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Febuxostat for treating chronic gout (Review)

Tayar JH, Lopez-Olivo MA, Suarez-Almazor ME

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TABLE OF CONTENTS

[Intervention Review]

Febuxostat for treating chronic gout

Jean H Tayar[1], Maria Angeles Lopez-Olivo[1], Maria E Suarez-Almazor[1]

[1]Department of General Internal Medicine, The University of Texas, M.D. Anderson Cancer Center, Houston, Texas, USA

Contact address: Maria Angeles Lopez-Olivo, Department of General Internal Medicine, The University of Texas, M.D. Anderson Cancer Center, 1515 Holcombe Blvd, Unit 1465, Houston, Texas, 77030, USA. amlopezo@mdanderson.org.

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ABSTRACT

Background

Gout is the most common inflammatory arthritis in men over 40 years and has an increasing prevalence among postmenopausal women. Lowering serum uric acid levels remains one of the primary goals in the treatment of chronic gout. In clinical trials, febuxostat has been shown to be effective in lowering serum uric acid levels to < 6.0 mg/dL.

Objectives

To evaluate the benefits and harms of febuxostat for chronic gout.

Search methods

We searched *The Cochrane Library,* MEDLINE, EMBASE, and International Pharmaceutical Abstracts from inception to July 2011. The ClinicalTrials.gov website was searched for references to trials of febuxostat. Our search did not include any restrictions.

Selection criteria

Two authors independently reviewed the search results and disagreements were resolved by discussion. We included any controlled clinical trial or open label trial (OLT) using febuxostat at any dose.

Data collection and analysis

Data and risk of bias were independently extracted by two authors and summarised in a meta-analysis. Continuous data were expressed as mean difference and dichotomous data as risk ratio (RR).

Main results

Four randomised trials and two OLTs with 3978 patients were included. Risk of bias differed by outcome, ranging from low to high risk of bias. Included studies failed to report on five to six of the nine outcome measures recommended by OMERACT. Patients taking febuxostat 120 mg and 240 mg reported more frequent gout flares than in the placebo group at 4 to 28 weeks (RR 1.7; 95% CI 1.3 to 2.3, and RR 2.6; 95% CI 1.8 to 3.7 respectively). No statistically significant differences were observed at 40 mg and 80 mg. Compared to placebo, patients on febuxostat 40 mg were 40.1 times more likely to achieve serum uric acid levels < 6.0 mg/dL at 4 weeks (95% CI 2.5 to 639), with an absolute treatment benefit of 56% (95% CI 37% to 71%). For febuxostat 80 mg and 120 mg, patients were 68.9 and 80.7 times more likely to achieve serum uric acid levels < 6.0 mg/dL at their final visit compared to placebo (95% CI 13.8 to 343.9, 95% CI 16.0 to 405.5), respectively; with an absolute treatment benefit of 75% and 87% (95% CI 68 to 80% and 81 to 91%), respectively. Total discontinuation rates were significantly higher in the febuxostat 80 mg group compared to placebo (RR 1.4; 95% CI 1.0 to 2.0, absolute risk increase 11%; 95% CI 3 to 19%). No other differences were observed.

When comparing allopurinol to febuxostat at 24 to 52 weeks, the number of gout flares was not significantly different between the two groups, except for febuxostat 240 mg (RR 2.3; 95% CI 1.7 to 3.0). Patients on febuxostat 40 mg showed no statistically significant differences in benefits or harms. Patients on febuxostat 80 mg and 120 mg were 1.8 and 2.2 times more likely to achieve serum uric acid levels < 6.0 mg/dL at their final visit (95% CI 1.6 to 2.2, 95% CI 1.9 to 2.5) with an absolute treatment benefit of 29% and 44% (95% CI 25% to 33%, 95% CI 38% to 50%), respectively, at 24 to 52 weeks. Total discontinuation rates were higher for febuxostat 80 mg and 120 mg compared to allopurinol (RR 1.5; 95% CI 1.2 to 1.8, absolute risk increase 11%; 95% CI 6% to 16%; and RR 2.6; 95% CI 2.0 to 3.3, absolute risk increase 20%; 95% CI 3% to 14%, respectively). Discontinuations due to adverse events were similar across groups. Total adverse events were lower for febuxostat 80 mg and 120 mg compared with allopurinol (RR 0.93; 95% CI 0.87 to 0.99, absolute risk increase 6%; 95% CI 0.7% to 11%; and RR 0.90; 95% CI 0.84 to 0.96, absolute risk increase 8%; 95% CI 3% to 13%, respectively). No other relevant differences were noted.

After 3 years of follow-up there were no statistically significant differences regarding effectiveness and harms between febuxostat 80 mg or 120 mg and allopurinol groups (adverse event rate per 100 patient-years 227, 216, and 246, respectively).

Authors' conclusions

Although the incidence of gout flares requiring treatment may be increased in patients taking febuxostat compared to placebo or allopurinol during early treatment, no such increase in gout flares was observed in the long-term follow-up study when compared to allopurinol. Febuxostat at any dose was shown to be beneficial in achieving serum uric acid levels < 6.0 mg/dL and reducing serum uric acid levels in the period from baseline to final visit when compared to placebo and to allopurinol. However, the grade of evidence ranged from low to high, which indicates that further research is needed.

PLAIN LANGUAGE SUMMARY

Febuxostat for treating chronic gout

This summary of a Cochrane review represents what we know from research about the effect of febuxostat for treating chronic gout.

From six studies including 3978 people with chronic gout, the review shows that,

In people with chronic gout:

- febuxostat probably reduces uric acid levels;

- febuxostat probably increases the incidence of gout flares during early treatment (while getting the uric acid levels down). The normalization of serum uric acid leads to mobilization of urate from tissue deposits, which in turn may increase the number of attacks;

- febuxostat probably shows similar benefits as allopurinol after three years of use.

We do not have information about febuxostat effects on joint imaging, musculoskeletal function, pain, overall assessment, and quality of life. Also, we do not have precise information about side effects and complications. This is particularly true for rare but serious side effects. Possible side effects may include liver enzyme elevations, high blood pressure and diarrhoea. Rare complications may include certain cardiovascular events (chest pain, coronary artery disease, myocardial infarction, or atrial fibrillation).

What is chronic gout and what is febuxostat?

Uric acid is a product normally present in the blood as a result of the breakdown of certain products called 'purines'. Gout is a disease caused by high uric acid levels in the blood leading to crystal formation in the joints, most commonly joints of the lower limbs such as the big toe, heels, ankles and knees. Gout usually presents as acute attacks causing joint swelling and pain, but also can lead to chronic arthritis. While there is no cure for the disease, treatment can prevent recurrent gout attacks and improve its chronic form.

Research shows that keeping uric acid levels below 6.0 mg/dL can reduce gout attacks over time. However, in the first months of therapy, there could be an increased number of gout attacks, due to the nature of the treatment.

Febuxostat is a new drug that can help lower uric acid levels in the blood in adults with gout.

Best estimate of what happens to people with chronic gout who take febuxostat:

Febuxostat was proven effective in lowering uric acid to less than 6.0 mg/dL.

In short-term studies (one year or less), when febuxostat was compared with placebo (a sham or fake medication):

- 6 patients out of 100 had more gout attacks taking febuxostat 80 mg (6% absolute increase in attacks);

- 75 more patients out of 100 taking febuxostat 80 mg reached their goal of uric acid level below 6.0 mg/dL (75% absolute benefit).

When febuxostat was compared with allopurinol, another medicine often used to lower uric acid:

- 2 patients out of 100 had more gout attacks taking febuxostat 80 mg (2% absolute increase in attacks);

- 29 more patients out of 100 on febuxostat 80 mg reached an acid level below 6.0 mg/dL (29% absolute benefit).

In studies of more than three years:

febuxostat at any dose had the same effect as allopurinol in reaching a uric acid level of less than 6.0 mg/dL, and there was no observed increase in gout attacks.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Febuxostat 40 mg/day versus placebo

Febuxostat 40 mg/day compared to placebo for chronic gout

Patient or population: patients with chronic gout
Settings: Primary care
Intervention: Febuxostat 40 mg/day
Comparison: Placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	**Febuxostat 40 mg/day**				
Incidence of gout flares Follow-up: 28 days	**368 per 1000**	**350 per 1000** (191 to 640)	**RR 0.95** (0.52 to 1.7)	75 (1 study)	++OO **low**[1,2]	Not statistically significant.
Serum uric acid <6.0 mg/dL at final visit Follow-up: 28 days	**27 per 1000**[4]	**1000 per 1000** (68 to 1000)[4]	**RR 40.1** (2.5 to 639.1)	69 (1 study)	++OO **low**[1,3]	NNT = 2 (95% CI 1 to 3)[4]; ATB = 56% (95% CI 37 to 71%); RRR = 39% (637% to 1.5%)[4].
Pain	See comment	See comment	See comment	See comment	See comment	Not assessed
Patient global assessment	See comment	See comment	See comment	See comment	See comment	Not assessed
Health Related Quality of Life	See comment	See comment	See comment	See comment	See comment	Not assessed
Serious Adverse Events Follow-up: 28 days	**26 per 1000**[4]	**26 per 1000** (0 to 0)[4]	**RR 1.0** (0 to 0)[4]	75 (1 study)	+++O **moderate**[1]	Not statistically significant .
Discontinuations due to adverse events Follow-up: 28 days	**26 per 1000**	**27 per 1000** (2 to 416)	**RR 1.0** (0.07 to 15.8)	75 (1 study)	+++O **moderate**[1]	Not statistically significant.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **NNT:** Number needed to treat; **ATB:** Absolute treatment benefit; **RRR:** Relative risk reduction; **NE:** Not estimable.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] High risk of bias in 1 item (intention to treat was not performed)
[2] Study include relatively few patients and few events and thus has wide confidence intervals around the estimate of the effect
[3] Outcome is a substitute measurement (surrogate endpoint).

[4] Numbers calculated adding a continuity correction value of 0.5 to each cell of the 2x2 table.

Summary of findings 2. Febuxostat 80 mg/day versus placebo

Febuxostat 80 mg/day compared to placebo for chronic gout

Patient or population: patients with chronic gout
Settings: Primary care
Intervention: Febuxostat 80 mg/day
Comparison: Placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	**Febuxostat 80 mg/day**				
Incidence of gout flares Follow-up: 4-28 weeks	**238 per 1000**	**314 per 1000** (228 to 431)	**RR 1.32** (0.96 to 1.8)	474 (2 studies)	++OO **low**[1,2]	Not statistically significant.
Serum uric acid <6.0 mg/dL at final visit Follow-up: 4-28 weeks	**7 per 1000**	**482 per 1000** (97 to 1000)	**RR 68.9** (13.8 to 343.9)	332 (2 studies)	++OO **low**[1,3]	NNT = 1 (95% CI 1 to 1); ATB = 75% (95% CI 68 to 80%); RRR = 10,000% (95% CI 71,500 to 13,300%).
Pain	See comment	See comment	See comment	See comment	See comment	Not assessed
Patient global assessment	See comment	See comment	See comment	See comment	See comment	Not assessed
Health Related Quality of Life	See comment	See comment	See comment	See comment	See comment	Not assessed
Serious Adverse Events Follow-up: 4-28 weeks	**12 per 1000**	**32 per 1000**[5] (8 to 125)	**RR 2.8** (0.72 to 10.7)	479 (2 studies)	+++O **moderate**[1]	Not statistically significant.

Discontinuations due to adverse events Follow-up: 4-28 weeks	**35 per 1000**	**63 per 1000** (26 to 156)	**RR 1.8** (0.74 to 4.5)	479 (2 studies)	+++O **moderate**	Not statistically significant.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **NNT:** Number needed to treat; **ATB:** Absolute treatment benefit; **RRR:** Relative risk reduction; **NE:** Not estimable.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] High risk of bias in 1 item (intention to treat was not performed)
[2] The Becker 2005b trial includes relatively few patients and few events and thus has wide confidence intervals around the estimate of the effect
[3] Outcome is a substitute measurement (surrogate endpoint).
[4] Heterogeneity exists across the studies

[5] In the placebo group 12 people out of 1000 had Serious Adverse Events over 4 to 28 weeks, compared to 32 (95% CI 8 to 125) out of 1000 for the febuxostat group. The reported serious adverse events were cardiovascular disorders (chest pain, coronary artery disease, myocardial infarction and atrial fibrillation).

Summary of findings 3. Febuxostat 120 mg/day versus placebo

Febuxostat 120 mg/day compared to placebo for chronic gout

Patient or population: patients with chronic cout
Settings: Primary care
Intervention: Febuxostat 120 mg/day
Comparison: Placebo

Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	Corresponding risk				
	Placebo	**Febuxostat 120 mg/day**				
Incidence of gout flares Follow-up: 4-28 weeks	**238 per 1000**	**407 per 1000** (300 to 552)	**RR 1.7** (1.3 to 2.3)	479 (2 studies)	+++O **moderate**[1]	NNT = 6 (95% CI 4 to 17); ATB = 15% (95% CI 6 to 23); RRR = 61%.

Serum uric acid <6.0 mg/dL at final visit Follow-up: 4-28 weeks	**7 per 1000**	**565 per 1000** (112 to 1000)	**RR 80.7** (16.0 to 405.5)	356 (2 studies)	++OO **low**[1,2,3]	NNT = NE; ATB = 87% (95% CI 81 to 91%); RRR = NE.
Pain	See comment	See comment	See comment	See comment	See comment	Not assessed
Patient global assessment	See comment	See comment	See comment	See comment	See comment	Not assessed
Health Related Quality of Life	See comment	See comment	See comment	See comment	See comment	Not assessed
Serious Adverse events Follow-up: 4-28 weeks	**12 per 1000**	**31 per 1000** (8 to 19)	**RR 2.7** (0.70 to 10.2)	479 (2 studies)	+++O **moderate**[1]	Not statistically significant.
Discontinuations due to adverse events Follow-up: 4-28 weeks	**35 per 1000**	**58 per 1000** (23 to 142)	**RR 1.7** (0.67 to 4.1)	479 (2 studies)	+++O **moderate**[1]	Not statistically significant.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **NNT:** Number needed to treat; **ATB:** Absolute treatment benefit; **RRR:** Relative risk reduction; **NE:** Not estimable.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] High risk of bias in 1 item (intention to treat was not performed)
[2] Outcome is a substitute measurement (surrogate endpoint).
[3] The Becker 2005b trial includes relatively few patients and few events and thus has wide confidence intervals around the estimate of the effect

Summary of findings 4. Febuxostat 40 mg/day versus allopurinol

Febuxostat 40 mg/day compared to allopurinol for chronic gout

Patient or population: patients with chronic gout
Settings: Primary care
Intervention: Febuxostat 40 mg/day
Comparison: Allopurinol

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Allopurinol	**Febuxostat 40 mg/day**				
Incidence of gout flares Follow-up: 24 weeks	**41 per 1000**	**40 per 1000** (23 to 68)	**RR 0.97** (0.57 to 1.65)	1324 (1 study)	++++ **high**	Not statistically significant.
Serum uric acid <6.0 mg/dL at final visit Follow-up: 24 weeks	**408 per 1000**	**432 per 1000** (384 to 494)	**RR 1.1** (0.94 to 1.2)	1324 (1 study)	+++O **moderate**[1]	Not statistically significant.
Pain	See comment	See comment	See comment	See comment	See comment	Not assessed
Patient global assessment	See comment	See comment	See comment	See comment	See comment	Not assessed
Health Related Quality of Life	See comment	See comment	See comment	See comment	See comment	Not assessed
Serious Adverse Events Follow-up: 24 weeks	**41 per 1000**	**25 per 1000** (14 to 44)	**RR 0.61** (0.35 to 1.07)	1513 (1 study)	++++ **high**	Not statistically significant.
Discontinuations due to adverse events Follow-up: 24 weeks	**85 per 1000**	**104 per 1000** (76 to 143)	**RR 1.2** (0.90 to 1.7)	1513 (1 study)	++++ **high**	Not statistically significant.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Outcome is a substitute measurement (surrogate endpoint).

Summary of findings 5. Febuxostat 80 mg/day versus allopurinol

Febuxostat 80 mg/day compared to allopurinol for chronic gout

Patient or population: patients with chronic gout
Settings: Primary care
Intervention: Febuxostat 80 mg/day
Comparison: Allopurinol

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Allopurinol	**Febuxostat 80 mg/day**				
Incidence of gout flares Follow-up: 8, 26, & 52 weeks	**204 per 1000**	**228 per 1000** (200 to 259)	**RR 1.1** (0.98 to 1.3)	2325 (3 studies)	++++ **high**	Not statistically significant.
Serum uric acid <6.0 mg/dL at final visit Follow-up: 8, 26, & 52 weeks	**398 per 1000**	**716 per 1000** (617 to 832)	**RR 1.8** (1.6 to 2.2)	2193 (3 studies)	++OO **low**[1,2]	NNT= 3 (95%CI 3 to 5); ATB = 29% (95% CI 25 to 33%); RRR = 73%.
Pain	See comment	See comment	See comment	See comment	See comment	Not assessed
Patient global assessment	See comment	See comment	See comment	See comment	See comment	Not assessed
Health Related Quality of Life	See comment	See comment	See comment	See comment	See comment	Not assessed
Serious Adverse Events Follow-up: 24. 28. & 52 weeks	**50 per 1000**	**45 per 1000** (17 to 122)	**RR 0.91** (0.34 to 2.4)	1044 (3 studies)	+++O **moderate**[1,4]	Not statistically significant.
Discontinuations due to adverse events Follow-up: 24. 28. & 52 weeks	**50 per 1000**	**65 per 1000** (39 to 107)	**RR 1.3** (0.79 to 2.1)	1044 (3 studies)	+++O **moderate**[4]	Not statistically significant.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **NNT:** Number needed to treat; **ATB:** Absolute treatment benefit; **RRR:** Relative risk reduction; **NE:** Not estimable.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

[1] Heterogeneity exists across the studies
[2] Outcome is a substitute measurement (surrogate endpoint).
[3] Pooled estimates are from 2 studies (Schumacher 2008 and Becker 2005a)

[4] High risk of bias in 1 item (intention to treat was not performed)

Summary of findings 6. Febuxostat 120 mg/day versus allopurinol

Febuxostat 120 mg/day compared to allopurinol for chronic gout

Patient or population: patients with chronic gout
Settings: Primary care
Intervention: Febuxostat 120 mg/day
Comparison: Allopurinol

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Allopurinol	**Febuxostat 120 mg/day**				
Incidence of gout flares Follow-up: 28 & 52 weeks	**420 per 1000**	**542 per 1000** (365 to 802)	**RR 1.3** (0.87 to 1.9)	986 (2 studies)	++++ **high**	Not statistically significant.
Serum uric acid <6.0 mg/dL at final visit Follow-up: 28 & 52 weeks	**384 per 1000**	**829 per 1000** (733 to 941)	**RR 2.2** (1.9 to 2.5)	880 (2 studies)	+++O **moderate**[1]	NNT= 3 (95%CI 2 to 3); ARR = 44% (95% CI 38 to 50%); RRR = NE.
Pain	See comment	See comment	See comment	See comment	See comment	Not assessed
Patient global assessment	See comment	See comment	See comment	See comment	See comment	Not assessed
Health Related Quality of Life	See comment	See comment	See comment	See comment	See comment	Not assessed
Serious Adverse Events Follow-up: 28 & 52 weeks	**50 per 1000**	**58 per 1000** (35 to 96)	**RR 1.2** (0.70 to 1.93)	1041 (3 studies)	++++ **high**	Not statistically significant.
Discontinuations due to adverse events	**50 per 1000**	**78 per 1000** (24 to 251)	**RR 1.6** (0.49 to 5.0)	1041 (3 studies)	++++ **high**	Not statistically significant.

Follow-up: 28 & 52 weeks

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **NNT:** Number needed to treat; **ARR:** Absolute risk reduction; **ARI:** Absolute risk increase; **RRR:** Relative risk reduction; **RRI:** Relative risk increase; **NE:** Not estimable.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Outcome is a substitute measurement (surrogate endpoint).

BACKGROUND

Description of the condition

Gout is the most common inflammatory arthritis in men over 40 years and has an increasing prevalence among postmenopausal women (Chohan 2009). It results from the deposition of monosodium uric acid crystals in and around the joints and soft tissues (Schlesinger 2004). It has been recognized that the formation of such crystals requires the presence of hyperuricaemia, defined as a serum uric acid concentration (serum uric acid levels) above its solubility limit (6.8 mg/dL) supersaturating the body fluids (Schumacher 2005). The disease can evolve from an asymptomatic stage of hyperuricaemia to recurrent gout attacks with inter-critical periods and subsequently chronic gouty arthritis. Formation of tophi and progression to chronic destructive arthritis can result from persistent monosodium uric acid crystal deposition that is left untreated. Furthermore, hyperuricaemia can be associated with renal damage secondary to interstitial monosodium uric acid crystal deposition and the formation of kidney stones (Schlesinger 2004).

Description of the intervention

Lowering serum uric acid levels below saturating levels, at a target < 6.0 mg/dL, remains one of the major goals in the treatment of chronic gout to reduce or reverse clinical events (Zhang 2006). The pharmacological methods currently employed for that purpose are i) reduction of uric acid production by use of the xanthine oxidase inhibitors; ii) enhancement of urinary uric acid excretion with uricosuric agents; and iii) promotion of the catabolism of uric acid with the pegylated recombinant uricase (pegloticase) (Anderson 2010). Among the xanthine oxidase inhibitors, allopurinol, a purine analogue has been the main drug available for decades. However, allopurinol's side effects, although rare, can be serious (hypersensitivity syndrome) and are more common in patients with renal dysfunction (Arellano 1993; Dalbeth 2007).

Febuxostat, a novel non-purine analogue xanthine oxidase inhibitor, at daily dosages of 40 mg to 240 mg has been shown in studies to be at least as good as allopurinol (dose ≤ 300 mg/day) in lowering serum uric acid levels to < 6.0 mg/dL, and may require fewer dose adjustments in patients with mild to moderate renal dysfunction (Bruce 2006; Edwards 2009). Approved doses in the US are 40 mg and 80 mg daily, and in Europe 80 mg and 120 mg.

How the intervention might work

The reversibility of monosodium uric acid crystal deposition by reducing the serum uric acid levels below saturation level has been recognized for years, making the reduction and maintenance of serum uric acid levels below 6.0 mg/dL a goal in managing chronic gout (Pascual 2007). Allopurinol has been the gold standard therapy for the past 40 years. However, there are patients who are refractory to allopurinol or with impaired renal function who may benefit from the newer alternative, febuxostat. The newer inhibitor of xanthine oxidase was approved for use in many countries in 2009. Individual studies found that it could be at least as effective as allopurinol. Furthermore, there were no reports of hypersensitivity reactions in patients on febuxostat, and it has been shown to be safe when used in patients with mild to moderate renal dysfunction (Becker 2010). A potential benefit with its uses could also be in allopurinol refractory patients.

Why it is important to do this review

The goal of this review was to systematically review the current data on febuxostat's benefit and harms in treating chronic gout (Bruce 2006; Stevenson 2011). Patients, clinicians and policy-makers need to keep abreast with the current literature in terms of benefit and harms of febuxostat.

To our knowledge there are only two systematic reviews to date on febuxostat for the treatment of chronic gout. This is the first systematic review of the literature with a meta-analysis of randomised controlled trials and it differs from other reviews in that it includes summary data on open label trials.

OBJECTIVES

To evaluate the benefits and harms of febuxostat alone or combined with non-steroidal antiinflammatory drugs or colchicine, or both, in comparison to allopurinol or placebo for the treatment of chronic gout.

METHODS

Criteria for considering studies for this review

Types of studies

Any randomised controlled trial (RCT), controlled clinical trial, or open label trial (OLT) comparing febuxostat (alone or combined with non-steroidal antiinflammatory drugs or colchicine, or both) in patients with gout with any control or placebo, with a minimum duration of three months.

Types of participants

Patients at least 16 years of age meeting the preliminary American College of Rheumatology (ACR) criteria for acute arthritis of primary gout (Wallace 1977) or given a diagnosis of gout as described by the authors.

Types of interventions

The following comparisons were eligible for inclusion: febuxostat alone or in combination with colchicine or non-steroidal antiinflammatory drugs (NSAIDs) or lifestyle changes versus placebo or any control alone or in combination with colchicine, NSAIDs or lifestyle changes. Any dosages were included.

Types of outcome measures

We used the primary outcome measures for response to gout treatment that were proposed by the American College of Rheumatology outcome measures for gout clinical trials and OMERACT 9 gout report (OMERACT 9).

Major outcomes

Benefit as assessed by the OMERACT 9 outcome domains for studies of acute and chronic gout (OMERACT 9).

1) G*out flares*: we extracted data on frequency of recurrent attacks in all ways reported.

2) *Serum urate*: change in serum uric acid levels, and per cent change in serum uric acid levels from baseline at final visit. Evidence suggests that lowering serum uric acid levels to < 6.0 mg/

dL increases crystal disappearance from synovial fluid (Edwards 1981; Li-Yu 2001).

3) *Harms* as assessed by the incidence of patients with adverse events (total and serious adverse events, liver function test abnormalities, skin reactions, cardiovascular events, hypertension, and diarrhoea) and the withdrawal rates (total withdrawals, withdrawals due to adverse events, withdrawals due to gout flares, withdrawals due to lack of efficacy, withdrawals due to other reasons).

Minor outcomes

The following secondary outcomes were also considered when reported.

1. *Tophus burden* as measured by size measurement of individual tophus (regression of tophi), including disappearance of tophi and velocity of tophus regression.
2. H*ealth-related quality of life* as assessed by measures: Short Form-36 (SF-36), Gout Assessment Questionnaire (GAQ), and the Gout Impact Scale (GIS).
3. *Pain*: on Likert scales as well as the visual analog scale (VAS), numeric rating scale (NRS), or qualitative scales.
4. *Musculoskeletal function*: function as assessed by activities of daily living scales including composite outcomes such as the Health Assessment Questionnaire (HAQ) or other activities of daily living scales (ADLs), and work productivity.
5. *Patient global and physician global assessment.*
6. *Joint imaging*: joint damage as assessed by the van der Heijde-Sharp radiographic score modified for gout.

We used the GRADE software to generate the 'Summary of findings' table and reported outcomes include: 1) incidence of gout flares, 2) serum uric acid levels < 6.0 mg/dL at final visit, 3) pain, 4) patient global assessment, 5) health-related quality of life, 6) total number of patients with serious adverse events, and 7) total number of withdrawals due to adverse events.

Search methods for identification of studies

Electronic searches

The following electronic databases were searched: *The Cochrane Library* (2011, Issue 6), including the Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE), and Health Technology Assessments (HTA); MEDLINE (1950 to July 2011); EMBASE (1980 to July 2011); and International Pharmaceutical Abstracts Database (IPAD). The ClinicalTrials.gov website was searched for references to trials of febuxostat.

The search was not limited by language, year of publication or type of publication. The full search strategy in Appendix 1 was developed for MEDLINE and was adapted for the other electronic databases.

Searching other resources

The reference lists from comprehensive reviews and identified clinical trials were also manually searched.

Websites of the following regulatory agencies were searched for reported adverse events using the terms 'gout', 'febuxostat' and 'uloric':

FDA's MedWatch, www.fda.gov/harms/medwatch/default.htm;
National Guideline Clearing House, www.guideline.gov;
National Institute for Health and Clinical Excellence, www.nice.org.uk/guidance/index.jsp?action=byID&o=11830;
Agency for Healthcare Research and Quality (AHRQ), www.ahrq.gov/;
Health Technology Assessment (HTAi), www.htai.org/;
Turning Research Into Practice (TRIP), www.tripdatabase.com.

Data collection and analysis

EndNote X2 software was used to manage the records retrieved from searches of electronic databases. Results from handsearches were tracked on a Microsoft Excel spreadsheet. A data extraction form was created in Word to capture all the information available for each individual trial.

Selection of studies

Results of the various searches were independently reviewed by two authors (JT, MLO). Titles and abstracts were reviewed and if additional information was required, the full text was obtained. A record of reasons for excluding studies was kept. Disagreements were resolved by discussion. Inter-rater agreement was calculated using Cohen's kappa.

Data extraction and management

Data were independently extracted from the included trials by two review authors (MLO, JT); then the collected data were entered into RevMan 5.0 using the double-entry system.

Data included the following.

1. General study information such as title, authors, contact address, publication source, publication year, country, and study sponsor.
2. Characteristics of the study: design, study setting, inclusion and exclusion criteria, quality criteria (e.g. randomisation method; allocation procedure; blinding of patients, caregivers and outcome assessors; withdrawals and dropouts, intention-to-treat (ITT) analysis).
3. Characteristics of the study population (age, sex, duration of disease, treatment history, presence of co-morbidity and peripheral disease, concurrent treatments).
4. Characteristics of the intervention, such as treatment comparators, dose, method of administration, frequency of administration, duration of treatment, and numbers in each intervention group.
5. Outcome measures as noted above.
6. Results for the ITT population (where possible); outcome measures at the end of the controlled phase; and any summary measures with standard deviations, confidence intervals and P values, where given; dropout rate and reasons for withdrawal.

Assessment of risk of bias in included studies

The risk of bias of the included studies was also assessed by two independent review authors. As recommended by the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008), the following methodological domains were assessed.

1. Random sequence generation.
2. Allocation sequence concealment.

3. Blinding of participants and personnel.
4. Blinding of outcome assessors.
5. Incomplete outcome data.
6. Selective reporting.
7. Other bias.

Each of these criteria were explicitly judged using: 'low risk of bias' ,'high risk of bias', or 'unclear' (uncertainty over the potential for bias).

Measures of treatment effect

The results of the studies were analysed using Review Manager 5.1. Data were summarised in a meta-analysis when they were sufficiently homogeneous, both clinically and statistically. Continuous data were expressed as mean difference (MD) or standardized mean difference (SMD) depending on similarity of scales measuring an outcome. Dichotomous data were expressed as risk ratios (RR) or, in the case of rare events (< 10%), Peto odds ratios (Peto OR) were used.

To establish equivalence between febuxostat and allopurinol we used the Becker et al definition where non-inferiority is a greater than 10% difference in achieving final serum uric acid levels < 6.0 mg/dL of the lower limit of the 95% confidence interval (CI) (Becker 2010).

Summary of findings tables were completed in order to improve the readability of the review. In addition to the absolute and relative magnitude of effect provided in the summary of findings table, the number needed to treat (NNT) was calculated from the control group event rate (unless the population event rate was known) and the risk ratio using the Visual Rx NNT calculator (Cates 2004). For continuous outcomes, the NNT was calculated using the Wells calculator available at the Cochrane Musculoskeletal Group editorial office. GRADE software was used to provide an overall grading of the quality of the evidence and to provide a comment on our confidence in the results. The possible grades of evidence are: 'high quality', 'moderate quality', 'low quality', 'very low quality'.

Unit of analysis issues

Treatment groups were analysed separately. No comparisons were added by combining all relevant experimental intervention groups of the study into a single group.

Dealing with missing data

We considered two strategies for handling withdrawals and dropouts.
i. Accounting for the numbers: were the numbers of withdrawals and dropouts reported for both groups?
ii. Accommodating withdrawals (ITT analysis, imputation): were the withdrawals and dropouts accounted for in the analysis (for example through ITT analysis using imputation methods) or the last observation carried forward (LOCF) was used.

Assessment of heterogeneity

Heterogeneity of the data was formally tested using the Chi^2 test with a P value < 0.10 indicating significant heterogeneity. The I^2 statistic (Higgins 2003) was also assessed. A value greater than 50% may indicate substantial heterogeneity. In the case of substantial heterogeneity, the data were further explored, including subgroup analyses, in an attempt to explain the heterogeneity.

Assessment of reporting biases

A funnel plot was not performed due to the limited number of publications retrieved.

Data synthesis

The fixed-effect model of meta-analysis was used to assess all outcomes. However, when significant heterogeneity was found and could not be explained, the random-effects model was used.

Subgroup analysis and investigation of heterogeneity

The following subgroup analyses were performed to explore possible effect size differences:

1. intervention (different dosage, duration of treatment), and
2. characteristics of participants (severity of baseline disease, age, disease duration, renal function).

Sensitivity analysis

We explored effect size differences and the robustness of conclusions by:

- effect of study quality that is defined as adequate allocation concealment and outcome assessor blinding, and
- effect of imputation of missing data or statistical transformations.

RESULTS

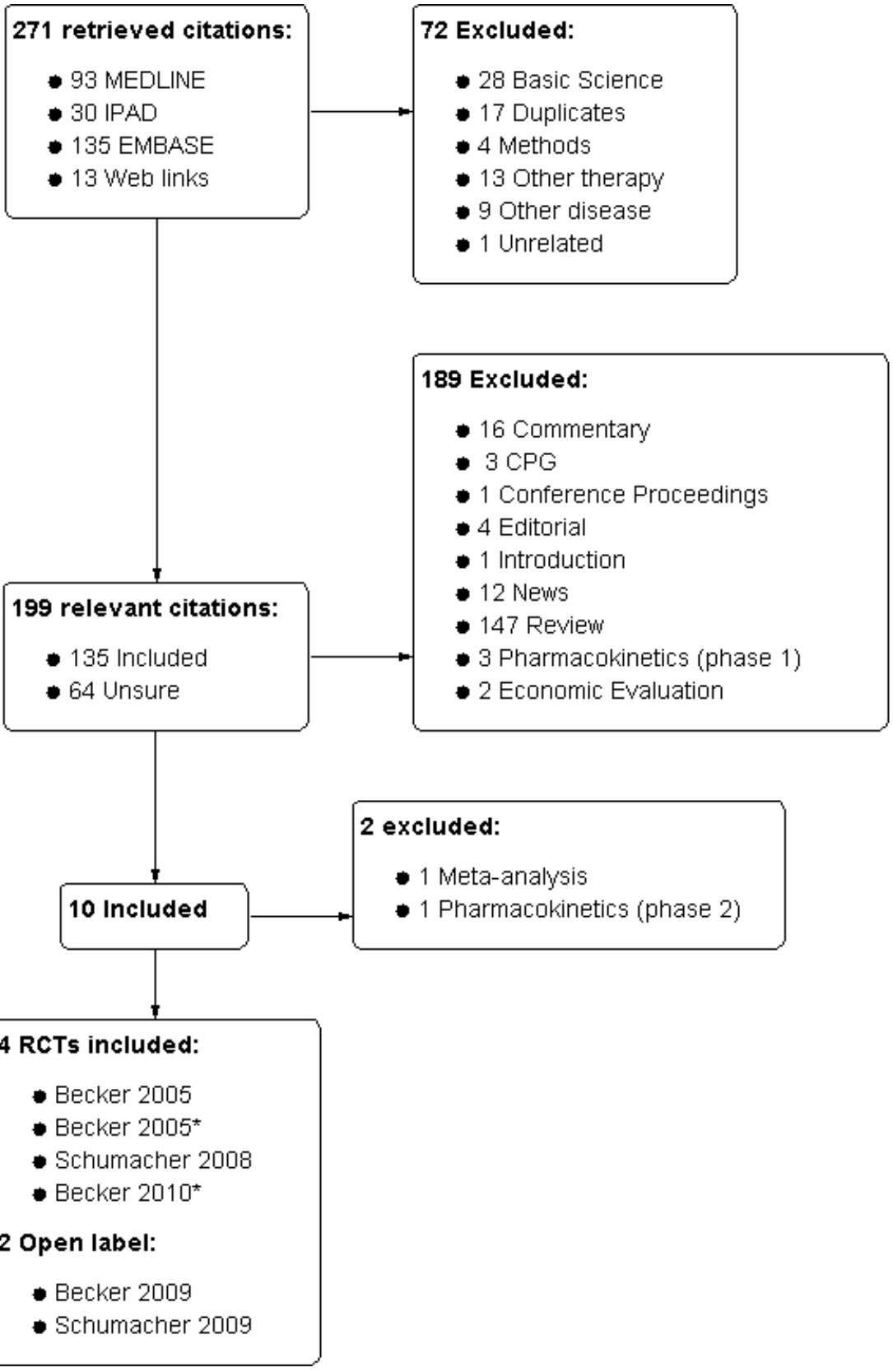
Description of studies

Studies are reported according to the follow-up duration. Characteristics of included studies are summarised in the tables section.

Results of the search

In our electronic search we retrieved a total of 271 citations: 93 from MEDLINE, 135 from EMBASE, 30 from IPAD, and 13 from web links. Searching other resources (described in the Methods paragraph) did not reveal additional records for review. In a first review based on abstracts and titles we excluded 72 citations. Of the remaining 199, 189 were excluded in a second step review mainly because of the type of citation (Figure 1). Of the 10 full texts then retrieved for our third and final review, two were excluded (see Characteristics of excluded studies for details) and a total of six met the inclusion criteria. The percentage of inter-rater agreement for the study selection was 93% (κ = 0.80). Four RCTs (six publications) were included in our efficacy and harms analysis (Becker 2005a; Becker 2005b; Becker 2010; Schumacher 2008) and two open label trials (OLTs) were included in effectiveness and harms analysis (Becker 2009; Schumacher 2009). We have also included two more tables: Studies awaiting classification and Ongoing studies, which may be useful for future updates of this review.

Figure 1. Diagram of study selection. * RCT plus abstract (2 publications)



Included studies

Design

There were four randomised, double-blind, placebo-controlled trials: Becker 2005b, Becker 2010, Schumacher 2008, Becker 2005a of 4-week, 26-week, 28-week, and 52-week duration, respectively. From these four RCTs, two were combined (Becker 2005a; Schumacher 2008) and followed over a three-year period in an OLT (Becker 2009), and one (Becker 2005b) had an OLT of five years (Schumacher 2009). Table 1 shows the characteristics of the two OLTs included in this review. In Becker 2010 patients completing either one of the OLTs were eligible to participate. Randomisation was reported in ratios of 1:1:1:1 for Becker 2005b, 1:1:1 for Becker 2010 and Becker 2005a, and 2:2:1:2:1 for Schumacher 2008. Schumacher 2008 had three febuxostat arms versus allopurinol versus placebo; Becker 2005b had three febuxostat arms versus placebo; and Becker 2010 and Becker 2005a had two febuxostat arms versus allopurinol.

Sample sizes

Sample sizes ranged from 153 in Becker 2005b to 2269 in the Becker 2010.

Setting

All trials were reported as 'multicentre' trials, with no specific information regarding the setting. Becker 2005a enrolled participants from 112 centres in US and Canada. The remaining three studies were from US centres (324 centres for Becker 2010, 167 centres for Schumacher 2008, and 24 centres for Becker 2005b).

Participants

A total of 3978 patients were included in this analysis (4254 in total, but we subtracted 276 patients from Becker 2010 that took part in previous trials); 2619 participants were randomised to febuxostat (696 to 40 mg, 1231 to 80 mg, 558 to 120 mg, and 134 to 240 mg), 172 to placebo, and 1187 to allopurinol (up to 300 mg). Of these, 84% to 97% were men and 75% to 89% were white. The mean age of participants ranged from 51.6 to 56.2 years. Mean disease duration, when reported, ranged from 10 to 12.6 years. Becker 2005b did not report participants' mean disease duration. Participants were at least 18 years old and met the preliminary criteria of the American College of Rheumatologists (ACR) for acute gout arthritis and had serum uric acid levels of ≥ 8.0 mg/dL. Common exclusion criteria included: serum creatinine > 1.5 mg/dL (Becker 2010 and Schumacher 2008 included participants with moderate renal dysfunction); body mass index (BMI) higher than 50; history of xanthinuria; pregnancy or lactation; active liver disease; history of alcohol abuse; and use of uric acid-lowering agents or medications that could interfere with the treatment.

Intervention

Febuxostat reported dosages were 40 mg/day, 80 mg/day, 120 mg/day, and 240 mg/day. If needed, patients underwent a washout period before the trial where only naproxen or colchicine or both were provided. After the washout period, patients were allowed to maintain naproxen or colchicine dosages for 2 to 26 weeks. Gout flares were treated at the investigator's discretion. No other gout medication was allowed. Becker 2010, Schumacher 2008, and Becker 2005a had a control group with allopurinol at 100, 200, or 300 mg/day. Becker 2005b and Schumacher 2008 included a placebo group.

Outcomes

All trials reported the proportion of participants with serum uric acid levels of < 6.0 mg/dL as a primary outcome measure. Becker 2005b and Becker 2010 measured the serum uric acid levels at the final visit. Schumacher 2008 and Becker 2005a required that the serum uric acid levels were maintained on the last three monthly measurements.

Secondary outcomes included the proportion of participants with a serum uric acid level of < 6.0 mg/dL at each visit, the per cent reduction of serum uric acid levels from baseline at each visit, the proportion of participants requiring treatment for a self reported gout flare between weeks 8 and 28, and the reduction in the number of tophi at each visit for participants with palpable tophi at baseline. Becker 2005b included the per cent reduction in daily urinary uric acid excretion from baseline to day 28. Becker 2005a also reported the per cent reduction from baseline in tophus area. Becker 2010 evaluated the proportion of participants with < 5.0 and < 4.0 mg/dL at each visit and stratified their results by renal function.

Reported adverse events were similar across trials. Trials reported any adverse event, serious adverse events, and those occurring in at least 2% to 5% of participants in any group. Only Schumacher 2008 reported liver function test results.

Funding

All trials were funded by TAP Pharmaceutical Products, Inc., which is now part of Takeda Global Research & Development Center, Inc.

Excluded studies

Two articles were excluded from the meta analysis. Becker 2008 was a meta-analysis of individual patient data and Komoriya 2004 was a pharmacokinetics (phase 2) study with no outcome of interest for this review (see table Characteristics of excluded studies).

Risk of bias in included studies

Summary assessment of the risk of bias tables is presented in Figure 2 and Figure 3. The studies included in the meta-analysis were rated as unclear in most domains due to a poor quality of reporting. High risk of bias was rated in Becker 2005b and Becker 2005a in terms of incomplete outcome data given the high dropout rates of participants and lack of ITT analyses. Additionally, all studies were sponsored by TAP Pharmaceutical Products, Inc.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

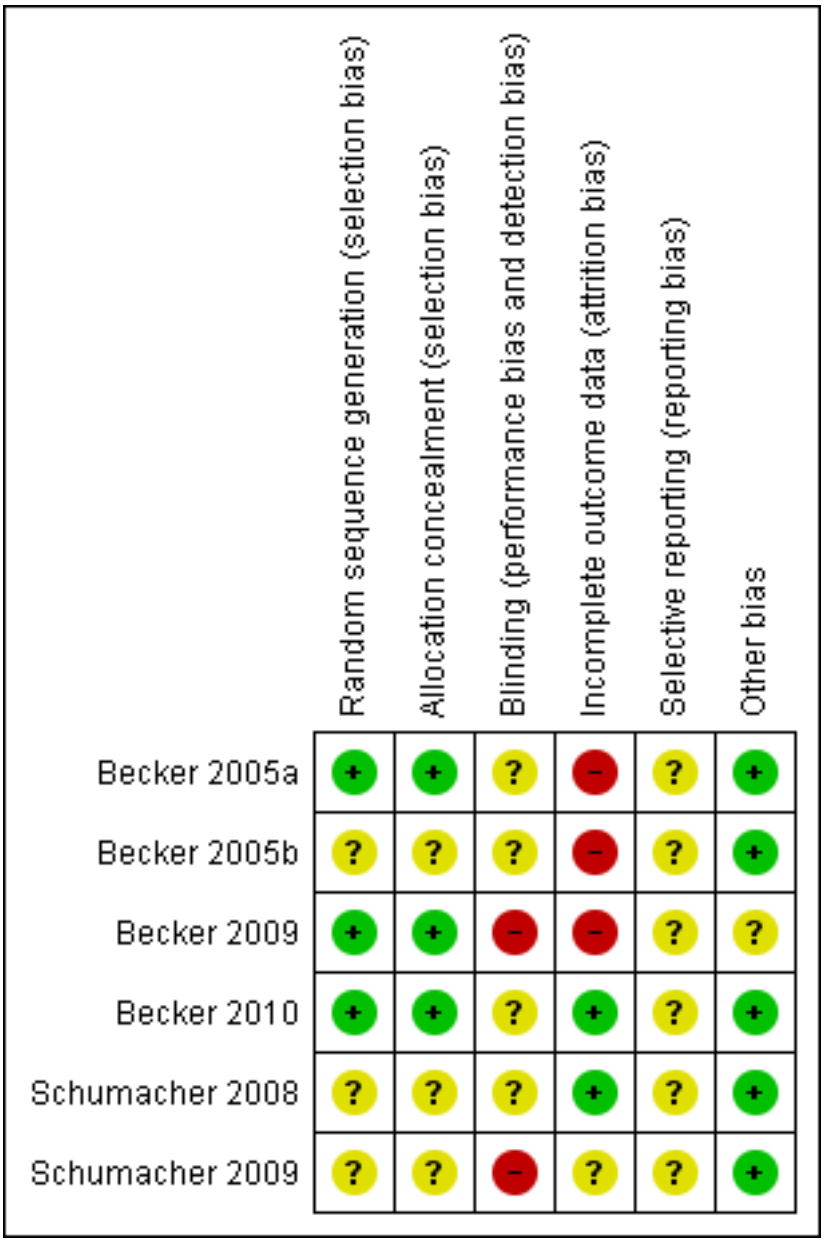
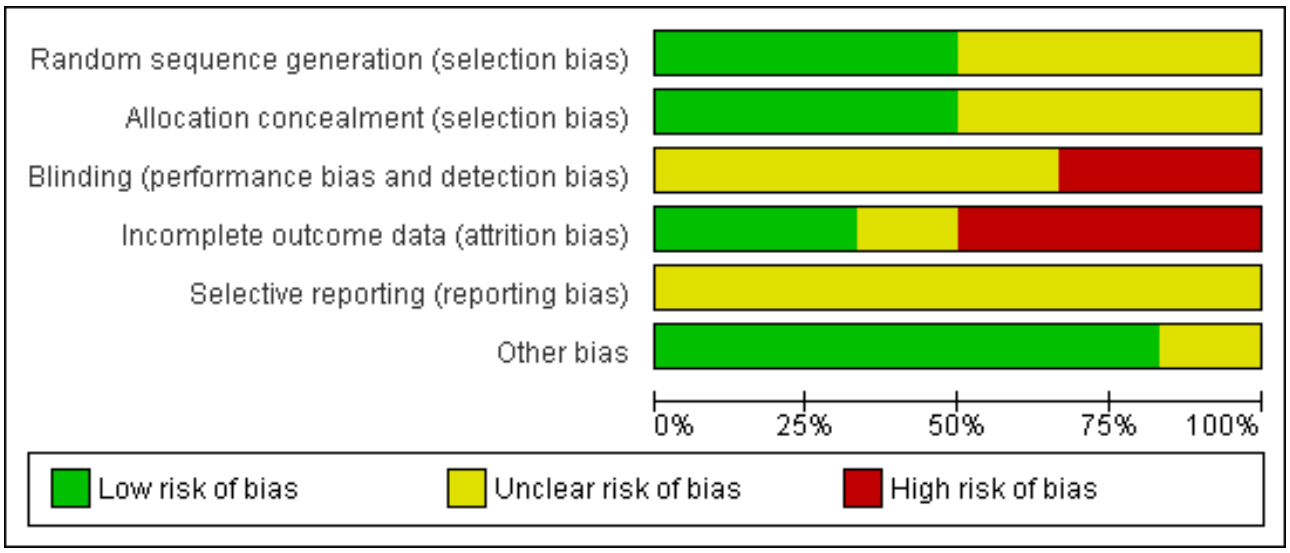


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

Adequate sequence generation was reported in two trials (Becker 2005a; Becker 2010). Becker 2010 described an interactive voice response system and stratified by baseline renal function and prior completion of either of two open label extension trials. A computer-generated central randomisation to allocate treatment was reported by Becker 2005a. For those reporting central randomisation we assumed that allocation was probably concealed. Methods of randomisation were not described by Schumacher 2008 and Becker 2005b.

