3,24), Febuxostat: 7.34 (3.72); Blinding details: Open label trial. Outcome assessor blinded.; Group 1 Number missing: 12, Reason: Adverse events: 2, withdrew consent: 5, other: 2, protocol violation: 2, lost to follow-up: 0, study terminated by sponsor: 0, noncompliance with study drug: 1; Group 2 Number missing: 11, Reason: Adverse events: 0, withdrew consent: 4, other: 3, protocol violation: 1, lost to follow-up: 1, study terminated by sponsor: 1, noncompliance with study drug: 0

Protocol outcome 2: Adverse events and complications of gout (radiographic joint damage, renal stones, tophi) at medium-term (3 to 12 months)
- Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Treatment emergent adverse events at During 38 week period (36 weeks treatment plus 2 weeks follow-up); Group 1: 63/98, Group 2: 51/99
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Difference in cardiovascular risk score:
Allopurinol group: 6.81 (3,24), Febuxostat: 7.34 (3.72); Blinding details: Open label trial. Outcome assessor blinded.; Group 1 Number missing: 12, Reason: Adverse events: 2, withdrew consent: 5, other: 2, protocol violation: 2, lost to follow-up: 0, study terminated by sponsor: 0, noncompliance with study drug: 1; Group 2 Number missing: 11, Reason: Adverse events: 0, withdrew consent: 4, other: 3, protocol violation: 1, lost to follow-up: 1, study terminated by sponsor: 1, noncompliance with study drug: 0

Protocol outcomes not reported by the study	Health-related quality of life at short (< 3 months); Health-related quality of life at medium (3 to 12 months); Health-related quality of life at long (>12 months); Pain at short (< 3 months); Pain at medium (3 to 12 months); Pain at long (>12 months); Joint swelling/joint inflammation at short (< 3 months); Joint swelling/joint inflammation at medium (3 to 12

	months); Joint swelling/joint inflammation at long (> 12 months); Joint tenderness at short (< 3 months); Joint tenderness at medium (3 to 12 months); Joint tenderness at long (> 12 months); Patient global assessment of treatment success (response to treatment) at short (< 3 months); Patient global assessment of treatment success (response to treatment) at medium (3 to 12 months); Patient global assessment of treatment success (response to treatment) at long (> 12 months); Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at short (< 3 months); Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at medium (3 to 12 months); Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at long (> 12 months); Admissions (hospital & A&E) at short (< 3 months); Admissions (hospital & A&E) at medium 3 to 12 months); Admissions (hospital & A&E) at long (> 12 months); Discontinuation of ULT at short (< 3 months); Discontinuation of ULT at medium (3 to 12 months); Discontinuation of ULT at long (> 12 months); Frequency of flares at short (< 3 months); Frequency of flares at medium (3 to 12 months); Frequency of flares at long (> 12 months); Serum urate levels at short (< 3 months); Serum urate levels at long (> 12 months); Adverse events and complications of gout (radiographic joint damage, renal stones, tophi) at short (< 3 months); Adverse events and complications of gout (radiographic joint damage, renal stones, tophi) at long (> 12 months)

Study	**Gunawardhana 2018[42]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=189)
Countries and setting	Conducted in USA; Setting: Outpatient follow up
Line of therapy	1st line
Duration of study	Intervention + follow up: 3 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Presence of gout based on criteria defined by the American Rheumatism Association
Stratum	People with chronic kidney disease (stage 3)
Subgroup analysis within study	Not applicable
Inclusion criteria	Men and women (age at least 18 years) who: provided informed consent; had a history or presence of gout based on criteria defined by the American Rheumatism Association; had a serum urate level at least 8.0 mg/dL at the day -4 screening visit or at

	the retest visit; had moderate renal impairment as defined by an eGFR (modification of diet in renal disease) at least 30 and <60mL/min at screening visit on day -21 for patients on urate lowering therapy and on day -4 for people not on urate lowering therapy at the test visit; had a self-reported history of at least 1 gout flare within the 12 months prior to the screening visit
Exclusion criteria	Received an investigational compound within 30 days prior to screening; secondary hyperuricaemia; history of xanthuria, known hypersensitivity to febuxostat or any components in its formulations; known hypersensitivity to naproxen; any other nonsteroidal anti-inflammatory drug, aspirin, lansoprazole, colchicine, or any components in their formulation; had experienced either a myocardial infarction, stroke, hospitalised unstable angina, cardiac or cerebrovascular revascularisation procedure, or hospitalised transient ischaemic attack; history of cancer (other than basal cell carcinoma of the skin) within 5 years prior to the screening visit; history of drug or alcohol abuse; presence of rheumatoid arthritis; active peptic ulcer disease; any significant medical condition that would interfere with the treatment, safety or compliance with the protocol
Recruitment/selection of patients	No additional information
Age, gender, and ethnicity	Age - Mean (SD): 63.1 (11.5). Gender (M:F): 134:55. Ethnicity: White = 126, Black or African American = 46
Further population details	1. Age: < 65 years 2. Setting: Not stated / Unclear
Extra comments	Baseline serum urate level (mean [SD]): 9.7 (1.3) mg/dL
Indirectness of population	No indirectness
Interventions	(n=37) Intervention 1: Xanthine oxidase inhibitor - Febuxostat 80mg. Febuxostat 80mg immediate release. Duration 3 months. Concurrent medication/care: All people systematically received gout flare prophylaxis for the duration of double-blind treatment from day 1 to the end of treatment, including colchicine 0.6mg every other day. However, if colchicine was contraindicated or not tolerated, naproxen (250mg BID) or other NSAIDs or prednisone were permitted at the investigator's discretion. Indirectness: No indirectness Further details: 1. Choice of drug (drugs within the class, based on the intervention arm only): Febuxostat 80mg (n=38) Intervention 2: Placebo. Duration 3 months. Concurrent medication/care: All people systematically received gout flare prophylaxis for the duration of double-blind treatment from day 1 to the end of treatment, including colchicine 0.6mg every other day. However, if colchicine was contraindicated or not tolerated, naproxen (250mg BID) or other NSAIDs or prednisone were permitted at the investigator's discretion. Indirectness: No indirectness Further details: 1. Choice of drug (drugs within the class, based on the intervention arm only): Placebo
Funding	Study funded by industry (This study was sponsored by Takeda Pharmaceutical international, Inc., Deerfield, IL, USA)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FEBUXOSTAT 80MG versus PLACEBO	

Protocol outcome 1: Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at medium (3 to 12 months)
- Actual outcome for People with chronic kidney disease (stage 3): Gastrointestinal adverse events at 3 months; Group 1: 0/37, Group 2: 0/38
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, sex, race, BMI, baseline serum urate level, approximate gout flares during the last year, baseline eGFR; Group 1 Number missing: 6, Reason: Pre-treatment event/adverse event = 1, major protocol deviation = 2, lost to follow up = 1, voluntary withdrawal = 1, other = 1; Group 2 Number missing: 5, Reason: Pre-treatment event/adverse event = 1, major protocol deviation = 1, voluntary withdrawal = 3
- Actual outcome for People with chronic kidney disease (stage 3): Renal/urinary adverse events (renal failure, nephrolithiasis) at 3 months; Group 1: 0/37, Group 2: 2/38
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, sex, race, BMI, baseline serum urate level, approximate gout flares during the last year, baseline eGFR; Group 1 Number missing: 6, Reason: Pre-treatment event/adverse event = 1, major protocol deviation = 2, lost to follow up = 1, voluntary withdrawal = 1, other = 1; Group 2 Number missing: 5, Reason: Pre-treatment event/adverse event = 1, major protocol deviation = 1, voluntary withdrawal = 3
- Actual outcome for People with chronic kidney disease (stage 3): Cardiac adverse events (palpitations) at 3 months; Group 1: 0/37, Group 2: 0/38
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, sex, race, BMI, baseline serum urate level, approximate gout flares during the last year, baseline eGFR; Group 1 Number missing: 6, Reason: Pre-treatment event/adverse event = 1, major protocol deviation = 2, lost to follow up = 1, voluntary withdrawal = 1, other = 1; Group 2 Number missing: 5, Reason: Pre-treatment event/adverse event = 1, major protocol deviation = 1, voluntary withdrawal = 3
- Actual outcome for People with chronic kidney disease (stage 3): Vascular adverse events (hypertension) at 3 months; Group 1: 1/37, Group 2: 1/38
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, sex, race, BMI, baseline serum urate level, approximate gout flares during the last year, baseline eGFR; Group 1 Number missing: 6, Reason: Pre-treatment event/adverse event = 1, major protocol deviation = 2, lost to follow up = 1, voluntary withdrawal = 1, other = 1; Group 2 Number missing: 5, Reason: Pre-treatment event/adverse event = 1, major protocol deviation = 1, voluntary withdrawal = 3

Protocol outcome 2: Frequency of flares at medium (3 to 12 months)
- Actual outcome for People with chronic kidney disease (stage 3): Frequency of flares at 3 months; Group 1: 14/37, Group 2: 4/38
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, sex, race, BMI, baseline serum urate level, approximate gout flares during the last year, baseline eGFR; Group 1 Number missing: 6, Reason: Pre-treatment event/adverse event = 1, major protocol deviation = 2, lost to follow up = 1, voluntary withdrawal = 1, other = 1; Group 2 Number missing: 5, Reason: Pre-treatment event/adverse event = 1, major protocol deviation = 1, voluntary withdrawal = 3

Protocol outcome 3: Serum urate levels at medium (3 to 12 months)
- Actual outcome for People with chronic kidney disease (stage 3): Number of people achieving sUA <6mg/dL at 3 months; Group 1: 22/37, Group 2: 0/38
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, sex, race, BMI, baseline serum urate level, approximate gout flares during the last year, baseline eGFR; Group 1 Number missing: 6, Reason: Pre-treatment event/adverse event = 1, major protocol deviation = 2, lost to follow up = 1, voluntary

withdrawal = 1, other = 1; Group 2 Number missing: 5, Reason: Pre-treatment event/adverse event = 1, major protocol deviation = 1, voluntary withdrawal = 3	
Protocol outcomes not reported by the study	Health-related quality of life at short (< 3 months); Health-related quality of life at medium (3 to 12 months); Health-related quality of life at long (>12 months); Pain at short (< 3 months); Pain at medium (3 to 12 months); Pain at long (>12 months); Joint swelling/joint inflammation at short (< 3 months); Joint swelling/joint inflammation at medium (3 to 12 months); Joint swelling/joint inflammation at long (> 12 months); Joint tenderness at short (< 3 months); Joint tenderness at medium (3 to 12 months); Joint tenderness at long (> 12 months); Patient global assessment of treatment success (response to treatment) at short (< 3 months); Patient global assessment of treatment success (response to treatment) at medium (3 to 12 months); Patient global assessment of treatment success (response to treatment) at long (> 12 months); Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at short (< 3 months); Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at long (> 12 months); Admissions (hospital & A&E) at short (< 3 months); Admissions (hospital & A&E) at medium 3 to 12 months); Admissions (hospital & A&E) at long (> 12 months); Discontinuation of ULT at short (< 3 months); Discontinuation of ULT at medium (3 to 12 months); Discontinuation of ULT at long (> 12 months); Frequency of flares at short (< 3 months); Frequency of flares at long (> 12 months); Serum urate levels at short (< 3 months); Serum urate levels at long (> 12 months); Adverse events and complications of gout (radiographic joint damage, renal stones, tophi) at short (< 3 months); Adverse events and complications of gout (radiographic joint damage, renal stones, tophi) at medium (3 to 12 months); Adverse events and complications of gout (radiographic joint damage, renal stones, tophi) at long (> 12 months)

Study	**Hill 2015[48]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=37)
Countries and setting	Conducted in USA; Setting: Outpatient follow up
Line of therapy	1st line
Duration of study	Intervention + follow up: 28 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: People with crystal-proven gout by arthrocentesis presenting with an acute gout attack within 72 hours after initial therapy
Stratum	Mixed population (people with chronic kidney disease and people without chronic kidney disease)
Subgroup analysis within study	Not applicable

Inclusion criteria	People with an acute gout attack were considered if they met at least 1 of the following additional criteria for starting urate-lowering therapy: the presence of gouty tophi; more than 1 acute gout attack per year; a history of nephrolithiasis; urate overproduction (>1000mg in 24-hour urine collection)
Exclusion criteria	Glomerular filtration rate of less than 50mL/min; aspartate and alanine aminotransferases or alkaline phosphatase greater than 1.25 times the upper limit of normal; prior use of allopurinol in the past 6 months; history of an adverse reaction to allopurinol; ongoing cancer treatment; myelodysplastic syndrome; leukaemia; women of childbearing potential; concomitant use of azathioprine or cyclophosphamide; inability to return for repeated examinations; premorbid pain in the involved joint of more than 3 on a 10-point numerical rating scale; neurologic deficit causing decreased pain sensation around the involved joint
Recruitment/selection of patients	No additional information
Age, gender, and ethnicity	Age - Mean (range): 56.6 (31-84). Gender (M:F): 33:2. Ethnicity: Not stated
Further population details	1. Age: < 65 years 2. Setting: Secondary care
Extra comments	Baseline serum urate: Not stated
Indirectness of population	No indirectness
Interventions	(n=16) Intervention 1: Xanthine oxidase inhibitor - Allopurinol for mild gout 100-200mg. Allopurinol initiated at 100mg daily for the first 14 days, and then increased to 200mg daily for the next 14 days. Duration 28 days. Concurrent medication/care: People were treated for acute gout as deemed appropriate by their referring physician. Each person was treated with prophylactic oral colchicine 0.6mg daily for the first 2 days, then 0.6mg twice daily from days 3-28. Dose reductions to 0.6mg daily were made for concomitant statin use or gastrointestinal intolerance. People unable to take colchicine because of prior adverse reactions received 15mg oral meloxicam daily for prophylaxis during allopurinol initiation. Indirectness: No indirectness Further details: 1. Choice of drug (drugs within the class, based on the intervention arm only): Allopurinol for mild gout 100-200mg (n=19) Intervention 2: Placebo. Duration 27 days. Concurrent medication/care: People were treated for acute gout as deemed appropriate by their referring physician. Each person was treated with prophylactic oral colchicine 0.6mg daily for the first 2 days, then 0.6mg twice daily from days 3-28. Dose reductions to 0.6mg daily were made for concomitant statin use or gastrointestinal intolerance. People unable to take colchicine because of prior adverse reactions received 15mg oral meloxicam daily for prophylaxis during allopurinol initiation. Indirectness: No indirectness Further details: 1. Choice of drug (drugs within the class, based on the intervention arm only): Placebo
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ALLOPURINOL FOR MILD GOUT 100-200MG versus PLACEBO

Protocol outcome 1: Joint swelling/joint inflammation at short (< 3 months)
- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Joint inflammation at 28 days; Group 1: 1/16, Group 2: 0/19. Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: Serious indirectness, Comments: Dichotomous outcome rather than continuous; Baseline details: Reported age, gender, disease duration, previous attacks, nephrolithiasis, tophi, erosions and initial treatment; Group 1 Number missing: 2, Reason: 1 unable to make visits, 1 epistaxis; Group 2 Number missing: 2, Reason: 1 nausea and vomiting, 1 elevated liver enzymes

Protocol outcome 2: Joint tenderness at short (< 3 months)
- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Joint tenderness at 28 days; Group 1: 2/16, Group 2: 1/19. Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: Serious indirectness, Comments: Dichotomous outcome rather than continuous; Baseline details: Reported age, gender, disease duration, previous attacks, nephrolithiasis, tophi, erosions and initial treatment; Group 1 Number missing: 2, Reason: 1 unable to make visits, 1 epistaxis; Group 2 Number missing: 2, Reason: 1 nausea and vomiting, 1 elevated liver enzymes

Protocol outcome 3: Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at short (< 3 months)
- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Withdrawal due to adverse events at 28 days; Group 1: 1/16, Group 2: 2/19. Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: Serious indirectness, Comments: Withdrawal outcome; Baseline details: Reported age, gender, disease duration, previous attacks, nephrolithiasis, tophi, erosions and initial treatment; Group 1 Number missing: 2, Reason: 1 unable to make visits, 1 epistaxis; Group 2 Number missing: 2, Reason: 1 nausea and vomiting, 1 elevated liver enzymes

Protocol outcomes not reported by the study	Health-related quality of life at short (< 3 months); Health-related quality of life at medium (3 to 12 months); Health-related quality of life at long (>12 months); Pain at short (< 3 months); Pain at medium (3 to 12 months); Pain at long (>12 months); Joint swelling/joint inflammation at medium (3 to 12 months); Joint swelling/joint inflammation at long (> 12 months); Joint tenderness at medium (3 to 12 months); Joint tenderness at long (> 12 months); Patient global assessment of treatment success (response to treatment) at short (< 3 months); Patient global assessment of treatment success (response to treatment) at medium (3 to 12 months); Patient global assessment of treatment success (response to treatment) at long (> 12 months); Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at medium (3 to 12 months); Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at long (> 12 months); Admissions (hospital & A&E) at short (< 3 months); Admissions (hospital & A&E) at medium 3 to 12 months); Admissions (hospital & A&E) at long (> 12 months); Discontinuation of ULT at short (< 3 months); Discontinuation of ULT at medium (3 to 12 months); Discontinuation of ULT at

	long (> 12 months); Frequency of flares at short (< 3 months); Frequency of flares at medium (3 to 12 months); Frequency of flares at long (> 12 months); Serum urate levels at short (< 3 months); Serum urate levels at medium (3 to 12 months); Serum urate levels at long (> 12 months); Adverse events and complications of gout (radiographic joint damage, renal stones, tophi) at short (< 3 months); Adverse events and complications of gout (radiographic joint damage, renal stones, tophi) at medium (3 to 12 months); Adverse events and complications of gout (radiographic joint damage, renal stones, tophi) at long (> 12 months)

Study	Huang 2014[53]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=516)
Countries and setting	Conducted in China; Setting: Outpatient follow up
Line of therapy	Mixed line
Duration of study	Intervention + follow up: 28 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: People with a diagnosis of gout fulfilling the American College of Rheumatology Association's preliminary criteria with a serum urate level of at least 8.0mg/dL
Stratum	Mixed population (people with chronic kidney disease and people without chronic kidney disease)
Subgroup analysis within study	Not applicable
Inclusion criteria	People aged 18-70 years with a diagnosis of gout fulfilling the American Rheumatology Association's preliminary criteria and with serum urate of at least 8.0mg/dL
Exclusion criteria	A serum creatinine concentration of more than 1.5mg/dL (135 micromol/L); active liver disease or hepatic dysfunction (alanine aminotransferase and aspartate aminotransferase values >1.5 times the upper limit of normal); people developing gouty arthritis or recovering from gouty arthritis less than 2 weeks previously; known allergy to febuxostat, allopurinol, non-steroidal anti-inflammatory drugs, colchicine, or any ingredient of these prescriptions
Recruitment/selection of patients	Subjects were enrolled at 14 sites in China
Age, gender, and ethnicity	Age - Mean (SD): 46.7 (11.2). Gender (M:F): 504:12. Ethnicity: Not stated
Further population details	1. Age: > 65 years 2. Setting: Secondary care
Extra comments	Baseline serum urate (mean [SD]): 9.9 (1.4) mg/dL.
Indirectness of population	No indirectness
Interventions	(n=172) Intervention 1: Xanthine oxidase inhibitor - Febuxostat 80mg. Febuxostat 80mg/day. Duration 28 weeks. Concurrent medication/care: People previously on a urate lowering therapy underwent a 2-week washout period before undergoing randomisation. Indirectness: No indirectness Further details: 1. Choice of drug (drugs within the class, based on the intervention arm only): Febuxostat 80mg (n=172) Intervention 2: Xanthine oxidase inhibitor - Allopurinol for moderate gout 300-600mg. Allopurinol 300mg/day. Duration 28 weeks. Concurrent medication/care: People previously on a urate lowering therapy underwent a 2-week washout

	period before undergoing randomisation. Indirectness: No indirectness Further details: 1. Choice of drug (drugs within the class, based on the intervention arm only): Allopurinol 300mg
Funding	Study funded by industry (This study was supported by Wanbang Biopharmaceuticals (ChiCTR: 2009L08759, 2009L11564))

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FEBUXOSTAT 80MG versus ALLOPURINOL FOR MODERATE GOUT 300-600MG

Protocol outcome 1: Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at medium (3 to 12 months)
- Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Gastrointestinal disorders at 28 weeks; Group 1: 5/172, Group 2: 1/172
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, sex, height, weight, BMI, serum urate level, gouty tophus status and concurrent disease; Group 1 Number missing: 18, Reason: 7 lost to follow up, 10 adverse events, 1 personal reason; Group 2 Number missing: 21, Reason: 8 lost to follow up, 12 adverse event, 1 personal reason

Protocol outcome 2: Frequency of flares at medium (3 to 12 months)
- Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Gout flares (subjects requiring treatment for acute gout flares at 28 weeks; Group 1: 7/172, Group 2: 16/172. Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, sex, height, weight, BMI, serum urate level, gouty tophus status and concurrent disease; Group 1 Number missing: 18, Reason: 7 lost to follow up, 10 adverse events, 1 personal reason; Group 2 Number missing: 21, Reason: 8 lost to follow up, 12 adverse event, 1 personal reason

Protocol outcome 3: Serum urate levels at medium (3 to 12 months)
- Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Reduction of serum urate level in the final visit against baseline at 28 weeks; Group 1: mean -4.17 mg/dL (SD 2.07); n=172, Group 2: mean -3.25 mg/dL (SD 2.11); n=172; Comments: Reported change scores and 95% confidence intervals. Reported febuxostat: -4.17 (-4.48, -3.86). Reported allopurinol: -3.25 (-3.57,-2.94). Baseline febuxostat: 9.98 (1.39). Baseline allopurinol: 9.95 (1.35). Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, sex, height, weight, BMI, serum urate level, gouty tophus status and concurrent disease; Group 1 Number missing: 18, Reason: 7 lost to follow up, 10 adverse events, 1 personal reason; Group 2 Number missing: 21, Reason: 8 lost to follow up, 12 adverse event, 1 personal reason

Protocol outcome 4: Adverse events and complications of gout (radiographic joint damage, renal stones, tophi) at medium (3 to 12 months)
- Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Change in number of Tophi from baseline at 28 weeks; Group 1: mean -0.28 (SD 1.17); n=172, Group 2: mean -0.15 (SD 1.17); n=172. Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, sex, height, weight,

BMI, serum urate level, gouty tophus status and concurrent disease; Group 1 Number missing: 18, Reason: 7 lost to follow up, 10 adverse events, 1 personal reason; Group 2 Number missing: 21, Reason: 8 lost to follow up, 12 adverse event, 1 personal reason. - Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: renal adverse events at 28 weeks; Group 1: 4/172, Group 2: 2/172 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, sex, height, weight, BMI, serum urate level, gouty tophus status and concurrent disease; Group 1 Number missing: 18, Reason: 7 lost to follow up, 10 adverse events, 1 personal reason; Group 2 Number missing: 21, Reason: 8 lost to follow up, 12 adverse event, 1 personal reason.	
Protocol outcomes not reported by the study	Health-related quality of life at short (< 3 months); Health-related quality of life at medium (3 to 12 months); Health-related quality of life at long (>12 months); Pain at short (< 3 months); Pain at medium (3 to 12 months); Pain at long (>12 months); Joint swelling/joint inflammation at short (< 3 months); Joint swelling/joint inflammation at medium (3 to 12 months); Joint swelling/joint inflammation at long (> 12 months); Joint tenderness at short (< 3 months); Joint tenderness at medium (3 to 12 months); Joint tenderness at long (> 12 months); Patient global assessment of treatment success (response to treatment) at short (< 3 months); Patient global assessment of treatment success (response to treatment) at medium (3 to 12 months); Patient global assessment of treatment success (response to treatment) at long (> 12 months); Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at short (< 3 months); Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at long (> 12 months); Admissions (hospital & A&E) at short (< 3 months); Admissions (hospital & A&E) at medium 3 to 12 months); Admissions (hospital & A&E) at long (> 12 months); Discontinuation of ULT at short (< 3 months); Discontinuation of ULT at medium (3 to 12 months); Discontinuation of ULT at long (> 12 months); Frequency of flares at short (< 3 months); Frequency of flares at long (> 12 months); Serum urate levels at short (< 3 months); Serum urate levels at long (> 12 months); Adverse events and complications of gout (radiographic joint damage, renal stones, tophi) at short (< 3 months); Adverse events and complications of gout (radiographic joint damage, renal stones, tophi) at long (> 12 months)

Study	**Huang 2020[54]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=156)
Countries and setting	Conducted in China; Setting: Outpatient follow up

Line of therapy	Mixed line
Duration of study	Intervention + follow up: 24 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Gout was diagnosed by the treating physician from the person's history and available laboratory data
Stratum	People without chronic kidney disease or people with CKD stages 1-2
Subgroup analysis within study	Not applicable
Inclusion criteria	Gout and hyperuricaemia (serum urate at least 8mg/dL); observation follow-up of at least 24 weeks; age between 17 and 70 years.
Exclusion criteria	A history of other autoimmune disease; people with nephropathy; people with cancer; people with haematopathy
Recruitment/selection of patients	People were recruited in the Department of Rheumatology, First Hospital of Jilin university, Changchun, Jilin Province, China
Age, gender, and ethnicity	Age - Mean (SD): 43.1 (10.9). Gender (M:F): Not stated. Ethnicity: All participants were Han Chinese
Further population details	1. Age: < 65 years 2. Setting: Secondary care
Extra comments	Baseline serum urate (mean [SD]): 594.6 (89.2) micromol/L
Indirectness of population	No indirectness
Interventions	(n=78) Intervention 1: Xanthine oxidase inhibitor - Febuxostat 80mg. Febuxostat 80mg dissolved in 200mL water once daily in the morning after breakfast for 24 weeks. Duration 24 weeks. Concurrent medication/care: No additional information. Indirectness: No indirectness Further details: 1. Choice of drug (drugs within the class, based on the intervention arm only): Febuxostat 80mg (n=78) Intervention 2: Placebo once a day in the morning for 24 weeks. Duration 24 weeks. Concurrent medication/care: No additional information. Indirectness: No indirectness

	Further details: 1. Choice of drug (drugs within the class, based on the intervention arm only): Placebo
Funding	Study funded by industry (This study was supported by funding from The National Natural Science Foundation of China (no. 81501343), The Bethune Plan Project of Jilin University (no. 2015410) and The Jilin Scientific and Technological Development Programme (no. 20170520010JH; no. 20150101152JC).)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FEBUXOSTAT 80MG versus PLACEBO Protocol outcome 1: Serum urate levels at short (< 3 months) - Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: number of people achieving sUA <6mg/dL at 2 months; Group 1: 22/78, Group 2: 0/78 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing:0 - Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: number of people achieving sUA <5mg/dL at 2 months; Group 1: 9/78, Group 2: 0/78 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0 Protocol outcome 2: Serum urate levels at medium (3 to 12 months) - Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: number of people achieving sUA <5mg/dL at 6 months; Group 1: 12/78, Group 2: 0/78 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing:0 - Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: number of people achieving sUA <6mg/dL at 6 months; Group 1: 25/78, Group 2: 0/78 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Health-related quality of life at short (< 3 months); Health-related quality of life at medium (3 to 12 months); Health-related quality of life at long (>12 months); Pain at short (< 3 months); Pain at medium (3 to 12 months); Pain at long (>12 months); Joint swelling/joint inflammation at short (< 3 months); Joint swelling/joint inflammation at medium (3 to 12 months); Joint

	swelling/joint inflammation at long (> 12 months); Joint tenderness at short (< 3 months); Joint tenderness at medium (3 to 12 months); Joint tenderness at long (> 12 months); Patient global assessment of treatment success (response to treatment) at short (< 3 months); Patient global assessment of treatment success (response to treatment) at medium (3 to 12 months); Patient global assessment of treatment success (response to treatment) at long (> 12 months); Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at short (< 3 months); Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at medium (3 to 12 months); Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at long (> 12 months); Admissions (hospital & A&E) at short (< 3 months); Admissions (hospital & A&E) at medium 3 to 12 months); Admissions (hospital & A&E) at long (> 12 months); Discontinuation of ULT at short (< 3 months); Discontinuation of ULT at medium (3 to 12 months); Discontinuation of ULT at long (> 12 months); Frequency of flares at short (< 3 months); Frequency of flares at medium (3 to 12 months); Frequency of flares at long (> 12 months); Serum urate levels at long (> 12 months); Adverse events and complications of gout (radiographic joint damage, renal stones, tophi) at short (< 3 months); Adverse events and complications of gout (radiographic joint damage, renal stones, tophi) at medium (3 to 12 months); Adverse events and complications of gout (radiographic joint damage, renal stones, tophi) at long (> 12 months)

Study	**Kim 2014[65]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=179)
Countries and setting	Conducted in South Korea; Setting: Outpatient follow up
Line of therapy	Mixed line
Duration of study	Intervention + follow up: 4 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Meeting the American College of Rheumatology criteria for gout
Stratum	Mixed population (people with chronic kidney disease and people without chronic kidney disease)
Subgroup analysis within study	Not applicable

Inclusion criteria	Meeting the preliminary criteria for the American College of Rheumatology for gout and had serum urate concentration of at least 8.0mg/dL at screening
Exclusion criteria	Serum creatinine concentration >1.5mg/dL (133 micromol/L); use of thiazide diuretics or medications containing aspirin or other salicylates; active liver disease; an alcohol intake of more than 14 drinks/week
Recruitment/selection of patients	The study was performed at 10 university affiliated hospitals in Korea
Age, gender, and ethnicity	Age - Mean (SD): 50.0 (11.8). Gender (M:F): 179:0. Ethnicity: Not stated
Further population details	1. Age: < 65 years 2. Setting: Secondary care
Extra comments	Baseline serum urate level (mean [SD]): 9.6 (1.2) mg/dL
Indirectness of population	No indirectness
Interventions	(n=36) Intervention 1: Xanthine oxidase inhibitor - Febuxostat 80mg. Febuxostat 80mg/day. Duration 4 weeks. Concurrent medication/care: No additional information. Indirectness: No indirectness Further details: 1. Choice of drug (drugs within the class, based on the intervention arm only): Febuxostat 80mg (n=38) Intervention 2: Xanthine oxidase inhibitor - Febuxostat 120mg. Febuxostat 120mg/day. Duration 4 weeks. Concurrent medication/care: No additional information. Indirectness: No indirectness Further details: 1. Choice of drug (drugs within the class, based on the intervention arm only): Febuxostat 120mg (n=38) Intervention 3: Xanthine oxidase inhibitor - Allopurinol for moderate gout 300-600mg. Allopurinol 300mg/day. Duration 4 weeks. Concurrent medication/care: No additional information. Indirectness: No indirectness Further details: 1. Choice of drug (drugs within the class, based on the intervention arm only): Allopurinol 300mg (n=39) Intervention 4: Placebo. Duration 4 weeks. Concurrent medication/care: No additional information. Indirectness: No indirectness Further details: 1. Choice of drug (drugs within the class, based on the intervention arm only):

Funding	Academic or government funding (This study was supported by a grant from Hallym University Medical Center Research Fun (01-2010-12))

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FEBUXOSTAT 80MG versus ALLOPURINOL FOR MODERATE GOUT 300-600MG

Protocol outcome 1: Serum urate levels at short-term (< 3 months)
- Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Serum urate levels at 4 weeks; Group 1: mean -3.76 mg/dL (SD 1.42); n=36, Group 2: mean -4.61 mg/dL (SD 1.38); n=35; Comments: Baseline febuxostat 80mg: 9.5 (1.3). Baseline allopurinol: 9.5 (1.0).
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Baseline details: Reported, age, BMI, blood pressure, BUN, creatinine, eGFR, uric acid, cholesterol, triglyceride, fasting glucose, AST, ALT and smoking status; Group 1 Number missing: 1, Reason: 1 missed a follow up or withdrew prematurely after week 2; Group 2 Number missing: 2, Reason: 2 missed a follow up or withdrew prematurely after week 2

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FEBUXOSTAT 80MG versus PLACEBO

Protocol outcome 1: Serum urate levels at short-term (< 3 months)
- Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Serum urate levels at 4 weeks; Group 1: mean -4.61 mg/dL (SD 1.38); n=35, Group 2: mean 0.07 mg/dL (SD 1.36); n=37; Comments: Baseline febuxostat 80mg: 9.5 (1.3). Baseline placebo: 9.7 (1.3).
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Baseline details: Reported, age, BMI, blood pressure, BUN, creatinine, eGFR, uric acid, cholesterol, triglyceride, fasting glucose, AST, ALT and smoking status; Group 1 Number missing: 1, Reason: 1 missed a follow up or withdrew prematurely after week 2; Group 2 Number missing: 2, Reason: 2 missed a follow up or withdrew prematurely after week 2

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FEBUXOSTAT 120MG versus FEBUXOSTAT 80MG

Protocol outcome 1: Serum urate levels at short-term (< 3 months)
- Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Serum urate levels at 4 weeks; Group 1: mean -5.26 mg/dL (SD 1.91); n=36, Group 2: mean -4.61 mg/dL (SD 1.38); n=35; Comments: Baseline febuxostat 120mg: 9.5 (1.0). Baseline febuxostat 80mg: 9.5 (1.3).
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Baseline details: Reported, age, BMI, blood pressure, BUN, creatinine, eGFR, uric acid, cholesterol, triglyceride, fasting glucose, AST, ALT and smoking status; Group 1 Number missing: 2, Reason: 2 missed a follow up or withdrew prematurely after week 2; Group 2 Number missing: 1, Reason: 1 missed a follow up or withdrew prematurely after week 2

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FEBUXOSTAT 120MG versus ALLOPURINOL FOR MODERATE GOUT 300-600MG

Protocol outcome 1: Serum urate levels at short-term (< 3 months)
- Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Serum urate levels at 4 weeks; Group 1: mean -5.26 mg/dL (SD 1.91); n=36, Group 2: mean -3.76 mg/dL (SD 1.42); n=36; Comments: Baseline febuxostat 120mg: 9.5 (1.0). Baseline allopurinol: 9.5 (1.0).
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Baseline details: Reported, age, BMI, blood pressure, BUN, creatinine, eGFR, uric acid, cholesterol, triglyceride, fasting glucose, AST, ALT and smoking status; Group 1 Number missing: 2, Reason: 2 missed a follow up or withdrew prematurely after week 2; Group 2 Number missing: 2, Reason: 2 missed a follow up or withdrew prematurely after week 2

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FEBUXOSTAT 120MG versus PLACEBO

Protocol outcome 1: Serum urate levels at short-term (< 3 months)
- Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Serum urate levels at 4 weeks; Group 1: mean -5.26 mg/dL (SD 1.91); n=36, Group 2: mean 0.07 mg/dL (SD 1.36); n=37; Comments: Baseline febuxostat 120mg: 9.5 (1.0). Baseline placebo: 9.7 (1.3).
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Baseline details: Reported, age, BMI, blood pressure, BUN, creatinine, eGFR, uric acid, cholesterol, triglyceride, fasting glucose, AST, ALT and smoking status; Group 1 Number missing: 2, Reason: 2 missed a follow up or withdrew prematurely after week 2; Group 2 Number missing: 2, Reason: 2 missed a follow up or withdrew prematurely after week 2

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ALLOPURINOL FOR MODERATE GOUT 300-600MG versus PLACEBO

Protocol outcome 1: Serum urate levels at short-term (< 3 months)
- Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Serum urate levels at 4 weeks; Group 1: mean -3.76 mg/dL (SD 1.42); n=36, Group 2: mean 0.07 mg/dL (SD 1.36); n=37; Comments: Baseline allopurinol: 9.5 (1.0). Baseline placebo: 9.7 (1.3).
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Baseline details: Reported, age, BMI, blood pressure, BUN, creatinine, eGFR, uric acid, cholesterol, triglyceride, fasting glucose, AST, ALT and smoking status; Group 1 Number missing: 2, Reason: 2 missed a follow up or withdrew prematurely after week 2; Group 2 Number missing: 2, Reason: 2 missed a follow up or withdrew prematurely after week 2

Protocol outcomes not reported by the study	Health-related quality of life at short (< 3 months); Health-related quality of life at medium (3 to 12 months); Health-related quality of life at long (>12 months); Pain at short (< 3 months); Pain at medium (3 to 12 months); Pain at long (>12 months); Joint swelling/joint inflammation at short (< 3 months); Joint swelling/joint inflammation at medium (3 to 12 months); Joint swelling/joint inflammation at long (> 12 months); Joint tenderness at short (< 3 months); Joint tenderness at medium (3 to 12

	months); Joint tenderness at long (> 12 months); Patient global assessment of treatment success (response to treatment) at short (< 3 months); Patient global assessment of treatment success (response to treatment) at medium (3 to 12 months); Patient global assessment of treatment success (response to treatment) at long (> 12 months); Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at short (< 3 months); Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at medium (3 to 12 months); Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at long (> 12 months); Admissions (hospital & A&E) at short (< 3 months); Admissions (hospital & A&E) at medium 3 to 12 months); Admissions (hospital & A&E) at long (> 12 months); Discontinuation of ULT at short (< 3 months); Discontinuation of ULT at medium (3 to 12 months); Discontinuation of ULT at long (> 12 months); Frequency of flares at short (< 3 months); Frequency of flares at medium (3 to 12 months); Frequency of flares at long (> 12 months); Serum urate levels at medium (3 to 12 months); Serum urate levels at long (> 12 months); Adverse events and complications of gout (radiographic joint damage, renal stones, tophi) at short (< 3 months); Adverse events and complications of gout (radiographic joint damage, renal stones, tophi) at medium (3 to 12 months); Adverse events and complications of gout (radiographic joint damage, renal stones, tophi) at long (> 12 months)

Study	**Mackenzie 2020[78]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=6128)
Countries and setting	Conducted in Denmark, Sweden, United Kingdom; Setting: Primary care
Line of therapy	2nd line
Duration of study	Intervention + follow up: Median follow-up time was 1467 days (IQR 1029–2052) and median on-treatment follow-up was 1324 days (IQR 870–1919).
Method of assessment of guideline condition	Adequate method of assessment/diagnosis

Stratum	Mixed population (people with chronic kidney disease and people without chronic kidney disease)
Subgroup analysis within study	Not applicable
Inclusion criteria	Eligible patients were aged 60 years or older, had gout, and, in the opinion of the recruiting physician, required urate-lowering therapy. No patients with asymptomatic hyperuricaemia were recruited to the study. Eligible participants also had at least one additional cardiovascular risk factor and were already receiving allopurinol therapy.
Exclusion criteria	Patients with a history of myocardial infarction or stroke in the previous 6 months and those with congestive heart failure (New York Heart Association [NYHA] class III or IV) or severe renal impairment were excluded.
Age, gender and ethnicity	Age - Mean (SD): 71 (6.4). Gender (M:F): 5225/903. Ethnicity: Allopurinol group – white 3036 (99.1%), Asian 14 (0.5%),Afro-Caribbean 8 (0.3%), Oriental 1 (<0.1%), Other 6 (0.2%) Febuxostat group - white 3034 (99.1%), Asian 11 (0.4%),Afro-Caribbean 10 (0.3%), Oriental 2 (0.1%), Other 6 (0.2%)
Further population details	1. Age: > 65 years (Allopurinol group 70.9(6.5), Febuxostat 71(6.4)). 2. Setting: Primary care
Indirectness of population	No indirectness
Interventions	(n=3065) Intervention 1: Xanthine oxidase inhibitor - Allopurinol for moderate gout 300-600mg. Allopurinol mixed severity dose mean: 279 mg. (100mg -10% of patients, 200mg - 23.3% of patients, 300mg - 50.9%, 400mg - 11.9%, 500-900 mg - 3.9% of patients). Patients in the allopurinol group were given allopurinol orally (100 mg or 300 mg tablets; Salutas Pharma [Barleben, Germany] or Teva Pharmaceutical Works[Debrecen, Hungary]) at the optimised dose determined pre-randomisation If serum urate was not controlled to the European League Against Rheumatism (EULAR)target of less than 0·357 mmol/L (<6 mg/dL)12 on the patient's pre-study allopurinol dose, the patient commenced a lead-in phase in which the dose was increased by 100 mg/day every 2 weeks until the patient's urate concentration was at target or until they reached the maximum licensed dose (900 mg/day) or maximum tolerated dose of allopurinol. This dose increase was done because 80 mg febuxostat is a more potent urate-lowering therapy than low-dose allopurinol. Patients could continue in the study even if the target urate concentration had not been reached after the maximum dose increase. Duration median on treatment follow up 1324 days. Concurrent medication/care: 6months of prophylaxis against gout flares was offered to all patients at the start of their randomly allocated therapy. First-line gout flare prophylaxis was with colchicine (0·5 mg once or twice daily), and

	second-line alternatives were non-steroidal anti-inflammatory drugs (NSAIDs; naproxen, diclofenac, ormeloxicam) with gastric protection (omeprazole or ranitidine). Patients could decline or discontinue gout flare prophylaxis at any time. Indirectness: No indirectness Further details: 1. Choice of drug (drugs within the class, based on the intervention arm only): Allopurinol mixed severity dose mean: 279 mg (n=3063) Intervention 2: Xanthine oxidase inhibitor - Febuxostat 80mg. Febuxostat mixed dose, mean 81 mg. (97.5% of patients were on 80 mg, 2.5 % were on 120mg).Patients in the febuxostat group were given febuxostat orally (80 mg and120 mg tablets; Patheon France [Bourgoin Jallieu, France] or Menarini [Dresden, Germany]) at 80 mg daily for the first 2 weeks after randomisation. After 2weeks, serum urate concentration was measured and, if not controlled to the EULAR target, the febuxostat dose was increased to 120 mg daily. Duration median on treatment follow up 1324. Concurrent medication/care: 6months of prophylaxis against gout flares was offered to all patients at the start of their randomly allocated therapy. First-line gout flare prophylaxis was with colchicine (0·5 mg once or twice daily), and second-line alternatives were non-steroidal anti-inflammatory drugs (NSAIDs; naproxen, diclofenac, ormeloxicam) with gastric protection (omeprazole or ranitidine). Patients could decline or discontinue gout flare prophylaxis at any time. Indirectness: No indirectness Further details: 1. Choice of drug (drugs within the class, based on the intervention arm only): Febuxostat 80mg
Funding	Other author(s) funded by industry (Menarini, Ipsen, and Teijin Pharma Ltd.

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ALLOPURINOL FOR MODERATE GOUT 300-600MG versus FEBUXOSTAT 80MG

Protocol outcome 1: Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at long (> 12 months)
- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Cardiovascular adverse events at >12 months; Group 1: 601/3050, Group 2: 570/3001
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Renal and urinary adverse events at >12 months; Group 1: 135/3050, Group 2: 129/3001
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Gastrointestinal adverse events at >12 months; Group 1: 285/3050, Group 2: 256/3001
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness

of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Admissions (hospital & A&E) at long (> 12 months)
- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Hospitalisation at >12 months; Group 1: 435/3065, Group 2: 424/3063
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Serum urate levels at long (> 12 months)
- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Number of people achieving sUA <6 mg/dL at 1 year; Group 1: 2362/2751, Group 2: 2237/2306
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 314; Group 2 Number missing: 757
- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Number of people achieving sUA <6 mg/dL at 2 years; Group 1: 2192/2547, Group 2: 2060/2121
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 518; Group 2 Number missing: 942
- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Number of people achieving sUA <6 mg/dL at 3 years; Group 1: 1622/1851, Group 2: 1464/1505
Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1214; Group 2 Number missing: 1558
- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Number of people achieving sUA <6 mg/dL at 4 years; Group 1: 1065/1223, Group 2: 1004/1034
Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1842; Group 2 Number missing: 2029
- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Number of people achieving sUA <6 mg/dL at 5 years; Group 1: 692/799, Group 2: 676/695
Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2266; Group 2 Number missing: 2368
- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Number of people achieving sUA <6 mg/dL at 6 years; Group 1: 360/406, Group 2: 335/347
Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2659; Group 2 Number missing: 2716
- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Number of people achieving sUA <6 mg/dL at 7 years; Group 1: 76/85, Group 2: 81/83

	Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2980; Group 2 Number missing: 2980 - Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Number of people achieving sUA <5 mg/dL at 1 year; Group 1: 1270/2751, Group 2: 2057/2306 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 314; Group 2 Number missing: 757 - Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Number of people achieving sUA <5 mg/dL at 2 years; Group 1: 1246/2547, Group 2: 1936/2121 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 518; Group 2 Number missing: 942 - Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Number of people achieving sUA <5 mg/dL at 3 years; Group 1: 948/1851, Group 2: 1378/1505 Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1214; Group 2 Number missing: 1558 - Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Number of people achieving sUA <5 mg/dL at 4 years; Group 1: 647/1223, Group 2: 937/1034 Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1842; Group 2 Number missing: 2029 - Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Number of people achieving sUA <5 mg/dL at 5 years; Group 1: 429/799, Group 2: 635/695 Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2266; Group 2 Number missing: 2368 - Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Number of people achieving sUA <5 mg/dL at 6 years; Group 1: 229/406, Group 2: 317/347 Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2659; Group 2 Number missing: 2716 - Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Number of people achieving sUA <5 mg/dL at 7 years; Group 1: 55/85, Group 2: 75/83 Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2980; Group 2 Number missing: 2980
Protocol outcomes not reported by the study	Health-related quality of life at short (< 3 months); Health-related quality of life at medium (3 to 12 months); Health-related quality of life at long (>12 months); Pain at short (< 3 months); Pain at medium (3 to 12 months); Pain at long (>12 months); Joint swelling/joint inflammation at short (< 3 months); Joint swelling/joint inflammation at medium (3 to 12 months); Joint

	swelling/joint inflammation at long (> 12 months); Joint tenderness at short (< 3 months); Joint tenderness at medium (3 to 12 months); Joint tenderness at long (> 12 months); Patient global assessment of treatment success (response to treatment) at short (< 3 months); Patient global assessment of treatment success (response to treatment) at medium (3 to 12 months); Patient global assessment of treatment success (response to treatment) at long (> 12 months); Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at short (< 3 months); Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at medium (3 to 12 months); Admissions (hospital & A&E) at short (< 3 months); Admissions (hospital & A&E) at medium 3 to 12 months); Discontinuation of ULT at short (< 3 months); Discontinuation of ULT at medium (3 to 12 months); Discontinuation of ULT at long (> 12 months); Frequency of flares at short (< 3 months); Frequency of flares at medium (3 to 12 months); Frequency of flares at long (> 12 months); Serum urate levels at short (< 3 months); Serum urate levels at medium (3 to 12 months); Adverse events and complications of gout (radiographic joint damage, renal stones, tophi) at short (< 3 months); Adverse events and complications of gout (radiographic joint damage, renal stones, tophi) at medium (3 to 12 months); Adverse events and complications of gout (radiographic joint damage, renal stones, tophi) at long (> 12 months)

Study	Saag 2019[96]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=1783)
Countries and setting	Conducted in USA; Setting: Outpatient follow up
Line of therapy	Mixed line
Duration of study	Intervention + follow up: 3 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Gout defined as fulfilling the American College of Rheumatology gout classification criteria
Stratum	Mixed population (people with chronic kidney disease and people without chronic kidney disease)
Subgroup analysis within study	Not applicable
Inclusion criteria	Age at least 18 years; a history or presence of gout; a serum urate level of at least 8.0 mg/dL on the day -4 screening visit; at least 1 gout flare within 12 months prior to screening; eGFR of at least 15mL/min at screening, and at least 30^ should have moderate-to-severe renal impairment.
Exclusion criteria	Secondary hyperuricaemia; history of xanthuria; known hypersensitivity to febuxostat; or any components in its formulations; know hypersensitivity to naproxen, any other NSAID, aspirin, lansoprazole, colchicine, or any components in their formulation; history of cardiovascular disease, including myocardial infarction, stroke, hospitalised unstable angina, cardiac or cerebrovascular revascularisation procedure, or hospitalised transient ischaemic attack (except in patients who had severe renal impairment); history of cancer (other than basal cell carcinoma of the skin) within 5 years prior to the screening visit; history of drug/alcohol abuse or consumption of >14 alcoholic beverages/week; presence of rheumatoid arthritis; active peptic ulcer disease; any significant medical condition that, in the investigator's opinion, would interfere with the treatment,

	safety, or compliance with the protocol. People with severe renal impairment who had a myocardial infarction or stroke within 90 days prior to screening or randomization were also excluded.
Recruitment/selection of patients	Multicentre trial conducted from April 18th 2015 to November 18th 2016
Age, gender, and ethnicity	Age - Mean (SD): 55.1 (11.7). Gender (M:F): 1577:206. Ethnicity: White = 1147, Black/African American = 474
Further population details	1. Age: < 65 years 2. Setting: Not stated / Unclear
Extra comments	Baseline serum urate level (mean [SD]): 9.6 (1.3) mg/dL. Renal function: Severely impaired = 100, moderately impaired = 483, mildly impaired = 965, normal = 235
Indirectness of population	No indirectness
Interventions	(n=357) Intervention 1: Xanthine oxidase inhibitor - Febuxostat 80mg. Febuxostat 80mg immediate release orally once daily for 3 months. Duration 3 months. Concurrent medication/care: No additional information. Indirectness: No indirectness Further details: 1. Choice of drug (drugs within the class, based on the intervention arm only): Febuxostat 80mg (n=357) Intervention 2: Placebo orally once a day for 3 months. Duration 3 months. Concurrent medication/care: No additional information. Indirectness: No indirectness Further details: 1. Choice of drug (drugs within the class, based on the intervention arm only): Placebo
Funding	Study funded by industry (Supported by Takeda Pharmaceuticals International)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FEBUXOSTAT 80MG versus PLACEBO

Protocol outcome 1: Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at medium-term (3 to 12 months)
- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Vascular adverse events - hypertension at 3 months; Group 1: 8/357, Group 2: 10/356
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, sex, race, BMI, baseline urate level, approximate gout flares during the past year and renal function at baseline; Group 1 Number missing: 68, Reason: 13 pre-treatment event/adverse event, 12 major protocol development, 18 lost to follow up, 15

voluntary withdrawal, 1 lack of efficacy, 9 other; Group 2 Number missing: 62, Reason: 9 pre-treatment event/adverse event, 9 major protocol deviation, 13 lost to follow up, 20 voluntary withdrawal, 1 gout flare, 10 other
- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Gastrointestinal adverse events at 3 months; Group 1: 21/357, Group 2: 13/356
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, sex, race, BMI, baseline urate level, approximate gout flares during the past year and renal function at baseline; Group 1 Number missing: 68, Reason: 13 pre-treatment event/adverse event, 12 major protocol development, 18 lost to follow up, 15 voluntary withdrawal, 1 lack of efficacy, 9 other; Group 2 Number missing: 62, Reason: 9 pre-treatment event/adverse event, 9 major protocol deviation, 13 lost to follow up, 20 voluntary withdrawal, 1 gout flare, 10 other