Blinding

All trials were reported as 'double-blind', but no further details were provided. Febuxostat and allopurinol were not provided by the same manufacturer.

Incomplete outcome data

We used the same judging criteria as Maxwell 2009, with a less than 80% completion rate in the treatment group considered as a high risk of bias, and reviewed how missing data were imputed and if the primary outcome was analysed on an ITT basis.

Although Becker 2005b reported ITT analysis, not all randomised patients were included in the efficacy analysis (13 patients out of 153 were excluded). Authors did not provide a description on how incomplete outcome data were analysed. In Becker 2010, only one participant (out of 2268 randomised) was not included in the efficacy analysis (baseline serum uric acid level was < 8.0 mg/dL). Also, in this study there was no report on how missing data were imputed. Schumacher 2008 was the only trial with a proper ITT analysis and considered participants to be non-responders if they discontinued the study before ≥ 3 serum uric acid levels were obtained. Statistical analysis in Becker 2005a was based on completers: four participants were excluded because they had serum uric acid levels < 8.0 mg/dL at baseline and three because they did not receive the study treatment. Missing data for the primary efficacy endpoint were considered as non-responses.

The completion rates ranged from 61% to 97% for the febuxostat group, 74% to 82% in the allopurinol-treated group, and 75% to 95% in the placebo group. Lower completion rates were observed in trials with longer follow-up periods and in higher dosage groups. Adverse events were the most common reason for discontinuation in all trials (not including gout flares).

Selective reporting

All trials assessed the expected outcomes. However, there was failure to report findings of some of the pre-specified secondary outcomes.

Other potential sources of bias

All trials were sponsored and partially designed by TAP Pharmaceutical products, and the specific role of the study sponsor and the potential conflicts of interest for each author were not reported in three trials.

Effects of interventions

See: **Summary of findings for the main comparison** Febuxostat 40 mg/day versus placebo; **Summary of findings 2** Febuxostat 80 mg/day versus placebo; **Summary of findings 3** Febuxostat 120 mg/day versus placebo; **Summary of findings 4** Febuxostat 40 mg/day versus allopurinol; **Summary of findings 5** Febuxostat 80 mg/day versus allopurinol; **Summary of findings 6** Febuxostat 120 mg/day versus allopurinol

Comparisons were analysed by febuxostat dosage and by the control group used: i) febuxostat 40 mg/day, 80 mg/day, 120 mg/day, or 240 mg/day versus placebo; and ii) febuxostat 40 mg/day, 80 mg/day, 120 mg/day, or 240 mg/day versus allopurinol. The current approved dosages for febuxostat in the US are 40 and 80 mg daily (FDA 2009), and 80 and 120 mg in Europe (EMEA 2008).

Efficacy

Outcomes are described in the following order: gout flares, per cent of patients achieving serum uric acid levels < 6.0 mg/dL, and per cent reduction in serum uric acid levels from baseline to the final

visit. Results for the following outcome measures were not reported in any of the included studies: joint imaging, musculoskeletal function, patient or physician global assessment, and pain. Tophi burden was measured differently in the trials, which prevented the analysis of this outcome. A summary of each trial result is provided at the end of this section. Mean serum uric acid levels at baseline ranged from 9.2 mg/dL to 9.9 mg/dL and the proportion of patients with a history or presence of tophi ranged from 16% to 33%.

Febuxostat versus placebo

1. Febuxostat 40 mg versus placebo

In Becker 2005b no statistically significant difference in the patients' self-reported gout flares was observed between patients assigned to febuxostat compared to those in the placebo group at 28 days (RR 0.95; 95% CI 0.52 to 1.7). However, patients in the febuxostat group were more likely to achieve serum uric acid levels < 6.0 mg/dL at 28 days (RR 40.1; 95% CI 2.5 to 639.1) and had a statistically significant reduction in serum uric acid levels from baseline at 28 days (MD -5.2; 95% CI -5.8 to -4.7) compared to patients in the placebo group (Analysis 1.1, Analysis 1.2, and Analysis 1.3).

2. Febuxostat 80 mg versus placebo

Two studies provided data on the incidence of gout flares at four to eight weeks (Becker 2005b; Schumacher 2008) with a pooled RR of 1.3 (95% CI 0.96 to 1.8). The combined RR for achieving serum uric acid levels < 6.0 mg/dL at the final visit was 68.9 (95% CI 13.8 to 343.9). The combined mean reduction observed in serum uric acid levels from baseline to the final visit of -5.0 was statistically significant in favour of febuxostat (95% CI -6.2 to -3.7) (Analysis 2.1, Analysis 2.2, and Analysis 2.3).

3. Febuxostat 120 mg versus placebo

Becker 2005b and Schumacher 2008 provided data for this comparison at four to eight weeks. Patients in the febuxostat group reported more frequent gout flares than in the placebo group (pooled RR 1.7; 95% CI 1.3 to 2.3). However, serum uric acid levels < 6.0 mg/dL at the final visit were 80.7 times more likely to be achieved in the febuxostat group compared to the placebo group (95% CI 16.0 to 405.5). The combined mean reduction in serum uric acid levels from baseline to the final visit between the febuxostat group and the placebo group was -5.3 (95% CI -5.7 to -4.9) (Analysis 3.1, Analysis 3.2, and Analysis 3.3).

4. Febuxostat 240 mg versus placebo

Only one study (Schumacher 2008) reported data on the incidence of gout flares for febuxostat 240 mg/day versus placebo with an observed RR at 28 weeks of 2.6 (95% CI 1.8 to 3.7). More febuxostat-treated patients achieved serum uric acid levels < 6.0 mg/dL at the final visit compared to placebo (RR 93.4; 95% CI 13.2 to 654.5). Furthermore, they had a greater decrease in their MD in serum uric acid levels from baseline at 28 weeks (MD -6.3; 95% CI -6.6 to -6.0) (Analysis 4.1, Analysis 4.2, and Analysis 4.3).

Febuxostat versus allopurinol

5. Febuxostat 40 mg versus allopurinol

One study provided data on the incidence of gout flares at 24 weeks (Becker 2010). The number of gout flares was not significantly different between the two groups (RR 0.97; 95% CI 0.57 to 1.7). Also, the two groups did not differ in the per cent achieving serum uric acid levels < 6.0 mg/dL (RR 1.1; 95% CI 0.94 to 1.2). Data on per cent reduction in serum uric acid levels from baseline to final visit were not provided (Analysis 5.1, Analysis 5.2).

6. Febuxostat 80 mg versus allopurinol

Three studies provided data on the efficacy of febuxostat 80 mg compared to allopurinol: Schumacher 2008 at 8 weeks, Becker 2010 at 26 weeks, and Becker 2005a at 52 weeks. The pooled RR for the incidence of gout flares was 1.1 (95% CI 0.98 to 1.3). Patients in the febuxostat group were 1.8 times more likely to achieve a serum uric acid level < 6.0 mg/dL at the final visit compared to those patients in the allopurinol group (95% CI 1.6 to 2.1). The pooled estimate for per cent reduction in serum uric acid levels from baseline to final visit did not reach statistical significance (MD -1.2; 95% CI -1.5 to -0.99) (Analysis 6.1, Analysis 6.2, and Analysis 6.3).

7. Febuxostat 120 mg versus allopurinol

At 28 to 52 weeks, the pooled RR from Schumacher 2008 and Becker 2005a for having gout flares, with febuxostat 120 mg, was 1.29 (95% CI 0.87 to 1.91). On the other hand, the pooled RR for achieving serum uric acid levels < 6.0 mg/dL at the final visit was 2.2 (95% CI 1.91 to 2.45). Similarly, there was a statistically significant reduction in serum uric acid levels from baseline to final visit (MD -1.9; 95% CI -2.2 to -1.7) (Analysis 7.1, Analysis 7.2, and Analysis 7.3).

8. Febuxostat 240 mg versus allopurinol

Patients on febuxostat 240 mg were 2.3 times more likely to report gout flares compared to those on allopurinol at 28 weeks (95% CI 1.7 to 3.0). They were also more likely to achieve serum uric acid levels < 6.0 mg/dL at the final visit (RR 93.0; 95% CI 13.2 to 654.5). Additionally, the reduction in serum uric acid levels from baseline to final visit was significantly greater in the febuxostat group compared to the allopurinol group at eight weeks (MD -3.4; 95% CI -3.6 to -3.1) (Analysis 8.1, Analysis 8.2, and Analysis 8.3).

Tophi burden

At 28 weeks, the mean per cent reduction in the number of tophi in the febuxostat 120 mg group was greater than in the placebo group (-1.2 versus -0.3, P ≤ 0.05) (Schumacher 2008). The presence of tophi at baseline was associated with a lower proportion of patients achieving serum uric acid levels < 6.0 mg/dL at the final visit: 48% versus 35% for febuxostat 40 mg, and 45% versus 32% for allopurinol (Becker 2010).

At 52 weeks, the median per cent reduction in tophus area was greater for patients receiving febuxostat 80 mg or 120 mg compared to allopurinol (83%, 66% versus 50%). However, the proportion of patients with a reduction in the tophus area and a median reduction in the number of tophi were similar between groups (54%, 40% versus 48%; and 1%, 0% versus 0%, respectively). The presence of tophi at baseline was associated with a lower proportion of patients achieving serum uric acid levels < 6.0 mg/dL at final visit: 70% versus 57% for febuxostat; and 45% versus 32% for allopurinol (Becker 2010).

Effectiveness

Only one OLT had a control group (Becker 2009). During three years of follow-up the authors did not find any differences across groups. The mean percentage of participants requiring treatment for an acute attack was 4.5% (0% to 10%) for the febuxostat 80 mg group, 6.6% (2% to 17%) for the febuxostat 120 mg group, compared

to 5.7% (0% to 11%) for the allopurinol group (numbers based on completers). Ninety per cent (109/120) of participants taking febuxostat 80 mg maintained serum uric acid levels < 6.0 mg/dL, 91% (43/47) of those taking febuxostat 120 mg, and 90% (9/10) of participants in the allopurinol group. Mean percentage reductions in serum uric acid levels from baseline to final visit were 47% and 53% for patients on febuxostat 80 mg and 120 mg respectively compared to 32% for patients on allopurinol. See Table 2.

In Becker 2009, the mean reduction in primary tophus size among participants with a history or the presence of tophi was -68%, -48%, and -52% for febuxostat 80 mg, 120 mg, and allopurinol, respectively. The mean reduction in total number of tophi was -60%, -58%, and -50%, respectively; and the proportion of participants with complete resolution of primary tophi at three years was 47%, 38%, and 30%, respectively. In Schumacher 2009, the incidence of gout flares was higher in participants with tophi compared with participants without tophi at one year (31% versus 10%). At four years only 10% of the participants with baseline tophi reported flares. Resolution of the tophi occurred in 18 of 26 (69%) of the participants at five years. However, the proportion of patients achieving serum urate levels < 6.0 mg/dL was similar between patients with or without a history or presence of tophi at baseline.

Withdrawals

We report five types of withdrawals: total withdrawals, due to adverse events, gout flares, lack of efficacy, and other reasons (as reported by authors).

Febuxostat versus placebo

9. Febuxostat 40 mg versus placebo

For the only study comparing febuxostat 40 mg versus placebo (Becker 2005b), withdrawals in both groups were mostly due to adverse events or gout flares, with no statistically significant differences between the two groups (RR 1.0; 95% CI 0.07 to 15.8, and RR 0.34; 95% CI 0.01 to 8.1, respectively). Also, looking at total withdrawals, there was no statistically significant difference between groups (RR 0.51; 95%CI 0.05 to 5.4) (Analysis 9.1, Analysis 9.2, Analysis 9.3, Analysis 9.4, and Analysis 9.5).

10. Febuxostat 80 mg versus placebo

The pooled RR for total withdrawals was 1.4 (95% CI 1.0 to 2.0) for patients in the febuxostat group compared to placebo. Otherwise, withdrawals because of adverse events, gout flares, lack of efficacy, and other reasons were not statistically higher in the febuxostat group compared to placebo (Analysis 10.1, Analysis 10.2, Analysis 10.3, Analysis 10.4, and Analysis 10.5).

11. Febuxostat 120 mg versus placebo

In the two trials included for this comparison (Becker 2005b; Schumacher 2008) there was no statistically significant difference between the groups for any withdrawal types (Analysis 11.1, Analysis 11.2, Analysis 11.3, Analysis 11.4, and Analysis 11.5).

12. Febuxostat 240 mg versus placebo

Patients in the febuxostat group were 1.5 times more likely to withdraw compared to placebo (95% CI 1.0 to 2.1). Also, there was a trend for a higher withdrawal rate due to gout flare (RR 17.0; 95% CI 0.99 to 291.6). Otherwise there were no observed differences (Analysis 12.1, Analysis 12.2, Analysis 12.3, Analysis 12.4, and Analysis 8.3).

Febuxostat versus allopurinol

13. Febuxostat 40 mg versus allopurinol

In (Becker 2010), again there was no statistically significant difference across groups in any type of withdrawal (Analysis 13.1, Analysis 13.2, Analysis 13.3, Analysis 13.4, and Analysis 8.3).

14. Febuxostat 80 mg versus allopurinol

Patients in the febuxostat group had a significantly higher total withdrawal rate than placebo with a pooled RR of 1.3 (95% CI 1.1 to 1.5) (Analysis 14.1). Also, patients in the febuxostat group were 1.3 times more likely to withdraw for reasons other than adverse events, gout flares, or lack of efficacy compared to allopurinol (95% CI 1.1 to 1.6) (Analysis 14.2, Analysis 14.3, Analysis 14.4, and Analysis 14.5).

15. Febuxostat 120 mg versus allopurinol

Trials included for this comparison were Schumacher 2008 and Becker 2005a. Patients in the febuxostat group were 1.4 times more likely to withdraw for any reason compared to the allopurinol group (95% CI 1.1 to 1.7) (Analysis 15.1). Furthermore, they were 3.4 times more likely to withdraw due to gout flares compared with allopurinol (95% CI 1.7 to 6.8). No other difference was found (Analysis 15.2, Analysis 15.3, Analysis 15.4, and Analysis 15.5).

16. Febuxostat 240 mg versus allopurinol

Similar to the 120 mg group, patients taking febuxostat 240 mg had increased total withdrawals and increased withdrawals due to gout flares when compared to allopurinol (RR 1.7; 95% CI 1.2 to 2.2, and RR 16.0; 95% CI 2.0 to 129.6, respectively). Again, no other differences were observed (Analysis 16.1, Analysis 16.2, Analysis 16.3, Analysis 16.4, and Analysis 16.5).

Adverse events

The most clinically relevant adverse events reported were: any adverse events, serious adverse events, liver function test abnormalities, skin reaction, cardiovascular events (chest pain, coronary artery disease, myocardial infarction, atrial fibrillation), hypertension, and diarrhoea. Adverse events were generally reported by treatment group. Three studies classified the events according to the definitions in the MedRA (Becker 2005b; Becker 2010; Schumacher 2008).

Febuxostat versus placebo

17. Febuxostat 40 mg versus placebo

Comparing febuxostat 40 mg to placebo we did not find any statistically significant difference between the two groups in any of the above adverse events. Of note, there were no reports in either group of any cardiovascular event, skin reaction, or hypertension (Analysis 17.1, Analysis 17.3, Analysis 17.4, Analysis 17.5, Analysis 17.6, and Analysis 17.7).

18. Febuxostat 80 mg versus placebo

No significant difference was noted between the two groups for the measure of any adverse event (RR 0.95; 95% CI 0.83 to 1.1). Pooled data from the studies included in this analysis (Becker 2005b; Schumacher 2008) showed that the febuxostat group tended

to have more liver enzyme abnormalities but without reaching statistical significance (RR 2.9; 95% CI 0.92 to 8.8). Otherwise there were no differences between both groups (Analysis 18.1, Analysis 18.3, Analysis 18.4, Analysis 18.5, Analysis 18.6, and Analysis 18.7).

19. Febuxostat 120 mg versus placebo

No statistically significant differences were noted between the two groups in any measure (Analysis 19.1, Analysis 19.3, Analysis 19.4, Analysis 19.5, Analysis 19.6, and Analysis 19.7).

20. Febuxostat 240 mg versus placebo

Similarly in this analysis there were no statistically significant differences noted between the two groups (Analysis 20.1, Analysis 20.3, Analysis 20.4, Analysis 20.5, Analysis 20.6, and Analysis 20.7).

Febuxostat versus allopurinol

21. Febuxostat 40 mg versus allopurinol

No statistically significant differences in any of the adverse events we reported were noted between these two groups (Analysis 21.1, Analysis 21.3, Analysis 21.4, Analysis 21.5, Analysis 21.6, and Analysis 21.7).

22. Febuxostat 80 mg versus allopurinol

Three studies provided data on adverse events for this comparison (Becker 2005a; Becker 2010, Schumacher 2008). Total adverse events were less likely to be reported in the febuxostat group compared with patients in the allopurinol group (RR 0.94; 95% CI 0.89 to 0.99) (Analysis 22.1). In one study, hypertension was 4.4 times more likely to be reported in the febuxostat group compared to the allopurinol group (RR 4.4; 95% CI 1.3 to 15.1) (Analysis 22.6). No other statistically significant differences in adverse events were found between the two groups (Analysis 22.3, Analysis 22.4, Analysis 22.5, and Analysis 22.7).

23. Febuxostat 120 mg versus allopurinol

From data provided by Schumacher 2008 and Becker 2005a, febuxostat-treated patients were 0.90 times less likely to report any adverse event compared to allopurinol-treated patients (95% CI 0.84 to 0.96). No other statistically significant differences were noted between the two groups (Analysis 23.1, Analysis 23.3, Analysis 23.4, Analysis 23.5, Analysis 23.6, and Analysis 23.7).

24. Febuxostat 240 mg versus allopurinol

In Schumacher 2008, hypertension and diarrhoea were more likely to be reported in the febuxostat group compared to the allopurinol group, with hypertension being 4.0 times more likely to develop (95% CI 1.0 to 15.8) and diarrhoea twice as likely (RR 2.1; 95% CI 1.1 to 4.0) (Analysis 24.1, Analysis 24.3, Analysis 24.4, Analysis 24.5, Analysis 24.6, and Analysis 24.7).

Long-term harms

There were no statistically significant differences regarding long-term harms over three years between febuxostat 80 mg or 120 mg and the allopurinol group in the only OLT with a control group (Becker 2009). The adverse events rate per 100 patient years were 227, 216, and 246, respectively (Table 3).

Subgroup and sensitivity analysis

Analyses by different dosage, duration of treatment, and renal function did not result in different effect sizes. Subgroups based on severity of baseline disease, age, and disease duration were not performed because these characteristics were similar across groups. No statistically significant differences were observed when data were analysed by renal function or considering effect of study quality.

DISCUSSION

This systematic review analysed and summarised evidence from all published RCTs of febuxostat for treating chronic gout. Four RCTs with 3978 participants were included, 2619 assigned to febuxostat, 172 to placebo, and 1187 to allopurinol. At the approved doses (40 mg, 80 mg, and 120 mg) febuxostat seemed to be beneficial in achieving serum uric acid levels < 6.0 mg/dL and reducing serum uric acid levels from baseline to the final visit. The benefit was noted for any dosage of febuxostat in comparison to placebo. When compared to allopurinol febuxostat showed benefit only at dosages of 80 and 120 mg. The incidence of gout flares requiring treatment may be increased in patients taking febuxostat compared to placebo or allopurinol during early treatment. However, no such increase in gout flares, compared to allopurinol, was observed in the long-term follow-up study. Additionally, trials did not report data on pain, functional assessment, quality of life, and patient and physician global assessments.

Summary of main results

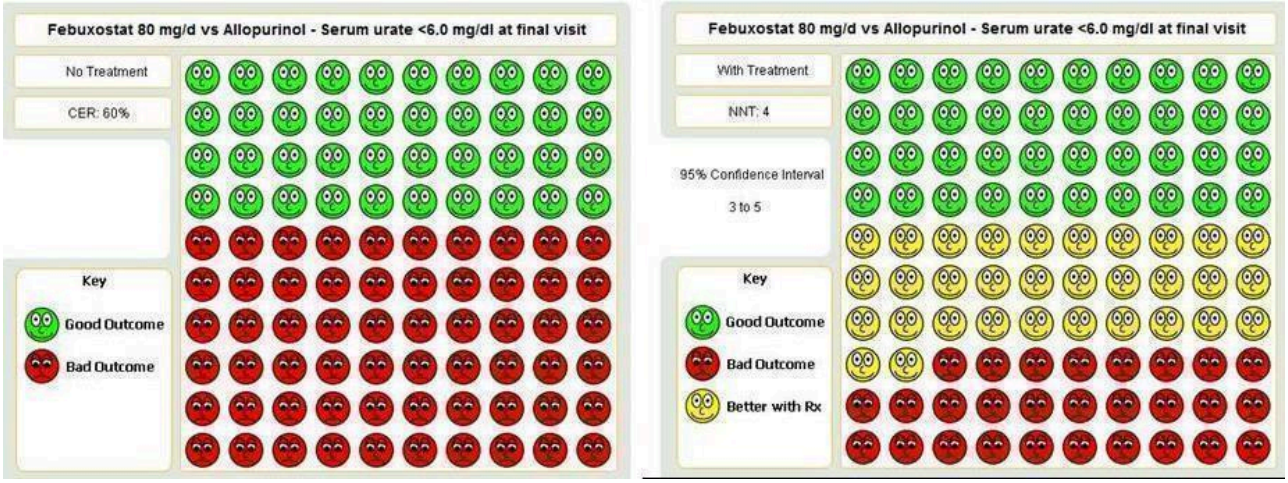
For our primary outcome acute gout flares, although there was only a statistically significant increase when comparing febuxostat 120 mg versus placebo (absolute risk increase 15%; 95% CI 6% to 23%, and a number need to treat to harm of 6, 95% CI 4 to 17), there was a strong trend towards such higher rates when comparing febuxostat 80 mg to placebo and febuxostat 80 mg or 120 mg to allopurinol.

Compared to placebo, febuxostat 40 mg had an absolute treatment benefit of 55% and a number needed to treat (NNT) of 1.8 people to achieve serum uric acid levels < 6.0 mg/dL at the final visit. Thus, patients taking febuxostat were 40 times more likely to achieve serum uric acid levels < 6.0 mg/dL at the final visit (Summary of findings for the main comparison). For febuxostat 80 mg and 120 mg, the absolute treatment benefit was 75% and 87% and the NNT 2 and 1, respectively (Figure 4). Patients were 69 and 81 times more likely to achieve serum uric acid levels < 6.0 mg/dL at the final visit, respectively (Summary of findings 2, and Summary of findings 3).

Figure 4. People not affected by a treatment (green faces for those with a good outcome and red for those with a bad outcome)
People for which treatment changes their category from a bad outcome to a good outcome (yellow faces)
People for which treatment causes an adverse event and changes their category from a good outcome to bad outcome (crossed out green faces)

Compared to allopurinol, febuxostat 40 mg showed no statistically significant difference between groups to achieve serum uric acid levels < 6.0 mg/dL at the final visit (Summary of findings 4). For febuxostat 80 mg and 120 mg, the absolute treatment benefit of achieving serum uric acid levels < 6.0 mg/dL at the final visit was 29% and 44% and the NNT was 3 people for both dosages (Figure 5). Patients were 1.8 and 1.2 times more likely to achieve serum uric acid levels < 6.0 mg/dL at the final visit (Summary of findings 5 and Summary of findings 6).

Figure 5. People not affected by a treatment (green faces for those with a good outcome and red for those with a bad outcome)
People for which treatment changes their category from a bad outcome to a good outcome (yellow faces)
People for which treatment causes an adverse event and changes their category from a good outcome to bad outcome (crossed out green faces)



For total discontinuation rates, compared to placebo only febuxostat 80 mg showed a significantly higher rate (11% absolute risk increase; 95% CI 6 to 16%, RR 1.4; 95% CI 1.2 to 1.8). Similarly, compared to allopurinol the rates were higher for febuxostat 80 mg and 120 mg (11% absolute risk increase; 95% CI 6 to 16%, RR 1.5; 95 % CI 1.2 to 1.8, and 20% absolute risk increase; 95% CI 3 to 14%, RR 2.6; 95% CI 2.0 to 3.3, respectively). There were no statistically significant differences between groups for discontinuation rates due to adverse events.

For total adverse events, there were no statistically significant differences except for a lower rate when comparing febuxostat 80 mg and 120 mg against allopurinol (ARR 6%; 95% CI 0.7 to 11%, RR 0.93; 95% CI 0.87 to 0.99, and ARR 8%; 95% CI 3 to 13%, RR 0.90; 95%

CI 0.84 to 0.96, respectively). No differences were observed between groups for serious adverse events rates.

Overall completeness and applicability of evidence

We have included all febuxostat RCTs published to date. All outcomes reported by each trial were analysed. However, the studies only evaluated four of the efficacy outcome measures listed by OMERACT 9 (OMERACT 9). Five relevant outcomes were not assessed in any of the studies including pain, functional assessment, quality of life, and patient and physician global assessment.

Listed study inclusion criteria were broad and general. Participants in the majority of the included studies had chronic gout with normal renal function and mild to moderate renal dysfunction. Patients included in these trials may not represent typical gout patients seen in daily clinical practice, where alcohol intake can be higher than 14 drinks per week or concomitant medications can interfere with the metabolism of febuxostat. Furthermore, patients selected for RCTs generally have few major co-morbidities.

On the other hand, included trials used a standard allopurinol dosage of 100 to 300 mg/day depending on renal function. This could contrast with what is considered best practice by major agencies guidelines (EULAR (Zhang 2006) and BSR (Jordan 2007)), which recommend dosage titration of allopurinol up to 900 mg daily when warranted to achieve the goal of a serum uric acid of < 6.0 mg/dL and if permitted by renal function. OMERACT 9 lists hyperuricaemia and incidence of gout flares as major outcome measures, among others, for RCTs including gout patients (OMERACT 9). In our review, all included studies had the goal of a serum uric acid of 6.0 mg/dL as the primary outcome and the incidence of gout flares, a more clinically relevant outcome, as a secondary one. While it is established that the target of uric lowering therapies in gout patients is maintaining uric acid levels at < 6.0 mg/dL, the indication to initiate such therapy is usually a clinical one, most commonly recurrent gout flares, and also uric acid renal stones or presence of tophi. Furthermore, all studies had a short-term follow-up, making the markedly higher incidence of gout flares in the febuxostat groups somewhat expected, especially when initiating uric lowering therapy with an increased pace of reducing uric acid levels. To be noted though, in the OLTs there were no observed differences in gout flares between the febuxostat and allopurinol groups.

Quality of the evidence

We used GRADEprofiler 3.6 to appraise the overall quality of evidence. Evidence quality ranged from low to high. There were two studies with high risk of bias in one item (ITT), one study included relatively few patients and few events providing wider confidence intervals, and all studies reported a surrogate endpoint as their primary outcome measure. Also, significant heterogeneity was noted in 20 out of the 59 analyses, ranging from 38% to 98%.

Regarding individual trial quality assessment, there were concerns about attrition bias given the dropout rates and some excluded participants from the efficacy analyses that were included in harms analyses. Of note, all studies failed to report on six of the nine outcome measures recommended by OMERACT, and were sponsored by the same pharmaceutical company; evidence shows that trials sponsored by industry may overestimate the treatment effect (Bhandari 2004).

A funnel plot was not created due to the limited number of studies included in this study.

Nonetheless, we concluded that the evidence provided in this review for short-term serum uric acid levels is unlikely to have an important impact on our confidence in the estimate. For long-term adverse events most trials that were included were not powered to detect adverse events, which can lead to type 2 error. Further studies are needed to assess long-term harms.

Potential biases in the review process

This review included a comprehensive search performed by an experience information specialist. Two review authors independently reviewed all abstracts and titles, abstracted data, and performed bias and quality assessment. Consensus was reached by discussing any discrepancies. Therefore, errors in selection and abstraction are minimized. Published trial reports did not provide enough details to adequately assess risk of bias, and we are unable to determine fully if there is selective outcome reporting since we do not have access to the protocols for these studies. Additionally, since most studies are designed primarily for efficacy outcomes, analyses on harms are somewhat limited. A lack of differences in the harms outcomes may be due either to lack of power to detect differences or lack of difference in these outcomes.

A protocol was published for this review. All analyses were specified a priori. However, the presence of significant heterogeneity poses a threat to the combinability of the included studies. Also, only one of the included open label trials (OLT) had a comparison group, which prevented us from pooling long-term data.

Agreements and disagreements with other studies or reviews

One health technology assessment, two reviews, one consensus statement, and one editorial have reviewed the evidence on the efficacy and harms of febuxostat for treating chronic gout.

Stevenson et al conducted a technology appraisal to evaluate the clinical and cost effectiveness of febuxostat (Stevenson 2011). The clinical evidence was derived from two RCTs. A simple pooled analysis of the individual patient-level data from the two trials was undertaken. There was substantial uncertainty in the relationships reported by the manufacturer regarding serum uric acid levels and the incidence of gout flares, and underlying patient utility. The study concluded that febuxostat is an option for the management of chronic hyperuricaemia in gout only for people who are intolerant to allopurinol or for whom allopurinol is contraindicated. Jansen et al published a position statement based on three RCTs and one OLT and concluded that, based on the available data, febuxostat should not be considered as first line drug treatment in patients with gout and associated hyperuricaemia (Jansen 2010). In an editorial for Arthritis Research and Therapy, Dr Singh (Singh 2010), conducted a meta-analysis to evaluate the cardiovascular risk with febuxostat treatment compared to allopurinol. Similar to our results, the author concluded that there were not statistically significant differences between febuxostat and allopurinol, although there was a non-significant trend towards more serious adverse events with febuxostat compared to placebo. Furthermore, in a systematic review, Bruce et al found

that febuxostat significantly reduces serum uric acid levels within two weeks after initiation of therapy, and up to 48% by the end of 104 weeks of therapy (Bruce 2006). Two thirds of the patients achieve serum uric acid levels < 6.0 mg/dL during the last three months following once-daily administration of febuxostat 80 mg or 120 mg for at least 52 weeks. However, he listed abnormal function tests and diarrhoea as the most common adverse event. Similar to our findings he concluded that patients on febuxostat are at an increased risk of experiencing gout flares (up to 70%).

AUTHORS' CONCLUSIONS

Implications for practice

Allopurinol is the first line treatment for chronic gout. However, both inadequate response and safety in patients with impaired renal function continue to be a concern. Febuxostat is approved at 40, 80, and 120 mg/day in the US and Europe. From our results, febuxostat has comparable efficacy as allopurinol. Thus, febuxostat is a promising alternative to allopurinol for the treatment of hyperuricaemia in chronic gout, especially in those who cannot tolerate allopurinol. Another benefit is the potential safety of febuxostat in patients with mild to moderate renal dysfunction. There are concerns about the initial increased rate of gout flares associated with the use of febuxostat, and the optimal length of prophylactic therapy is unclear.

Implications for research

On-going post-marketing surveillance is required to determine the incidence of adverse events and sustainability of the treatment response. Also needed are studies comparing febuxostat to higher allopurinol doses, and its harms in patients with severe renal dysfunction.

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NCT01082640 *{unpublished data only}*

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Becker 2005a

Methods	Phase 3, randomised, double-blind, allopurinol-controlled trial. 52-week, multicentre study. No of patients randomised = 762. No of patients analysed = 756 (2 withdrew without receiving study drug, 4 excluded because baseline serum uric acid was < 8.0mg/dL).
Participants	Inclusion criteria: preliminary criteria of the ACR for gout and serum uric acid ≥ 8.0 mg/dL. Adults. Exclusion criteria: serum creatinine > 1.5 mg/dL or estimated creatinine clearance rate < 50 ml/min; pregnancy or lactation; use of uric acid-lowering agents, azathioprine, 6-mercaptopurine, thiazide diuretics, or medications containing aspirin (> 325 mg/day) or other salicylates; BMI > 50; history of xanthinuria, active liver disease, or hepatic dysfunction; use of prednisone at > 10 mg/day; change in hormone-replacement therapy or oral-contraceptive therapy within the previous 3 months; and history of alcohol abuse or alcohol intake of more than 14 drinks/week. Location: Centers in the USA and Canada.
Interventions	Patient randomised to 3 groups 1. Febuxostat 80 mg/day N = 257(256 received ≥1dose) 2. Febuxostat 120 mg/day N = 251 3. Allopurinol 300 mg/day N = 254 (253 received ≥1dose) Two-weeks washout period before randomisation for subjects already on uric acid-lowering therapy. Prophylaxis with naproxen (250 mg BID) or colchicine (0.6 mg daily) given to all subjects during the washout period and the first 8 weeks of the trial. Subsequent gout flares treated at the investigators' discretion. Duration: 52 weeks.
Outcomes	Primary efficacy endpoint: - serum uric acid < 6.0 mg/dL at each of the last three monthly measurements. Secondary efficacy endpoints: - proportion of subjects with serum uric acid < 6.0 mg/dL at each visit - percentage reduction from baseline in the serum uric acid concentration at each visit. - percentage reduction from baseline in tophus area. - change in the number of tophi at each visit. - proportion of subjects requiring treatment for gout flares from weeks 9 through 52. Adverse events.
Notes	Source of funding: TAP Pharmaceutical Products, Inc.
Risk of bias	

Becker 2005a *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer-generated central randomisation schedule with a block size of three was used to assign each subject to one of the three groups.
Allocation concealment (selection bias)	Low risk	Not described, but considered probable due to central randomisation.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No details provided other than stating that this is a double-blind trial.
Incomplete outcome data (attrition bias) All outcomes	High risk	Some study participants were not accounted for in the efficacy analysis: 4 subjects excluded because they had sUA < 8mg/dL at baseline and 3 because they did not receive the study treatment.
Selective reporting (reporting bias)	Unclear risk	The study protocol is not available, but the authors did not report on 5 of the 9 outcomes recommended by OMERACT (OMERACT 9).
Other bias	Low risk	Representatives of TAP Pharmaceutical Products collected the data, and statisticians at TAP conducted all statistical analyses.

Becker 2005b

Methods	Phase 2, randomised, double-blind, placebo-controlled, dose-response trial. 28-day multicentre study. No of patients randomised = 153. No of patients analysed for efficacy = 140 (13 excluded because baseline serum uric acid was collected outside the day -2 window). No of patients analysed for harms and gout flares = 153.
Participants	Inclusion criteria: preliminary criteria of the ACR for gout and serum uric acid ≥ 8.0 mg/dL. Exclusion criteria: serum creatinine > 1.5 mg/dL or estimated creatinine clearance (eCLcr) < 50 ml/min; pregnancy or lactation; use of uric acid-lowering agents, azathioprine, 6-mercaptopurine, or medications containing aspirin (> 325 mg/day) or other salicylates; BMI > 50; history of xanthinuria, active liver disease, or hepatic dysfunction; use of prednisone at > 10 mg/day; change in thiazide or steroid therapy (within 1 month of study) or hormone-replacement therapy or oral-contraceptive therapy (within 3 months of study); and history of alcohol abuse or alcohol intake of ≥ 14 drinks/week. Location: centres in the USA.
Interventions	Patient randomised to 4 groups: 1. Febuxostat 40 mg/day N = 37 2. Febuxostat 80 mg/day N = 40 3. Febuxostat 120 mg/day N = 38 4.Placebo N = 38 Two-weeks washout period before randomisation for subjects already on uric acid-lowering therapy. Prophylaxis with colchicine (0.6 mg BID) given to all subjects during the washout period and the first 2 weeks of the trial.

Becker 2005b *(Continued)*

	Subsequent gout flares treated at the investigators' discretion.
Outcomes	The primary efficacy endpoint: - serum uric acid < 6.0 mg/dL at day 28. Secondary efficacy endpoints: - proportion of subjects with serum uric acid < 6.0 mg/dL at each visit. - percentage reduction from baseline in the serum uric acid concentration at day 28. - incidence of gout flares. Adverse events.
Notes	Source of funding: TAP Pharmaceutical Products, Inc.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Reported as a double-blind trial, but methods of masking were not described (only 2 weeks of double blind treatment).
Incomplete outcome data (attrition bias) All outcomes	High risk	Efficacy analyses were based on a modified intention-to-treat population (only those that received treatment). There is no description on how incomplete outcome data was analysed
Selective reporting (reporting bias)	Unclear risk	The study protocol is not available, but the authors did not report on 6 of the 9 outcomes recommended by OMERACT(OMERACT 9).
Other bias	Low risk	Drs Becker, Schumacher, and Wortmann have received consulting fees from TAP Pharmaceutical Products, but role of the sponsor was not stated. 4 of the 7 authors are from TAP Pharmaceutical Products.

Becker 2009

Methods	Open label extension study (3 years findings). No of patients randomised =1280 subjects who previously completed one of the 2 Phase III double-blind trials (Becker 2005a; Schumacher 2008). No. of patients completing the study = 1086. No. of patients analysed for harms and gout flares = 664
Participants	Inclusion criteria: preliminary criteria of the ACR for gout. Exclusion criteria: pregnancy or lactation; serious drug-related AE in the prior study; other significant medical conditions that would interfere with treatment harms or compliance; or known intolerance to allopurinol..

Becker 2009 *(Continued)*

	Location: 174 centres in the USA and Canada.
Interventions	3 groups: 1. Febuxostat 80 mg/day N = 606 2. Febuxostat 120 mg/day N = 388 3.Allopurinol N = 92 During the first six months of treatment, subjects could switch their febuxostat doses if necessary. Subsequent gout flares treated at the investigators' discretion.
Outcomes	The primary efficacy endpoint: - serum uric acid < 6.0 mg/dL at each visit. Secondary efficacy endpoints: - proportion of subjects with serum uric acid < 6.0 mg/dL at each visit. - percentage reduction from baseline in the serum uric acid concentration at each visit. - incidence of gout flares. - reduction in number of tophi - reduction in the size or disappearance of the index tophus Adverse events.
Notes	Source of funding: TAP Pharmaceutical Products, Inc.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Open label extension from FACT and APEX studies
Allocation concealment (selection bias)	Low risk	Open label extension from FACT and APEX studies
Blinding (performance bias and detection bias) All outcomes	High risk	Open label extension study
Incomplete outcome data (attrition bias) All outcomes	High risk	Efficacy analyses were based on a modified intention-to-treat population (only those that received treatment). There is no description on how incomplete outcome data was analysed
Selective reporting (reporting bias)	Unclear risk	The study protocol is not available, but the authors did not report on 5 of the 9 outcomes recommended by OMERACT(OMERACT 9).
Other bias	Unclear risk	Source of funding: TAP Pharmaceutical Products, Inc.

Becker 2010

Methods	Randomized, double-blind, allopurinol-controlled. 6-month multicentre study.

Becker 2010 *(Continued)*

	Stratification by renal function (normal, mildly impaired = eCLcr 60 to 89 ml/min, or moderately impaired = eCLcr 30 to 59 ml/min) and prior completion of either of two open-label febuxostat or febuxostat/allopurinol extension trials. No of patients randomised = 2269. No of patients analysed (modified intent-to-treat cohort) = 2268 (one subject randomised to allopurinol was excluded from the efficacy analyses because baseline sUA was < 8.0 mg/dL).
Participants	Inclusion criteria: preliminary criteria of the ACR for gout, serum uric acid of ≥ 8.0 mg/dL, age 18-85. Subjects successfully completing either of two prior open label extension studies were eligible (subjects from FACT, FOCUS, APEX were eligible for one of these two open label studies) . Exclusion criteria: secondary hyperuricaemia; xanthinuria; severe renal dysfunction (eCLcr < 30 ml/min);hepatic dysfunction (ALT and AST > 1.5 times 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, harms, or adherence to the protocol. Location: centres in the USA.
Interventions	Patient randomised to 3 groups: 1. Febuxostat 40 mg/day N = 757 2. Febuxosatat 80 mg/day N = 756 3. Allopurinol 200/300 mg (for moderately impaired/ normal to mildly impaired renal function respectively) N = 755 (145/610) [modified intent-to-treat cohort]. 30-day washout period before randomisation for subjects already on uric acid-lowering therapy. Prophylaxis with naproxen (250 mg BID) or colchicine (0.6 mg daily) given to all subjects during the washout period and the study period (6 months). All subjects receiving naproxen prophylaxis also received lansoprazole 15 mg daily. Subjects with eCLcr < 50 ml/min were not to receive naproxen. Gout flares were regarded as expected gout manifestations rather than as AEs. Serum uric acid was blinded after baseline determination at Day-4.
Outcomes	The primary efficacy endpoint: - serum uric acid < 6.0 mg/dL at the final visit. Treatment with febuxostat 40 mg was compared with allopurinol with regard to non-inferiority in uric acid lowering. If non-inferiority of febuxostat 40 mg was established, superiority to allopurinol was to be assessed. Treatment with febuxostat 80 mg was compared with the allopurinol and febuxostat 40 mg for superiority. "In subgroup analyses, the primary endpoint was stratified by baseline serum uric acid, renal functional status, presence of tophi at baseline, and prior participation in a ULT trial" Secondary efficacy endpoints: - patients with renal impairment and serum uric acid < 6.0 mg/dL at the final visit. - patients with serum uric acid < 6.0mg/dL, < 5.0mg/dL, < 4.0mg/dL at each visit. Pairwise comparisons were made between treatment groups.

Becker 2010 *(Continued)*

	Adverse events.
Notes	Source of funding: TAP Pharmaceutical Products, Inc.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Authors stated that "An Interactive Voice Response System was utilized by site personnel during screening visits to initiate double blind randomisation. Subjects were randomised 1:1:1 on Day 1 to receive daily febuxostat 40 mg, febuxostat 80 mg, or allopurinol".
Allocation concealment (selection bias)	Low risk	No details provided, but considered probable due to randomisation type.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No details provided other than stating that this is a double-blind trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only one subject out of 2268 was not included in the efficacy analysis because his serum uric acid was < 8 mg/dL; the rest included in a modified ITT analysis.
Selective reporting (reporting bias)	Unclear risk	The study protocol is not available, but the authors did not report on 5 of the 9 outcomes recommended by OMERACT (OMERACT 9).
Other bias	Low risk	Source of funding: TAP Pharmaceutical Products, Inc.