Protocol outcome 2: Frequency of flares at medium-term (3 to 12 months)
- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Frequency of flares at 3 months; Group 1: 97/357, Group 2: 74/357
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, sex, race, BMI, baseline urate level, approximate gout flares during the past year and renal function at baseline; Group 1 Number missing: 68, Reason: 13 pre-treatment event/adverse event, 12 major protocol development, 18 lost to follow up, 15 voluntary withdrawal, 1 lack of efficacy, 9 other; Group 2 Number missing: 62, Reason: 9 pre-treatment event/adverse event, 9 major protocol deviation, 13 lost to follow up, 20 voluntary withdrawal, 1 gout flare, 10 other

Protocol outcome 3: Serum urate levels at medium-term (3 to 12 months)
- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): number of people achieving sUA <6mg/dL at 3 months; Group 1: 206/357, Group 2: 2/357
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, sex, race, BMI, baseline urate level, approximate gout flares during the past year and renal function at baseline; Group 1 Number missing: 68, Reason: 13 pre-treatment event/adverse event, 12 major protocol development, 18 lost to follow up, 15 voluntary withdrawal, 1 lack of efficacy, 9 other; Group 2 Number missing: 62, Reason: 9 pre-treatment event/adverse event, 9 major protocol deviation, 13 lost to follow up, 20 voluntary withdrawal, 1 gout flare, 10 other
- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): number of people achieving sUA <5mg/dL at 3 months; Group 1: 152/357, Group 2: 1/357
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, sex, race, BMI, baseline urate level, approximate gout flares during the past year and renal function at baseline; Group 1 Number missing: 68, Reason: 13 pre-treatment event/adverse event, 12 major protocol development, 18 lost to follow up, 15 voluntary withdrawal, 1 lack of efficacy, 9 other; Group 2 Number missing: 62, Reason: 9 pre-treatment event/adverse event, 9 major protocol deviation, 13 lost to follow up, 20 voluntary withdrawal, 1 gout flare, 10 other

Protocol outcomes not reported by the study	Health-related quality of life at short (< 3 months); Health-related quality of life at medium (3 to 12 months); Health-related quality of life at long (>12 months); Pain at short (< 3 months); Pain at medium (3 to 12 months); Pain at long (>12 months); Joint swelling/joint inflammation at short (< 3 months); Joint swelling/joint inflammation at medium (3 to 12 months); Joint swelling/joint inflammation at long (> 12 months); Joint tenderness at short (< 3 months); Joint tenderness at medium (3 to 12 months); Joint tenderness at long (> 12 months); Patient global assessment of treatment success (response to treatment) at short (< 3 months); Patient global assessment of treatment success (response to treatment) at medium (3 to 12 months); Patient global assessment of treatment success (response to treatment) at long (> 12 months); Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at short (< 3 months); Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at long (> 12 months); Admissions (hospital & A&E) at short (< 3 months); Admissions (hospital & A&E) at medium 3 to 12 months); Admissions (hospital & A&E) at long (> 12 months); Discontinuation of ULT at short (< 3 months); Discontinuation of ULT at medium (3 to 12 months); Discontinuation of ULT at long (> 12 months); Frequency of flares at short (< 3 months); Frequency of flares at long (> 12 months); Serum urate levels at short (< 3 months); Serum urate levels at long (> 12 months); Adverse events and complications of gout (radiographic joint damage, renal stones, tophi) at short (< 3 months); Adverse events and complications of gout (radiographic joint damage, renal stones, tophi) at medium (3 to 12 months); Adverse events and complications of gout (radiographic joint damage, renal stones, tophi) at long (> 12 months)

Study	**Schumacher 2008[100]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=1072)
Countries and setting	Conducted in USA; Setting: Outpatient follow up
Line of therapy	Mixed line
Duration of study	Intervention + follow up: 28 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Gout defined by the American College of Rheumatology

Stratum	Mixed population (people with chronic kidney disease and people without chronic kidney disease)
Subgroup analysis within study	Not applicable
Inclusion criteria	People of either sex and 18-85 years of age, inclusive, with gout (defined by the American College of Rheumatology preliminary criteria), hyperuricemia (defined for this study as a serum urate level of at least 8.0mg/dL) and normal (serum creatinine level no more than 1.5mg/dL) or impaired (serum creatinine level >1.5 to no more than 2.0mg/dL) renal function at day -2
Exclusion criteria	Intolerance to allopurinol, naproxen, or colchicine; history of renal calculi; alcohol intake of at least 14 drinks/week; hepatic dysfunction with alanine aminotransferase and aspartate aminotransferase both >1.5 times the upper limit of normal; or any other significant medical conditions
Recruitment/selection of patients	Multicentre trial
Age, gender, and ethnicity	Age - Mean (SD): 51.8 (12.2). Gender (M:F): 1005:67. Ethnicity: White = 835, Minority = 237
Further population details	1. Age: < 65 years 2. Setting: Primary care (The majority of investigators were primary care physicians).
Extra comments	Serum urate level: Not stated. Mild to moderate renal impairment: 40
Indirectness of population	No indirectness
Interventions	(n=267) Intervention 1: Xanthine oxidase inhibitor - Febuxostat 80mg. Febuxostat 80mg a day. Duration 28 weeks. Concurrent medication/care: A washout of previous therapy for a period of 2 weeks was achieved with people being offered either colchicine 0.6mg once daily or naproxen 250mg twice daily during the period. They were continued for the first 8 weeks of the study. Indirectness: No indirectness Further details: 1. Choice of drug (drugs within the class, based on the intervention arm only): Febuxostat 80mg (n=269) Intervention 2: Xanthine oxidase inhibitor - Febuxostat 120mg. Febuxostat 120mg a day. Duration 28 weeks. Concurrent medication/care: A washout of previous therapy for a period of 2 weeks was achieved with people being offered either colchicine 0.6mg once daily or naproxen 250mg twice daily during the period. They were continued for the first 8 weeks of the study. Indirectness: No indirectness

	Further details: 1. Choice of drug (drugs within the class, based on the intervention arm only): Febuxostat 120mg (n=268) Intervention 3: Xanthine oxidase inhibitor - Allopurinol for moderate gout 300-600mg. Allopurinol 300mg a day. Duration 28 weeks. Concurrent medication/care: A washout of previous therapy for a period of 2 weeks was achieved with people being offered either colchicine 0.6mg once daily or naproxen 250mg twice daily during the period. They were continued for the first 8 weeks of the study. Indirectness: No indirectness Further details: 1. Choice of drug (drugs within the class, based on the intervention arm only): Allopurinol 300mg (n=134) Intervention 4: Placebo each day. Duration 28 weeks. Concurrent medication/care: A washout of previous therapy for a period of 2 weeks was achieved with people being offered either colchicine 0.6mg once daily or naproxen 250mg twice daily during the period. They were continued for the first 8 weeks of the study. Indirectness: No indirectness Further details: 1. Choice of drug (drugs within the class, based on the intervention arm only): Placebo
Funding	Study funded by industry (Supported by Takeda Global Research & Development Center, Inc., Deerfield, Illinois. Dr. Schumacher's work was supported by grants from Takeda Global Research & Development Center, Inc.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FEBUXOSTAT 80MG versus ALLOPURINOL FOR MODERATE GOUT 300-600MG

Protocol outcome 1: Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at medium (3 to 12 months)
- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Cardiovascular adverse events at 28 weeks; Group 1: 5/267, Group 2: 1/268
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, gender, race, BMI, hypercholesterolemia, hyperlipidaemia, hypertension, cardiovascular disease, gout history, history/presence of tophi, recent use of allopurinol, low-dose aspirin use, mild to moderate renal impairment; Group 1 Number missing: 93, Reason: Febuxostat 80mg: 93 withdrew. 18 adverse events. 6 protocol violation. 16 personal reasons. 19 lost to follow up. 6 therapeutic failure. 13 gout flare. 15 others; Group 2 Number missing: 57, Reason: Allopurinol: 57 withdrew. 18 adverse events. 6 protocol violation. 9 personal reasons. 17 lost to follow up. 1 therapeutic failure. 1 gout flare. 5 other.

- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Gastrointestinal adverse events (diarrhoea) at 28 weeks; Group 1: 16/267, Group 2: 17/268 - denominator unclear. Use with caution). Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete

outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, gender, race, BMI, hypercholesterolemia, hyperlipidaemia, hypertension, cardiovascular disease, gout history, history/presence of tophi, recent use of allopurinol, low-dose aspirin use, mild to moderate renal impairment; Group 1 Number missing: 93, Reason: Febuxostat 80mg: 93 withdrew. 18 adverse events. 6 protocol violation. 16 personal reasons. 19 lost to follow up. 6 therapeutic failure. 13 gout flare. 15 other; Group 2 Number missing: 57, Reason: Allopurinol: 57 withdrew. 18 adverse events. 6 protocol violation. 9 personal reasons. 17 lost to follow up. 1 therapeutic failure. 1 gout flare. 5 other.

- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Gastrointestinal adverse events (nausea and vomiting symptoms)at 28 weeks; Group 1: 12/267, Group 2: 6/268; - denominator unclear. Use with caution).
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, gender, race, BMI, hypercholesterolemia, hyperlipidaemia, hypertension, cardiovascular disease, gout history, history/presence of tophi, recent use of allopurinol, low-dose aspirin use, mild to moderate renal impairment; Group 1 Number missing: 93, Reason: Febuxostat 80mg: 93 withdrew. 18 adverse events. 6 protocol violation. 16 personal reasons. 19 lost to follow up. 6 therapeutic failure. 13 gout flare. 15 other; Group 2 Number missing: 57, Reason: Allopurinol: 57 withdrew. 18 adverse events. 6 protocol violation. 9 personal reasons. 17 lost to follow up. 1 therapeutic failure. 1 gout flare. 5 other.

- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Gastrointestinal adverse events (gastrointestinal and abdominal pains) at 28 weeks; Group 1: 6/267, Group 2: 6/268; - denominator unclear. Use with caution).
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, gender, race, BMI, hypercholesterolemia, hyperlipidaemia, hypertension, cardiovascular disease, gout history, history/presence of tophi, recent use of allopurinol, low-dose aspirin use, mild to moderate renal impairment; Group 1 Number missing: 93, Reason: Febuxostat 80mg: 93 withdrew. 18 adverse events. 6 protocol violation. 16 personal reasons. 19 lost to follow up. 6 therapeutic failure. 13 gout flare. 15 other; Group 2 Number missing: 57, Reason: Allopurinol: 57 withdrew. 18 adverse events. 6 protocol violation. 9 personal reasons. 17 lost to follow up. 1 therapeutic failure. 1 gout flare. 5 other.
Protocol outcome 2: Frequency of flares at short (< 3 months)
- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): People requiring treatment for gout flare at 8 weeks; Group 1: 73/267, Group 2: 61/268
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, gender, race, BMI, hypercholesterolemia, hyperlipidaemia, hypertension, cardiovascular disease, gout history, history/presence of tophi, recent use of allopurinol, low-dose aspirin use, mild to moderate renal impairment; Group 1 Number missing: 93, Reason: Febuxostat 80mg: 93 withdrew. 18 adverse events. 6 protocol violation. 16 personal reasons. 19 lost to follow up. 6 therapeutic failure. 13 gout flare. 15 other; Group 2 Number missing: 57, Reason: Allopurinol: 57 withdrew. 18 adverse events. 6 protocol violation. 9 personal reasons. 17 lost to follow up. 1 therapeutic failure. 1 gout flare. 5 other.

Protocol outcome 3: Serum urate levels at medium (3 to 12 months)

- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Number of people achieving sUA <6mg/dL at 28 weeks; Group 1: 183/253, Group 2: 102/263
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, gender, race, BMI, hypercholesterolemia, hyperlipidaemia, hypertension, cardiovascular disease, gout history, history/presence of tophi, recent use of allopurinol, low-dose aspirin use, mild to moderate renal impairment; Group 1 Number missing: 93, Reason: Febuxostat 80mg: 93 withdrew. 18 adverse events. 6 protocol violation. 16 personal reasons. 19 lost to follow up. 6 therapeutic failure. 13 gout flare. 15 other; Group 2 Number missing: 57, Reason: Allopurinol: 57 withdrew. 18 adverse events. 6 protocol violation. 9 personal reasons. 17 lost to follow up. 1 therapeutic failure. 1 gout flare. 5 other.

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FEBUXOSTAT 80MG versus PLACEBO

Protocol outcome 1: Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at medium-term (3 to 12 months)
- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Cardiovascular adverse events at 28 weeks; Group 1: 5/267, Group 2: 1/134
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Baseline details: Reported age, gender, race, BMI, hypercholesterolemia, hyperlipidaemia, hypertension, cardiovascular disease, gout history, history/presence of tophi, recent use of allopurinol, low-dose aspirin use, mild to moderate renal impairment; Group 1 Number missing: 93, Reason: Febuxostat 80mg: 93 withdrew. 18 adverse events. 6 protocol violation. 16 personal reasons. 19 lost to follow up. 6 therapeutic failure. 13 gout flare. 15 other; Group 2 Number missing: 33, Reason: Placebo: 33 withdrew. 5 adverse events. 3 protocol violation. 9 personal reasons. 10 lost to follow up. 3 therapeutic failure. 0 gout flare. 3 other.
- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Gastrointestinal adverse events (diarrhoea) at 28 weeks; Group 1: 16/267, Group 2: 11/134; Comments: - denominator unclear. Use with caution.
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, gender, race, BMI, hypercholesterolemia, hyperlipidaemia, hypertension, cardiovascular disease, gout history, history/presence of tophi, recent use of allopurinol, low-dose aspirin use, mild to moderate renal impairment; Group 1 Number missing: 93, Reason: Febuxostat 80mg: 93 withdrew. 18 adverse events. 6 protocol violation. 16 personal reasons. 19 lost to follow up. 6 therapeutic failure. 13 gout flare. 15 other; Group 2 Number missing: 33, Reason: Placebo: 33 withdrew. 5 adverse events. 3 protocol violation. 9 personal reasons. 10 lost to follow up. 3 therapeutic failure. 0 gout flare. 3 other.

- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Gastrointestinal adverse events (nausea and vomiting symptoms) at 28 weeks; Group 1: 12/267, Group 2: 5/134; Comments: denominator unclear. Use with caution). Placebo: Diarrhoea = 11, nausea and vomiting symptoms = 5, gastrointestinal and abdominal pains = 3 (19 - denominator unclear. Use with caution).
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, gender, race, BMI, hypercholesterolemia, hyperlipidaemia, hypertension, cardiovascular disease, gout history, history/presence of tophi, recent use of allopurinol, low-dose aspirin use, mild to moderate renal impairment; Group 1

Number missing: 93, Reason: Febuxostat 80mg: 93 withdrew. 18 adverse events. 6 protocol violation. 16 personal reasons. 19 lost to follow up. 6 therapeutic failure. 13 gout flare. 15 other; Group 2 Number missing: 33, Reason: Placebo: 33 withdrew. 5 adverse events. 3 protocol violation. 9 personal reasons. 10 lost to follow up. 3 therapeutic failure. 0 gout flare. 3 other.

- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Gastrointestinal adverse events (gastrointestinal and abdominal pains)at 28 weeks; Group 1: 6/267, Group 2: 3/134; Comments: denominator unclear. Use with caution).
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, gender, race, BMI, hypercholesterolemia, hyperlipidaemia, hypertension, cardiovascular disease, gout history, history/presence of tophi, recent use of allopurinol, low-dose aspirin use, mild to moderate renal impairment; Group 1 Number missing: 93, Reason: Febuxostat 80mg: 93 withdrew. 18 adverse events. 6 protocol violation. 16 personal reasons. 19 lost to follow up. 6 therapeutic failure. 13 gout flare. 15 other; Group 2 Number missing: 33, Reason: Placebo: 33 withdrew. 5 adverse events. 3 protocol violation. 9 personal reasons. 10 lost to follow up. 3 therapeutic failure. 0 gout flare. 3 other.

Protocol outcome 2: Frequency of flares at short (< 3 months)
- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): People requiring treatment for gout flare at 8 weeks; Group 1: 73/267, Group 2: 27/134
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, gender, race, BMI, hypercholesterolemia, hyperlipidaemia, hypertension, cardiovascular disease, gout history, history/presence of tophi, recent use of allopurinol, low-dose aspirin use, mild to moderate renal impairment; Group 1 Number missing: 93, Reason: Febuxostat 80mg: 93 withdrew. 18 adverse events. 6 protocol violation. 16 personal reasons. 19 lost to follow up. 6 therapeutic failure. 13 gout flare. 15 other; Group 2 Number missing: 33, Reason: Placebo: 33 withdrew. 5 adverse events. 3 protocol violation. 9 personal reasons. 10 lost to follow up. 3 therapeutic failure. 0 gout flare. 3 other.

Protocol outcome 3: Serum urate levels at medium (3 to 12 months)
- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Number of people achieving sUA <6mg/dL at 28 weeks; Group 1: 183/253, Group 2: 1/127
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, gender, race, BMI, hypercholesterolemia, hyperlipidaemia, hypertension, cardiovascular disease, gout history, history/presence of tophi, recent use of allopurinol, low-dose aspirin use, mild to moderate renal impairment; Group 1 Number missing: 93, Reason: Febuxostat 80mg: 93 withdrew. 18 adverse events. 6 protocol violation. 16 personal reasons. 19 lost to follow up. 6 therapeutic failure. 13 gout flare. 15 other; Group 2 Number missing: 33, Reason: Placebo: 33 withdrew. 5 adverse events. 3 protocol violation. 9 personal reasons. 10 lost to follow up. 3 therapeutic failure. 0 gout flare. 3 other.

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FEBUXOSTAT 120MG versus FEBUXOSTAT 80MG

Protocol outcome 1: Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at medium (3 to 12 months)
- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Cardiovascular adverse events at 28 weeks; Group 1: 5/269, Group 2: 5/267
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, gender, race, BMI, hypercholesterolemia, hyperlipidaemia, hypertension, cardiovascular disease, gout history, history/presence of tophi, recent use of allopurinol, low-dose aspirin use, mild to moderate renal impairment; Group 1 Number missing: 69, Reason: Febuxostat 120mg: 69 withdrew. 16 adverse events. 3 protocol violation. 16 personal reasons. 17 lost to follow up. 3 therapeutic failure. Gout flare 6. Other 8.; Group 2 Number missing: 93, Reason: Febuxostat 80mg: 93 withdrew. 18 adverse events. 6 protocol violation. 16 personal reasons. 19 lost to follow up. 6 therapeutic failure. 13 gout flare. 15 other.

- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Gastrointestinal adverse events(diarrhoea) at 28 weeks; Group 1: 19/269, Group 2: 16/267; Comments: denominator unclear. Use with caution.
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, gender, race, BMI, hypercholesterolemia, hyperlipidaemia, hypertension, cardiovascular disease, gout history, history/presence of tophi, recent use of allopurinol, low-dose aspirin use, mild to moderate renal impairment; Group 1 Number missing: 69, Reason: Febuxostat 120mg: 69 withdrew. 16 adverse events. 3 protocol violation. 16 personal reasons. 17 lost to follow up. 3 therapeutic failure. Gout flare 6. Other 8.; Group 2 Number missing: 93, Reason: Febuxostat 80mg: 93 withdrew. 18 adverse events. 6 protocol violation. 16 personal reasons. 19 lost to follow up. 6 therapeutic failure. 13 gout flare. 15 other.

- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Gastrointestinal adverse events (nausea and vomiting symptoms) at 28 weeks; Group 1: 10/269, Group 2: 12/267; Comments: denominator unclear. Use with caution.
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, gender, race, BMI, hypercholesterolemia, hyperlipidaemia, hypertension, cardiovascular disease, gout history, history/presence of tophi, recent use of allopurinol, low-dose aspirin use, mild to moderate renal impairment; Group 1 Number missing: 69, Reason: Febuxostat 120mg: 69 withdrew. 16 adverse events. 3 protocol violation. 16 personal reasons. 17 lost to follow up. 3 therapeutic failure. Gout flare 6. Other 8.; Group 2 Number missing: 93, Reason: Febuxostat 80mg: 93 withdrew. 18 adverse events. 6 protocol violation. 16 personal reasons. 19 lost to follow up. 6 therapeutic failure. 13 gout flare. 15 other.

- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Gastrointestinal adverse events(gastrointestinal and abdominal pains) at 28 weeks; Group 1: 7/269, Group 2: 6/267; Comments: denominator unclear. Use with caution.
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, gender, race, BMI, hypercholesterolemia, hyperlipidaemia, hypertension, cardiovascular disease, gout history, history/presence of tophi, recent use of allopurinol, low-dose aspirin use, mild to moderate renal impairment; Group 1

Number missing: 69, Reason: Febuxostat 120mg: 69 withdrew. 16 adverse events. 3 protocol violation. 16 personal reasons. 17 lost to follow up. 3 therapeutic failure. Gout flare 6. Other 8.; Group 2 Number missing: 93, Reason: Febuxostat 80mg: 93 withdrew. 18 adverse events. 6 protocol violation. 16 personal reasons. 19 lost to follow up. 6 therapeutic failure. 13 gout flare. 15 other.

Protocol outcome 2: Frequency of flares at short (< 3 months)
- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): People requiring treatment for gout flare at 8 weeks; Group 1: 97/269, Group 2: 73/267
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, gender, race, BMI, hypercholesterolemia, hyperlipidaemia, hypertension, cardiovascular disease, gout history, history/presence of tophi, recent use of allopurinol, low-dose aspirin use, mild to moderate renal impairment; Group 1 Number missing: 69, Reason: Febuxostat 120mg: 69 withdrew. 16 adverse events. 3 protocol violation. 16 personal reasons. 17 lost to follow up. 3 therapeutic failure. Gout flare 6. Other 8.; Group 2 Number missing: 93, Reason: Febuxostat 80mg: 93 withdrew. 18 adverse events. 6 protocol violation. 16 personal reasons. 19 lost to follow up. 6 therapeutic failure. 13 gout flare. 15 other.

Protocol outcome 3: Serum urate levels at medium (3 to 12 months)
- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Number of people achieving sUA <6mg/dL at 28 weeks; Group 1: 209/265, Group 2: 183/253
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, gender, race, BMI, hypercholesterolemia, hyperlipidaemia, hypertension, cardiovascular disease, gout history, history/presence of tophi, recent use of allopurinol, low-dose aspirin use, mild to moderate renal impairment; Group 1 Number missing: 69, Reason: Febuxostat 120mg: 69 withdrew. 16 adverse events. 3 protocol violation. 16 personal reasons. 17 lost to follow up. 3 therapeutic failure. Gout flare 6. Other 8.; Group 2 Number missing: 93, Reason: Febuxostat 80mg: 93 withdrew. 18 adverse events. 6 protocol violation. 16 personal reasons. 19 lost to follow up. 6 therapeutic failure. 13 gout flare. 15 other.

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FEBUXOSTAT 120MG versus ALLOPURINOL FOR MODERATE GOUT 300-600MG

Protocol outcome 1: Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at medium (3 to 12 months)
- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Cardiovascular adverse events at 28 weeks; Group 1: 5/269, Group 2: 1/268
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low,

Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, gender, race, BMI, hypercholesterolemia, hyperlipidaemia, hypertension, cardiovascular disease, gout history, history/presence of tophi, recent use of allopurinol, low-dose aspirin use, mild to moderate renal impairment; Group 1 Number missing: 69, Reason: Febuxostat 120mg: 69 withdrew. 16 adverse events. 3 protocol violation. 16 personal reasons. 17 lost to follow up. 3 therapeutic failure. Gout flare 6. Other 8.; Group 2 Number missing: 57, Reason: Allopurinol: 57 withdrew. 18 adverse events. 6 protocol violation. 9 personal reasons. 17 lost to follow up. 1 therapeutic failure. 1 gout flare. 5 other.

- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Gastrointestinal adverse events(diarrhoea) at 28 weeks; Group 1: 19/269, Group 2: 17/267; Comments: denominator unclear. Use with caution).
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, gender, race, BMI, hypercholesterolemia, hyperlipidaemia, hypertension, cardiovascular disease, gout history, history/presence of tophi, recent use of allopurinol, low-dose aspirin use, mild to moderate renal impairment; Group 1 Number missing: 69, Reason: Febuxostat 120mg: 69 withdrew. 16 adverse events. 3 protocol violation. 16 personal reasons. 17 lost to follow up. 3 therapeutic failure. Gout flare 6. Other 8.; Group 2 Number missing: 93, Reason: Febuxostat 80mg: 93 withdrew. 18 adverse events. 6 protocol violation. 16 personal reasons. 19 lost to follow up. 6 therapeutic failure. 13 gout flare. 15 other.

- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Gastrointestinal adverse events(nausea and vomiting symptoms) at 28 weeks; Group 1: 10/269, Group 2: 16/267; Comments: denominator unclear. Use with caution.
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, gender, race, BMI, hypercholesterolemia, hyperlipidaemia, hypertension, cardiovascular disease, gout history, history/presence of tophi, recent use of allopurinol, low-dose aspirin use, mild to moderate renal impairment; Group 1 Number missing: 69, Reason: Febuxostat 120mg: 69 withdrew. 16 adverse events. 3 protocol violation. 16 personal reasons. 17 lost to follow up. 3 therapeutic failure. Gout flare 6. Other 8.; Group 2 Number missing: 93, Reason: Febuxostat 80mg: 93 withdrew. 18 adverse events. 6 protocol violation. 16 personal reasons. 19 lost to follow up. 6 therapeutic failure. 13 gout flare. 15 other.

- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Gastrointestinal adverse events(gastrointestinal and abdominal pains) at 28 weeks; Group 1: 7/269, Group 2: 6/267; Comments: denominator unclear. Use with caution).
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, gender, race, BMI, hypercholesterolemia, hyperlipidaemia, hypertension, cardiovascular disease, gout history, history/presence of tophi, recent use of allopurinol, low-dose aspirin use, mild to moderate renal impairment; Group 1 Number missing: 69, Reason: Febuxostat 120mg: 69 withdrew. 16 adverse events. 3 protocol violation. 16 personal reasons. 17 lost to follow up. 3 therapeutic failure. Gout flare 6. Other 8.; Group 2 Number missing: 93, Reason: Febuxostat 80mg: 93 withdrew. 18 adverse events. 6 protocol violation. 16 personal reasons. 19 lost to follow up. 6 therapeutic failure. 13 gout flare. 15 other.

Protocol outcome 2: Frequency of flares at short (< 3 months)
- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): People requiring treatment for gout flare at 8 weeks; Group 1: 97/269, Group 2: 61/268
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, gender, race, BMI, hypercholesterolemia, hyperlipidaemia, hypertension, cardiovascular disease, gout history, history/presence of tophi, recent use of allopurinol, low-dose aspirin use, mild to moderate renal impairment; Group 1 Number missing: 69, Reason: Febuxostat 120mg: 69 withdrew. 16 adverse events. 3 protocol violation. 16 personal reasons. 17 lost to follow up. 3 therapeutic failure. Gout flare 6. Other 8.; Group 2 Number missing: 57, Reason: Allopurinol: 57 withdrew. 18 adverse events. 6 protocol violation. 9 personal reasons. 17 lost to follow up. 1 therapeutic failure. 1 gout flare. 5 other.

Protocol outcome 3: Serum urate levels at medium-term (3 to 12 months)
- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Number of people achieving sUA <6mg/dL at 28 weeks; Group 1: 209/265, Group 2: 102/263
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, gender, race, BMI, hypercholesterolemia, hyperlipidaemia, hypertension, cardiovascular disease, gout history, history/presence of tophi, recent use of allopurinol, low-dose aspirin use, mild to moderate renal impairment; Group 1 Number missing: 69, Reason: Febuxostat 120mg: 69 withdrew. 16 adverse events. 3 protocol violation. 16 personal reasons. 17 lost to follow up. 3 therapeutic failure. Gout flare 6. Other 8.; Group 2 Number missing: 57, Reason: Allopurinol: 57 withdrew. 18 adverse events. 6 protocol violation. 9 personal reasons. 17 lost to follow up. 1 therapeutic failure. 1 gout flare. 5 other.

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FEBUXOSTAT 120MG versus PLACEBO

Protocol outcome 1: Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at medium (3 to 12 months)
- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Cardiovascular adverse events at 28 weeks; Group 1: 5/269, Group 2: 1/134
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, gender, race, BMI, hypercholesterolemia, hyperlipidaemia, hypertension, cardiovascular disease, gout history, history/presence of tophi, recent use of allopurinol, low-dose aspirin use, mild to moderate renal impairment; Group 1 Number missing: 69, Reason: Febuxostat 120mg: 69 withdrew. 16 adverse events. 3 protocol violation. 16 personal reasons. 17 lost to follow up. 3 therapeutic failure. Gout flare 6. Other 8.; Group 2 Number missing: 33, Reason: Placebo: 33 withdrew. 5 adverse events. 3 protocol violation. 9 personal reasons. 10 lost to follow up. 3 therapeutic failure. 0 gout flare. 3 other.

- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Gastrointestinal adverse events(diarrhoea) at 28 weeks; Group 1: 19/269, Group 2: 11/267; Comments: denominator unclear. Use with caution.
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, gender, race, BMI, hypercholesterolemia, hyperlipidaemia, hypertension, cardiovascular disease, gout history, history/presence of tophi, recent use of allopurinol, low-dose aspirin use, mild to moderate renal impairment; Group 1 Number missing: 69, Reason: Febuxostat 120mg: 69 withdrew. 16 adverse events. 3 protocol violation. 16 personal reasons. 17 lost to follow up. 3 therapeutic failure. Gout flare 6. Other 8.; Group 2 Number missing: 93, Reason: Febuxostat 80mg: 93 withdrew. 18 adverse events. 6 protocol violation. 16 personal reasons. 19 lost to follow up. 6 therapeutic failure. 13 gout flare. 15 other.

- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Gastrointestinal adverse events (nausea and vomiting symptoms) at 28 weeks; Group 1: 10/269, Group 2: 5/267; Comments: denominator unclear. Use with caution.
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, gender, race, BMI, hypercholesterolemia, hyperlipidaemia, hypertension, cardiovascular disease, gout history, history/presence of tophi, recent use of allopurinol, low-dose aspirin use, mild to moderate renal impairment; Group 1 Number missing: 69, Reason: Febuxostat 120mg: 69 withdrew. 16 adverse events. 3 protocol violation. 16 personal reasons. 17 lost to follow up. 3 therapeutic failure. Gout flare 6. Other 8.; Group 2 Number missing: 93, Reason: Febuxostat 80mg: 93 withdrew. 18 adverse events. 6 protocol violation. 16 personal reasons. 19 lost to follow up. 6 therapeutic failure. 13 gout flare. 15 other.

- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Gastrointestinal adverse events(gastrointestinal and abdominal pains) at 28 weeks; Group 1: 7/269, Group 2: 3/267; Comments: denominator unclear. Use with caution.
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, gender, race, BMI, hypercholesterolemia, hyperlipidaemia, hypertension, cardiovascular disease, gout history, history/presence of tophi, recent use of allopurinol, low-dose aspirin use, mild to moderate renal impairment; Group 1 Number missing: 69, Reason: Febuxostat 120mg: 69 withdrew. 16 adverse events. 3 protocol violation. 16 personal reasons. 17 lost to follow up. 3 therapeutic failure. Gout flare 6. Other 8.; Group 2 Number missing: 93, Reason: Febuxostat 80mg: 93 withdrew. 18 adverse events. 6 protocol violation. 16 personal reasons. 19 lost to follow up. 6 therapeutic failure. 13 gout flare. 15 other.

Protocol outcome 2: Frequency of flares at short (< 3 months)
- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): People requiring treatment for gout flare at 8 weeks; Group 1: 97/269, Group 2: 27/134
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, gender, race, BMI, hypercholesterolemia, hyperlipidaemia, hypertension, cardiovascular disease, gout history, history/presence of tophi, recent use of allopurinol, low-dose aspirin use, mild to moderate renal impairment; Group 1

Number missing: 93, Reason: Febuxostat 80mg: 93 withdrew. 18 adverse events. 6 protocol violation. 16 personal reasons. 19 lost to follow up. 6 therapeutic failure. 13 gout flare. 15 other; Group 2 Number missing: 33, Reason: Placebo: 33 withdrew. 5 adverse events. 3 protocol violation. 9 personal reasons. 10 lost to follow up. 3 therapeutic failure. 0 gout flare. 3 other.

Protocol outcome 3: Serum urate levels at medium (3 to 12 months)
- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Number of people achieving sUA <6mg/dL at 28 weeks; Group 1: 209/265, Group 2: 1/127
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, gender, race, BMI, hypercholesterolemia, hyperlipidaemia, hypertension, cardiovascular disease, gout history, history/presence of tophi, recent use of allopurinol, low-dose aspirin use, mild to moderate renal impairment; Group 1 Number missing: 69, Reason: Febuxostat 120mg: 69 withdrew. 16 adverse events. 3 protocol violation. 16 personal reasons. 17 lost to follow up. 3 therapeutic failure. Gout flare 6. Other 8.; Group 2 Number missing: 33, Reason: Placebo: 33 withdrew. 5 adverse events. 3 protocol violation. 9 personal reasons. 10 lost to follow up. 3 therapeutic failure. 0 gout flare. 3 other.

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ALLOPURINOL FOR MODERATE GOUT 300-600MG versus PLACEBO

Protocol outcome 1: Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at medium (3 to 12 months)
- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Cardiovascular adverse events at 28 weeks; Group 1: 1/268, Group 2: 1/134
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, gender, race, BMI, hypercholesterolemia, hyperlipidaemia, hypertension, cardiovascular disease, gout history, history/presence of tophi, recent use of allopurinol, low-dose aspirin use, mild to moderate renal impairment; Group 1 Number missing: 57, Reason: Allopurinol: 57 withdrew. 18 adverse events. 6 protocol violation. 9 personal reasons. 17 lost to follow up. 1 therapeutic failure. 1 gout flare. 5 other; Group 2 Number missing: 33, Reason: Placebo: 33 withdrew. 5 adverse events. 3 protocol violation. 9 personal reasons. 10 lost to follow up. 3 therapeutic failure. 0 gout flare. 3 other.

- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Gastrointestinal adverse events(diarrhoea) at 28 weeks; Group 1: 17/269, Group 2: 11/267; Comments: denominator unclear. Use with caution.
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, gender, race, BMI, hypercholesterolemia, hyperlipidaemia, hypertension, cardiovascular disease, gout history, history/presence of tophi, recent use of allopurinol, low-dose aspirin use, mild to moderate renal impairment; Group 1 Number missing: 69, Reason: Febuxostat 120mg: 69 withdrew. 16 adverse events. 3 protocol violation. 16 personal reasons. 17 lost to follow up. 3 therapeutic failure. Gout flare 6. Other 8.; Group 2 Number missing: 93, Reason: Febuxostat 80mg: 93 withdrew. 18 adverse events. 6 protocol violation. 16 personal reasons. 19 lost to follow up. 6 therapeutic failure. 13 gout flare. 15 other.

- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Gastrointestinal adverse events (nausea and vomiting symptoms) at 28 weeks; Group 1: 6/269, Group 2: 5/267; Comments: denominator unclear. Use with caution.
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, gender, race, BMI, hypercholesterolemia, hyperlipidaemia, hypertension, cardiovascular disease, gout history, history/presence of tophi, recent use of allopurinol, low-dose aspirin use, mild to moderate renal impairment; Group 1 Number missing: 69, Reason: Febuxostat 120mg: 69 withdrew. 16 adverse events. 3 protocol violation. 16 personal reasons. 17 lost to follow up. 3 therapeutic failure. Gout flare 6. Other 8.; Group 2 Number missing: 93, Reason: Febuxostat 80mg: 93 withdrew. 18 adverse events. 6 protocol violation. 16 personal reasons. 19 lost to follow up. 6 therapeutic failure. 13 gout flare. 15 other.

- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Gastrointestinal adverse events(gastrointestinal and abdominal pains) at 28 weeks; Group 1: 6/269, Group 2: 3/267; Comments: denominator unclear. Use with caution.
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, gender, race, BMI, hypercholesterolemia, hyperlipidaemia, hypertension, cardiovascular disease, gout history, history/presence of tophi, recent use of allopurinol, low-dose aspirin use, mild to moderate renal impairment; Group 1 Number missing: 69, Reason: Febuxostat 120mg: 69 withdrew. 16 adverse events. 3 protocol violation. 16 personal reasons. 17 lost to follow up. 3 therapeutic failure. Gout flare 6. Other 8.; Group 2 Number missing: 93, Reason: Febuxostat 80mg: 93 withdrew. 18 adverse events. 6 protocol violation. 16 personal reasons. 19 lost to follow up. 6 therapeutic failure. 13 gout flare. 15 other.

Protocol outcome 2: Frequency of flares at short (< 3 months)
- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): People requiring treatment for gout flare at 8 weeks; Group 1: 61/268, Group 2: 27/134
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, gender, race, BMI, hypercholesterolemia, hyperlipidaemia, hypertension, cardiovascular disease, gout history, history/presence of tophi, recent use of allopurinol, low-dose aspirin use, mild to moderate renal impairment; Group 1 Number missing: 57, Reason: Allopurinol: 57 withdrew. 18 adverse events. 6 protocol violation. 9 personal reasons. 17 lost to follow up. 1 therapeutic failure. 1 gout flare. 5 other; Group 2 Number missing: 33, Reason: Placebo: 33 withdrew. 5 adverse events. 3 protocol violation. 9 personal reasons. 10 lost to follow up. 3 therapeutic failure. 0 gout flare. 3 other.

Protocol outcome 3: Serum urate levels at medium (3 to 12 months)
- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Number of people achieving sUA <6mg/dL at 28 weeks; Group 1: 102/263, Group 2: 1/127
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, gender, race, BMI, hypercholesterolemia, hyperlipidaemia,

hypertension, cardiovascular disease, gout history, history/presence of tophi, recent use of allopurinol, low-dose aspirin use, mild to moderate renal impairment; Group 1 Number missing: 57, Reason: Allopurinol: 57 withdrew. 18 adverse events. 6 protocol violation. 9 personal reasons. 17 lost to follow up. 1 therapeutic failure. 1 gout flare. 5 other; Group 2 Number missing: 33, Reason: Placebo: 33 withdrew. 5 adverse events. 3 protocol violation. 9 personal reasons. 10 lost to follow up. 3 therapeutic failure. 0 gout flare. 3 other.	
Protocol outcomes not reported by the study	Health-related quality of life at short (< 3 months); Health-related quality of life at medium (3 to 12 months); Health-related quality of life at long (>12 months); Pain at short (< 3 months); Pain at medium (3 to 12 months); Pain at long (>12 months); Joint swelling/joint inflammation at short (< 3 months); Joint swelling/joint inflammation at medium (3 to 12 months); Joint swelling/joint inflammation at long (> 12 months); Joint tenderness at short (< 3 months); Joint tenderness at medium (3 to 12 months); Joint tenderness at long (> 12 months); Patient global assessment of treatment success (response to treatment) at short (< 3 months); Patient global assessment of treatment success (response to treatment) at medium (3 to 12 months); Patient global assessment of treatment success (response to treatment) at long (> 12 months); Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at short (< 3 months); Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at long (> 12 months); Admissions (hospital & A&E) at short (< 3 months); Admissions (hospital & A&E) at medium 3 to 12 months); Admissions (hospital & A&E) at long (> 12 months); Discontinuation of ULT at short (< 3 months); Discontinuation of ULT at medium (3 to 12 months); Discontinuation of ULT at long (> 12 months); Frequency of flares at medium (3 to 12 months); Frequency of flares at long (> 12 months); Serum urate levels at short (< 3 months); Serum urate levels at long (> 12 months); Adverse events and complications of gout (radiographic joint damage, renal stones, tophi) at short (< 3 months); Adverse events and complications of gout (radiographic joint damage, renal stones, tophi) at medium (3 to 12 months); Adverse events and complications of gout (radiographic joint damage, renal stones, tophi) at long (> 12 months)

Study	**Taylor 2012[119]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=57)
Countries and setting	Conducted in USA
Line of therapy	1st line
Duration of study	Intervention + follow up: 30 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	People without chronic kidney disease or people with CKD stages 1-2
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients presenting within 7 days of onset of an acute gout attack were evaluated, and American College of Rheumatology criteria for acute arthritis of gout were met, including the presence of monosodium urate crystals on arthrocentesis of the primary joint on the day of study entry
Exclusion criteria	Exclusion criteria included secondary gout (because it is dependent on the treatment of the underlying disease); the presence of tophaceous gout (because of concern that tophi could make evaluation of resolution and exacerbations difficult); a history of congestive heart failure; anticoagulant use; a recent serum creatinine greater than 1.3 mg/dL (because these patients should not receive indomethacin); or the use of steroids, colchicine, allopurinol, uricosuric drugs, chemotherapy, or immunosuppressive therapy in the past 6 months. Although all subjects brought to the attention of the principal investigator were screened consecutively, primary providers also made decisions regarding eligibility and subjects were highly selected by study criteria; thus, information regarding the number and characteristics of those excluded could not be reliably tracked.

Age, gender, and ethnicity	Age - Mean (SD): Allopurinol 57(14); Placebo 61(11). Gender (M:F): male 51 (100%). Ethnicity:
Further population details	1. Age: < 65 years 2. Setting: Primary care
Indirectness of population	No indirectness
Interventions	(n=31) Intervention 1: Xanthine oxidase inhibitor - Allopurinol for moderate gout 300-600mg. Allopurinol 300mg. Duration 10 days. Concurrent medication/care: In addition to the 10-day course of allopurinol or placebo, all patients received indomethacin 50 mg 3 times per day for 10 days and colchicine 0.6 mg 2 times per day for 90 days. All patients were started on open-label allopurinol 300 mg daily on day 11 and followed for 30 days. Indirectness: No indirectness Further details: 1. Choice of drug (drugs within the class, based on the intervention arm only): Allopurinol 300mg. (n=26) Intervention 2: Placebo. Duration 10 days. Concurrent medication/care: In addition to the 10-day course of allopurinol or placebo, all patients received indomethacin 50 mg 3 times per day for 10 days and colchicine 0.6 mg 2 times per day for 90 days. All patients were started on open-label allopurinol 300 mg daily on day 11 and followed for 30 days. Indirectness: No indirectness Further details: 1. Choice of drug (drugs within the class, based on the intervention arm only): Placebo
Funding	No funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ALLOPURINOL FOR MODERATE GOUT 300-600MG versus Placebo

Protocol outcome 1: Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at short (< 3 months)
- Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Adverse events (colchicine reductions due to gastrointestinal symptoms) at 30 days; Group 1: 8/26, Group 2: 12/25
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5; Group 2 Number missing: 1

Protocol outcome 2: Frequency of flares at short (< 3 months)
- Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: New or recurrent flares at 30 days; Group 1: 2/26, Group 2: 3/25
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness

of outcome: No indirectness ; Group 1 Number missing: 5; Group 2 Number missing: 1	
Protocol outcomes not reported by the study	Health-related quality of life at short (< 3 months); Health-related quality of life at medium (3 to 12 months); Health-related quality of life at long (>12 months); Pain at short (< 3 months); Pain at medium (3 to 12 months); Pain at long (>12 months); Joint swelling/joint inflammation at short (< 3 months); Joint swelling/joint inflammation at medium (3 to 12 months); Joint swelling/joint inflammation at long (> 12 months); Joint tenderness at short (< 3 months); Joint tenderness at medium (3 to 12 months); Joint tenderness at long (> 12 months); Patient global assessment of treatment success (response to treatment) at short (< 3 months); Patient global assessment of treatment success (response to treatment) at medium (3 to 12 months); Patient global assessment of treatment success (response to treatment) at long (> 12 months); Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at medium (3 to 12 months); Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at long (> 12 months); Admissions (hospital & A&E) at short (< 3 months); Admissions (hospital & A&E) at medium 3 to 12 months); Admissions (hospital & A&E) at long (> 12 months); Discontinuation of ULT at short (< 3 months); Discontinuation of ULT at medium (3 to 12 months); Discontinuation of ULT at long (> 12 months); Frequency of flares at medium (3 to 12 months); Frequency of flares at long (> 12 months); Serum urate levels at short (< 3 months); Serum urate levels at medium (3 to 12 months); Serum urate levels at long (> 12 months); Adverse events and complications of gout (radiographic joint damage, renal stones, tophi) at short (< 3 months); Adverse events and complications of gout (radiographic joint damage, renal stones, tophi) at medium (3 to 12 months); Adverse events and complications of gout (radiographic joint damage, renal stones, tophi) at long (> 12 months)

Study	Wang 2018[122]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=160)
Countries and setting	Conducted in China; Setting: Outpatient follow up
Line of therapy	1st line
Duration of study	Intervention + follow up: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diagnosed with gout and hyperuricemia in their hospital meeting the diagnostic criteria for acute gouty arthritis of the American College of Rheumatology with a history of gout attack
Stratum	People without chronic kidney disease or people with CKD stages 1-2
Subgroup analysis within study	Not applicable
Inclusion criteria	Meeting the diagnostic criteria of acute gouty arthritis of the American College of Rheumatology, history of gout attack; in the gout remission period before admission; signed formal informed consent
Exclusion criteria	Liver and kidney dysfunction; contraindications to the use of febuxostat or allopurinol; severe abnormality in white blood cells or platelet counts; coagulation disorder
Recruitment/selection of patients	Patients at the study hospital
Age, gender, and ethnicity	Age - Mean (SD): 61.7 (3.7). Gender (M:F): 88:72. Ethnicity: Not stated
Further population details	1. Age: < 65 years 2. Setting: Secondary care
Extra comments	Baseline urate level: 617.5 (79.2) micromol/L
Indirectness of population	No indirectness
Interventions	(n=80) Intervention 1: Xanthine oxidase inhibitor - Febuxostat 80mg. Febuxostat 80mg once a day. Duration 6 months. Concurrent medication/care: Both groups were given information with health publicity and education, including a diet program, advice on quitting smoking and alcohol, reducing the intake of high purine foods, such as animal organs, seafood, and soy products, avoiding excessive exercise, and maintaining good sleep. Indirectness: No indirectness Further details: 1. Choice of drug (drugs within the class, based on the intervention arm only): Febuxostat 80mg (n=80) Intervention 2: Xanthine oxidase inhibitor - Allopurinol for moderate gout 300-600mg. Allopurinol 100mg three times a day. Duration 6 months. Concurrent medication/care: Both groups were given information with health publicity and education, including a diet program, advice on quitting smoking and alcohol, reducing the intake of high purine foods, such as

	animal organs, seafood, and soy products, avoiding excessive exercise, and maintaining good sleep. Indirectness: No indirectness Further details: 1. Choice of drug (drugs within the class, based on the intervention arm only): Allopurinol 300mg
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FEBUXOSTAT 80MG versus ALLOPURINOL FOR MODERATE GOUT 300-600MG

Protocol outcome 1: Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at medium-term (3 to 12 months)
- Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Gastrointestinal adverse events (digestive tract symptom) at 6 months; Group 1: 1/80, Group 2: 4/80
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported baseline values of gender, age and blood uric acid levels; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Frequency of flares at medium-term (3 to 12 months)
- Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Acute gout attack rate at 6 months; Group 1: 3/80, Group 2: 10/80
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported baseline values of gender, age and blood uric acid levels; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Serum urate levels at short-term (< 3 months)
- Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Blood uric acid at 3 months; Group 1: mean 467.89 micromol/L (SD 92.03); n=80, Group 2: mean 420.57 micromol/L (SD 90.58); n=80; Comments: Baseline febuxostat: 614.39 (80.13). Baseline allopurinol: 620.55 (78.05).
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Baseline details: Reported baseline values of gender, age and blood uric acid levels; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Number of people achieving <6mg/dL at 1 month; Group 1: 45/60, Group 2: 60/80. Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Baseline details: Reported baseline values of gender, age and blood uric acid levels; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Number of people achieving <6mg/dL at 6 months; Group 1: 70/80, Group 2: 80/80. Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Baseline details: Reported baseline values of gender, age and blood uric acid levels; Group 1

Number missing: 0; Group 2 Number missing: 0 Protocol outcome 4: Serum urate levels at medium-term (3 to 12 months) - Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Blood uric acid at 6 months; Group 1: mean 400.03 micrmol/L (SD 75.48); n=80, Group 2: mean 372.06 micrmol/L (SD 76.46); n=80; Comments: Baseline febuxostat: 614.39 (80.13). Baseline allopurinol: 620.55 (78.05). Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported baseline values of gender, age, and blood uric acid levels; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Health-related quality of life at short (< 3 months); Health-related quality of life at medium (3 to 12 months); Health-related quality of life at long (>12 months); Pain at short (< 3 months); Pain at medium (3 to 12 months); Pain at long (>12 months); Joint swelling/joint inflammation at short (< 3 months); Joint swelling/joint inflammation at medium (3 to 12 months); Joint swelling/joint inflammation at long (> 12 months); Joint tenderness at short (< 3 months); Joint tenderness at medium (3 to 12 months); Joint tenderness at long (> 12 months); Patient global assessment of treatment success (response to treatment) at short (< 3 months); Patient global assessment of treatment success (response to treatment) at medium (3 to 12 months); Patient global assessment of treatment success (response to treatment) at long (> 12 months); Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at short (< 3 months); Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at long (> 12 months); Admissions (hospital & A&E) at short (< 3 months); Admissions (hospital & A&E) at medium 3 to 12 months); Admissions (hospital & A&E) at long (> 12 months); Discontinuation of ULT at short (< 3 months); Discontinuation of ULT at medium (3 to 12 months); Discontinuation of ULT at long (> 12 months); Frequency of flares at short (< 3 months); Frequency of flares at long (> 12 months); Serum urate levels at long (> 12 months); Adverse events and complications of gout (radiographic joint damage, renal stones, tophi) at short (< 3 months); Adverse events and complications of gout (radiographic joint damage, renal stones, tophi) at medium (3 to 12 months); Adverse events and complications of gout (radiographic joint damage, renal stones, tophi) at long (> 12 months)

Study	**Xu 2015[129]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=504)
Countries and setting	Conducted in China; Setting: Outpatient follow up
Line of therapy	1st line

Duration of study	Intervention + follow up: 24 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Gout defined by the American Rheumatism Association criteria
Stratum	People without chronic kidney disease or people with CKD stages 1-2
Subgroup analysis within study	Not applicable
Inclusion criteria	People of either sex and 18-70 years of age, inclusive, with gout, hyperuricemia (defined for the study as a serum urate level at least 480 micromol/L), normal renal function (serum creatinine concentration no more than 135 micromol/L) and free of gout flare 2 weeks beforehand and during the 2 week run-in period
Exclusion criteria	Pregnancy or lactation; concurrent therapy with azathioprine, 6-mercaptopurine, thiazide diuretics, or medications containing aspirin (>325mg) or other salicylates; a history of active liver disease, or hepatic dysfunction (alanine aminotransferase and aspartate aminotransferase values >1.5 times the upper limit of normal); a history of bronchial asthma; a history of renal calculi or thyroid disease; secondary gout joint diseases induced by rheumatoid arthritis, psoriatic arthritis and bone tumour; intolerance to allopurinol and ibuprofen; alcohol intake of at least 14 drinks/week; clinically significant medical conditions
Recruitment/selection of patients	Multicentre trial
Age, gender, and ethnicity	Age - Mean (SD): 46.8 (11.6). Gender (M:F): 453:24. Ethnicity: Not stated
Further population details	1. Age: < 65 years 2. Setting: Not stated / Unclear
Extra comments	Serum urate level:
Indirectness of population	No indirectness
Interventions	(n=168) Intervention 1: Xanthine oxidase inhibitor - Febuxostat 80mg. Febuxostat 80mg/day at a fixed dose for 24 weeks. Duration 24 weeks. Concurrent medication/care: No additional information. Indirectness: No indirectness. Further details: 1. Choice of drug (drugs within the class, based on the intervention arm only): Febuxostat 80mg (n=168) Intervention 2: Xanthine oxidase inhibitor - Allopurinol for moderate gout 300-600mg. Allopurinol 300mg/day at a fixed dose for 24 weeks. Duration 24 weeks. Concurrent medication/care: No additional information. Indirectness: No indirectness. Further details: 1. Choice of drug (drugs within the class, based on the intervention arm only): Allopurinol 300mg
Funding	Study funded by industry (The study was funded by Qingdao Shengbang Pharmaceutical Corporation Limited, Shandong, China)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FEBUXOSTAT 80MG versus ALLOPURINOL FOR MODERATE GOUT 300-600MG