Schumacher 2008

Methods	Phase 3, randomised, double-blind, allopurinol- and placebo-controlled, parallel-group trial. 28-week multicentre study. 2:2:1:2:1 febuxostat 80 mg, febuxostat 120 mg, febuxostat 240 mg, allopurinol, or placebo of random assignment. Stratification by renal function (serum creatinine ≤ 1.5mg/dL or >1.5mg/dL to ≤ 2mg/dL). No of patients randomised = 1072. No of patients analysed = 1072.
Participants	Inclusion criteria: preliminary criteria of the ACR for gout, serum uric acid concentrations of ≥ 8.0 mg/dL, age 18-85, serum creatinine ≤ 2mg/dL. Exclusion criteria: intolerance to allopurinol, naproxen, or colchicine; history of renal calculi; alcohol intake of ≥ 14 drinks/week; hepatic dysfunction (ALT and AST > 1.5 times upper limit of normal); any other significant medical conditions. Location: centres in the USA.
Interventions	Patient randomised to 5 groups: 1. Febuxostat 80 mg/day N = 267 2. Febuxostat 120 mg/day N = 269 3. Febuxostat 240 mg/day N = 134

Schumacher 2008 *(Continued)*

	4. Allopurinol 100 mg/day or 300 mg/day (for serum creatinine > 1.5 mg/dL to ≤ 2 mg/dL or ≤ 1.5 mg/dL respectively) N = 268 5. Placebo N = 134 Two-weeks washout period before randomisation for subjects already on uric acid-lowering therapy. Prophylaxis with naproxen (250 mg BID) or colchicine (0.6 mg daily) given to all subjects during the washout period and the first 8 weeks of the trial. Subsequent gout flares treated at the investigators' discretion.
Outcomes	The primary efficacy endpoint: - serum uric acid < 6.0 mg/dL at each of the last three monthly measurements. Secondary efficacy endpoints: - proportion of subjects with serum uric acid < 6.0 mg/dL at each visit. - percentage reduction from baseline in the serum uric acid concentration at each visit. - percentage reduction from baseline in tophus area.. - proportion of subjects requiring treatment for gout flares from weeks 8 through 28. - change in the number of tophi at each visit - percent reduction in primary tophus size at each visit. Adverse events.
Notes	Study supported by Takeda Global Research & Development Center, Inc. (of which TAP Pharmaceutical Products, Inc., is a subsidiary).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Authors stated that “subjects were randomised in a 2:2:1:2:1 ratio to once-daily febuxostat 80 mg, febuxostat 120 mg, febuxostat 240 mg, allopurinol, or placebo".The randomisation was stratified by renal function, but not further details about the sequence generation were given.
Allocation concealment (selection bias)	Unclear risk	No details were provided
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No details were provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	All efficacy analyses were performed on the intention-to-treat population. If a subject discontinued the study before ≥ 3 serum uric acid levels were obtained, the subject was considered a non-responder.
Selective reporting (reporting bias)	Unclear risk	The study protocol is not available, but the authors did not report on 5 of the 9 outcomes recommended by OMERACT(OMERACT 9).
Other bias	Low risk	Study supported by a pharmaceutical company. Representatives of Takeda Global Research & Development Center, Inc., collected the data and statisticians at Takeda Global Research & Development Center, Inc., conducted all statistical analyses

Schumacher 2009

Methods	Open label extension study (5 years findings). No. of patients randomised =145 subjects who previously completed one of the 1 Phase II double-blind trial (Becker 2005b). No. of patients completing the study.=.116. No. of patients analysed for harms and gout flares.= 116
Participants	Inclusion criteria: enrolment and completion of the 28-day Phase II study. Exclusion criteria: pregnancy or lactation;use of uric acid-lowering agents, azathioprine, 6-mercaptopurine, or medications containing aspirin (> 325 mg/day) or other salicylates; BMI > 50; history of xanthinuria, active liver disease, or hepatic dysfunction; use of prednisone at > 10 mg/day; change in thiazide or steroid therapy (within 1 month of study) or hormone-replacement therapy or oral-contraceptive therapy (within 3 months of study); and history of alcohol abuse or alcohol intake of ≥ 14 drinks/week. Location: centres in the USA.
Interventions	3 groups: 1. Febuxostat 40 mg/day N = 8 2. Febuxostat 80 mg/day N = 79 3. Febuxostat 120 mg/day N = 29 Subsequent gout flares treated at the investigators' discretion.
Outcomes	The primary efficacy endpoint: - proportion of subjects with serum uric acid < 6.0 mg/dL at each visit. Secondary efficacy endpoints: - percentage reduction from baseline in the serum uric acid concentration at each visit. - incidence of gout flares. - disappearance of the index tophus Adverse events.
Notes	Source of funding: TAP Pharmaceutical Products, Inc.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Open label extension from FOCUS study
Allocation concealment (selection bias)	Unclear risk	Open label extension from FOCUS study
Blinding (performance bias and detection bias) All outcomes	High risk	Open label extension study

Schumacher 2009 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Efficacy analyses were based on a modified intent-to-treat population (only those that received treatment). There is no description on how incomplete outcome data was analysed
Selective reporting (reporting bias)	Unclear risk	The study protocol is not available, but the authors did not report on 5 of the 9 outcomes recommended by OMERACT(OMERACT 9).
Other bias	Low risk	Source of funding: TAP Pharmaceutical Products, Inc.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Becker 2008	Meta-analysis of individual data
Komoriya 2004	Pharmacokinetics (Phase 2)

Characteristics of studies awaiting assessment *[ordered by study ID]*

NCT00821392

Methods	Phase 3, randomised, double-blind, allopurinol- and placebo-controlled, parallel-group trial. No. randomised = 181
Participants	Inclusion criteria:18 Years to 85 Years; female: either postmenopausal for at least 2 years, surgically sterile, or using a medically accepted means of contraception; negative serum pregnancy test; satisfy ARA; serum creatinine ≤ 1.5 mg/dL <Day -1>; serum uric acid level ≥ 8.0mg/dL Exclusion Criteria: women who are breast-feeding or pregnant; xanthinuria; allopurinol intolerance; thiazide diuretic therapy; secondary hyperuricaemia; required > 10mg/day of prednisone during the study; therapy containing aspirin or other salicylates (stable low doses aspirin allowed); change in hormone replacement therapy or oral contraceptive therapy within 3 months of the screening visit; alcohol abuse within 5 years prior to the Screening; more than14 alcoholic beverages per week;therapy with any uric acid-lowering therapy; active liver disease or hepatic dysfunction; unable to take colchicine; rheumatoid arthritis or any active arthritis; cancer (other than basal cell carcinoma of the skin) within 5 years prior to the screening visit; participated in another investigational trial within the 30days prior to the screening visit; significant medical condition
Interventions	Patients randomised to 5 groups: 1. Febuxostat 40 mg/day 2. Febuxostat 80 mg/day 3. Febuxostat 120 mg/day 4. Allopurinol 300mg/day 5. Placebo Colchicine 0.6 mg QD is given to minimize the risk of gout flares during the washout/run-in period and during the study period
Outcomes	harms/Efficacy Study

NCT00821392 *(Continued)*

Notes	No Contacts or Locations Provided Responsible Party: SK Chemicals Co.,Ltd Health Authority: Korea: Food and Drug Administration

Characteristics of ongoing studies *[ordered by study ID]*

NCT01078389

Trial name or title	A Multicenter, Randomized, Double-Blind, Phase 2 Study to Evaluate the Effect of Febuxostat Versus Placebo in Joint Damage in Hyperuricemic Subjects With Early Gout
Methods	Phase 2, randomised, double-blind, parallel assignment efficacy trial. 24 months multicentre study Estimated enrolment 240
Participants	Inclusion criteria: ≥18 years old; preliminary ACR criteria for gout and have experienced only one gout flare; hyperuricaemia. Exclusion criterias: secondary hyperuricaemia; Previously on uric acid-lowering therapy; xanthinuria; known hypersensitivity to any component of the febuxostat formulation; rheumatoid arthritis; cancer, except basal cell carcinoma of the skin, not in remission for at least 5 years prior to the first dose of study medication; MI or stroke within 90 days prior to the Screening visit; ALT and/or AST > 2.0 times the upper limit of normal;significant medical condition and/or conditions; eCLcr ≥ 60 mL/min; serum creatinine at Screening > 2.0 mg/dL; known history of hepatitis B, hepatitis C or HIV; hypersensitivity to gadolinium; severe asthma; electronically, magnetically or mechanically activated implanted device; object as potential hazard or interfere with MRI interpretation
Interventions	Patients will be randomised to 2 groups: 1. Febuxostat 40 mg/day or 80 mg/day (based on serum uric acid levels) 2. Placebo
Outcomes	Primary Outcome Measures: - Mean Change from Baseline to Month 24 in a modified Sharp/van der Heijde Erosion Score of the single affected joint Secondary Outcome Measures: - Mean Change from Baseline to Month 24 in the modified Sharp/van der Heijde Total Scores from full hand and foot radiographs. - Mean Change from Baseline to Month 24 in the modified Sharp/van der Heijde Erosion Scores from full hand and foot radiographs. - Mean change from baseline to Month 24 in the Rheumatoid Arthritis MRI Scoring System (RAMRIS) score. - Mean change from baseline to Month 24 in a modified Sharp/van der Heijde Total Score of the single affected joint.
Starting date	March 2010
Contact information	Takeda Study Registration Call Center 800-778-2860 medicalinformation@tpna.com
Notes	

NCT01082640

Trial name or title	A Multicenter, Randomized, Double-Blind, Phase 2 Study to Evaluate the Effect of Febuxostat Versus Placebo on Renal Function in Gout Subjects With Hyperuricemia and Moderate to Severe Renal Impairment
Methods	Phase 2, randomised, double-blind,parallel assignment efficacy trial. 12 months multicentre study. Estimated Enrollment 7500.
Participants	Inclusion criteria: ≥18 years old; inadequate response to treatment with allopurinol, defined as:current use of allopurinol and a serum uric acid greater than 7.0 mg/dL OR a past history of allopurinol use that was discontinued due to lack of therapeutic effect or due to adverse effects and a serum uric acid greater than 7.0 mg/dL; history or presence of gout defined as having one or more of the American Rheumatism Association criteria for the diagnosis of gout (the criteria related to tophi have been excluded for the purpose of the study); estimated Glomerular Filtration Rate (eGFR) > 20 and ≤ 45 mL/min, AND a serum creatinine > 1.5 mg/dL at all 3 Screening Visits (Day -49//35, Day -14 and Day -7). Exclusion criteria: secondary hyperuricaemia; tophaceous gout; history of xanthinuria; received aspirin > 325 mg/day within 35 days prior to Day 1/Randomization Visit; known hypersensitivity or allergy to allopurinol or febuxostat or colchicine or any component in their formulation; myocardial infarction or stroke within the 90 days prior to the Screening Visit; ALT and/or AST > 2.0 times the upper limit of normal; end stage renal disease or is likely to be a candidate for dialysis over the 1 year study period; eCLcr ≤ 20 mL/min or > 45 mL/min; serum creatinine ≤ 1.5 mg/dL, or an eGFR at any of the screening visits ≥ 20 mL/min or > 45 mL/min; required to take excluded medications
Interventions	Patients will be randomised to 3 groups: 1. Febuxostat 40 mg/day or 80 mg/day (based on serum uric acid levels) 2. Febuxostat 30 mg BID 3. Placebo
Outcomes	Primary Outcome Measures: - Change from Baseline to Month 12 in Serum Creatinine Secondary Outcome Measures: - Change from Baseline to Month 12 in 24-HR measured creatinine clearance (mCLcr). - Mean Clearance (CL/F) of febuxostat during the study. - Mean Area Under the Concentration-Time Curve (AUC) of Febuxostat during the study. - Percentage of subjects with Serum uric acid (sUA) < 6 mg/dL at Month 12. - Change from baseline to Month 12 in estimated Glomerular Filtration Rate (eGFR) using the Modification of Diet in Renal Disease (MDRD) formula (as calculated by the central laboratory).
Starting date	April 2010
Contact information	Takeda Study Registration Call Center 800-778-2860 medicalinformation@tpna.com
Notes	

NCT01101035

Trial name or title	A Multicenter, Randomized, Active-Control, Phase 3B Study to Evaluate the Cardiovascular harms of Febuxostat and Allopurinol in Subjects With Gout and Cardiovascular Comorbidities

NCT01101035 *(Continued)*

Methods	Phase 3, randomised, double-blind, parallel assignment harms trial. 60 months multicentre study. Estimated Enrollment 240.
Participants	Inclusion criteria: ≥ 50 years old; a major cardiovascular or cerebrovascular disease (MI, unstable angina, cardiac or cerebrovascular revascularization procedure, stroke, hospitalised for transient Ischaemic attack, peripheral vascular disease, diabetes mellitus with evidence of micro- or macrovascular disease); ACR criteria for gout; serum uric acid level ≥ 7.0 mg/dL at the Day -7 Visit OR ≥ 6.0 mg/dL at the Day -7 Visit AND inadequately controlled gout Exclusion criteria: secondary hyperuricaemia; on uric acid-lowering therapy; xanthinuria; known hypersensitivity to any component of the febuxostat or allopurinol formulation; active peptic ulcer disease; cancer within 5 years prior to the first dose of study medication; MI or stroke within 60 days prior to the Screening visit; ALT and/or AST > 2.0 times the upper limit of normal; eCLcr < 30 mL/min; known history of hepatitis B, hepatitis C or HIV; history of drug abuse or a history of alcohol abuse within 5 years prior to the Screening; more than14 alcoholic beverages per week; received any investigational medicinal product within the 30 days prior to the Screening Visit and throughout the study; required to take excluded medications
Interventions	Patients will be randomised to 2 groups: 1. Febuxostat 40 mg/day or 80 mg/day (dependent on serum uric acid levels) 2. Allopurinol 200 mg/day to 600 mg/day (dependent on renal function)
Outcomes	Primary Outcome Measures: - First occurrence of any event in the predefined Major Adverse Cardiovascular Events Composite (Cardiovascular death, Non-fatal Myocardial Infarction, Nonfatal Stroke and Unstable Angina with Urgent Coronary Revascularization) Secondary Outcome Measures: - First occurrence of any Antiplatelet Trialists' Collaborative Event (Cardiovascular Death, Non-fatal Myocardial Infarction or Non-fatal Stroke) - First occurrence of Cardiovascular Death death - First occurrence of Non-fatal Myocardial Infarction - First occurrence of Non-fatal stroke - First occurrence of Unstable Angina with Urgent Coronary Revascularization
Starting date	May 2010
Contact information	Takeda Study Registration Call Center 800-778-2860 medicalinformation@tpna.com
Notes	

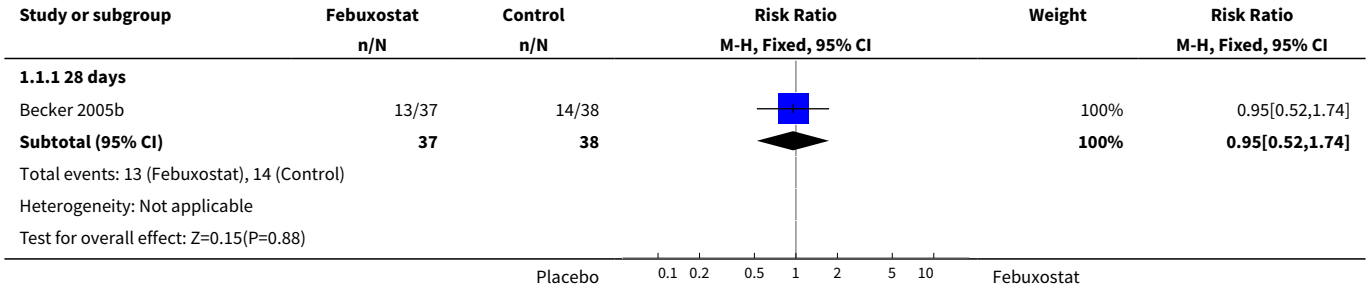
DATA AND ANALYSES

Comparison 1. Efficacy - febuxostat 40 mg/day versus placebo

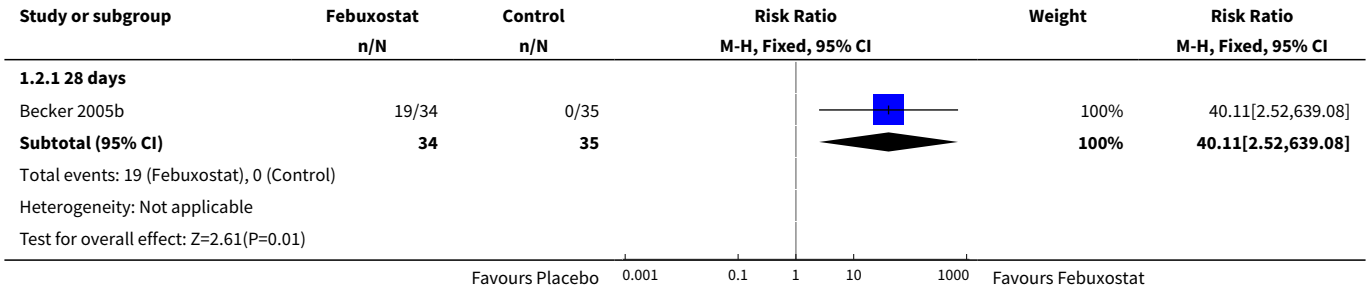
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of gout flares	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1.1 28 days	1	75	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.52, 1.74]
2 Serum uric acid <6.0 mg/dL at final visit	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 28 days	1	69	Risk Ratio (M-H, Fixed, 95% CI)	40.11 [2.52, 639.08]
3 Change in serum uric acid concentration from baseline at final visit	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 28 days	1	69	Mean Difference (IV, Fixed, 95% CI)	-5.23 [-5.78, -4.69]

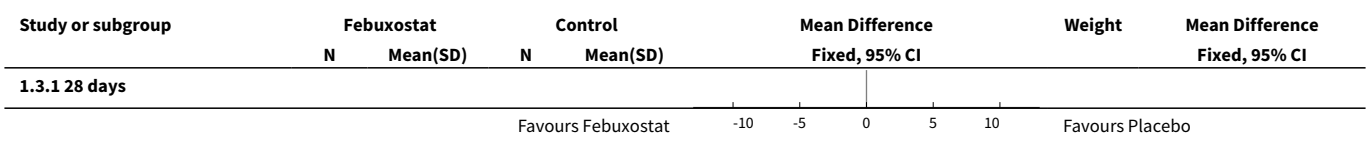
Analysis 1.1. Comparison 1 Efficacy - febuxostat 40 mg/day versus placebo, Outcome 1 Incidence of gout flares.

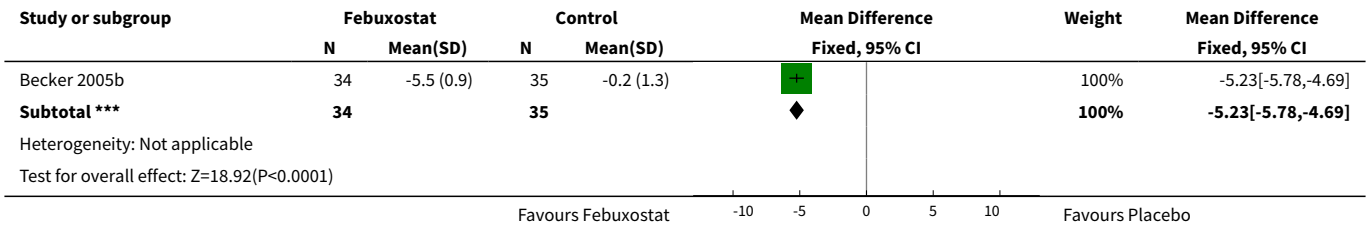


Analysis 1.2. Comparison 1 Efficacy - febuxostat 40 mg/day versus placebo, Outcome 2 Serum uric acid <6.0 mg/dL at final visit.



Analysis 1.3. Comparison 1 Efficacy - febuxostat 40 mg/day versus placebo, Outcome 3 Change in serum uric acid concentration from baseline at final visit.

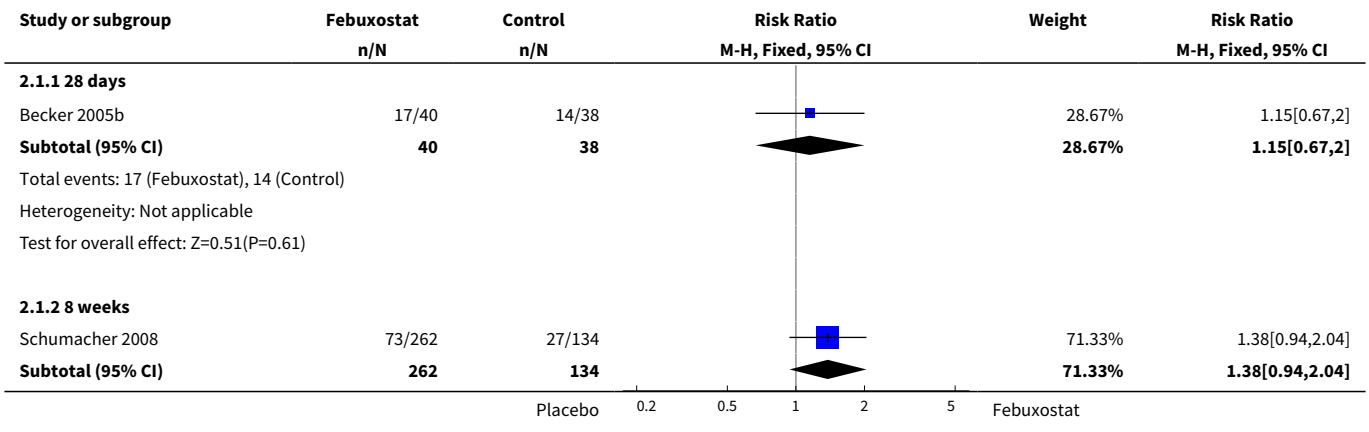


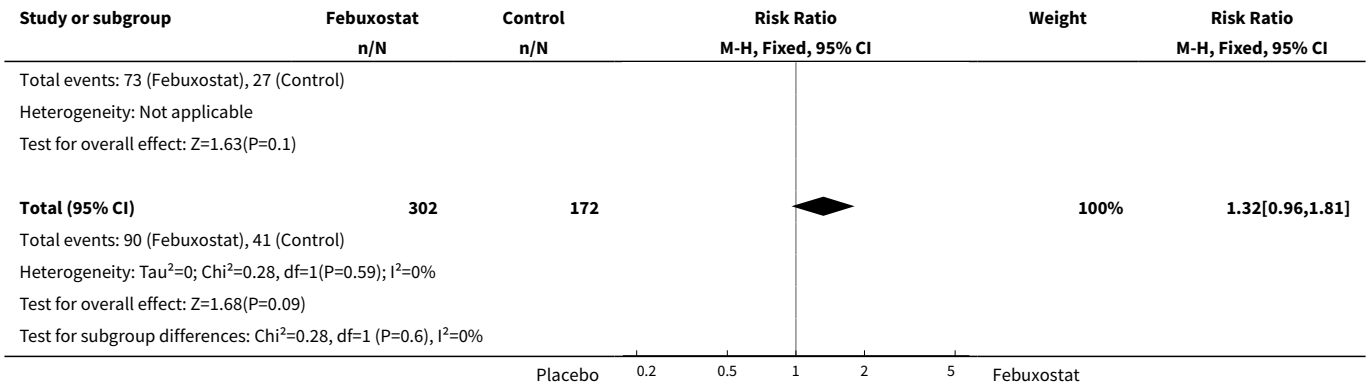


Comparison 2. Efficacy - febuxostat 80 mg/day versus placebo

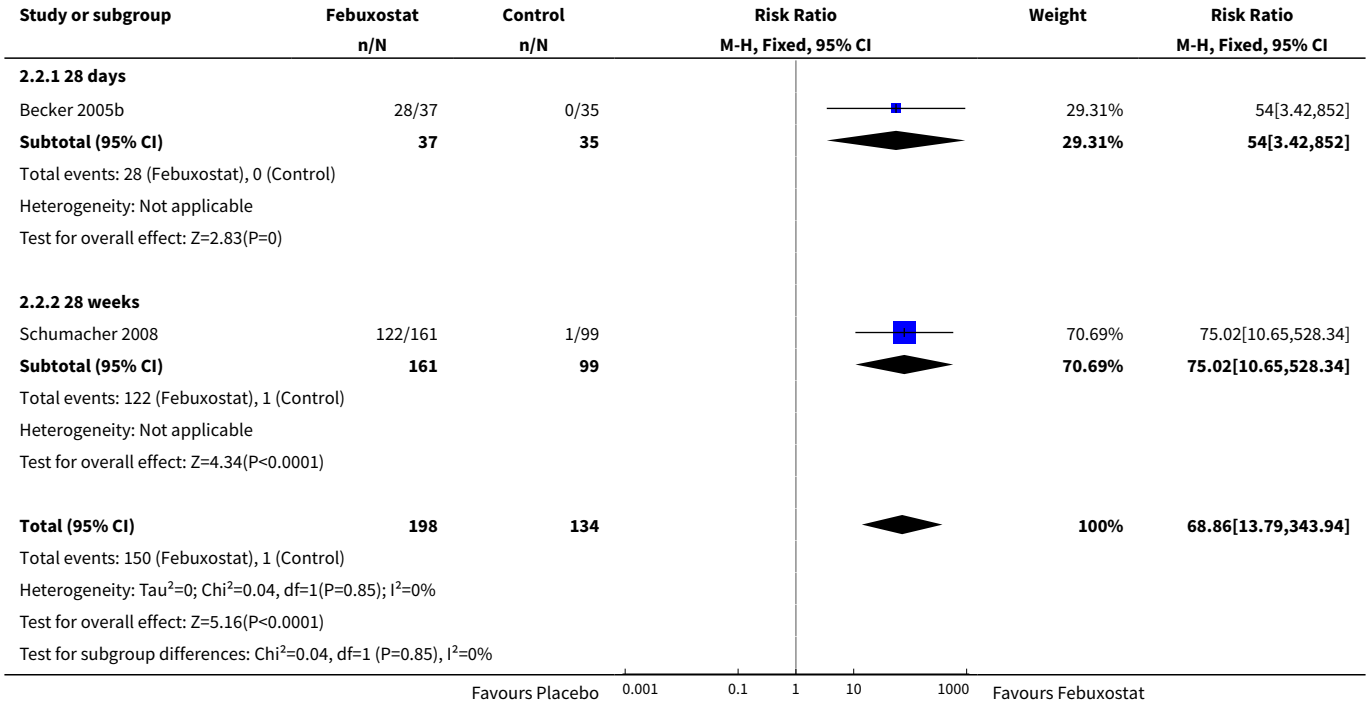
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of gout flares	2	474	Risk Ratio (M-H, Fixed, 95% CI)	1.32 [0.96, 1.81]
1.1 28 days	1	78	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.67, 2.00]
1.2 8 weeks	1	396	Risk Ratio (M-H, Fixed, 95% CI)	1.38 [0.94, 2.04]
2 Serum uric acid <6.0 mg/dL at final visit	2	332	Risk Ratio (M-H, Fixed, 95% CI)	68.86 [13.79, 343.94]
2.1 28 days	1	72	Risk Ratio (M-H, Fixed, 95% CI)	54.0 [3.42, 852.00]
2.2 28 weeks	1	260	Risk Ratio (M-H, Fixed, 95% CI)	75.02 [10.65, 528.34]
3 Change in serum uric acid concentration from baseline at final visit	2	332	Mean Difference (IV, Random, 95% CI)	-4.96 [-6.23, -3.68]
3.1 28 days	1	72	Mean Difference (IV, Random, 95% CI)	-5.63 [-6.24, -5.03]
3.2 28 weeks	1	260	Mean Difference (IV, Random, 95% CI)	-4.33 [-4.65, -4.02]

Analysis 2.1. Comparison 2 Efficacy - febuxostat 80 mg/day versus placebo, Outcome 1 Incidence of gout flares.

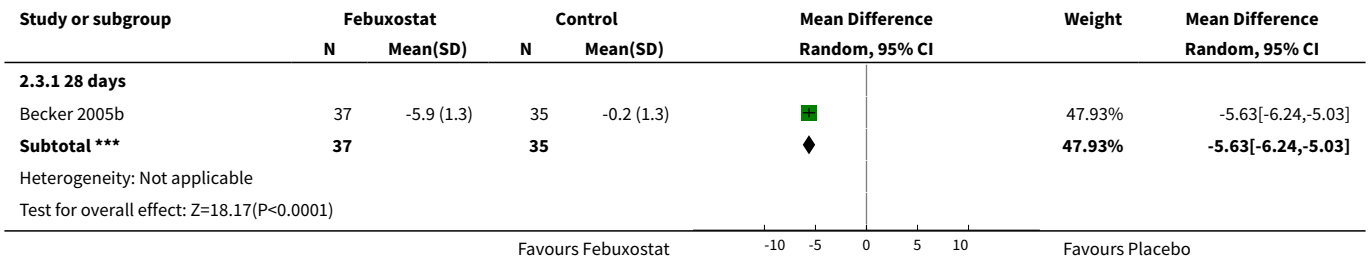


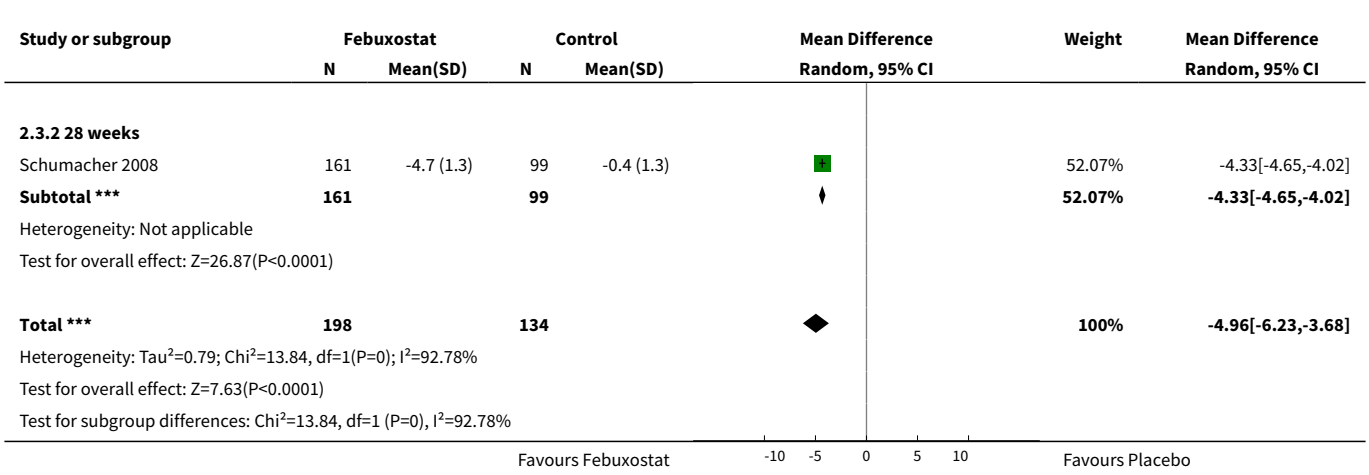


Analysis 2.2. Comparison 2 Efficacy - febuxostat 80 mg/day versus placebo, Outcome 2 Serum uric acid <6.0 mg/dL at final visit.



Analysis 2.3. Comparison 2 Efficacy - febuxostat 80 mg/day versus placebo, Outcome 3 Change in serum uric acid concentration from baseline at final visit.

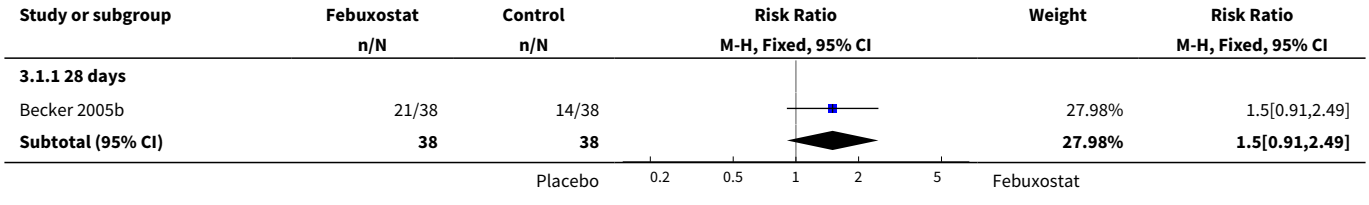


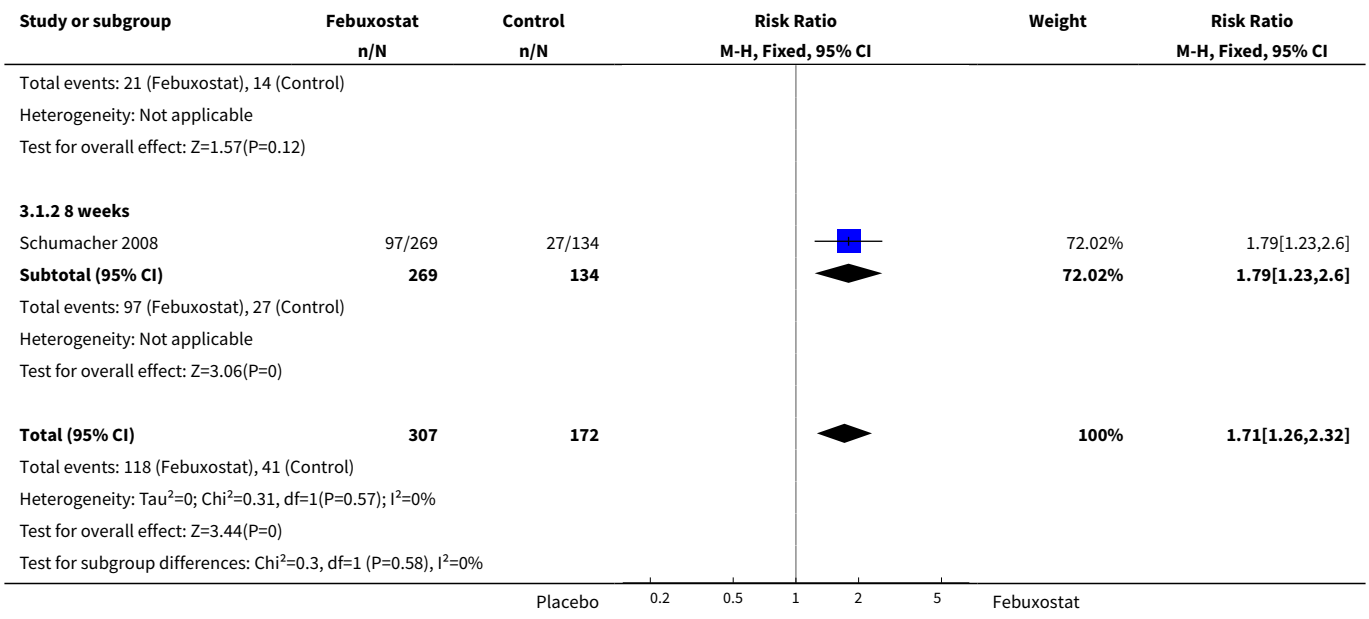


Comparison 3. Efficacy - febuxostat 120 mg/day versus placebo

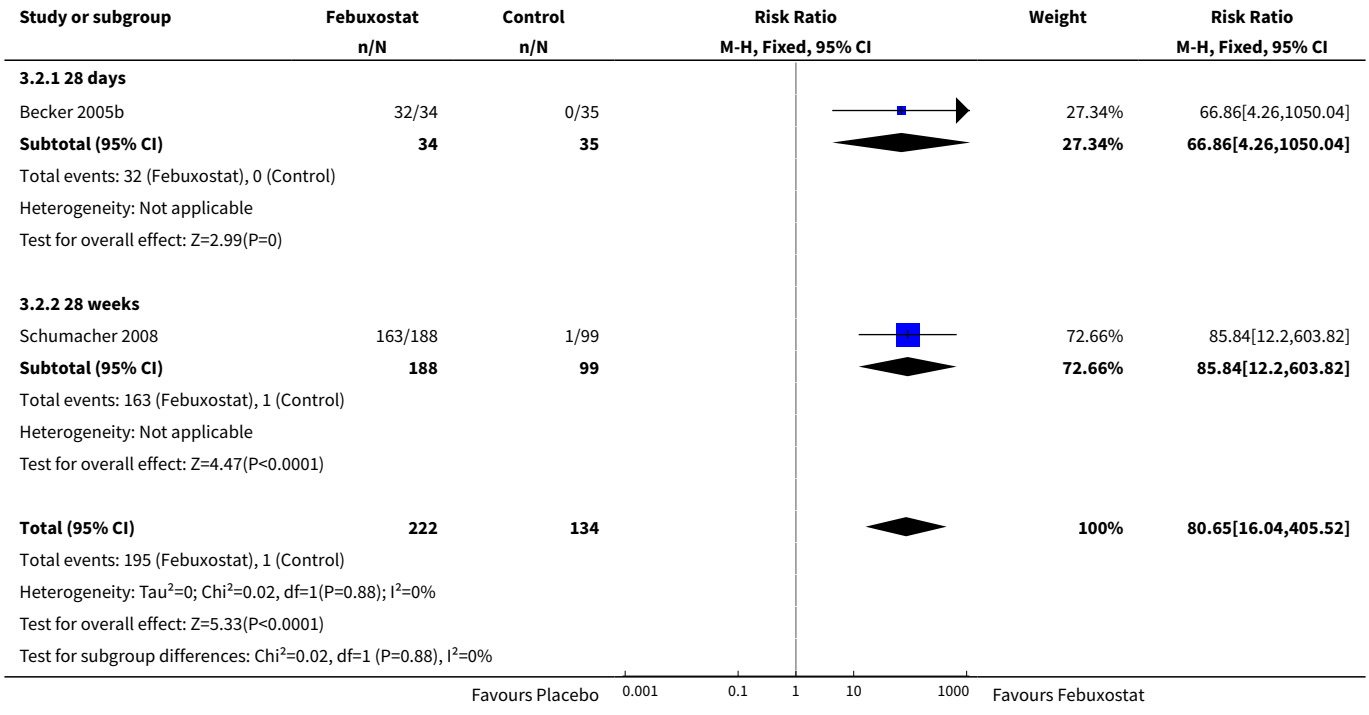
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of gout flares	2	479	Risk Ratio (M-H, Fixed, 95% CI)	1.71 [1.26, 2.32]
1.1 28 days	1	76	Risk Ratio (M-H, Fixed, 95% CI)	1.5 [0.91, 2.49]
1.2 8 weeks	1	403	Risk Ratio (M-H, Fixed, 95% CI)	1.79 [1.23, 2.60]
2 Serum uric acid <6.0 mg/dL at final visit	2	356	Risk Ratio (M-H, Fixed, 95% CI)	80.65 [16.04, 405.52]
2.1 28 days	1	69	Risk Ratio (M-H, Fixed, 95% CI)	66.86 [4.26, 1050.04]
2.2 28 weeks	1	287	Risk Ratio (M-H, Fixed, 95% CI)	85.84 [12.20, 603.82]
3 Change in serum uric acid concentration from baseline at final visit	2	472	Mean Difference (IV, Random, 95% CI)	-5.31 [-5.68, -4.94]
3.1 28 days	1	69	Mean Difference (IV, Random, 95% CI)	-5.02 [-5.60, -4.45]
3.2 28 weeks	1	403	Mean Difference (IV, Random, 95% CI)	-5.44 [-5.70, -5.17]

Analysis 3.1. Comparison 3 Efficacy - febuxostat 120 mg/day versus placebo, Outcome 1 Incidence of gout flares.



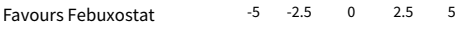


Analysis 3.2. Comparison 3 Efficacy - febuxostat 120 mg/day versus placebo, Outcome 2 Serum uric acid <6.0 mg/dL at final visit.



Analysis 3.3. Comparison 3 Efficacy - febuxostat 120 mg/day versus placebo, Outcome 3 Change in serum uric acid concentration from baseline at final visit.

Study or subgroup	Experimental N	Experimental Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
3.3.1 28 days							
Becker 2005b	34	-5.4 (1.1)	35	-0.4 (1.3)		29.65%	-5.02[-5.6,-4.45]
Subtotal ***	**34**		**35**			**29.65%**	**-5.02[-5.6,-4.45]**
Heterogeneity: Not applicable							
Test for overall effect: Z=17.05(P<0.0001)							
3.3.2 28 weeks							
Schumacher 2008	269	-5.7 (1.3)	134	-0.2 (1.3)		70.35%	-5.44[-5.7,-5.17]
Subtotal ***	**269**		**134**			**70.35%**	**-5.44[-5.7,-5.17]**
Heterogeneity: Not applicable							
Test for overall effect: Z=40.7(P<0.0001)							
Total ***	**303**		**169**			**100%**	**-5.31[-5.68,-4.94]**
Heterogeneity: Tau^2=0.03; Chi^2=1.62, df=1(P=0.2); I^2=38.24%							
Test for overall effect: Z=28.27(P<0.0001)							
Test for subgroup differences: Chi^2=1.62, df=1 (P=0.2), I^2=38.24%							

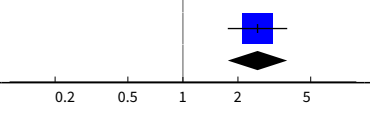


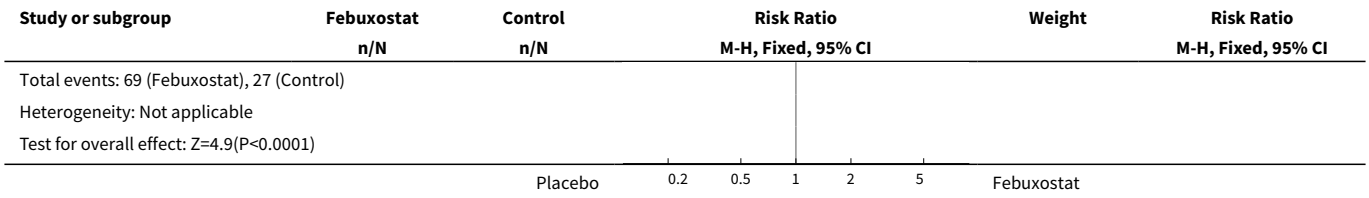
Comparison 4. Efficacy - febuxostat 240 mg/day versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of gout flares	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 28 weeks	1	268	Risk Ratio (M-H, Fixed, 95% CI)	2.56 [1.76, 3.72]
2 Serum urate <6.0 mg/dl at final visit	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 28 weeks	1	182	Risk Ratio (M-H, Fixed, 95% CI)	93.04 [13.23, 654.45]
3 Change in serum urate concentration from baseline at final visit	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 28 weeks	1	268	Mean Difference (IV, Fixed, 95% CI)	-6.31 [-6.61, -6.00]

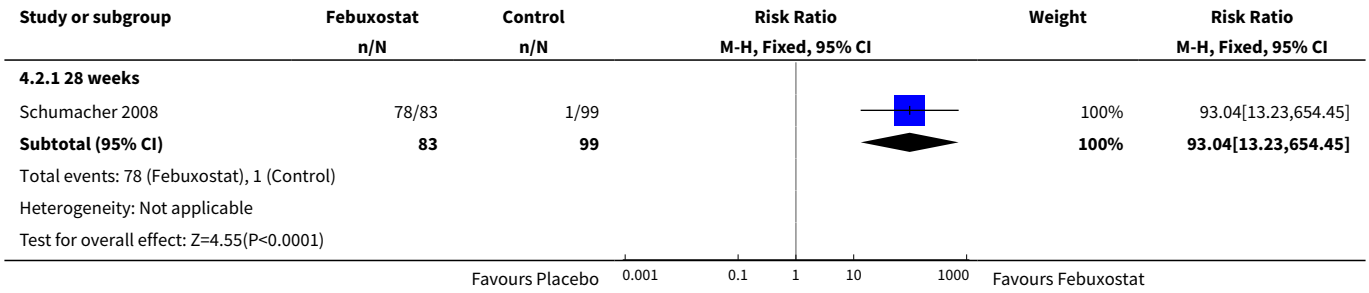
Analysis 4.1. Comparison 4 Efficacy - febuxostat 240 mg/day versus placebo, Outcome 1 Incidence of gout flares.

Study or subgroup	Febuxostat n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.1.1 28 weeks					
Schumacher 2008	69/134	27/134		100%	2.56[1.76,3.72]
Subtotal (95% CI)	**134**	**134**		**100%**	**2.56[1.76,3.72]**

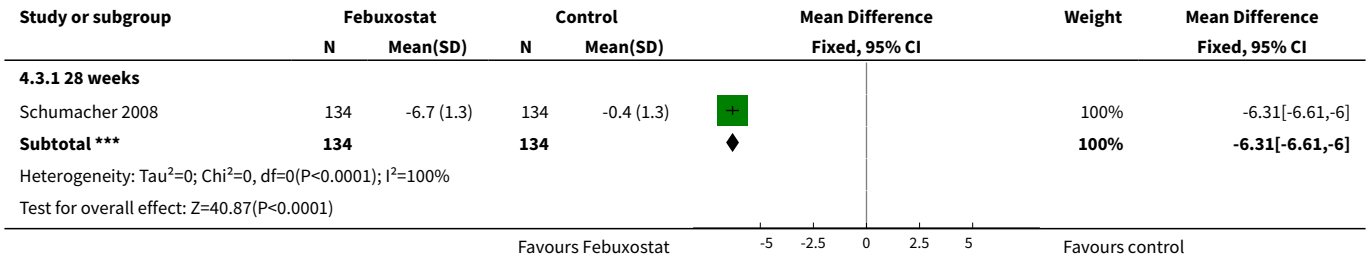




Analysis 4.2. Comparison 4 Efficacy - febuxostat 240 mg/day versus placebo, Outcome 2 Serum urate <6.0 mg/dl at final visit.



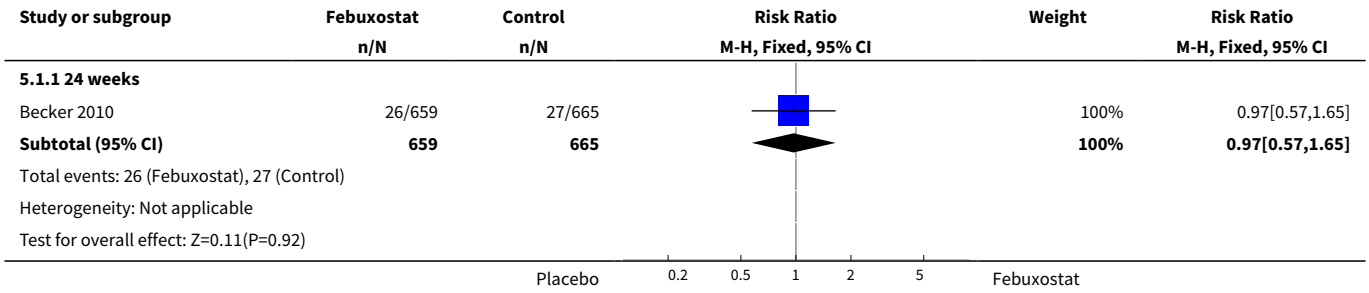
Analysis 4.3. Comparison 4 Efficacy - febuxostat 240 mg/day versus placebo, Outcome 3 Change in serum urate concentration from baseline at final visit.



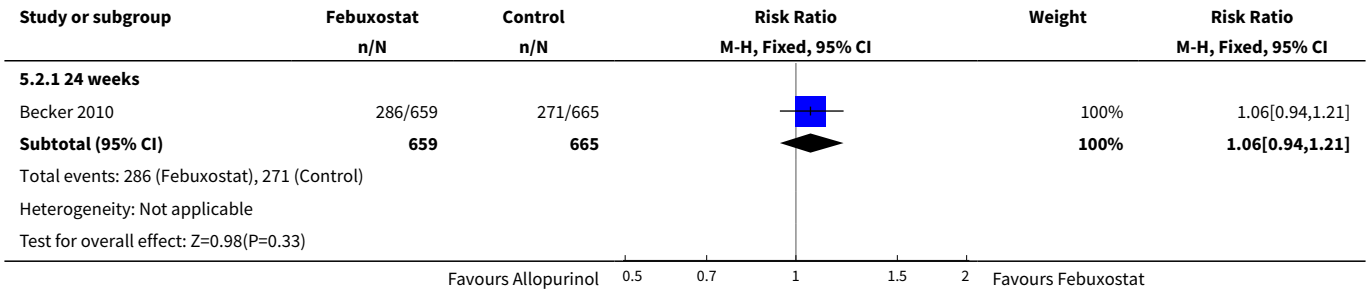
Comparison 5. Efficacy - Febuxostat 40 mg/day versus allopurinol 200 or 300 mg/day

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Incidence of gout flares	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 24 weeks	1	1324	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.57, 1.65]
2 Serum urate <6.0 mg/dL at final visit	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 24 weeks	1	1324	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.94, 1.21]

Analysis 5.1. Comparison 5 Efficacy - Febuxostat 40 mg/day versus allopurinol 200 or 300 mg/day, Outcome 1 Incidence of gout flares.



Analysis 5.2. Comparison 5 Efficacy - Febuxostat 40 mg/day versus allopurinol 200 or 300 mg/day, Outcome 2 Serum urate <6.0 mg/dL at final visit.

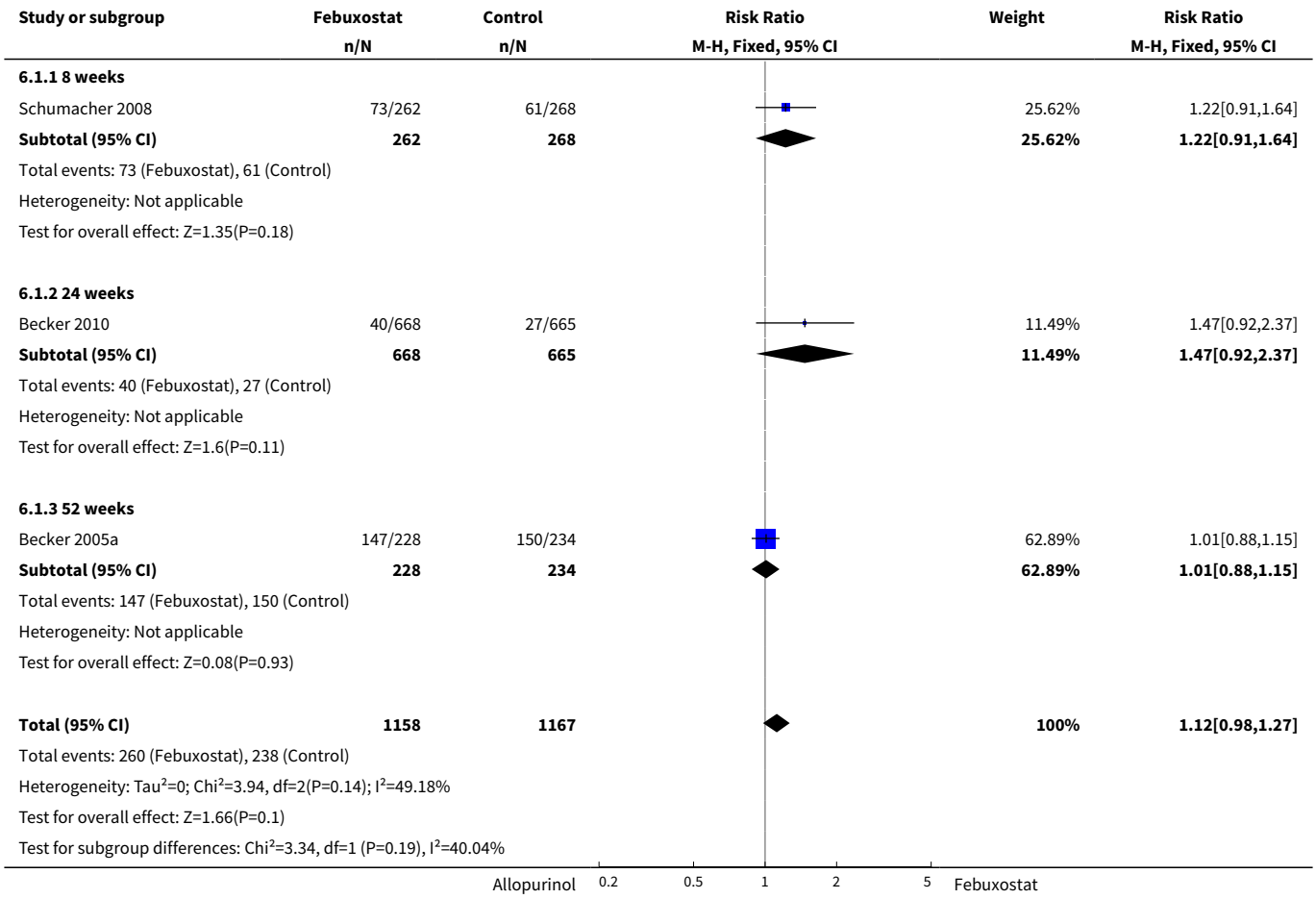


Comparison 6. Efficacy - febuxostat 80 mg/day versus allopurinol 200 or 300 mg/day

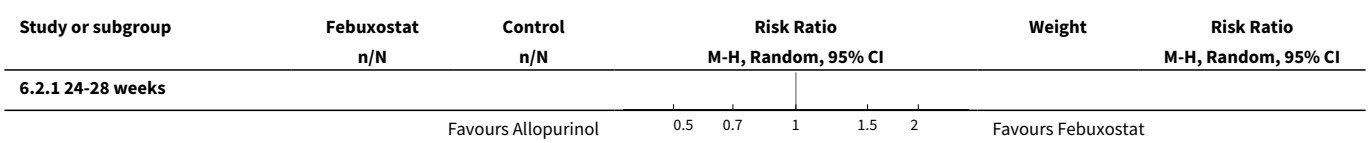
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of gout flares	3	2325	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.98, 1.27]
1.1 8 weeks	1	530	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.91, 1.64]
1.2 24 weeks	1	1333	Risk Ratio (M-H, Fixed, 95% CI)	1.47 [0.92, 2.37]
1.3 52 weeks	1	462	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.88, 1.15]
2 Serum uric acid <6.0 mg/dL at final visit	3	2193	Risk Ratio (M-H, Random, 95% CI)	1.80 [1.55, 2.09]
2.1 24-28 weeks	2	1702	Risk Ratio (M-H, Random, 95% CI)	1.69 [1.49, 1.93]
2.2 52 weeks	1	491	Risk Ratio (M-H, Random, 95% CI)	2.04 [1.70, 2.45]
3 Change in serum uric acid concentration from baseline at final visit	2	1041	Mean Difference (IV, Random, 95% CI)	-1.24 [-1.50, -0.99]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
3.1 8 weeks	1	535	Mean Difference (IV, Random, 95% CI)	-1.38 [-1.59, -1.16]
3.2 52 weeks	1	506	Mean Difference (IV, Random, 95% CI)	-1.12 [-1.30, -0.94]

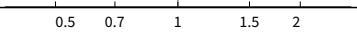
Analysis 6.1. Comparison 6 Efficacy - febuxostat 80 mg/day versus allopurinol 200 or 300 mg/day, Outcome 1 Incidence of gout flares.



Analysis 6.2. Comparison 6 Efficacy - febuxostat 80 mg/day versus allopurinol 200 or 300 mg/day, Outcome 2 Serum uric acid <6.0 mg/dL at final visit.



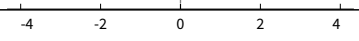
Study or subgroup	Febuxostat n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Becker 2010	439/668	271/665		41.62%	1.61[1.45,1.79]
Schumacher 2008	122/161	85/208		28.95%	1.85[1.54,2.23]
Subtotal (95% CI)	**829**	**873**		**70.57%**	**1.69[1.49,1.93]**
Total events: 561 (Febuxostat), 356 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.64, df=1(P=0.2); I^2=39.07%					
Test for overall effect: Z=7.91(P<0.0001)					
6.2.2 52 weeks					
Becker 2005a	185/249	88/242		29.43%	2.04[1.7,2.45]
Subtotal (95% CI)	**249**	**242**		**29.43%**	**2.04[1.7,2.45]**
Total events: 185 (Febuxostat), 88 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=7.7(P<0.0001)					
Total (95% CI)	**1078**	**1115**		**100%**	**1.8[1.55,2.09]**
Total events: 746 (Febuxostat), 444 (Control)					
Heterogeneity: Tau^2=0.01; Chi^2=5.39, df=2(P=0.07); I^2=62.91%					
Test for overall effect: Z=7.8(P<0.0001)					
Test for subgroup differences: Chi^2=2.71, df=1 (P=0.1), I^2=63.13%					



Favours Allopurinol — Favours Febuxostat

Analysis 6.3. Comparison 6 Efficacy - febuxostat 80 mg/day versus allopurinol 200 or 300 mg/day, Outcome 3 Change in serum uric acid concentration from baseline at final visit.

Study or subgroup	Febuxostat N	Febuxostat Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
6.3.1 8 weeks							
Schumacher 2008	267	-4.7 (1.3)	268	-3.3 (1.3)		47.32%	-1.38[-1.59,-1.16]
Subtotal ***	**267**		**268**			**47.32%**	**-1.38[-1.59,-1.16]**
Heterogeneity: Not applicable							
Test for overall effect: Z=12.63(P<0.0001)							
6.3.2 52 weeks							
Becker 2005a	255	-4.4 (1)	251	-3.3 (1)		52.68%	-1.12[-1.3,-0.94]
Subtotal ***	**255**		**251**			**52.68%**	**-1.12[-1.3,-0.94]**
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%							
Test for overall effect: Z=12.29(P<0.0001)							
Total ***	**522**		**519**			**100%**	**-1.24[-1.5,-0.99]**
Heterogeneity: Tau^2=0.02; Chi^2=3.39, df=1(P=0.07); I^2=70.47%							
Test for overall effect: Z=9.51(P<0.0001)							
Test for subgroup differences: Chi^2=3.39, df=1 (P=0.07), I^2=70.47%							



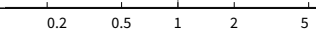
Favours Febuxostat — Favours Allopurinol

Comparison 7. Efficacy - febuxostat 120 mg/day versus allopurinol 300 mg/day

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of gout flares	2	986	Risk Ratio (M-H, Random, 95% CI)	1.29 [0.87, 1.91]
1.1 8 weeks	1	537	Risk Ratio (M-H, Random, 95% CI)	1.58 [1.21, 2.08]
1.2 52 weeks	1	449	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.96, 1.24]
2 Serum uric acid <6.0 mg/dL at final visit	2	880	Risk Ratio (M-H, Fixed, 95% CI)	2.16 [1.91, 2.45]
2.1 28 weeks	1	396	Risk Ratio (M-H, Fixed, 95% CI)	2.12 [1.78, 2.52]
2.2 52 weeks	1	484	Risk Ratio (M-H, Fixed, 95% CI)	2.19 [1.83, 2.62]
3 Change in serum uric acid concentration from baseline at final visit	2	1038	Mean Difference (IV, Random, 95% CI)	-1.93 [-2.19, -1.67]
3.1 8 weeks	1	537	Mean Difference (IV, Random, 95% CI)	-2.07 [-2.28, -1.85]
3.2 52 weeks	1	501	Mean Difference (IV, Random, 95% CI)	-1.80 [-1.98, -1.62]

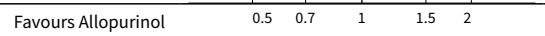
Analysis 7.1. Comparison 7 Efficacy - febuxostat 120 mg/day versus allopurinol 300 mg/day, Outcome 1 Incidence of gout flares.

Study or subgroup	Febuxostat n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
7.1.1 8 weeks					
Schumacher 2008	97/269	61/268		45.44%	1.58[1.21,2.08]
Subtotal (95% CI)	**269**	**268**		**45.44%**	**1.58[1.21,2.08]**
Total events: 97 (Febuxostat), 61 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=3.32(P=0)					
7.1.2 52 weeks					
Becker 2005a	150/215	150/234		54.56%	1.09[0.96,1.24]
Subtotal (95% CI)	**215**	**234**		**54.56%**	**1.09[0.96,1.24]**
Total events: 150 (Febuxostat), 150 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.28(P=0.2)					
Total (95% CI)	**484**	**502**		**100%**	**1.29[0.87,1.91]**
Total events: 247 (Febuxostat), 211 (Control)					
Heterogeneity: Tau^2=0.07; Chi^2=6.88, df=1(P=0.01); I^2=85.46%					
Test for overall effect: Z=1.27(P=0.2)					
Test for subgroup differences: Chi^2=5.96, df=1 (P=0.01), I^2=83.21%					



Analysis 7.2. Comparison 7 Efficacy - febuxostat 120 mg/day versus allopurinol 300 mg/day, Outcome 2 Serum uric acid <6.0 mg/dL at final visit.

Study or subgroup	Febuxostat n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
7.2.1 28 weeks					
Schumacher 2008	163/188	85/208		47.84%	2.12[1.78,2.52]
Subtotal (95% CI)	**188**	**208**		**47.84%**	**2.12[1.78,2.52]**
Total events: 163 (Febuxostat), 85 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=8.53(P<0.0001)					
7.2.2 52 weeks					
Becker 2005a	193/242	88/242		52.16%	2.19[1.83,2.62]
Subtotal (95% CI)	**242**	**242**		**52.16%**	**2.19[1.83,2.62]**
Total events: 193 (Febuxostat), 88 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=8.63(P<0.0001)					
Total (95% CI)	**430**	**450**		**100%**	**2.16[1.91,2.45]**
Total events: 356 (Febuxostat), 173 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.07, df=1(P=0.79); I^2=0%					
Test for overall effect: Z=12.11(P<0.0001)					
Test for subgroup differences: Chi^2=0.07, df=1 (P=0.79), I^2=0%					



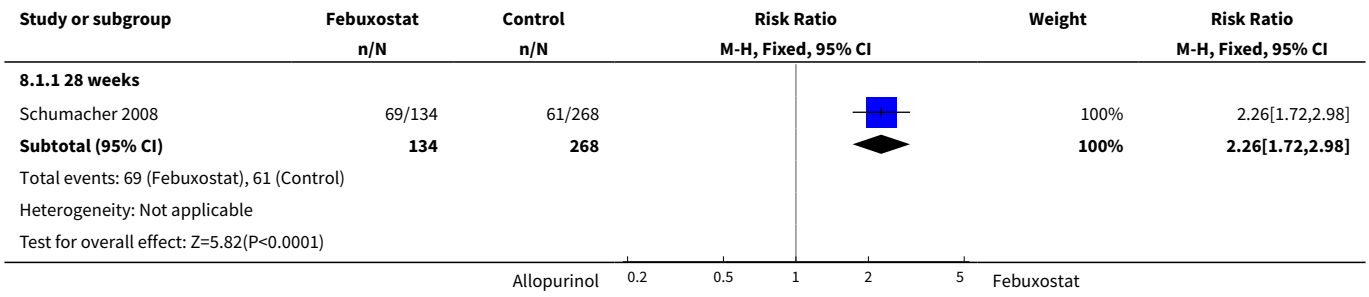
Analysis 7.3. Comparison 7 Efficacy - febuxostat 120 mg/day versus allopurinol 300 mg/day, Outcome 3 Change in serum uric acid concentration from baseline at final visit.

Study or subgroup	Febuxostat N	Febuxostat Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
7.3.1 8 weeks							
Schumacher 2008	269	-5.4 (1.3)	268	-3.3 (1.3)		47.51%	-2.07[-2.28,-1.85]
Subtotal ***	**269**		**268**			**47.51%**	**-2.07[-2.28,-1.85]**
Heterogeneity: Not applicable							
Test for overall effect: Z=18.98(P<0.0001)							
7.3.2 52 weeks							
Becker 2005a	250	-5.1 (1)	251	-3.3 (1)		52.49%	-1.8[-1.98,-1.62]
Subtotal ***	**250**		**251**			**52.49%**	**-1.8[-1.98,-1.62]**
Heterogeneity: Not applicable							
Test for overall effect: Z=19.69(P<0.0001)							
Total ***	**519**		**519**			**100%**	**-1.93[-2.19,-1.67]**
Heterogeneity: Tau^2=0.02; Chi^2=3.46, df=1(P=0.06); I^2=71.12%							
Test for overall effect: Z=14.58(P<0.0001)							
Test for subgroup differences: Chi^2=3.46, df=1 (P=0.06), I^2=71.12%							

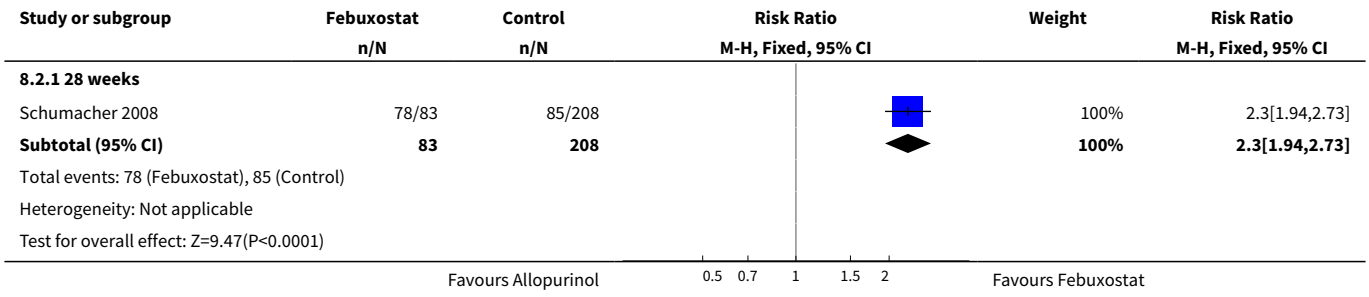
Comparison 8. Efficacy - febuxostat 240 mg/day versus allopurinol 300 mg/day

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of gout flares	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 28 weeks	1	402	Risk Ratio (M-H, Fixed, 95% CI)	2.26 [1.72, 2.98]
2 Serum uric acid <6.0 mg/dL at final visit	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 28 weeks	1	291	Risk Ratio (M-H, Fixed, 95% CI)	2.30 [1.94, 2.73]
3 Change in serum uric acid concentration from baseline at final visit	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 8 weeks	1	402	Mean Difference (IV, Fixed, 95% CI)	-3.35 [-3.61, -3.09]

Analysis 8.1. Comparison 8 Efficacy - febuxostat 240 mg/day versus allopurinol 300 mg/day, Outcome 1 Incidence of gout flares.

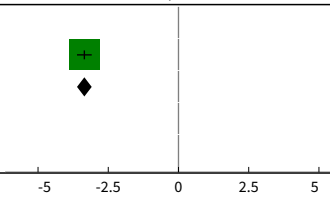


Analysis 8.2. Comparison 8 Efficacy - febuxostat 240 mg/day versus allopurinol 300 mg/day, Outcome 2 Serum uric acid <6.0 mg/dL at final visit.



Analysis 8.3. Comparison 8 Efficacy - febuxostat 240 mg/day versus allopurinol 300 mg/day, Outcome 3 Change in serum uric acid concentration from baseline at final visit.

Study or subgroup	Febuxostat N	Febuxostat Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
8.3.1 8 weeks							
Schumacher 2008	134	-6.7 (1.3)	268	-3.3 (1.3)		100%	-3.35[-3.61,-3.09]
Subtotal ***	**134**		**268**			**100%**	**-3.35[-3.61,-3.09]**
Heterogeneity: Not applicable							
Test for overall effect: Z=25.08(P<0.0001)							

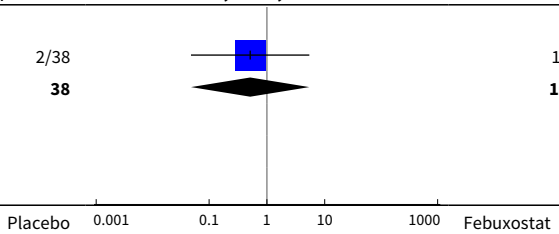


Comparison 9. Withdrawals - febuxostat 40 mg/day versus placebo

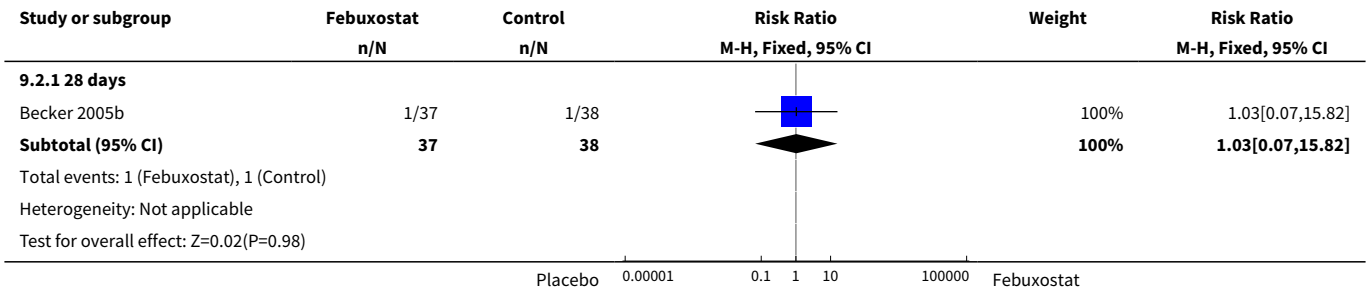
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 TOTAL	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 28 days	1	75	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.05, 5.42]
2 Adverse event	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 28 days	1	75	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.07, 15.82]
3 Gout flare	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 28 days	1	75	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.01, 8.14]
4 Lack of efficacy	1		Risk Difference (M-H, Fixed, 95% CI)	Subtotals only
4.1 28 days	1	75	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.05, 0.05]
5 Other reasons	1		Risk Difference (M-H, Fixed, 95% CI)	Subtotals only
5.1 28 days	1	75	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.05, 0.05]

Analysis 9.1. Comparison 9 Withdrawals - febuxostat 40 mg/day versus placebo, Outcome 1 TOTAL.

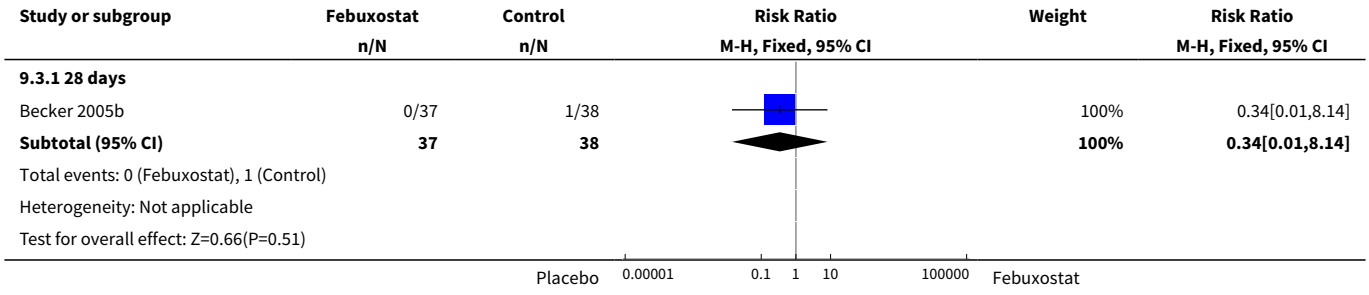
Study or subgroup	Febuxostat n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
9.1.1 28 days					
Becker 2005b	1/37	2/38		100%	0.51[0.05,5.42]
Subtotal (95% CI)	**37**	**38**		**100%**	**0.51[0.05,5.42]**
Total events: 1 (Febuxostat), 2 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.55(P=0.58)					



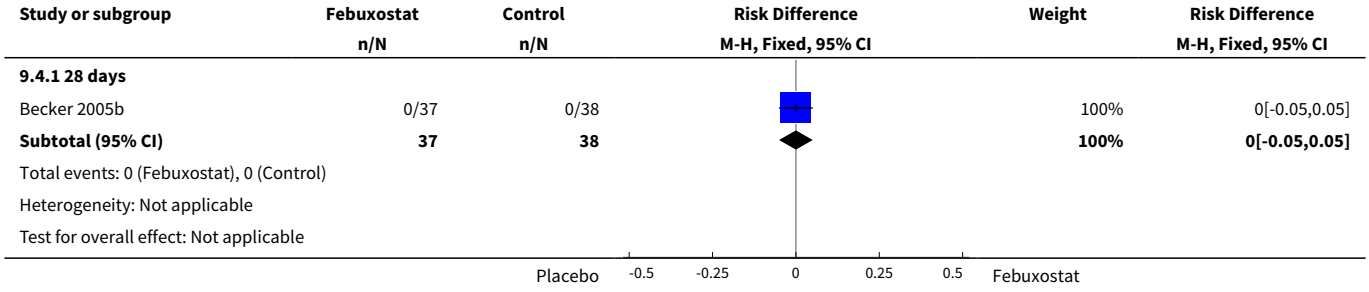
Analysis 9.2. Comparison 9 Withdrawals - febuxostat 40 mg/day versus placebo, Outcome 2 Adverse event.



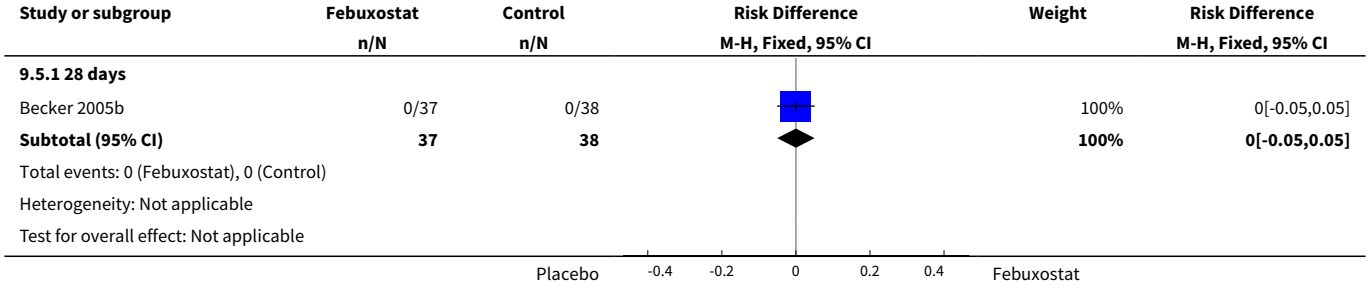
Analysis 9.3. Comparison 9 Withdrawals - febuxostat 40 mg/day versus placebo, Outcome 3 Gout flare.



Analysis 9.4. Comparison 9 Withdrawals - febuxostat 40 mg/day versus placebo, Outcome 4 Lack of efficacy.



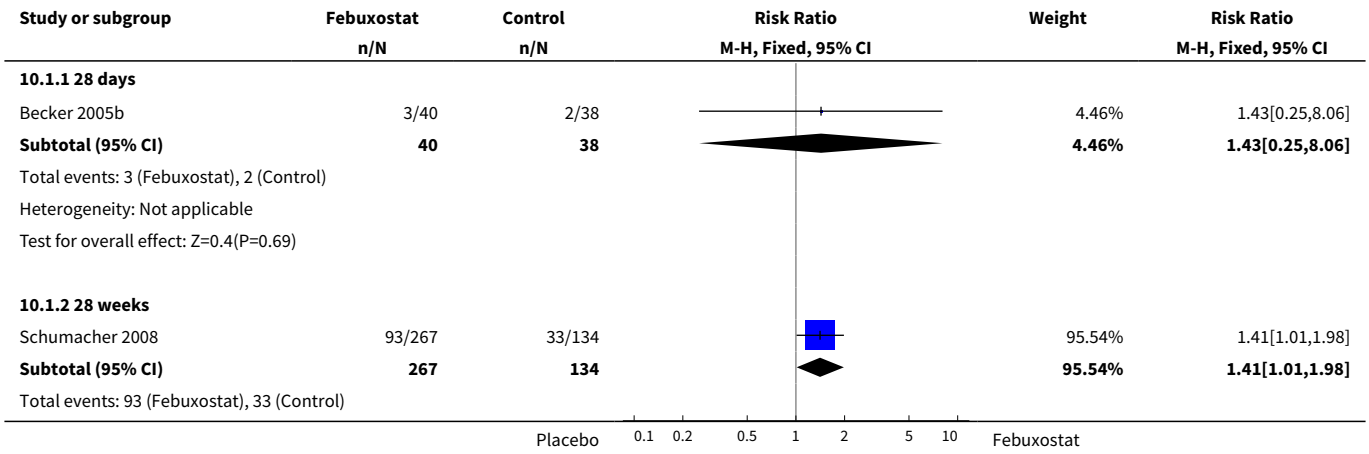
Analysis 9.5. Comparison 9 Withdrawals - febuxostat 40 mg/day versus placebo, Outcome 5 Other reasons.

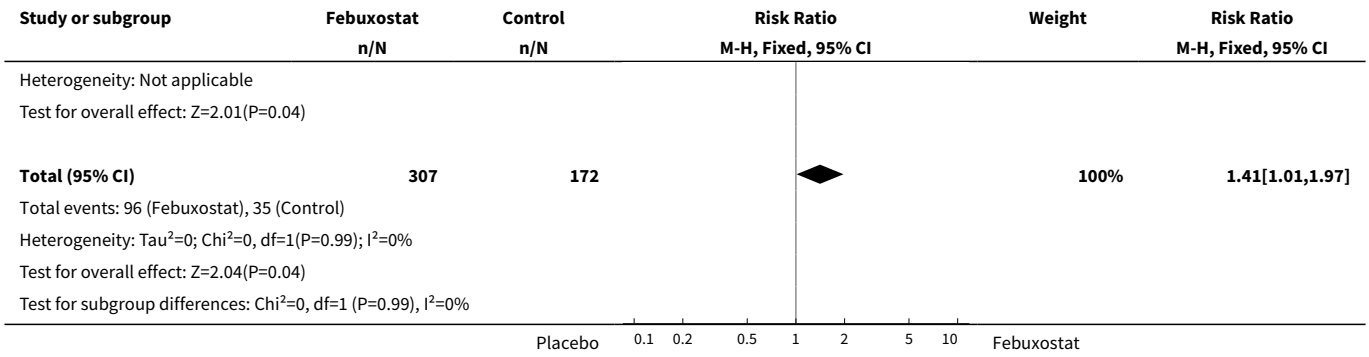


Comparison 10. Withdrawals - febuxostat 80 mg/day versus placebo

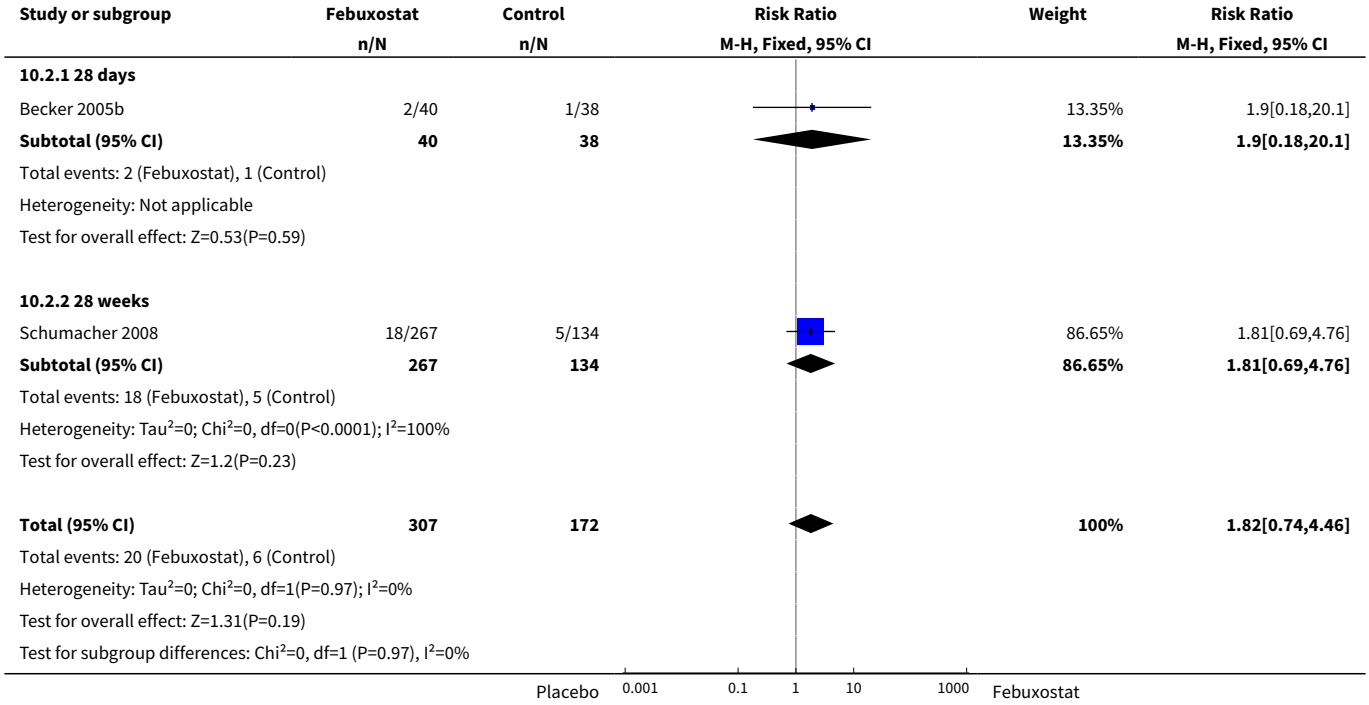
Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 TOTAL	2	479	Risk Ratio (M-H, Fixed, 95% CI)	1.41 [1.01, 1.97]
1.1 28 days	1	78	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [0.25, 8.06]
1.2 28 weeks	1	401	Risk Ratio (M-H, Fixed, 95% CI)	1.41 [1.01, 1.98]
2 Adverse event	2	479	Risk Ratio (M-H, Fixed, 95% CI)	1.82 [0.74, 4.46]
2.1 28 days	1	78	Risk Ratio (M-H, Fixed, 95% CI)	1.9 [0.18, 20.10]
2.2 28 weeks	1	401	Risk Ratio (M-H, Fixed, 95% CI)	1.81 [0.69, 4.76]
3 Gout flare	2	479	Risk Ratio (M-H, Random, 95% CI)	2.22 [0.05, 101.12]
3.1 28 days	1	78	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.01, 7.55]
3.2 28 weeks	1	401	Risk Ratio (M-H, Random, 95% CI)	13.60 [0.81, 227.06]
4 Lack of efficacy	2	479	Risk Difference (M-H, Fixed, 95% CI)	0.00 [-0.03, 0.03]
4.1 28 days	1	78	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.05, 0.05]
4.2 28 weeks	1	401	Risk Difference (M-H, Fixed, 95% CI)	0.00 [-0.03, 0.03]
5 Other reasons	2	479	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.76, 1.75]
5.1 28 days	1	78	Risk Ratio (M-H, Fixed, 95% CI)	2.85 [0.12, 67.97]
5.2 28 weeks	1	401	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.74, 1.72]

Analysis 10.1. Comparison 10 Withdrawals - febuxostat 80 mg/day versus placebo, Outcome 1 TOTAL.

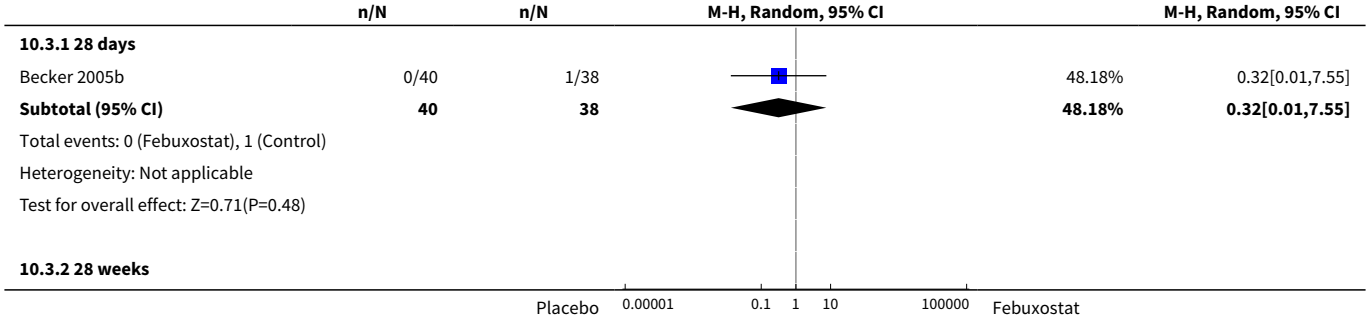


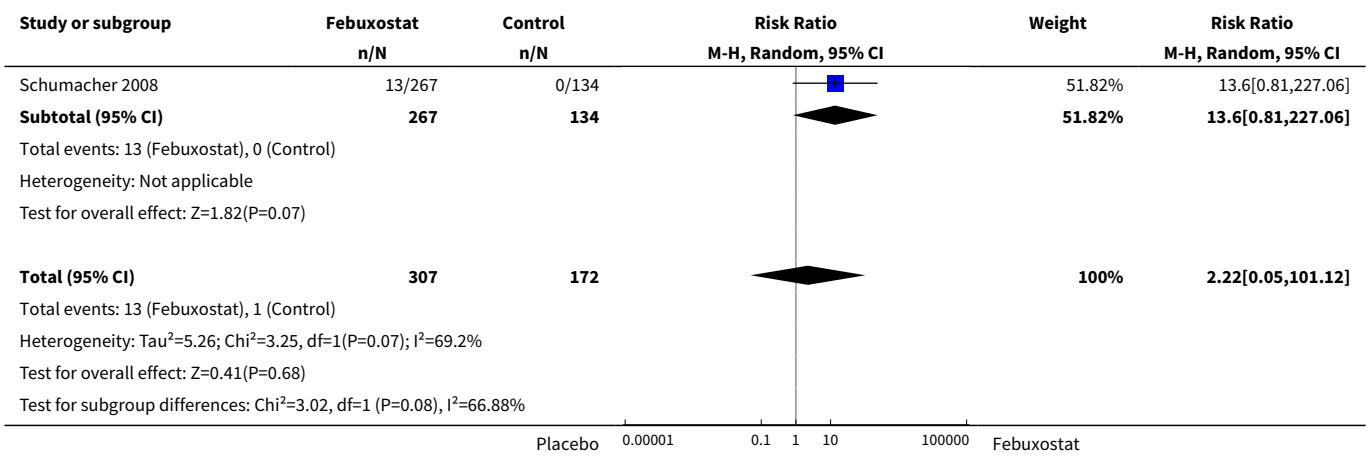


Analysis 10.2. Comparison 10 Withdrawals - febuxostat 80 mg/day versus placebo, Outcome 2 Adverse event.

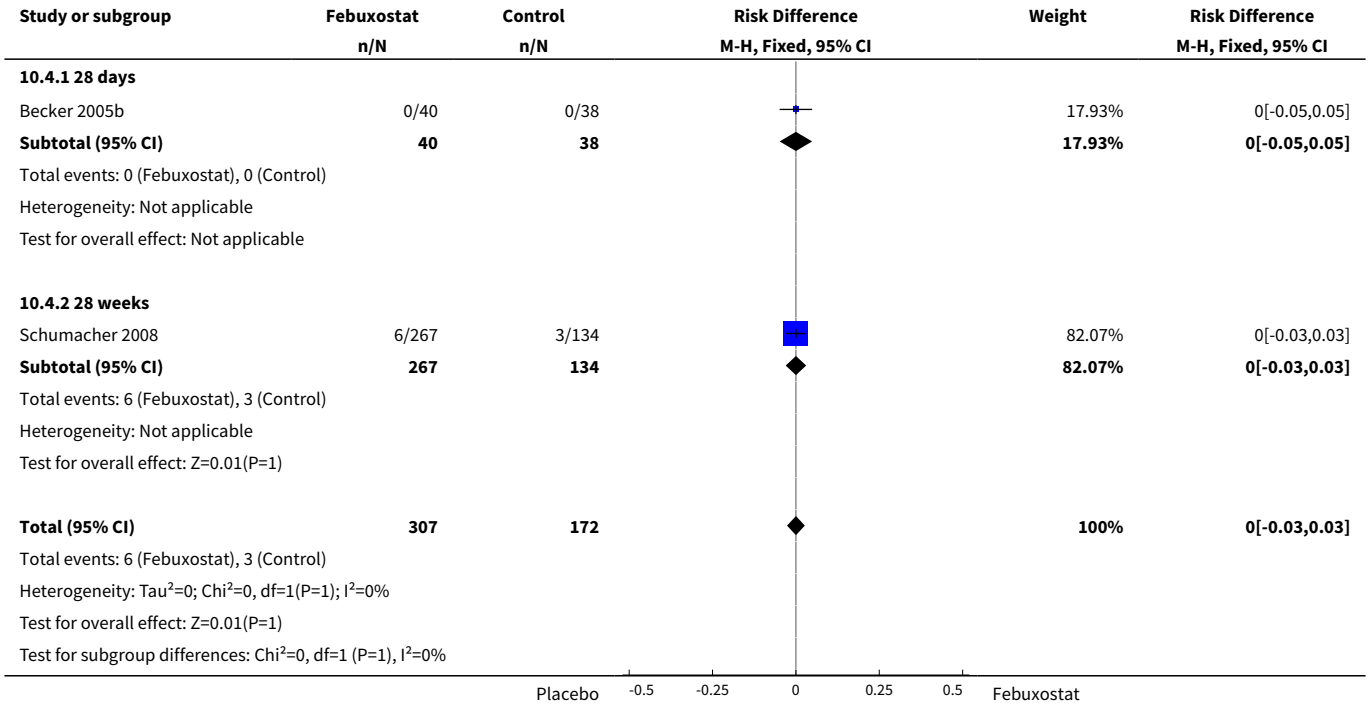


Analysis 10.3. Comparison 10 Withdrawals - febuxostat 80 mg/day versus placebo, Outcome 3 Gout flare.