Protocol outcome 1: Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at medium (3 to 12 months)
- Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Cardiovascular adverse events (abnormal electrocardiograph) at 24 weeks; Group 1: 0/168, Group 2: 1/168
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, sex, height, body mass, BMI, systolic and diastolic blood pressure, serum urate level, time with gout, history of presence of tophi, previous urate-lowering therapy, drug allergy and coexisting conditions; Group 1 Number missing: 27, Reason: 27 discontinued. 11 lost to follow-up, 3 adverse events, 1 gout flare, 4 protocol violation, 2 personal reason, 5 other reason; Group 2 Number missing: 36, Reason: 36 discontinued. 17 lost to follow up, 3 adverse event, 4 gout flare, 3 protocol violation, 7 personal reason, 1 other reason
- Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Renal adverse events (renal function test abnormality) at 24 weeks; Group 1: 7/168, Group 2: 2/168
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, sex, height, body mass, BMI, systolic and diastolic blood pressure, serum urate level, time with gout, history of presence of tophi, previous urate-lowering therapy, drug allergy and coexisting conditions; Group 1 Number missing: 27, Reason: 27 discontinued. 11 lost to follow-up, 3 adverse events, 1 gout flare, 4 protocol violation, 2 personal reason, 5 other reason; Group 2 Number missing: 36, Reason: 36 discontinued. 17 lost to follow up, 3 adverse event, 4 gout flare, 3 protocol violation, 7 personal reason, 1 other reason
- Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Gastrointestinal adverse events at 24 weeks; Group 1: 2/168, Group 2: 4/168
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, sex, height, body mass, BMI, systolic and diastolic blood pressure, serum urate level, time with gout, history of presence of tophi, previous urate-lowering therapy, drug allergy and coexisting conditions; Group 1 Number missing: 27, Reason: 27 discontinued. 11 lost to follow-up, 3 adverse events, 1 gout flare, 4 protocol violation, 2 personal reason, 5 other reason; Group 2 Number missing: 36, Reason: 36 discontinued. 17 lost to follow up, 3 adverse event, 4 gout flare, 3 protocol violation, 7 personal reason, 1 other reason

Protocol outcome 2: Serum urate levels at medium-term (3 to 12 months)
- Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Serum urate levels at 24 weeks; Group 1: mean -216 micromol/L (SD 137.2); n=158, Group 2: mean -170.4 micromol/L (SD 132.6); n=159; Comments: Baseline febuxostat: 565.1 (75.5). Baseline allopurinol: 574.2 (77.8).
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, sex, height, body mass, BMI, systolic and diastolic blood pressure, serum urate level, time with gout, history of presence of tophi, previous urate-lowering therapy, drug allergy and coexisting conditions; Group 1 Number missing: 27, Reason: 27 discontinued. 11 lost to follow-up, 3 adverse events, 1 gout flare, 4 protocol violation, 2 personal reason, 5 other reason; Group 2 Number missing: 36, Reason: 36 discontinued. 17 lost to follow up, 3 adverse event, 4 gout flare, 3 protocol violation, 7 personal reason, 1 other reason
- Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Number of people achieving sUA <6mg/dL at 24 weeks; Group 1: 55/159, Group 2: 93/158

Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, sex, height, body mass, BMI, systolic and diastolic blood pressure, serum urate level, time with gout, history of presence of tophi, previous urate-lowering therapy, drug allergy and coexisting conditions; Group 1 Number missing: 27, Reason: 27 discontinued. 11 lost to follow-up, 3 adverse events, 1 gout flare, 4 protocol violation, 2 personal reason, 5 other reason; Group 2 Number missing: 36, Reason: 36 discontinued. 17 lost to follow up, 3 adverse event, 4 gout flare, 3 protocol violation, 7 personal reason, 1 other reason.	
Protocol outcomes not reported by the study	Health-related quality of life at short (< 3 months); Health-related quality of life at medium (3 to 12 months); Health-related quality of life at long (>12 months); Pain at short (< 3 months); Pain at medium (3 to 12 months); Pain at long (>12 months); Joint swelling/joint inflammation at short (< 3 months); Joint swelling/joint inflammation at medium (3 to 12 months); Joint swelling/joint inflammation at long (> 12 months); Joint tenderness at short (< 3 months); Joint tenderness at medium (3 to 12 months); Joint tenderness at long (> 12 months); Patient global assessment of treatment success (response to treatment) at short (< 3 months); Patient global assessment of treatment success (response to treatment) at medium (3 to 12 months); Patient global assessment of treatment success (response to treatment) at long (> 12 months); Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at short (< 3 months); Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at long (> 12 months); Admissions (hospital & A&E) at short (< 3 months); Admissions (hospital & A&E) at medium 3 to 12 months); Admissions (hospital & A&E) at long (> 12 months); Discontinuation of ULT at short (< 3 months); Discontinuation of ULT at medium (3 to 12 months); Discontinuation of ULT at long (> 12 months); Frequency of flares at short (< 3 months); Frequency of flares at medium (3 to 12 months); Frequency of flares at long (> 12 months); Serum urate levels at short (< 3 months); Serum urate levels at long (> 12 months); Adverse events and complications of gout (radiographic joint damage, renal stones, tophi) at short (< 3 months); Adverse events and complications of gout (radiographic joint damage, renal stones, tophi) at medium (3 to 12 months); Adverse events and complications of gout (radiographic joint damage, renal stones, tophi) at long (> 12 months)

Study	Yu 2016[136]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=109)
Countries and setting	Conducted in Taiwan; Setting: Outpatient follow up
Line of therapy	Mixed line
Duration of study	Intervention + follow up: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Gout based on the American College of Rheumatology criteria
Stratum	Mixed population (people with chronic kidney disease and people without chronic kidney disease)
Subgroup analysis within study	Not applicable
Inclusion criteria	20-65 years old; diagnosed with gout based on the American College of Rheumatology criteria; were not taking urate-lowering agents with serum urate levels of at least 8.0mg/dL
Exclusion criteria	Breastfeeding or pregnancy; history of xanthinuria; allopurinol intolerance (i.e. hypersensitivity, Stevens-Johnson syndrome, topic epidermal necrolysis); use of allopurinol at >300mg/day and serum urate level >8mg/dL at the screening visit; presence of the HLA-B*5801 allele; use of thiazide diuretic therapy; secondary hyperuricaemia; requirement for concurrent therapy with any systemic or topical medication (prescribed or non-prescribed) that contained aspirin or other salicylates at the screening visit or during the study (although stable, low-dose aspirin 325mg/day was allowed); requirement for therapy with prednisone of at least 10mg/day during the study period; change in hormone replacement or oral contraceptive therapy within 3 months of the screening visit; alcohol intake of 14 or more drinks per week or alcohol abuse within the previous 5 years; requirement for concurrent therapy with any urate-lowering agent; active liver disease or hepatic dysfunction (ALT and AST more than 1.5 times the upper limits of normal); serum creatinine of 1.5mg/dL or more at the screening visit; inability to take the protocol-required gout flare prophylactic medication of colchicine due to intolerance; hypersensitivity; active gastric ulcer disease; renal impairment; changes in liver enzymes; presence of any other significant medical condition that would interfere with treatment, safety or compliance; history of cancer (other than basal cell carcinoma); use of any systemic cancer chemotherapy within 6 years prior to the screening visit; participation in a clinical study in which febuxostat was administered; participation in another investigational trial in the 30 days prior to the screening visit
Recruitment/selection of patients	Multicentre trial
Age, gender, and ethnicity	Age - Mean (SD): 45.6 (11.5). Gender (M:F): 106:3. Ethnicity: Han Chinese patients
Further population details	1. Age: < 65 years 2. Setting: Secondary care

Extra comments	Serum urate level: Not stated
Indirectness of population	No indirectness
Interventions	(n=54) Intervention 1: Xanthine oxidase inhibitor - Febuxostat 80mg. Febuxostat 80mg once a day for 12 weeks. Duration 12 weeks. Concurrent medication/care: Colchicine 0.5mg twice a day was used for prophylaxis of gout flares. Indirectness: No indirectness Further details: 1. Choice of drug (drugs within the class, based on the intervention arm only): Febuxostat 80mg (n=55) Intervention 2: Xanthine oxidase inhibitor - Allopurinol for moderate gout 300-600mg. Allopurinol 300mg once a day. Duration 12 weeks. Concurrent medication/care: Colchicine 0.5mg twice a day was used for prophylaxis of gout flares. Indirectness: No indirectness Further details: 1. Choice of drug (drugs within the class, based on the intervention arm only): Allopurinol 300mg
Funding	Academic or government funding (This study was funded by Astellas Pharma Taiwan, inc and is registered as NCT01736514 on clinicaltrials.gov.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FEBUXOSTAT 80MG versus ALLOPURINOL FOR MODERATE GOUT 300-600MG

Protocol outcome 1: Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at medium (3 to 12 months)
- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Total adverse events at 3 months (12 weeks); Group 1: 38/54, Group 2: 35/55
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, gender, palpable tophus, height, weight, BMI, alcohol use, concentration of preferred alcoholic beverage, tobacco use, caffeine use, previous urate-lowering therapy, uric acid in urine, urine creatinine, chromium chloride; Group 1 Number missing: 0, Reason: Unclear, stated that it included this number of participants, but not if any people withdrew from the trial; Group 2 Number missing: 0

Protocol outcome 2: Frequency of flares at medium (3 to 12 months)
- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Frequency of flares at 3 months (12 weeks); Group 1: 22/54, Group 2: 19/55
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, gender, palpable tophus, height, weight, BMI, alcohol use, concentration of preferred alcoholic beverage, tobacco use, caffeine use, previous urate-lowering therapy, uric acid in urine, urine creatinine, chromium chloride; Group 1 Number missing: 0, Reason: Unclear, stated that it included this number of participants, but not if any people withdrew from the trial; Group 2 Number missing: 0

Protocol outcome 3: Serum urate levels at short (< 3 months) - Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Number of people achieving sUA <6mg/dL at 2 months (8 weeks); Group 1: 38/54, Group 2: 13/55 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, gender, palpable tophus, height, weight, BMI, alcohol use, concentration of preferred alcoholic beverage, tobacco use, caffeine use, previous urate-lowering therapy, uric acid in urine, urine creatinine, chromium chloride; Group 1 Number missing: 0, Reason: Unclear, stated that it included this number of participants, but not if any people withdrew from the trial; Group 2 Number missing: 0 Protocol outcome 4: Serum urate levels at medium (3 to 12 months) - Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Number of people achieving sUA <6mg/dL at 3 months (12 weeks); Group 1: 32/54, Group 2: 6/55 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported age, gender, palpable tophus, height, weight, BMI, alcohol use, concentration of preferred alcoholic beverage, tobacco use, caffeine use, previous urate-lowering therapy, uric acid in urine, urine creatinine, chromium chloride; Group 1 Number missing: 0, Reason: Unclear, stated that it included this number of participants, but not if any people withdrew from the trial; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Health-related quality of life at short (< 3 months); Health-related quality of life at medium (3 to 12 months); Health-related quality of life at long (>12 months); Pain at short (< 3 months); Pain at medium (3 to 12 months); Pain at long (>12 months); Joint swelling/joint inflammation at short (< 3 months); Joint swelling/joint inflammation at medium (3 to 12 months); Joint swelling/joint inflammation at long (> 12 months); Joint tenderness at short (< 3 months); Joint tenderness at medium (3 to 12 months); Joint tenderness at long (> 12 months); Patient global assessment of treatment success (response to treatment) at short (< 3 months); Patient global assessment of treatment success (response to treatment) at medium (3 to 12 months); Patient global assessment of treatment success (response to treatment) at long (> 12 months); Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at short (< 3 months); Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at long (> 12 months); Admissions (hospital & A&E) at short (< 3 months); Admissions (hospital & A&E) at medium 3 to 12 months); Admissions (hospital & A&E) at long (> 12 months); Discontinuation of ULT at short (< 3 months); Discontinuation of ULT at medium (3 to 12 months); Discontinuation of ULT at long (> 12 months); Frequency of flares at short (< 3 months); Frequency of flares at long (> 12 months); Serum urate levels at long (> 12 months); Adverse events and complications of gout (radiographic joint damage, renal stones, tophi) at short (< 3 months); Adverse events and complications of gout (radiographic joint damage, renal stones, tophi) at medium (3 to 12 months); Adverse events and complications of gout (radiographic joint damage, renal stones, tophi) at long (> 12 months)

Study	**Zhang 2019[137]**

Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=599)
Countries and setting	Conducted in China; Setting: Outpatient follow up
Line of therapy	1st line
Duration of study	Intervention + follow up: 24 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Serum urate levels of >7.0mg/dL with a history of gout or serum urate levels of at least 8.0mg/dL with complications or serum urate levels of at least 9mg/dL without complications
Stratum	People without chronic kidney disease or people with CKD stages 1-2
Subgroup analysis within study	Not applicable
Inclusion criteria	Men or women aged between 18 and 85 years, with serum urate levels of >7.0mg/dL with a history of gout, serum urate levels of at least 8.0mg/dL with complications 9defined as the need for pharmacologic or other treatment for lithangiuria, hypertension, hyperlipidaemia, or abnormal glucose tolerance) or serum urate levels of at least 9.0mg/dL without complications
Exclusion criteria	Reported an acute attack of gouty arthritis at the screening visit or the randomisation visit (day -1) or if they had recovered for less than 2 weeks from a previous gouty arthritis attack; had been routinely receiving no-steroidal anti-inflammatory drugs or corticosteroids (not including topical application) for a disease other than gouty arthritis; had a medical condition that would interfere with treatment, safety or adherence to the protocol; were pregnant or lactating; had a history of drug-induced allergy or hypersensitivity; had renal dysfunction (serum creatinine at least 1.5mg/dL or 133 micromol/L); had severe hypertension (systolic blood pressure at least 180mmHg or diastolic blood pressure at least 110mmHg) or blood pressure that was not well controlled with antihypertensive agents; or had received any investigational product within 90 days prior to the start of screening
Recruitment/selection of patients	Multicentre trial
Age, gender, and ethnicity	Age - Mean (SD): 47.3 (12.7). Gender (M:F): 546:7. Ethnicity: All subjects were of Asian race
Further population details	1. Age: < 65 years 2. Setting: Not stated / Unclear
Extra comments	Serum urate at baseline (mean [SD]): 9.7 (1.5)
Indirectness of population	No indirectness: 12 people did not have gout, but this was less than 10% and so was not downgraded for indirectness
Interventions	(n=201) Intervention 1: Xanthine oxidase inhibitor - Febuxostat 80mg. Febuxostat 80mg (up-titrated from 20mg/day during weeks 1-4, 40mg/day weeks 5-8, 60mg/day weeks 9-16 and finally 80mg/day weeks 17-24). Duration 24 weeks (7 weeks at target dose). Concurrent medication/care: Subjects were prohibited from taking any uric acid-reducing medication or any

	drugs for the prophylaxis of gout flares, such as colchicine, during the study. Subjects who took one or more prohibited medications during the 2 weeks prior to providing informed consent underwent a washout period of at least 2 weeks prior to randomisation. Indirectness: No indirectness Further details: 1. Choice of drug (drugs within the class, based on the intervention arm only): (n=200) Intervention 2: Xanthine oxidase inhibitor - Allopurinol for moderate gout 300-600mg. Allopurinol 300mg (up-titrated with 100mg/day for weeks 1-2, 200mg/day for weeks 3-4, and 300mg/day from weeks 5-24). Duration 24 weeks (19 weeks at target dose). Concurrent medication/care: Subjects were prohibited from taking any uric acid-reducing medication or any drugs for the prophylaxis of gout flares, such as colchicine, during the study. Subjects who took one or more prohibited medications during the 2 weeks prior to providing informed consent underwent a washout period of at least 2 weeks prior to randomisation. Indirectness: No indirectness Further details: 1. Choice of drug (drugs within the class, based on the intervention arm only): Allopurinol 300mg
Funding	Study funded by industry (Astellas Pharma Global Development, inc. funded this work and the journal's Rapid Service Fee)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FEBUXOSTAT 80MG versus ALLOPURINOL FOR MODERATE GOUT 300-600MG

Protocol outcome 1: Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at medium (3 to 12 months)
- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Renal adverse events (renal and urinary disorders) at 24 weeks; ; Group 1: 6/197, Group 2: 16/200
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported gender, age, ethnicity, BMI, alcohol abuse, serum urate level and clinical diagnosis; Group 1 Number missing: 38, Reason: 38 discontinued. 14 withdrew consent, 11 serum urate no more than 7.0mg/dL at Day-1, 8 investigator/sub-investigator decision, 2 lost to follow-up, 1 failed to meet inclusion/exclusion criteria, 2 other; Group 2 Number missing: 43, Reason: 43 discontinued. 10 withdrew consent, 8 serum urate no more than 7.0 mg/dL at day -1, 6 lost to follow up, 3 failed to meet inclusion/exclusion criteria, 4 other

Protocol outcome 2: Frequency of flares at medium (3 to 12 months)
- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Frequency of flares at 24 weeks; Group 1: 101/197, Group 2: 102/200
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reported gender, age, ethnicity, BMI, alcohol abuse, serum urate level and clinical diagnosis; Group 1 Number missing: 38, Reason: 38 discontinued. 14 withdrew consent, 11 serum urate no more than 7.0mg/dL at Day-1, 8 investigator/sub-investigator decision, 2 lost to follow-up, 1 failed to meet inclusion/exclusion criteria, 2 other; Group 2 Number missing: 43, Reason: 43 discontinued. 10 withdrew consent, 8 serum

urate no more than 7.0 mg/dL at day -1, 6 lost to follow up, 3 failed to meet inclusion/exclusion criteria, 4 other	
Protocol outcomes not reported by the study	Health-related quality of life at short (< 3 months); Health-related quality of life at medium (3 to 12 months); Health-related quality of life at long (>12 months); Pain at short (< 3 months); Pain at medium (3 to 12 months); Pain at long (>12 months); Joint swelling/joint inflammation at short (< 3 months); Joint swelling/joint inflammation at medium (3 to 12 months); Joint swelling/joint inflammation at long (> 12 months); Joint tenderness at short (< 3 months); Joint tenderness at medium (3 to 12 months); Joint tenderness at long (> 12 months); Patient global assessment of treatment success (response to treatment) at short (< 3 months); Patient global assessment of treatment success (response to treatment) at medium (3 to 12 months); Patient global assessment of treatment success (response to treatment) at long (> 12 months); Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at short (< 3 months); Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at long (> 12 months); Admissions (hospital & A&E) at short (< 3 months); Admissions (hospital & A&E) at medium 3 to 12 months); Admissions (hospital & A&E) at long (> 12 months); Discontinuation of ULT at short (< 3 months); Discontinuation of ULT at medium (3 to 12 months); Discontinuation of ULT at long (> 12 months); Frequency of flares at short (< 3 months); Frequency of flares at long (> 12 months); Serum urate levels at short (< 3 months); Serum urate levels at medium (3 to 12 months); Serum urate levels at long (> 12 months); Adverse events and complications of gout (radiographic joint damage, renal stones, tophi) at short (< 3 months); Adverse events and complications of gout (radiographic joint damage, renal stones, tophi) at medium (3 to 12 months); Adverse events and complications of gout (radiographic joint damage, renal stones, tophi) at long (> 12 months)

Appendix E – Forest plots

E.1 First-line treatment

Figure 2: non-CKD population – allopurinol 300mg versus placebo – Flares (new or recurrent) at <3 months (30 days)

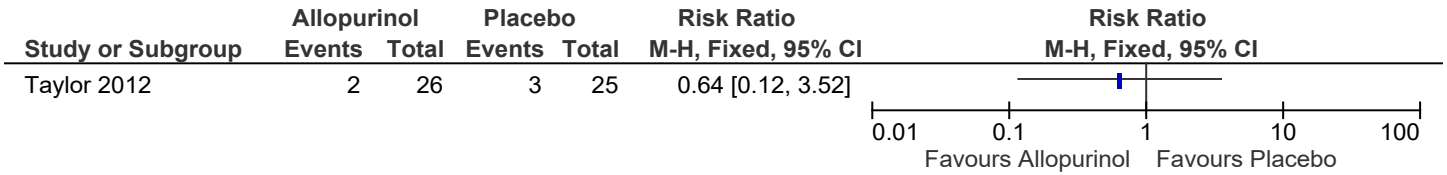


Figure 3: non-CKD population – allopurinol 300mg vs placebo – Gastrointestinal adverse events (colchicine reductions due to gastrointestinal symptoms) at <3 months (30 days)

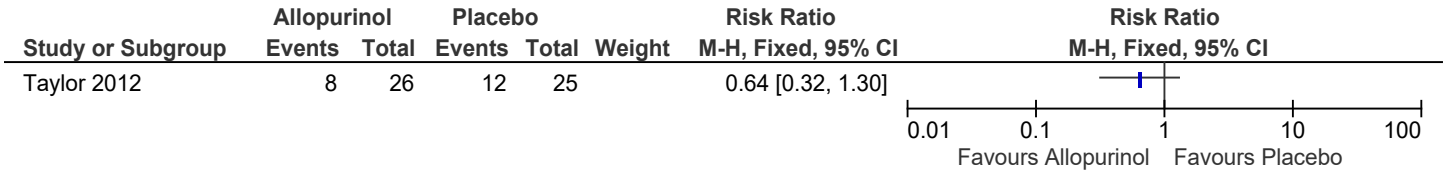


Figure 4: non-CKD population – allopurinol 300mg versus febuxostat 80 mg – Frequency of flares (acute gout attack rate) at 3 – 12 months (24 weeks)

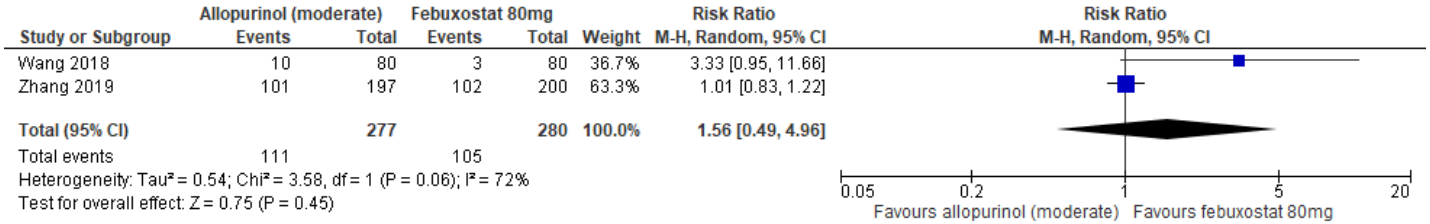


Figure 5: non-CKD population – allopurinol 300mg versus febuxostat 80mg – Renal adverse events (renal and urinary disorders) at 3 – 12 months (24 weeks)

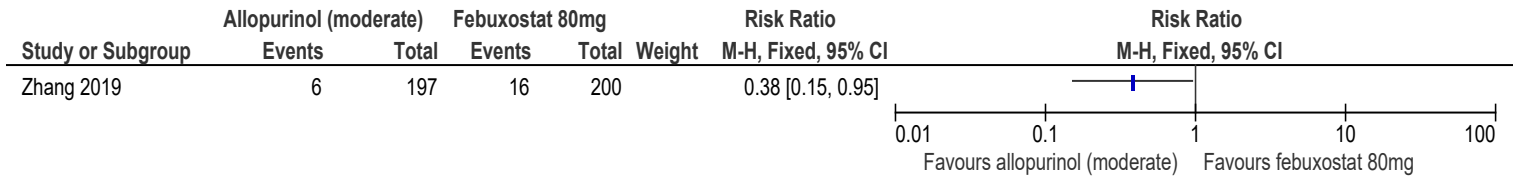


Figure 6: non-CKD population – allopurinol 300mg versus febuxostat 80mg - Gastrointestinal adverse events at 3 – 12 months (6 months)

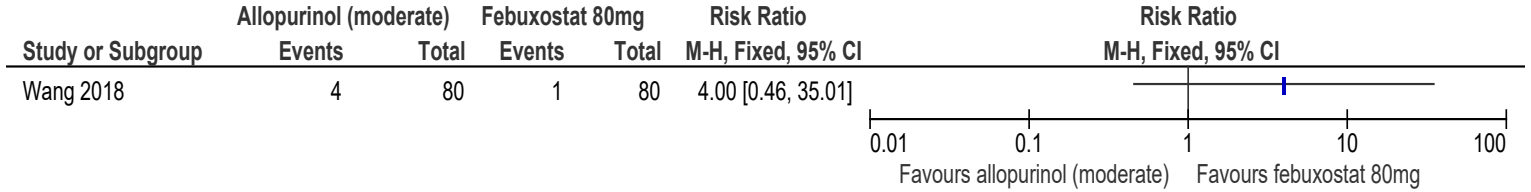


Figure 7: non-CKD population – allopurinol 300mg versus febuxostat 80 mg – Serum urate level (final value) at <3 months (1 month post-treatment)

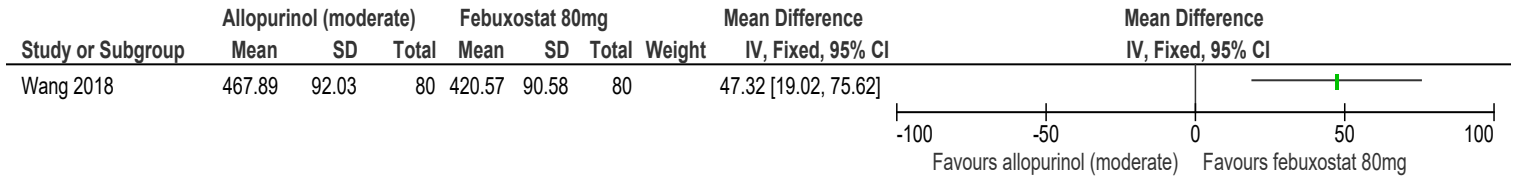


Figure 8: non-CKD population – allopurinol 300mg versus febuxostat 80mg – Serum urate level (final value) at 3 - 12 months (6 months post-treatment)

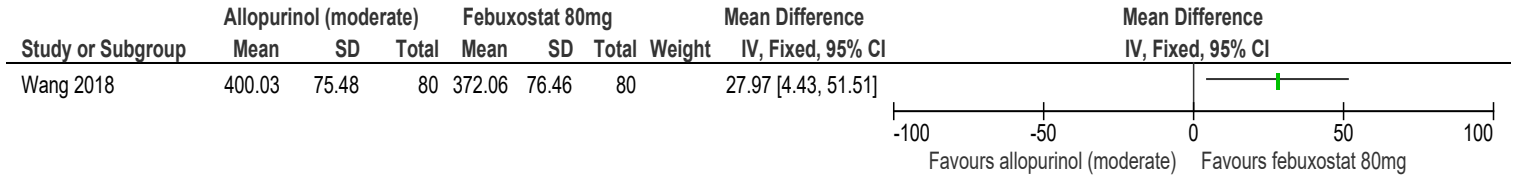


Figure 9: non-CKD population – allopurinol 300mg versus febuxostat 80mg – Serum urate level (number of patients reaching sUA of <6mg/dL) at <3 months (1 month post-treatment)

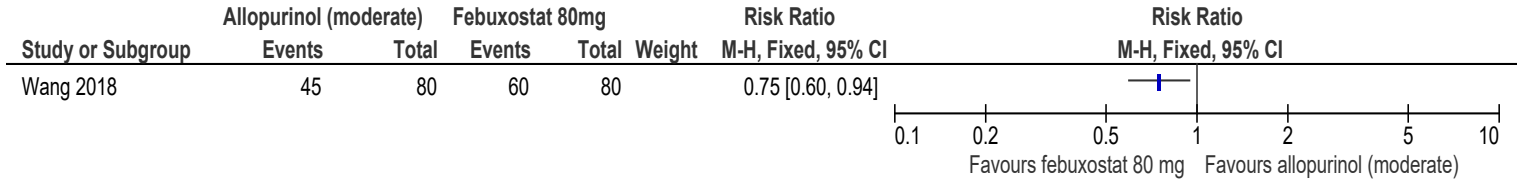


Figure 10: non-CKD population – allopurinol 300mg versus febuxostat 80 mg – Serum urate level (number of patients reaching sUA of <6mg/dL) at 3 – 12 months (6 months post-treatment)

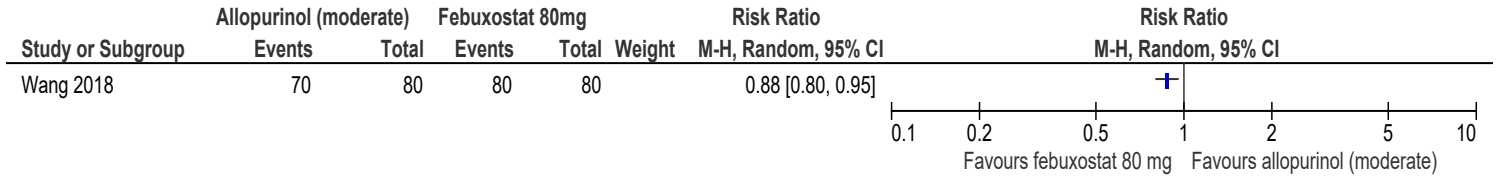


Figure 11: non-CKD population – febuxostat 80mg versus placebo - Serum urate level (number of patients reaching sUA of <6mg/dL) at <3 months (8 weeks)

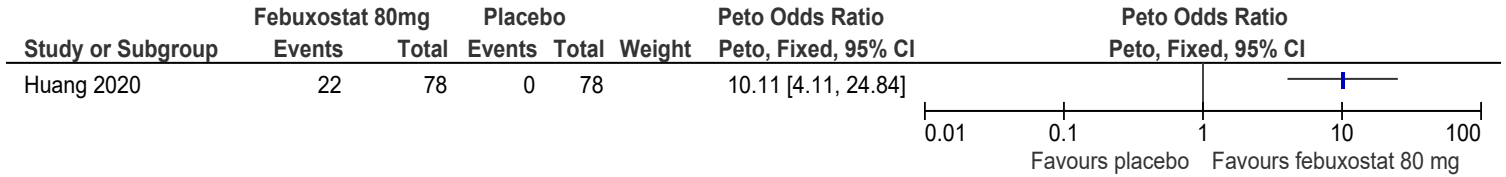


Figure 12: non-CKD population – febuxostat 80mg versus placebo - Serum urate level (number of patients reaching sUA of <6mg/dL) at 3 -12 months (24 weeks)

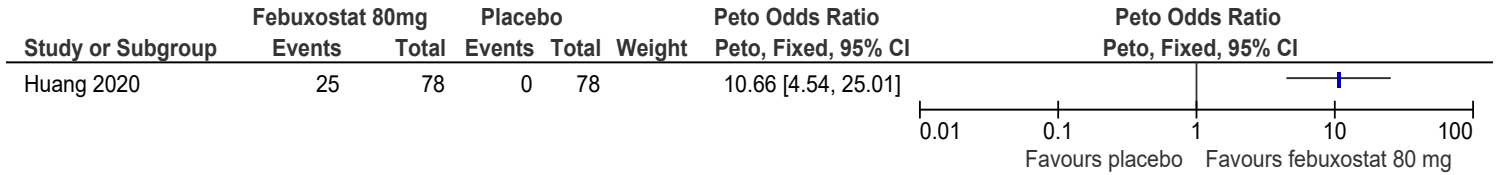


Figure 13: non-CKD population – febuxostat 80 mg versus placebo - Serum urate level (number of patients reaching sUA of <5mg/dL) at <3 months (8 weeks)

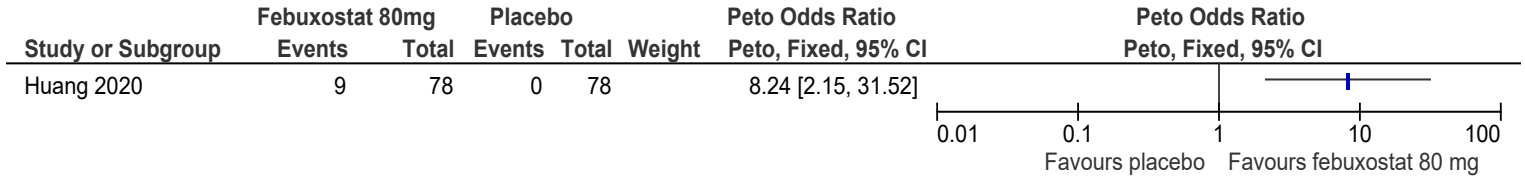


Figure 14: non-CKD population – febuxostat 80 mg versus placebo - Serum urate level (number of patients reaching sUA of <5mg/dL) at 3 - 12 months (24 weeks)

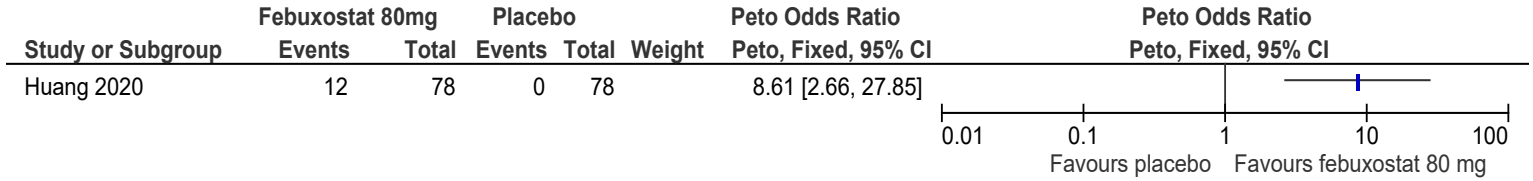


Figure 15: mixed CKD population – allopurinol 100 - 200mg versus placebo - Joint inflammation at <3 months (28 days)

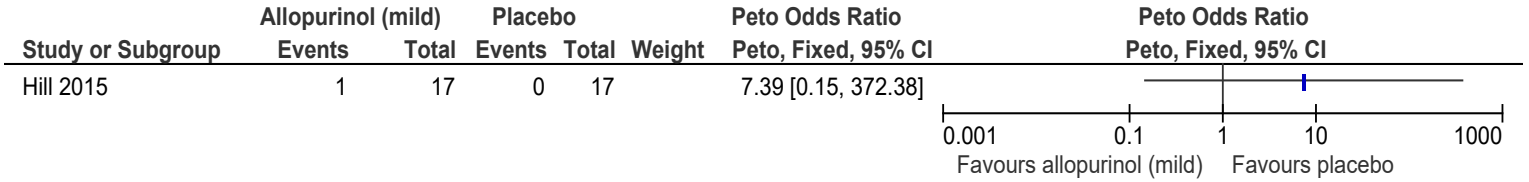


Figure 16: mixed CKD population – allopurinol 100 - 200mg vs placebo – Joint tenderness at <3 months (28 days)

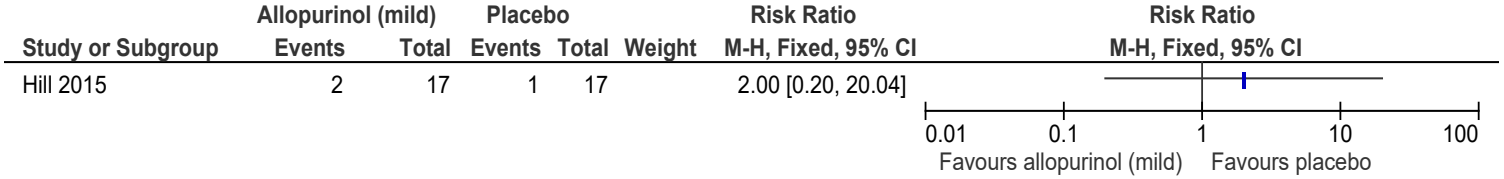
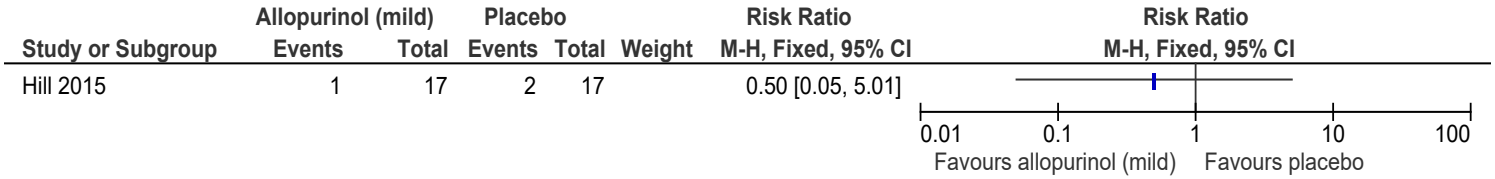


Figure 17: mixed CKD population – allopurinol 100 - 200mg versus placebo – Adverse events (withdrawal due to AE) at <3 months (28 days)



Unclear or mixed treatment line

Figure 18: Stage 3 CKD population - febuxostat 80 mg versus placebo – Frequency of flares (number of participants with 1 or more flares) at 3-12 months (3 months)

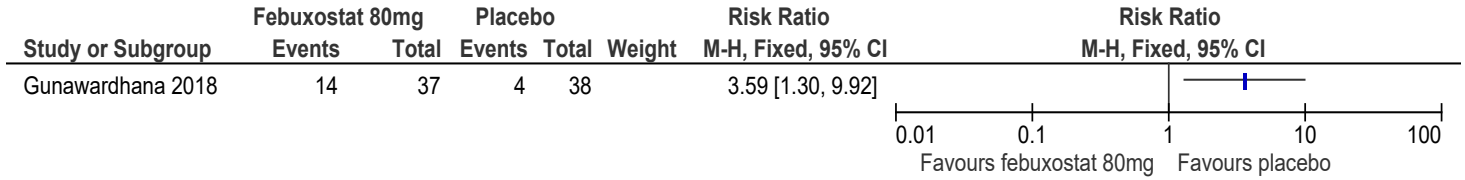


Figure 19: Stage 3 CKD population - febuxostat 80mg versus placebo – Cardiovascular adverse events (hypertension) at 3 - 12 months (3 months)

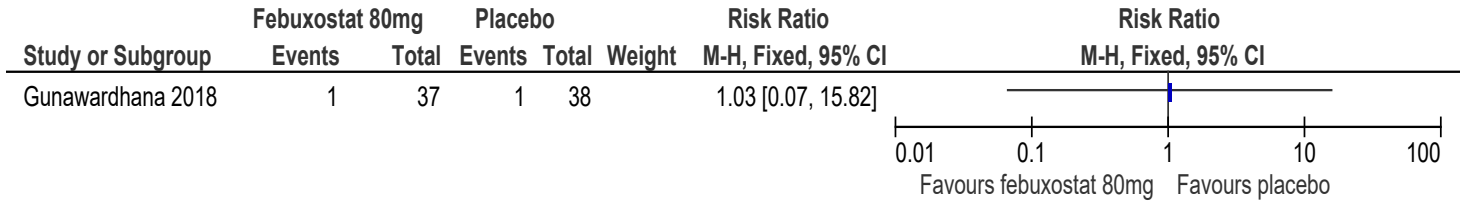


Figure 20: Stage 3 CKD population - febuxostat 80mg versus placebo – Renal adverse events (renal failure) at 3 – 12 months (3 months)

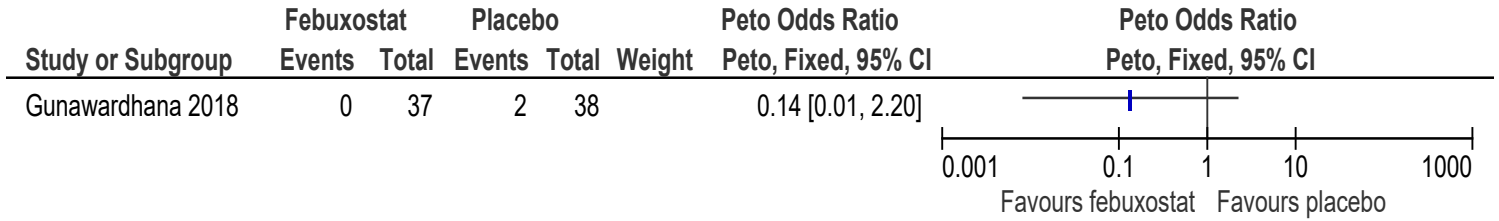


Figure 21: Stage 3 CKD population - febuxostat 80mg versus placebo – Gastrointestinal adverse events at 3 – 12 months (3 months)

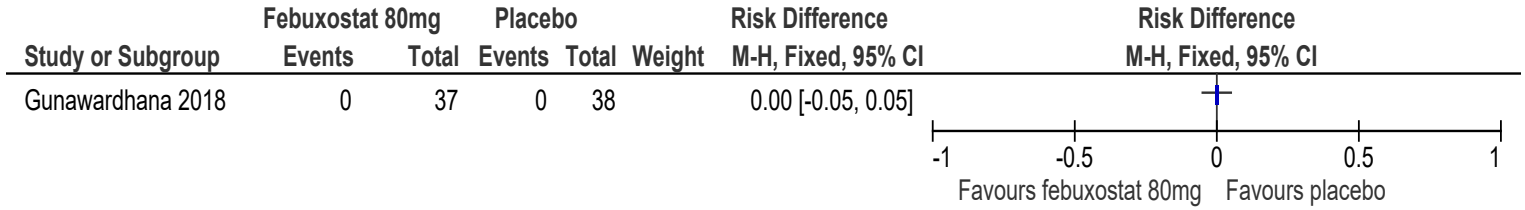


Figure 22: Stage 3 CKD population - febuxostat 80mg versus placebo – number of people achieving serum urate level <6mg/dL at 3-12 months (3 months)

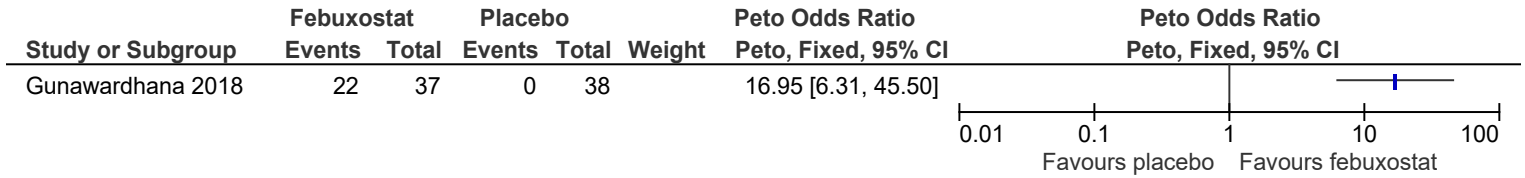


Figure 23: non-CKD population – allopurinol 300mg versus febuxostat 80mg – Cardiovascular adverse events at 3 - 12 months

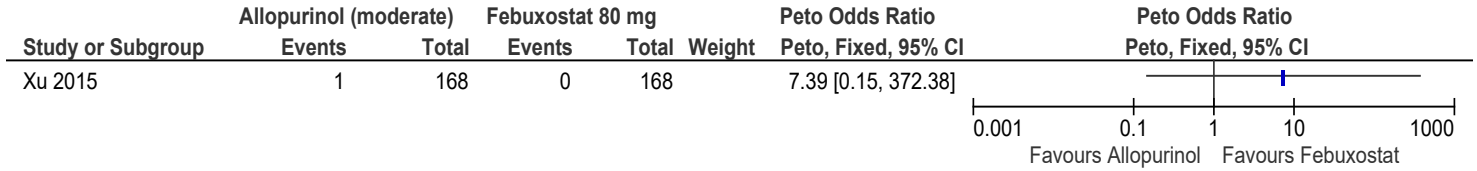


Figure 24: non-CKD population – allopurinol 300mg versus febuxostat 80mg – Renal adverse events at 3 - 12 months (24 weeks)

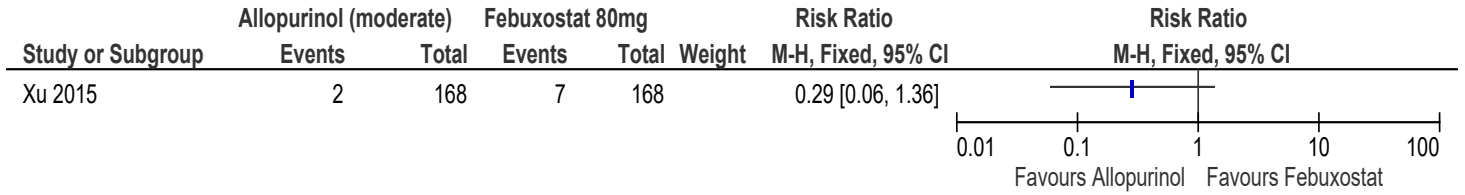


Figure 25: non-CKD population – allopurinol 300mg versus febuxostat 80mg – Gastrointestinal adverse events at 3 - 12 months (24 weeks)

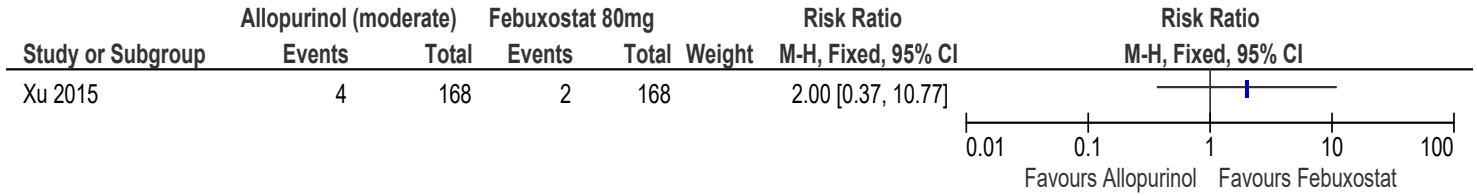


Figure 26: non-CKD population – allopurinol 300mg versus febuxostat 80mg – Serum urate level, change score at 3 - 12 months (24 weeks)

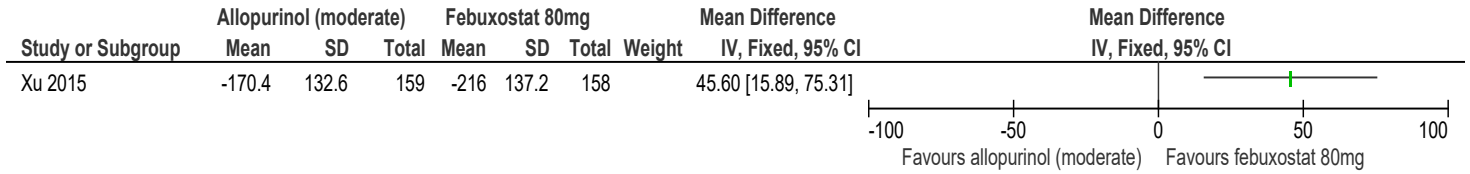


Figure 27: non-CKD population – allopurinol 300mg versus febuxostat 80mg – Serum urate level, number of patients achieving serum urate level of 6mg/dL at 3 - 12 months (24 weeks)

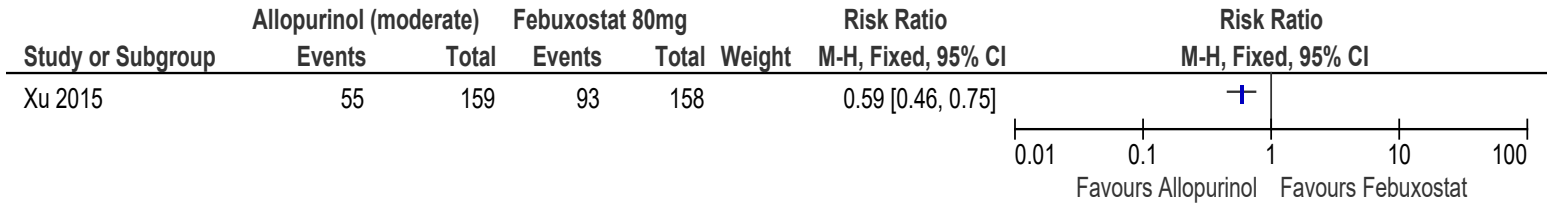


Figure 28: **non-CKD population – allopurinol 300mg versus febuxostat 80mg - Number of people achieving SUA concentrations of ≤6mg/dL at Week 36 – treat-to-target**

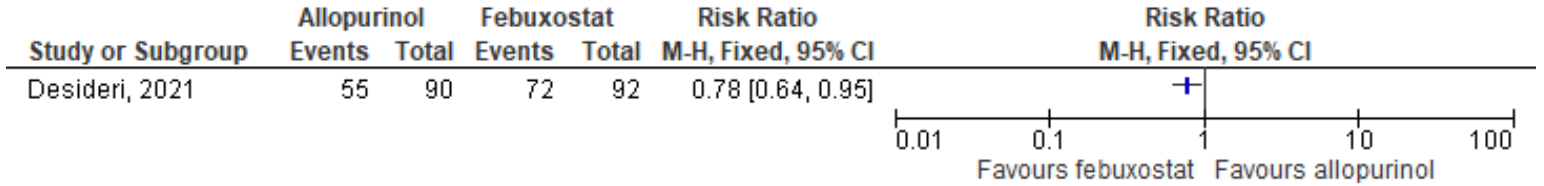


Figure 29: no CKD population – allopurinol 300mg versus placebo - Treatment emergent adverse events (during 36 week treatment period and 2 week follow-up) – treat-to-target

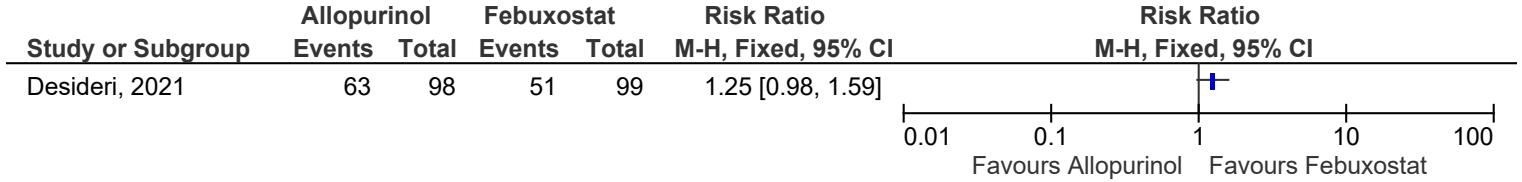


Figure 30: mixed CKD population – allopurinol 300mg versus placebo – Frequency of flares at <3 months (28 weeks)

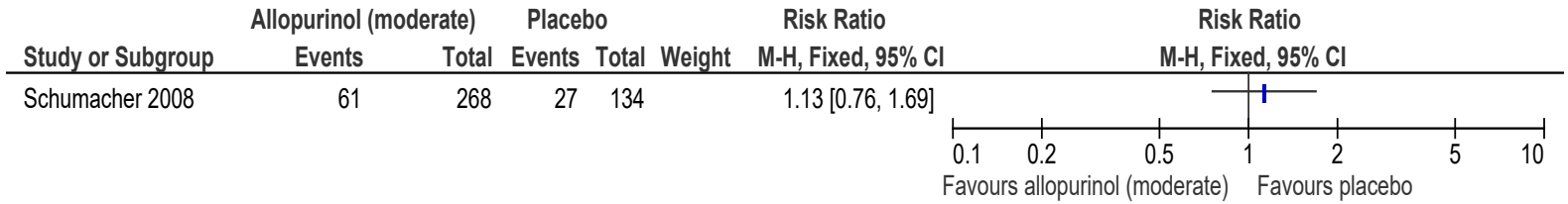


Figure 31: mixed CKD population – allopurinol 300mg versus placebo – Cardiovascular adverse events at 3-12 months (28 weeks)

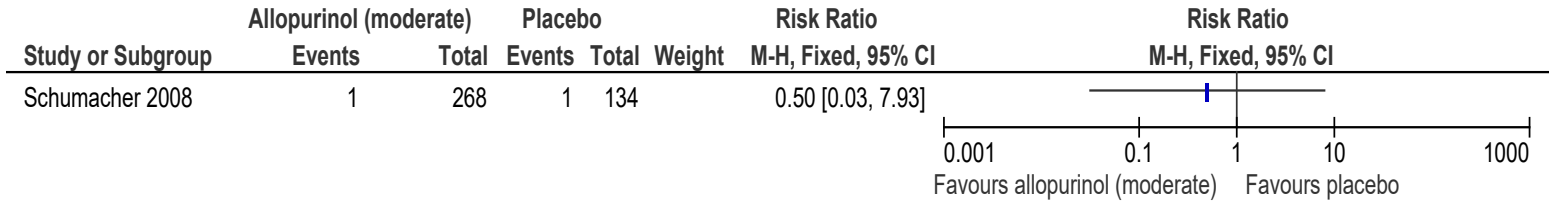


Figure 32: mixed CKD population – allopurinol 300mg versus placebo – Gastrointestinal adverse events (diarrhoea) at 3-12 months (28 weeks)

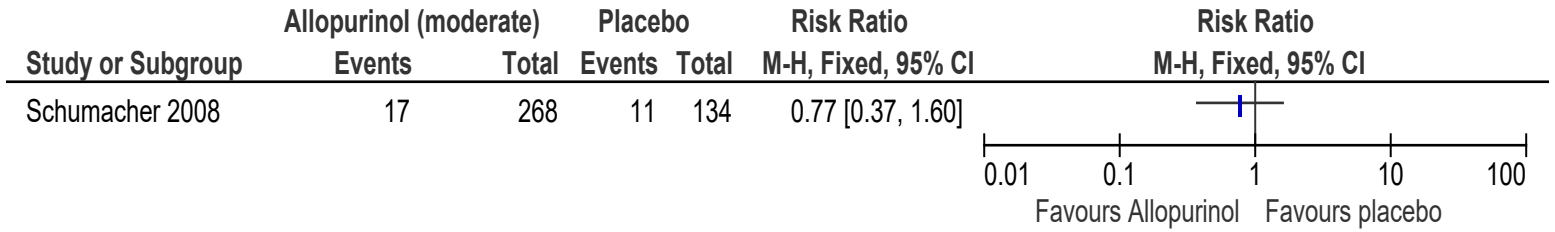


Figure 33: mixed CKD population – allopurinol 300mg versus placebo – Gastrointestinal adverse events (nausea and vomiting) at 3-12 months (28 weeks)

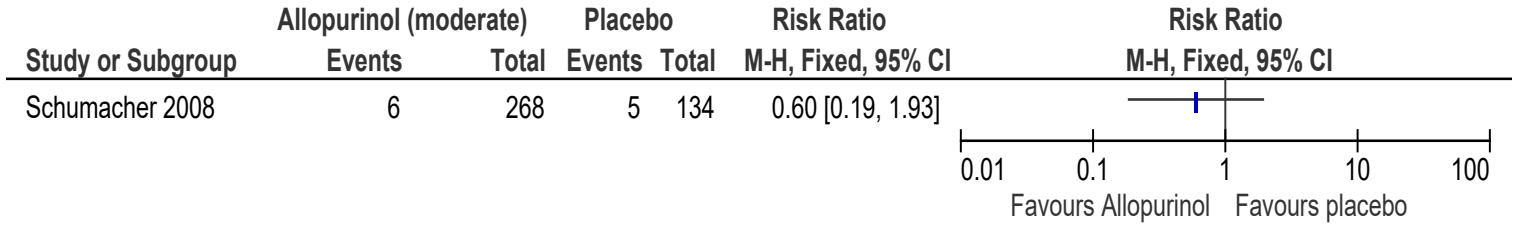


Figure 34: mixed CKD population – allopurinol 300mg versus placebo – Gastrointestinal adverse events (diarrhoea) at 3-12 months (28 weeks)

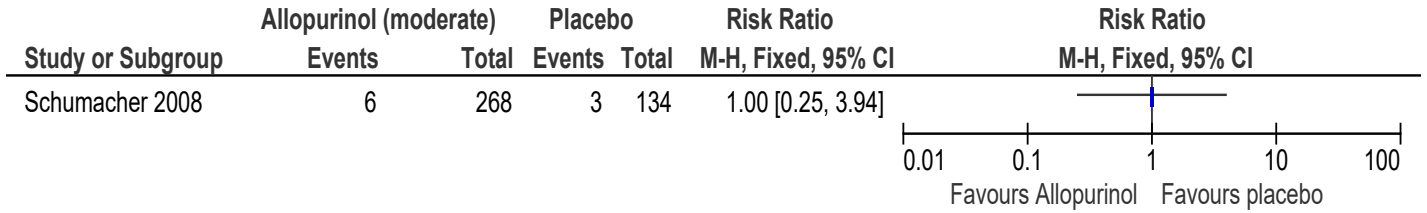


Figure 35: mixed CKD population – allopurinol 300mg versus placebo – serum urate level (change from baseline) at <3 months

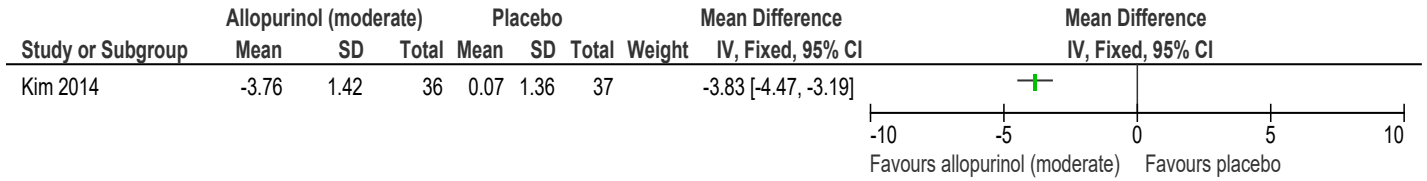


Figure 36: mixed CKD population – allopurinol 300mg versus placebo – serum urate level (number of people achieving sUA <6mg/dL) at 3 - 12 months

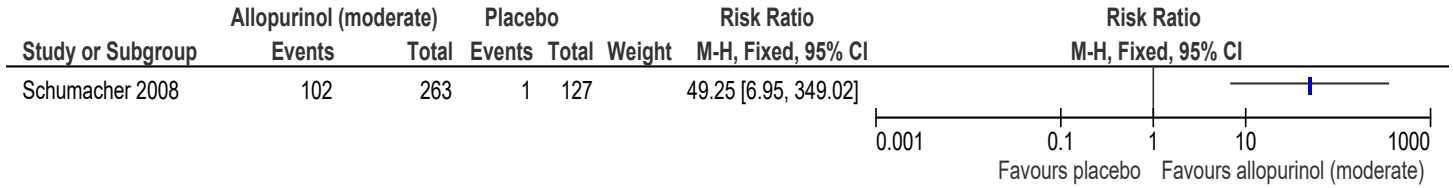


Figure 37: mixed CKD population – allopurinol 300mg versus febuxostat 80mg – Frequency of flares at <3 months

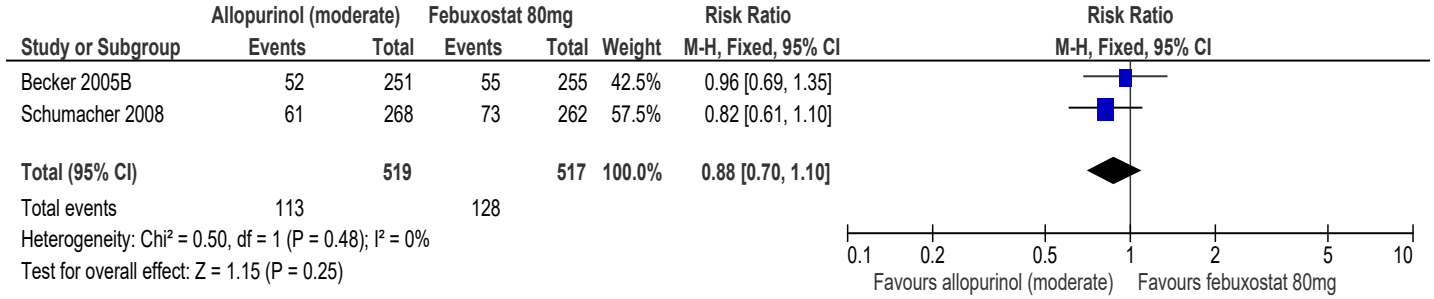


Figure 38: mixed CKD population – allopurinol 300mg versus febuxostat 80mg – Frequency of flares at 3 - 12 months

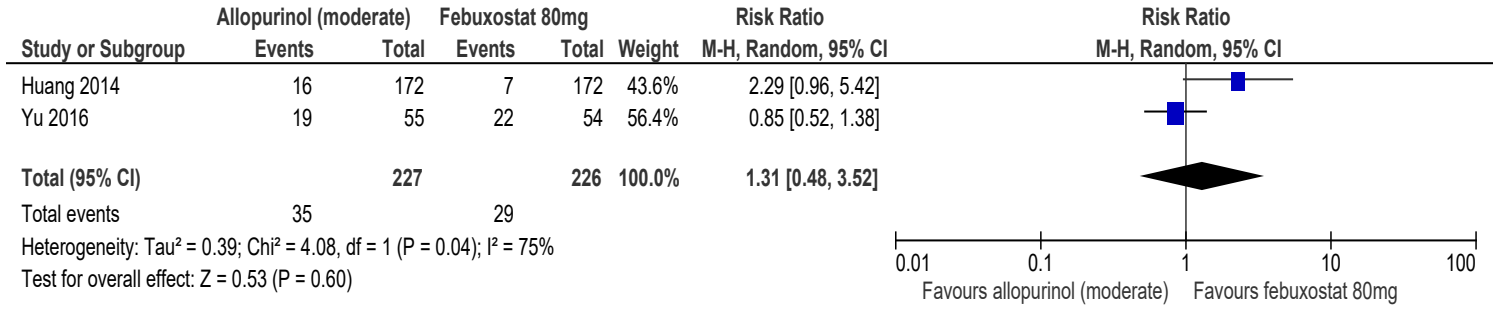


Figure 39: mixed CKD population – allopurinol 300mg versus febuxostat 80mg – Cardiovascular adverse events at 3-12 months

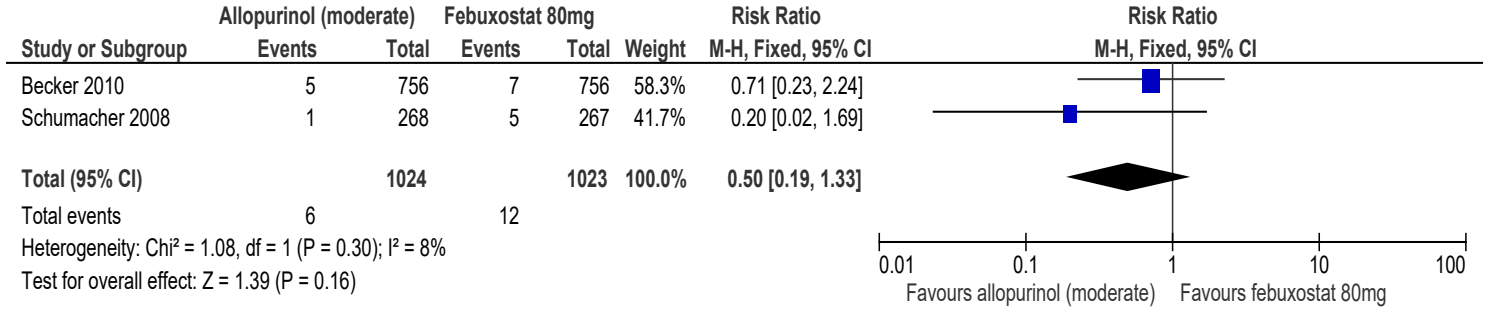


Figure 40: mixed CKD population – allopurinol 300mg versus febuxostat 80mg – Renal adverse events at 3 – 12 months

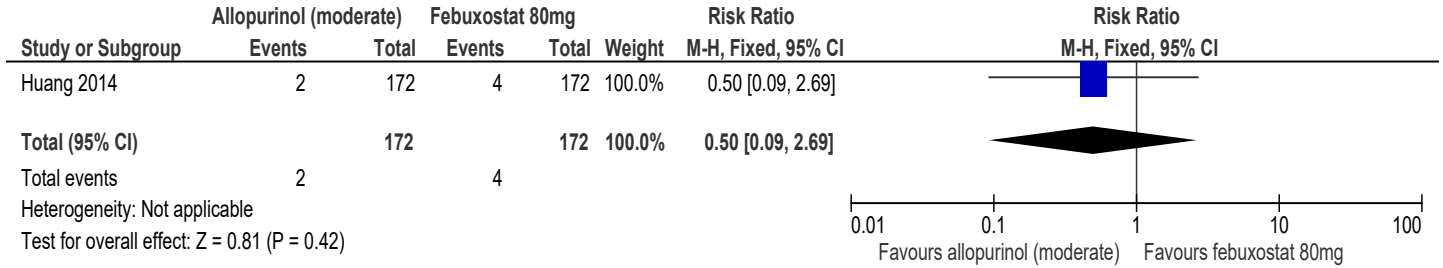


Figure 41: mixed CKD population – allopurinol 300mg versus febuxostat 80mg – Gastrointestinal adverse events (diarrhoea) at 3 – 12 months

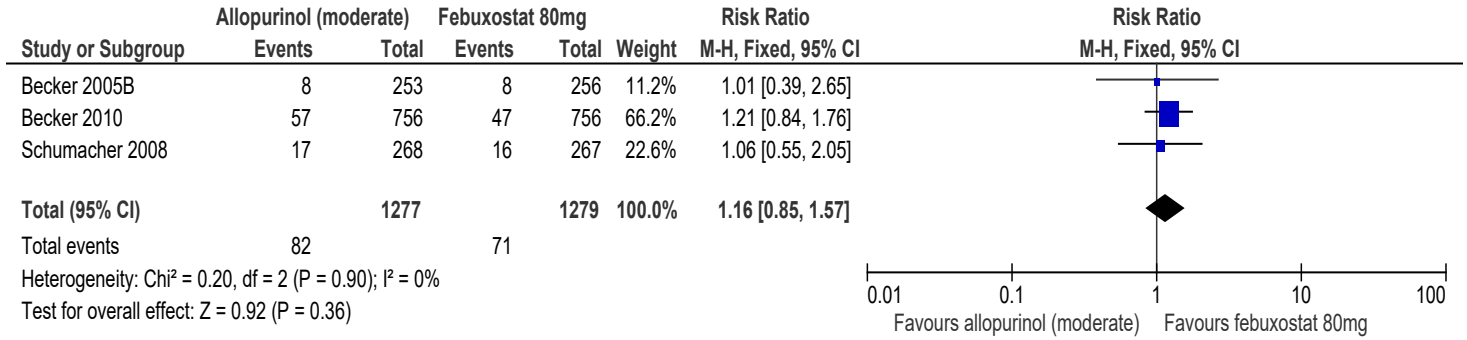


Figure 42: mixed CKD population – allopurinol 300mg versus febuxostat 80mg – Gastrointestinal adverse events (nausea and vomiting) at 3 – 12 months

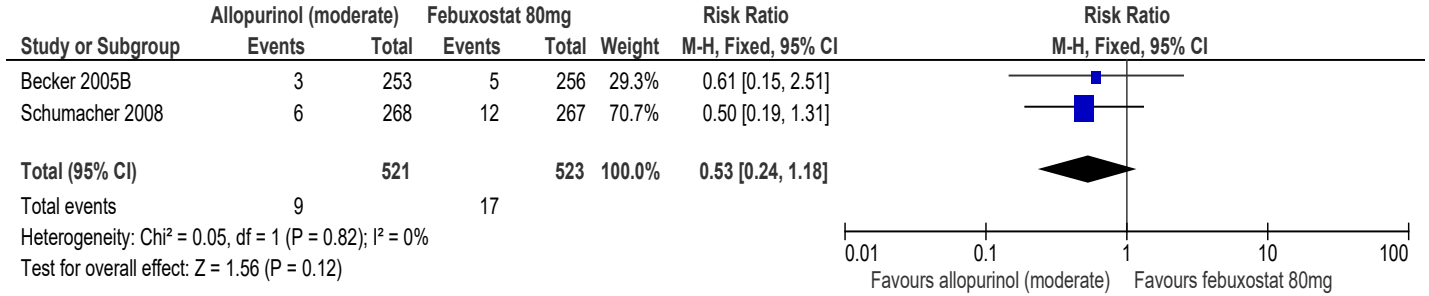
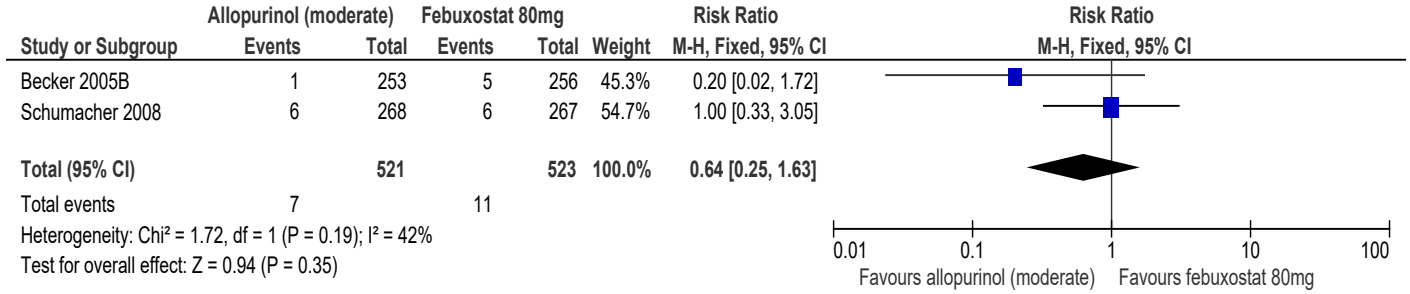
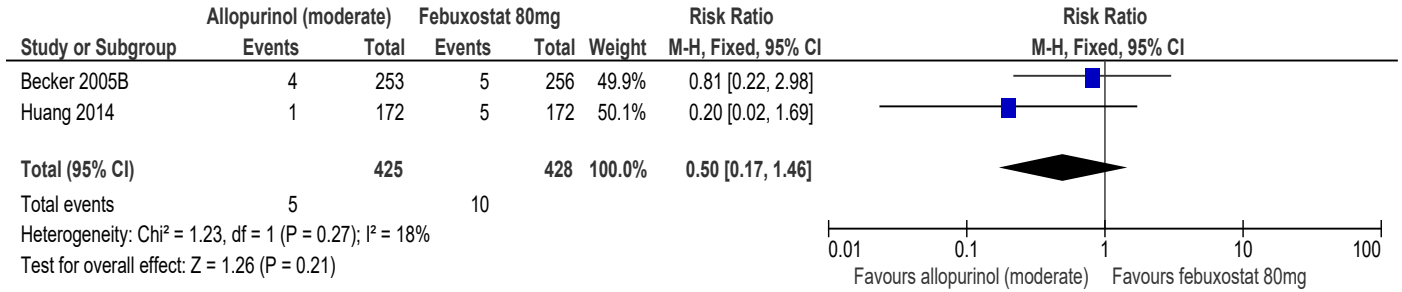


Figure 43: mixed CKD population – allopurinol 300mg versus febuxostat 80mg – Gastrointestinal adverse events (pain and discomfort) at 3 – 12 months



One study (Becker 2005B) included signs and symptoms (epigastric and stomach discomfort) and the other (Schumacher 2008) included gastro and abdominal pain (excluding oral and throat).

Figure 44: mixed CKD population – allopurinol 300mg versus febuxostat 80mg – Gastrointestinal adverse events (disorders) at 3 – 12 months



One study (Huang 2014) reported 'gastrointestinal disorders' whereas the other (Becker 2005B) included gastrointestinal and hypomotility disorders (constipation, gastro-oesophageal reflux disease).

Figure 45: mixed CKD population – allopurinol 300mg versus febuxostat 80 mg – Total adverse events at 3 – 12 months

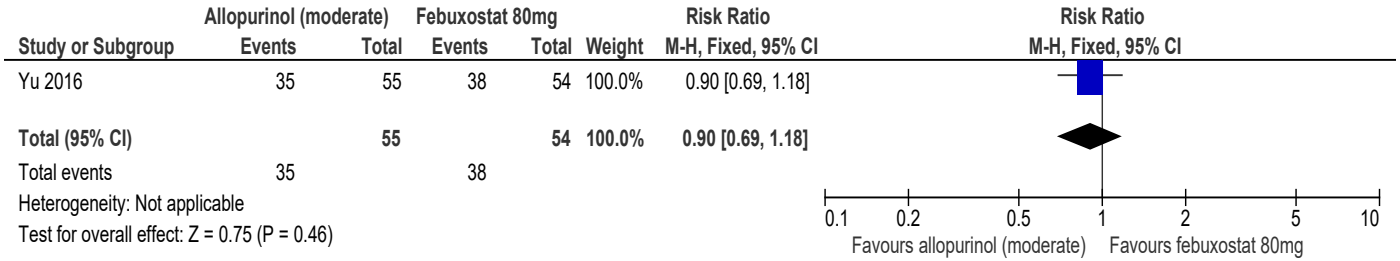


Figure 46: mixed CKD population – allopurinol 300mg versus febuxostat 80mg – Tophi at 3 – 12 months

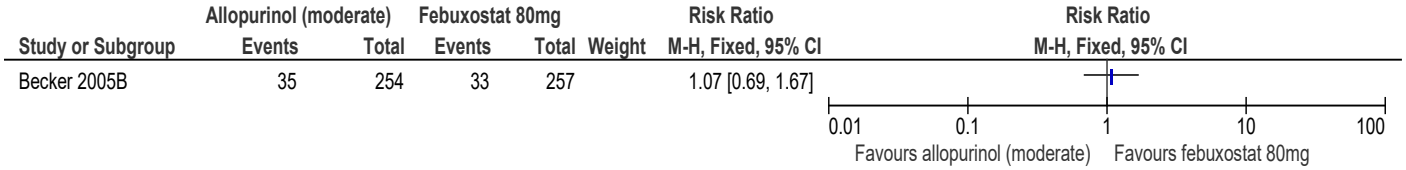


Figure 47: mixed CKD population – allopurinol 300mg versus febuxostat 80mg – Tophi (change from baseline) at 3 – 12 months

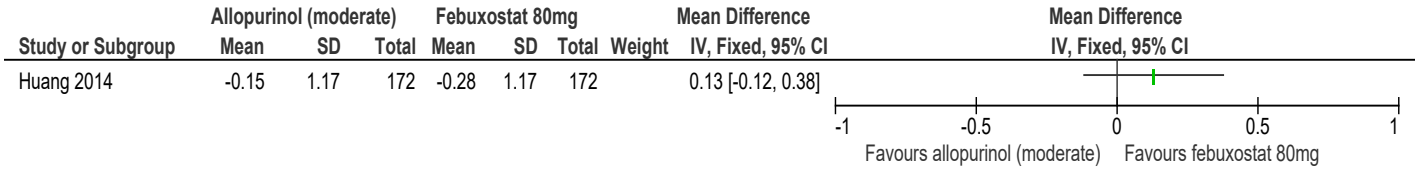


Figure 48: mixed CKD population – allopurinol 300mg versus febuxostat 80mg – Serum urate level (change score) at 3 – 12 months

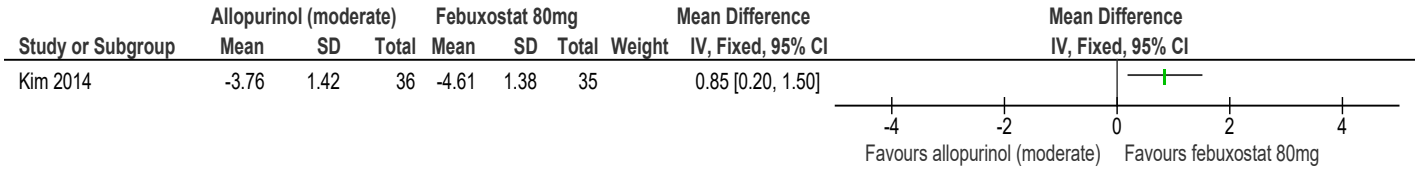


Figure 49: mixed CKD population – allopurinol 300mg versus febuxostat 80mg – Serum urate level (% change) at 3 – 12 months

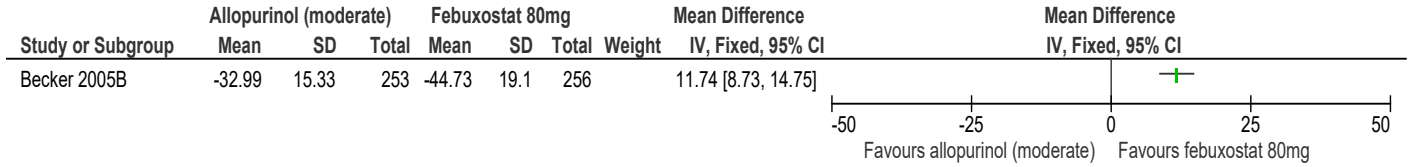


Figure 50: mixed CKD population – allopurinol 300mg versus febuxostat 80mg – Serum urate level (change score) at 3 – 12 months

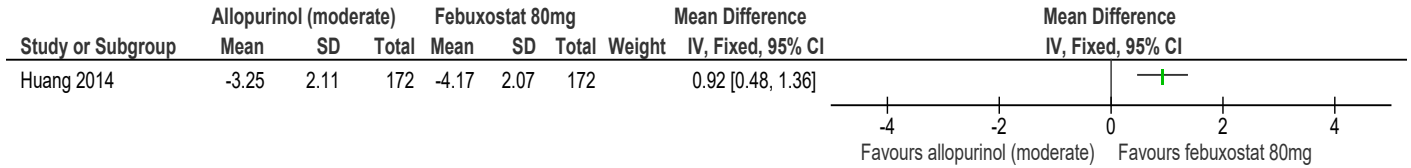


Figure 51: mixed CKD population – allopurinol 300mg versus febuxostat 80mg – Serum urate level (number of people achieving sUA <6.0 mg/dL) at <3 months (8 weeks)

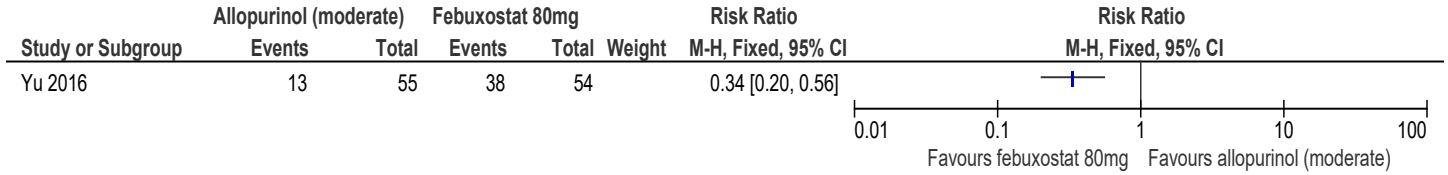


Figure 52: mixed CKD population – allopurinol 300mg versus febuxostat 80mg – Serum urate level (number of people achieving sUA <6.0 mg/dL) at 3 – 12 months

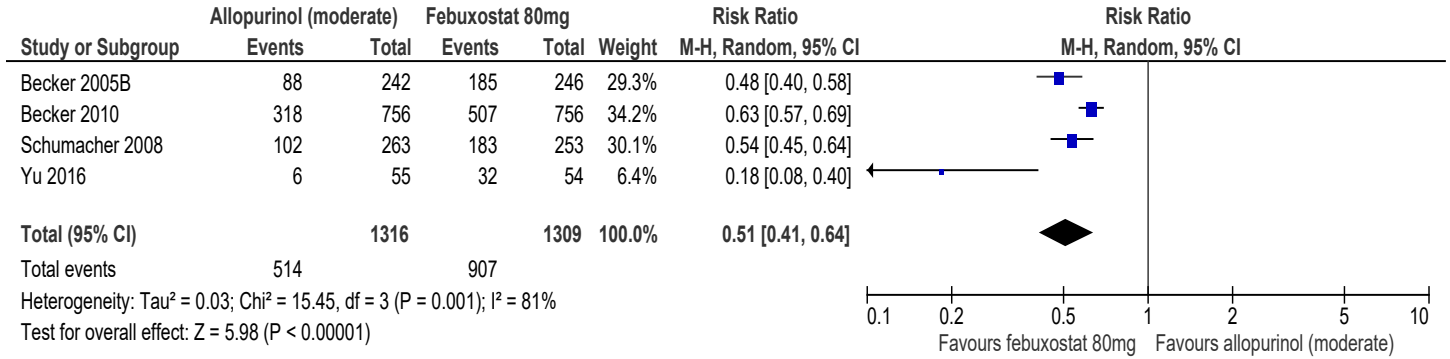


Figure 53: mixed CKD population – allopurinol 300mg versus febuxostat 120 mg – Frequency of flares at <3 months

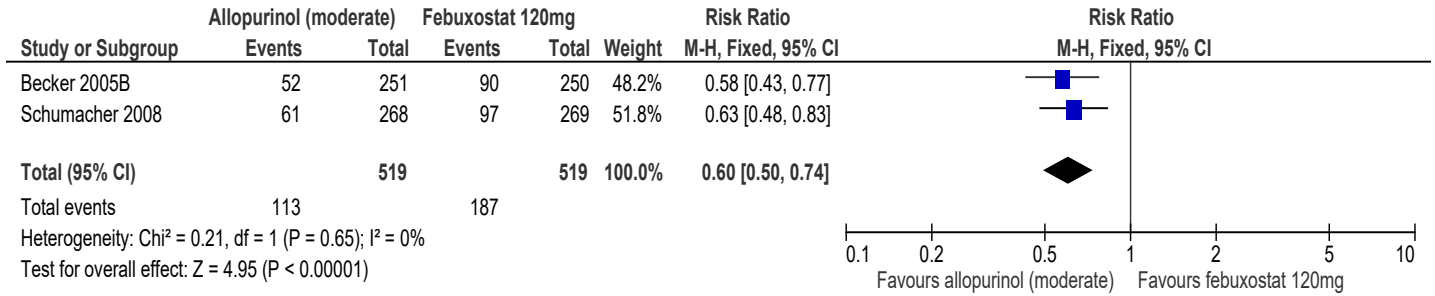


Figure 54: mixed CKD population – allopurinol 300mg versus febuxostat 120 mg – Cardiovascular adverse events at 3 – 12 months

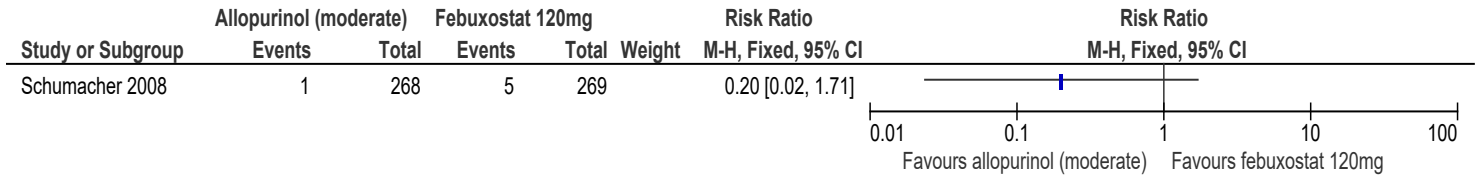


Figure 55: mixed CKD population – allopurinol 300mg versus febuxostat 120 mg – Gastrointestinal adverse events (diarrhoea) at 3-12 months

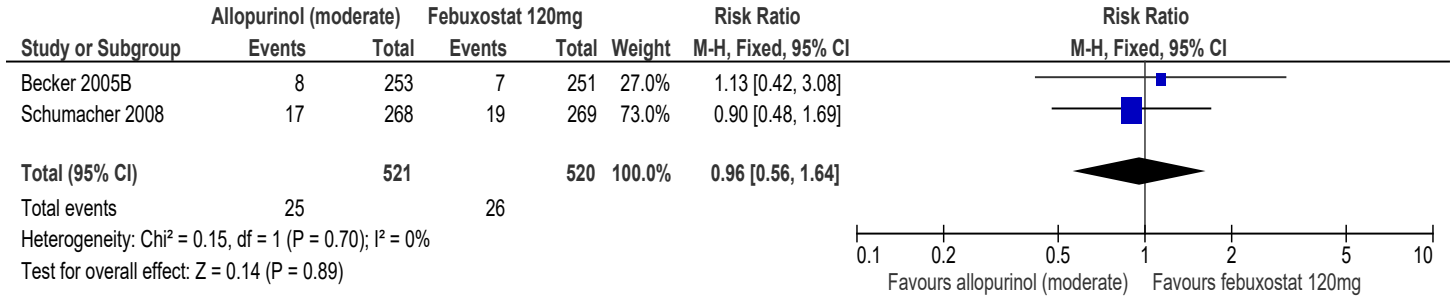


Figure 56: mixed CKD population – allopurinol 300mg versus febuxostat 120 mg – Gastrointestinal adverse events (nausea and vomiting) at 3-12 months

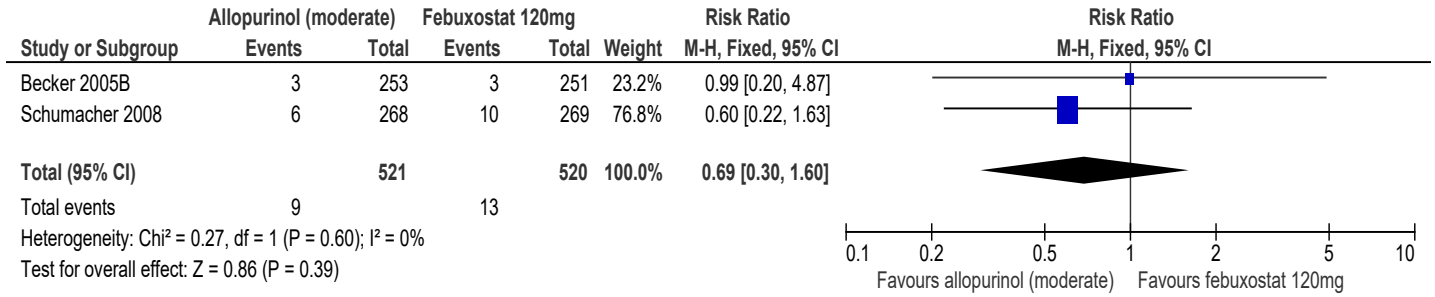


Figure 57: mixed CKD population – allopurinol 300mg versus febuxostat 120 mg – Gastrointestinal adverse events (gastro and abdominal pain) at 3-12 months

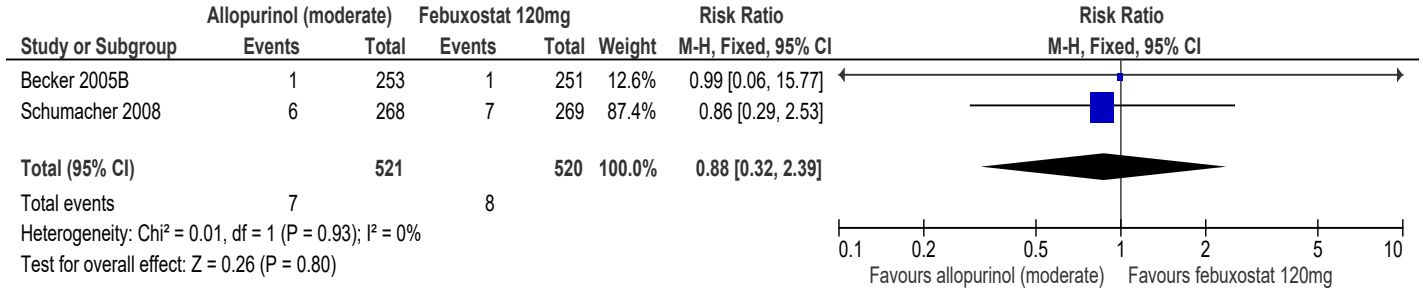


Figure 58: mixed CKD population – allopurinol 300mg versus febuxostat 120 mg – Tophi at 3 – 12 months

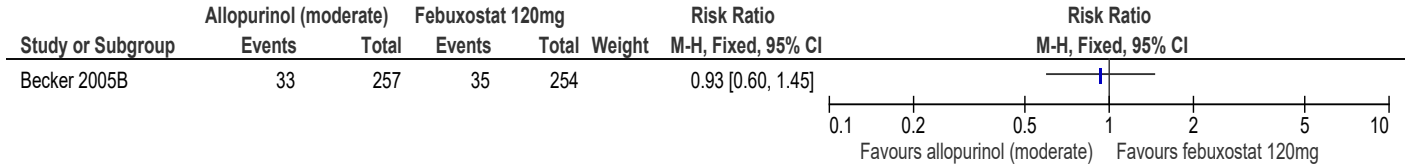


Figure 59: mixed CKD population – allopurinol 300mg versus febuxostat 120mg – Serum urate level (change score) at <3 months

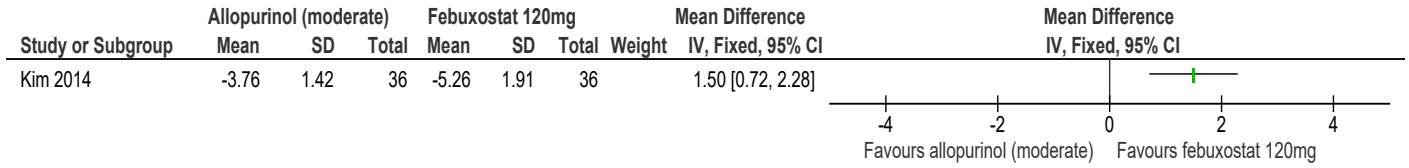


Figure 60: mixed CKD population – allopurinol 300mg versus febuxostat 120mg – Serum urate level (change score) at 3 – 12 months

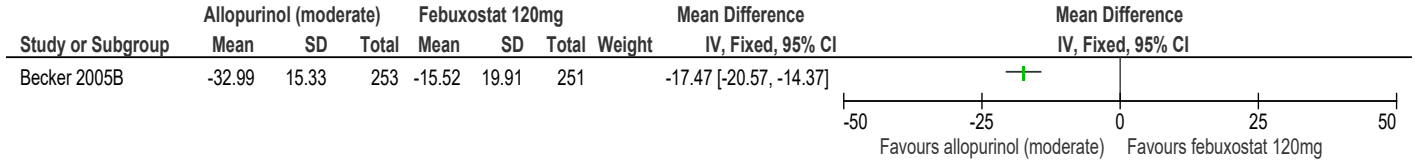


Figure 61: mixed CKD population – allopurinol 300mg versus febuxostat 120 mg – Serum urate level (number of people achieving sUA <6mg/dL) at 3 – 12 months

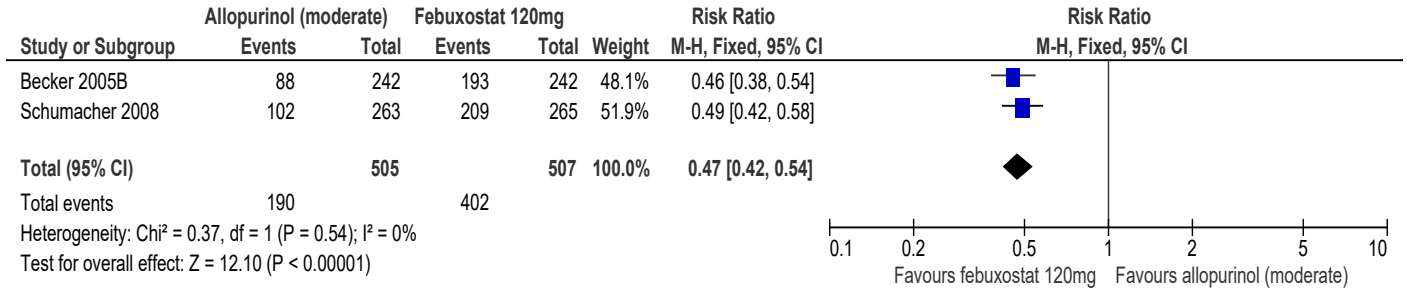


Figure 62: mixed CKD population – febuxostat 80 mg versus placebo – Frequency of flares at <3 months

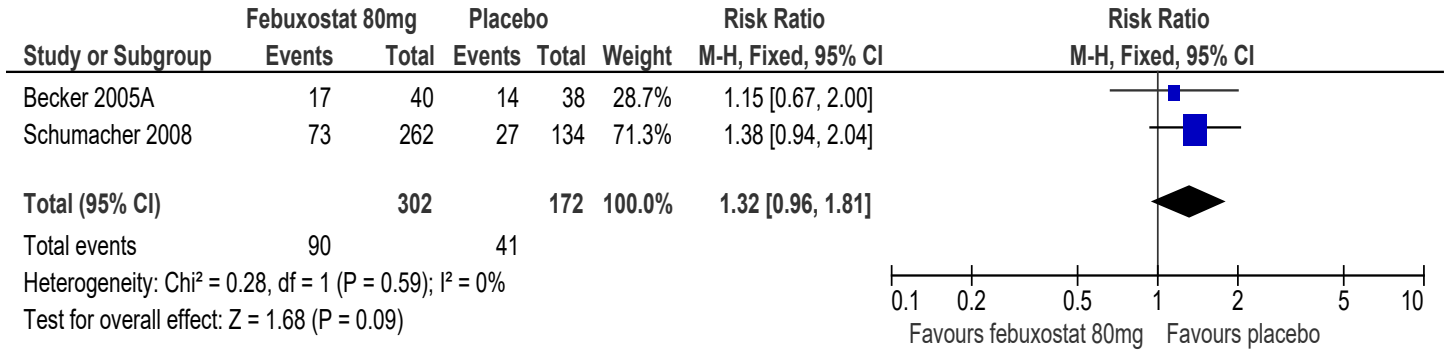


Figure 63: mixed CKD population – febuxostat 80mg versus placebo – Frequency of flares at 3-12 months

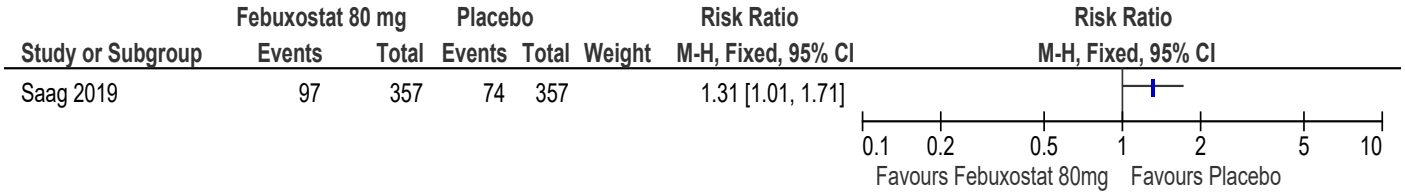


Figure 64: mixed CKD population – febuxostat 80mg versus placebo – Cardiovascular adverse events at 3 – 12 months

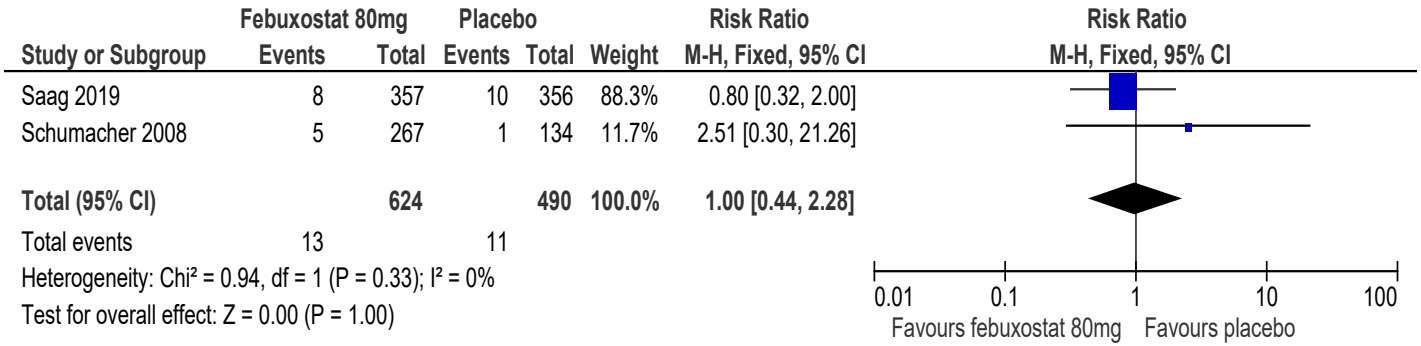


Figure 65: mixed CKD population – febuxostat 80 mg versus placebo – Gastrointestinal adverse events (abdominal pain) at <3 months

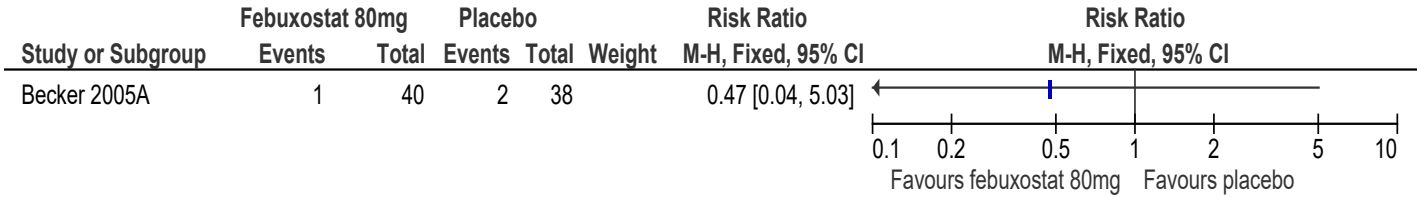


Figure 59: mixed CKD population – febuxostat 80 mg versus placebo – Gastrointestinal adverse events (diarrhoea) at <3 months

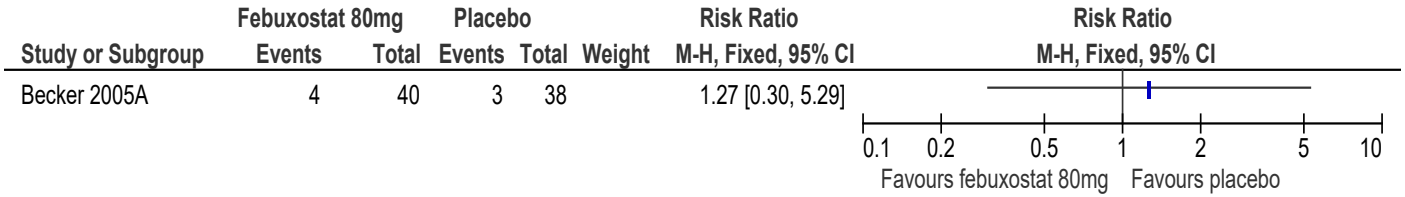


Figure 66: mixed CKD population – febuxostat 80mg versus placebo – Gastrointestinal adverse events (diarrhoea) at 3 - 12 months

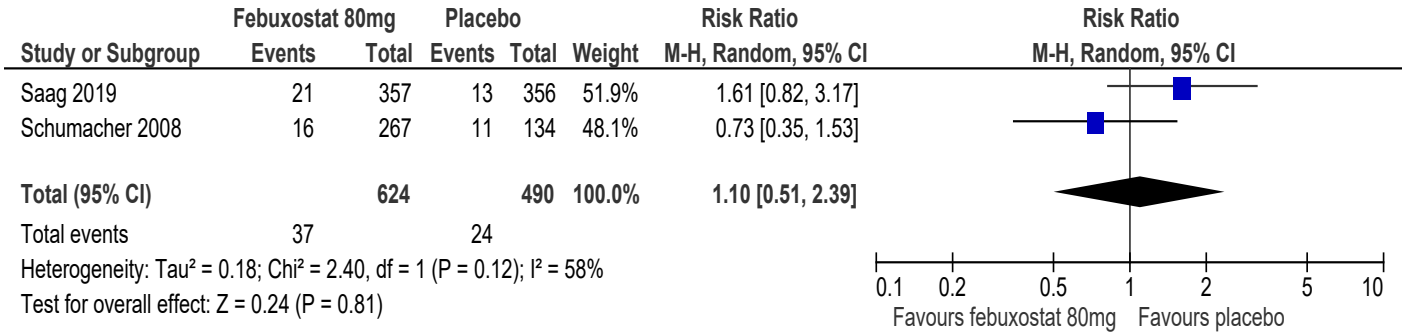


Figure 67: mixed CKD population – febuxostat 80mg versus placebo – Gastrointestinal adverse events (nausea and vomiting) at 3 - 12 months (28 weeks)