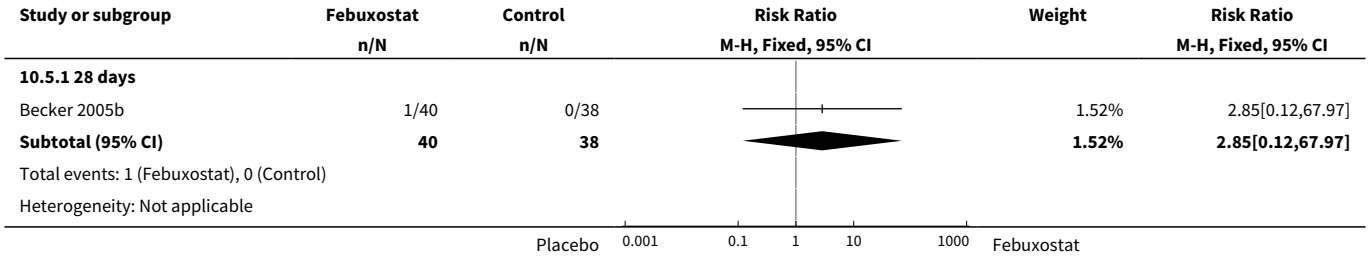


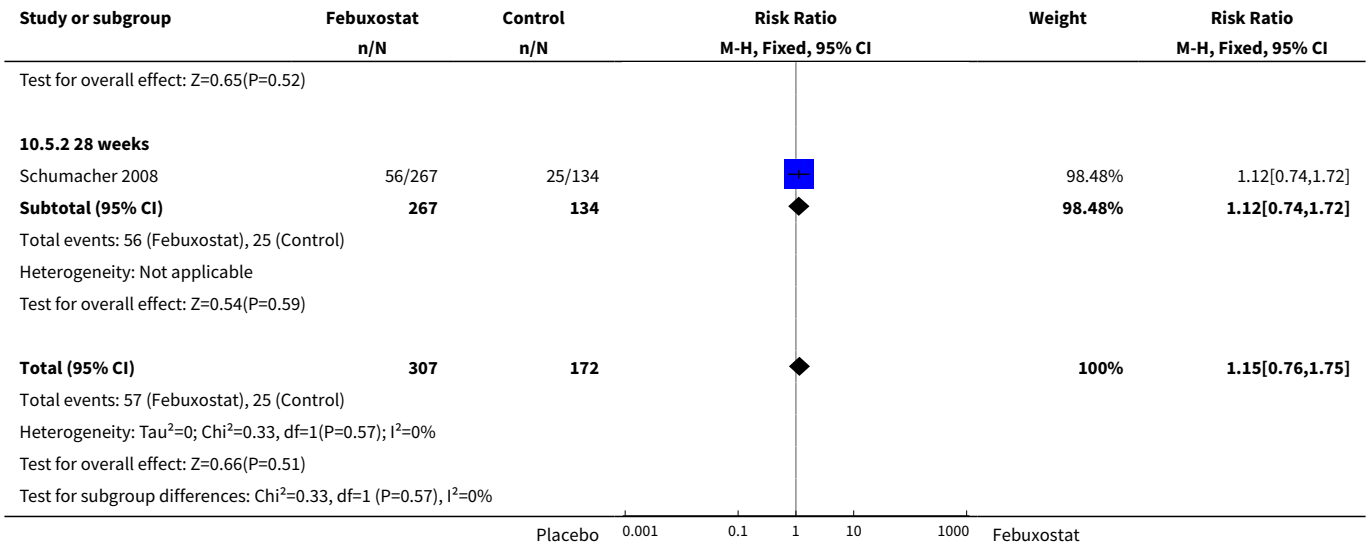


Analysis 10.4. Comparison 10 Withdrawals - febuxostat 80 mg/day versus placebo, Outcome 4 Lack of efficacy.



Analysis 10.5. Comparison 10 Withdrawals - febuxostat 80 mg/day versus placebo, Outcome 5 Other reasons.



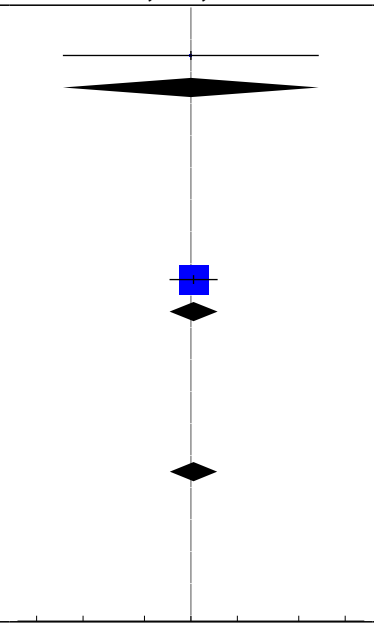


Comparison 11. Withdrawals - febuxostat 120 mg/day versus placebo

Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 TOTAL	2	479	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.73, 1.48]
1.1 28 days	1	76	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.15, 6.74]
1.2 28 weeks	1	403	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.73, 1.49]
2 Adverse event	2	479	Risk Ratio (M-H, Fixed, 95% CI)	1.65 [0.67, 4.08]
2.1 28 days	1	76	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.19, 21.14]
2.2 28 weeks	1	403	Risk Ratio (M-H, Fixed, 95% CI)	1.59 [0.60, 4.26]
3 Gout flare	2	479	Risk Ratio (M-H, Fixed, 95% CI)	2.23 [0.40, 12.57]
3.1 28 days	1	76	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.93]
3.2 28 weeks	1	403	Risk Ratio (M-H, Fixed, 95% CI)	6.5 [0.37, 114.53]
4 Lack of efficacy	2	479	Risk Difference (M-H, Fixed, 95% CI)	-0.01 [-0.03, 0.02]
4.1 28 days	1	76	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.05, 0.05]
4.2 28 weeks	1	403	Risk Difference (M-H, Fixed, 95% CI)	-0.01 [-0.04, 0.02]
5 Other reasons	2	479	Risk Difference (M-H, Fixed, 95% CI)	-0.02 [-0.09, 0.05]
5.1 28 days	1	76	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.05, 0.05]
5.2 28 weeks	1	403	Risk Difference (M-H, Fixed, 95% CI)	-0.02 [-0.10, 0.06]

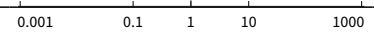
Analysis 11.1. Comparison 11 Withdrawals - febuxostat 120 mg/day versus placebo, Outcome 1 TOTAL.

Study or subgroup	Febuxostat n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
11.1.1 28 days					
Becker 2005b	2/38	2/38		4.34%	1[0.15,6.74]
Subtotal (95% CI)	**38**	**38**		**4.34%**	**1[0.15,6.74]**
Total events: 2 (Febuxostat), 2 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
11.1.2 28 weeks					
Schumacher 2008	69/269	33/134		95.66%	1.04[0.73,1.49]
Subtotal (95% CI)	**269**	**134**		**95.66%**	**1.04[0.73,1.49]**
Total events: 69 (Febuxostat), 33 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.22(P=0.82)					
Total (95% CI)	**307**	**172**		**100%**	**1.04[0.73,1.48]**
Total events: 71 (Febuxostat), 35 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=0.97); I^2=0%					
Test for overall effect: Z=0.22(P=0.83)					
Test for subgroup differences: Chi^2=0, df=1 (P=0.97), I^2=0%					



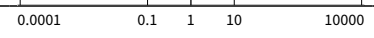
Analysis 11.2. Comparison 11 Withdrawals - febuxostat 120 mg/day versus placebo, Outcome 2 Adverse event.

Study or subgroup	Febuxostat n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
11.2.1 28 days					
Becker 2005b	2/38	1/38		13.03%	2[0.19,21.14]
Subtotal (95% CI)	**38**	**38**		**13.03%**	**2[0.19,21.14]**
Total events: 2 (Febuxostat), 1 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.58(P=0.56)					
11.2.2 28 weeks					
Schumacher 2008	16/269	5/134		86.97%	1.59[0.6,4.26]
Subtotal (95% CI)	**269**	**134**		**86.97%**	**1.59[0.6,4.26]**
Total events: 16 (Febuxostat), 5 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.93(P=0.35)					
Total (95% CI)	**307**	**172**		**100%**	**1.65[0.67,4.08]**
Total events: 18 (Febuxostat), 6 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.03, df=1(P=0.86); I^2=0%					
Test for overall effect: Z=1.08(P=0.28)					
Test for subgroup differences: Chi^2=0.03, df=1 (P=0.86), I^2=0%					



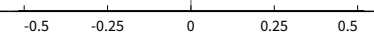
Analysis 11.3. Comparison 11 Withdrawals - febuxostat 120 mg/day versus placebo, Outcome 3 Gout flare.

Study or subgroup	Febuxostat n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
11.3.1 28 days					
Becker 2005b	0/38	1/38		69.23%	0.33[0.01,7.93]
Subtotal (95% CI)	**38**	**38**		**69.23%**	**0.33[0.01,7.93]**
Total events: 0 (Febuxostat), 1 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.68(P=0.5)					
11.3.2 28 weeks					
Schumacher 2008	6/269	0/134		30.77%	6.5[0.37,114.53]
Subtotal (95% CI)	**269**	**134**		**30.77%**	**6.5[0.37,114.53]**
Total events: 6 (Febuxostat), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.28(P=0.2)					
Total (95% CI)	**307**	**172**		**100%**	**2.23[0.4,12.57]**
Total events: 6 (Febuxostat), 1 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.92, df=1(P=0.17); I^2=47.79%					
Test for overall effect: Z=0.91(P=0.36)					
Test for subgroup differences: Chi^2=1.85, df=1 (P=0.17), I^2=46.07%					



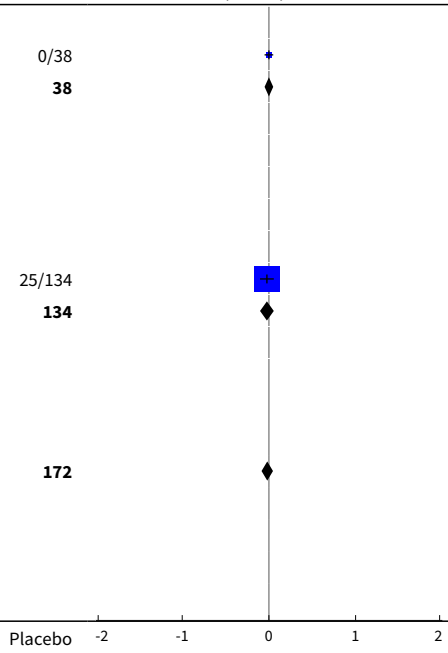
Analysis 11.4. Comparison 11 Withdrawals - febuxostat 120 mg/day versus placebo, Outcome 4 Lack of efficacy.

Study or subgroup	Febuxostat n/N	Control n/N	Risk Difference M-H, Fixed, 95% CI	Weight	Risk Difference M-H, Fixed, 95% CI
11.4.1 28 days					
Becker 2005b	0/38	0/38		17.52%	0[-0.05,0.05]
Subtotal (95% CI)	**38**	**38**		**17.52%**	**0[-0.05,0.05]**
Total events: 0 (Febuxostat), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
11.4.2 28 weeks					
Schumacher 2008	3/269	3/134		82.48%	-0.01[-0.04,0.02]
Subtotal (95% CI)	**269**	**134**		**82.48%**	**-0.01[-0.04,0.02]**
Total events: 3 (Febuxostat), 3 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=0.79(P=0.43)					
Total (95% CI)	**307**	**172**		**100%**	**-0.01[-0.03,0.02]**
Total events: 3 (Febuxostat), 3 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.15, df=1(P=0.7); I^2=0%					
Test for overall effect: Z=0.73(P=0.46)					
Test for subgroup differences: Chi^2=0.15, df=1 (P=0.7), I^2=0%					



Analysis 11.5. Comparison 11 Withdrawals - febuxostat 120 mg/day versus placebo, Outcome 5 Other reasons.

Study or subgroup	Febuxostat n/N	Control n/N	Risk Difference M-H, Fixed, 95% CI	Weight	Risk Difference M-H, Fixed, 95% CI
11.5.1 28 days					
Becker 2005b	0/38	0/38		17.52%	0[-0.05,0.05]
Subtotal (95% CI)	**38**	**38**		**17.52%**	**0[-0.05,0.05]**
Total events: 0 (Febuxostat), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
11.5.2 28 weeks					
Schumacher 2008	44/269	25/134		82.48%	-0.02[-0.1,0.06]
Subtotal (95% CI)	**269**	**134**		**82.48%**	**-0.02[-0.1,0.06]**
Total events: 44 (Febuxostat), 25 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.57(P=0.57)					
Total (95% CI)	**307**	**172**		**100%**	**-0.02[-0.09,0.05]**
Total events: 44 (Febuxostat), 25 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.56, df=1(P=0.45); I^2=0%					
Test for overall effect: Z=0.56(P=0.57)					
Test for subgroup differences: Chi^2=0.23, df=1 (P=0.63), I^2=0%					



Comparison 12. Withdrawals - febuxostat 240 mg/day versus placebo

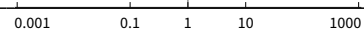
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 TOTAL	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 28 weeks	1	268	Risk Ratio (M-H, Fixed, 95% CI)	1.45 [1.00, 2.11]
2 Adverse event	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 28 weeks	1	268	Risk Ratio (M-H, Fixed, 95% CI)	2.2 [0.79, 6.16]
3 Gout flare	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 28 weeks	1	268	Risk Ratio (M-H, Fixed, 95% CI)	17.0 [0.99, 291.60]
4 Lack of efficacy	1		Risk Ratio (IV, Fixed, 95% CI)	Subtotals only
4.1 28 weeks	1	268	Risk Ratio (IV, Fixed, 95% CI)	0.67 [0.11, 3.93]
5 Other reasons	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 28 weeks	1	268	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.66, 1.76]

Analysis 12.1. Comparison 12 Withdrawals - febuxostat 240 mg/day versus placebo, Outcome 1 TOTAL.

Study or subgroup	Febuxostat n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
12.1.1 28 weeks					
Schumacher 2008	48/134	33/134		100%	1.45[1,2.11]
Subtotal (95% CI)	**134**	**134**		**100%**	**1.45[1,2.11]**
Total events: 48 (Febuxostat), 33 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.97(P=0.05)					

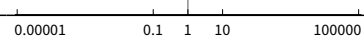
Analysis 12.2. Comparison 12 Withdrawals - febuxostat 240 mg/day versus placebo, Outcome 2 Adverse event.

Study or subgroup	Febuxostat n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
12.2.1 28 weeks					
Schumacher 2008	11/134	5/134		100%	2.2[0.79,6.16]
Subtotal (95% CI)	**134**	**134**		**100%**	**2.2[0.79,6.16]**
Total events: 11 (Febuxostat), 5 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.5(P=0.13)					



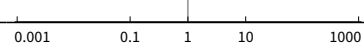
Analysis 12.3. Comparison 12 Withdrawals - febuxostat 240 mg/day versus placebo, Outcome 3 Gout flare.

Study or subgroup	Febuxostat n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
12.3.1 28 weeks					
Schumacher 2008	8/134	0/134		100%	17[0.99,291.6]
Subtotal (95% CI)	**134**	**134**		**100%**	**17[0.99,291.6]**
Total events: 8 (Febuxostat), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.95(P=0.05)					

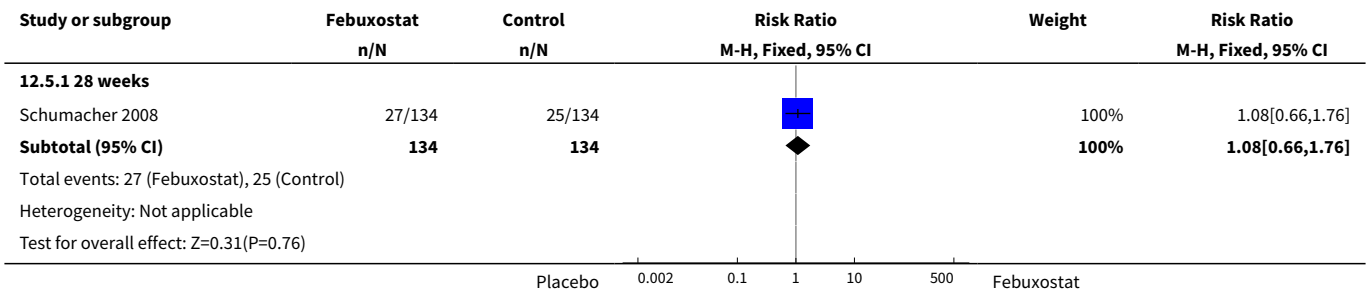


Analysis 12.4. Comparison 12 Withdrawals - febuxostat 240 mg/day versus placebo, Outcome 4 Lack of efficacy.

Study or subgroup	Febuxostat n/N	Control n/N	Risk Ratio IV, Fixed, 95% CI	Weight	Risk Ratio IV, Fixed, 95% CI
12.4.1 28 weeks					
Schumacher 2008	2/134	3/134		100%	0.67[0.11,3.93]
Subtotal (95% CI)	**134**	**134**		**100%**	**0.67[0.11,3.93]**
Total events: 2 (Febuxostat), 3 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.45(P=0.65)					



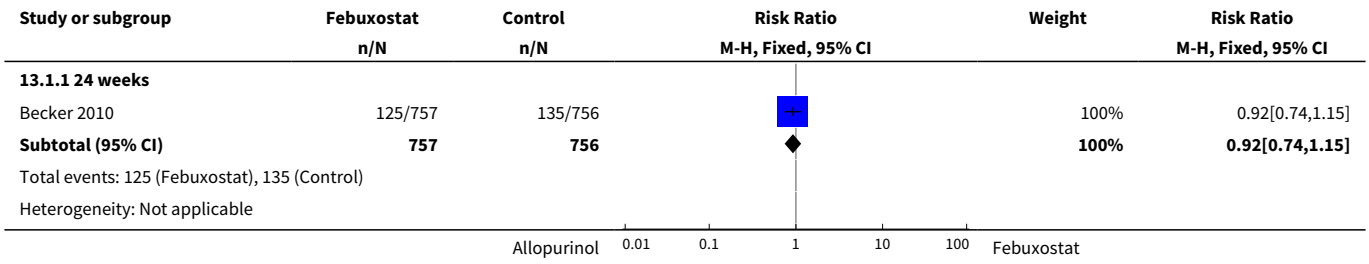
Analysis 12.5. Comparison 12 Withdrawals - febuxostat 240 mg/day versus placebo, Outcome 5 Other reasons.

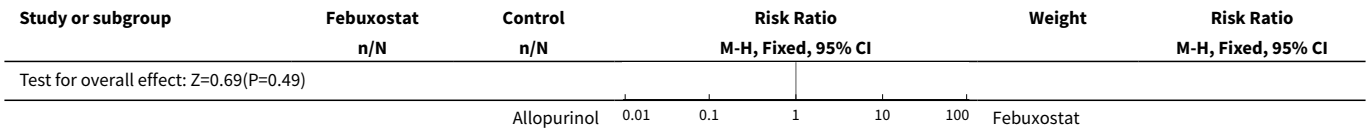


Comparison 13. Withdrawals - febuxostat 40 mg/day versus allopurinol 200 or 300 mg/day

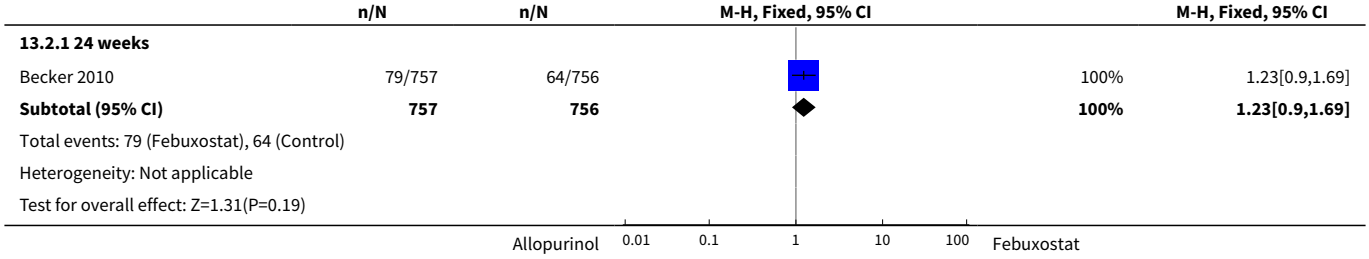
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 TOTAL	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 24 weeks	1	1513	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.74, 1.15]
2 Adverse event	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 24 weeks	1	1513	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [0.90, 1.69]
3 Gout flare	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 24 weeks	1	1513	Risk Ratio (M-H, Fixed, 95% CI)	1.50 [0.25, 8.94]
4 Lack of efficacy	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 24 weeks	1	1513	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.06, 15.94]
5 Other reasons	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 24 weeks	1	1512	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.77, 1.45]

Analysis 13.1. Comparison 13 Withdrawals - febuxostat 40 mg/day versus allopurinol 200 or 300 mg/day, Outcome 1 TOTAL.

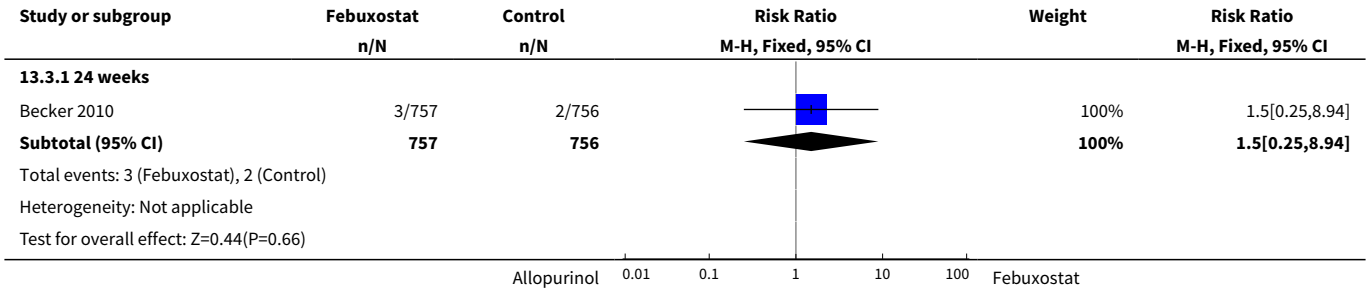




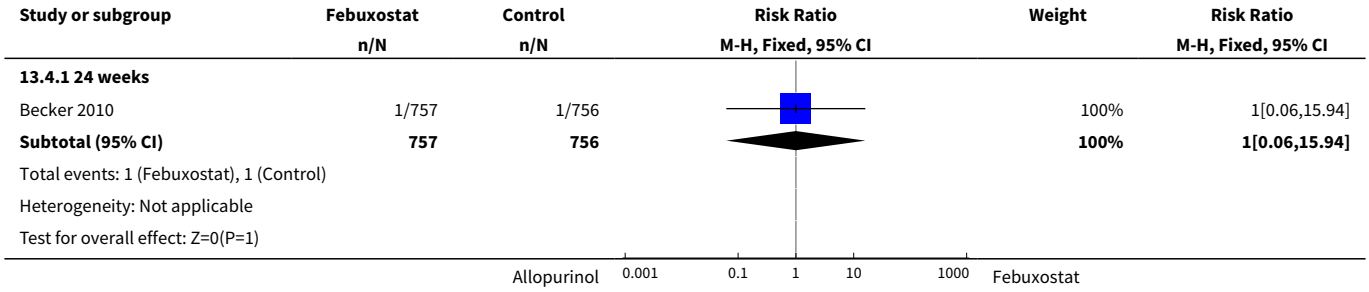
Analysis 13.2. Comparison 13 Withdrawals - febuxostat 40 mg/ day versus allopurinol 200 or 300 mg/day, Outcome 2 Adverse event.



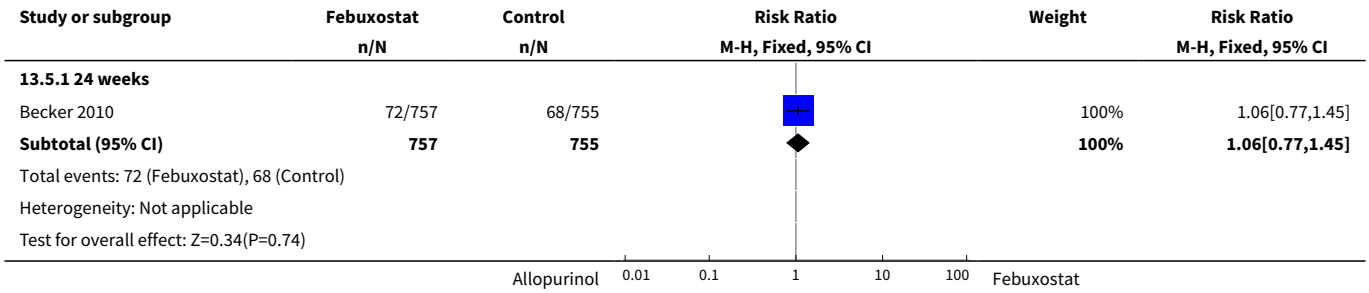
Analysis 13.3. Comparison 13 Withdrawals - febuxostat 40 mg/ day versus allopurinol 200 or 300 mg/day, Outcome 3 Gout flare.



Analysis 13.4. Comparison 13 Withdrawals - febuxostat 40 mg/ day versus allopurinol 200 or 300 mg/day, Outcome 4 Lack of efficacy.



Analysis 13.5. Comparison 13 Withdrawals - febuxostat 40 mg/ day versus allopurinol 200 or 300 mg/day, Outcome 5 Other reasons.

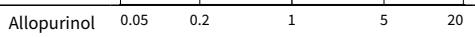


Comparison 14. Withdrawals - febuxostat 80 mg/day versus allopurinol 200 or 300 mg/day

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 TOTAL	3	2555	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [1.14, 1.51]
1.1 24-28 weeks	2	2046	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [1.11, 1.54]
1.2 52 weeks	1	509	Risk Ratio (M-H, Fixed, 95% CI)	1.32 [1.01, 1.72]
2 Adverse event	3	2555	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.80, 1.39]
2.1 24-28 weeks	2	2046	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.72, 1.30]
2.2 52 weeks	1	509	Risk Ratio (M-H, Fixed, 95% CI)	1.98 [0.86, 4.54]
3 Gout flare	3	2555	Risk Ratio (M-H, Random, 95% CI)	2.99 [0.70, 12.79]
3.1 24-28 weeks	2	2046	Risk Ratio (M-H, Random, 95% CI)	5.79 [1.59, 21.05]
3.2 52 weeks	1	509	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.45, 2.66]
4 Lack of efficacy	3	2555	Risk Ratio (M-H, Random, 95% CI)	3.08 [0.55, 17.20]
4.1 24-28 weeks	2	2046	Risk Ratio (M-H, Random, 95% CI)	3.08 [0.55, 17.20]
4.2 52 weeks	1	509	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5 Other reasons	3	2555	Risk Ratio (M-H, Random, 95% CI)	1.34 [1.10, 1.62]
5.1 28 weeks	2	2046	Risk Ratio (M-H, Random, 95% CI)	1.38 [1.09, 1.75]
5.2 52 weeks	1	509	Risk Ratio (M-H, Random, 95% CI)	1.25 [0.90, 1.74]

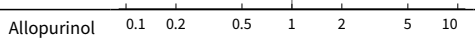
Analysis 14.1. Comparison 14 Withdrawals - febuxostat 80 mg/ day versus allopurinol 200 or 300 mg/day, Outcome 1 TOTAL.

Study or subgroup	Febuxostat n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
14.1.1 24-28 weeks					
Becker 2010	158/756	135/755		52.28%	1.17[0.95,1.44]
Schumacher 2008	93/267	57/268		22.02%	1.64[1.23,2.17]
Subtotal (95% CI)	**1023**	**1023**		**74.3%**	**1.31[1.11,1.54]**
Total events: 251 (Febuxostat), 192 (Control)					
Heterogeneity: Tau^2=0; Chi^2=3.57, df=1(P=0.06); I^2=71.98%					
Test for overall effect: Z=3.16(P=0)					
14.1.2 52 weeks					
Becker 2005a	88/256	66/253		25.7%	1.32[1.01,1.72]
Subtotal (95% CI)	**256**	**253**		**25.7%**	**1.32[1.01,1.72]**
Total events: 88 (Febuxostat), 66 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.02(P=0.04)					
Total (95% CI)	**1279**	**1276**		**100%**	**1.31[1.14,1.51]**
Total events: 339 (Febuxostat), 258 (Control)					
Heterogeneity: Tau^2=0; Chi^2=3.57, df=2(P=0.17); I^2=43.95%					
Test for overall effect: Z=3.75(P=0)					
Test for subgroup differences: Chi^2=0, df=1 (P=0.96), I^2=0%					



Analysis 14.2. Comparison 14 Withdrawals - febuxostat 80 mg/ day versus allopurinol 200 or 300 mg/day, Outcome 2 Adverse event.

Study or subgroup	Febuxostat n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
14.2.1 24-28 weeks					
Becker 2010	61/756	64/755		71.11%	0.95[0.68,1.33]
Schumacher 2008	18/267	18/268		19.95%	1[0.53,1.89]
Subtotal (95% CI)	**1023**	**1023**		**91.06%**	**0.96[0.72,1.3]**
Total events: 79 (Febuxostat), 82 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.02, df=1(P=0.88); I^2=0%					
Test for overall effect: Z=0.25(P=0.8)					
14.2.2 52 weeks					
Becker 2005a	16/256	8/253		8.94%	1.98[0.86,4.54]
Subtotal (95% CI)	**256**	**253**		**8.94%**	**1.98[0.86,4.54]**
Total events: 16 (Febuxostat), 8 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.61(P=0.11)					
Total (95% CI)	**1279**	**1276**		**100%**	**1.05[0.8,1.39]**
Total events: 95 (Febuxostat), 90 (Control)					
Heterogeneity: Tau^2=0; Chi^2=2.58, df=2(P=0.28); I^2=22.4%					
Test for overall effect: Z=0.37(P=0.71)					
Test for subgroup differences: Chi^2=2.55, df=1 (P=0.11), I^2=60.8%					

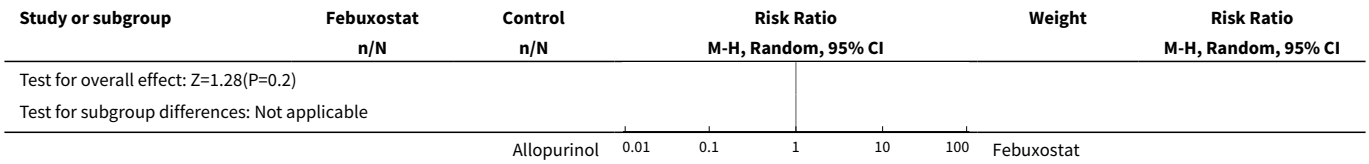


Analysis 14.3. Comparison 14 Withdrawals - febuxostat 80 mg/ day versus allopurinol 200 or 300 mg/day, Outcome 3 Gout flare.

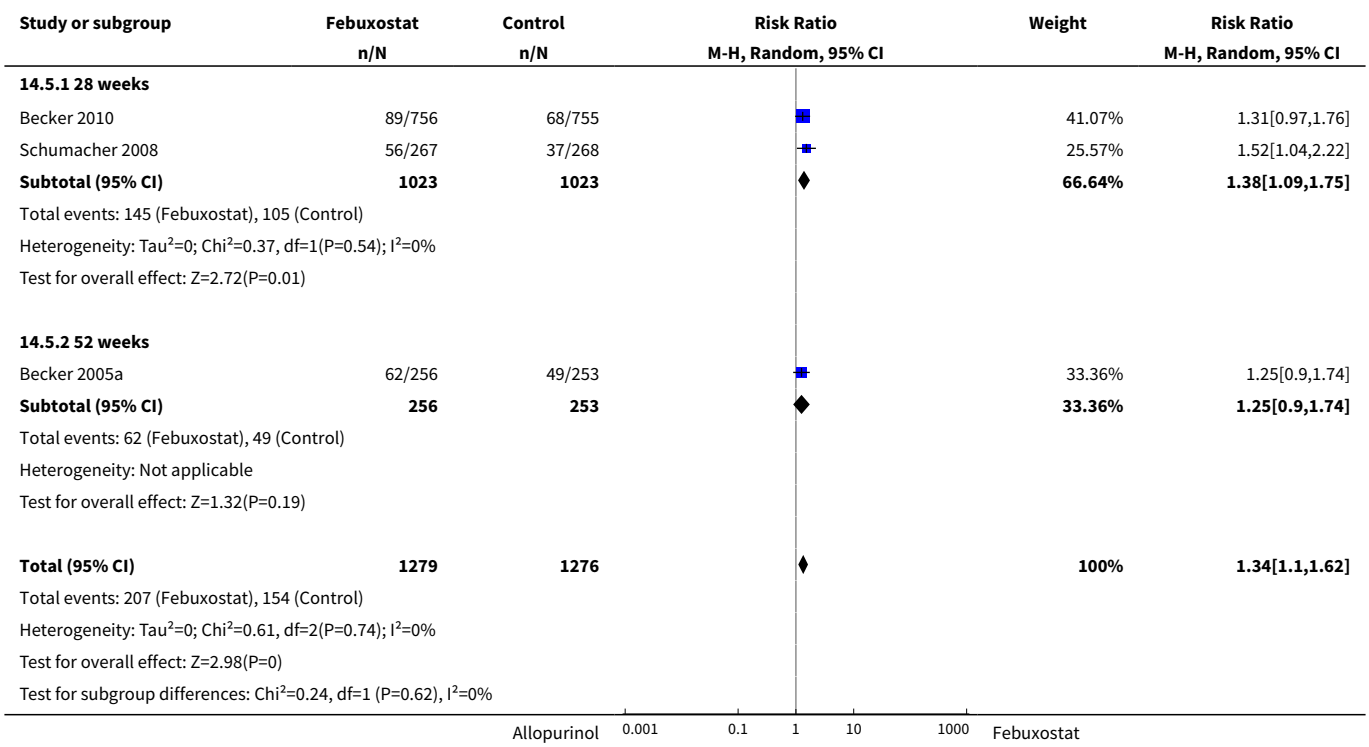
Study or subgroup	Febuxostat n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
14.3.1 24-28 weeks					
Becker 2010	7/756	2/755		31.85%	3.5[0.73,16.77]
Schumacher 2008	13/267	1/268		25.52%	13.05[1.72,99.04]
Subtotal (95% CI)	**1023**	**1023**		**57.37%**	**5.79[1.59,21.05]**
Total events: 20 (Febuxostat), 3 (Control)					
Heterogeneity: Tau^2=0.06; Chi^2=1.07, df=1(P=0.3); I^2=6.87%					
Test for overall effect: Z=2.67(P=0.01)					
14.3.2 52 weeks					
Becker 2005a	10/256	9/253		42.63%	1.1[0.45,2.66]
Subtotal (95% CI)	**256**	**253**		**42.63%**	**1.1[0.45,2.66]**
Total events: 10 (Febuxostat), 9 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.21(P=0.84)					
Total (95% CI)	**1279**	**1276**		**100%**	**2.99[0.7,12.79]**
Total events: 30 (Febuxostat), 12 (Control)					
Heterogeneity: Tau^2=1.09; Chi^2=6.04, df=2(P=0.05); I^2=66.87%					
Test for overall effect: Z=1.47(P=0.14)					
Test for subgroup differences: Chi^2=4.34, df=1 (P=0.04), I^2=76.95%					

Analysis 14.4. Comparison 14 Withdrawals - febuxostat 80 mg/ day versus allopurinol 200 or 300 mg/day, Outcome 4 Lack of efficacy.

Study or subgroup	Febuxostat n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
14.4.1 24-28 weeks					
Becker 2010	1/756	1/755		37.26%	1[0.06,15.94]
Schumacher 2008	6/267	1/268		62.74%	6.02[0.73,49.69]
Subtotal (95% CI)	**1023**	**1023**		**100%**	**3.08[0.55,17.2]**
Total events: 7 (Febuxostat), 2 (Control)					
Heterogeneity: Tau^2=0.07; Chi^2=1.04, df=1(P=0.31); I^2=4.05%					
Test for overall effect: Z=1.28(P=0.2)					
14.4.2 52 weeks					
Becker 2005a	0/256	0/253			Not estimable
Subtotal (95% CI)	**256**	**253**			**Not estimable**
Total events: 0 (Febuxostat), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**1279**	**1276**		**100%**	**3.08[0.55,17.2]**
Total events: 7 (Febuxostat), 2 (Control)					
Heterogeneity: Tau^2=0.07; Chi^2=1.04, df=1(P=0.31); I^2=4.05%					



Analysis 14.5. Comparison 14 Withdrawals - febuxostat 80 mg/ day versus allopurinol 200 or 300 mg/day, Outcome 5 Other reasons.



Comparison 15. Withdrawals - febuxostat 120 mg/day versus allopurinol 300 mg/day

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 TOTAL	2	1041	Risk Ratio (M-H, Fixed, 95% CI)	1.36 [1.12, 1.66]
1.1 28 weeks	1	537	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.89, 1.64]
1.2 52 weeks	1	504	Risk Ratio (M-H, Fixed, 95% CI)	1.50 [1.16, 1.94]
2 Adverse event	2	1041	Risk Ratio (M-H, Random, 95% CI)	1.57 [0.49, 5.03]
2.1 28 weeks	1	537	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.46, 1.70]
2.2 52 weeks	1	504	Risk Ratio (M-H, Random, 95% CI)	2.90 [1.32, 6.36]

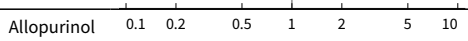
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Gout flare	2	1041	Risk Ratio (M-H, Fixed, 95% CI)	3.42 [1.72, 6.81]
3.1 28 weeks	1	537	Risk Ratio (M-H, Fixed, 95% CI)	5.98 [0.72, 49.32]
3.2 52 weeks	1	504	Risk Ratio (M-H, Fixed, 95% CI)	3.14 [1.51, 6.51]
4 Lack of efficacy	2	1041	Risk Difference (M-H, Fixed, 95% CI)	0.00 [-0.00, 0.01]
4.1 28 weeks	1	537	Risk Difference (M-H, Fixed, 95% CI)	0.01 [-0.01, 0.02]
4.2 52 weeks	1	504	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.01, 0.01]
5 Other reasons	2	1042	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.87, 1.47]
5.1 28 weeks	1	537	Risk Ratio (M-H, Fixed, 95% CI)	1.35 [0.91, 1.99]
5.2 52 weeks	1	505	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.68, 1.39]

Analysis 15.1. Comparison 15 Withdrawals - febuxostat 120 mg/day versus allopurinol 300 mg/day, Outcome 1 TOTAL.

Study or subgroup	Febuxostat n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
15.1.1 28 weeks					
Schumacher 2008	69/269	57/268		46.49%	1.21[0.89,1.64]
Subtotal (95% CI)	**269**	**268**		**46.49%**	**1.21[0.89,1.64]**
Total events: 69 (Febuxostat), 57 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.19(P=0.23)					
15.1.2 52 weeks					
Becker 2005a	98/251	66/253		53.51%	1.5[1.16,1.94]
Subtotal (95% CI)	**251**	**253**		**53.51%**	**1.5[1.16,1.94]**
Total events: 98 (Febuxostat), 66 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=3.06(P=0)					
Total (95% CI)	**520**	**521**		**100%**	**1.36[1.12,1.66]**
Total events: 167 (Febuxostat), 123 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.11, df=1(P=0.29); I^2=10.1%					
Test for overall effect: Z=3.06(P=0)					
Test for subgroup differences: Chi^2=1.11, df=1 (P=0.29), I^2=9.9%					

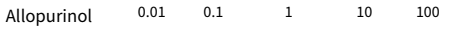
Analysis 15.2. Comparison 15 Withdrawals - febuxostat 120 mg/ day versus allopurinol 300 mg/day, Outcome 2 Adverse event.

Study or subgroup	Febuxostat n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
15.2.1 28 weeks					
Schumacher 2008	16/269	18/268		51.77%	0.89[0.46,1.7]
Subtotal (95% CI)	**269**	**268**		**51.77%**	**0.89[0.46,1.7]**
Total events: 16 (Febuxostat), 18 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.37(P=0.71)					
15.2.2 52 weeks					
Becker 2005a	23/251	8/253		48.23%	2.9[1.32,6.36]
Subtotal (95% CI)	**251**	**253**		**48.23%**	**2.9[1.32,6.36]**
Total events: 23 (Febuxostat), 8 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.66(P=0.01)					
Total (95% CI)	**520**	**521**		**100%**	**1.57[0.49,5.03]**
Total events: 39 (Febuxostat), 26 (Control)					
Heterogeneity: Tau^2=0.57; Chi^2=5.21, df=1(P=0.02); I^2=80.82%					
Test for overall effect: Z=0.76(P=0.45)					
Test for subgroup differences: Chi^2=5.18, df=1 (P=0.02), I^2=80.71%					



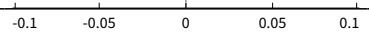
Analysis 15.3. Comparison 15 Withdrawals - febuxostat 120 mg/ day versus allopurinol 300 mg/day, Outcome 3 Gout flare.

Study or subgroup	Febuxostat n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
15.3.1 28 weeks					
Schumacher 2008	6/269	1/268		10.05%	5.98[0.72,49.32]
Subtotal (95% CI)	**269**	**268**		**10.05%**	**5.98[0.72,49.32]**
Total events: 6 (Febuxostat), 1 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.66(P=0.1)					
15.3.2 52 weeks					
Becker 2005a	28/251	9/253		89.95%	3.14[1.51,6.51]
Subtotal (95% CI)	**251**	**253**		**89.95%**	**3.14[1.51,6.51]**
Total events: 28 (Febuxostat), 9 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=3.07(P=0)					
Total (95% CI)	**520**	**521**		**100%**	**3.42[1.72,6.81]**
Total events: 34 (Febuxostat), 10 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.32, df=1(P=0.57); I^2=0%					
Test for overall effect: Z=3.5(P=0)					
Test for subgroup differences: Chi^2=0.32, df=1 (P=0.57), I^2=0%					



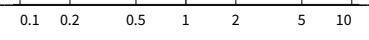
Analysis 15.4. Comparison 15 Withdrawals - febuxostat 120 mg/ day versus allopurinol 300 mg/day, Outcome 4 Lack of efficacy.

Study or subgroup	Febuxostat n/N	Control n/N	Risk Difference M-H, Fixed, 95% CI	Weight	Risk Difference M-H, Fixed, 95% CI
15.4.1 28 weeks					
Schumacher 2008	3/269	1/268		51.59%	0.01[-0.01,0.02]
Subtotal (95% CI)	**269**	**268**		**51.59%**	**0.01[-0.01,0.02]**
Total events: 3 (Febuxostat), 1 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1(P=0.32)					
15.4.2 52 weeks					
Becker 2005a	0/251	0/253		48.41%	0[-0.01,0.01]
Subtotal (95% CI)	**251**	**253**		**48.41%**	**0[-0.01,0.01]**
Total events: 0 (Febuxostat), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**520**	**521**		**100%**	**0[-0,0.01]**
Total events: 3 (Febuxostat), 1 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.18, df=1(P=0.28); I^2=14.9%					
Test for overall effect: Z=0.9(P=0.37)					
Test for subgroup differences: Chi^2=0.78, df=1 (P=0.38), I^2=0%					



Analysis 15.5. Comparison 15 Withdrawals - febuxostat 120 mg/ day versus allopurinol 300 mg/day, Outcome 5 Other reasons.

Study or subgroup	Febuxostat n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
15.5.1 28 weeks					
Schumacher 2008	50/269	37/268		43.22%	1.35[0.91,1.99]
Subtotal (95% CI)	**269**	**268**		**43.22%**	**1.35[0.91,1.99]**
Total events: 50 (Febuxostat), 37 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.49(P=0.13)					
15.5.2 52 weeks					
Becker 2005a	47/251	49/254		56.78%	0.97[0.68,1.39]
Subtotal (95% CI)	**251**	**254**		**56.78%**	**0.97[0.68,1.39]**
Total events: 47 (Febuxostat), 49 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.16(P=0.87)					
Total (95% CI)	**520**	**522**		**100%**	**1.13[0.87,1.47]**
Total events: 97 (Febuxostat), 86 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.46, df=1(P=0.23); I^2=31.52%					
Test for overall effect: Z=0.93(P=0.35)					
Test for subgroup differences: Chi^2=1.46, df=1 (P=0.23), I^2=31.48%					

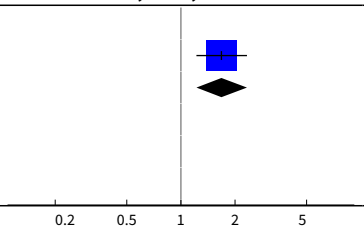


Comparison 16. Withdrawals - febuxostat 240 mg/day versus allopurinol 300 mg/day

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 TOTAL	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 28 weeks	1	402	Risk Ratio (M-H, Fixed, 95% CI)	1.68 [1.22, 2.33]
2 Adverse event	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 28 weeks	1	402	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.59, 2.51]
3 Gout flare	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 28 weeks	1	402	Risk Ratio (M-H, Fixed, 95% CI)	16.0 [2.02, 126.61]
4 Lack of efficacy	1		Risk Difference (M-H, Fixed, 95% CI)	Subtotals only
4.1 28 weeks	1	402	Risk Difference (M-H, Fixed, 95% CI)	0.01 [-0.01, 0.03]
5 Other reasons	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 28 weeks	1	402	Risk Ratio (M-H, Fixed, 95% CI)	1.46 [0.93, 2.29]

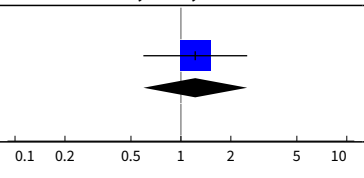
Analysis 16.1. Comparison 16 Withdrawals - febuxostat 240 mg/day versus allopurinol 300 mg/day, Outcome 1 TOTAL.