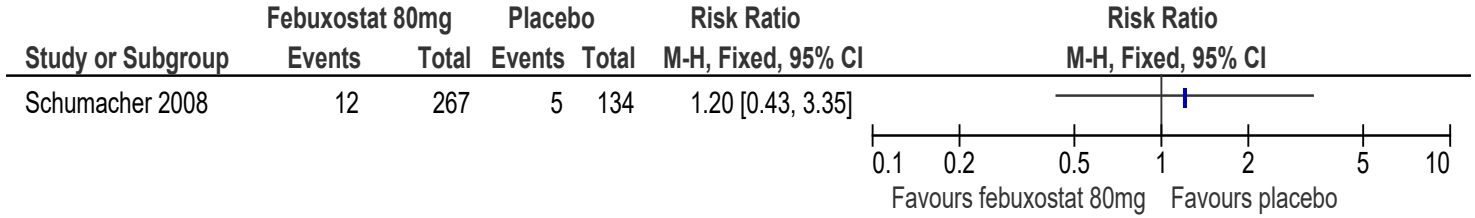


Figure 68: mixed CKD population – febuxostat 80mg versus placebo – Gastrointestinal adverse events (nausea and vomiting) at 3 - 12 months (28 weeks)

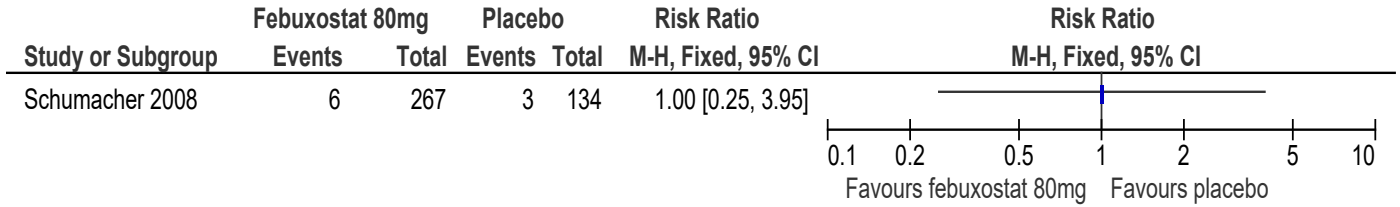


Figure 69: mixed CKD population – febuxostat 80mg versus placebo – Serum urate level (change score) at <3 months

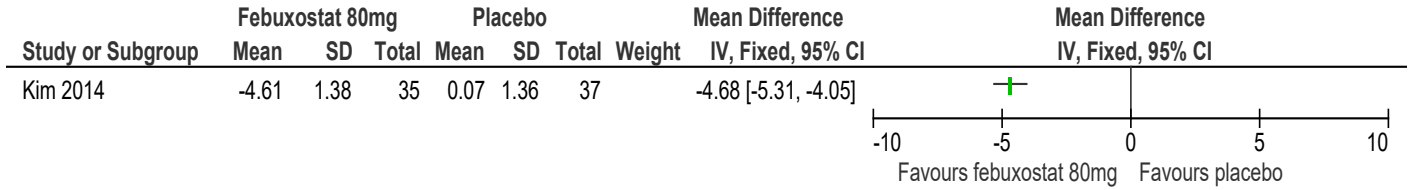


Figure 70: mixed CKD population – febuxostat 80mg versus placebo – Serum urate level (number of patients achieving sUA <6 mg/dL) at 3 - 12 months

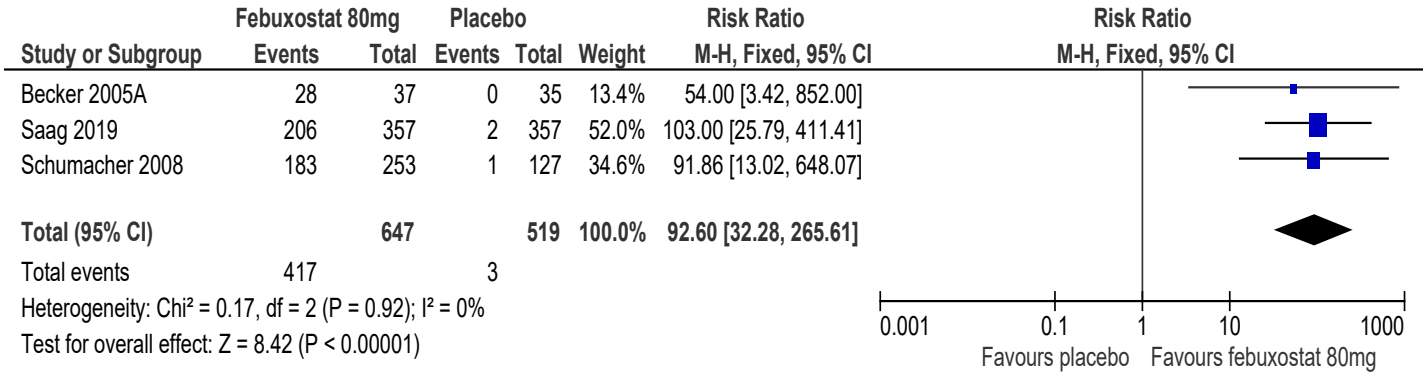


Figure 71: mixed CKD population – febuxostat 80mg versus placebo – Serum urate level (number of patients achieving sUA <5 mg/dL) at 3 - 12 months

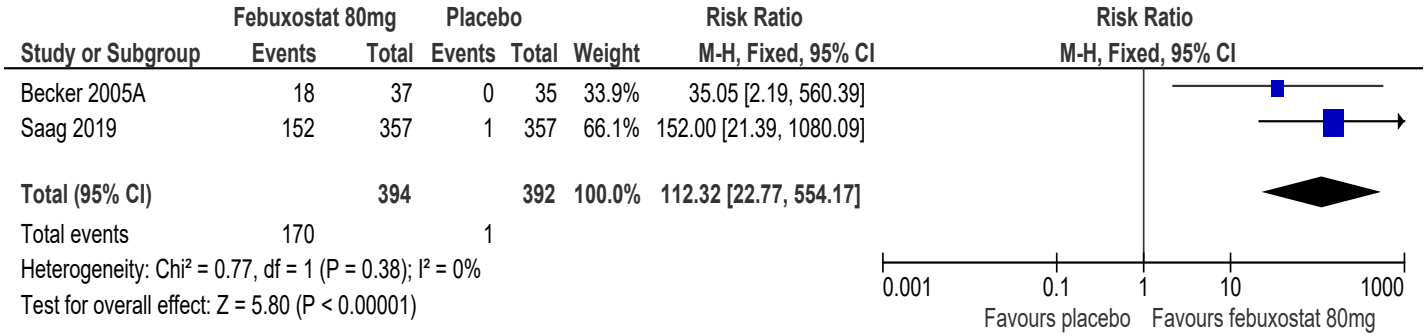


Figure 72: mixed CKD population – febuxostat 80mg versus placebo – Serum urate level (number of patients achieving sUA <4 mg/dL) at 3 - 12 months

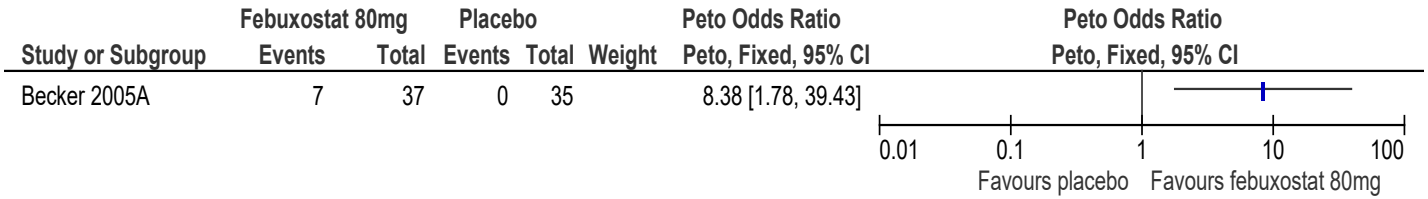


Figure 73: mixed CKD population – febuxostat 120mg versus placebo – Frequency of flares at <3months

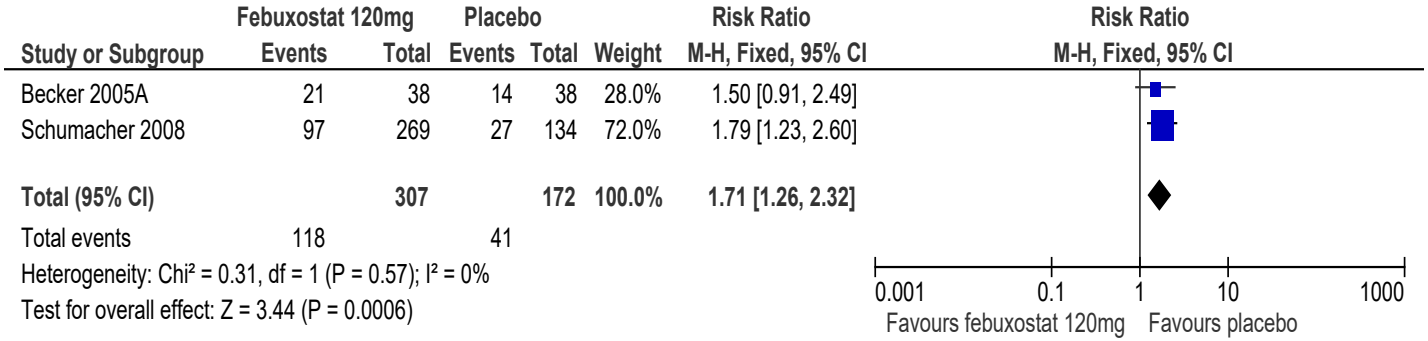


Figure 74: mixed CKD population – febuxostat 120mg versus placebo – Cardiovascular adverse events at 3 – 12 months

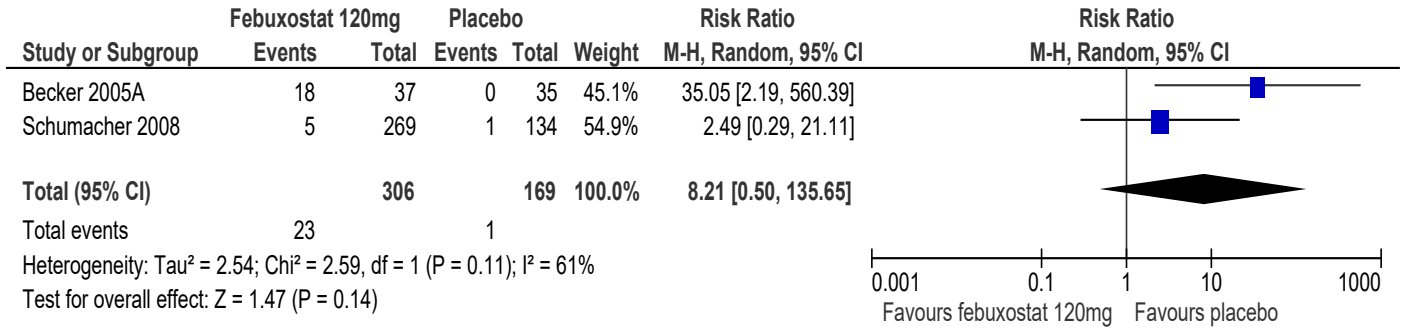


Figure 75: mixed CKD population – febuxostat 120mg versus placebo – Gastrointestinal adverse events (abdominal pain)at <3 months

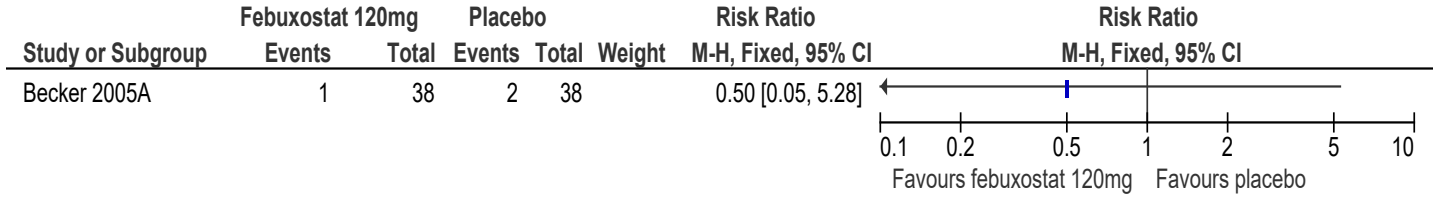


Figure 67: mixed CKD population – febuxostat 120mg versus placebo – Gastrointestinal adverse events (diarrhoea)at <3 months

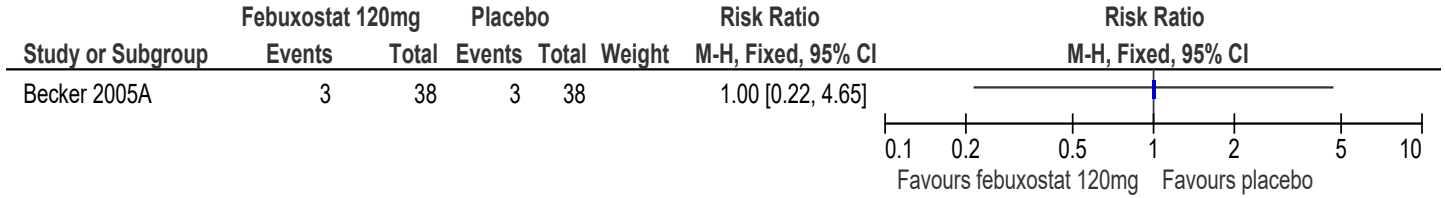


Figure 76: mixed CKD population – febuxostat 120mg versus placebo – Gastrointestinal adverse events at 3 – 12 months

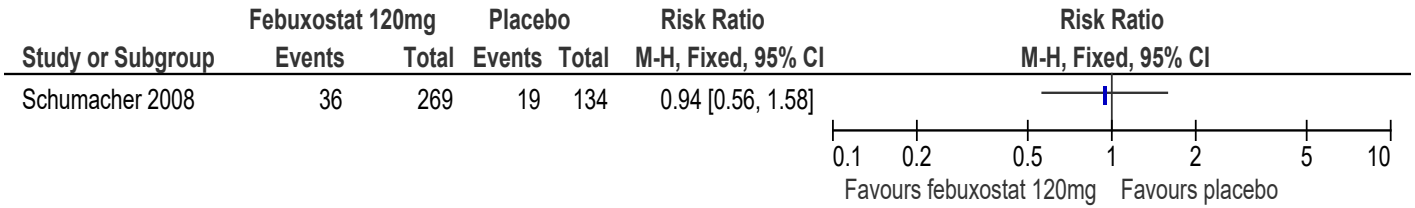


Figure 77: mixed CKD population – febuxostat 120mg versus placebo – Serum urate level, change from baseline at <3 months

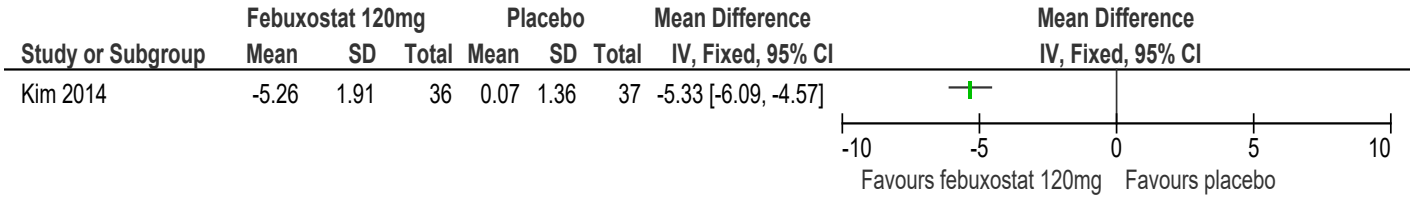


Figure 78: mixed CKD population – febuxostat 120mg versus placebo – Serum urate level (number of people achieving sUA <6 mg/dL) at 3 – 12 months

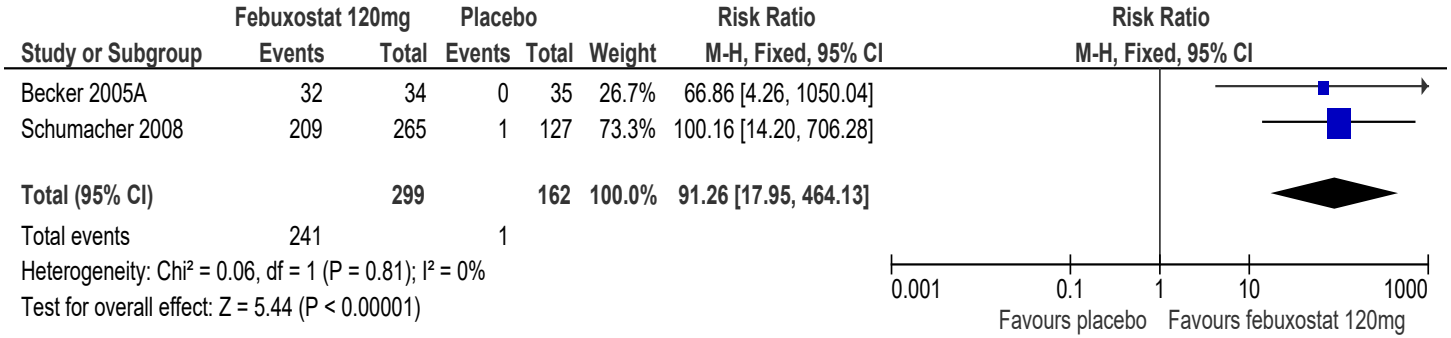


Figure 79: mixed CKD population – febuxostat 120mg versus placebo – Serum urate level (number of people achieving sUA <5 mg/dL) at 3 – 12 months

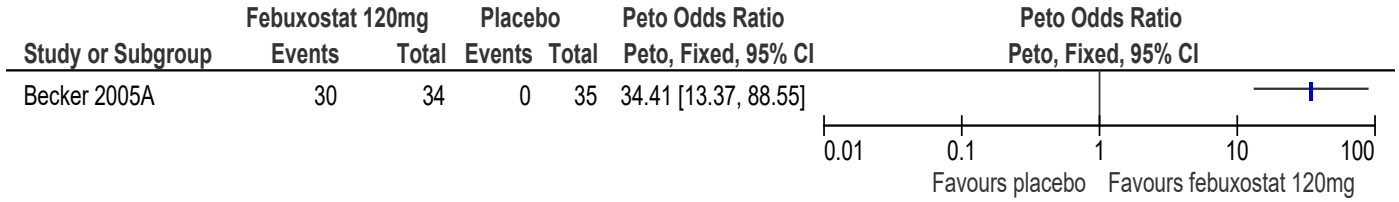
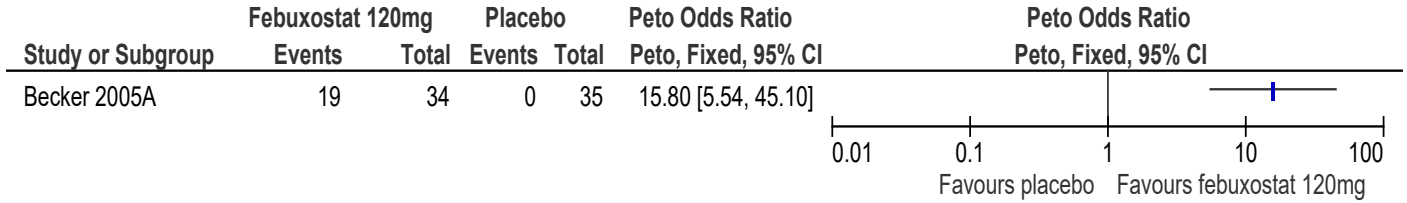


Figure 80: mixed CKD population – febuxostat 120mg versus placebo – Serum urate level (number of people achieving sUA <4 mg/dL) at 3 – 12 months



E.2 Second-line treatment

Figure 81: No CKD population – allopurinol 300mg versus placebo – Joint tenderness (arthralgia) at 3 -12 months

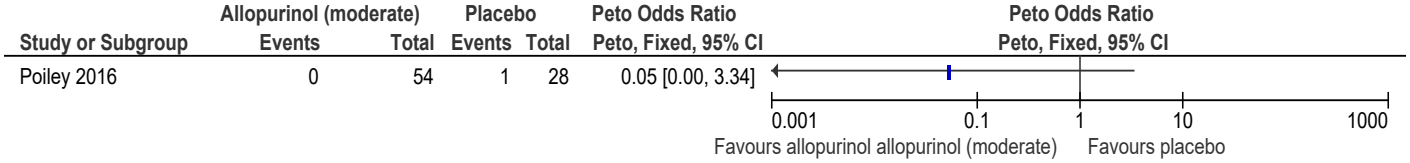


Figure 82: No CKD population – allopurinol 300mg versus placebo – Cardiovascular adverse events at 3 – 12 months

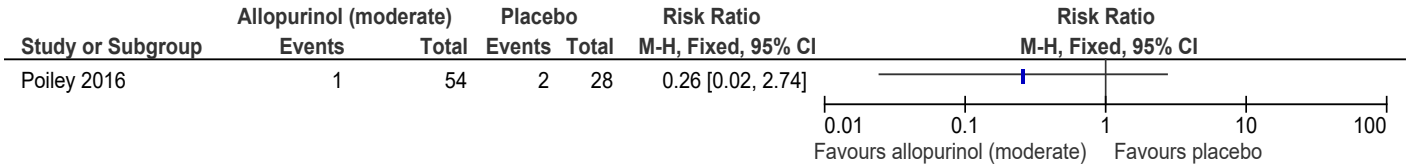


Figure 83: No CKD population – allopurinol 300mg versus placebo – Serum urate level (change score) at 3 – 12 months

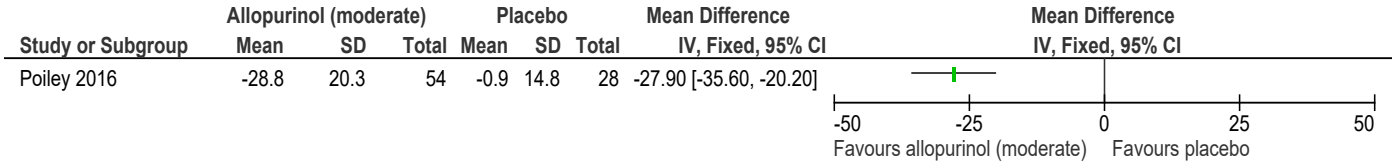


Figure 84: No CKD population – allopurinol 300mg versus placebo – Serum urate level (number of patients sUA <6mg/dL) at 3 – 12 months

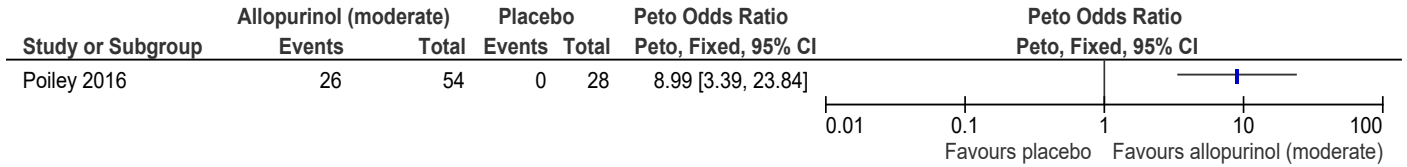
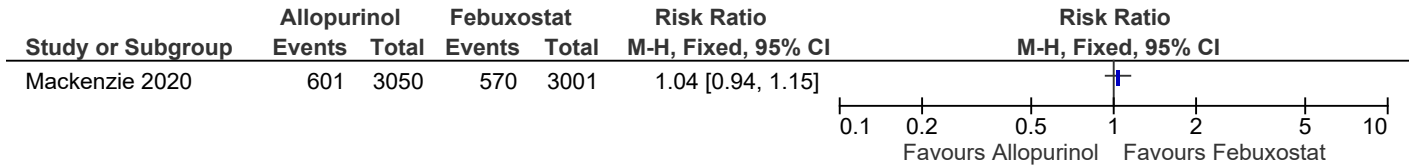


Figure 85: Mixed CKD population – allopurinol (mixed dose 279 mg on average) versus febuxostat (mixed dose 81 mg on average) - Cardiovascular disorders (number of patients with at least 1 event) at >12 months



This was reported separately in the study as cardiac disorders and vascular disorders, numbers were patients with at least one event (overall and within each system organ class).

Figure 86: Mixed CKD population – allopurinol (mixed dose 279 mg on average) versus febuxostat (mixed dose 81 mg on average) - Renal and urinary disorders (number of patients with at least 1 event) at >12 months

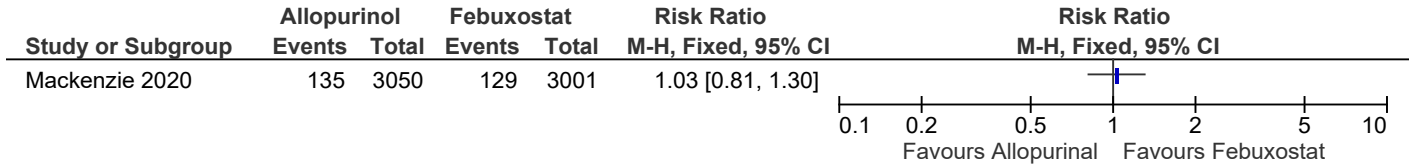


Figure 87: Mixed CKD population – allopurinol (mixed dose 279 mg on average) versus febuxostat (mixed dose 81 mg on average) - Gastrointestinal disorders (number of patients with at least 1 event) at >12 months

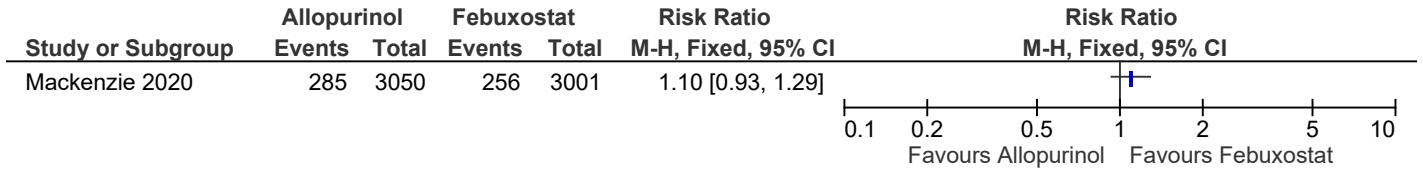


Figure 88: Mixed CKD population – allopurinol (mixed dose 279 mg on average) versus febuxostat (mixed dose 81 mg on average) - Number of people achieving sUA <6 mg/dL at 1 year

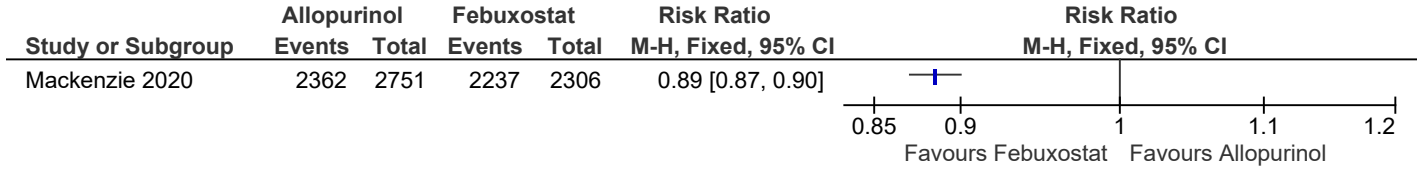


Figure 89: Mixed CKD population – allopurinol (mixed dose 279 mg on average) versus febuxostat (mixed dose 81 mg on average) - Number of people achieving sUA <6 mg/dL at 2 years

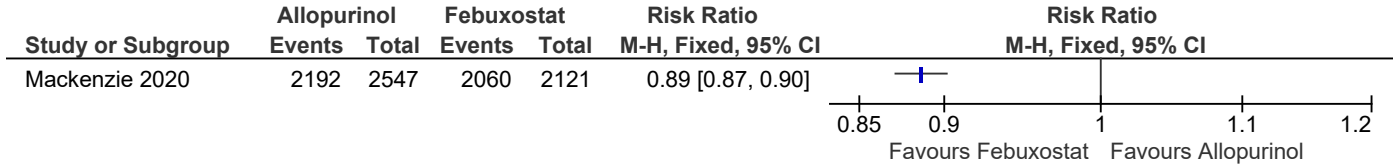


Figure 90: Mixed CKD population – allopurinol (mixed dose 279 mg on average) versus febuxostat (mixed dose 81 mg on average) - Number of people achieving sUA <6 mg/dL at 3 years

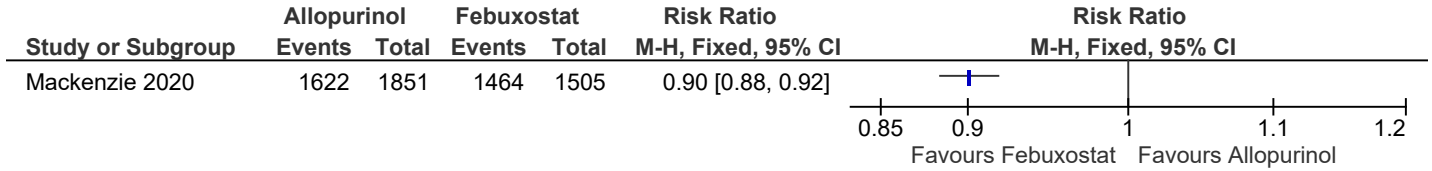


Figure 91: Mixed CKD population – allopurinol (mixed dose 279 mg on average) versus febuxostat (mixed dose 81 mg on average) - Number of people achieving sUA <6 mg/dL at 4 years

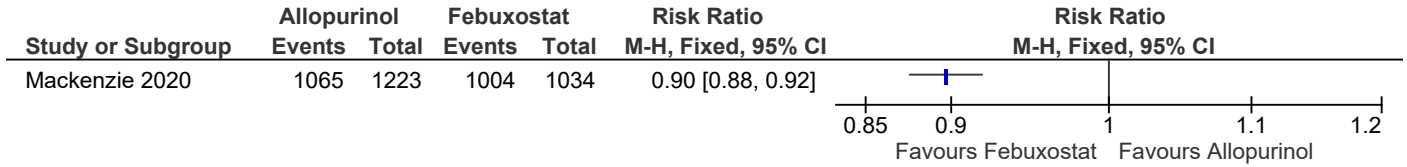


Figure 92: Mixed CKD population – allopurinol (mixed dose 279 mg on average) versus febuxostat (mixed dose 81 mg on average) - Number of people achieving sUA <6 mg/dL at 5 years

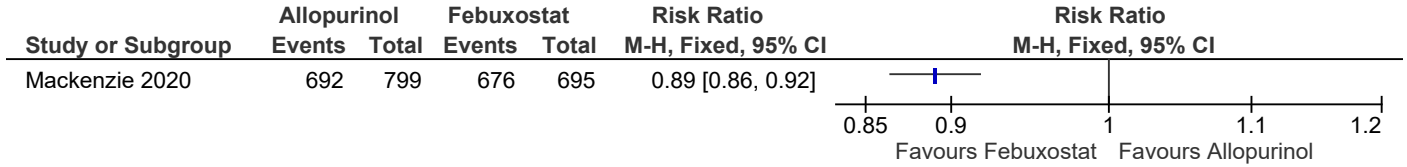


Figure 93: Mixed CKD population – allopurinol (mixed dose 279 mg on average) versus febuxostat (mixed dose 81 mg on average) - Number of people achieving sUA <6 mg/dL at 6 years

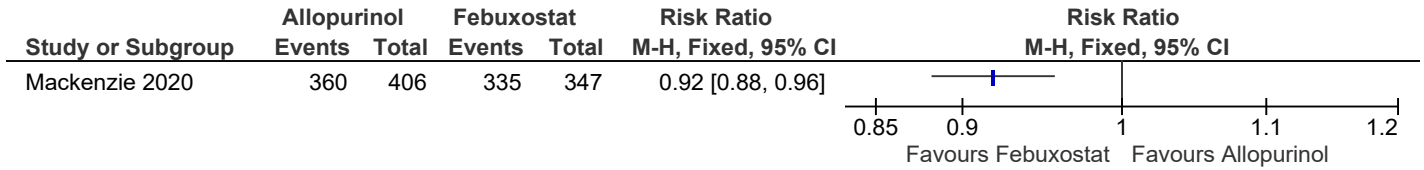


Figure 94: Mixed CKD population – allopurinol (mixed dose 279 mg on average) versus febuxostat (mixed dose 81 mg on average) - Number of people achieving sUA <6 mg/dL at 7 years

Study or Subgroup	Allopurinol Events	Allopurinol Total	Febuxostat Events	Febuxostat Total	Risk Ratio M-H, Fixed, 95% CI
Mackenzie 2020	76	85	81	83	0.92 [0.85, 0.99]

Figure 95: Mixed CKD population – allopurinol (mixed dose 279 mg on average) versus febuxostat (mixed dose 81 mg on average) - Number of people achieving sUA <5mg/dL at 1 year

Study or Subgroup	Allopurinol Events	Allopurinol Total	Febuxostat Events	Febuxostat Total	Risk Ratio M-H, Fixed, 95% CI
Mackenzie 2020	1270	2751	2057	2306	0.52 [0.50, 0.54]

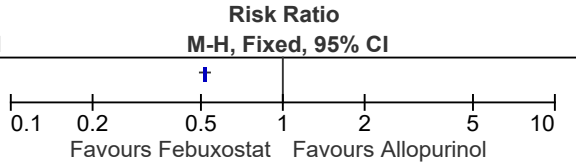


Figure 96: Mixed CKD population – allopurinol (mixed dose 279 mg on average) versus febuxostat (mixed dose 81 mg on average) - Number of people achieving sUA <5mg/dL at 2 years

Study or Subgroup	Allopurinol Events	Allopurinol Total	Febuxostat Events	Febuxostat Total	Risk Ratio M-H, Fixed, 95% CI
Mackenzie 2020	1246	2547	1936	2121	0.54 [0.51, 0.56]

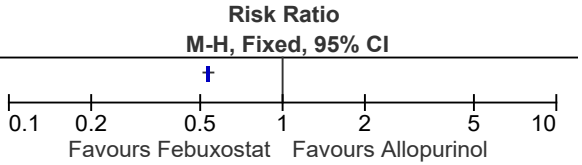


Figure 97: Mixed CKD population – allopurinol (mixed dose 279 mg on average) versus febuxostat (mixed dose 81 mg on average) - Number of people achieving sUA <5mg/dL at 3 years

Study or Subgroup	Allopurinol Events	Allopurinol Total	Febuxostat Events	Febuxostat Total	Risk Ratio M-H, Fixed, 95% CI
Mackenzie 2020	948	1851	1378	1505	0.56 [0.53, 0.59]

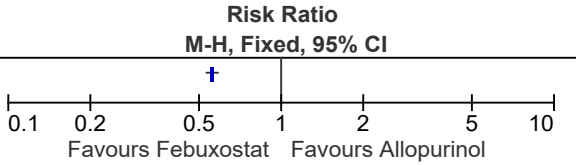


Figure 98: Mixed CKD population – allopurinol (mixed dose 279 mg on average) versus febuxostat (mixed dose 81 mg on average) - Number of people achieving sUA <5mg/dL at 4 years

Study or Subgroup	Allopurinol Events	Allopurinol Total	Febuxostat Events	Febuxostat Total	Risk Ratio M-H, Fixed, 95% CI
Mackenzie 2020	647	1223	937	1034	0.58 [0.55, 0.62]

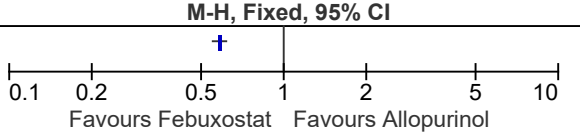


Figure 99: Mixed CKD population – allopurinol (mixed dose 279 mg on average) versus febuxostat (mixed dose 81 mg on average) - Number of people achieving sUA <5mg/dL at 5 years

Study or Subgroup	Allopurinol Events	Allopurinol Total	Febuxostat Events	Febuxostat Total	Risk Ratio M-H, Fixed, 95% CI
Mackenzie 2020	429	799	635	695	0.59 [0.55, 0.63]

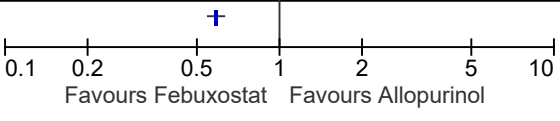


Figure 100: Mixed CKD population – allopurinol (mixed dose 279 mg on average) versus febuxostat (mixed dose 81 mg on average) - Number of people achieving sUA <5mg/dL at 6 years

Study or Subgroup	Allopurinol Events	Allopurinol Total	Febuxostat Events	Febuxostat Total	Risk Ratio M-H, Fixed, 95% CI
Mackenzie 2020	229	406	317	347	0.62 [0.56, 0.68]

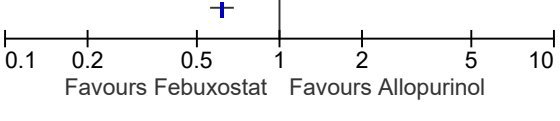


Figure 101: Mixed CKD population – allopurinol (mixed dose 279 mg on average) versus febuxostat (mixed dose 81 mg on average) - Number of people achieving sUA <5mg/dL at 7 years

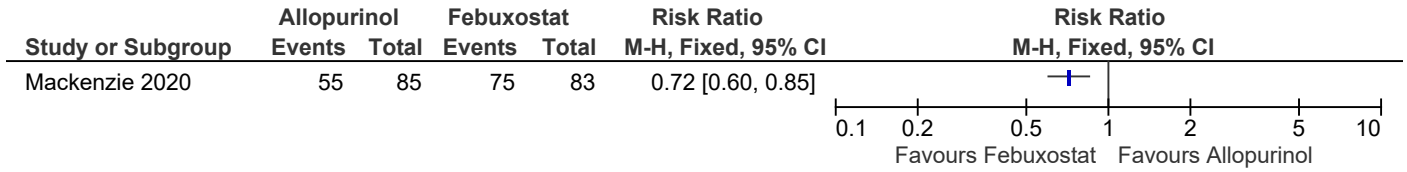
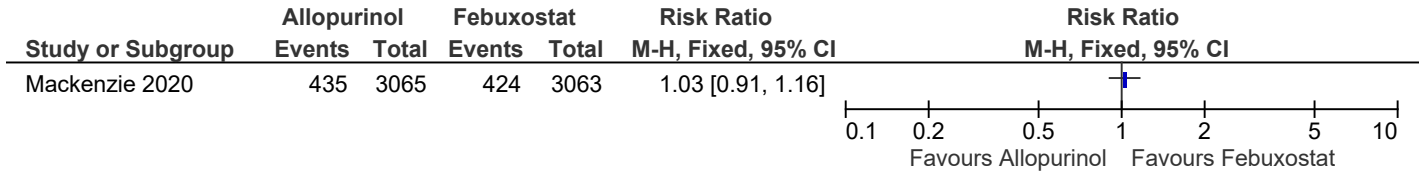


Figure 102: Mixed CKD population – allopurinol (mixed dose 279 mg on average) versus febuxostat (mixed dose 81 mg on average) - Hospitalisation at >12 months



This is a sum of all hospitalisations reported in the study: hospitalisation for non-fatal myocardial infarction or biomarker-positive acute coronary syndrome; hospitalisation for heart failure; hospitalisation for unstable, new or worsening angina; hospitalisation for coronary revascularisation; hospitalisation for cerebrovascular revascularisation; hospitalisation for transient ischaemic attack; hospitalisation for non-fatal cardiac arrest; hospitalisation for venous and peripheral arterial vascular thrombotic event; hospitalisation for arrhythmia with no evidence of ischaemia.

Appendix F – GRADE tables

First-line treatment

Table 26: Clinical evidence summary: non-CKD population – allopurinol 300mg vs placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Allopurinol 300mg	Placebo	Relative (95% CI)	Absolute (95% CI)		
Flares (new or recurrent flares) – short-term (< 3 months) (30 days)												
1	randomised trials	not serious	not serious	not serious	very serious [a]	none	2/26 (7.7%)	3/25 (12.0%)	RR 0.64 (0.12 to 3.52)	43 fewer per 1,000 (from 106 fewer to 302 more)	⊕⊕◯◯ LOW	CRITICAL
Adverse events (Colchicine reductions due to gastrointestinal symptoms)												
1	randomised trials	not serious	not serious	not serious	very serious [a]	none	8/26 (30.8%)	12/25 (48.0%)	RR 0.64 (0.32 to 1.30)	173 fewer per 1,000 (from 326 fewer to 144 more)	⊕⊕◯◯ LOW	CRITICAL

a. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. GRADE default MIDs used for all outcomes. For dichotomous outcomes MIDs were taken to be RRs of 0.8 and 1.25.

Table 27: Clinical evidence summary: non-CKD population – allopurinol (300mg) vs febuxostat (80 mg)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Allopurinol 300mg	Febuxostat 80 mg	Relative (95% CI)	Absolute (95% CI)		
Frequency of flares at 3-12 months												
2	randomised trials	serious [a]	serious [b]	not serious	very serious [c]	none	111/277 (40.1%)	105/280 (37.5%)	**RR 1.56** (0.49 to 4.96)	**210 more per 1,000** (from 191 fewer to 1,000 more)	⊕◯◯◯ VERY LOW	CRITICAL
Renal adverse events at 3-12 months												
1	randomised trials	serious [a]	not serious	not serious	not serious	none	6/197 (3%)	16/200 (8%)	**RR 0.38** (0.15 to 0.95)	**50 fewer per 1,000** (from 68 fewer to 4 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Gastrointestinal adverse events at 3-12 months												
1	randomised trials	serious [a]	not serious	not serious	very serious [c]	none	4/80 (5.0%)	1/80 (1.3%)	**RR 4.00** (0.46 to 35.01)	**38 more per 1,000** (from 7 fewer to 425 more)	⊕◯◯◯ VERY LOW	CRITICAL
Serum urate level, final value (high is poor) at <3 months												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Allopurinol 300mg	Febuxostat 80 mg	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	not serious	serious [c]	none	80	80	-	MD **47.32 higher** (19.02 higher to 75.62 higher)	⨁⨁◯◯ LOW	CRITICAL

Changed Serum urate level, final value (high is poor) at 3-12 months

1	randomised trials	serious [a]	not serious	not serious	serious [c]	none	80	80	-	MD **27.97 higher** (4.43 higher to 51.51 higher)	⨁⨁◯◯ LOW	CRITICAL

Serum urate level number of patients reaching 6mg/dL(<360micromol)/L at <3 months

1	randomised trials	serious [a]	not serious	not serious	serious [c]	none	45/80 (56.3%)	60/80 (75.0%)	**RR 0.75** (0.60 to 0.94)	**188 fewer per 1,000** (from 300 fewer to 45 fewer)	⨁⨁◯◯ LOW	CRITICAL

Serum urate level number of patients reaching 6mg/dL(<360micromol)/L at 3-12 months

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Allopurinol 300mg	Febuxostat 80 mg	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	not serious	not serious	none	70/80 (87.5%)	80/80 (100.0%)	**RR 0.88** (0.80 to 0.95)	**120 fewer per 1,000** (from 200 fewer to 50 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 or 2 increments because: The point estimate varies widely across studies,I2=72%, subgroup analysis could not be performed so a random effects model was used.

c. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. GRADE default MIDs used for all outcomes. For dichotomous outcomes MIDs were taken to be RRs of 0.8 and 1.25. For continuous outcomes 0.5 x baseline SD was calculated, serum urate level: 39 µmol/L.

Table 28: Clinical evidence summary: non-CKD population – febuxostat 80 mg vs placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	First line - no CKD - Febuxostat (80mg)	placebo	Relative (95% CI)	Absolute (95% CI)		
Serum urate levels (number of patients achieving sUA 6mg/dL; 2 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	First line - no CKD - Febuxostat (80mg)	placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	not serious	none	22/78 (28.2%)	0/78 (0.0%)	**Peto OR 10.11** (4.11 to 24.84)	**280 more per 1,000** (from 180 more to 380 more)	⊕⊕⊕⊕ HIGH[a]	CRITICAL

Serum urate levels (number of patients achieving sUA 6mg/dL; 3-12 months)

1	randomised trials	not serious	not serious	not serious	not serious	none	25/78 (32.1%)	0/78 (0.0%)	**Peto OR 10.66** (4.54 to 25.01)	**320 more per 1,000** (from 220 more to 430 more)	⊕⊕⊕⊕ HIGH[a]	CRITICAL

Serum urate levels (number of patients achieving sUA 5mg/dL; 2 months)

1	randomised trials	not serious	not serious	not serious	not serious	none	9/78 (11.5%)	0/78 (0.0%)	**Peto OR 8.24** (2.15 to 31.52)	**120 more per 1,000** (from 40 more to 190 more)	⊕⊕⊕⊕ HIGH[a]	CRITICAL

Serum urate levels (number of patients achieving sUA 5mg/dL; 3-12 months)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	First line - no CKD - Febuxostat (80mg)	placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	not serious	none	12/78 (15.4%)	0/78 (0.0%)	**Peto OR 8.61** (2.66 to 27.85)	**150 more per 1,000** (from 70 more to 240 more)	⨁⨁⨁⨁ HIGH[a]	CRITICAL

a. GRADE default MIDs used for all outcomes. For dichotomous outcomes MIDs were taken to be RRs of 0.8 and 1.25.

Table 29: Clinical evidence summary: mixed CKD population – allopurinol (mild severity dose 100 - 200mg) vs placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	First line - Mixed CKD - Allopurinol (mild 100-200mg)	placebo	Relative (95% CI)	Absolute (95% CI)		

Joint inflammation (evidence of new joint inflammation, <3 months)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	First line - Mixed CKD - Allopurinol (mild 100-200mg)	placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	very serious [a]	none	1/17 (5.9%)	0/17 (0.0%)	**OR 7.39** (0.15 to 372.38)	**60 more per 1,000** (from 90 fewer to 210 more)	⨁⨁◯◯ LOW	CRITICAL
Joint tenderness (pain in a new joint, <3 months)												
1	randomised trials	not serious	not serious	not serious	very serious [a]	none	2/17 (11.8%)	1/17 (5.9%)	**RR 2.00** (0.20 to 20.04)	**59 more per 1,000** (from 47 fewer to 1,000 more)	⨁⨁◯◯ LOW	CRITICAL
Adverse events (withdrawal due to AE, <3 months)												
1	randomised trials	not serious	not serious	not serious	very serious [a]	none	1/17 (5.9%)	2/17 (11.8%)	**RR 0.50** (0.05 to 5.01)	**59 fewer per 1,000** (from 112 fewer to 472 more)	⨁⨁◯◯ LOW	CRITICAL

a. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. GRADE default MIDs used for all outcomes. For dichotomous outcomes MIDs were taken to be RRs of 0.8 and 1.25.

Unclear/mixed treatment line

Table 30: Clinical evidence summary: stage 3 CKD population - febuxostat 80 mg vs placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	First line - Stage 3 CKD - Febuxostat (80mg)	placebo	Relative (95% CI)	Absolute (95% CI)		
Frequency of flares (number of participants with 1 or more flares; 3 months)												
1	randomised trials	not serious	not serious	not serious	not serious	none	14/37 (37.8%)	4/38 (10.5%)	**RR 3.59** (1.30 to 9.92)	**273 more per 1,000** (from 32 more to 939 more)	⨁⨁⨁⨁ HIGH	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	First line - Stage 3 CKD - Febuxostat (80mg)	placebo	Relative (95% CI)	Absolute (95% CI)		
Adverse events (Cardiovascular [hypertension]; >3 months)												
1	randomised trials	not serious	not serious	not serious	very serious [a]	none	1/38 (2.6%)	1/38 (2.6%)	**RR 1.00** (0.06 to 15.41)	**0 fewer per 1,000** (from 25 fewer to 379 more)	⊕⊕◯◯ LOW	CRITICAL
Adverse events (renal/urinary [renal failure, nephrolithiasis (kidney stones)]; >3 months)												
1	randomised trials	not serious	not serious	not serious	very serious [a]	none	0/38 (0.0%)	2/38 (5.3%)	**OR 0.13** (0.01 to 2.15)	**45 fewer per 1,000** (from 52 fewer to 54 more)	⊕⊕◯◯ LOW	CRITICAL
Adverse events (gastrointestinal; >3 months)												
1	randomised trials	not serious	not serious	not serious	not serious	none	0/38 (0.0%)	0/38 (0.0%)	not estimable	0 fewer per 1,000 (from 50 fewer to 50 more)	⊕⊕⊕⊕ HIGH	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	First line - Stage 3 CKD - Febuxostat (80mg)	placebo	Relative (95% CI)	Absolute (95% CI)		
Serum urate levels (number of patients achieving sUA 6mg/dL; 3 months)												
1	randomised trials	not serious	not serious	not serious	not serious	none	22/37 (59.5%)	0/38 (0.0%)	OR 16.95 (6.31 to 45.50)	590 more per 1,000 (from 430 more to 750 more)	⨁⨁⨁⨁ HIGH	CRITICAL

a. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. GRADE default MIDs used for all outcomes. For dichotomous outcomes MIDs were taken to be RRs of 0.8 and 1.25.

b. Zero events in both arms - Imprecision was measured using sample size: no imprecision (sample size>350, serious imprecision (sample size >70 to <350), very serious imprecision (sample size<70)

Table 31: Clinical evidence summary: non-CKD population – allopurinol 300mg vs febuxostat 80 mg

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Allopurinol 300mg	febuxostat 80mg	Relative (95% CI)	Absolute (95% CI)		
Cardiovascular adverse events at 3-12 months												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Allopurinol 300mg	febuxostat 80mg	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	1/168 (0.6%)	0/168 (0.0%)	OR 7.39 (0.15 to 372.38)	10 more per 1,000 (from 10 fewer to 20 more)	⨁◯◯◯ VERY LOW	CRITICAL

Renal adverse events at 3-12 months

1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	2/168 (1.2%)	7/168 (4.2%)	RR 0.29 (0.06 to 1.36)	30 fewer per 1,000 (from 39 fewer to 15 more)	⨁◯◯◯ VERY LOW	CRITICAL

Gastrointestinal adverse events at 3-12 months

1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	4/168 (2.4%)	2/168 (1.2%)	RR 2.00 (0.37 to 10.77)	12 more per 1,000 (from 8 fewer to 116 more)	⨁◯◯◯ VERY LOW	CRITICAL

Serum urate level, change score (high is poor) at 3-12 months

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Allopurinol 300mg	febuxostat 80mg	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	159	158	-	MD **45.6 higher** (15.89 higher to 75.31 higher)	⨁⨁◯◯ LOW	CRITICAL

Serum urate level number of patients reaching 6mg/dL(<360micromol) at 3 -12 months

1	randomised trials	serious [a]	not serious	not serious	not serious	none	55/159 (34.6%)	93/158 (58.9%)	**RR 0.59** (0.46 to 0.75)	**241 fewer per 1,000** (from 318 fewer to 147 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. GRADE default MIDs used for all outcomes. For dichotomous outcomes MIDs were taken to be RRs of 0.8 and 1.25. For continuous outcomes 0.5 x baseline SD was calculated, serum urate level: 68.6.

Table 32: Clinical evidence summary: mixed CKD population – allopurinol 300mg vs placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Allopurinol 300mg	placebo	Relative (95% CI)	Absolute (95% CI)		
Frequency of flares at <3 months												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	61/268 (22.8%)	27/134 (20.1%)	**RR 1.13** (0.76 to 1.69)	**26 more per 1,000** (from 48 fewer to 139 more)	⊕◯◯◯ VERY LOW	CRITICAL
Cardiovascular adverse events at 3-12 months												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	1/268 (0.4%)	1/134 (0.7%)	**RR 0.50** (0.03 to 7.93)	**4 fewer per 1,000** (from 7 fewer to 52 more)	⊕◯◯◯ VERY LOW	CRITICAL
Gastrointestinal adverse events (diarrhoea) at 3-12 months												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	17/268 (6.3%)	11/134 (8.2%)	**RR 0.77** (0.37 to 1.6)	**19 fewer per 1000 (from 52 fewer to 49 more)**	⊕◯◯◯ VERY LOW	CRITICAL
Gastrointestinal adverse events (nausea and vomiting) at 3-12 months												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Allopurinol 300mg	placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	Very serious [a]	not serious	not serious	very serious [b]	none	6/268 (2.2%)	5/134 (3.7%)	**RR 0.6 (0.19 to 1.93)**	**15 fewer per 1000 (from 30 fewer to 34 more)**	⊕◯◯◯ VERY LOW	CRITICAL
Gastrointestinal adverse events (gastro and abdominal pain) at 3-12 months												
1	randomised trials	Very serious [a]	not serious	not serious	very serious [b]	none	6/268 (2.2%)	3/134 (2.2%)	**RR 1 (0.25 to 3.94)**)	**0 fewer per 1000 (from 17 fewer to 66 more)**	⊕◯◯◯ VERY LOW	CRITICAL
Serum urate level (change from baseline; mg/dL; <3 months)												
1	randomised trials	serious [a]	not serious	not serious	not serious	none	36	37	-	MD **3.83 lower** (4.47 lower to 3.19 lower)	⊕⊕⊕◯ MODERATE	CRITICAL
Number of people achieving sUA <6.0 mg/dL at 3-12 months												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Allopurinol 300mg	placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	not serious	none	102/263 (38.8%)	1/127 (0.8%)	**RR 49.25** (6.95 to 349.02)	**380 more per 1,000** (from 47 more to 1,000 more)	⨁⨁◯◯ LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. GRADE default MIDs used for all outcomes For dichotomous outcomes MIDs were taken to be RRs of 0.8 and 1.25. For continuous outcomes 0.5 x baseline SD was calculated, serum urate level: 0.55.

Table 33: Clinical evidence summary: mixed CKD population – allopurinol 300mg vs febuxostat 80 mg

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Allopurinol 300mg	febuxostat 80mg	Relative (95% CI)	Absolute (95% CI)		
Frequency of flares at <3 months												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Allopurinol 300mg	febuxostat 80mg	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	113/519 (21.8%)	128/517 (24.8%)	**RR 0.88** (0.70 to 1.10)	**30 fewer per 1,000** (from 74 fewer to 25 more)	⨁◯◯◯ VERY LOW	CRITICAL

Frequency of flares at 3-12 months (1 study - YU 2016 reported outcomes at 3 months exactly)

2	randomised trials	very serious [a]	very serious [c]	not serious	very serious [b]	none	35/227 (15.4%)	29/226 (12.8%)	**RR 1.31** (0.48 to 3.52)	**40 more per 1,000** (from 67 fewer to 323 more)	⨁◯◯◯ VERY LOW	CRITICAL

Cardiovascular adverse events at 3-12 months

2	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	6/1024 (0.6%)	12/1023 (1.2%)	**RR 0.50** (0.19 to 1.33)	**6 fewer per 1,000** (from 10 fewer to 4 more)	⨁◯◯◯ VERY LOW	CRITICAL

Renal adverse events at 3-12 months

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Allopurinol 300mg	febuxostat 80mg	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	very serious [b]	none	2/172 (1.2%)	4/172 (2.3%)	**RR 0.50** (0.09 to 2.69)	**12 fewer per 1,000** (from 21 fewer to 39 more)	⊕⊕◯◯ LOW	CRITICAL
Gastrointestinal adverse events (diarrhoea) at 3-12 months												
3	randomised trials	serious [a]	not serious	not serious	serious [b]	none	82/1277 (6.4%)	71/1279 (5.6%)	**RR 1.16** (0.85 to 1.57)	**10 more per 1000 (from 9 fewer to 34 more)**	⊕⊕◯◯ LOW	CRITICAL
Gastrointestinal adverse events (nausea and vomiting) at 3-12 months												
2	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	9/521 (1.7%)	17/523 (3.3%)	**RR 0.53** (0.24 to 1.18)	**15 fewer per 1000 (from 24 fewer to 6 more)**	⊕◯◯◯ VERY LOW	CRITICAL
Gastrointestinal adverse events (pain/discomfort) at 3-12 months												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Allopurinol 300mg	febuxostat 80mg	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	very serious [a]	not serious	not serious	Very serious [b]	none	7/521 (1.3%)	11/523 (2.1%)	**RR 0.64** (0.25 to 1.63)	**8** fewer per 1000 (from 16 fewer to 13 more)	⨁◯◯◯ VERY LOW	CRITICAL
Gastrointestinal adverse events (disorders) at 3-12 months												
2	randomised trials	very serious [a]	not serious	not serious	Very serious [b]	none	5/425 (1.2%	10/428 (2.3%)	**RR 0.5** (0.17 to 1.46)	**12** fewer per 1000 (from 20 fewer to 11 more)	⨁◯◯◯ VERY LOW	CRITICAL
Total adverse events at 3-12 months (1 study - YU 2016 reported outcomes at 3 months exactly)												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	35/55 (63.6%)	38/54 (70.4%)	**RR 0.90** (0.69 to 1.18)	**70 fewer per 1,000** (from 218 fewer to 127 more)	⨁⨁◯◯ LOW	CRITICAL
Tophi at 3-12 months												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Allopurinol 300mg	febuxostat 80mg	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	35/254 (13.8%)	33/257 (12.8%)	**RR 1.07** (0.69 to 1.67)	**9 more per 1,000** (from 40 fewer to 86 more)	⊕◯◯◯ VERY LOW	CRITICAL

Tophi - (change in number of Tophi from baseline) at 3 - 12 months

1	randomised trials	not serious	not serious	not serious	not serious	none	172	172	-	MD **0.13 higher** (0.12 lower to 0.38 higher)	⊕⊕⊕⊕ HIGH	CRITICAL

Serum urate levels (change from baseline; <3 months)

1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	36	35	-	MD **0.85 higher** (0.2 higher to 1.5 higher)	⊕⊕◯◯ LOW	CRITICAL

Serum urate level, % change at 3-12 months

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Allopurinol 300mg	febuxostat 80mg	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	253	256	-	MD **11.74 higher** (8.73 higher to 14.75 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Serum urate level, change score (high is poor) at 3-12 months

1	randomised trials	not serious	not serious	not serious	serious [b]	none	172	172	-	MD **0.92 higher** (0.48 higher to 1.36 higher)	⨁⨁⨁◯ MODERATE	CRITICAL

Number of patients with sUA <6mg/dL at <3 months

1	randomised trials	serious [a]	not serious	not serious	not serious	none	13/55 (23.6%)	38/54 (70.4%)	**RR 0.34** (0.20 to 0.56)	**464 fewer per 1,000** (from 563 fewer to 310 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL

Number of people achieving sUA <6.0 mg/dL at 3-12 months (1 study - YU 2016 reported outcomes at 3 months exactly)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Allopurinol 300mg	febuxostat 80mg	Relative (95% CI)	Absolute (95% CI)		
4	randomised trials	very serious [a]	very serious [c]	not serious	not serious	none	514/1316 (39.1%)	907/1309 (69.3%)	**RR 0.51** (0.41 to 0.64)	**340 fewer per 1,000** (from 409 fewer to 249 fewer)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.; GRADE default MIDs used for all other outcomes. For dichotomous outcomes MIDs were taken to be RRs of 0.8 and 1.25. For continuous outcomes 0.5 x baseline SD was calculated: serum urate level 0.62, tophi 3.29. c. Downgraded by 1 or 2 increments because: The point estimate varies widely across studies, could not be explained by subgroup analysis.

Table 34: Clinical evidence summary: mixed CKD population – allopurinol 300mg vs febuxostat 120mg

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Allopurinol 300mg	febuxostat 120mg	Relative (95% CI)	Absolute (95% CI)		
Frequency of flares at <3 months												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Allopurinol 300mg	febuxostat 120mg	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	very serious [a]	not serious	not serious	not serious	none	113/519 (21.8%)	187/519 (36.0%)	**RR 0.60** (0.50 to 0.74)	**144 fewer per 1,000** (from 180 fewer to 94 fewer)	⨁⨁◯◯ LOW	CRITICAL
Cardiovascular adverse events at 3-12 months												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	1/268 (0.4%)	5/269 (1.9%)	**RR 0.20** (0.02 to 1.71)	**15 fewer per 1,000** (from 18 fewer to 13 more)	⨁◯◯◯ VERY LOW	CRITICAL
Gastrointestinal adverse events (diarrhoea) at 3-12 months												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	25/521 (4.8%)	26/520 (5%)	**RR 0.96** (0.56 to 1.64)	**2 fewer per 1,000** (from 22 fewer to 31 more)	⨁◯◯◯ VERY LOW	CRITICAL
Gastrointestinal adverse events (nausea and vomiting) at 3-12 months												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Allopurinol 300mg	febuxostat 120mg	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	9/521 (1.7%)	13/520 (2.5%)	**RR 0.69** (0.3 to 1.6)	**25 fewer per 1,000** (from 18 fewer to 15 more)	⨁◯◯◯ VERY LOW	CRITICAL
Gastrointestinal adverse events (gastro and abdominal pain) at 3-12 months												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	7/521 (1.3%)	8/520 (1.5%)	**RR 0.88** (0.32 to 2.39)	**2 fewer per 1,000** (from 10 fewer to 21 more)	⨁◯◯◯ VERY LOW	CRITICAL

Tophi 3 -12 months

1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	33/257 (12.8%)	35/254 (13.8%)	**RR 0.93** (0.60 to 1.45)	**10 fewer per 1,000** (from 55 fewer to 62 more)	⨁◯◯◯ VERY LOW	CRITICAL

Serum urate levels (change from baseline; <3 months)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Allopurinol 300mg	febuxostat 120mg	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	36	36	-	MD **1.5 higher** (0.72 higher to 2.28 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Serum urate level, change score (high is poor) at 3-12 months												
1	randomised trials	very serious [a]	not serious	not serious	not serious	none	253	251	-	MD **17.47 lower** (20.57 lower to 14.37 lower)	⨁⨁◯◯ LOW	CRITICAL
Number of people achieving sUA <6.0 mg/dL at 3-12 months												
2	randomised trials	very serious [a]	not serious	not serious	not serious	none	190/505 (37.6%)	402/507 (79.3%)	**RR 0.47** (0.42 to 0.54)	**420 fewer per 1,000** (from 460 fewer to 365 fewer)	⨁⨁◯◯ LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. GRADE default MIDs used for all other outcomes. For dichotomous outcomes MIDs were taken to be RRs of 0.8 and 1.25. For continuous outcomes 0.5 x baseline SD was calculated, serum urate level: 0.56.

Table 35: Clinical evidence summary: mixed CKD population – febuxostat 80 mg vs placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Febuxostat 80mg	placebo	Relative (95% CI)	Absolute (95% CI)		
Frequency of flares at <3 months												
2	randomised trials	very serious [b]	not serious	not serious	serious [a]	none	90/302 (29.8%)	41/172 (23.8%)	**RR 1.32** (0.96 to 1.81)	**76 more per 1,000** (from 10 fewer to 193 more)	⨁◯◯◯ VERY LOW	CRITICAL
Frequency of flares at 3-12 months												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	97/357 (27.2%)	74/357 (20.7%)	**RR 1.31** (1.01 to 1.71)	**64 more per 1,000** (from 2 more to 147 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Cardiovascular adverse events at 3-12 months												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Febuxostat 80mg	placebo	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	not serious	not serious	not serious	very serious [a]	none	13/624 (2.1%)	11/490 (2.2%)	**RR 1.00** (0.44 to 2.28)	**0 fewer per 1,000** (from 13 fewer to 29 more)	⨁⨁◯◯ LOW	CRITICAL
Gastrointestinal adverse events (abdominal pain) at <3 months												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	1/40 (2.5%)	2/38 (5.3%)	**RR 0.47** (0.04 to 5.03)	**28 fewer per 1,000** (from 51 fewer to 212 more)	⨁◯◯◯ VERY LOW	CRITICAL
Gastrointestinal adverse events (diarrhoea) at <3months												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	4/40 (10.0%)	3/38 (7.9%)	**RR 1.27** (0.30 to 5.29)	**21 more per 1,000** (from 55 fewer to 339 more)	⨁◯◯◯ VERY LOW	CRITICAL
Gastrointestinal adverse events (diarrhoea) at 3-12 months												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Febuxostat 80mg	placebo	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	very serious [b]	serious[c]	not serious	Very serious [a]	none	37/624 (5.9%)	24/490 (4.9%)	**RR 1.10** (0.51 to 2.39)	**5 more per 1,000** (from 24 fewer to 68 more)	⨁◯◯◯ VERY LOW	CRITICAL
Gastrointestinal adverse events (nausea and vomiting) at 3-12 months												
1	randomised trials	very serious [b]	not serious	not serious	Very serious [a]	none	12/267 (4.5%)	5/134 (3.7%)	**RR 1.2** (0.43 to 3.35)	**7 more per 1,000** (from 21 fewer to 87 more)	⨁◯◯◯ VERY LOW	CRITICAL
Gastrointestinal adverse events (gastro and abdominal pain) at 3-12 months												
1	randomised trials	very serious [b]	not serious	not serious	Very serious [a]	none	6/267 (2.2%)	3/134 (2.2%)	**RR 1** (0.25 to 3.95)	**0 fewer per 1,000** (from 16 fewer to 65 more)	⨁◯◯◯ VERY LOW	CRITICAL

Serum urate levels (change from baseline; mg/dL; <3 months)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Febuxostat 80mg	placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [b]	not serious	not serious	not serious	none	35	37	-	MD **4.68 lower** (5.31 lower to 4.05 lower)	⊕⊕⊕◯ MODERATE	CRITICAL

Number of people achieving sUA <6.0 mg/dL at 3-12 months

3	randomised trials	not serious	not serious	not serious	not serious	none	417/647 (64.5%)	3/519 (0.6%)	**RR 92.60** (32.28 to 265.61)	**529 more per 1,000** (from 181 more to 1,000 more)	⊕⊕⊕⊕ HIGH	CRITICAL

Number of people achieving sUA <5.0 mg/dL at 3-12 months

2	randomised trials	not serious	not serious	not serious	not serious	none	170/394 (43.1%)	1/392 (0.3%)	**RR 112.32** (22.77 to 554.17)	**284 more per 1,000** (from 56 more to 1,000 more)	⊕⊕⊕⊕ HIGH	CRITICAL

Number of people achieving sUA <4.0 mg/dL at 3-12 months

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Febuxostat 80mg	placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [b]	not serious	not serious	not serious	none	7/37 (18.9%)	0/35 (0.0%)	**OR 8.38** (1.78 to 39.43)	**190 more per 1,000** (from 60 more to 320 more)	⨁⨁⨁◯ MODERATE	CRITICAL

a. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. GRADE default MIDs used for all other outcomes. For dichotomous outcomes MIDs were taken to be RRs of 0.8 and 1.25. For continuous outcomes 0.5 x baseline SD was calculated, serum urate level: 0.65.

b. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

c. The point estimates varied widely and the I^2 = 58%, no subgroup analysis could be conducted so a random effects model was used.

Table 36: Clinical evidence summary: mixed CKD population – febuxostat 120 mg vs placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Febuxostat 120mg	placebo	Relative (95% CI)	Absolute (95% CI)		
Frequency of flares at <3 months												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Febuxostat 120mg	placebo	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	very serious [a]	not serious	not serious	not serious	none	118/307 (38.4%)	41/172 (23.8%)	**RR 1.71** (1.26 to 2.32)	**169 more per 1,000** (from 62 more to 315 more)	⨁⨁◯◯ LOW	CRITICAL

Cardiovascular adverse events at 3-12 months

2	randomised trials	very serious [a]	not serious	not serious	not serious	none	23/306 (7.5%)	1/169 (0.6%)	**RR 8.21** (0.50 to 135.65)	**43 more per 1,000** (from 3 fewer to 797 more)	⨁⨁◯◯ LOW	CRITICAL

Gastrointestinal adverse events (abdominal pain) at <3 months

1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	1/38 (2.6%)	2/38 (5.3%)	**RR 0.50** (0.05 to 5.28)	**26 fewer per 1,000** (from 50 fewer to 225 more)	⨁◯◯◯ VERY LOW	CRITICAL

Gastrointestinal adverse events (diarrhoea) at <3 months

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Febuxostat 120mg	placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	3/38 (7.9%)	3/38 (7.9%)	**RR 1.00** (0.22 to 4.65)	**0 fewer per 1,000** (from 62 fewer to 288 more)	⨁◯◯◯ VERY LOW	CRITICAL

Serum urate levels (change from baseline mg/dl; <3 months)

1	randomised trials	serious [a]	not serious	not serious	not serious	none	36	37	-	MD **5.33 lower** (6.09 lower to 4.57 lower)	⨁⨁⨁◯ MODERATE	CRITICAL

Number of people achieving sUA <6.0 mg/dL at 3-12 months

2	randomised trials	very serious [a]	not serious	not serious	not serious	none	241/299 (80.6%)	1/162 (0.6%)	**RR 91.26** (17.95 to 464.13)	**557 more per 1,000** (from 105 more to 1,000 more)	⨁⨁◯◯ LOW	CRITICAL

Number of people achieving sUA <5.0 mg/dL at 3-12 months

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Febuxostat 120mg	placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	not serious	not serious	none	30/34 (88.2%)	0/35 (0.0%)	**OR 34.41** (13.37 to 88.55)	**880 more per 1,000** (from 770 more to 1,000 more)	⨁⨁⨁◯ MODERATE	CRITICAL

Number of people achieving sUA <4.0 mg/dL at 3-12 months

1	randomised trials	serious [a]	not serious	not serious	not serious	none	19/34 (55.9%)	0/35 (0.0%)	**OR 15.80** (5.54 to 45.10)	**560 more per 1,000** (from 390 more to 730 more)	⨁⨁⨁◯ MODERATE	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. GRADE default MIDs used for all other outcomes. For dichotomous outcomes MIDs were taken to be RRs of 0.8 and 1.25. For continuous outcomes 0.5 x baseline SD for continuous outcomes was calculated, serum urate level: 0.58.

c. I^2=61% and subgroup analysis could not be conducted so a random effects model was used.

Treat-to-target

Table 37: Non-CKD population – treat-to-target Allopurinol 300mg versus febuxostat 80 mg or 120mg

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Allopurinol	Febuxostat	Relative (95% CI)	Absolute (95% CI)		
number of patients with SUA < or equal to 6mg/dL (follow up: 36 weeks)												
1	randomised trials	not serious	not serious	not serious	serious [b]	none	55/90 (61.1%)	72/92 (78.3%)	**RR 0.78** (0.64 to 0.95)	**172 fewer per 1,000** (from 282 fewer to 39 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Treatment emergent adverse events (follow up: 38 weeks)												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	63/98 (64.3%)	51/99 (51.5%)	**RR 1.25** (0.98 to 1.59)	**129 more per 1,000** (from 10 fewer to 304 more)	⨁⨁◯◯ LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. GRADE default MIDs used for all outcomes.

Second-line treatment

Table 38: Clinical evidence summary: Non-CKD population – allopurinol (300mg) vs placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Allopurinol 300mg	placebo	Relative (95% CI)	Absolute (95% CI)		
Joint tenderness (arthralgia, 3 months)												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	0/54 (0.0%)	1/28 (3.6%)	**OR 0.05** (0.00 to 3.34)	**34 fewer per 1,000** (from -- to 74 more)	⊕◯◯◯ VERY LOW	CRITICAL
Adverse events (Cardiovascular [hypertension]; 3 months)												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	1/54 (1.9%)	2/28 (7.1%)	**RR 0.26** (0.02 to 2.74)	**53 fewer per 1,000** (from 70 fewer to 124 more)	⊕◯◯◯ VERY LOW	CRITICAL
Serum urate level (change from baseline; %;												
1	randomised trials	serious [a]	not serious	not serious	not serious	none	54	28	-	MD **27.9 lower** (35.6 lower to 20.2 lower)	⊕⊕⊕◯ MODERATE	CRITICAL
Serum urate level (patients with sUA <6mg/dL; 3 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Allopurinol 300mg	placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	not serious	not serious	none	26/54 (48.1%)	0/28 (0.0%)	**OR 8.99** (3.39 to 23.84)	**480 more per 1,000** (from 340 more to 620 more)	⨁⨁⨁◯ MODERATE	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. GRADE default MIDs used for all other outcomes. For dichotomous outcomes MIDs were taken to be RRs of 0.8 and 1.25. For continuous outcomes 0.5 x baseline SD for continuous outcomes was calculated, serum urate level: 0.7.

Mixed CKD population treat-to-target

Table 39: Clinical evidence summary: Mixed CKD population – allopurinol (mixed dose, mean 279 mg) vs febuxostat (mixed dose, mean 81 mg)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Allopurinol(mixed dose 279 mg on average)	febuxostat (mixed dose 81 mg on average)	Relative (95% CI)	Absolute (95% CI)		
Cardiovascular disorders (number of patients with at least 1 event) at >12 months												
1	randomised trials	not serious	not serious	serious [a]	not serious	none	601/3050 (19.7%)	570/3001 (19.0%)	**RR 1.04** (0.94 to 1.15)	**8 more per 1,000** (from 11 fewer to 28 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Renal and urinary disorders (number of patients with at least 1 event) at >12 months												
1	randomised trials	not serious	not serious	serious [a]	serious [b]	none	135/3050 (4.4%)	129/3001 (4.3%)	**RR 1.03** (0.81 to 1.30)	**1 more per 1,000** (from 8 fewer to 13 more)	⊕⊕◯◯ LOW	CRITICAL
Gastrointestinal disorders (number of patients with at least 1 event) at >12 months												
1	randomised trials	not serious	not serious	serious [a]	serious [b]	none	285/3050 (9.3%)	256/3001 (8.5%)	**RR 1.10** (0.93 to 1.29)	**9 more per 1,000** (from 6 fewer to 25 more)	⊕⊕◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Allopurinol(mixed dose 279 mg on average)	febuxostat (mixed dose 81 mg on average)	Relative (95% CI)	Absolute (95% CI)		
Number of people achieving sUA <6 mg/dL at 1 year												
1	randomised trials	serious [c]	not serious	serious [a]	not serious	none	2362/2751 (85.9%)	2237/2306 (97.0%)	**RR 0.89** (0.87 to 0.90)	**107 fewer per 1,000** (from 126 fewer to 97 fewer)	⨁⨁◯◯ LOW	CRITICAL
Number of people achieving sUA <6 mg/dL at 2 years												
1	randomised trials	serious [c]	not serious	serious [a]	not serious	none	2192/2547 (86.1%)	2060/2121 (97.1%)	**RR 0.89** (0.87 to 0.90)	**107 fewer per 1,000** (from 126 fewer to 97 fewer)	⨁⨁◯◯ LOW	CRITICAL
Number of people achieving sUA <6 mg/dL at 3 years												
1	randomised trials	very serious [c]	not serious	serious [a]	not serious	none	1622/1851 (87.6%)	1464/1505 (97.3%)	**RR 0.90** (0.88 to 0.92)	**97 fewer per 1,000** (from 117 fewer to 78 fewer)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Allopurinol(mixed dose 279 mg on average)	febuxostat (mixed dose 81 mg on average)	Relative (95% CI)	Absolute (95% CI)		
Number of people achieving sUA <6 mg/dL at 4 years												
1	randomised trials	very serious [c]	not serious	serious [a]	not serious	none	1065/1223 (87.1%)	1004/1034 (97.1%)	**RR 0.90** (0.88 to 0.92)	**97 fewer per 1,000** (from 117 fewer to 78 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Number of people achieving sUA <6 mg/dL at 5 years												
1	randomised trials	very serious [c]	not serious	serious [a]	not serious	none	692/799 (86.6%)	676/695 (97.3%)	**RR 0.89** (0.86 to 0.92)	**107 fewer per 1,000** (from 136 fewer to 78 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Number of people achieving sUA <6 mg/dL at 6 years												
1	randomised trials	very serious [c]	not serious	serious [a]	not serious	none	360/406 (88.7%)	335/347 (96.5%)	**RR 0.92** (0.88 to 0.96)	**77 fewer per 1,000** (from 116 fewer to 39 fewer)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Allopurinol(mixed dose 279 mg on average)	febuxostat (mixed dose 81 mg on average)	Relative (95% CI)	Absolute (95% CI)		
Number of people achieving sUA <6 mg/dL at 7 years												
1	randomised trials	very serious [c]	not serious	serious [a]	not serious	none	76/85 (89.4%)	81/83 (97.6%)	**RR 0.92** (0.85 to 0.99)	**78 fewer per 1,000** (from 146 fewer to 10 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Number of people achieving sUA <5mg/dL at 1 year												
1	randomised trials	serious [c]	not serious	serious [a]	not serious	none	1270/2751 (46.2%)	2057/2306 (89.2%)	**RR 0.52** (0.50 to 0.54)	**428 fewer per 1,000** (from 446 fewer to 410 fewer)	⨁⨁◯◯ LOW	CRITICAL
Number of people achieving sUA <5mg/dL at 2 years												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Allopurinol(mixed dose 279 mg on average)	febuxostat (mixed dose 81 mg on average)	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [c]	not serious	serious [a]	not serious	none	1246/2547 (48.9%)	1936/2121 (91.3%)	**RR 0.54** (0.51 to 0.56)	**420 fewer per 1,000** (from 447 fewer to 402 fewer)	⨁⨁◯◯ LOW	CRITICAL

Number of people achieving sUA <5mg/dL at 3 years

1	randomised trials	very serious [c]	not serious	serious [a]	not serious	none	948/1851 (51.2%)	1378/1505 (91.6%)	**RR 0.56** (0.53 to 0.59)	**403 fewer per 1,000** (from 430 fewer to 375 fewer)	⨁◯◯◯ VERY LOW	CRITICAL

Number of people achieving sUA <5mg/dL at 4 years

1	randomised trials	very serious [c]	not serious	serious [a]	not serious	none	647/1223 (52.9%)	937/1034 (90.6%)	**RR 0.58** (0.55 to 0.62)	**381 fewer per 1,000** (from 408 fewer to 344 fewer)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Allopurinol(mixed dose 279 mg on average)	febuxostat (mixed dose 81 mg on average)	Relative (95% CI)	Absolute (95% CI)		
Number of people achieving sUA <5mg/dL at 5 years												
1	randomised trials	very serious [c]	not serious	serious [a]	not serious	none	429/799 (53.7%)	635/695 (91.4%)	**RR 0.59** (0.55 to 0.63)	**375 fewer per 1,000** (from 411 fewer to 338 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Number of people achieving sUA <5mg/dL at 6 years												
1	randomised trials	very serious [c]	not serious	serious [a]	not serious	none	229/406 (56.4%)	317/347 (91.4%)	**RR 0.62** (0.56 to 0.68)	**347 fewer per 1,000** (from 402 fewer to 292 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Number of people achieving sUA <5mg/dL at 7 years												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Allopurinol(mixed dose 279 mg on average)	febuxostat (mixed dose 81 mg on average)	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [c]	not serious	serious [a]	serious [b]	none	55/85 (64.7%)	75/83 (90.4%)	**RR 0.72** (0.60 to 0.85)	**253 fewer per 1,000** (from 361 fewer to 136 fewer)	⊕◯◯◯ VERY LOW	CRITICAL

Hospitalisation at >12 months

1	randomised trials	not serious	not serious	serious [a]	not serious	none	435/3065 (14.2%)	424/3063 (13.8%)	**RR 1.03** (0.91 to 1.16)	**4 more per 1,000** (from 12 fewer to 22 more)	⊕⊕⊕◯ MODERATE	CRITICAL

a. Downgraded by 1 or 2 increments because the majority of the evidence included an indirect or very indirect interventions respectively. Mixed dose Allopurinol (279 mg on average) and mixed dose Febuxostat (81 mg on average)

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. GRADE default MIDs used for all outcomes. For dichotomous outcomes MIDs were taken to be RRs of 0.8 and 1.25.

c. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

Appendix G – Economic evidence tables

Study	NICE 2008, Stevenson 2009, Stevenson 2011, Ipsen 2008 [56, 80, 111, 112]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** Probabilistic decision analytic model. **Approach to analysis:** Decision tree. The model was split into two time periods because of the initial flare-triggering period: 1. An initial period of 3 months, during which patients may, or may not, suffer from a treatment-initiated flare. 2. A treatment maintenance period from months 4 to 24, during which patients were grouped into four subgroups according the clinical effect achieved i.e., sUA level: – ≤ 360 µmol/L (6 mg/dL)	**Population:** Adults with hyperuricaemia in whom urate deposition has already occurred (including a history or presence of, tophus and/or gouty arthritis). sUA levels of at least 8 mg/dl (0.48 mmol/l). **Cohort settings:** Start age: 61.4 Male: 78% **Intervention 1:** fixed-dose allopurinol, 300 mg once daily **Intervention 2:** Febuxostat, 80 mg or 120 mg once daily Patients on 80 mg/d febuxostat treatment assumed to have a dose increase to 120 mg/d if the sUA level was not	**Total costs (mean per patient):** Intervention 1: £2,606 Intervention 2: £3,145 Incremental (2−1): £539 (95% CI: £347, £776 p=NR) **Currency & cost year:** 2006 UK pounds **Cost components incorporated:** Cost of flares (hospitalisation, diagnostics and outpatient visits), maintenance cost of gout treatment (outpatient visits, diagnostic laboratory tests, procedures and hospitalisation due to complications of gout) and drug costs (febuxostat 80mg or 120 mg was £0.87 per day and allopurinol 300mg was £0.065 per day).	**QALYs (mean per patient):** Intervention 1: 1.399 Intervention 2: 1.432 Incremental (2−1): 0.033 (95% CI: -0.017, 0.083; p=NR)	**ICER (Intervention 2 versus Intervention 1):** £16,324 per QALY gained (pa) 95% CI: £6,281, £239,928 Probability Intervention 2 cost effective (£20K): 63% **Analysis of uncertainty:** Univariate sensitivity analyses undertaken: - time horizon (3,4 and 5 years) - protective effect provided by colchicine prophylaxis (0% and 100%) - discount rates (0% and 6%) - the assumed cost of febuxostat (£0.5/day and £1.25 per day) - the disutility associated with each incremental level of sUA (0.02 and 0.05) - the proportion of patients < 360 µmol/L in months 4 to 24 for febuxostat (0.7). The results were most sensitive to: - the assumed cost of febuxostat (when increased to £1.25, ICER = £23,386 per QALY)

– > 360 µmol/L (6 mg/dL) and ≤ 480 µmol/L (8 mg/dL) – > 480 µmol/L (8 mg/dL) and ≤ 600 µmol/L (10 mg/dL) – > 600 µmol/L (10 mg/dL). After 3 months, the incidence of flares is dependent on the sUA level. QOL gains were assumed to be achieved through the reduction of flares (decreased utility) and in a long-term increase in utility associated with improved sUA categorization. **Perspective:** UK NHS **Time horizon:** 2 years **Treatment effect duration:**[(a)] n/a **Discounting:** Costs: 3.5%; Outcomes: 3.5%	≤360 µmol/L (6 mg/dL) after the initial 3 months of febuxostat treatment. The sUA levels of patients who changed dose from 80 mg/d to 120 mg/d were assumed to be identical to a cohort of patients that had been prescribed 120 mg/d from the initiation of treatment. Dose titration of allopurinol was not permitted, regardless of the sUA level of the patient.			- the disutility associated with each incremental level of sUA (0.02, ICER = £26,018) - the proportion of patients < 360 µmol/L in months 4 to 24 for febuxostat (0.7, ICER = £24,645). Exploratory modelling done by manufacturer following appraisal consultation document, whereby the model explicitly included a comparison of febuxostat versus placebo in a population contraindicated to allopurinol. The ICER was £3,727 per QALY. The process timelines for this appraisal did not permit an assessment of this exploratory modelling by the ERG.
Data sources				
Health outcomes: Baseline sUA level based on two RCTs (FACT [Becker 2005][10] and APEX [Schumacher 2008][100]). Other cohort settings listed above based on IMS observational study (unpublished) of primary care gout patients in UK, France and Germany as part of manufacturer's submission. First 3 months number of gout flares based on two RCTs (FACT [Becker 2005][10] and APEX [Schumacher 2008][,100]). Data pooled rather than meta-analysed. In the initial 3-months an assumption that prophylactic colchicine treatment reduced the incidence of flares by 78% was applied (Borstad 2004 and Paulus 1974). IMS observational study bivariate analysis used to link sUA levels to number of gout flares. Model assumed sUA levels constant between 4 and 24				

months. Mortality was not accounted for since the time horizon is only 2 years and there is no increased mortality related with gout. The mortality was assumed to be the same in both treatment groups. Adverse events of drugs assumed to be similar between groups and not accounted for. **Quality-of-life weights:** The utility data applied in the model were derived from IMS observational study. EQ-5D quality-of life data from study participants (patients with gout from France, UK and Germany), with UK tariff applied (values commercial in confidence and therefore not resented). The model assigned a utility penalty associated with experiencing one flare and a baseline utility per sUA level. **Cost sources:** Resource use from IMS observational UK data. The maintenance costs of gout were assumed to be the same regardless of disease severity and uric acid level. National Health Service Diagnosis Related Group unit costs used for hospitalisation, laboratory, and diagnostic procedures. Unit costs for allopurinol from BNF, unit cost of febuxostat based on anticipated daily price estimated by manufacturer. Drug costs applied to all patients as model assumed no attrition over 2 years.
Comments
Source of funding: Manufacturer of febuxostat. **Limitations:** No subgrouping for renal impairment. First line comparison only and does not include allopurinol given in a titrated regimen, model uses a fixed dose of 300mg which is not best practice. Does not include other comparators or treatment sequences. ERG had concerns regarding QoL assumptions that lower sUA levels would produce utility gains independently of the incidence of gout flares. In addition, it noted that EQ-5D values from some patients were not plausible, with some without a flare rating their utility as worse than death. Model structure and comparators do not allow for sequential treatment or treatment discontinuation. Clinical data pooled not meta-analysed. Concern regarding use of serum uric acid concentration as a surrogate outcome for gout flares. Model based on bivariate analysis that did not include other confounders rather than multivariate analysis. The NICE appraisal committee concluded that the relationship was not fully understood, but it was accepted that as sUA concentration levels increased above 6mg/100mL it was likely that symptoms would be more frequent. ERG raised concerns with reasons why manufacturer discarded 77% of the UK data set, and 51% of the overall data set from IMS observational study, which was used to link sUA levels and number of gout flares expected. Impact of prophylactic colchicine treatment on reduction of incidence of flares overestimated in model due to calculation error. Concerns regarding inputs included (costs of intervention)/excluded (prophylaxis success rate) in PSA, contributing to uncertainty in results presented. Model does not include monitoring of theophylline levels for febuxostat as per SPC. **Other:** ERG recommend manufacturer amend model to include treatment strategies, but this was declined by manufacturer. ERG was unable to undertake any of their own analyses as the deemed the model so fundamentally flawed that there was insufficient time to undertake modifications. They did calculate what proportion of QALY gain was associated with the incidence of gout flares (first 3 months of model) versus the long-term utility gain associated with a lower sUA category. The latter was 5 times greater than the former. The QALY gain was largely driven by this. Concerns raised as to accuracy of ICER given the relationship between sUA and gout flares is not clearly established.
Overall applicability: Partially applicable[a] **Overall quality: Potentially serious limitations**[b]

Abbreviations: 95% CI= 95% confidence interval; CUA= cost–utility analysis; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ERG = evidence review group; ICER= incremental cost-effectiveness ratio; NR= not reported; pa= probabilistic analysis; PSA = probabilistic sensitivity analysis; QALYs= quality-adjusted life years; SPC = summary of product characteristics; sUA = serum uric acid
(a) Directly applicable / Partially applicable / Not applicable
(b) Minor limitations / Potentially serious limitations / Very serious limitations

<table>
<tr><th>Study</th><th colspan="4">Beard 2013[5]</th></tr>
<tr><th>Study details</th><th>Population & interventions</th><th>Costs</th><th>Health outcomes</th><th>Cost effectiveness</th></tr>
<tr>
<td>Economic analysis:
CUA (health outcome: QALYs)

Study design:
Probabilistic decision analytic model.
Approach to analysis:
Decision tree and Markov model.
- Initial treatment: The first 3 months of treatment, which included an assessment of sUA response and the flare triggering effect of initiating ULT (decision tree)
- Maintenance treatment: A period used to estimate the costs and outcomes over a longer time horizon (represented as a Markov 3-month time cycle health-state structure). Health states included:
- sUA response (defined as achieving an sUA level of 6 mg/dl (0.36 mmol/l) or less)</td>
<td>Population:
Adults with chronic gout and established hyperuricaemia who are typically treated with allopurinol (300mg once daily). sUA levels of at least 8 mg/dl (0.48 mmol/l).

Cohort settings:
Start age: NR
Male: NR

Intervention 1:
Base case no treatment (NT)

Intervention 2:
Sequence 1: allopurinol 300 mg → febuxostat 80 mg → febuxostat 120 mg → NT

Intervention 3:
Sequence 2: febuxostat 80 mg → febuxostat 120 mg → allopurinol 300 mg → NT

Intervention 4:</td>
<td>Total costs (mean per patient):
See full incremental analysis.
Currency & cost year:
2009 UK pounds
Cost components incorporated:
Cost of flares (hospitalisation, diagnostics and outpatient visits: £295.60), maintenance cost of gout treatment (outpatient visits, diagnostic laboratory tests, procedures and hospitalisation due to complications of gout, total monthly cost: £89.52) and drug costs (febuxostat 80mg or 120 mg was £0.87 per day and allopurinol 300mg was £0.047 per day).</td>
<td>QALYs (mean per patient):
See full incremental analysis.</td>
<td>Full incremental analysis (pa):[(c) (d)]
<table>
<tr><th>Int</th><th>Cost (e)</th><th>QALY</th><th>Inc cost</th><th>Inc QALY</th><th>ICER</th></tr>
<tr><td>1</td><td>£6,821</td><td>3.016</td><td colspan="3">Baseline</td></tr>
<tr><td>4</td><td>£7,043</td><td>3.090</td><td>£222</td><td>0.073</td><td>£3,020</td></tr>
<tr><td>5</td><td>£7,721</td><td>3.198</td><td colspan="3">Dominated by 2</td></tr>
<tr><td>3</td><td>£7,808</td><td>3.238</td><td colspan="3">Dominated by 2</td></tr>
<tr><td>2</td><td>£7,578</td><td>3.239</td><td>£535</td><td>0.149</td><td>£3,591</td></tr>
</table>
Probability second line febuxostat cost effective (£20K threshold): ~98% (read from graph)

Analysis of uncertainty:
Subgroup analyses undertaken:
- patients unresponsive to first-line allopurinol (ICER £5,529 compared with no treatment)
- mild to moderate renal impairment using allopurinol 100 or 200mg (ICER £3,613 compared with allopurinol 100mg or 200mg)

Univariate sensitivity analyses undertaken, ICERs for second line treatment with febuxostat following allopurinol compared with allopurinol alone:
- Lifetime time horizon £3,290
- 1-year time horizon £7,165
- Utility drop: 50 % of default (0.017) at all levels £7,032
- Utility drop: 25 % of default (0.0085) at all levels £14,348</td>
</tr>
</table>

- sUA non-response which was split into three non-response sUA groups (>6 to ≤8 mg/dl), (>8 to≤10 mg/dl), and (>10 mg/dl). In each of the sUA categories there was a probability of having an acute flare (1 week duration). When patients failed to gain an adequate sUA response or lost a previously attained response because of treatment dropout, the model switched patients to the next treatment in the sequence. Patients at the end of the treatment sequence were distributed across the sUA levels associated with the no treatment health state. QOL gains were assumed to be achieved through the reduction of flares and in a long-term increase in utility associated with improved sUA categorization.	Sequence 3: allopurinol 300 mg →NT **Intervention 5:** Sequence 4: febuxostat 80 mg → febuxostat 120 mg → NT			- Baseline sUA level (disease severity) <9 mg/dl £3,621 - Baseline sUA level (disease severity) ≥9 and <10 mg/dl £3,237 - Baseline sUA level (disease severity) ≥10 mg/dL £3,886 - sUA response threshold <5 mg/dL £3,776 - Low-dose (300 mg efficacy and 100 mg cost) allopurinol titration and initial flare rate of 0 % for first 3-month cycle £2,555 - High-dose (600 mg efficacy with 80 % response rate and 600 mg cost) allopurinol titration £3,681 - High-dose (900 mg efficacy with 100 % response rate and limited to 600 mg cost) allopurinol titration £3,764 - Low-dose (100–200 mg) and high-dose (600 mg) allopurinol titration £2,567 - Low-dose (100–200 mg) and high-dose (900 mg) allopurinol titration £2,578 - Extended prophylaxis in initial 3-month flares, avoiding all treatment-initiated flares, according to CONFIRMS £2,550 - Long-term dropouts are lost to further treatment for the remaining model time horizon £3,573

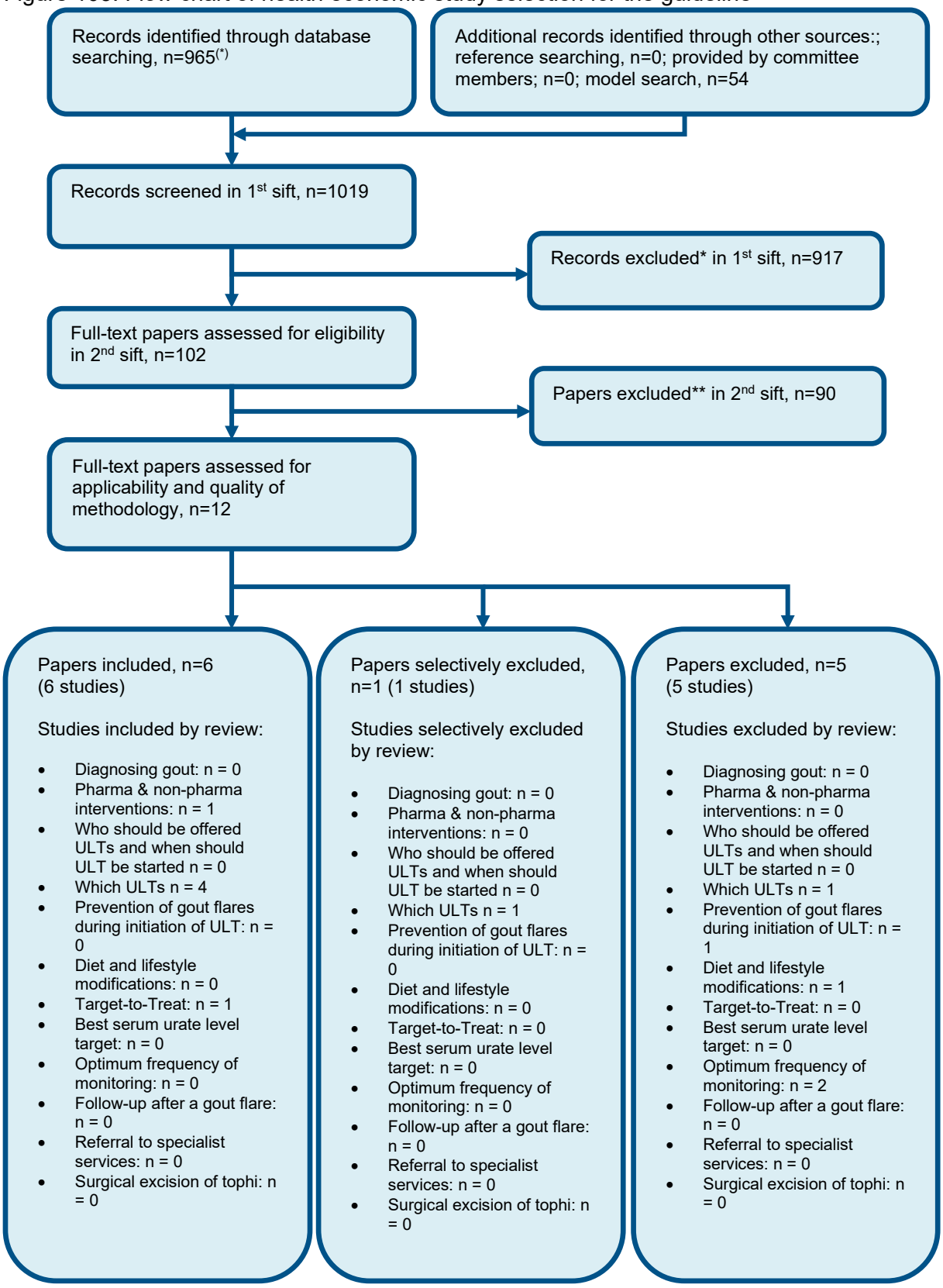
Perspective: Scottish NHS **Time horizon:** 5 years **Treatment effect duration:**[(a)] n/a **Discounting:** Costs: 3.5%; Outcomes: 3.5%				
Data sources				
Health outcomes: Cohort settings (age, gender) unclear. Source used for baseline sUA unclear, likely to be from two RCTs (FACT [Becker 2005][10] and APEX [Schumacher 2008][100]). General age-related mortality rates were derived from the Office for National Statistics. First 3 months number of gout flares based on two RCTs (FACT [Becker 2005][10] and APEX [Schumacher 2008][100]). Data pooled rather than meta-analysed. In the initial 3-months an assumption that prophylactic colchicine treatment given for 8 weeks to reduce the incidence of flares (adapted from Borstad 2004). Probability of experiencing flare after first 3 months by sUA category taken from IMS observational study (unpublished) of primary care gout patients in UK, France and Germany. Proportion of non-responsive patients in each sUA category from APEX[100] and FACT[10] studies. Drop out and discontinuation rates taken from APEX[100] and FACT[10]and from EXCEL[12] (non-randomised long term study) after first 12 months of treatment. CONFIRMS[9] study used for subgroup analysis of a population with renal impairment. **Quality-of-life weights:** The model assigned a utility penalty associated with experiencing one flare and a baseline utility per sUA level. The utility data by sUA level was derived from a multivariate analysis of the IMS observational study (unpublished) evaluating the impact of sUA on EQ-5D. An sUA level of 6 mg/dl (360 µmol/l) or less had an EQ-5D value of 0.746 (95 % CI 0.703–0.789). For sUA levels above 6 mg/dl (360 µmol/l), each 2-mg/dl (120-µmol/l) increase correspondingly decreased the EQ-5D value by 0.034. The same study provided an estimate of overall utility loss per acute flare (0.0097). Study participants were patients with gout from France, UK and Germany. UK tariff applied. **Cost sources:** Resource use from IMS observational UK data (unpublished). The maintenance costs of gout were assumed to be the same regardless of disease severity and uric acid level. National Health Service Diagnosis Related Group unit costs used for hospitalisation, laboratory, and diagnostic procedures, these were inflated from 2007 to 2009 using Hospital and Community Health Services Pay index. Unit costs for allopurinol from BNF, unit cost of febuxostat based on anticipated daily price estimated by manufacturer.				
Comments				
Source of funding: Manufacturer of febuxostat. **Limitations:** Model uses a fixed dose of 300mg which is not best practice. Concerns had been raised by NICE TA regarding QoL assumptions that lower sUA levels would produce utility gains independently of the incidence of gout flares and that EQ-5D values from some patients were not plausible, with some without a flare rating their utility as worse than death. Sensitivity analyses in this model explored the utility weights. Clinical data pooled not meta-analysed. Concern regarding use of serum uric acid concentration as a surrogate outcome for gout flares. Correlation between sUA and gout flares and QoL data based on unpublished IMS observational study sponsored by manufacturer. Note, ERG for NICE TA raised concerns with reasons why manufacturer discarded 77% of the UK data set, and 51% of the overall data set from this unpublished IMS observational study, unclear if this was addressed in this analysis. Furthermore, concern that the link between sUA gout flares based on bivariate rather than multivariate analysis, unclear if this was addressed in this analysis. SMC highlighted following weaknesses in the model: basecase time horizon (lifetime preferrable), lack of data to estimate the impact of potential dose titration above 300mg/day for allopurinol, uncertainty over the impact of prophylaxis on short term flare rates, and uncertainty over the quality of life impact (and disutility) associated with sUA level.				

Overall applicability: Partially applicable(a) **Overall quality: Potentially serious limitations**(b)

Abbreviations: 95% CI= 95% confidence interval; CUA= cost–utility analysis; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ERG = evidence review group; ICER= incremental cost-effectiveness ratio; NR= not reported; pa= probabilistic analysis; PSA = probabilistic sensitivity analysis; QALYs= quality-adjusted life years; SMC = Scottish Medicines Consortium; SPC = summary of product characteristics; sUA = serum uric acid
(a) Directly applicable / Partially applicable / Not applicable
(b) Minor limitations / Potentially serious limitations / Very serious limitations

Appendix H – Economic evidence study selection

Figure 103: Flow chart of health economic study selection for the guideline



* excludes conference abstracts (n=280)

**Non-relevant population, intervention, comparison, design or setting; non-English language

Appendix I – Health economic model

No original economic modelling was undertaken for this review question, but a costing analysis was developed to aid consideration of cost effectiveness.

Overview of the analysis

The costing analysis had a one-year time horizon and assessed the differences in costs between allopurinol and febuxostat using a treat-to-target management strategy. For the proportion of people receiving doses greater than 100mg allopurinol and 80mg febuxostat a treat-to-target management strategy was assumed whereby people were up titrated to higher doses of their ULT monthly. The costing analysis included the costs of:

- ULT
- Prophylaxis
- Initiation of ULT
- Up-titration of ULT
- Flares from initiating ULT (in the first 3 months)
- Flares from up-titrating ULT
- Flares post initiation / up titration for the remainder of the year

The costing analysis had 21 different scenarios.

Data inputs

The proportion of people receiving each ULT

In the base case analysis data from the FAST trial[78] was used to obtain the proportion of people receiving each ULT and the proportion of people achieving target serum urate levels. Data on the proportion of people receiving each ULT was also identified in the FORWARD[28] and Doherty[29] trials. However, data was only available on the proportion of people receiving allopurinol in the Doherty trial because this was a treat-to-target study where the majority of trial participants received allopurinol. This study was therefore used in sensitivity analyses to alter the proportion of people receiving different doses of allopurinol.

The FAST trial[78] was selected as the base case over the FORWARD[28] trial because participants were recruited from primary care (in the UK, Sweden, and Denmark) and therefore more reflective of how the majority of the gout population are treated compared to those recruited in the FORWARD[28] trial. In the FORWARD[28] trial, participants were recruited from twenty-nine secondary care centres across Europe. The FAST trial also had a larger population size (6,128 compared with 197) and the committee noted the manufacturer of febuxostat (Menarini) were the sole sponsors of the FORWARD trial.