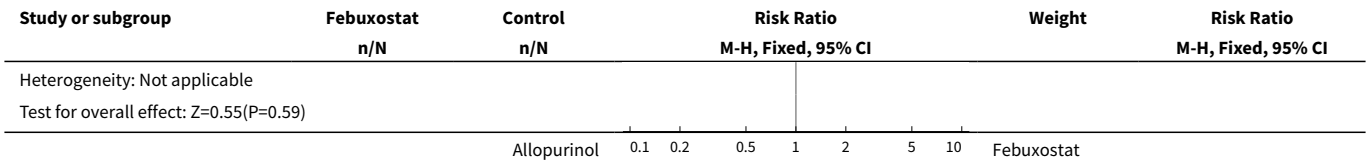
Study or subgroup	Febuxostat n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
16.1.1 28 weeks					
Schumacher 2008	48/134	57/268		100%	1.68[1.22,2.33]
Subtotal (95% CI)	**134**	**268**		**100%**	**1.68[1.22,2.33]**
Total events: 48 (Febuxostat), 57 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=3.16(P=0)					



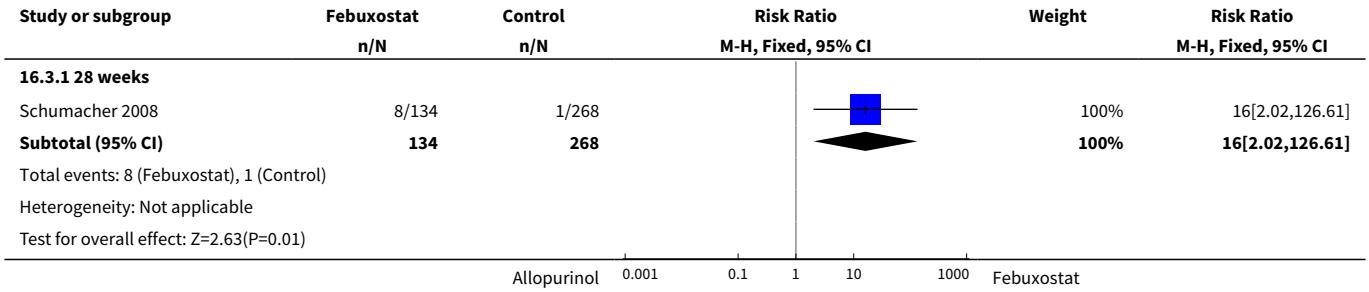
Analysis 16.2. Comparison 16 Withdrawals - febuxostat 240 mg/day versus allopurinol 300 mg/day, Outcome 2 Adverse event.

Study or subgroup	Febuxostat n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
16.2.1 28 weeks					
Schumacher 2008	11/134	18/268		100%	1.22[0.59,2.51]
Subtotal (95% CI)	**134**	**268**		**100%**	**1.22[0.59,2.51]**
Total events: 11 (Febuxostat), 18 (Control)					

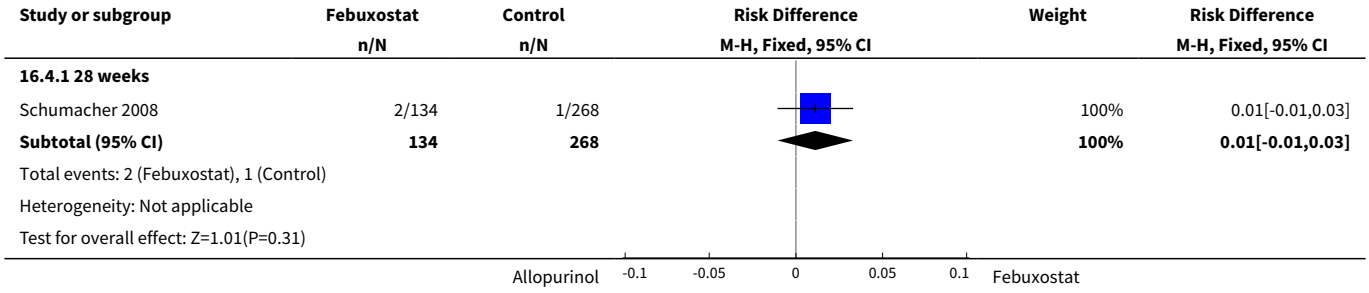




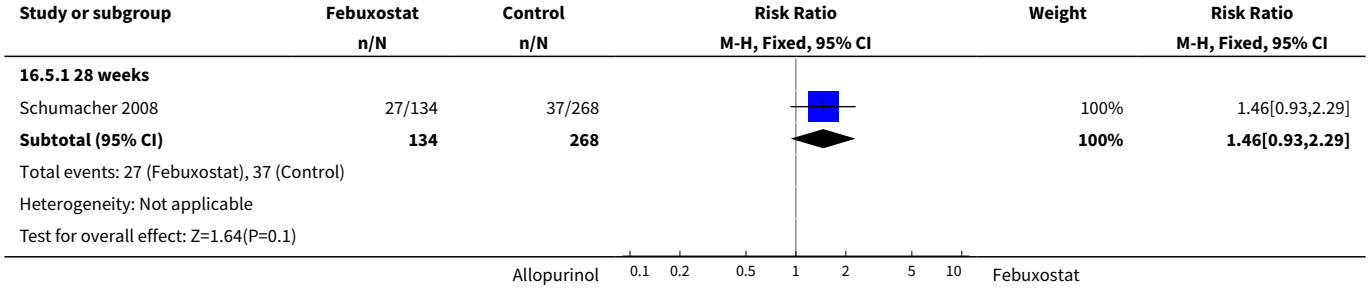
Analysis 16.3. Comparison 16 Withdrawals - febuxostat 240 mg/ day versus allopurinol 300 mg/day, Outcome 3 Gout flare.



Analysis 16.4. Comparison 16 Withdrawals - febuxostat 240 mg/ day versus allopurinol 300 mg/day, Outcome 4 Lack of efficacy.



Analysis 16.5. Comparison 16 Withdrawals - febuxostat 240 mg/ day versus allopurinol 300 mg/day, Outcome 5 Other reasons.

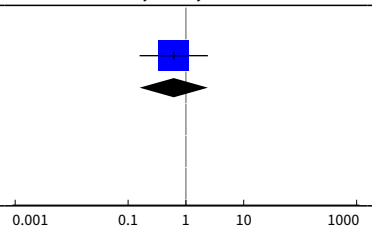


Comparison 17. Adverse events - febuxostat 40 mg/day versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 TOTAL	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 28 days	1	75	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.16, 2.40]
2 Serious	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 28 days	1	75	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Liver function test abnormalities	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 28 days	1	75	Risk Ratio (M-H, Fixed, 95% CI)	5.13 [0.25, 103.41]
4 Skin reaction	1		Risk Difference (M-H, Fixed, 95% CI)	Subtotals only
4.1 28 days	1	75	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.05, 0.05]
5 Cardiovascular events (chest pain, coronary artery disease, myocardial infarction, atrial fibrillation)	1		Risk Difference (M-H, Fixed, 95% CI)	Subtotals only
5.1 28 days	1	75	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.05, 0.05]
6 Hypertension	1		Risk Difference (M-H, Fixed, 95% CI)	Subtotals only
6.1 28 days	1	75	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.05, 0.05]
7 Diarrhea	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 28 days	1	75	Risk Ratio (M-H, Fixed, 95% CI)	0.15 [0.01, 2.74]

Analysis 17.1. Comparison 17 Adverse events - febuxostat 40 mg/day versus placebo, Outcome 1 TOTAL.

Study or subgroup	Febuxostat n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
17.1.1 28 days					
Becker 2005b	3/37	5/38		100%	0.62[0.16,2.4]
Subtotal (95% CI)	**37**	**38**		**100%**	**0.62[0.16,2.4]**
Total events: 3 (Febuxostat), 5 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.7(P=0.48)					

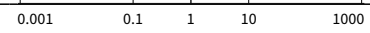


Analysis 17.2. Comparison 17 Adverse events - febuxostat 40 mg/day versus placebo, Outcome 2 Serious.

Study or subgroup	Febuxostat n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
17.2.1 28 days					
Becker 2005b	0/37	0/38			Not estimable
Subtotal (95% CI)	**37**	**38**			**Not estimable**
Total events: 0 (Febuxostat), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					

Analysis 17.3. Comparison 17 Adverse events - febuxostat 40 mg/day versus placebo, Outcome 3 Liver function test abnormalities.

Study or subgroup	Febuxostat n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
17.3.1 28 days					
Becker 2005b	2/37	0/38		100%	5.13[0.25,103.41]
Subtotal (95% CI)	**37**	**38**		**100%**	**5.13[0.25,103.41]**
Total events: 2 (Febuxostat), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.07(P=0.29)					

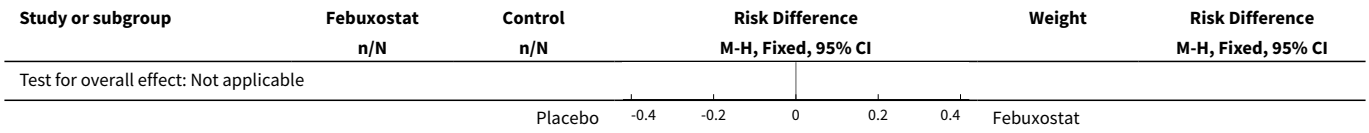


Analysis 17.4. Comparison 17 Adverse events - febuxostat 40 mg/day versus placebo, Outcome 4 Skin reaction.

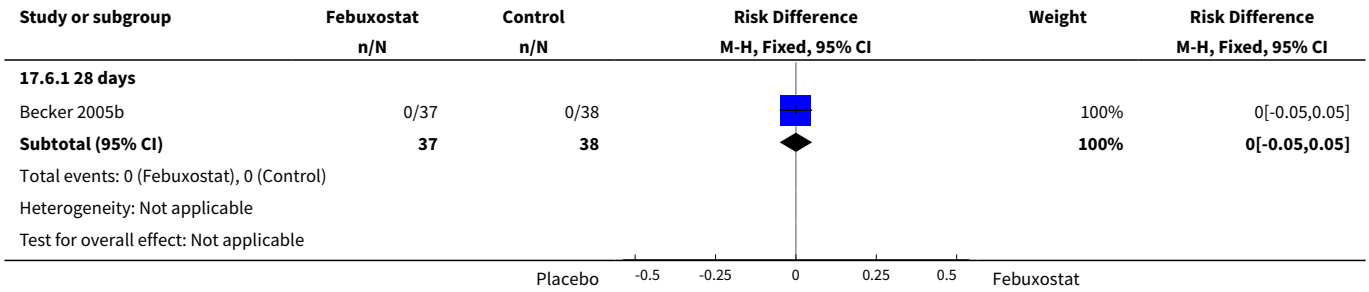
Study or subgroup	Febuxostat n/N	Control n/N	Risk Difference M-H, Fixed, 95% CI	Weight	Risk Difference M-H, Fixed, 95% CI
17.4.1 28 days					
Becker 2005b	0/37	0/38		100%	0[-0.05,0.05]
Subtotal (95% CI)	**37**	**38**		**100%**	**0[-0.05,0.05]**
Total events: 0 (Febuxostat), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					

Analysis 17.5. Comparison 17 Adverse events - febuxostat 40 mg/day versus placebo, Outcome 5 Cardiovascular events (chest pain, coronary artery disease, myocardial infarction, atrial fibrillation).

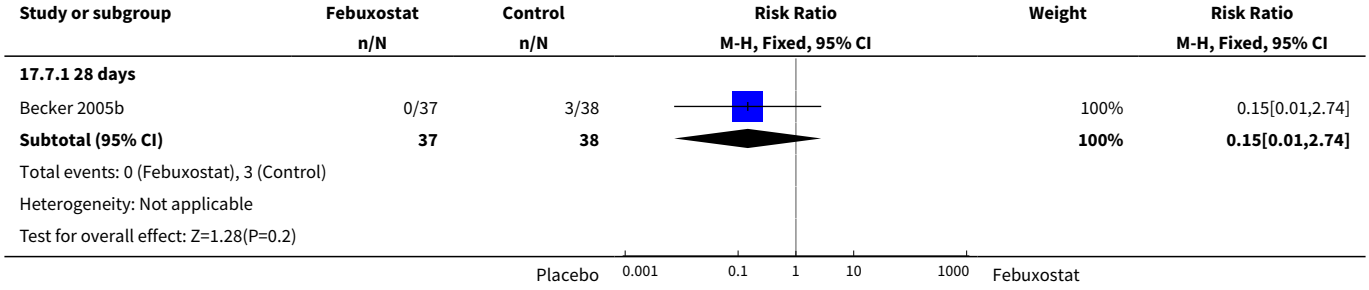
Study or subgroup	Febuxostat n/N	Control n/N	Risk Difference M-H, Fixed, 95% CI	Weight	Risk Difference M-H, Fixed, 95% CI
17.5.1 28 days					
Becker 2005b	0/37	0/38		100%	0[-0.05,0.05]
Subtotal (95% CI)	**37**	**38**		**100%**	**0[-0.05,0.05]**
Total events: 0 (Febuxostat), 0 (Control)					
Heterogeneity: Not applicable					



Analysis 17.6. Comparison 17 Adverse events - febuxostat 40 mg/day versus placebo, Outcome 6 Hypertension.



Analysis 17.7. Comparison 17 Adverse events - febuxostat 40 mg/day versus placebo, Outcome 7 Diarrhea.

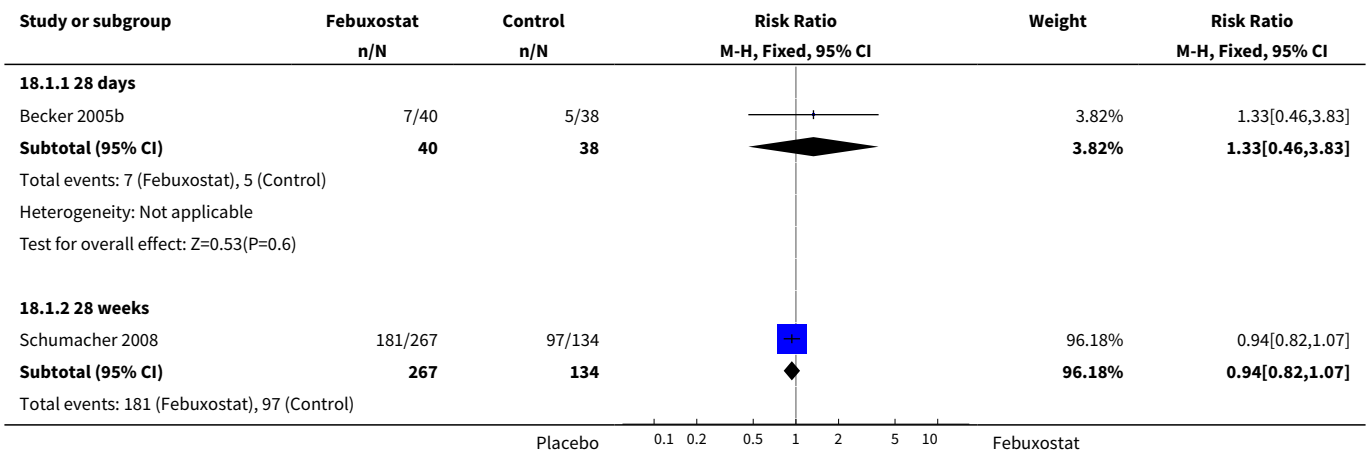


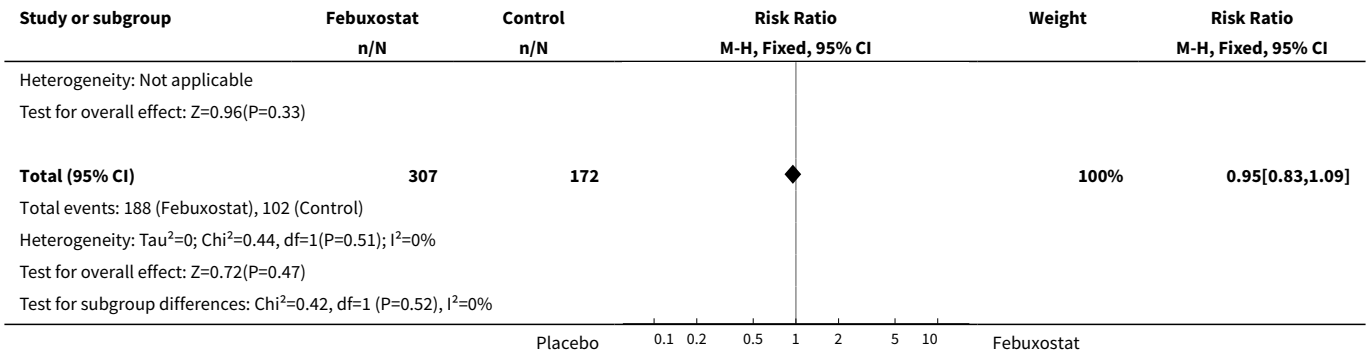
Comparison 18. Adverse events - febuxostat 80 mg/day versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 TOTAL	2	479	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.83, 1.09]
1.1 28 days	1	78	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.46, 3.83]
1.2 28 weeks	1	401	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.82, 1.07]
2 Serious	2	479	Risk Ratio (M-H, Fixed, 95% CI)	2.78 [0.72, 10.72]
2.1 28 days	1	78	Risk Ratio (M-H, Fixed, 95% CI)	2.85 [0.12, 67.97]
2.2 28 weeks	1	401	Risk Ratio (M-H, Fixed, 95% CI)	2.76 [0.62, 12.28]

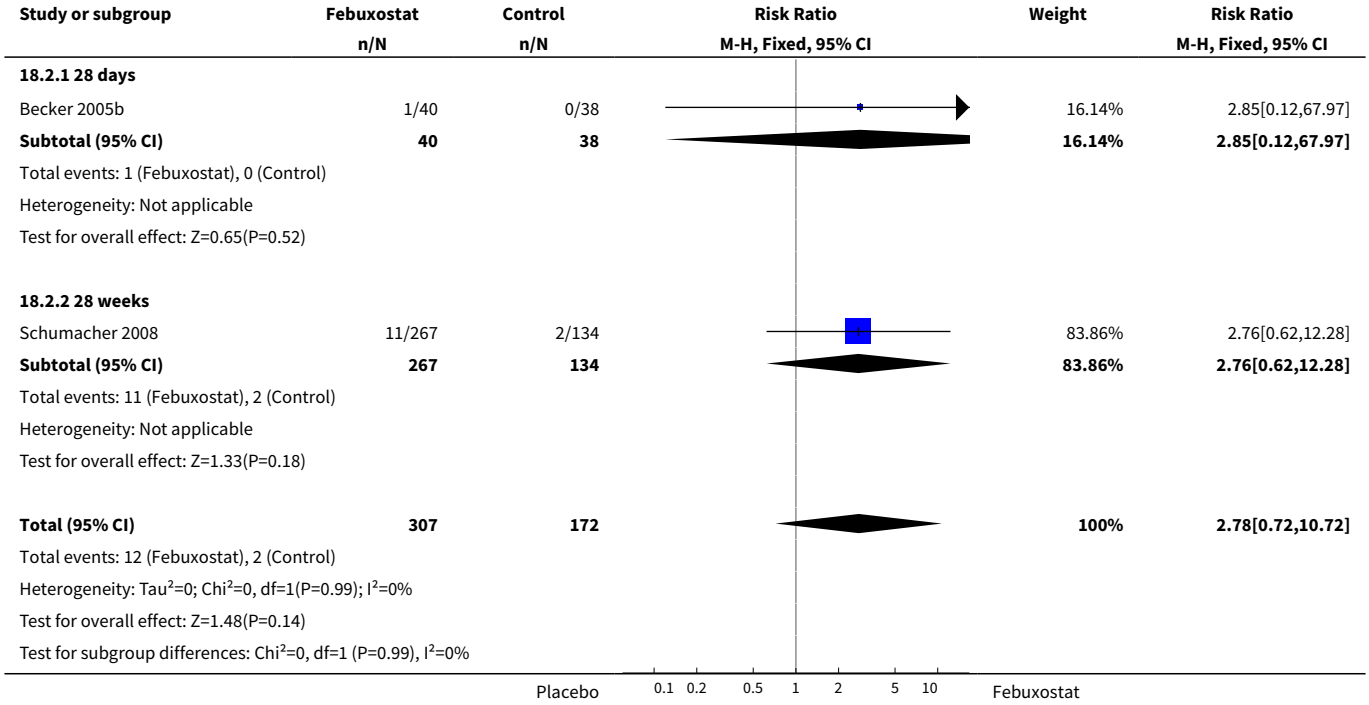
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Liver function test abnormalities	2	479	Risk Ratio (M-H, Fixed, 95% CI)	2.85 [0.92, 8.82]
3.1 28 days	1	78	Risk Ratio (M-H, Fixed, 95% CI)	2.85 [0.12, 67.97]
3.2 28 weeks	1	401	Risk Ratio (M-H, Fixed, 95% CI)	2.84 [0.85, 9.53]
4 Skin reaction	2	479	Risk Difference (M-H, Fixed, 95% CI)	0.00 [-0.04, 0.04]
4.1 28 days	1	78	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.05, 0.05]
4.2 28 weeks	1	401	Risk Difference (M-H, Fixed, 95% CI)	0.00 [-0.05, 0.05]
5 Cardiovascular events (chest pain, coronary artery disease, myocardial infarction, atrial fibrillation)	2		Risk Difference (M-H, Fixed, 95% CI)	Subtotals only
5.1 28 days	1	78	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.05, 0.05]
5.2 28 weeks	1	401	Risk Difference (M-H, Fixed, 95% CI)	0.01 [-0.01, 0.03]
6 Hypertension	2	479	Risk Difference (M-H, Fixed, 95% CI)	-0.01 [-0.05, 0.03]
6.1 28 days	1	78	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.05, 0.05]
6.2 28 weeks	1	401	Risk Difference (M-H, Fixed, 95% CI)	-0.01 [-0.06, 0.04]
7 Diarrhea	2	479	Risk Difference (M-H, Fixed, 95% CI)	-0.01 [-0.06, 0.04]
7.1 28 days	1	78	Risk Difference (M-H, Fixed, 95% CI)	0.02 [-0.11, 0.15]
7.2 28 weeks	1	401	Risk Difference (M-H, Fixed, 95% CI)	-0.02 [-0.08, 0.03]

Analysis 18.1. Comparison 18 Adverse events - febuxostat 80 mg/day versus placebo, Outcome 1 TOTAL.

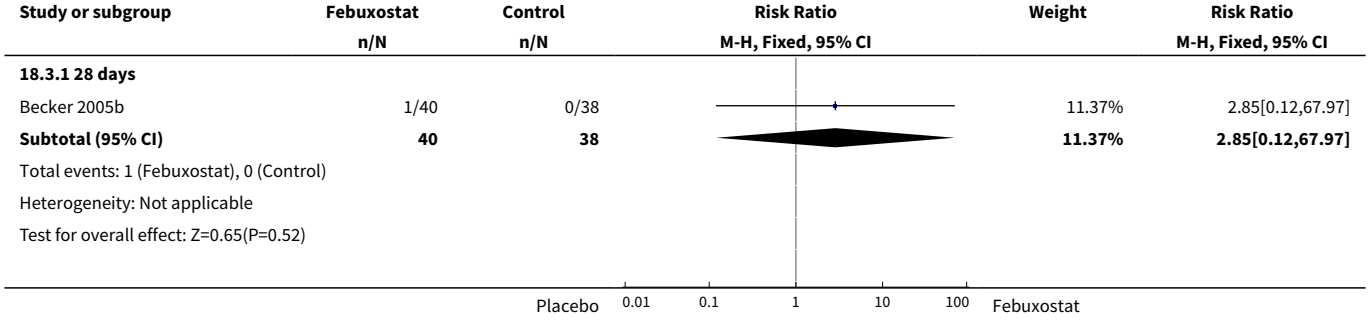


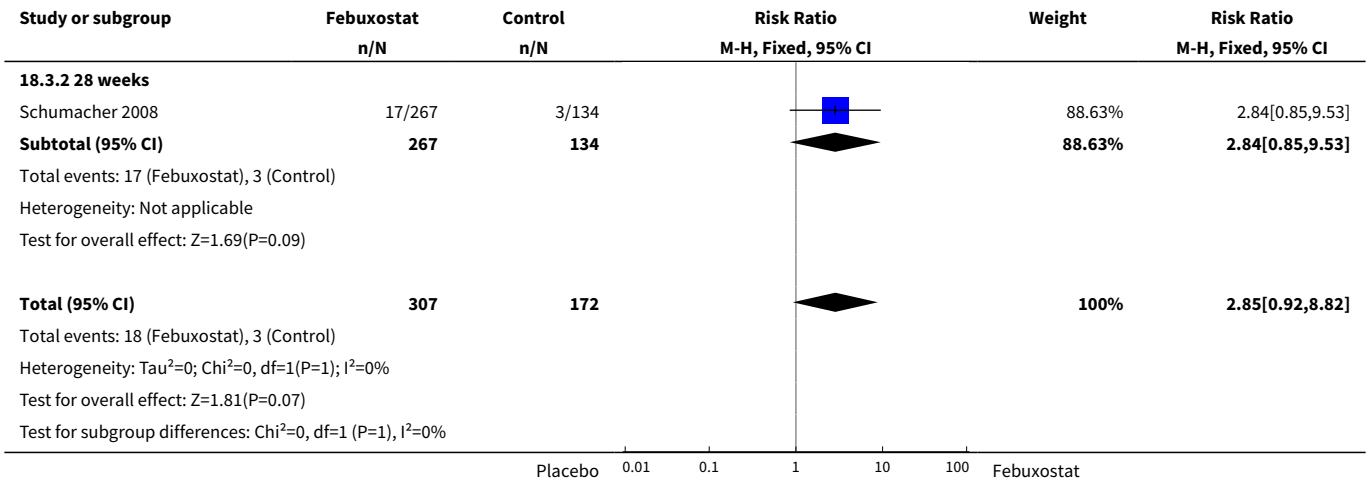


Analysis 18.2. Comparison 18 Adverse events - febuxostat 80 mg/day versus placebo, Outcome 2 Serious.

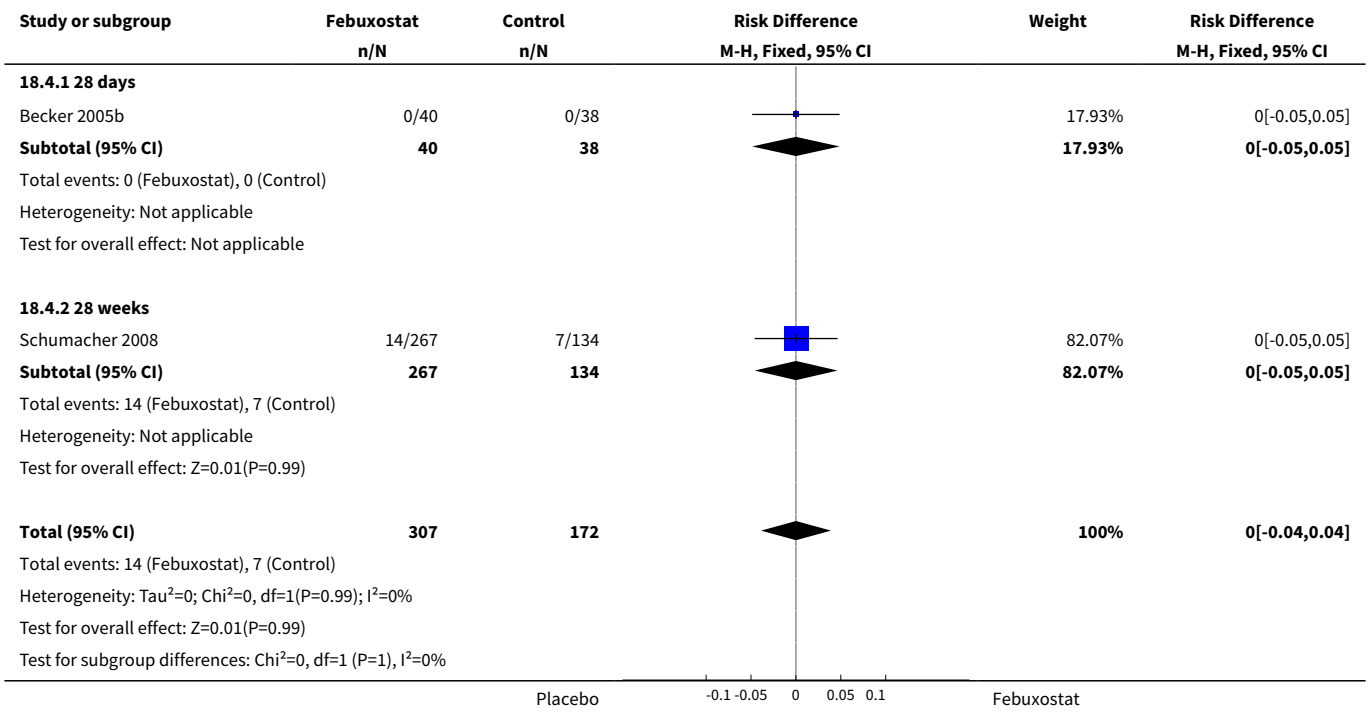


Analysis 18.3. Comparison 18 Adverse events - febuxostat 80 mg/day versus placebo, Outcome 3 Liver function test abnormalities.

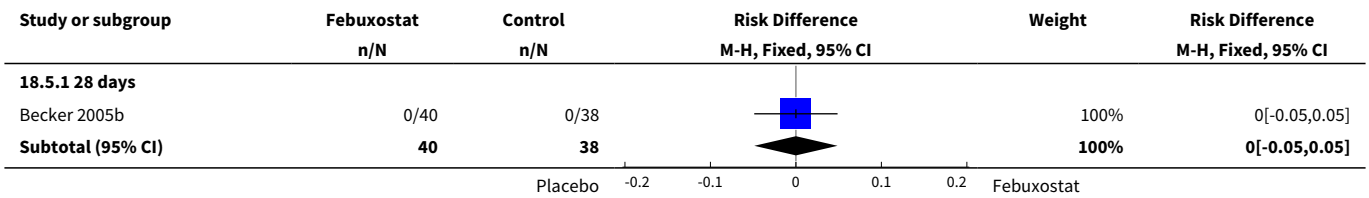


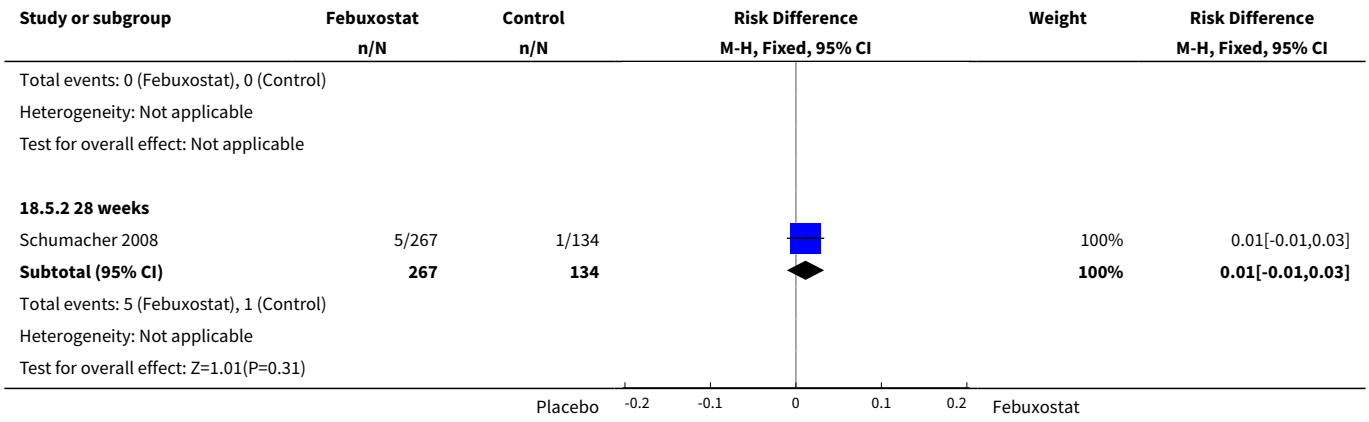


Analysis 18.4. Comparison 18 Adverse events - febuxostat 80 mg/day versus placebo, Outcome 4 Skin reaction.

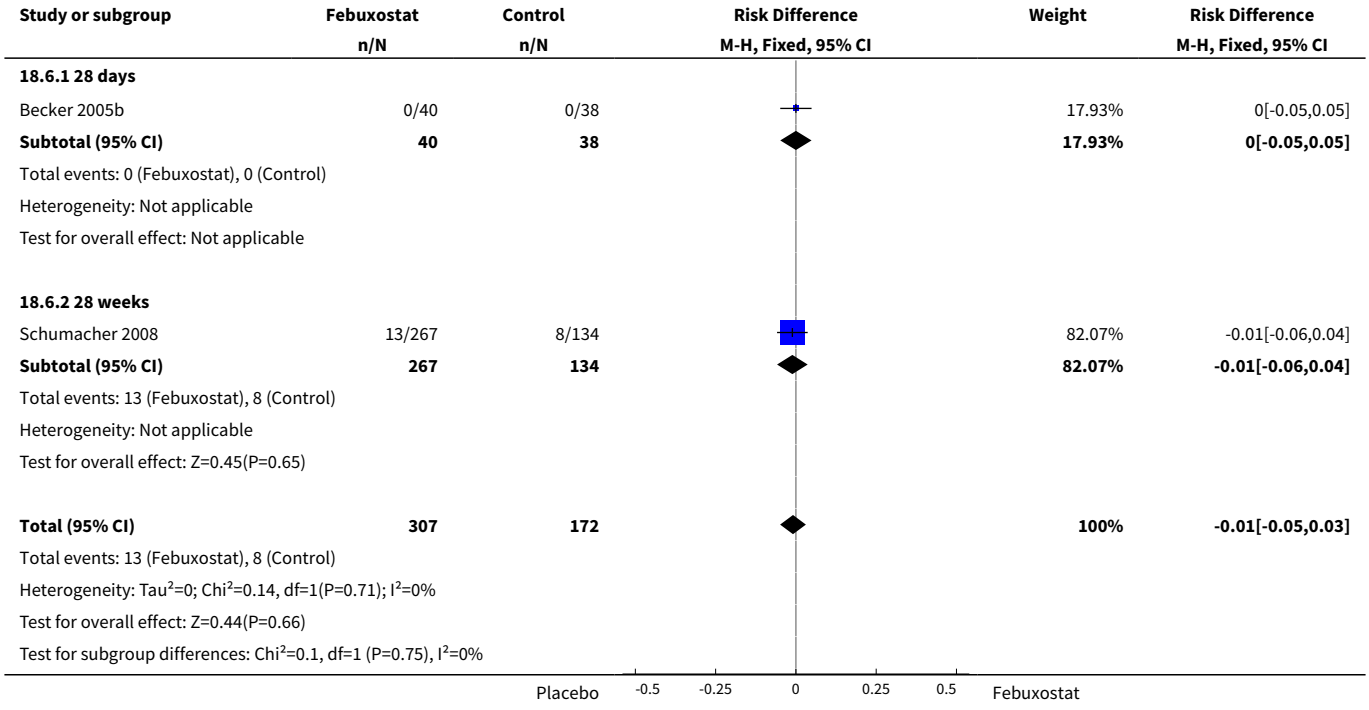


Analysis 18.5. Comparison 18 Adverse events - febuxostat 80 mg/day versus placebo, Outcome 5 Cardiovascular events (chest pain, coronary artery disease, myocardial infarction, atrial fibrillation).

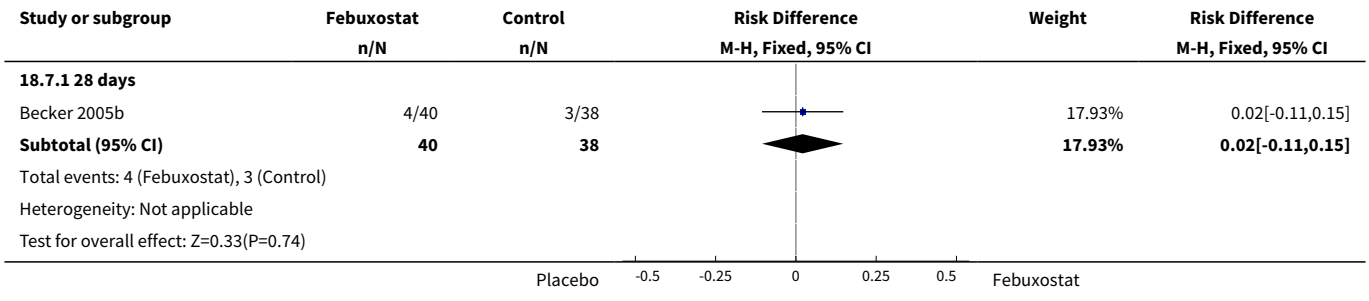


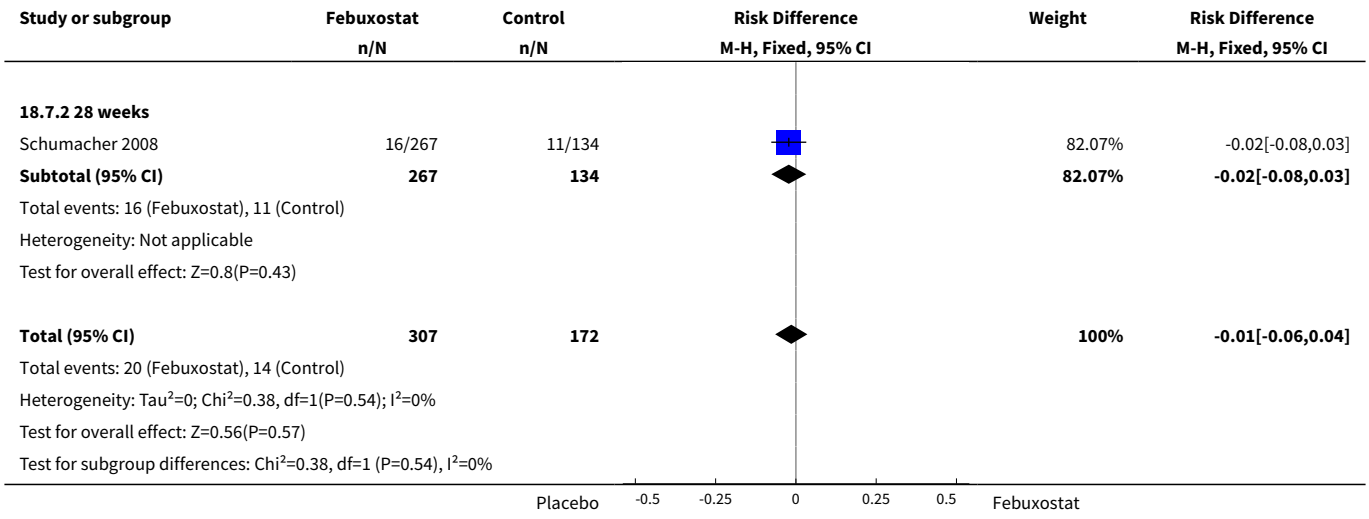


Analysis 18.6. Comparison 18 Adverse events - febuxostat 80 mg/day versus placebo, Outcome 6 Hypertension.



Analysis 18.7. Comparison 18 Adverse events - febuxostat 80 mg/day versus placebo, Outcome 7 Diarrhea.





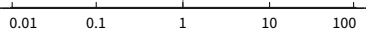
Comparison 19. Adverse events - febuxostat 120 mg/day versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 TOTAL	2	479	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.84, 1.10]
1.1 28 days	1	76	Risk Ratio (M-H, Fixed, 95% CI)	1.4 [0.49, 4.02]
1.2 28 weeks	1	403	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.82, 1.07]
2 Serious	2	479	Risk Ratio (M-H, Fixed, 95% CI)	2.68 [0.70, 10.20]
2.1 28 days	1	76	Risk Ratio (M-H, Fixed, 95% CI)	5.0 [0.25, 100.80]
2.2 28 weeks	1	403	Risk Ratio (M-H, Fixed, 95% CI)	2.24 [0.49, 10.23]
3 Liver function test abnormalities	2	479	Risk Ratio (M-H, Fixed, 95% CI)	1.81 [0.56, 5.86]
3.1 28 days	1	76	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.13, 71.40]
3.2 28 weeks	1	403	Risk Ratio (M-H, Fixed, 95% CI)	1.66 [0.46, 5.93]
4 Skin reaction	2	479	Risk Difference (M-H, Fixed, 95% CI)	0.01 [-0.03, 0.05]
4.1 28 days	1	76	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.05, 0.05]
4.2 28 weeks	1	403	Risk Difference (M-H, Fixed, 95% CI)	0.01 [-0.04, 0.06]
5 Cardiovascular events (chest pain, coronary artery disease, myocardial infarction, atrial fibrillation)	2		Risk Difference (M-H, Fixed, 95% CI)	Subtotals only
5.1 28 days	1	76	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.05, 0.05]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.2 28 weeks	1	403	Risk Difference (M-H, Fixed, 95% CI)	0.01 [-0.01, 0.03]
6 Hypertension	2		Risk Difference (M-H, Fixed, 95% CI)	Subtotals only
6.1 28 days	1	76	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.05, 0.05]
6.2 28 weeks	1	403	Risk Difference (M-H, Fixed, 95% CI)	-0.04 [-0.08, 0.01]
7 Diarrhea	2		Risk Difference (M-H, Fixed, 95% CI)	Subtotals only
7.1 28 days	1	76	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.12, 0.12]
7.2 28 weeks	1	403	Risk Difference (M-H, Fixed, 95% CI)	-0.01 [-0.07, 0.04]

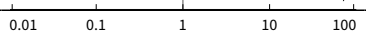
Analysis 19.1. Comparison 19 Adverse events - febuxostat 120 mg/day versus placebo, Outcome 1 TOTAL.