Of note, the FAST trial[78] stipulated that 3.9% of people in the trial received a dose of allopurinol of 500mg or more. It was assumed 70% of the 3.9% of people received 500mg of allopurinol, 11% received 600mg, 9% received 700mg, 6% received 800mg, and 4% received 900mg. The proportion of people receiving the respective doses of allopurinol and febuxostat are presented in Table 40.

Table 40: The proportion of people receiving allopurinol and febuxostat from the FAST trial

Drug and drug dosage	Proportion of people receiving each drug
Allopurinol 100mg	10.0%
Allopurinol 200mg	23.30%
Allopurinol 300mg	50.90%
Allopurinol 400mg	11.90%
Allopurinol 500mg	2.73%
Allopurinol 600mg	0.43%
Allopurinol 700mg	0.35%
Allopurinol 800mg	0.23%
Allopurinol 900mg	0.16%
Febuxostat 80mg	97.50%
Febuxostat 120mg	2.50%

Source: FAST trial[78]. 3.9% of people received a dose of 500mg or more. It was assumed 70% of the 3.9% of people received 500mg of allopurinol, 11% received 600mg, 9% received 700mg, 6% received 800mg, and 4% received 900mg

Overall, 86% of people receiving allopurinol in the FAST trial[78] achieved target serum urate levels and 97% of people receiving febuxostat (80mg & 120mg combined) achieved target serum urate levels.

The cost of ULT

The ULT costs for one year were estimated for different drug dosages. It was assumed people would be up titrated to the next dose of their drug monthly. The unit costs for ULTs are presented in Table 41.

Table 41: Cost of ULTs

Drug	Cost per pack	Units per pack	Cost per unit
Allopurinol 100mg	£0.99	28	£0.04
Allopurinol 300mg	£1.37	28	£0.05
Febuxostat 80mg	£2.43	28	£0.09
Febuxostat 120mg	£24.36	28	£0.87

Source: British National Formulary (BNF)[15]; Accessed 18/02/2022

Based on the unit costs presented in Table 41 the total cost for each drug dose was estimated for one year assuming 100% adherence to medication. 100% adherence was assumed throughout the costing analysis due to the lack of supporting evidence available on the relationship between adherence and the effect on serum urate levels.

The yearly cost for each final drug dose includes the lower drugs doses received as part of monthly up titration. For example, the cost for those who eventually receive 400mg of allopurinol includes the cost of; one month of receiving 100mg of allopurinol, one month of receiving 200mg allopurinol, one month of receiving 300mg of allopurinol, and the cost of receiving 400mg allopurinol for the remainder of the year (9 months).

The cost of prophylaxis

Based on committee opinion, it was assumed people would also receive prophylaxis for one month for each drug dose they received. For example, someone who was up titrated to 400mg of allopurinol, and remained on this dose for the rest of the year, would receive 4 months of prophylaxis.

It was assumed people receiving prophylaxis would receive 1mg of colchicine per day (£0.12 per day). Unit costs for colchicine are presented in Table 42.

Table 42: Cost of Colchicine

Cost per pack	Units per pack	mg per unit	Cost per unit	No. tablets per day	Cost per day
£6.07	100	0.5	£0.06	2	£0.12

Source: British National Formulary (BNF)[15]; Accessed 02/08/21

The cost of prophylaxis and the cost for ULTs for each drug dosage were multiplied by the proportion of people receiving each drug dosage (as reported in Table 40) to obtain the total drug costs for one year of treatment.

The cost of initiating ULT

Initiation of ULT costs were included for all people. The cost of initiating ULT included the cost of nurse and GP time, the cost of a blood test to measure serum urate levels, and the cost of a renal function test. Unit costs for initiating ULT are presented in Table 43.

Table 43: Cost of initiating ULT

Resource	Cost per hour	Cost per min	Time (mins)	Cost
Nurse (Band 5)[(a)]	£42	£0.70	7.5[(b)]	£5.25
GP[(a)]	£238	£3.96	5[(b)]	£19.82
Blood test[(c)]	-	-	-	£3.10
Renal function test[(d)]	-	-	-	£6.00
Total cost				**£34.17**

Sources:(a) PSSRU 2020[13], including qualification costs (excluding individual and productivity costs)

(b) Based on committee opinion

(c) NHS reference costs 2019/20[84]

(d) NICE guidance, Chronic kidney disease 2014[81]

The cost of up titrating ULT

Up-titration costs included nurse and GP time, and the cost of a blood test to measure serum urate levels. The cost of up-titration was included for all people receiving a drug dose greater than 100mg allopurinol and 80mg of febuxostat. The total cost of up-titration for each drug dosage was dependent on how many times a person was up-titrated. For example, someone receiving 300mg of allopurinol incurred the cost of up titrating ULT twice and the cost of initiating ULT once. Unit costs for up titrating ULT are presented in Table 44.

Table 44: Cost of up titrating ULT

Resource	Cost per hour	Cost per min	Time (mins)	Cost
Nurse (Band 5)[(a)]	£42	£0.70	5[(b)]	£3.50
GP[(a)]	£238	£3.96	2[(b)]	£7.93

Resource	Cost per hour	Cost per min	Time (mins)	Cost
Blood test[c]	-	-	-	£3.10
Total cost				**£14.53**

Sources:(a) PSSRU 2020[13], including qualification costs (excluding individual and productivity costs)
(b) Based on committee opinion
(c) NHS reference costs 2019/20[84]

The cost of initiating and up titrating ULT for each drug dosage was multiplied the proportion of people receiving each drug dosage and presented in one column in the results section.

The cost of a gout flare

The cost of a gout flare was estimated by calculating the cost of a:

- Hospital treated gout flare
- GP visit treated gout flare
- Repeat prescription (via telephone or online)
- Self-managed gout flare

The estimated cost of a gout flare was subsequently used in calculations for calculating the cost of flares associated with initiating ULT, up titrating ULT, and the cost of flares based on the probability of having a gout flare for the remainder of the one-year time horizon.

The estimated cost of a gout flare in each respective setting was multiplied by the estimates for the proportion of people treated in each setting (based on committee opinion) to obtain the total cost of a gout flare. Due to the uncertainty surrounding the proportion of people being treated for a gout flare in each respective setting the cost of a gout flare was estimated for 8 different scenarios varying these proportions. All eight estimated costs of a flare were applied to the base case setting. In additional scenarios the highest and lowest cost of a gout flare were applied. The proportions of people treated in each respective setting for the 8 scenarios are presented in Table 45.

Table 45: The proportion of people treated for a gout flare in each setting

Scenario	Hospital	GP visit	Repeat prescription	Self-managed
Scenario 1	1%	25%	54%	20%
Scenario 2	5%	25%	50%	20%
Scenario 3	1%	25%	44%	30%
Scenario 4	5%	25%	40%	30%
Scenario 5	1%	15%	64%	20%
Scenario 6	5%	15%	60%	20%
Scenario 7	1%	15%	54%	30%
Scenario 8	5%	15%	50%	30%

Source: Based on committee opinion

The cost components and methodology for estimating the total cost of a gout flare treated in each respective setting are detailed below.

Drug costs

Drug costs were included for the costs of; a hospital treated gout flare, a GP visit treated gout flare, and for obtaining a repeat prescription. The proportion of people obtaining each type of drug for treatment for a gout flare was obtained from CPRD data. This CPRD data was sourced as part of the collaborative research project between NICE and the University of Edinburgh (Multimorbidity and clinical guidelines: using epidemiology to quantify the applicability of trial evidence to Inform guideline development)[43]. The proportion of people receiving each drug was multiplied by the total cost for each course of drug and summed to obtain the total cost of drugs prescribed for a gout flare.

It was assumed PPIs were prescribed for people receiving NSAIDs (assuming people would receive 10mg of omeprazole for 7 days, costing £2.33)[15] and oral corticosteroids (assuming 50% of people receiving an oral corticosteroid would receive 10mg of omeprazole for 4 days, costing £1.33 for four days of treatment).

Details for the cost of drugs for the treatment of a gout flare are presented in Table 46.

Table 46: Cost of drugs for treatment of a gout flare

Drug	Cost per day	Number of days	Cost per course (including PPI for naproxen)	Weighting	Total cost
NSAIDs (naproxen)[(a)]	£0.35 day one £0.21 remainder of course	7	£3.93	58.63%[(b)]	£2.30
Colchicine[(c)]	£0.18	4	£0.73	33.79%[(b)]	£0.25
Oral corticosteroid[(d)]	£0.26	4	£1.05	7.21%[(b)]	£0.12
Injectable corticosteroid[(e)]	£3.44	1	£3.44	0.37%[(b)]	£0.01
Total cost					**£2.69**

Sources:(a) British National Formulary (BNF)[15], assuming people receive 750mg of naproxen initially and then 250mg every eight hours

(b) Multimorbidity and clinical guidelines: using epidemiology to quantify the applicability of trial evidence to inform guideline development (University of Edinburgh) [43]

(c) British National Formulary (BNF)[15], assuming people receive 0.5mg 3 times daily

(d) British National Formulary (BNF)[15], assuming 30mg per day

(e) British National Formulary (BNF)[15], assuming one injection of methylprednisolone acetate (40 mg per 1 ml)

Hospital treated gout flare

The cost of a hospital treated gout flare was calculated in two stages. Firstly, we estimated the cost of accessing hospital via different routes of admission. Secondly, we estimated the costs attributed to people once they were treated in hospital.

People could be admitted to hospital for gout flare treatment via; GP home visit, GP consultation, ambulance, or by admitting themselves to A&E. The costs for each route of admission were multiplied by estimates provided by the committee on the proportion of people admitted via each respective route. Unit costs for admissions to hospital for treatment of a gout flare are presented in Table 47.

Table 47: Cost of a hospital treated gout flare – admission costs

Resource	Cost per hour	Cost per min	Time (mins)	Proportion of people	Total cost
GP home visit[a]	£238	£3.96	40[b]	7.50%[b]	£11.89
GP consultation[a]	£238	£3.96	12.5[b]	42.5%[b]	£21.06
Ambulance[c]	-	-	-	20.0%[b]	£42.54
Self-admitted[d]	-	-	-	30.0%[b]	£0.00
Total					**£75.49**

Sources:(a) PSSRU 2020[13], including qualification costs (excluding individual and productivity costs)

(b) Based on committee opinion

(c) NHS reference costs 2019/20[84]; Total weighted average cost for ambulance (currency code: ASC1, ASH1, ASS01, ASS02)

(d) The cost of self-admission is zero because no cost to the NHS is incurred prior to admission

The costs for people once they received treatment for a gout flare in hospital comprised of the cost of; an A&E visit, orthopaedics review (with and without admission), investigations undertaken, and the cost of acute treatment drugs prescribed. Once again, the committee provided estimates for the proportion of people who would incur costs associated with each resource use. Unit costs associated with hospital treatment for a gout flare can be found in Table 48.

Table 48: Cost of a hospital treated gout flare – treatment costs

Resource	Unit cost	Proportion of people	Total cost
A&E visit without admission[a]	£155.28	100%[b]	£155.28
Orthopaedics review without admission[c]	£129	56%[b]	£72.41
Orthopaedics review with admission[d]	£521.84	14%[b]	£73.06
X-ray[e]	£28.62	95%[b]	£27.19
Blood test[f]	£3.10	95%[b]	£2.95
Joint aspiration[g]	£598.26	40%[b]	£239.30
Drug costs[h]	£2.64	100%[b]	£2.69
Total			**£572.87**

Sources:(a) NHS reference costs 2019/20[84]; Total weighted average cost for accident & emergency, non-admitted (VB01Z – VB09Z & VB11Z, Type 01 – 04 for all currency codes)

(b) Based on committee opinion

(c) NHS reference costs 2019/20[84], Trauma and orthopaedics, Non-consultant-led non-admitted face-to-face, first

(d) NHS reference cost 2019/20[84]; Total weighted average cost for Inflammatory, Spine, Joint or Connective Tissue Disorders (HD23D – HD23H & HD23J)

(e) NHS reference costs 2019/20[84]; Direct access plain film (DAPF)

(f) NHS reference costs 2019/20[84]; Average of phlebotomy and haematology directly accessed pathology services

(g) NHS reference costs 2019/20[84]; Total weighted average cost for Percutaneous Aspiration of Joint, 19 years and over (YH30A)

(h) Cost estimated in Table 46.

The resulting total cost for a hospital treated gout flare was £648.36 (the sum of the totals in Table 47 and Table 48).

As highlighted in Table 48, in the base case analysis we assumed 100% of people receiving treatment for a gout flare visited A&E. However, we also conducted a sensitivity analysis assuming only 50% of people visited A&E.

GP visit treated gout flare

The cost of a flare attributed to a GP visit included the cost of GP's time and the cost of drugs prescribed for treatment of a gout flare. Unit costs are presented in Table 49.

Table 49: Cost of a GP visit for treatment of a gout flare

Resource	Cost per hour	Cost per min	Time (mins)	Total cost
GP consultation[(a)]	£238	£3.96	12.5[(b)]	£49.55
Drug costs[(b)]	-	-	-	£2.69
Total cost				**£52.24**

Sources:(a) PSSRU 2020[13], including qualification costs (excluding individual and productivity costs)
(b) Cost estimated in Table 46.

Repeat prescription (via telephone or online)

Cost for a repeat prescription were split into four distinct categories:

- People who obtain a repeat prescription via telephone which consists of receptionist time and GP task time.
- People who obtain a repeat prescription via telephone which consists of receptionist time and a GP consultation.
- People submit an online task to a GP to obtain a repeat prescription which consists of receptionists' time and GP task time.
- People submit an online task to a GP to obtain a repeat prescription which consists of receptionists' time, GP task time, and a GP consultation.

The costs for the respective categories outlined above are presented in the tables below (Table 50, Table 51, Table 52, Table 53).

Table 50: Cost of obtaining a repeat prescription via telephone – receptionist time & GP task

Resource	Cost per hour	Cost per min	Time (mins)	Total cost
Receptionist time (telephone)[(a)]	£11	£0.19	3.5[(b)]	£0.66
GP task time (non-patient contact)[(c)]	£153	£2.55	3.5[(b)]	£8.92
Drug costs[(d)]	-	-	-	£2.69
Total cost				**£12.26**

Sources:(a) Receptionist time was estimated obtaining the salary of a Band 2 and 3 receptionists (<1 year

& 2+ years' experience) for inner and outer London and the rest of England from the Agenda for pay rates 2020[47]. To calculate the annual average salary of a receptionist in England the total number of GP practices in England and London were obtained to calculate the proportion of GP practices in England and London. The committee assumed 60% of receptionists were Band 2 and 30% had >1 year experience. It was assumed 5% of Band 3 receptionists had >1 year experience. In addition, it was assumed 40% of GP practices in London were in Inner London.

(b) Committee opinion

(c) PSSRU 2020[13], Non-patient contact GP time including qualification costs (excluding individual and productivity costs)

(d) Cost estimated in Table 46.

Table 51: Cost of obtaining a repeat prescription via telephone – receptionist time & GP consultation

Resource	Cost per hour	Cost per min	Time (mins)	Total cost
Receptionist time (telephone) [(a)]	£11	£0.19	3.5[(b)]	£0.66
GP consultation (patient contact) [(c)]	£238	£3.96	7.5[(b)]	£29.73
Drug costs[(d)]	-	-	-	£2.69
Total cost				**£33.08**

Sources:(a) Receptionist time was estimated obtaining the salary of a Band 2 and 3 receptionists (<1 year & 2+ years' experience) for inner and outer London and the rest of England from the Agenda for pay rates 2020[47]. To calculate the annual average salary of a receptionist in England the total number of GP practices in England and London were obtained to calculate the proportion of GP practices in England and London. The committee assumed 60% of receptionists were Band 2 and 30% had >1 year experience. It was assumed 5% of Band 3 receptionists had >1 year experience. In addition, it was assumed 40% of GP practices in London were in Inner London.

(b) Committee opinion

(c) PSSRU 2020[13], Patient contact GP time including qualification costs (excluding individual and productivity costs)

(d) Cost estimated in Table 46.

Table 52: Cost of obtaining a repeat prescription online – receptionist time & GP task

Resource	Cost per hour	Cost per min	Time (mins)	Total cost
Receptionist time (online) [(a)]	£11	£0.19	1.5[(b)]	£0.28
GP task time (non-patient contact) [(c)]	£153	£2.55	3.5[(b)]	£8.92
Drug costs[(d)]	-	-	-	£2.69
Total cost				**£11.89**

Sources:(a) Receptionist time was estimated obtaining the salary of a Band 2 and 3 receptionists (<1 year & 2+ years' experience) for inner and outer London and the rest of England from the Agenda for pay rates 2020[47]. To calculate the annual average salary of a receptionist in England the total number of GP practices in England and London were obtained to calculate the proportion of GP practices in England and London. The committee assumed 60% of receptionists were Band 2 and 30% had >1 year experience. It was assumed 5% of Band 3 receptionists had >1 year experience. In addition, it was assumed 40% of GP practices in London were in Inner London.

(b) Committee opinion

(c) PSSRU 2020[13], Non-patient contact GP time including qualification costs (excluding individual and productivity costs)

(d) Cost estimated in Table 46.

Table 53: Cost of obtaining a repeat prescription online – receptionist time, GP task & GP consultation

Resource	Cost per hour	Cost per min	Time (mins)	Total cost
Receptionist time (online) [a]	£11	£0.19	1.5[b]	£0.28
GP task time (non-patient contact) [c]	£153	£2.55	3.5[b]	£8.92
GP consultation (patient contact) [d]	£238	£3.96	7.5[b]	£29.73
Drug costs[e]	-	-	-	£2.69
Total cost				**£41.62**

Sources:(a) Receptionist time was estimated obtaining the salary of a Band 2 and 3 receptionists (<1 year & 2+ years' experience) for inner and outer London and the rest of England from the Agenda for pay rates 2020[47]. To calculate the annual average salary of a receptionist in England the total number of GP practices in England and London were obtained to calculate the proportion of GP practices in England and London. The committee assumed 60% of receptionists were Band 2 and 30% had >1 year experience. It was assumed 5% of Band 3 receptionists had >1 year experience. In addition, it was assumed 40% of GP practices in London were in Inner London.

(b) Committee opinion

(c) PSSRU 2020[13], Non-patient contact GP time including qualification costs (excluding individual and productivity costs)

(d) PSSRU 2020[13], Patient contact GP time including qualification costs (excluding individual and productivity costs)

(e) Cost estimated in Table 46.

The costs presented in the above tables were multiplied by estimates provided by the committee on the proportion of people obtaining a repeat prescription via the different modes stated above. The committee acknowledged that there was a high degree of uncertainty with regards to how repeat prescriptions are prescribed and how people will be treated in primary care in the future due to a current shift in practice because of new technologies (for example, online booking systems), and Covid-19. Therefore, to try and account for this uncertainty we varied the proportion of people obtaining a repeat prescription based on whether in Scenario 1 – Scenario 8 (Table 45) the proportion of people visiting a GP was 25% or 15%.

When the proportion of people visiting a GP was 25% (Scenario 1 – Scenario 4 for the cost of a gout flare). The costs presented above (Table 50, Table 51, Table 52, Table 53) where multiplied by the following proportions presented in Table 54.

Table 54: The proportion of people obtaining a repeat prescription via different routes when the proportion of people visiting a GP is 25%

Mode of obtaining a repeat prescription	Proportion of people
Telephone – receptionist time & GP task	45%
Telephone – receptionist time & GP consultation	25%
Online – receptionist time & GP task	20%
Online – receptionist time, GP task & GP consultation	10%

Source: Based on committee opinion

When the proportion of people visiting a GP was 15% (Scenario 5 – Scenario 8). The costs presented above (Table 50, Table 51, Table 52, Table 53) where multiplied by the proportions presented in Table 55.

Table 55: The proportion of people obtaining a repeat prescription via different routes when the proportion of people visiting a GP is 15%

Mode of obtaining a repeat prescription	Proportion of people
Telephone – receptionist time & GP task	35%
Telephone – receptionist time & GP consultation	35%
Online – receptionist time & GP task	15%
Online – receptionist time, GP task & GP consultation	15%

Source: Based on committee opinion

As highlighted in Table 54 and Table 55, when the proportion of people visiting a GP for treatment for a gout flare is lower (15%, Table 55) a higher proportion of people receive a GP consultation when obtaining a repeat prescription (50% compared to 35% in Table 54). This is to account for the fact that fewer people in this instance are receiving face-to-face appointment for treatment of a gout flare and therefore, more time is required to assess the person's condition and treatment when obtaining a repeat prescription.

Self-managed gout flare

The cost of a self-managed flare was assumed to be £0.00 because people who self-manage their gout flares at home manage their pain with over-the-counter medications, thus incurring no cost to the NHS.

Total cost of a gout a flare

The total cost of a gout flare for each scenario is presented in Table 56.

Table 56: Total cost of a gout flare for each scenario

Scenario	Hospital	GP visit	Repeat prescription	Self-managed	Total cost of a gout flare
Scenario 1	1%	25%	54%	20%	£30.52
Scenario 2	5%	25%	50%	20%	£55.64
Scenario 3	1%	25%	44%	30%	£28.49
Scenario 4	5%	25%	40%	30%	£53.61
Scenario 5	1%	15%	64%	20%	£29.61
Scenario 6	5%	15%	60%	20%	£54.59
Scenario 7	1%	15%	54%	30%	£27.22
Scenario 8	5%	15%	50%	30%	£ 52.20

The lowest cost of a gout flare is £27.22, and the highest cost of a gout flare is £55.64. The cost of a gout flare is sensitive to the proportion of people being treated in hospital. When 1% of people are treated in hospital the cost of a gout flare ranges from £27.22 - £30.52 and when 5% of people are treated in hospital the cost of a gout flare ranges from £52.20 - £55.64.

The cost of a gout flare in the first 3 months of treatment

The average number of flares for the first three months of treatment for ULT with allopurinol were obtained from Borstad 2004[17] and the average number of flares for the first three months of treatment with febuxostat were obtained from the FACT and APEX trials[10,100]. In all of the studies people received prophylaxis on initiation of ULT. The average number of flares for the first three months of treatment with ULT are presented in Table 57.

Table 57: Average number of flares for the first 3 months of treatment with ULT

Drug	Average number of flares for the first three months of treatment
Allopurinol (all doses)[(a)]	0.57
Febuxostat 80mg[(b)]	1.121
Febuxostat 120mg[(b)]	1.546

Sources: (a) Borstad 2004[17]

(b) FACT and APEX trial[10,100]

The average number of flares reported in Table 57 were multiplied by the total cost of a gout flare to obtain the cost of gout flares for the first three months of treatment.

To obtain the total cost for flares for the first 3 months of treatment for allopurinol and febuxostat. The cost for each drug dosage was multiplied by the proportion of people receiving each drug and summed together for each respective ULT. For example, for febuxostat, the cost of flares for the first three months of treatment were calculated by; multiplying the cost of a gout flares for 80mg of febuxostat for the first three months of treatment by 97.5% (the proportion of people receiving 80mg febuxostat), multiplying the cost of gout flares for 120mg febuxostat for the first three months of treatment by 2.50% (the proportion of people receiving 120mg febuxostat), and adding these values together.

To note, the FACT and APEX[10,100] trial also reported the mean number of flares for allopurinol. However, in the FACT and APEX trial[10,100] people received a fixed dose of 300mg allopurinol. The committee noted this would likely induce a higher flare triggering effect from initiation of ULT compared to if people were up titrated from 100mg, as required, to achieve target serum urate levels. Therefore, the committee concluded the average number of flares from Borstad 2004[17] should be used in the base case analysis (where people were up titrated from 100mg of allopurinol), and the average number of flares reported in the FACT and APEX trials[10,100] should be used in additional scenario analyses. In Borstad 2004[17] people were up titrated up to achieve target serum urate levels and the average dose of allopurinol was 265mg.

The cost of a gout flare from up titrating ULT post three months of treatment

For people receiving doses greater than 300mg of allopurinol we calculated the cost of a flare for people up titrating ULT. Costs of flares for up titrating for doses of less than 300mg allopurinol and 120mg febuxostat were not calculated separately because the average number of flares in the first three months of treatment included flares associated with up titration for people receiving febuxostat and up to 300mg allopurinol. Costs for up titrating ULT were based on the assumption that people were up titrated monthly.

The cost of a flare for people receiving allopurinol post three months and up titrating ULT was calculated by dividing the mean number of flares in the first three months of treatment for allopurinol (0.57) by three (to obtain a monthly mean number of flares) and multiplying this value by 0.8 to account for the fact people will experience a greater number of flares when they initiate ULT as opposed to up titrating. These adjustments to the mean number of flares were based on assumptions by the committee due to the absence of published data. People receiving allopurinol increase their dosage in increments of 100mg per month. Therefore, for each dose of allopurinol greater than 300mg a value of 0.152 ([0.57/3]*0.8) was multiplied by the number of times a person had up-titrated post three months. For example, for people receiving 500mg of allopurinol they would up titrate an additional **two** times after 3 months of initial treatment and therefore the value of 0.152 was multiplied by two.

This figure was then multiplied by the cost of a gout flare and the proportion of people receiving each dose to obtain the total cost for flares related to up titration for each dose of allopurinol above 300mg. The total cost of flares related to up titration for allopurinol was the sum of these calculated values.

The total average number of flares people experience from up titrating ULT post three months over the course of the year for each dose of allopurinol above 300mg are presented in Table 58. For example, a person receiving 500mg allopurinol will experience a total of 0.304 (0.152*2) flares as a result of up titration for the remainder of the year post three months of treatment.

Table 58: Total number of flares people experience from up titration post three months over a one-year period for each dose of allopurinol

Dose	Total number of flares from up titration for each dose of allopurinol
Allopurinol 400mg	0.152
Allopurinol 500mg	0.304
Allopurinol 600mg	0.456
Allopurinol 700mg	0.608
Allopurinol 800mg	0.760
Allopurinol 900mg	0.912

The cost of flares for the remainder of the year

The cost of flares for the remainder of the year (excluding the cost of flares from up-titration of ULT) were calculated by estimating the mean number of flares for the duration of this period based on data used in the previous TA[56, 80, 111, 112] (including unpublished data from the IMS observational study) and the proportion of people achieving target serum urate levels from the FAST trial[78] (86% allopurinol and 97% febuxostat). The data used from the previous TA[56, 80, 111, 112] was data on:

- the number of flares dependent on serum urate levels (IMS study)
- the proportion of people in each serum urate level band who were non-responsive (e.g., had a serum urate level above 360 micromol/L [6mg/dl]) (based on pooled data from FACT and APEX trials[10,100]).

The IMS study was an unpublished study on the economic assessment of febuxostat for the management of gout. The committee acknowledged there were additional limitations in conjunction to the study being unpublished. Mainly, that 77% of the UK data set, and 51% of the overall data set linking serum urate levels and the number of gout flares expected was discarded. However, no additional evidence was available and therefore this data was used to estimate the cost of flares for the remainder of the year.

The committee selected the FAST trial as the base case for the proportion of people achieving target serum urate levels due to the more applicable population and treatment strategy compared to the other trials. FAST was selected over Doherty because Doherty had a mixed treatment strategy (where the majority of people received allopurinol) and separate data was not available for the proportion of people achieving target serum urate levels for allopurinol and febuxostat. The FAST trial was selected over the FORWARD trial because the FAST trial was more representative of the UK gout population and had a significantly larger sample size. In addition, the FORWARD trial only included people without CKD (or CKD stages 1-2).

Data for the number of flares people experienced based on their serum urate levels and the proportion of non-responsive people in each serum urate level band is presented in Table 59 and Table 60.

Table 59: Number of flares each month dependent on serum urate levels

	Number of flares per month according to serum urate level band
<6mg/dl	0.0874
≥6mg/dl and <8mg/dl	0.0989
≥8mg/dl and <10mg/dl	0.1085
≥10mg/dl	0.1161

Source: Unpublished IMS study

Table 60: Proportion on non-responsive people in each serum urate level band

Drug	≥6mg/dl and <8mg/dl	≥8mg/dl and <10mg/dl	≥10mg/dl
Allopurinol	79.00%	21.30%	4.60%
Febuxostat 80mg	74.10%	21.30%	4.60%
Febuxostat 120mg	67.20%	29.50%	3.30%

Source: Pooled data from the FACT and APEX trials[10,100] (trial end points at 52 and 28 weeks respectively)

The mean number of flares experienced for each serum urate level category was calculated as follows:

<6mg/dl

$$Prop_{\geq 6mg/dl} \times No.flares_{\geq 6mg/dl}$$

≥6mg/dl and <8mg/dl

$$\left(1 - Prop._{\geq 6mg/dl}\right) \times Prop.no\ respone_{\geq 6\text{mg/dl and } <8\text{mg/dl}} \times No.flares_{\geq 6\text{mg/dl and } <8\text{mg/dl}}$$

≥8mg/dl and <10mg/dl

$$\left(1 - Prop._{\geq 6mg/dl}\right) \times Prop.no\ respone_{\geq 8\text{mg/dl and } <10\text{mg/dl}} \times No.flares_{\geq 8\text{mg/dl and } <10\text{mg/dl}}$$

≥10mg/dl

$$\left(1 - Prop._{\geq 6mg/dl}\right) \times Prop.no\ respone_{\geq 10\text{mg/dl}} \times No.flares_{\geq 10\text{mg/dl}}$$

Where Prop. is proportion.

For example, for ≥8mg/dl and <10mg/dl, this reads as:
One minus the proportion of people achieving target serum urate levels (less than 360 micromol/L [6mg/dl]), multiplied by the proportion of people not responding to treatment for those people in the serum urate level band of ≥8mg/dl and <10mg/dl, multiplied by the number of flares for people in the serum urate level band of ≥8mg/dl and <10mg/dl.

The mean number of flares calculated for each serum urate level band (<6mg/dl - ≥10mg/dl, as detailed above) were summed together and multiplied by nine to obtain the total number of gout flares experienced for the remainder of the year. These are presented in Table 61.

Table 61: Mean number of flares experienced for the remainder of the year

	Number of flares
Allopurinol	0.8041
Febuxostat	0.7905

The mean number of flares presented in Table 61 were multiplied by the cost of a gout flare to obtain the total cost of gout flares for the remainder of the year for each dose of allopurinol and febuxostat. Total cost of a gout flare for the remainder of the year for both allopurinol and febuxostat were calculated by weighting the cost of each drug dosage by the proportion of people receiving each dose and summing these values together.

Scenario analyses

A total of 21 different scenarios were run for the costing analysis. Details of these are provided below.

Scenario 1

Scenario 1 through to Scenario 8 used all base case data inputs and the cost of a gout flare was varied with those reported in Table 45.

In Scenario 1 the cost of a gout flare used in the analysis was £30.52.

Scenario 2

In Scenario 2 the cost of a gout flare used in the analysis was £55.64.

Scenario 3

In Scenario 3 the cost of a gout flare used in the analysis was £28.49.

Scenario 4

In scenario 4 the cost of a gout flare used in the analysis was £53.61.

Scenario 5

In scenario 5 the cost of a gout flare used in the analysis was £29.61.

Scenario 6

In scenario 6 the cost of a gout flare used in the analysis was £54.59.

Scenario 7

In scenario 7 the cost of a gout flare used in the analysis was £27.22.

Scenario 8

In scenario 8 the cost of a gout flare used in the analysis was £52.20.

Scenario 9

In scenario 9 data for the proportion of people receiving each drug dosage was obtained from the FORWARD trial[28]. Data from the FORWARD[28] trial was used as an alternative data source for the proportion of people receiving each drug dose and the proportion of people achieving target serum urate levels due to the uncertainty surrounding these data inputs. This scenario analysis was conducted because, in general, the committee noted care for people with gout is sub-optimal, and it is therefore difficult know what proportion of people require what dose of drug to achieve target serum urate levels.

The committee acknowledged that the time horizon for the FORWARD trial[28] was 36 weeks and therefore shorter than the time horizon of our costing analysis. However, people will achieve target serum urate levels within one month if they are on the correct dose of ULT. The FORWARD trial employed a treat-to-target management strategy but because the maximum dose of allopurinol in the study was 600mg (as opposed to 900mg in the FAST trial) all people in the trial would have been up titrated to the maximum dose of allopurinol within the 36-week time horizon.

Data for the proportion of people receiving each drug dosage in the FORWARD trial[28] is presented in Table 62.

Table 62: The proportion of people receiving allopurinol and febuxostat from the FORWAD trial

Drug and drug dosage	Proportion of people receiving each drug[(a)]	Base case values[(b)]
Allopurinol 100mg	17.80%	10.00%
Allopurinol 200mg	25.60%	23.30%
Allopurinol 300mg	43.30%	50.90%
Allopurinol 400mg	7.80%	11.90%
Allopurinol 500mg	2.22%	2.73%
Allopurinol 600mg	3.30%	0.43%
Allopurinol 700mg	0.00%	0.35%

Drug and drug dosage	Proportion of people receiving each drug[(a)]	Base case values[(b)]
Allopurinol 800mg	0.00%	0.23%
Allopurinol 900mg	0.00%	0.16%
Febuxostat 80mg	78.30%	97.50%
Febuxostat 120mg	21.70%	2.50%

Sources:(a) FORWARD trial[28]

Data for the number of people achieving target serum urate levels was also obtained from this trial with 61% of people receiving allopurinol achieving target serum urate levels and 78% of people receiving febuxostat achieving target serum urate levels.

Of note, less people achieved target serum urate levels in the FORWARD trial[28] for both allopurinol and febuxostat compared to the base case (FAST trial[78]). In addition, more people received 120mg febuxostat (21.70% compared to 2.50%) and nobody received a dose of more than 600mg allopurinol.

In Scenario 9 the lowest cost of a gout flare was used (£27.22). Apart from these differences, all other data inputs where the same as the base case analysis.

Scenario 10

Scenario 10 was the same as Scenario 9 with exception that the highest cost of a gout flare was used in this scenario analysis (£55.64).

Scenario 11

In Scenario 11 data on the proportion of people receiving each drug dosage and the proportion of people achieving target serum urate levels was the same as the base case (FAST trial[78]). The lowest cost of a gout flare was used in the analysis (£27.22). However, the average number of flares for allopurinol for the first 3 months of treatment was obtained from the FACT and APEX trial (0.917)[10,100].

Scenario 12

Scenario 12 used the highest cost for a gout flare (£55.64), but in all other aspects was identical to Scenario 11.

Scenario 13

This scenario analysis used the same data inputs as Scenario 9 (FORWARD trial[28] data for the proportion of people receiving each drug dosage [Table 62] and achieving target serum urate levels, and the lowest cost for a gout flare [£27.22]). However, in this scenario the average number of flares for allopurinol was obtained from the FACT and APEX study (0.917)[10,100].

Scenario 14

Scenario 14 was identical to Scenario 13 apart from the fact the highest cost of a gout flare (£55.64) was used in this analysis.

Scenario 15

Scenario 15 used the pooled data from the FACT and APEX trial[10,100] (as used in the previous NICE TA) to obtain the proportion of people receiving each dose of allopurinol and

febuxostat, the proportion of people achieving target serum urate levels, and the average number of flares in the first three months of treatment. In this analysis people received a fixed dose of 300mg allopurinol. The proportion of people receiving each drug dose is reported in Table 63.

Table 63: The proportion of people receiving allopurinol and febuxostat from the FACT and APEX trial

Drug and drug dosage	Proportion of people receiving each drug
Allopurinol (fixed dose 300mg)	100.0%
Febuxostat 80mg	49.75%
Febuxostat 120mg	50.25%

Source: FACT and APEX trial[10,100]

In the FACT and APEX trial[10,100], 38% of people achieved target serum urate levels receiving a fixed dose of 300mg allopurinol, 73% of people achieved target serum urate levels receiving 80mg febuxostat, and 79% of people achieved target serum urate levels receiving 120mg of febuxostat.

In this scenario the lowest cost of a gout flare was used £27.22.

Scenario 16

This scenario was identical to Scenario 15 except in this analysis the highest cost for a gout flare was used (£55.64).

Scenario 17

Scenario 17 used data from the Doherty trial[29] for the proportion of people receiving different doses of allopurinol. The Doherty trial only provided data for the proportion of people receiving different doses of allopurinol because this study assessed the cost effectiveness of a treat-to-target management strategy where the majority of the trial population received allopurinol. In our costing analysis, we used data from the Doherty trial[29] for the proportion of people receiving allopurinol in the treat-to-target management arm at one year.

The committee acknowledged that although the Doherty trial specified a target serum urate level of 360 micromol/L, a large proportion of people (87.82%) also achieved target serum urate levels of less than 300micromol/L at one year (5mg/dl). Of note, the target serum urate level in the FAST[78], FORWARD[28], and FACT & APEX trials[10,100] was less than 360 micromol/L (6mg/dl). In general, the committee noted that it is easier to obtain a target serum urate level of less than 360 micromol/L, as opposed to less than 300 micromol/L, because serum urate levels do not need to decrease as much from baseline.

The committee discussed that the high proportion of people achieving a target serum urate level of less than 360 micromol/L and less than 300 micromol/L (94.96% and 87.82% respectively) in the Doherty trial likely explains why higher doses of allopurinol were received in this study as compared to the FAST[78] and FORWARD[28] trials. Although, our recommendations made as part of this guideline recommend a target serum urate level of less than 360 micromol/L. We also stipulated that for people who have tophi or chronic gouty arthritis, or for people who continue to have ongoing frequent flares despite having a serum urate level below 360 micromol/litre, a target serum urate level of less than 300 micromol/L may be appropriate. Therefore, to account for this and to vary the proportions of people receiving different doses of allopurinol we used the proportion of people receiving different doses of allopurinol at one year in the treat-to-target arm from the Doherty trial[29].

In general, the committee noted the proportion of people receiving different doses of allopurinol and achieving target serum urate levels likely falls between the range of doses observed in the FAST[78] and Doherty[29] trials, whereby more people may require higher doses of allopurinol than observed in the FAST trial[78]. However, the committee emphasised that in clinical practice, once employing a treat-to-target management strategy, it is easy and simple to up titrate people to higher doses of allopurinol when needed.

For this scenario analysis, the proportion of people receiving febuxostat was obtained from the FAST[78] trial in addition to the proportion of people achieving target serum urate levels.

In Doherty[29] it was noted 53% of people received 500mg or more of allopurinol. Therefore, synonymous to the base case analysis, we assumed 70% of the 53% of people received 500mg of allopurinol, 11% received 600mg, 9% received 700mg, 6% received 800mg, and 4% received 900mg. The proportion of people receiving each drug is detailed in Table 64.

Table 64: The proportion of people receiving allopurinol from the Doherty trial and febuxostat from the FAST trial

Drug and drug dosage	Proportion of people receiving each drug[(a)]	Base case values[(b)]
Allopurinol 100mg	0.49%	10.00%
Allopurinol 200mg	2.96%	23.30%
Allopurinol 300mg	16.75%	50.90%
Allopurinol 400mg	27.09%	11.90%
Allopurinol 500mg	36.90%	2.73%
Allopurinol 600mg	5.80%	0.43%
Allopurinol 700mg	4.74%	0.35%
Allopurinol 800mg	3.16%	0.23%
Allopurinol 900mg	2.11%	0.16%
Febuxostat 80mg	97.50%	97.50%
Febuxostat 120mg	2.50%	2.50%

Source: (a) Doherty trial [29] and FAST trial for the proportion of people receiving febuxostat[78]
(b) Doherty trial[29]. 53% of people received a dose of 500mg or more. It was assumed 70% of the 53% of people received 500mg of allopurinol, 11% received 600mg, 9% received 700mg, 6% received 800mg, and 4% received 900mg

This scenario analysis used the average number of flares for allopurinol from Borstad 2004[17] and the lowest cost of a gout flare (£27.22).

Scenario 18

This scenario was identical to Scenario 17 but the highest cost for a gout flare was used (£55.64) as opposed to the lowest cost for a gout flare.

Scenario 19

Scenario 19 was identical to Scenario 17 except the proportion of people receiving different dose of febuxostat and the proportion of people obtaining target serum urate levels was obtained from the FORWARD trial[28].

Overall, this scenario analysis used the Doherty trial for the proportion of people receiving allopurinol, the FORWARD trial[28] for the proportion of people receiving different doses of

febuxostat and achieving target serum urate levels, the average number of flares for allopurinol was taken Borstad 2004[17], and the lowest cost of a gout flare was used (£27.22). The proportion of people receiving each drug is detailed in Table 65.

Table 65: The proportion of people receiving allopurinol from the Doherty trial and febuxostat from the FORWARD trial

Drug and drug dosage	Proportion of people receiving each drug
Allopurinol 100mg	0.49%
Allopurinol 200mg	2.96%
Allopurinol 300mg	16.75%
Allopurinol 400mg	27.09%
Allopurinol 500mg	36.90%
Allopurinol 600mg	5.80%
Allopurinol 700mg	4.74%
Allopurinol 800mg	3.16%
Allopurinol 900mg	2.11%
Febuxostat 80mg	78.30%
Febuxostat 120mg	21.70%

Source: Doherty trial [29] and FORWARD trial[28]

Scenario 20

This Scenario used the highest cost for a gout flare (£55.64) but apart from this was identical to Scenario 19.

Scenario 21

Scenario 21 was the same as the base case analysis and used the following data; the FAST trial[78] data for the proportion of people receiving each drug dosage and achieving target serum urate levels, and Borstad 2004[17] for the average number of flares for allopurinol. The lowest cost of a gout flare settings were used, as in Scenario 7, but differed in that it assumed 50% of people go to A&E for a hospital treated flare as opposed to 100% used in all other analyses.

Results

A summary of the results is presented in Table 66. The base case data inputs for Scenario 1 – Scenario 8 include the proportion of people receiving each drug dosage and achieving target serum urate levels from the FAST trial[78], the number of gout flares for the first three months of treatment for allopurinol taken from Borstad[17], and the number of flares from the first three months of treatment for febuxostat taken from the FACT and APEX trials[10,100]. Scenarios 1, 3, 5 and 7 are the base case scenarios when 1% of people receive hospital treatment for a gout flare and scenarios 2, 4, 6 and 8 are the base case scenarios when 5% of people receive hospital treatment for a gout flare.

Table 66: Results summary

Scenario	Scenario description	Total cost allopurinol	Total cost febuxostat	Difference in cost (febuxostat vs allopurinol)	Cheapest intervention
Scenario 1, 3, 5, 7	Base case data inputs and the cost of a gout flare of £27.22 to £30.52	£137.67 to £142.31	£128.87 to £135.21	-£8.80 to -£7.10	Febuxostat
Scenario 2, 4, 6, 8	Base case data inputs and the cost of a gout flare of £52.20 to £55.64	£172.83 to £176.20	£176.89 to £183.50	£4.05 to £5.82	Allopurinol
Scenario 9	FORWARD trial[28] data for the proportion of people receiving each drug dose and achieving target serum urate levels. Lowest cost of a gout flare (£27.22)	£130.85	£185.57	£54.73	Allopurinol
Scenario 10	FORWARD trial data[28] for the proportion of people receiving each drug dose and achieving target serum urate levels. Highest cost of a gout flare (£55.64)	£171.73	£243.21	£71.48	Allopurinol
Scenario 11	FAST trial[78] data (base case) for the proportion of people receiving each drug dose and achieving target serum urate levels. The average number of flares for allopurinol for the first 3 months was obtained from the FACT and APEX trial[10,100]. Lowest cost of a gout flare (£27.22)	£147.67	£128.87	-£18.80	Febuxostat
Scenario 12	FAST trial[78] data (base case) for the proportion of people receiving each drug dose and achieving target serum urate levels. The average number of flares for allopurinol for the first 3 months was obtained from the FACT and APEX trial[10,100]. Highest cost of a gout flare (£55.64)	£198.13	£183.50	-£14.63	Febuxostat

Scenario	Scenario description	Total cost allopurinol	Total cost febuxostat	Difference in cost (febuxostat vs allopurinol)	Cheapest intervention
Scenario 13	FORWARD trial[28] data for the proportion of people receiving each drug dose and achieving target serum urate levels. The average number of flares for allopurinol for the first 3 months was obtained from the FACT and APEX trial[10,100]. Lowest cost of a gout flare (£27.22)	£140.85	£185.57	£44.72	Allopurinol
Scenario 14	FORWARD trial[28] data for the proportion of people receiving each drug dose and achieving target serum urate levels. The average number of flares for allopurinol for the first 3 months was obtained from the FACT and APEX trial[10,100]. Highest cost of a gout flare (£55.64)	£192.17	£243.21	£51.03	Allopurinol
Scenario 15	FACT and APEX trial[10,100] for the proportion of people receiving each drug dose, achieving target serum urate levels, and the average number of flares for allopurinol for the first 3 months. Lowest cost of a gout flare (£27.22)	£111.83	£268.87	£157.14	Allopurinol
Scenario 16	FACT and APEX trial[10,100] for the proportion of people receiving each drug dose, achieving target serum urate levels, and the average number of flares for allopurinol for the first 3 months. Highest cost of a gout flare (£55.64)	£162.43	£330.15	£167.72	Allopurinol
Scenario 17	Doherty trial[29] for the proportion of people receiving different doses of allopurinol. FAST trial[78] for the proportion of people receiving different doses of febuxostat and achieving target serum urate levels. Lowest cost of a gout flare (£27.22)	£184.51	£128.87	-£55.64	Febuxostat
Scenario 18	Doherty trial[29] for the proportion of people receiving different doses of allopurinol. FAST trial[78] for the proportion of people receiving different doses of febuxostat and achieving target serum urate levels. Highest cost of a gout flare (£55.64)	£230.72	£183.50	-£47.23	Febuxostat
Scenario 19	Doherty trial[29] for the proportion of people receiving different doses of allopurinol. FORWARD trial[28] for the proportion of people receiving different doses of febuxostat	£185.35	£185.57	£0.22	Allopurinol

Scenario	Scenario description	Total cost allopurinol	Total cost febuxostat	Difference in cost (febuxostat vs allopurinol)	Cheapest intervention
	and achieving target serum urate levels. Lowest cost of a gout flare (£27.22)				
Scenario 20	Doherty trial[29] for the proportion of people receiving different doses of allopurinol. FORWARD trial[28] for the proportion of people receiving different doses of febuxostat and achieving target serum urate levels. Highest cost of a gout flare (£55.64)	£232.43	£243.21	£10.78	Allopurinol
Scenario 21	Base case data inputs and 50% of people go to A&E for a hospital treated flare as opposed to 100%. Lowest cost of a gout flare settings for all additional cost of a gout flare inputs.	£138.36	£129.81	-£8.54	Febuxostat

Individual Scenario analysis results

The breakdown of results for the individual scenario analyses are presented below.

Scenario 1 – Base case data inputs and the cost of a gout flare of £30.52

Table 67: Scenario 1 results

Drug and drug dosage	Trial weighting	ULT cost 1 year	Prophylaxis	Total drug cost with weighting	Initiation & up titration costs	Cost of flares in the first 3 months	Cost of flares from up titration	Probability of a flare post 3 months	Cost of a flare post 3 months
Allopurinol 100mg	10.0%	£12.91	£3.69	£1.66	£3.42	£17.40	£0.00	80%	£24.54
Allopurinol 200mg	23.30%	£24.74	£7.39	£7.48	£11.35		£0.00		
Allopurinol 300mg	50.90%	£18.11	£11.08	£14.86	£32.19		£0.00		
Allopurinol 400mg	11.90%	£34.74	£14.77	£5.89	£9.25		£0.55		
Allopurinol 500mg	2.73%	£36.31	£18.46	£1.50	£5.65		£0.25		
Allopurinol 600mg	0.43%	£31.75	£22.16	£0.23	£4.38		£0.06		

Drug and drug dosage	Trial weighting	ULT cost 1 year	Prophylaxis	Total drug cost with weighting	Initiation & up titration costs	Cost of flares in the first 3 months	Cost of flares from up titration	Probability of a flare post 3 months	Cost of a flare post 3 months
Allopurinol 700mg	0.35%	£38.21	£25.85	£0.22	£0.43		£0.07		
Allopurinol 800mg	0.23%	£43.51	£29.54	£0.17	£0.32		£0.05		
Allopurinol 900mg	0.16%	£40.93	£33.23	£0.12	£0.23		£0.04		
Febuxostat 80mg	97.50%	£31.68	£3.69	£34.49	£33.32	£34.21	£0.00	79%	£24.12
Febuxostat 120mg	2.50%	£293.73	£7.39	£7.53	£1.22	£47.18	£0.00	79%	£24.13
Allopurinol all				**£32.13**	**£67.21**	**£17.40**	**£1.03**		**£24.554**
Febuxostat all				**£42.01**	**£34.54**	**£34.54**	**£0.00**		**£24.12**

The total costs of one year of treatment with allopurinol were £142.31 and the total costs for Febuxostat were £135.21

Scenario 2 – Base case data inputs and the cost of a gout flare of £55.64

Table 68: Scenario 2 results

Drug and drug dosage	Trial weighting	ULT cost 1 year	Prophylaxis	Total drug cost with weighting	Initiation & up titration costs	Cost of flares in the first 3 months	Cost of flares from up titration	Probability of a flare post 3 months	Cost of a flare post 3 months
Allopurinol 100mg	10.0%	£12.91	£3.69	£1.66	£3.42	£31.72	£0.00	80%	£44.74
Allopurinol 200mg	23.30%	£24.74	£7.39	£7.48	£11.35		£0.00		
Allopurinol 300mg	50.90%	£18.11	£11.08	£14.86	£32.19		£0.00		
Allopurinol 400mg	11.90%	£34.74	£14.77	£5.89	£9.25		£1.01		
Allopurinol 500mg	2.73%	£36.31	£18.46	£1.50	£5.65		£0.46		
Allopurinol 600mg	0.43%	£31.75	£22.16	£0.23	£4.38		£0.11		
Allopurinol 700mg	0.35%	£38.21	£25.85	£0.22	£0.43		£0.12		
Allopurinol 800mg	0.23%	£43.51	£29.54	£0.17	£0.32		£0.10		
Allopurinol 900mg	0.16%	£40.93	£33.23	£0.12	£0.23		£0.08		
Febuxostat 80mg	97.50%	£31.68	£3.69	£34.49	£33.32	£62.37	£0.00	79%	£43.98
Febuxostat 120mg	2.50%	£293.73	£7.39	£7.53	£1.22	£86.02	£0.00	79%	£43.99
Allopurinol all				**£32.13**	**£67.21**	**£31.72**	**£1.87**		**£44.74**
Febuxostat all				**£42.01**	**£34.54**	**£62.97**	**£0.00**		**£43.98**

The total cost of allopurinol for one year of treatment was £177.68 and the total cost for febuxostat was £183.50

Scenario 3 – Base case data inputs and the cost of a gout flare of £28.49

Table 69: Scenario 3 results

Drug and drug dosage	Trial weighting	ULT cost 1 year	Prophylaxis	Total drug cost with weighting	Initiation & up titration costs	Cost of flares in the first 3 months	Cost of flares from up titration	Probability of a flare post 3 months	Cost of a flare post 3 months
Allopurinol 100mg	10.0%	£12.91	£3.69	£1.66	£3.42	£16.24	£0.00	80%	£22.91
Allopurinol 200mg	23.30%	£24.74	£7.39	£7.48	£11.35		£0.00		
Allopurinol 300mg	50.90%	£18.11	£11.08	£14.86	£32.19		£0.00		
Allopurinol 400mg	11.90%	£34.74	£14.77	£5.89	£9.25		£0.52		
Allopurinol 500mg	2.73%	£36.31	£18.46	£1.50	£5.65		£0.24		
Allopurinol 600mg	0.43%	£31.75	£22.16	£0.23	£4.38		£0.06		
Allopurinol 700mg	0.35%	£38.21	£25.85	£0.22	£0.43		£0.06		
Allopurinol 800mg	0.23%	£43.51	£29.54	£0.17	£0.32		£0.05		
Allopurinol 900mg	0.16%	£40.93	£33.23	£0.12	£0.23		£0.04		
Febuxostat 80mg	97.50%	£31.68	£3.69	£34.49	£33.32	£31.93	£0.00	79%	£22.52
Febuxostat 120mg	2.50%	£293.73	£7.39	£7.53	£1.22	£44.04	£0.00	79%	£22.52
Allopurinol all				**£32.13**	**£67.21**	**£16.24**	**£0.96**		**£22.91**
Febuxostat all				**£42.01**	**£34.54**	**£32.24**	**£0.00**		**£22.52**

The total cost of allopurinol for one year of treatment was £139.45 and the total cost for febuxostat was £131.30.