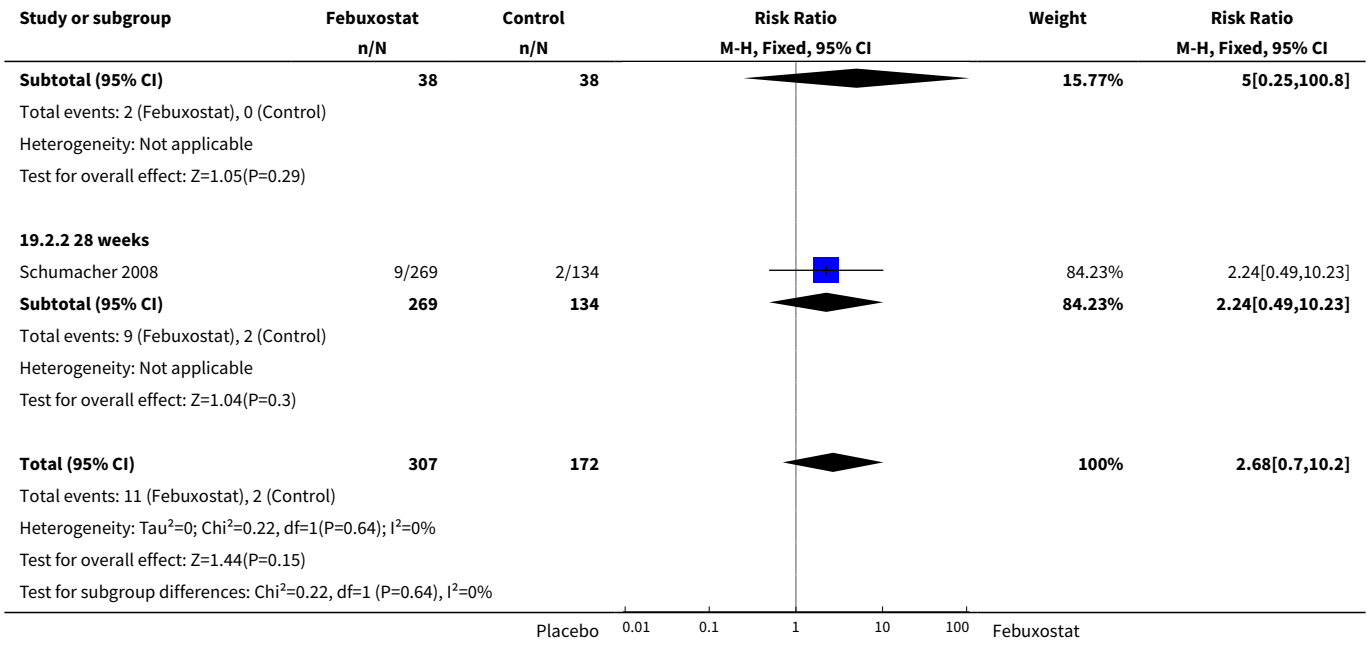
Study or subgroup	Febuxostat n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
19.1.1 28 days					
Becker 2005b	7/38	5/38		3.72%	1.4[0.49,4.02]
Subtotal (95% CI)	**38**	**38**		**3.72%**	**1.4[0.49,4.02]**
Total events: 7 (Febuxostat), 5 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.62(P=0.53)					
19.1.2 28 weeks					
Schumacher 2008	183/269	97/134		96.28%	0.94[0.82,1.07]
Subtotal (95% CI)	**269**	**134**		**96.28%**	**0.94[0.82,1.07]**
Total events: 183 (Febuxostat), 97 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.92(P=0.36)					
Total (95% CI)	**307**	**172**		**100%**	**0.96[0.84,1.1]**
Total events: 190 (Febuxostat), 102 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.57, df=1(P=0.45); I^2=0%					
Test for overall effect: Z=0.64(P=0.52)					
Test for subgroup differences: Chi^2=0.54, df=1 (P=0.46), I^2=0%					



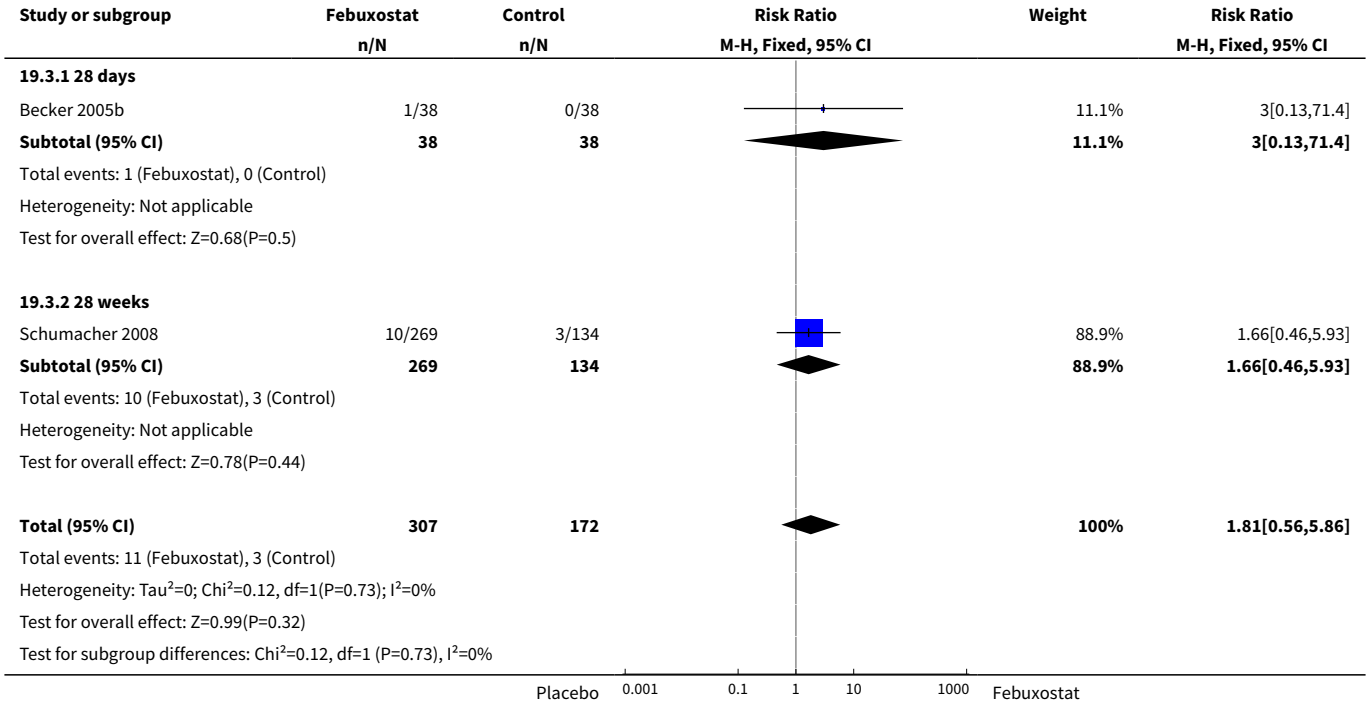
Analysis 19.2. Comparison 19 Adverse events - febuxostat 120 mg/day versus placebo, Outcome 2 Serious.

Study or subgroup	Febuxostat n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
19.2.1 28 days					
Becker 2005b	2/38	0/38		15.77%	5[0.25,100.8]



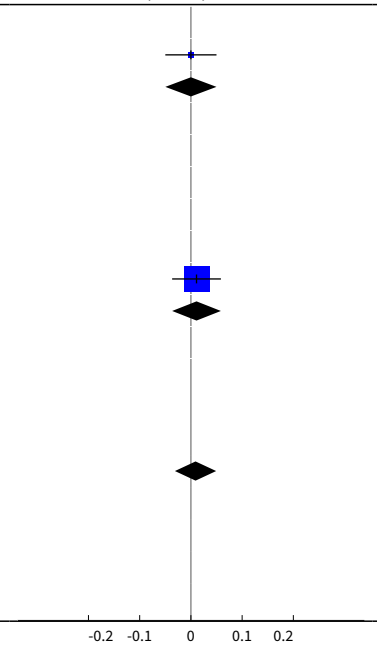


Analysis 19.3. Comparison 19 Adverse events - febuxostat 120 mg/ day versus placebo, Outcome 3 Liver function test abnormalities.



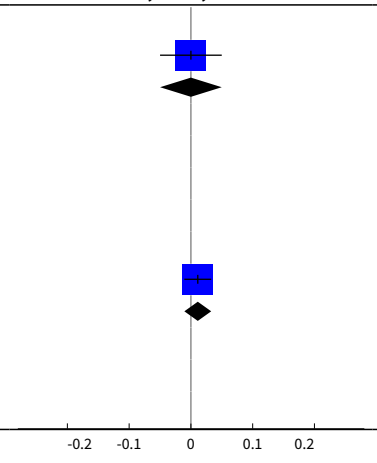
Analysis 19.4. Comparison 19 Adverse events - febuxostat 120 mg/day versus placebo, Outcome 4 Skin reaction.

Study or subgroup	Febuxostat n/N	Control n/N	Risk Difference M-H, Fixed, 95% CI	Weight	Risk Difference M-H, Fixed, 95% CI
19.4.1 28 days					
Becker 2005b	0/38	0/38		17.52%	0[-0.05,0.05]
Subtotal (95% CI)	**38**	**38**		**17.52%**	**0[-0.05,0.05]**
Total events: 0 (Febuxostat), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
19.4.2 28 weeks					
Schumacher 2008	17/269	7/134		82.48%	0.01[-0.04,0.06]
Subtotal (95% CI)	**269**	**134**		**82.48%**	**0.01[-0.04,0.06]**
Total events: 17 (Febuxostat), 7 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.45(P=0.65)					
Total (95% CI)	**307**	**172**		**100%**	**0.01[-0.03,0.05]**
Total events: 17 (Febuxostat), 7 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.13, df=1(P=0.72); I^2=0%					
Test for overall effect: Z=0.44(P=0.66)					
Test for subgroup differences: Chi^2=0.1, df=1 (P=0.76), I^2=0%					



Analysis 19.5. Comparison 19 Adverse events - febuxostat 120 mg/day versus placebo, Outcome 5 Cardiovascular events (chest pain, coronary artery disease, myocardial infarction, atrial fibrillation).

Study or subgroup	Febuxostat n/N	Control n/N	Risk Difference M-H, Fixed, 95% CI	Weight	Risk Difference M-H, Fixed, 95% CI
19.5.1 28 days					
Becker 2005b	0/38	0/38		100%	0[-0.05,0.05]
Subtotal (95% CI)	**38**	**38**		**100%**	**0[-0.05,0.05]**
Total events: 0 (Febuxostat), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
19.5.2 28 weeks					
Schumacher 2008	5/269	1/134		100%	0.01[-0.01,0.03]
Subtotal (95% CI)	**269**	**134**		**100%**	**0.01[-0.01,0.03]**
Total events: 5 (Febuxostat), 1 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1(P=0.32)					

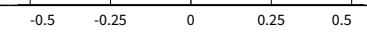


Analysis 19.6. Comparison 19 Adverse events - febuxostat 120 mg/day versus placebo, Outcome 6 Hypertension.

Study or subgroup	Febuxostat n/N	Control n/N	Risk Difference M-H, Fixed, 95% CI	Weight	Risk Difference M-H, Fixed, 95% CI
19.6.1 28 days					
Becker 2005b	0/38	0/38		100%	0[-0.05,0.05]
Subtotal (95% CI)	**38**	**38**		**100%**	**0[-0.05,0.05]**
Total events: 0 (Febuxostat), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
19.6.2 28 weeks					
Schumacher 2008	6/269	8/134		100%	-0.04[-0.08,0.01]
Subtotal (95% CI)	**269**	**134**		**100%**	**-0.04[-0.08,0.01]**
Total events: 6 (Febuxostat), 8 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.67(P=0.09)					

Analysis 19.7. Comparison 19 Adverse events - febuxostat 120 mg/day versus placebo, Outcome 7 Diarrhea.

Study or subgroup	Febuxostat n/N	Control n/N	Risk Difference M-H, Fixed, 95% CI	Weight	Risk Difference M-H, Fixed, 95% CI
19.7.1 28 days					
Becker 2005b	3/38	3/38		100%	0[-0.12,0.12]
Subtotal (95% CI)	**38**	**38**		**100%**	**0[-0.12,0.12]**
Total events: 3 (Febuxostat), 3 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
19.7.2 28 weeks					
Schumacher 2008	19/269	11/134		100%	-0.01[-0.07,0.04]
Subtotal (95% CI)	**269**	**134**		**100%**	**-0.01[-0.07,0.04]**
Total events: 19 (Febuxostat), 11 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.4(P=0.69)					



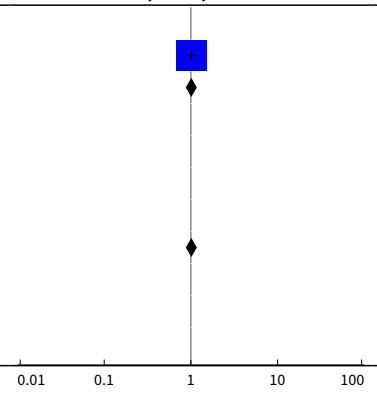
Comparison 20. Adverse events - febuxostat 240 mg/day versus placebo

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 TOTAL	1	268	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.87, 1.17]
1.1 28 weeks	1	268	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.87, 1.17]
2 Serious	1	268	Risk Ratio (M-H, Fixed, 95% CI)	2.5 [0.49, 12.66]
2.1 28 weeks	1	268	Risk Ratio (M-H, Fixed, 95% CI)	2.5 [0.49, 12.66]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Liver function test abnormalities	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 28 weeks	1	268	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.51, 7.83]
4 Skin reaction	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 28 weeks	1	268	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.30, 2.48]
5 Cardiovascular events (chest pain, coronary artery disease, myocardial infarction, atrial fibrillation)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 28 weeks	1	268	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.06, 15.82]
6 Hypertension	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 28 weeks	1	268	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.27, 2.10]
7 Diarrhea	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 28 weeks	1	268	Risk Ratio (M-H, Fixed, 95% CI)	1.64 [0.80, 3.33]

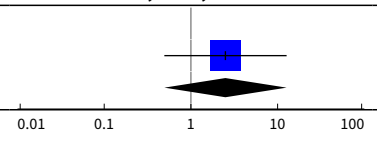
Analysis 20.1. Comparison 20 Adverse events - febuxostat 240 mg/day versus placebo, Outcome 1 TOTAL.

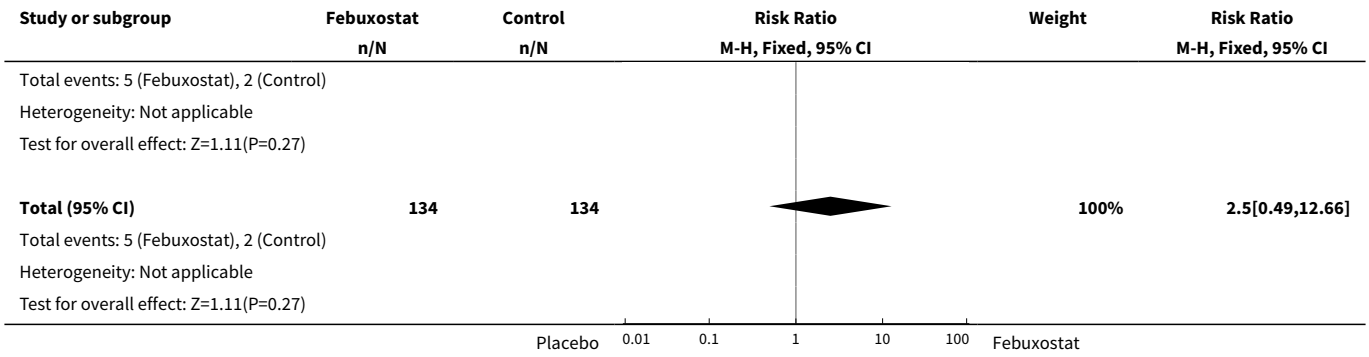
Study or subgroup	Febuxostat n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
20.1.1 28 weeks					
Schumacher 2008	98/134	97/134		100%	1.01[0.87,1.17]
Subtotal (95% CI)	**134**	**134**		**100%**	**1.01[0.87,1.17]**
Total events: 98 (Febuxostat), 97 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.14(P=0.89)					
Total (95% CI)	**134**	**134**		**100%**	**1.01[0.87,1.17]**
Total events: 98 (Febuxostat), 97 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.14(P=0.89)					



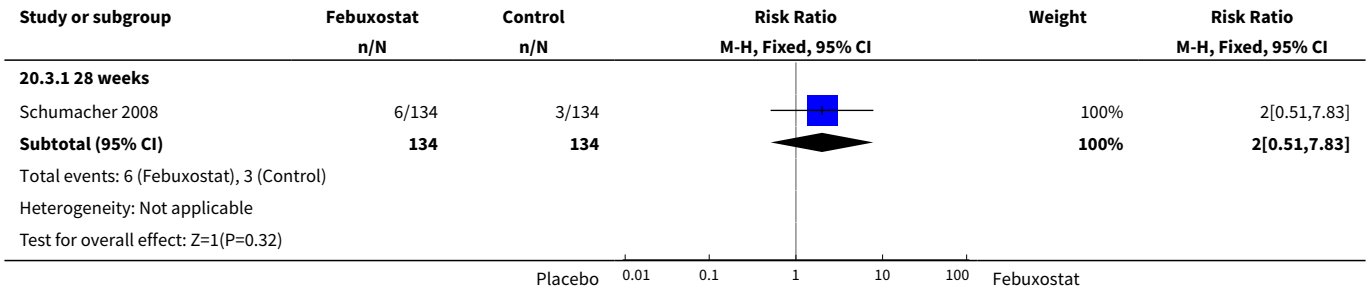
Analysis 20.2. Comparison 20 Adverse events - febuxostat 240 mg/day versus placebo, Outcome 2 Serious.

Study or subgroup	Febuxostat n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
20.2.1 28 weeks					
Schumacher 2008	5/134	2/134		100%	2.5[0.49,12.66]
Subtotal (95% CI)	**134**	**134**		**100%**	**2.5[0.49,12.66]**

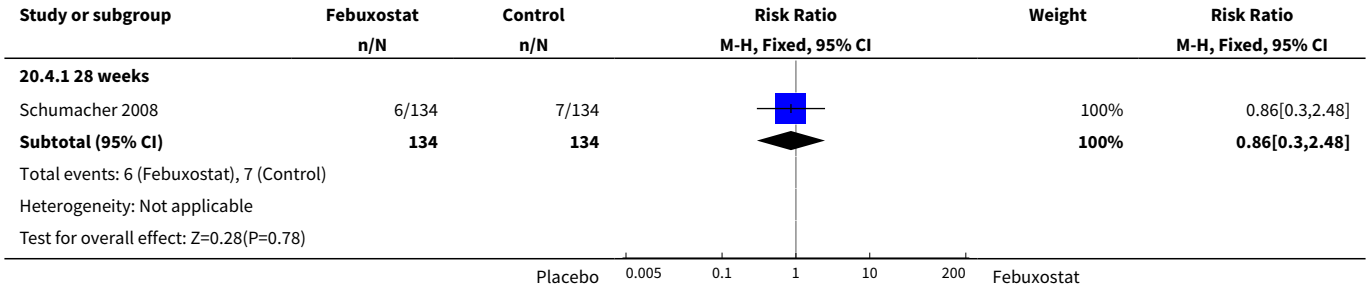




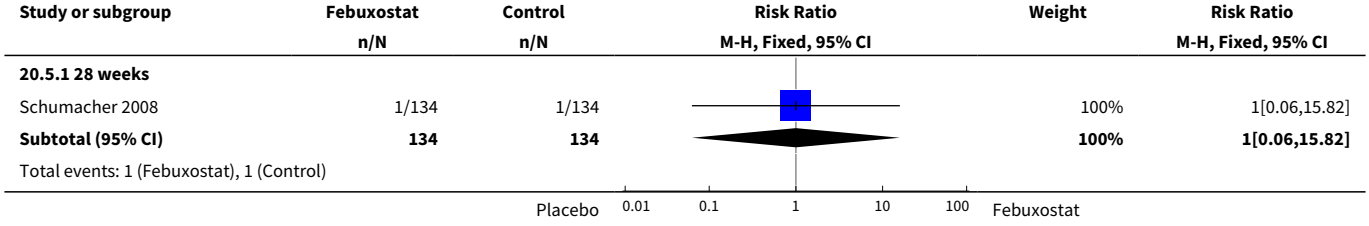
Analysis 20.3. Comparison 20 Adverse events - febuxostat 240 mg/day versus placebo, Outcome 3 Liver function test abnormalities.

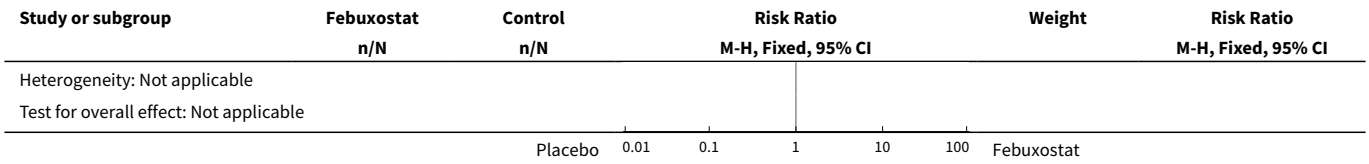


Analysis 20.4. Comparison 20 Adverse events - febuxostat 240 mg/day versus placebo, Outcome 4 Skin reaction.

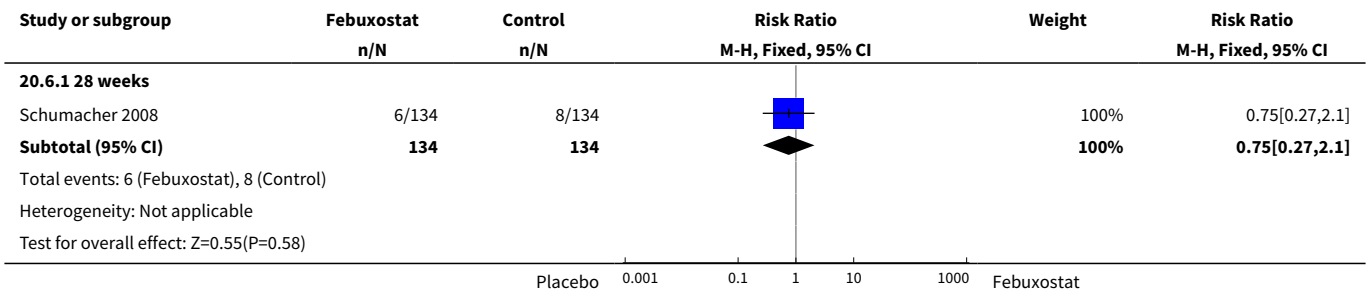


Analysis 20.5. Comparison 20 Adverse events - febuxostat 240 mg/day versus placebo, Outcome 5 Cardiovascular events (chest pain, coronary artery disease, myocardial infarction, atrial fibrillation).

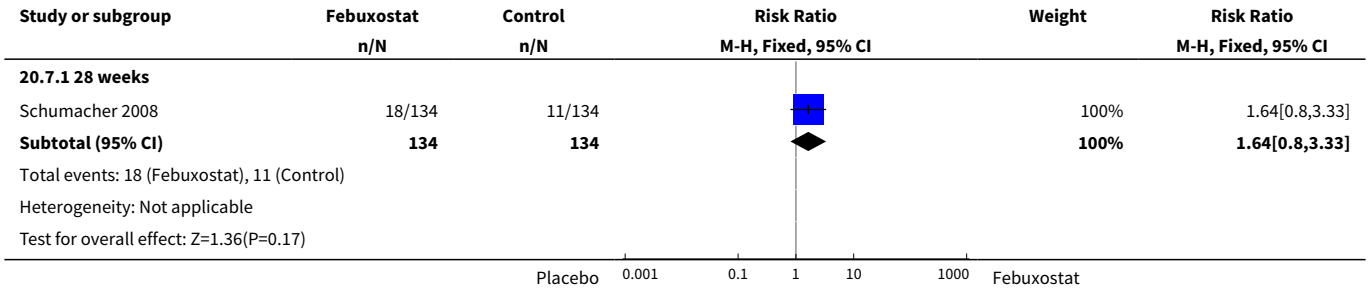




Analysis 20.6. Comparison 20 Adverse events - febuxostat 240 mg/day versus placebo, Outcome 6 Hypertension.



Analysis 20.7. Comparison 20 Adverse events - febuxostat 240 mg/day versus placebo, Outcome 7 Diarrhea.



Comparison 21. Adverse events - febuxostat 40 mg/day versus allopurinol 200 or 300 mg/day

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 TOTAL	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 24 weeks	1	1513	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.91, 1.08]
2 Serious	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 24 weeks	1	1513	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.35, 1.07]
3 Liver function test abnormalities	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 24 weeks	1	1213	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.53, 1.08]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Skin reaction	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 24 weeks	1	1513	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.54, 1.17]
5 Cardiovascular events (chest pain, coronary artery disease, myocardial infarction, atrial fibrillation)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 24 weeks	1	1513	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.55, 1.28]
6 Hypertension	1		Risk Difference (M-H, Fixed, 95% CI)	Subtotals only
6.1 24 weeks	1	1513	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.00, 0.00]
7 Diarrhea	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 24 weeks	1	1513	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.54, 1.15]

Analysis 21.1. Comparison 21 Adverse events - febuxostat 40 mg/day versus allopurinol 200 or 300 mg/day, Outcome 1 TOTAL.

Study or subgroup	Febuxostat n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
21.1.1 24 weeks					
Becker 2010	429/757	433/756		100%	0.99[0.91,1.08]
Subtotal (95% CI)	**757**	**756**		**100%**	**0.99[0.91,1.08]**
Total events: 429 (Febuxostat), 433 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.24(P=0.81)					

Allopurinol Febuxostat

Analysis 21.2. Comparison 21 Adverse events - febuxostat 40 mg/day versus allopurinol 200 or 300 mg/day, Outcome 2 Serious.

Study or subgroup	Febuxostat n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
21.2.1 24 weeks					
Becker 2010	19/757	31/756		100%	0.61[0.35,1.07]
Subtotal (95% CI)	**757**	**756**		**100%**	**0.61[0.35,1.07]**
Total events: 19 (Febuxostat), 31 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.71(P=0.09)					

Allopurinol Febuxostat

Analysis 21.3. Comparison 21 Adverse events - febuxostat 40 mg/day versus allopurinol 200 or 300 mg/day, Outcome 3 Liver function test abnormalities.

Study or subgroup	Febuxostat n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
21.3.1 24 weeks					
Becker 2010	63/757	50/456		100%	0.76[0.53,1.08]
Subtotal (95% CI)	**757**	**456**		**100%**	**0.76[0.53,1.08]**
Total events: 63 (Febuxostat), 50 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.53(P=0.13)					

Analysis 21.4. Comparison 21 Adverse events - febuxostat 40 mg/day versus allopurinol 200 or 300 mg/day, Outcome 4 Skin reaction.

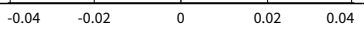
Study or subgroup	Febuxostat n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
21.4.1 24 weeks					
Becker 2010	44/757	55/756		100%	0.8[0.54,1.17]
Subtotal (95% CI)	**757**	**756**		**100%**	**0.8[0.54,1.17]**
Total events: 44 (Febuxostat), 55 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.15(P=0.25)					

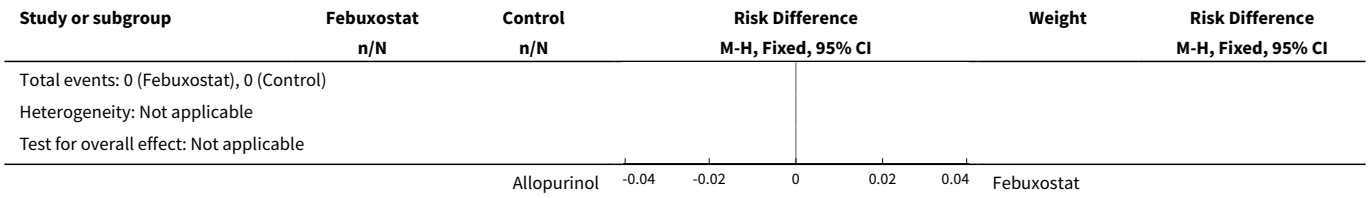
Analysis 21.5. Comparison 21 Adverse events - febuxostat 40 mg/day versus allopurinol 200 or 300 mg/day, Outcome 5 Cardiovascular events (chest pain, coronary artery disease, myocardial infarction, atrial fibrillation).

Study or subgroup	Febuxostat n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
21.5.1 24 weeks					
Becker 2010	38/757	45/756		100%	0.84[0.55,1.28]
Subtotal (95% CI)	**757**	**756**		**100%**	**0.84[0.55,1.28]**
Total events: 38 (Febuxostat), 45 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.8(P=0.43)					

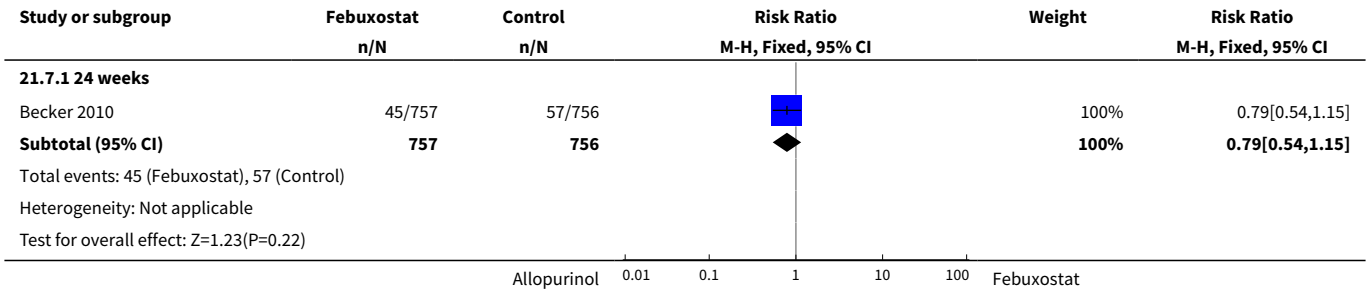
Analysis 21.6. Comparison 21 Adverse events - febuxostat 40 mg/day versus allopurinol 200 or 300 mg/day, Outcome 6 Hypertension.

Study or subgroup	Febuxostat n/N	Control n/N	Risk Difference M-H, Fixed, 95% CI	Weight	Risk Difference M-H, Fixed, 95% CI
21.6.1 24 weeks					
Becker 2010	0/757	0/756		100%	0[-0,0]
Subtotal (95% CI)	**757**	**756**		**100%**	**0[-0,0]**





Analysis 21.7. Comparison 21 Adverse events - febuxostat 40 mg/ day versus allopurinol 200 or 300 mg/day, Outcome 7 Diarrhea.



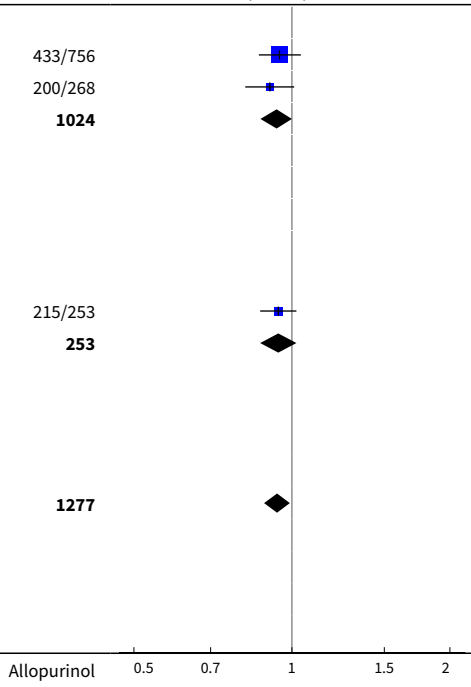
Comparison 22. Adverse events - febuxostat 80 mg/day versus allopurinol 200 or 300 mg/day

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 TOTAL	3	2556	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.89, 0.99]
1.1 24-28 weeks	2	2047	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.87, 1.00]
1.2 52 weeks	1	509	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.87, 1.02]
2 Serious	3	2556	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.55, 1.42]
2.1 24-28 weeks	2	2047	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.65, 1.65]
2.2 52 weeks	1	509	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.28, 1.18]
3 Liver function test abnormali-ties	3	2556	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.76, 1.39]
3.1 24-28 weeks	2	2047	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.77, 1.47]
3.2 52 weeks	1	509	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.34, 1.92]
4 Skin reaction	3	2556	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.56, 1.09]
4.1 24-28 weeks	2	2047	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.58, 1.14]
4.2 52 weeks	1	509	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.03, 2.20]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5 Cardiovascular events (chest pain, coronary artery disease, myocardial infarction, atrial fibrillation)	3	2556	Risk Difference (M-H, Fixed, 95% CI)	-0.00 [-0.02, 0.01]
5.1 24-28 weeks	2	2047	Risk Difference (M-H, Fixed, 95% CI)	-0.00 [-0.02, 0.01]
5.2 52 weeks	1	509	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.01, 0.01]
6 Hypertension	3	2556	Risk Ratio (M-H, Fixed, 95% CI)	4.35 [1.25, 15.09]
6.1 24-28 weeks	2	2047	Risk Ratio (M-H, Fixed, 95% CI)	4.35 [1.25, 15.09]
6.2 52 weeks	1	509	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Diarrhea	3	2556	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.64, 1.18]
7.1 24-28 weeks	2	2047	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.62, 1.18]
7.2 52 weeks	1	509	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.38, 2.59]

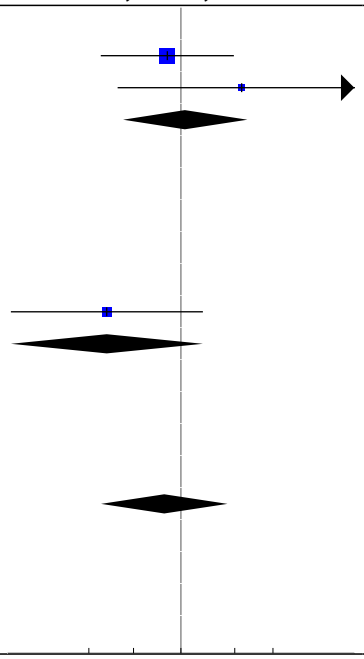
Analysis 22.1. Comparison 22 Adverse events - febuxostat 80 mg/day versus allopurinol 200 or 300 mg/day, Outcome 1 TOTAL.

Study or subgroup	Febuxostat n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
22.1.1 24-28 weeks					
Becker 2010	410/756	433/756		51.01%	0.95[0.87,1.04]
Schumacher 2008	181/267	200/268		23.52%	0.91[0.82,1.01]
Subtotal (95% CI)	**1023**	**1024**		**74.52%**	**0.93[0.87,1]**
Total events: 591 (Febuxostat), 633 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.35, df=1(P=0.56); I^2=0%					
Test for overall effect: Z=1.88(P=0.06)					
22.1.2 52 weeks					
Becker 2005a	205/256	215/253		25.48%	0.94[0.87,1.02]
Subtotal (95% CI)	**256**	**253**		**25.48%**	**0.94[0.87,1.02]**
Total events: 205 (Febuxostat), 215 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.45(P=0.15)					
Total (95% CI)	**1279**	**1277**		**100%**	**0.94[0.89,0.99]**
Total events: 796 (Febuxostat), 848 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.39, df=2(P=0.82); I^2=0%					
Test for overall effect: Z=2.28(P=0.02)					
Test for subgroup differences: Chi^2=0.02, df=1 (P=0.88), I^2=0%					



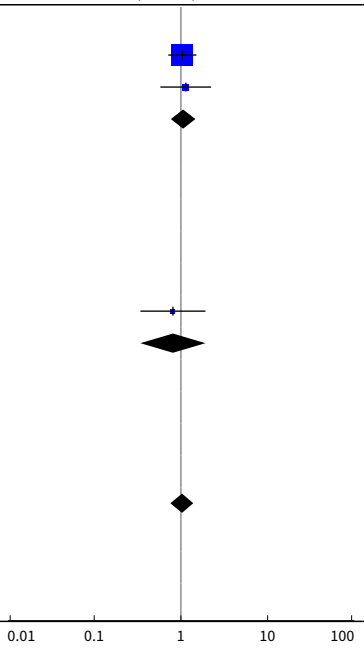
Analysis 22.2. Comparison 22 Adverse events - febuxostat 80 mg/day versus allopurinol 200 or 300 mg/day, Outcome 2 Serious.

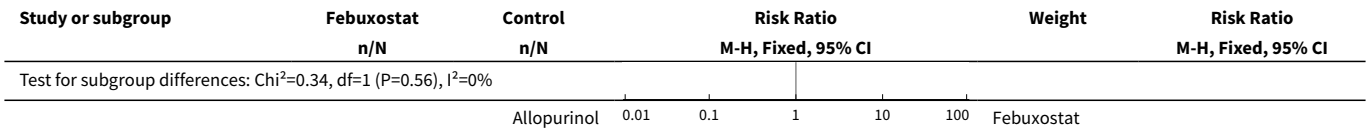
Study or subgroup	Febuxostat n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
22.2.1 24-28 weeks					
Becker 2010	28/756	31/756		48.48%	0.9[0.55,1.49]
Schumacher 2008	11/267	7/268		20.83%	1.58[0.62,4.01]
Subtotal (95% CI)	**1023**	**1024**		**69.32%**	**1.03[0.65,1.65]**
Total events: 39 (Febuxostat), 38 (Control)					
Heterogeneity: Tau^2=0.01; Chi^2=1.07, df=1(P=0.3); I^2=6.2%					
Test for overall effect: Z=0.14(P=0.89)					
22.2.2 52 weeks					
Becker 2005a	11/256	19/253		30.68%	0.57[0.28,1.18]
Subtotal (95% CI)	**256**	**253**		**30.68%**	**0.57[0.28,1.18]**
Total events: 11 (Febuxostat), 19 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.52(P=0.13)					
Total (95% CI)	**1279**	**1277**		**100%**	**0.88[0.55,1.42]**
Total events: 50 (Febuxostat), 57 (Control)					
Heterogeneity: Tau^2=0.06; Chi^2=2.88, df=2(P=0.24); I^2=30.55%					
Test for overall effect: Z=0.52(P=0.6)					
Test for subgroup differences: Chi^2=1.81, df=1 (P=0.18), I^2=44.86%					



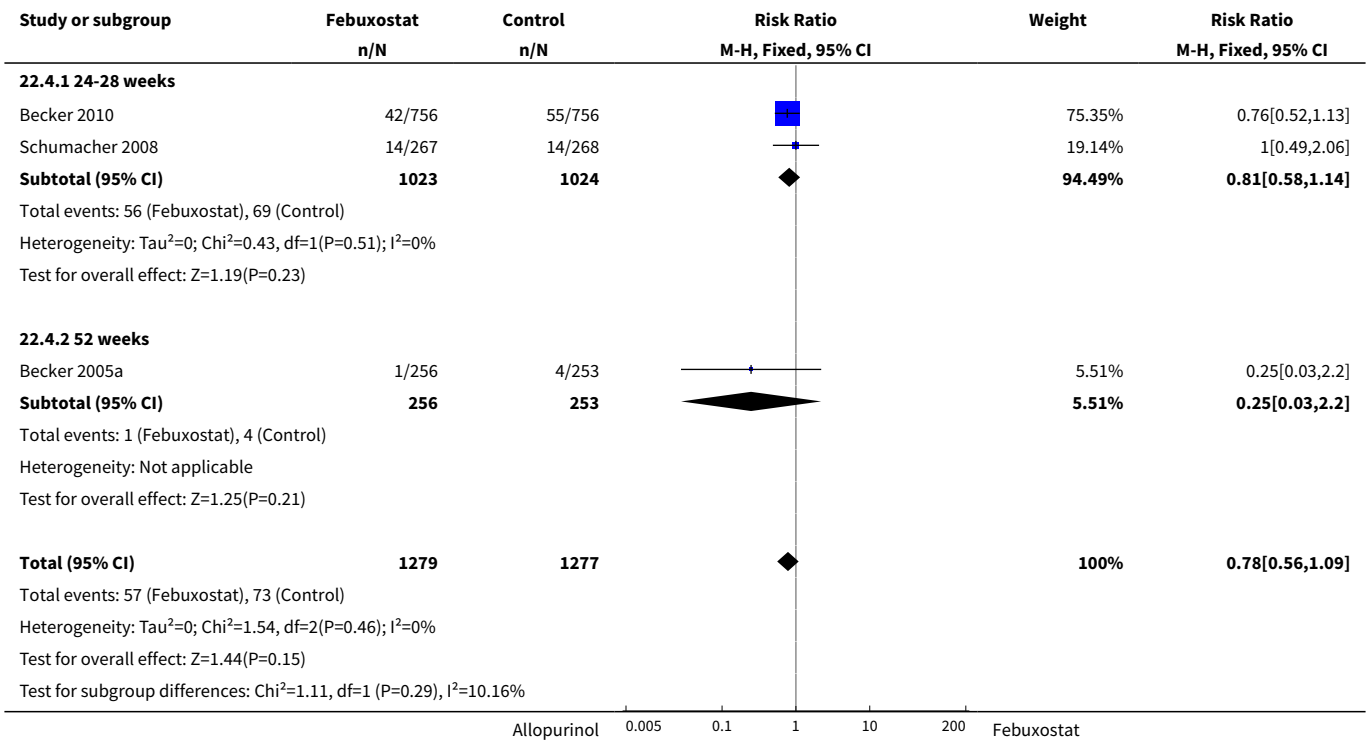
Analysis 22.3. Comparison 22 Adverse events - febuxostat 80 mg/day versus allopurinol 200 or 300 mg/day, Outcome 3 Liver function test abnormalities.

Study or subgroup	Febuxostat n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
22.3.1 24-28 weeks					
Becker 2010	52/756	50/756		65.76%	1.04[0.71,1.51]
Schumacher 2008	17/267	15/268		19.69%	1.14[0.58,2.23]
Subtotal (95% CI)	**1023**	**1024**		**85.45%**	**1.06[0.77,1.47]**
Total events: 69 (Febuxostat), 65 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.05, df=1(P=0.82); I^2=0%					
Test for overall effect: Z=0.36(P=0.72)					
22.3.2 52 weeks					
Becker 2005a	9/256	11/253		14.55%	0.81[0.34,1.92]
Subtotal (95% CI)	**256**	**253**		**14.55%**	**0.81[0.34,1.92]**
Total events: 9 (Febuxostat), 11 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.48(P=0.63)					
Total (95% CI)	**1279**	**1277**		**100%**	**1.03[0.76,1.39]**
Total events: 78 (Febuxostat), 76 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.39, df=2(P=0.82); I^2=0%					
Test for overall effect: Z=0.16(P=0.87)					

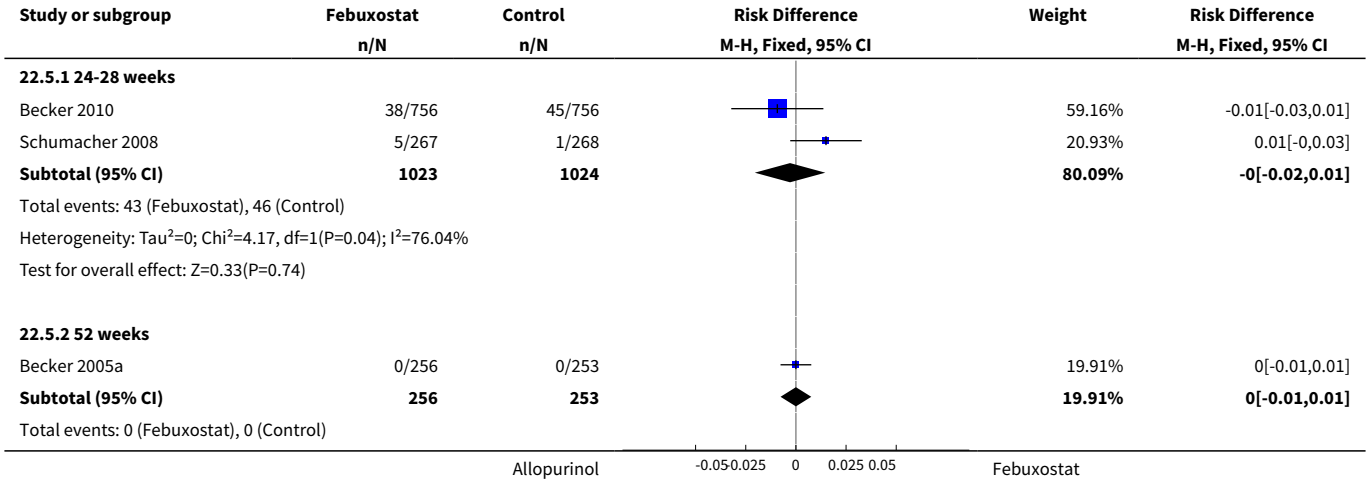


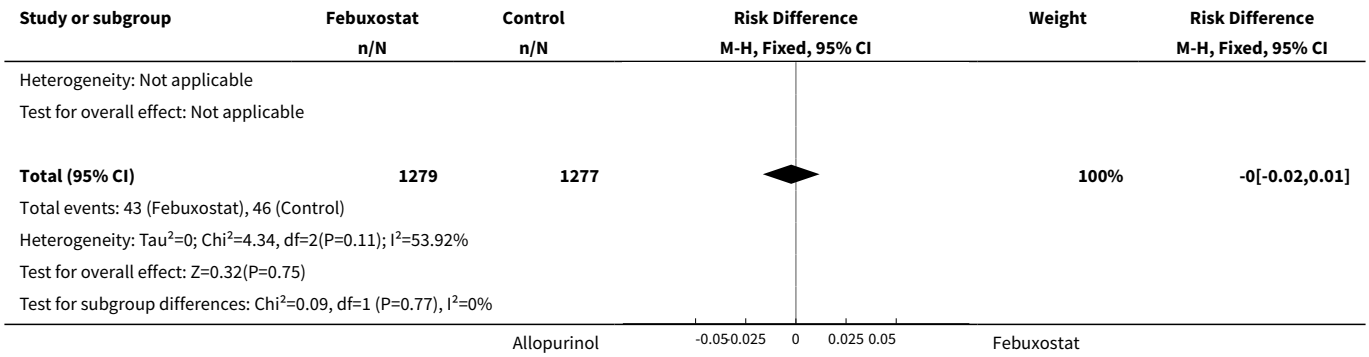


Analysis 22.4. Comparison 22 Adverse events - febuxostat 80 mg/ day versus allopurinol 200 or 300 mg/day, Outcome 4 Skin reaction.

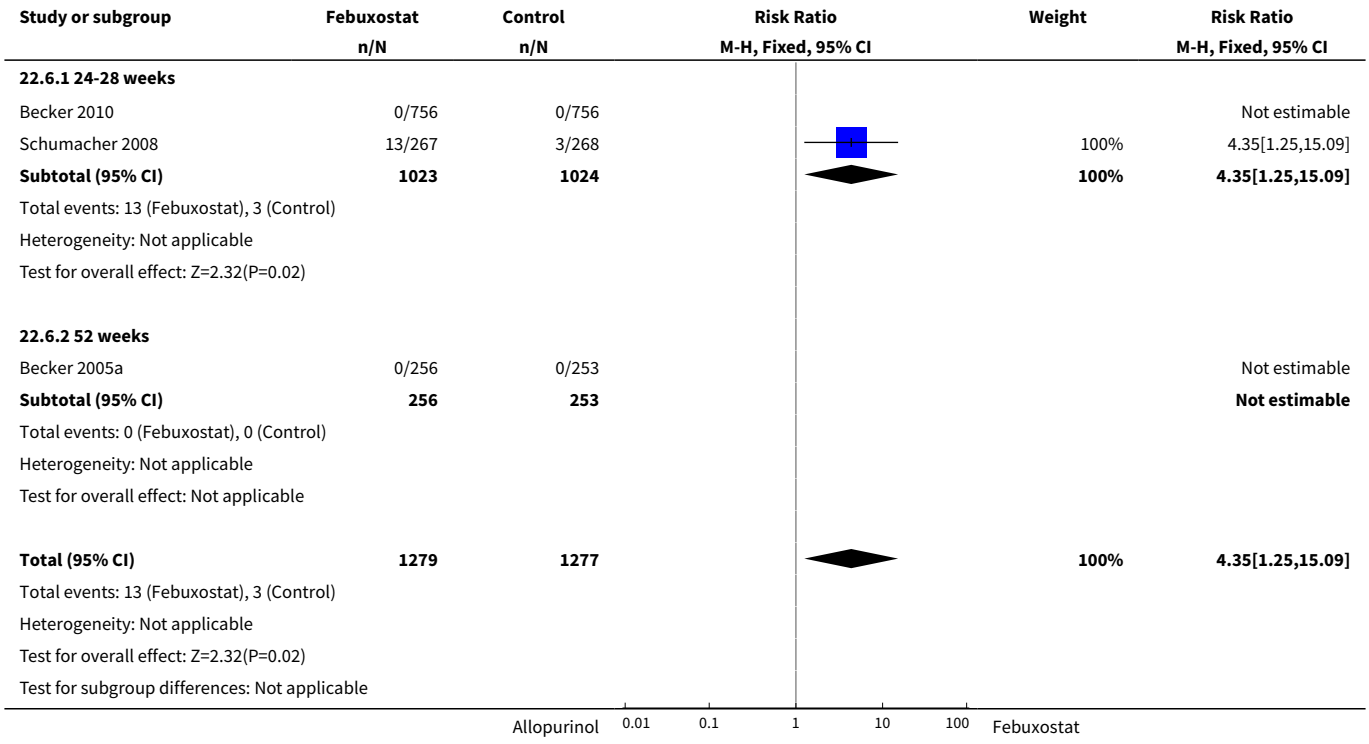


Analysis 22.5. Comparison 22 Adverse events - febuxostat 80 mg/day versus allopurinol 200 or 300 mg/day, Outcome 5 Cardiovascular events (chest pain, coronary artery disease, myocardial infarction, atrial fibrillation).

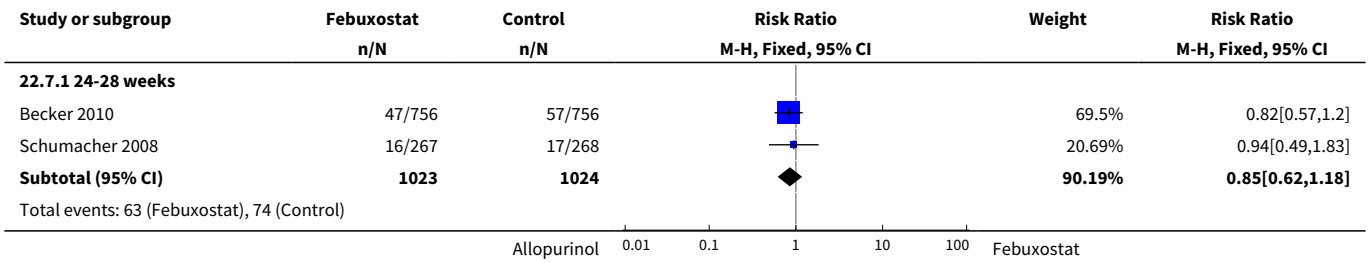


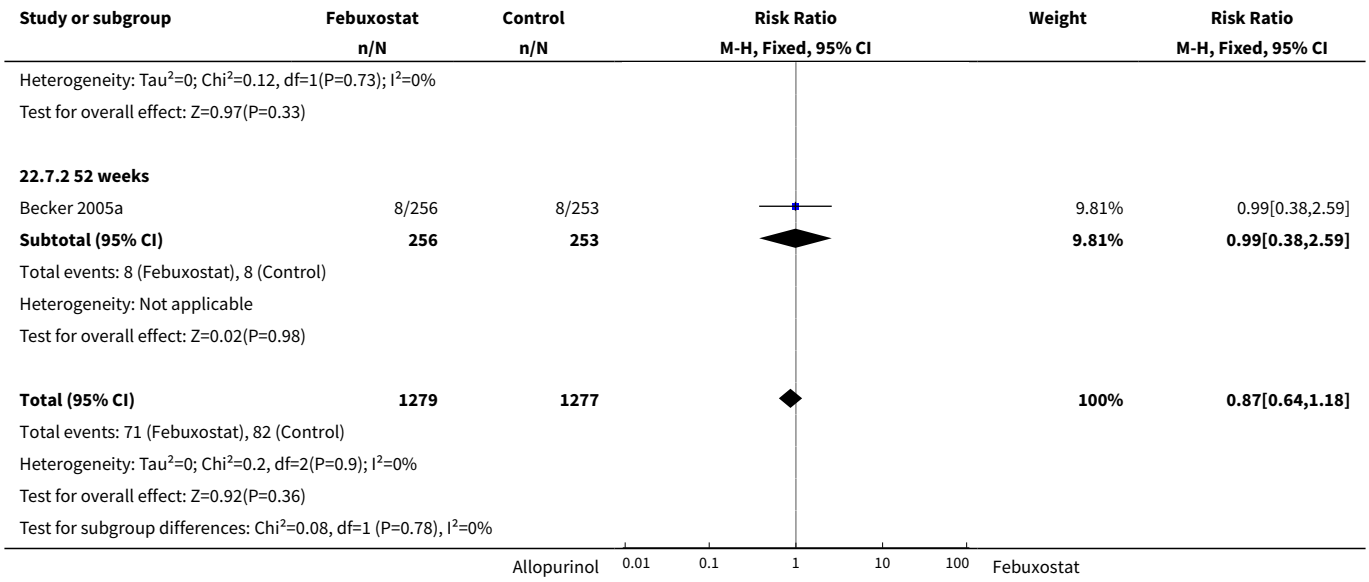


Analysis 22.6. Comparison 22 Adverse events - febuxostat 80 mg/ day versus allopurinol 200 or 300 mg/day, Outcome 6 Hypertension.



Analysis 22.7. Comparison 22 Adverse events - febuxostat 80 mg/ day versus allopurinol 200 or 300 mg/day, Outcome 7 Diarrhea.





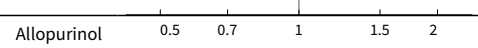
Comparison 23. Adverse events - febuxostat 120 mg/day versus allopurinol 300 mg/day

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 TOTAL	2	1041	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.84, 0.96]
1.1 28 weeks	1	537	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.82, 1.02]
1.2 52 weeks	1	504	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.81, 0.97]
2 Serious	2	1041	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.70, 1.93]
2.1 28 weeks	1	537	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [0.48, 3.39]
2.2 52 weeks	1	504	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.61, 2.02]
3 Liver function test abnormalities	2	1041	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.51, 1.53]
3.1 28 weeks	1	537	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.30, 1.45]
3.2 52 weeks	1	504	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.54, 2.61]
4 Skin reaction	2	1041	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.53, 1.89]
4.1 28 weeks	1	537	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.61, 2.40]
4.2 52 weeks	1	504	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.03, 2.24]
5 Cardiovascular events (chest pain, coronary artery disease, myocardial infarction, atrial fibrillation)	2	1041	Risk Difference (M-H, Fixed, 95% CI)	0.01 [-0.00, 0.02]

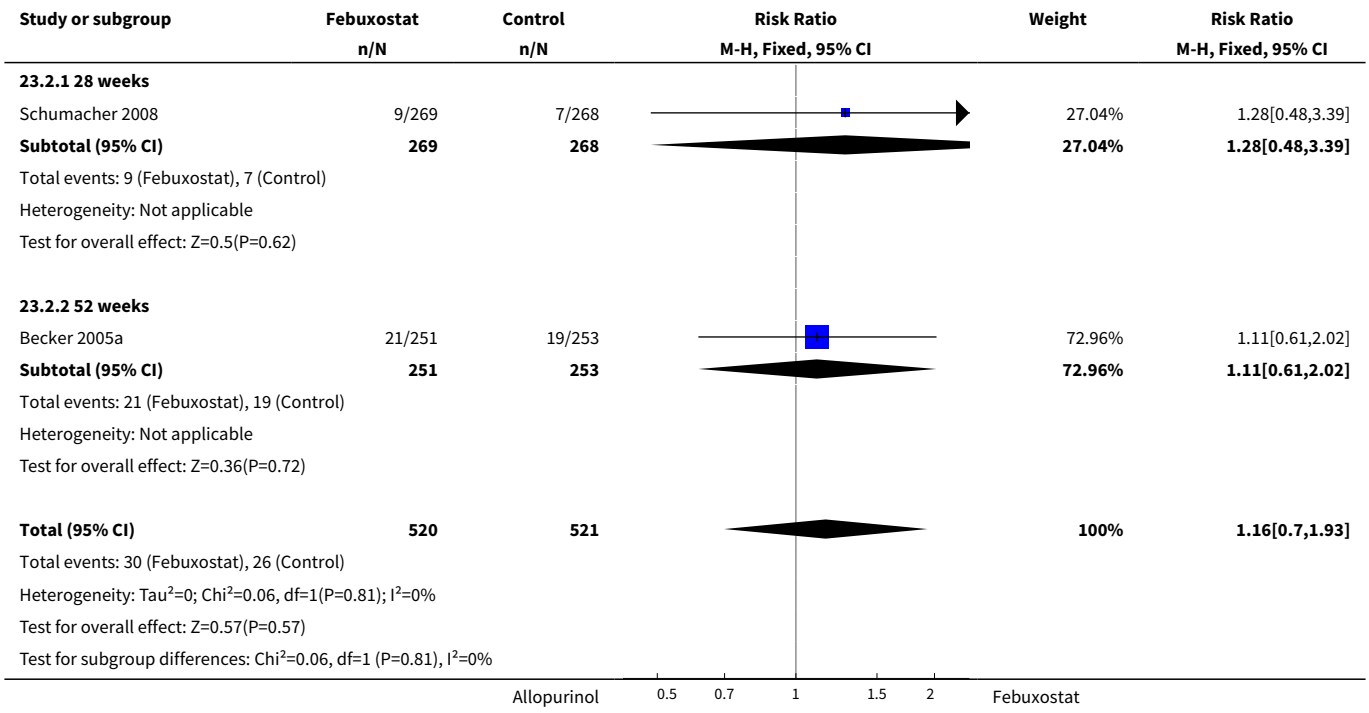
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
5.1 28 weeks	1	537	Risk Difference (M-H, Fixed, 95% CI)	0.01 [-0.00, 0.03]
5.2 52 weeks	1	504	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.01, 0.01]
6 Hypertension	2	1041	Risk Difference (M-H, Fixed, 95% CI)	0.01 [-0.01, 0.02]
6.1 28 weeks	1	537	Risk Difference (M-H, Fixed, 95% CI)	0.01 [-0.01, 0.03]
6.2 52 weeks	1	504	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.01, 0.01]
7 Diarrhea	2	1041	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.61, 1.77]
7.1 28 weeks	1	537	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.59, 2.10]
7.2 52 weeks	1	504	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.32, 2.40]

Analysis 23.1. Comparison 23 Adverse events - febuxostat 120 mg/day versus allopurinol 300 mg/day, Outcome 1 TOTAL.

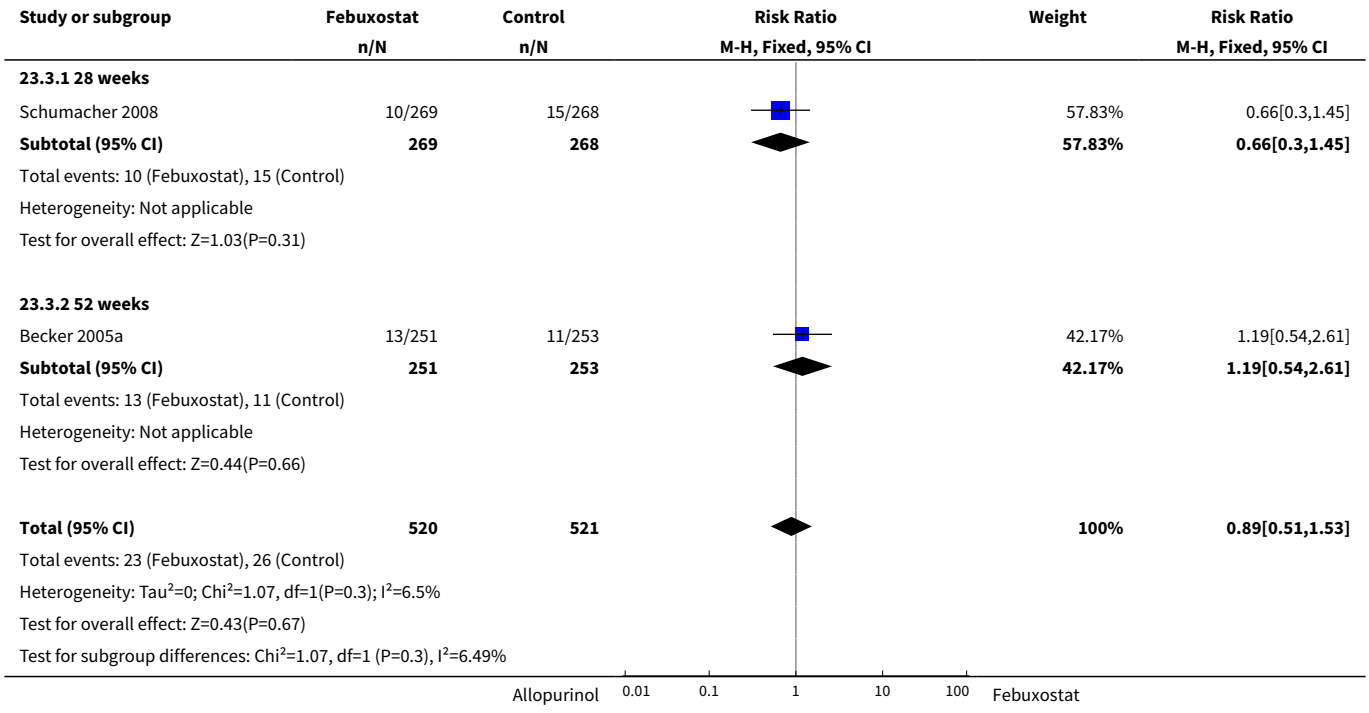
Study or subgroup	Febuxostat n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
23.1.1 28 weeks					
Schumacher 2008	183/269	200/268		48.34%	0.91[0.82,1.02]
Subtotal (95% CI)	**269**	**268**		**48.34%**	**0.91[0.82,1.02]**
Total events: 183 (Febuxostat), 200 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.69(P=0.09)					
23.1.2 52 weeks					
Becker 2005a	189/251	215/253		51.66%	0.89[0.81,0.97]
Subtotal (95% CI)	**251**	**253**		**51.66%**	**0.89[0.81,0.97]**
Total events: 189 (Febuxostat), 215 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.7(P=0.01)					
Total (95% CI)	**520**	**521**		**100%**	**0.9[0.84,0.96]**
Total events: 372 (Febuxostat), 415 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.17, df=1(P=0.68); I^2=0%					
Test for overall effect: Z=3.04(P=0)					
Test for subgroup differences: Chi^2=0.16, df=1 (P=0.69), I^2=0%					



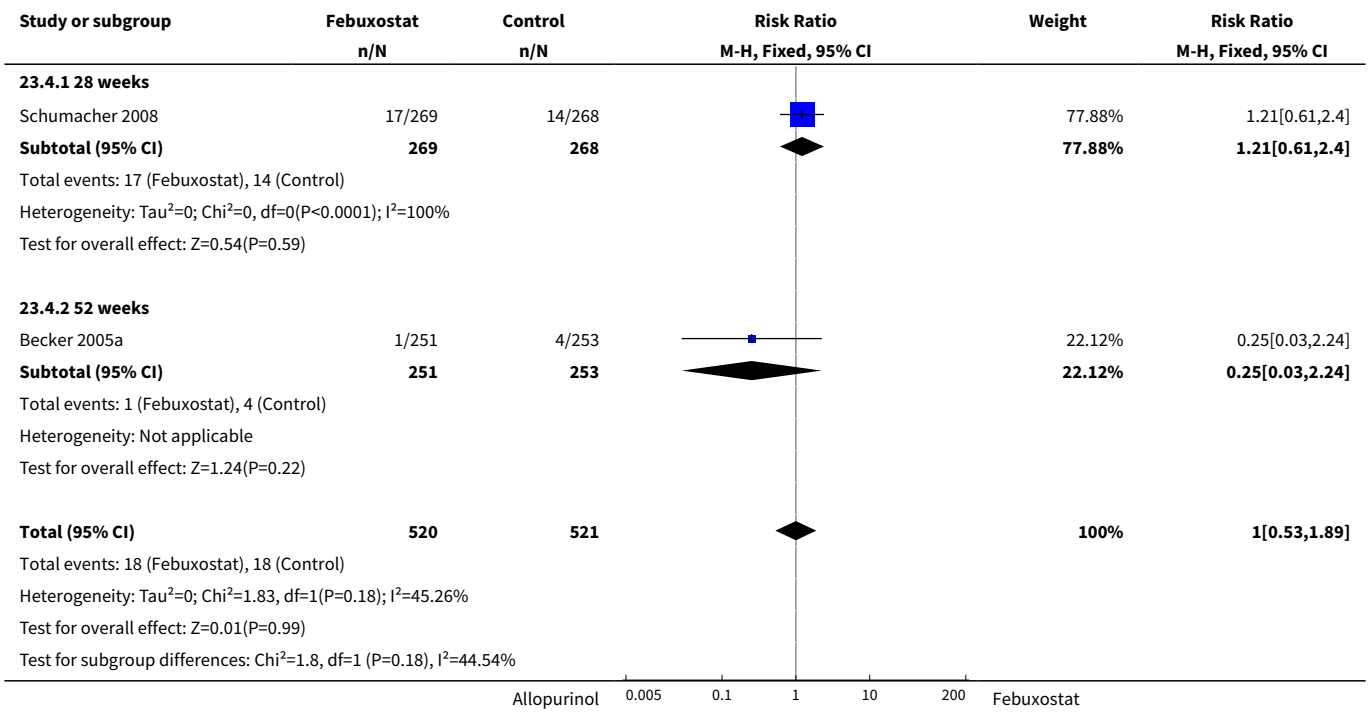
Analysis 23.2. Comparison 23 Adverse events - febuxostat 120 mg/day versus allopurinol 300 mg/day, Outcome 2 Serious.



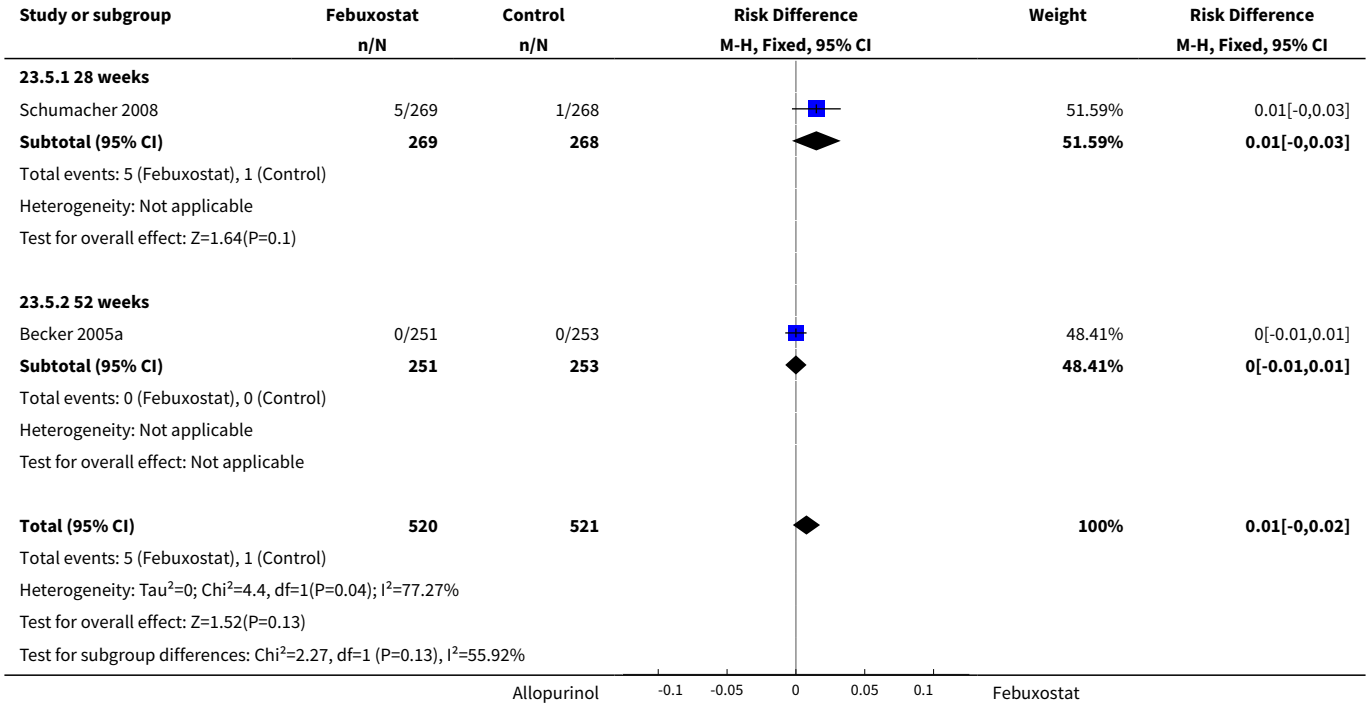
Analysis 23.3. Comparison 23 Adverse events - febuxostat 120 mg/day versus allopurinol 300 mg/day, Outcome 3 Liver function test abnormalities.



Analysis 23.4. Comparison 23 Adverse events - febuxostat 120 mg/day versus allopurinol 300 mg/day, Outcome 4 Skin reaction.

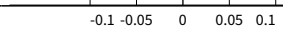


Analysis 23.5. Comparison 23 Adverse events - febuxostat 120 mg/day versus allopurinol 300 mg/day, Outcome 5 Cardiovascular events (chest pain, coronary artery disease, myocardial infarction, atrial fibrillation).



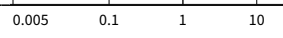
Analysis 23.6. Comparison 23 Adverse events - febuxostat 120 mg/day versus allopurinol 300 mg/day, Outcome 6 Hypertension.

Study or subgroup	Febuxostat n/N	Control n/N	Risk Difference M-H, Fixed, 95% CI	Weight	Risk Difference M-H, Fixed, 95% CI
23.6.1 28 weeks					
Schumacher 2008	6/269	3/268		51.59%	0.01[-0.01,0.03]
Subtotal (95% CI)	**269**	**268**		**51.59%**	**0.01[-0.01,0.03]**
Total events: 6 (Febuxostat), 3 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1(P=0.32)					
23.6.2 52 weeks					
Becker 2005a	0/251	0/253		48.41%	0[-0.01,0.01]
Subtotal (95% CI)	**251**	**253**		**48.41%**	**0[-0.01,0.01]**
Total events: 0 (Febuxostat), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**520**	**521**		**100%**	**0.01[-0.01,0.02]**
Total events: 6 (Febuxostat), 3 (Control)					
Heterogeneity: Tau^2=0; Chi^2=2.34, df=1(P=0.13); I^2=57.32%					
Test for overall effect: Z=0.95(P=0.34)					
Test for subgroup differences: Chi^2=0.89, df=1 (P=0.34), I^2=0%					



Analysis 23.7. Comparison 23 Adverse events - febuxostat 120 mg/day versus allopurinol 300 mg/day, Outcome 7 Diarrhea.

Study or subgroup	Febuxostat n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
23.7.1 28 weeks					
Schumacher 2008	19/269	17/268		68.13%	1.11[0.59,2.1]
Subtotal (95% CI)	**269**	**268**		**68.13%**	**1.11[0.59,2.1]**
Total events: 19 (Febuxostat), 17 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.33(P=0.74)					
23.7.2 52 weeks					
Becker 2005a	7/251	8/253		31.87%	0.88[0.32,2.4]
Subtotal (95% CI)	**251**	**253**		**31.87%**	**0.88[0.32,2.4]**
Total events: 7 (Febuxostat), 8 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.25(P=0.81)					
Total (95% CI)	**520**	**521**		**100%**	**1.04[0.61,1.77]**
Total events: 26 (Febuxostat), 25 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.15, df=1(P=0.7); I^2=0%					
Test for overall effect: Z=0.14(P=0.89)					
Test for subgroup differences: Chi^2=0.15, df=1 (P=0.7), I^2=0%					

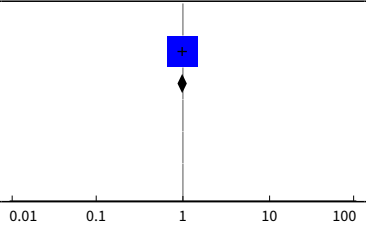


Comparison 24. Adverse events - febuxostat 240 mg/day versus allopurinol 300 mg/day

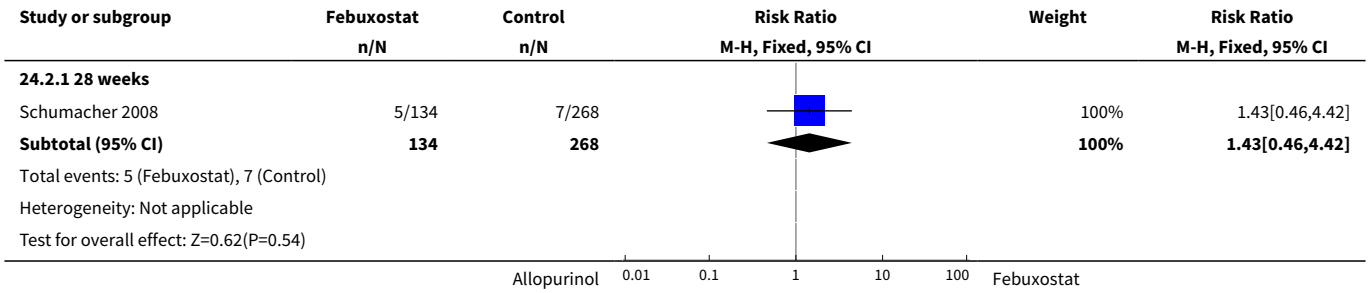
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 TOTAL	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 28 weeks	1	402	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.87, 1.11]
2 Serious	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 28 weeks	1	402	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [0.46, 4.42]
3 Liver function test abnormalities	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 28 weeks	1	402	Risk Ratio (M-H, Fixed, 95% CI)	0.8 [0.32, 2.02]
4 Skin reaction	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 28 weeks	1	402	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.34, 2.18]
5 Cardiovascular events (chest pain, coronary artery disease, myocardial infarction, atrial fibrillation)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 28 weeks	1	402	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.13, 31.73]
6 Hypertension	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 28 weeks	1	402	Risk Ratio (M-H, Fixed, 95% CI)	4.0 [1.02, 15.75]
7 Diarrhea	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 28 weeks	1	402	Risk Ratio (M-H, Fixed, 95% CI)	2.12 [1.13, 3.97]

Analysis 24.1. Comparison 24 Adverse events - febuxostat 240 mg/day versus allopurinol 300 mg/day, Outcome 1 TOTAL.

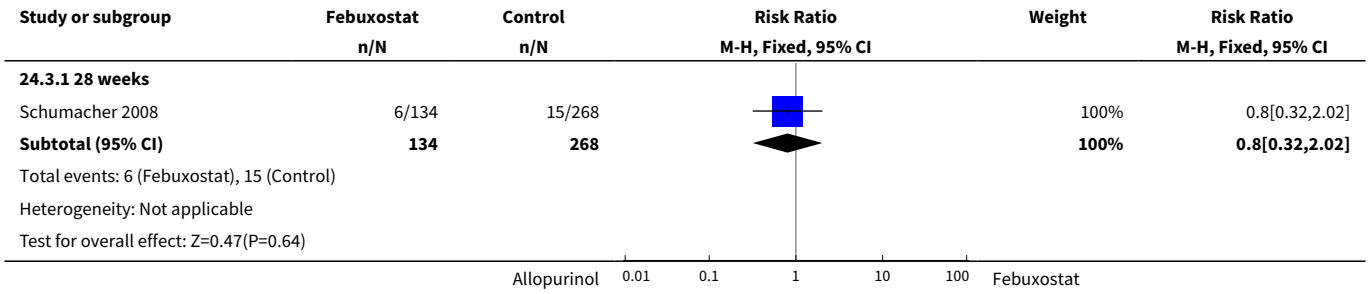
Study or subgroup	Febuxostat n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
24.1.1 28 weeks					
Schumacher 2008	98/134	200/268		100%	0.98[0.87,1.11]
Subtotal (95% CI)	**134**	**268**		**100%**	**0.98[0.87,1.11]**
Total events: 98 (Febuxostat), 200 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=0.32(P=0.75)					



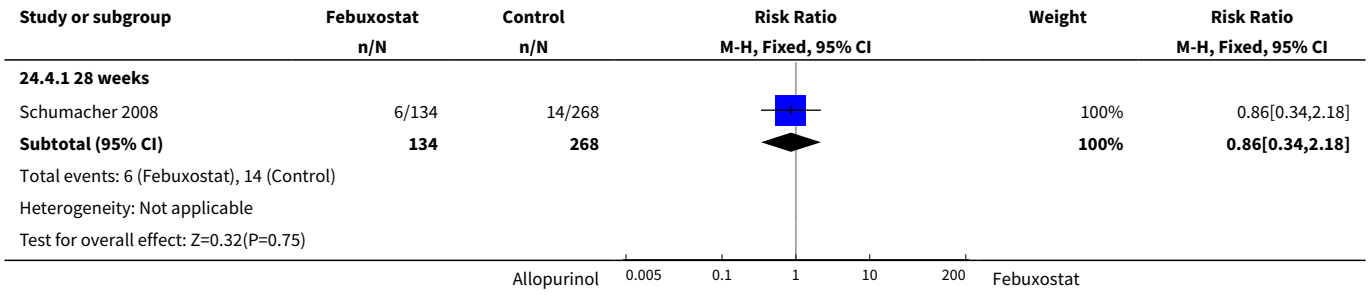
Analysis 24.2. Comparison 24 Adverse events - febuxostat 240 mg/day versus allopurinol 300 mg/day, Outcome 2 Serious.



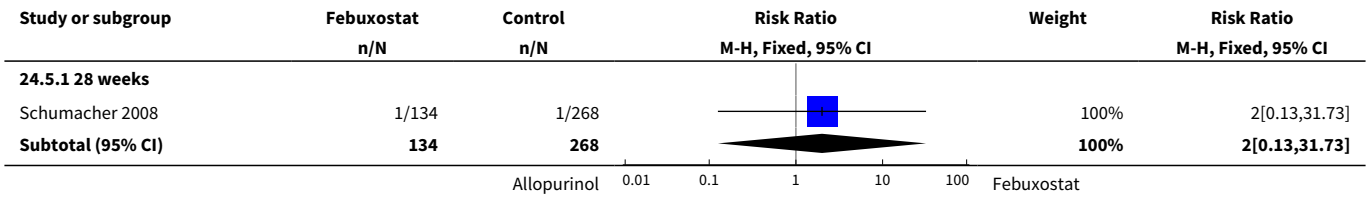
Analysis 24.3. Comparison 24 Adverse events - febuxostat 240 mg/day versus allopurinol 300 mg/day, Outcome 3 Liver function test abnormalities.

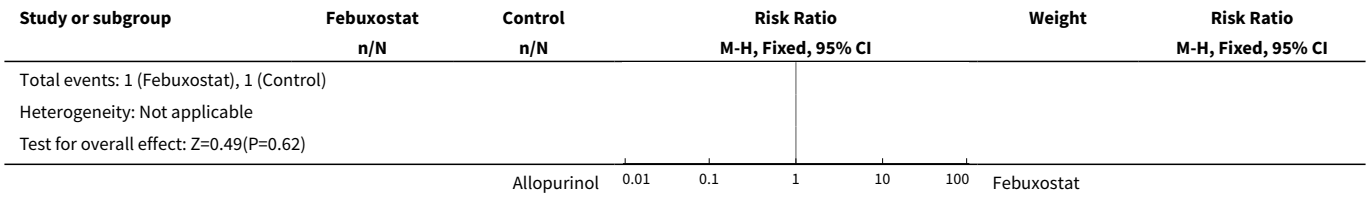


Analysis 24.4. Comparison 24 Adverse events - febuxostat 240 mg/day versus allopurinol 300 mg/day, Outcome 4 Skin reaction.

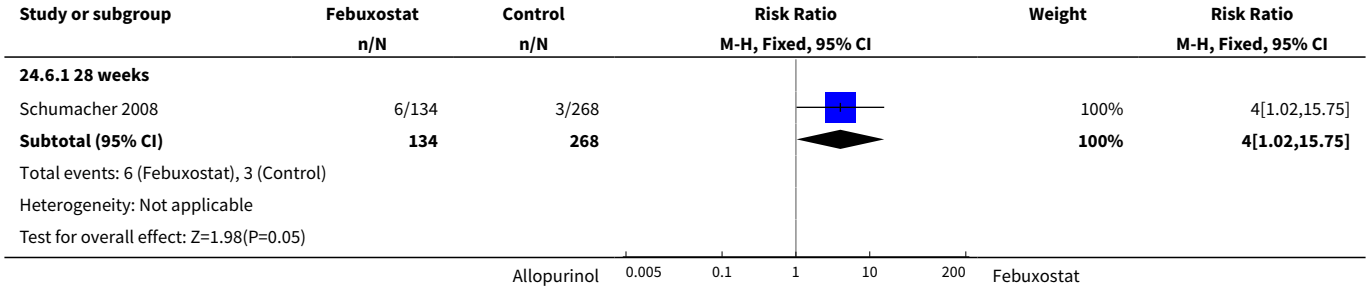


Analysis 24.5. Comparison 24 Adverse events - febuxostat 240 mg/day versus allopurinol 300 mg/day, Outcome 5 Cardiovascular events (chest pain, coronary artery disease, myocardial infarction, atrial fibrillation).

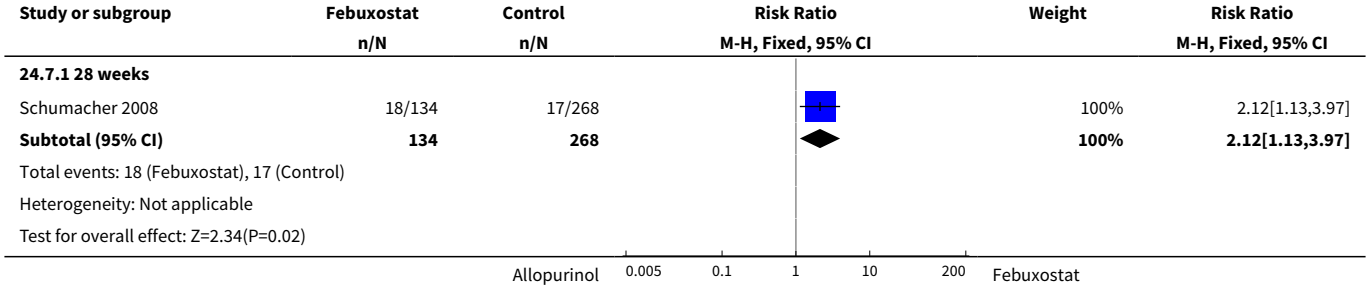




Analysis 24.6. Comparison 24 Adverse events - febuxostat 240 mg/ day versus allopurinol 300 mg/day, Outcome 6 Hypertension.



Analysis 24.7. Comparison 24 Adverse events - febuxostat 240 mg/day versus allopurinol 300 mg/day, Outcome 7 Diarrhea.



ADDITIONAL TABLES

Table 1. Open label trials characteristics

	Schumacher 2009	Becker 2009
Name	Febuxostat in the treatment of gout: 5-yr findings of the FOCUS efficacy and harms study	Clinical efficacy and harms of successful long term uric acid lowering with febuxostat or allopurinol in subjects with gout FACT and APEX open label trial
Duration of RCT	28 days	52 weeks and 28 weeks
Duration of open label trial	60 months	40 months

Table 1. Open label trials characteristics *(Continued)*

Arms	Febuxostat 40mg	Febuxostat 80mg	Febuxostat 120mg	Febuxostat 80mg	Febuxostat 120mg	Allopurinol
Subjects enrolled in open label trial	8	79	29	606	388	92
Subjects completed open label trial	6	41	11	412	217	35
Primary endpoint	Proportion of subjects that achieved and maintained SUA < 6mg/dL			Proportion of subjects with sUA < 6mg/dL at each visit		
Secondary endpoints	Percentage reduction from baseline sUA; Proportion of subjects with sUA < 5mg/dL and 4 mg/dL;Proportion of subjects with flares requiring treatment; resolution of palpable tophi			Percentage reduction from baseline sUA; proportion of subjects with sUA decreasing to < 6mg/dL across treatment changes; reduction in the incidence of flares requiring treatment; percentage reduction in number of tophi; reduction in the size or disappearance of the index tophus		

Table 2. Effectiveness data from open label trials

		1year n/N (%)	2year n/N (%)	3year n/N (%)	4year n/N (%)	5year n/N (%)
Schumacher 2009	Febuxostat 40 mg	4/7 (57)	5/8 (63)	4/ 6 (67)	5/ 6 (83)	6/6 (100)
	Febuxostat 80 mg	47/55 (85)	37/49 (76)	38/ 45 (84)	36/39 (92)	38/41 (93)
	Febuxostat 120 mg	12/18 (67)	12/13 (92)	12/13 (92)	11/13 (85)	10/11 (91)
Becker 2009	Febuxostat 80 mg	375/422 (89)	325/364 (89)	109/120 (91)	-	-
	Febuxostat 120 mg	145/168 (86)	123/141 (87)	43/47 (92)	-	-
	Allopurinol 300 mg	37/45 (82)	33/42 (79)	9/10 (90)	-	-

Proportion of subjects with serum uric acid < 6 mg/dL

Table 3. Adverse events data from open label trials

		AEs Rate per 100 patient-year
Schumacher 2009	Febuxostat 40 mg	274
	Febuxostat 80 mg	385
	Febuxostat 120 mg	259

Table 3. Adverse events data from open label trials *(Continued)*

Becker 2009	Febuxostat 80 mg	227
	Febuxostat 120 mg	216
	Allopurinol 300 mg	245

APPENDICES

Appendix 1. Search strategy

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1950 to Present> 201107.up.

Search Strategy:

---

1. 1 gout/ (7747)
2. 2 (gout or gout?).mp. (10434)
3. 3 1 or 2 (10434)
4. 4 Hyperuricemia/ (775)
5. 5 hyperuricemi*.mp. (3483)
6. 6 4 or 5 (3483)
7. 7 3 or 6 (12596)
8. 8 Febuxostat.af. (101)
9. 9 144060-53-7.af. (60)
10. 10 Uloric.af. (1)
11. 11 "TMX-67".af. (8)
12. 12 "TEI 6720".af. (11)
13. 13 Adenuric.af. (0)
14. 14 UNII-101V0R1N2E.af. (0)
15. 15 "2-3-cyano-4-isobutoxyphenyl-4-methyl-5-thiazolecarboxylic acid".af. (5)
16. 16 or/8-15 (104)
17. 17 16 and 3 (69)
18. 18 16 and 6 (45)
19. 19 18 not 17 (4)
20. 20 18 or 17 (73)

Database: International Pharmaceutical Abstracts <1970 to July 2011> [201107.em]

Search Strategy:

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1. 1 gout/ (268)
2. 2 (gout or gout?).mp. (412)
3. 3 1 or 2 (412)
4. 4 Hyperuricemia/ (33)
5. 5 hyperuricemi*.mp. (216)
6. 6 4 or 5 (216)
7. 7 3 or 6 (536)
8. 8 Febuxostat.af. (32)
9. 9 144060-53-7.af. (32)
10. 10 Uloric.af. (2)

11.11 "TMX-67".af. (4)
12.12 "TEI 6720".af. (3)
13.13 Adenuric.af. (0)
14.14 UNII-101V0R1N2E.af. (0)
15.15 "2-3-cyano-4-isobutoxyphenyl-4-methyl-5-thiazolecarboxylic acid".af. (0)
16.16 or/8-15 (33)
17.17 16 and 3 (28)
18.18 16 and 6 (13)
19.19 18 not 17 (0)
20.20 18 or 17 (28)
21.21 from 20 keep 1-28 (28)

Database: EMBASE <1980 to 2011 Week 31> [201131.up.]

Search Strategy:

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1. 1 exp gout/ (5306)
2. 2 hyperuricemia/ (4546)
3. 3 exp febuxostat/ (168)
4. 4 144060-53-7.rn. (168)
5. 5 Uloric.af. (7)
6. 6 "TMX-67".af. (19)
7. 7 "TEI 6720".af. (19)
8. 8 Adenuric.af. (11)
9. 9 UNII-101V0R1N2E.af. (0)
10. 10 "2-3-cyano-4-isobutoxyphenyl-4-methyl-5-thiazolecarboxylic acid".af. (6)
11. 11 or/3-10 (169)
12. 12 1 or 2 (8644)
13. 13 11 and 12 (141)
14. 14 from 13 keep 1-141 (141)

Cochrane Database of Systematic Reviews, Cochrane Methodology Register, Database of Abstracts of Reviews of Effects, NHA Economic Evaluation Database, Health Technology Assessment Database

1. There are **0** results out of **5933 records** for**: "gout* or Hyperuricemi*** and **Febuxostat or 144060-53-7 or Uloric or TMX-67 or TEI 6720 or Adenuric or UNII-101V0R1N2E or "2-3-cyano-4-isobutoxyphenyl-4-methyl-5-thiazolecarboxylic acid" in Cochrane Database of Systematic Reviews**"
2. There are 0 results out of 12200 records for: "gout* or Hyperuricemi* and Febuxostat or 144060-53-7 or Uloric or TMX67 or "TMX 67" or TMX-67 or TEI6720 or "TEI 6720" or Adenuric or UNII-101V0R1N2E or "2-3-cyano-4-isobutoxyphenyl-4-methyl-5-thiazolecarboxylic acid" in Cochrane Methodology Register"
3. There are 0 results out of 7596 records for: "gout* or Hyperuricemi* and Febuxostat or 144060-53-7 or Uloric or TMX67 or "TMX 67" or TMX-67 or TEI6720 or "TEI 6720" or Adenuric or UNII-101V0R1N2E or "2-3-cyano-4-isobutoxyphenyl-4-methyl-5-thiazolecarboxylic acid" in Record Title in Database of Abstacts of Reviews of Effects"
4. There are 0 results out of 27436 records for: "gout* or Hyperuricemi* and Febuxostat or 144060-53-7 or Uloric or TMX67 or "TMX 67" or TMX-67 or TEI6720 or "TEI 6720" or Adenuric or UNII-101V0R1N2E or "2-3-cyano-4-isobutoxyphenyl-4-methyl-5-thiazolecarboxylic acid" in NHS Economic Evaluation Database"

Cochrane Central Register of Controlled Trials

1. There are 5 results out of 600472 records for: "gout* or Hyperuricemi* and Febuxostat or 144060-53-7 or Uloric or TMX-67 or TEI 6720 or Adenuric or UNII-101V0R1N2E or "2-3-cyano-4-isobutoxyphenyl-4-

Health Technology Assessment

1. There are 3 results out of 7596 records for: "gout* or Hyperuricemi* and Febuxostat or 144060-53-7 or Uloric or TMX67 or "TMX 67" or TMX-67 or TEI6720 or "TEI 6720" or Adenuric or UNII-101V0R1N2E or "2-3-cyano-4-isobutoxyphenyl-4-methyl-5-thiazolecarboxylic acid" in Record Title in Health Technology Assessment Database

HISTORY

Protocol first published: Issue 8, 2010
Review first published: Issue 11, 2012

Date	Event	Description
2 July 2010	Amended	CMSG ID: C201-R

CONTRIBUTIONS OF AUTHORS

Link with editorial base and co-ordinate contributions from co-authors (MSA)
Draft protocol (JT, MLO, MSA)
Run search (SF)
Identify relevant titles and abstracts from searches (JT, MLO)
Obtain copies of trials (MLO)
Selection of trials (JT, MLO, MSA)
Extract data from trials (JT, MLO)
Enter data into RevMan (MLO)
Carry out analysis (MLO, MSA)
Interpret data (JT, MLO, MSA)
Draft final review (MSA with contributions from all)
Update review (JT, MLO, MSA)

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  Computer Access and Office Space

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None

NOTES

None

INDEX TERMS

Medical Subject Headings (MeSH)

Allopurinol [adverse effects] [therapeutic use]; Chronic Disease; Febuxostat; Gout [blood] [*drug therapy]; Gout Suppressants [adverse effects] [*therapeutic use]; Hyperuricemia [drug therapy]; Randomized Controlled Trials as Topic; Thiazoles [adverse effects] [*therapeutic use]

MeSH check words

Female; Humans; Male