Scenario 4 – Base case data inputs and the cost of a gout flare of £53.61

Table 70: Scenario 4 results

Drug and drug dosage	Trial weighting	ULT cost 1 year	Prophylaxis	Total drug cost with weighting	Initiation & up titration costs	Cost of flares in the first 3 months	Cost of flares from up titration	Probability of a flare post 3 months	Cost of a flare post 3 months
Allopurinol 100mg	10.0%	£12.91	£3.69	£1.66	£3.42	£30.56	£0.00	80%	£43.11
Allopurinol 200mg	23.30%	£24.74	£7.39	£7.48	£11.35		£0.00		
Allopurinol 300mg	50.90%	£18.11	£11.08	£14.86	£32.19		£0.00		
Allopurinol 400mg	11.90%	£34.74	£14.77	£5.89	£9.25		£0.97		
Allopurinol 500mg	2.73%	£36.31	£18.46	£1.50	£5.65		£0.44		
Allopurinol 600mg	0.43%	£31.75	£22.16	£0.23	£4.38		£0.10		
Allopurinol 700mg	0.35%	£38.21	£25.85	£0.22	£0.43		£0.11		
Allopurinol 800mg	0.23%	£43.51	£29.54	£0.17	£0.32		£0.10		
Allopurinol 900mg	0.16%	£40.93	£33.23	£0.12	£0.23		£0.08		
Febuxostat 80mg	97.50%	£31.68	£3.69	£34.49	£33.32	£60.10	£0.00	79%	£42.38
Febuxostat 120mg	2.50%	£293.73	£7.39	£7.53	£1.22	£82.88	£0.00	79%	£42.38
Allopurinol all				**£32.13**	**£67.21**	**£30.56**	**£1.81**		**£43.11**
Febuxostat all				**£42.01**	**£34.54**	**£60.67**	**£0.00**		**£42.38**

The total cost of allopurinol for one year of treatment was £174.82 and the total cost for febuxostat was £179.59.

Scenario 5 – Base case data inputs and the cost of a gout flare of £29.61

Table 71: Scenario 5 results

Drug and drug dosage	Trial weighting	ULT cost 1 year	Prophylaxis	Total drug cost with weighting	Initiation & up titration costs	Cost of flares in the first 3 months	Cost of flares from up titration	Probability of a flare post 3 months	Cost of a flare post 3 months
Allopurinol 100mg	10.0%	£12.91	£3.69	£1.66	£3.42	£16.88	£0.00	80%	£23.81
Allopurinol 200mg	23.30%	£24.74	£7.39	£7.48	£11.35		£0.00		
Allopurinol 300mg	50.90%	£18.11	£11.08	£14.86	£32.19		£0.00		
Allopurinol 400mg	11.90%	£34.74	£14.77	£5.89	£9.25		£0.54		
Allopurinol 500mg	2.73%	£36.31	£18.46	£1.50	£5.65		£0.25		
Allopurinol 600mg	0.43%	£31.75	£22.16	£0.23	£4.38		£0.06		
Allopurinol 700mg	0.35%	£38.21	£25.85	£0.22	£0.43		£0.06		
Allopurinol 800mg	0.23%	£43.51	£29.54	£0.17	£0.32		£0.05		
Allopurinol 900mg	0.16%	£40.93	£33.23	£0.12	£0.23		£0.04		
Febuxostat 80mg	97.50%	£31.68	£3.69	£34.49	£33.32	£33.20	£0.00	79%	£23.41
Febuxostat 120mg	2.50%	£293.73	£7.39	£7.53	£1.22	£45.78	£0.00	79%	£23.41
Allopurinol all				**£32.13**	**£67.21**	**£16.88**	**£1.00**		**£23.81**
Febuxostat all				**£42.01**	**£34.54**	**£33.51**	**£0.00**		**£23.41**

The total cost of allopurinol for one year of treatment was £141.03 and the total cost for febuxostat was £133.47.

Scenario 6 – Base case data inputs and the cost of a gout flare of £54.59

Table 72: Scenario 6 results

Drug and drug dosage	Trial weighting	ULT cost 1 year	Prophylaxis	Total drug cost with weighting	Initiation & up titration costs	Cost of flares in the first 3 months	Cost of flares from up titration	Probability of a flare post 3 months	Cost of a flare post 3 months
Allopurinol 100mg	10.0%	£12.91	£3.69	£1.66	£3.42	£31.12	£0.00	80%	£43.90
Allopurinol 200mg	23.30%	£24.74	£7.39	£7.48	£11.35		£0.00		
Allopurinol 300mg	50.90%	£18.11	£11.08	£14.86	£32.19		£0.00		
Allopurinol 400mg	11.90%	£34.74	£14.77	£5.89	£9.25		£0.99		
Allopurinol 500mg	2.73%	£36.31	£18.46	£1.50	£5.65		£0.45		
Allopurinol 600mg	0.43%	£31.75	£22.16	£0.23	£4.38		£0.11		
Allopurinol 700mg	0.35%	£38.21	£25.85	£0.22	£0.43		£0.12		
Allopurinol 800mg	0.23%	£43.51	£29.54	£0.17	£0.32		£0.10		
Allopurinol 900mg	0.16%	£40.93	£33.23	£0.12	£0.23		£0.08		
Febuxostat 80mg	97.50%	£31.68	£3.69	£34.49	£33.32	£61.20	£0.00	79%	£43.15
Febuxostat 120mg	2.50%	£293.73	£7.39	£7.53	£1.22	£84.40	£0.00	79%	£43.16
Allopurinol all				**£32.13**	**£67.21**	**£31.20**	**£1.84**		**£43.90**
Febuxostat all				**£42.01**	**£34.54**	**£61.78**	**£0.00**		**£43.15**

The total cost of allopurinol for one year of treatment was £176.20 and the total cost for febuxostat was £181.48.

Scenario 7 – Base case data inputs and the cost of a gout flare of £27.22

Table 73: Scenario 7 results

Drug and drug dosage	Trial weighting	ULT cost 1 year	Prophylaxis	Total drug cost with weighting	Initiation & up titration costs	Cost of flares in the first 3 months	Cost of flares from up titration	Probability of a flare post 3 months	Cost of a flare post 3 months
Allopurinol 100mg	10.0%	£12.91	£3.69	£1.66	£3.42	£15.52	£0.00	80%	£21.89
Allopurinol 200mg	23.30%	£24.74	£7.39	£7.48	£11.35		£0.00		
Allopurinol 300mg	50.90%	£18.11	£11.08	£14.86	£32.19		£0.00		
Allopurinol 400mg	11.90%	£34.74	£14.77	£5.89	£9.25		£0.49		
Allopurinol 500mg	2.73%	£36.31	£18.46	£1.50	£5.65		£0.23		
Allopurinol 600mg	0.43%	£31.75	£22.16	£0.23	£4.38		£0.05		
Allopurinol 700mg	0.35%	£38.21	£25.85	£0.22	£0.43		£0.06		
Allopurinol 800mg	0.23%	£43.51	£29.54	£0.17	£0.32		£0.05		
Allopurinol 900mg	0.16%	£40.93	£33.23	£0.12	£0.23		£0.04		
Febuxostat 80mg	97.50%	£31.68	£3.69	£34.49	£33.32	£30.52	£0.00	79%	£21.52
Febuxostat 120mg	2.50%	£293.73	£7.39	£7.53	£1.22	£42.09	£0.00	79%	£21.52
Allopurinol all				**£32.13**	**£67.21**	**£15.52**	**£0.92**		**£21.89**
Febuxostat all				**£42.01**	**£34.54**	**£30.81**	**£0.00**		**£21.52**

The total cost of allopurinol for one year of treatment was £137.67 and the total cost for febuxostat was £128.87.

Scenario 8 – Base case data inputs and the cost of a gout flare of £52.20

Table 74: Scenario 8 results

Drug and drug dosage	Trial weighting	ULT cost 1 year	Prophylaxis	Total drug cost with weighting	Initiation & up titration costs	Cost of flares in the first 3 months	Cost of flares from up titration	Probability of a flare post 3 months	Cost of a flare post 3 months
Allopurinol 100mg	10.0%	£12.91	£3.69	£1.66	£3.42	£29.75	£0.00	80%	£41.98
Allopurinol 200mg	23.30%	£24.74	£7.39	£7.48	£11.35		£0.00		
Allopurinol 300mg	50.90%	£18.11	£11.08	£14.86	£32.19		£0.00		
Allopurinol 400mg	11.90%	£34.74	£14.77	£5.89	£9.25		£0.94		
Allopurinol 500mg	2.73%	£36.31	£18.46	£1.50	£5.65		£0.43		
Allopurinol 600mg	0.43%	£31.75	£22.16	£0.23	£4.38		£0.10		
Allopurinol 700mg	0.35%	£38.21	£25.85	£0.22	£0.43		£0.11		
Allopurinol 800mg	0.23%	£43.51	£29.54	£0.17	£0.32		£0.09		
Allopurinol 900mg	0.16%	£40.93	£33.23	£0.12	£0.23		£0.07		
Febuxostat 80mg	97.50%	£31.68	£3.69	£34.49	£33.32	£58.52	£0.00	79%	£41.26
Febuxostat 120mg	2.50%	£293.73	£7.39	£7.53	£1.22	£80.70	£0.00	79%	£41.27
Allopurinol all				**£32.13**	**£67.21**	**£29.75**	**£1.76**		**£41.98**
Febuxostat all				**£42.01**	**£34.54**	**£59.07**	**£0.00**		**£41.26**

The total cost of allopurinol for one year of treatment was £172.83 and the total cost for febuxostat was £176.89.

Scenario 9 – FORWARD trial data for the proportion of people receiving each drug and achieving target serum urate levels. Lowest cost of a gout flare (£27.22)

Table 75: Scenario 9 results

Drug and drug dosage	Trial weighting	ULT cost 1 year	Prophylaxis	Total drug cost with weighting	Initiation & up titration costs	Cost of flares in the first 3 months	Cost of flares from up titration	Probability of a flare post 3 months	Cost of a flare post 3 months
Allopurinol 100mg	17.80%	£12.91	£3.69	£2.95	£6.08	£15.52	£0.00	83%	£22.73
Allopurinol 200mg	25.60%	£24.74	£7.39	£8.22	£12.47		£0.00		
Allopurinol 300mg	43.30%	£18.11	£11.08	£12.64	£27.38		£0.00		
Allopurinol 400mg	7.80%	£34.74	£14.77	£3.86	£6.07		£0.32		
Allopurinol 500mg	2.22%	£36.31	£18.46	£1.22	£3.96		£0.18		
Allopurinol 600mg	3.30%	£31.75	£22.16	£1.78	£5.06		£0.41		
Allopurinol 700mg	0.00%	£38.21	£25.85	£0.00	£0.00		£0.00		
Allopurinol 800mg	0.00%	£43.51	£29.54	£0.00	£0.00		£0.00		
Allopurinol 900mg	0.00%	£40.93	£33.23	£0.00	£0.00		£0.00		
Febuxostat 80mg	78.30%	£31.68	£3.69	£27.69	£26.76	£30.52	£0.00	81%	£22.18
Febuxostat 120mg	21.70%	£293.73	£7.39	£65.34	£10.57	£42.09	£0.00	82%	£22.21
Allopurinol all				**£30.67**	**£61.02**	**£15.52**	**£0.92**		**£22.73**
Febuxostat all				**£93.04**	**£37.33**	**£32.03**	**£0.00**		**£22.18**

The total cost of allopurinol for one year of treatment was £130.85 and the total cost for febuxostat was £185.57.

Scenario 10 – FORWARD trial data for the proportion of people receiving each drug and achieving target serum urate levels. Highest cost of a gout flare (£55.64)

Table 76: Scenario 10 results

Drug and drug dosage	Trial weighting	ULT cost 1 year	Prophylaxis	Total drug cost with weighting	Initiation & up titration costs	Cost of flares in the first 3 months	Cost of flares from up titration	Probability of a flare post 3 months	Cost of a flare post 3 months
Allopurinol 100mg	17.80%	£12.91	£3.69	£2.95	£6.08	£31.72	£0.00	83%	£46.45
Allopurinol 200mg	25.60%	£24.74	£7.39	£8.22	£12.47		£0.00		
Allopurinol 300mg	43.30%	£18.11	£11.08	£12.64	£27.38		£0.00		
Allopurinol 400mg	7.80%	£34.74	£14.77	£3.86	£6.07		£0.66		
Allopurinol 500mg	2.22%	£36.31	£18.46	£1.22	£3.96		£0.38		
Allopurinol 600mg	3.30%	£31.75	£22.16	£1.78	£5.06		£0.84		
Allopurinol 700mg	0.00%	£38.21	£25.85	£0.00	£0.00		£0.00		
Allopurinol 800mg	0.00%	£43.51	£29.54	£0.00	£0.00		£0.00		
Allopurinol 900mg	0.00%	£40.93	£33.23	£0.00	£0.00		£0.00		
Febuxostat 80mg	78.30%	£31.68	£3.69	£27.69	£26.76	£62.37	£0.00	81%	£45.33
Febuxostat 120mg	21.70%	£293.73	£7.39	£65.34	£10.57	£86.02	£0.00	82%	£45.39
Allopurinol all				**£30.67**	**£61.02**	**£31.72**	**£1.87**		**£46.45**
Febuxostat all				**£93.04**	**£37.33**	**£67.51**	**£0.00**		**£45.34**

The total cost of allopurinol for one year of treatment was £171.73 and the total cost for febuxostat was £243.21.

Scenario 11 – FAST trial data (base case) for the proportion of people receiving each drug and achieving target serum urate levels. The average number of flares for allopurinol for the first 3 months was obtained from the FACT and APEX trial. Lowest cost of a gout flare (£27.22)

Table 77: Scenario 11 results

Drug and drug dosage	Trial weighting	ULT cost 1 year	Prophylaxis	Total drug cost with weighting	Initiation & up titration costs	Cost of flares in the first 3 months	Cost of flares from up titration	Probability of a flare post 3 months	Cost of a flare post 3 months
Allopurinol 100mg	10.0%	£12.91	£3.69	£1.66	£3.42	£24.96	£0.00	80%	£21.89
Allopurinol 200mg	23.30%	£24.74	£7.39	£7.48	£11.35		£0.00		
Allopurinol 300mg	50.90%	£18.11	£11.08	£14.86	£32.19		£0.00		
Allopurinol 400mg	11.90%	£34.74	£14.77	£5.89	£9.25		£0.79		
Allopurinol 500mg	2.73%	£36.31	£18.46	£1.50	£5.65		£0.36		
Allopurinol 600mg	0.43%	£31.75	£22.16	£0.23	£4.38		£0.09		
Allopurinol 700mg	0.35%	£38.21	£25.85	£0.22	£0.43		£0.09		
Allopurinol 800mg	0.23%	£43.51	£29.54	£0.17	£0.32		£0.08		
Allopurinol 900mg	0.16%	£40.93	£33.23	£0.12	£0.23		£0.06		
Febuxostat 80mg	97.50%	£31.68	£3.69	£34.49	£33.32	£30.53	£0.00	79%	£21.52
Febuxostat 120mg	2.50%	£293.73	£7.39	£7.53	£1.22	£42.09	£0.00	79%	£21.52
Allopurinol all				**£32.13**	**£67.21**	**£24.96**	**£1.47**		**£21.89**
Febuxostat all				**£42.01**	**£34.54**	**£30.81**	**£0.00**		**£21.52**

The total cost of allopurinol for one year of treatment was £147.67 and the total cost for febuxostat was £128.87.

Scenario 12 – FAST trial data (base case) for the proportion of people receiving each drug and achieving target serum urate levels. The average number of flares for allopurinol for the first 3 months was obtained from the FACT and APEX trial. Highest cost of a gout flare (£55.64)

Table 78: Scenario 12 results

Drug and drug dosage	Trial weighting	ULT cost 1 year	Prophylaxis	Total drug cost with weighting	Initiation & up titration costs	Cost of flares in the first 3 months	Cost of flares from up titration	Probability of a flare post 3 months	Cost of a flare post 3 months
Allopurinol 100mg	10.0%	£12.91	£3.69	£1.66	£3.42	£51.09	£0.00	80%	£44.74
Allopurinol 200mg	23.30%	£24.74	£7.39	£7.48	£11.35		£0.00		
Allopurinol 300mg	50.90%	£18.11	£11.08	£14.86	£32.19		£0.00		
Allopurinol 400mg	11.90%	£34.74	£14.77	£5.89	£9.25		£1.62		
Allopurinol 500mg	2.73%	£36.31	£18.46	£1.50	£5.65		£0.74		
Allopurinol 600mg	0.43%	£31.75	£22.16	£0.23	£4.38		£0.17		
Allopurinol 700mg	0.35%	£38.21	£25.85	£0.22	£0.43		£0.19		
Allopurinol 800mg	0.23%	£43.51	£29.54	£0.17	£0.32		£0.16		
Allopurinol 900mg	0.16%	£40.93	£33.23	£0.12	£0.23		£0.13		
Febuxostat 80mg	97.50%	£31.68	£3.69	£34.49	£33.32	£62.37	£0.00	79%	£43.98
Febuxostat 120mg	2.50%	£293.73	£7.39	£7.53	£1.22	£86.02	£0.00	79%	£43.99
Allopurinol all				**£32.13**	**£67.21**	**£51.02**	**£3.01**		**£44.74**
Febuxostat all				**£42.01**	**£34.54**	**£62.97**	**£0.00**		**£43.99**

The total cost of allopurinol for one year of treatment was £198.13 and the total cost for febuxostat was £183.50.

Scenario 13 – FORWARD trial data for the proportion of people receiving each drug and achieving target serum urate levels. The average number of flares for allopurinol for the first 3 months was obtained from the FACT and APEX trial. Lowest cost of a gout flare (£27.22)

Table 79: Scenario 13 results

Drug and drug dosage	Trial weighting	ULT cost 1 year	Prophylaxis	Total drug cost with weighting	Initiation & up titration costs	Cost of flares in the first 3 months	Cost of flares from up titration	Probability of a flare post 3 months	Cost of a flare post 3 months
Allopurinol 100mg	17.80%	£12.91	£3.69	£2.95	£6.08	£24.96	£0.00	83%	£22.73
Allopurinol 200mg	25.60%	£24.74	£7.39	£8.22	£12.47		£0.00		
Allopurinol 300mg	43.30%	£18.11	£11.08	£12.64	£27.38		£0.00		
Allopurinol 400mg	7.80%	£34.74	£14.77	£3.86	£6.07		£0.52		
Allopurinol 500mg	2.22%	£36.31	£18.46	£1.22	£3.96		£0.30		
Allopurinol 600mg	3.30%	£31.75	£22.16	£1.78	£5.06		£0.66		
Allopurinol 700mg	0.00%	£38.21	£25.85	£0.00	£0.00		£0.00		
Allopurinol 800mg	0.00%	£43.51	£29.54	£0.00	£0.00		£0.00		
Allopurinol 900mg	0.00%	£40.93	£33.23	£0.00	£0.00		£0.00		
Febuxostat 80mg	78.30%	£31.68	£3.69	£27.69	£26.76	£30.52	£0.00	81%	£22.18
Febuxostat 120mg	21.70%	£293.73	£7.39	£65.34	£10.57	£42.09	£0.00	82%	£22.21
Allopurinol all				**£30.67**	**£61.02**	**£24.96**	**£1.47**		**£22.73**
Febuxostat all				**£93.04**	**£37.33**	**£33.03**	**£0.00**		**£22.18**

The total cost of allopurinol for one year of treatment was £140.85 and the total cost for febuxostat was £185.57.

Scenario 14 – FORWARD trial data for the proportion of people receiving each drug and achieving target serum urate levels. The average number of flares for allopurinol for the first 3 months was obtained from the FACT and APEX trial. Highest cost of a gout flare (£55.64)

Table 80: Scenario 14 results

Drug and drug dosage	Trial weighting	ULT cost 1 year	Prophylaxis	Total drug cost with weighting	Initiation & up titration costs	Cost of flares in the first 3 months	Cost of flares from up titration	Probability of a flare post 3 months	Cost of a flare post 3 months
Allopurinol 100mg	17.80%	£12.91	£3.69	£2.95	£6.08	£51.02	£0.00	83%	£46.45
Allopurinol 200mg	25.60%	£24.74	£7.39	£8.22	£12.47		£0.00		
Allopurinol 300mg	43.30%	£18.11	£11.08	£12.64	£27.38		£0.00		
Allopurinol 400mg	7.80%	£34.74	£14.77	£3.86	£6.07		£1.06		
Allopurinol 500mg	2.22%	£36.31	£18.46	£1.22	£3.96		£0.60		
Allopurinol 600mg	3.30%	£31.75	£22.16	£1.78	£5.06		£1.35		
Allopurinol 700mg	0.00%	£38.21	£25.85	£0.00	£0.00		£0.00		
Allopurinol 800mg	0.00%	£43.51	£29.54	£0.00	£0.00		£0.00		
Allopurinol 900mg	0.00%	£40.93	£33.23	£0.00	£0.00		£0.00		
Febuxostat 80mg	78.30%	£31.68	£3.69	£27.69	£26.76	£62.37	£0.00	81%	£45.33
Febuxostat 120mg	21.70%	£293.73	£7.39	£65.34	£10.57	£86.02	£0.00	82%	£45.39
Allopurinol all				**£30.67**	**£61.02**	**£51.02**	**£3.01**		**£46.45**
Febuxostat all				**£93.04**	**£37.33**	**£67.51**	**£0.00**		**£45.34**

The total cost of allopurinol for one year of treatment was £192.17 and the total cost for febuxostat was £243.21.

Scenario 15 – FACT and APEX trial for the proportion of people receiving each drug, achieving target serum urate levels, and the average number of flares for allopurinol for the first 3 months. Lowest cost of a gout flare (£27.22)

Table 81: Scenario 15 results

Drug and drug dosage	Trial weighting	ULT cost 1 year	Prophylaxis	Total drug cost with weighting	Initiation & up titration costs	Cost of flares in the first 3 months	Cost of flares from up titration	Probability of a flare post 3 months	Cost of a flare post 3 months
Allopurinol 100mg	0.00%	£12.91	£3.69	£0.00	£0.00	£24.96	£0.00	86%	£23.51
Allopurinol 200mg	0.00%	£24.74	£7.39	£0.00	£0.00		£0.00		
Allopurinol 300mg	100.00%	£18.11	£11.08	£29.19	£34.17		£0.00		
Allopurinol 400mg	0.00%	£34.74	£14.77	£0.00	£0.00		£0.00		
Allopurinol 500mg	0.00%	£36.31	£18.46	£0.00	£0.00		£0.00		
Allopurinol 600mg	0.00%	£31.75	£22.16	£0.00	£0.00		£0.00		
Allopurinol 700mg	0.00%	£38.21	£25.85	£0.00	£0.00		£0.00		
Allopurinol 800mg	0.00%	£43.51	£29.54	£0.00	£0.00		£0.00		
Allopurinol 900mg	0.00%	£40.93	£33.23	£0.00	£0.00		£0.00		
Febuxostat 80mg	49.75%	£31.68	£3.69	£17.60	£17.00	£30.52	£0.00	82%	£22.36
Febuxostat 120mg	50.25%	£293.73	£7.39	£151.53	£24.47	£42.09	£0.00	81%	£22.18
Allopurinol all				**£29.19**	**£34.17**	**£24.96**	**£0.00**		**£23.51**
Febuxostat all				**£169.90**	**£41.47**	**£36.33**	**£0.00**		**£22.27**

The total cost of allopurinol for one year of treatment was £111.83 and the total cost for febuxostat was £268.97.

Scenario 16 – FACT and APEX trial for the proportion of people receiving each drug, achieving target serum urate levels, and the average number of flares for allopurinol for the first 3 months. Highest cost of a gout flare (£55.64)

Table 82: Scenario 16 results

Drug and drug dosage	Trial weighting	ULT cost 1 year	Prophylaxis	Total drug cost with weighting	Initiation & up titration costs	Cost of flares in the first 3 months	Cost of flares from up titration	Probability of a flare post 3 months	Cost of a flare post 3 months
Allopurinol 100mg	0.00%	£12.91	£3.69	£0.00	£0.00	£51.02	£0.00	86%	£48.05
Allopurinol 200mg	0.00%	£24.74	£7.39	£0.00	£0.00		£0.00		
Allopurinol 300mg	100.00%	£18.11	£11.08	£29.19	£34.17		£0.00		
Allopurinol 400mg	0.00%	£34.74	£14.77	£0.00	£0.00		£0.00		
Allopurinol 500mg	0.00%	£36.31	£18.46	£0.00	£0.00		£0.00		
Allopurinol 600mg	0.00%	£31.75	£22.16	£0.00	£0.00		£0.00		
Allopurinol 700mg	0.00%	£38.21	£25.85	£0.00	£0.00		£0.00		
Allopurinol 800mg	0.00%	£43.51	£29.54	£0.00	£0.00		£0.00		
Allopurinol 900mg	0.00%	£40.93	£33.23	£0.00	£0.00		£0.00		
Febuxostat 80mg	49.75%	£31.68	£3.69	£17.60	£17.00	£62.37	£0.00	82%	£45.71
Febuxostat 120mg	50.25%	£293.73	£7.39	£151.53	£24.47	£86.02	£0.00	81%	£45.33
Allopurinol all				**£29.19**	**£34.17**	**£51.02**	**£0.00**		**£48.05**
Febuxostat all				**£168.905**	**£41.47**	**£74.26**	**£0.00**		**£45.52**

The total cost of allopurinol for one year of treatment was £162.43 and the total cost for febuxostat was £330.15.

Scenario 17 – Doherty trial for the proportion of people receiving allopurinol. FAST trial for the proportion of people receiving febuxostat and achieving target serum urate levels. Lowest cost of a gout flare (£27.22)

Table 83: Scenario 17 results

Drug and drug dosage	Trial weighting	ULT cost 1 year	Prophylaxis	Total drug cost with weighting	Initiation & up titration costs	Cost of flares in the first 3 months	Cost of flares from up titration	Probability of a flare post 3 months	Cost of a flare post 3 months
Allopurinol 100mg	0.49%	£12.91	£3.69	£0.08	£0.17	£15.52	£0.00	80%	£21.89
Allopurinol 200mg	2.96%	£24.74	£7.39	£0.95	£1.44		£0.00		
Allopurinol 300mg	16.75%	£18.11	£11.08	£4.89	£10.59		£0.00		
Allopurinol 400mg	27.09%	£34.74	£14.77	£13.41	£21.07		£1.12		
Allopurinol 500mg	36.90%	£36.31	£18.46	£21.21	£30.70		£3.05		
Allopurinol 600mg	5.80%	£31.75	£22.16	£3.13	£13.47		£0.72		
Allopurinol 700mg	4.74%	£38.21	£25.85	£3.04	£5.76		£0.79		
Allopurinol 800mg	3.16%	£43.51	£29.54	£2.31	£4.30		£0.65		
Allopurinol 900mg	2.11%	£40.93	£33.23	£1.56	£3.17		£0.52		
Febuxostat 80mg	97.50%	£31.68	£3.69	£34.49	£33.32	£30.52	£0.00	79%	£21.52
Febuxostat 120mg	2.50%	£293.73	£7.39	£7.53	£1.22	£42.09	£0.00	79%	£21.52
Allopurinol all				**£49.58**	**£90.67**	**£15.52**	**£6.86**		**£21.89**
Febuxostat all				**£42.01**	**£34.54**	**£30.81**	**£0.00**		**£21.52**

The total cost of allopurinol for one year of treatment was £184.51 and the total cost for febuxostat was £128.87.

Scenario 18 – Doherty trial for the proportion of people receiving allopurinol. FORWARD trial for the proportion of people receiving febuxostat and achieving target serum urate levels. Highest cost of a gout flare (£55.64)

Table 84: Scenario 18 results

Drug and drug dosage	Trial weighting	ULT cost 1 year	Prophylaxis	Total drug cost with weighting	Initiation & up titration costs	Cost of flares in the first 3 months	Cost of flares from up titration	Probability of a flare post 3 months	Cost of a flare post 3 months
Allopurinol 100mg	0.49%	£12.91	£3.69	£0.08	£0.17	£31.72	£0.00	80%	£44.74
Allopurinol 200mg	2.96%	£24.74	£7.39	£0.95	£1.44		£0.00		
Allopurinol 300mg	16.75%	£18.11	£11.08	£4.89	£10.59		£0.00		
Allopurinol 400mg	27.09%	£34.74	£14.77	£13.41	£21.07		£2.29		
Allopurinol 500mg	36.90%	£36.31	£18.46	£21.21	£30.70		£6.24		
Allopurinol 600mg	5.80%	£31.75	£22.16	£3.13	£13.47		£1.47		
Allopurinol 700mg	4.74%	£38.21	£25.85	£3.04	£5.76		£1.60		
Allopurinol 800mg	3.16%	£43.51	£29.54	£2.31	£4.30		£1.34		
Allopurinol 900mg	2.11%	£40.93	£33.23	£1.56	£3.17		£1.07		
Febuxostat 80mg	97.50%	£31.68	£3.69	£34.49	£33.32	£62.37	£0.00	79%	£43.98
Febuxostat 120mg	2.50%	£293.73	£7.39	£7.53	£1.22	£86.02	£0.00	79%	£43.99
Allopurinol all				**£49.58**	**£90.67**	**£31.72**	**£14.02**		**£44.74**
Febuxostat all				**£42.01**	**£34.54**	**£62.97**	**£0.00**		**£43.98**

The total cost of allopurinol for one year of treatment was £230.72 and the total cost for febuxostat was £183.50.

Scenario 19 – Doherty trial for the proportion of people receiving allopurinol. FORWARD trial for the proportion of people receiving febuxostat and achieving target serum urate levels. Lowest cost of a gout flare (£27.22)

Table 85: Scenario 19 results

Drug and drug dosage	Trial weighting	ULT cost 1 year	Prophylaxis	Total drug cost with weighting	Initiation & up titration costs	Cost of flares in the first 3 months	Cost of flares from up titration	Probability of a flare post 3 months	Cost of a flare post 3 months
Allopurinol 100mg	0.49%	£12.91	£3.69	£0.08	£0.17	£15.52	£0.00	83%	£22.73
Allopurinol 200mg	2.96%	£24.74	£7.39	£0.95	£1.44		£0.00		
Allopurinol 300mg	16.75%	£18.11	£11.08	£4.89	£10.59		£0.00		
Allopurinol 400mg	27.09%	£34.74	£14.77	£13.41	£21.07		£1.12		
Allopurinol 500mg	36.90%	£36.31	£18.46	£21.21	£30.70		£3.05		
Allopurinol 600mg	5.80%	£31.75	£22.16	£3.13	£13.47		£0.72		
Allopurinol 700mg	4.74%	£38.21	£25.85	£3.04	£5.76		£0.79		
Allopurinol 800mg	3.16%	£43.51	£29.54	£2.31	£4.30		£0.65		
Allopurinol 900mg	2.11%	£40.93	£33.23	£1.56	£3.17		£0.52		
Febuxostat 80mg	78.30%	£31.68	£3.69	£27.69	£26.76	£30.52	£0.00	81%	£22.18
Febuxostat 120mg	21.70%	£293.73	£7.39	£65.34	£10.57	£42.09	£0.00	82%	£22.21
Allopurinol all				**£49.58**	**£90.67**	**£15.52**	**£6.86**		**£22.73**
Febuxostat all				**£93.04**	**£37.33**	**£33.03**	**£0.00**		**£22.18**

The total cost of allopurinol for one year of treatment was £185.35 and the total cost for febuxostat was £185.57.

Scenario 20 – Doherty trial for the proportion of people receiving allopurinol. FORWARD trial for the proportion of people receiving febuxostat and achieving target serum urate levels. Highest cost of a gout flare (£55.64)

Table 86: Scenario 20 results

Drug and drug dosage	Trial weighting	ULT cost 1 year	Prophylaxis	Total drug cost with weighting	Initiation & up titration costs	Cost of flares in the first 3 months	Cost of flares from up titration	Probability of a flare post 3 months	Cost of a flare post 3 months
Allopurinol 100mg	0.49%	£12.91	£3.69	£0.08	£0.17	£31.72	£0.00	83%	£46.45
Allopurinol 200mg	2.96%	£24.74	£7.39	£0.95	£1.44		£0.00		
Allopurinol 300mg	16.75%	£18.11	£11.08	£4.89	£10.59		£0.00		
Allopurinol 400mg	27.09%	£34.74	£14.77	£13.41	£21.07		£2.29		
Allopurinol 500mg	36.90%	£36.31	£18.46	£21.21	£30.70		£6.24		
Allopurinol 600mg	5.80%	£31.75	£22.16	£3.13	£13.47		£1.47		
Allopurinol 700mg	4.74%	£38.21	£25.85	£3.04	£5.76		£1.60		
Allopurinol 800mg	3.16%	£43.51	£29.54	£2.31	£4.30		£1.34		
Allopurinol 900mg	2.11%	£40.93	£33.23	£1.56	£3.17		£1.07		
Febuxostat 80mg	78.30%	£31.68	£3.69	£27.69	£26.76	£62.37	£0.00	81%	£45.33
Febuxostat 120mg	21.70%	£293.73	£7.39	£65.34	£10.57	£86.02	£0.00	82%	£45.39
Allopurinol all				**£49.58**	**£90.67**	**£31.72**	**£14.02**		**£46.45**
Febuxostat all				**£93.04**	**£37.33**	**£67.51**	**£0.00**		**£45.34**

The total cost of allopurinol for one year of treatment was £232.43 and the total cost for febuxostat was £243.21.

Scenario 21 – Base case data inputs and 50% of people go to A&E for a hospital treated flare as opposed to 100%. Lowest cost of a gout flare settings

Table 87: Scenario 21 results

Drug and drug dosage	Trial weighting	ULT cost 1 year	Prophylaxis	Total drug cost with weighting	Initiation & up titration costs	Cost of flares in the first 3 months	Cost of flares from up titration	Probability of a flare post 3 months	Cost of a flare post 3 months
Allopurinol 100mg	10.0%	£12.91	£3.69	£1.66	£3.42	£15.80	£0.00	80%	£22.28
Allopurinol 200mg	23.30%	£24.74	£7.39	£7.48	£11.35		£0.00		
Allopurinol 300mg	50.90%	£18.11	£11.08	£14.86	£32.19		£0.00		
Allopurinol 400mg	11.90%	£34.74	£14.77	£5.89	£9.25		£0.50		
Allopurinol 500mg	2.73%	£36.31	£18.46	£1.50	£5.65		£0.23		
Allopurinol 600mg	0.43%	£31.75	£22.16	£0.23	£4.38		£0.05		
Allopurinol 700mg	0.35%	£38.21	£25.85	£0.22	£0.43		£0.06		
Allopurinol 800mg	0.23%	£43.51	£29.54	£0.17	£0.32		£0.05		
Allopurinol 900mg	0.16%	£40.93	£33.23	£0.12	£0.23		£0.04		
Febuxostat 80mg	97.50%	£31.68	£3.69	£34.49	£33.32	£31.06	£0.00	79%	£21.90
Febuxostat 120mg	2.50%	£293.73	£7.39	£7.53	£1.22	£42.84	£0.00	79%	£21.91
Allopurinol all				**£32.13**	**£67.21**	**£15.80**	**£0.93**		**£22.28**
Febuxostat all				**£42.01**	**£34.54**	**£31.36**	**£0.00**		**£21.90**

The total cost of allopurinol for one year of treatment was £138.36 and the total cost for febuxostat was £129.81.

Discussion

The results indicated allopurinol was the cheapest intervention in 12 out of the 21 scenarios. In the base case scenarios data for the proportion of people receiving each drug dosage and the proportion of people achieving target serum urate levels was obtained from the FAST trial, and data on the mean number of flares for allopurinol was obtained from Borstad 2004. In the base case scenarios (Scenario 1 – Scenario 8) the cost of a gout flare was varied using all eight estimated costs of a gout flare. In these scenarios the difference in costs ranged from £4.05 to £8.80 for one year of treatment and the results of the costing analysis were sensitive to whether 1% or 5% of people received treatment for a gout flare in hospital. When 1% of people received treatment for a gout flare in hospital febuxostat was cheaper (range £4.06 to £5.82). However, when 5% of people received treatment in hospital for a gout flare allopurinol was cheaper (range £7.10 to £8.80).

Allopurinol was cheaper when data from the FORWARD trial was used for the proportion of people receiving allopurinol and febuxostat and the proportion of people achieving target serum urate levels (Scenario 9 & Scenario 10). The higher total cost for febuxostat can be attributed to the fact a higher proportion of people receive the more expensive 120mg dose of febuxostat (21.7% compared to 2.5% in the base case), In addition, in all scenario analyses a greater number of flares are observed for febuxostat upon initiation of ULT as a result of a greater flare triggering effect associated with initiating febuxostat. The cost of flares post three months for the remainder of the year in these scenarios were similar.

Scenario 11 and Scenario 12 were the same as the base case analysis except the average number of flares for the first three months of treatment for people receiving allopurinol were obtained from the FACT and APEX trials (0.917) as opposed to Borstad 2004 (0.57). When the lowest cost for a gout flare was used, febuxostat was £15.56 cheaper and when the highest cost for a gout flare was used febuxostat was £11.39 cheaper. Compared to the base case, febuxostat was cheaper in this scenario because more people receiving allopurinol experienced flares in the first three months of treatment and when up-titrating ULT. The committee did however note the number of flares reported in the FACT and APEX trial were likely an overestimate because initiating people on a fixed dose of 300mg allopurinol would likely induce a higher flare triggering affect compared to when people are up titrated from 100mg allopurinol.

In Scenario 13 and 14, allopurinol was cheaper by £44.72 and £51.03 respectively. In these scenarios data from the FAST trial was used for the proportion of people receiving different doses of allopurinol and febuxostat, and the proportion of people achieving target serum urate levels (as in Scenario 9 & Scenario 10). The average number of flares for the first three months of treatment were taken from the FACT and APEX trials. Once again, allopurinol was cheaper in these scenarios primarily due to the fact a higher proportion of people received 120mg febuxostat.

As anticipated, allopurinol was cheaper when data from the FACT and APEX trials were used (Scenario 15 & Scenario 16), whereby people receiving allopurinol received a fixed dose of 300mg. When the lower cost of a flare was used allopurinol was £157.14 cheaper compared to febuxostat and when the highest cost of a gout flare was used allopurinol was £167.72. In this analysis, allopurinol was significantly cheaper because a high proportion of people (50.25%) in the FACT and APEX trials received 120mg febuxostat which is more expensive than 80mg febuxostat (£0.87 compared to £0.09). In addition, because people received a fixed dose of allopurinol up-titration costs were not incurred for people receiving allopurinol. The committee noted this scenario was not reflective of best practice as people receiving allopurinol should be up titrated until they achieve target serum urate levels. In

addition, in current practice you would not expect over half of people receiving febuxostat (50.25%) to require 120mg.

The Doherty treat-to-target trial was used to obtain the proportion of people receiving different doses of allopurinol in Scenario 17 – Scenario 20. In scenarios 17 & 18 the proportion of people receiving different doses of febuxostat and achieving target serum urate levels was obtained from the FAST trial. In scenarios 19 & 20 the proportion of people receiving different doses of febuxostat and achieving target serum urate levels was obtained from the FORWARD trial. In Scenarios 17 and 18 febuxostat was cheaper by £55.64 and £47.23 (when the lowest and highest cost of a gout flare were used respectively). In Scenarios 19 and 20 allopurinol was cheaper by £0.22 and £10.78 respectively. Overall febuxostat was cheaper in Scenario 17 and 18 due to a higher proportion of people receiving higher doses of allopurinol. This cost was offset in Scenarios 19 and 20 because a higher proportion of people received 120mg febuxostat.

Scenario 21 used the base case lowest cost of a gout flare assumptions (Scenario 7) but only 50% of people visited A&E when being treated for a gout flare in hospital (as opposed to 100%). Apart from this change, all other data inputs where the same as Scenario 7 where the results indicated febuxostat was £8.80 cheaper than allopurinol. This scenario analysis was conducted to see if the conclusions of the results were sensitive to the proportion of people visiting A&E prior to hospital treatment. The results of Scenario 21 showed febuxostat was £8.54 cheaper compared to allopurinol, indicating the results were not sensitive to the proportion of people visiting A&E prior to treatment for a gout flare in hospital.

Appendix J – Excluded studies

Clinical studies

Table 88: Studies excluded from the clinical review

Study	Exclusion reason
Agarwal 2013[1]	Systematic review - references checked
Anonymous 2009[2]	Incorrect study design - Article, literature review
Azzeh 2017[3]	Incorrect study design - non-randomised study
Bastow 1988[4]	Incorrect population - ten men with persistent hyperglyceridaemia
Becker 2008[8]	Incorrect study design - overview of two randomised trials, references checked
Becker 2009[12]	Incorrect study design - open label extension study, non-randomised
Becker 2011[6]	Secondary analysis of Confirms trial - no relevant outcomes
Becker 2013[7]	Secondary analysis of Confirms trial - no relevant outcomes
Beslon 2018[14]	Systematic review - references checked
Borghi 2016[16]	Systematic review - references checked
Cada 2009[18]	Incorrect study design - literature review
Castrejon[19]	Systematic review - references checked
Chohan 2012[20]	Incorrect study design - retrospective analysis/overview of RCT's (FACT APEX and CONFIRMS) already included in this review
Choi 2009[22]	Incorrect study design - prospective non-randomised study
Choi 2018[21]	Incorrect study design - literature review
Choudhury 2016[23]	Incorrect population - study excluded patients with gouty arthritis
Cuenca 2019[24]	Systematic review - references checked
Cutolo 2017[25]	Systematic review - references checked
Dalbeth 2017[26]	Incorrect intervention - febuxostat 40 mg (increased to 80 mg if the serum UA level was ≥6.0 mg/dl on day 14)
Derosa 2015[27]	Systematic review - references checked
Faruque 2013[30]	Systematic review - references checked
Feher 2003 [31]	Incorrect study design - non-randomised cross-over study
Foody 2017[32]	Incorrect study design - retrospective cohort study
Frampton 2015[33]	Systematic review - references checked
Gaffo 2009[34]	Systematic review - references checked
Gandhi 2015[35]	Incorrect study design - Markov model, cost-analysis

Study	Exclusion reason
Gibson 1980[37]	Incorrect comparison - colchicine versus colchicine plus allopurinol
Gibson 1982[36]	Incorrect comparison - Colchicine versus Colchicine plus allopurinol
Goldfarb 2013[38]	Incorrect population - people were excluded if they had gout
Goldfarb 2011[39]	Sub-study of Becker 2005 which is included in the review. Study analysed effectiveness of ULT in patients who were either overproducers or underexcretors of uric acid
Gray 2011[40]	Incorrect study design - literature review
Grewal 2014[41]	Incorrect study design - literature review
Hanvivadhanakul 2002[44]	Incorrect study design - non-randomised observational study
Hay 2020[45]	Systematic review - references checked
He 2017[46]	Incorrect study design - literature review
Hosoya 2014[49]	Incorrect study design - protocol of RCT
Houpt 1965[50]	Incorrect study design - non-randomised study
Hu 2020[51]	Systematic review - references checked
Huang 2005[52]	Incorrect population - adult non-smokers
Inokuchi 2009[55]	Incorrect comparison - Allopurinol vs benzbromarone
Jackson 2012[57]	Secondary analysis of Confirms trial - no relevant outcomes
Jennings 2014[58]	Incorrect analysis - pre-randomisation data was analysed
Juraschek 2011[59]	Systematic review - references checked
Kamatani 2011[60]	Incorrect intervention - low dose febuxostat 40 mg or 60 mg
Kamatani 2011[63]	Incorrect population - population mixed (40% without gout but with hyperuricemia)
Kamatani 2011[62]	Incorrect comparison - febuxostat 40mg vs febuxostat 60 mg
Kamatani 2011[61]	Incorrect intervention - Febuxostat 10 mg/d vs allopurinol 100 mg/d
Khan 2012[64]	Incorrect comparison - allopurinol plus candisartan versus allopurinol plus losartan
Kim 2006[66]	Incorrect study design - literature review
Kimura 2018[67]	Incorrect intervention – the following doses were used: loading daily dose, 10 mg given as one 10 mg tablet once daily on days 1 to 28 after study onset; escalated daily dose, 20 mg given as one 20-mg tablet at weeks 4 to 7; and maintenance daily dose, 40 mg given as one 40-mg tablet once daily at weeks 8 to 108.
Kumar 2013[68]	Incorrect intervention - Febuxostat 40mg once per day versus Allopurinol 100mg 3xday
Kydd 2014[70]	Systematic review references checked

Study	Exclusion reason
Kydd 2014[69]	Cochrane review - included incorrect comparisons: benzbromarone versus allopurinol; benzbromarone versus probenecid and probenecid versus allopurinol
Li 2016[71]	Systematic review - references checked
Liang 2019[72]	Incorrect intervention - benzbromarone
Lin 2017[73]	Incorrect study design - non-randomised study
Lin 2020[74]	Systematic review - references checked
Liu 2019[75]	Systematic review - references checked
Love 2010[76]	Incorrect study design - literature review
MacDonald 2014[77]	Incorrect study design - protocol for FAST trial
Mu 2019[79]	Incorrect study design - Post-hoc analysis of randomised controlled trial
Perez-Ruiz 1998[85]	Incorrect study design - non-randomised parallel study
Perez-Ruiz 2019[86]	Incorrect study design - literature review
Pohar 2006[88]	Incorrect study design - overview of the trial
Pui 2002[89]	Incorrect study design - literature review
Ramasamy 2013[90]	Systematic review references checked
Reinders 2009[92]	Incorrect comparison - Allopurinol vs benzbromarone
Robinson 2018[93]	Systematic review - references checked
Roddy 2020[94]	Incorrect intervention/comparison - naproxen vs colchicine
Rogers 2016[95]	Incorrect study design - description of pharmacy system
Saag 2016[97]	Incorrect intervention - febuxostat 40/80mg (80 mg if at the month 1 visit if their serum UA level was >=6.0 mg/dl)
Saddekni 2016[98]	Incorrect study design - protocol only
Schumacher 2009[99]	Incorrect study design - non-randomised study, open label extension study of another study
Scott 1966[101]	Incorrect comparison - Allopurinol versus Probenecid
Seth 2014[102]	Cochrane review – included non-randomised studies as well as randomised controlled trials, analysis combined both types of studies.
Singh 2012[103]	Incorrect study design - literature review
Smolen 2016[104]	Incorrect study design - cost effectiveness analysis
Sorbera 2001[105]	Incorrect study design - description/overview of drug TMX-67 (febuxostat)
Stamp 2013[109]	Incorrect analysis/incorrect intervention - unclear dose of allopurinol. The dose changes throughout the study
Stamp 2017[107]	Incorrect comparison - treat-to-target versus usual care

Study	Exclusion reason
Stamp 2018[106]	Systematic review - references checked
Stamp 2018[108]	Systematic review - references checked
Steinberg 2017[110]	Incorrect intervention - Arhalofenate
Stevenson 2009[112]	Meta-analysis - references checked
Stevenson 2011[111]	Incorrect study design - NICE technology appraisal
Sun 2020[114]	Systematic review - references checked
Sun 2020[113]	Incorrect comparison - febuxostat 40 mg daily for attacks versus control febuxostat 40 mg after the attacks
Takahashi 2003[115]	Incorrect study design - expert opinion
Tani 2014[116]	Incorrect study design - conference paper
Tausche 2014[117]	Incorrect study design - non-randomised trial
Tayar 2012[118]	Cochrane review - analysis was not stratified by CKD and by line of treatment, some outcomes extracted at last time point even though it does not start from the baseline (for instance incidence of gout flares)
Villazor-Isidro 2014[120]	Systematic review - references checked
Waldman 2018[121]	Incorrect population - patients with type 2 diabetes, not confirmed gout
Wells 2012[123]	Secondary analysis of Confirms trial - no relevant outcomes
Whelton 2013[124]	Incorrect analysis/incorrect study design - during the study any participant could switch which dose they were on/which drug. Study reports results for anyone who received febuxostat of any dose during the trial.
White 2012[125]	Incorrect study design - Overview of the study, protocol
White 2018[126]	Incorrect dose - febuxostat 40 mg or 80 mg (61% of the patients received 40 mg)
Wolff 2015[127]	Systematic review - references checked
Wurzner 2001[128]	Incorrect comparison - losartan compared to irbesartan
Yamamoto 1997[130]	Incorrect study design, non-randomised before and after study
Yamanaka 2018[131]	Incorrect intervention - Febuxostat stepwise (10 to 40 mg per day) versus febuxostat 40 mg plus colchicine versus febuxostat 40 mg
Ye 2013[132]	Systematic review - references checked
Yen 2020[133]	Incorrect study design - cohort study
Yin 2018[134]	Systematic review - references checked
Yu 2007[135]	Incorrect study design - literature review
Zhang 2017[138]	Systematic review - references checked
Zhang 2021[139]	Systematic review - references checked

Health Economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2005 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below. See the health economic protocol for more details.

Table 89: Studies excluded from the health economic review

Reference	Reason for exclusion
Perez-Ruiz 2016[87]	This study was assessed as partially applicable (Spanish setting may not reflect current NHS context); however, given that a more applicable UK analysis by Beard 2013 [5] was available based on the same RCTs and model structure this study was selectively excluded.