

**SUPPLEMENTARY APPENDIX 6: Network Meta-Analyses (NMA) to Support Decision-Making Regarding Use of ULT**

**2020 American College of Rheumatology Guideline for the Management of Gout**

**PICO 10: For patients diagnosed with gout with an indication for ULT, what is the relative impact of starting allopurinol, febuxostat, probenecid, allopurinol/lesinurad 200mg combination, febuxostat/lesinurad 200mg combination, pegasitase, or no treatment?**

**Evidence from randomized clinical trials**

**Summary**

We found 21 studies (reported in 31 publications) addressing this question (1-31).

Note that some agents could not be analyzed in the NMA (or not analyzed for all possible outcomes) because their outcomes were reported differently which precluded their ability to be pooled, or the comparisons between interventions were not connected to the rest of the network. As a result, pegloticase was not included in the NMA for the outcome gout flares (due to different measurement of gout flares) and tophus (not connected to the network). We summarize results about how Pegloticase compares to placebo for the outcome tophus. The summary of the evidence below is informed by the synthesis of the data provided in Table 1 below.

The evidence shows:

- There may be no differences among the (non-placebo) drugs regarding their effectiveness to reduce the risk of gout flares for patients followed between 6-13 months (assessed in final month of the trial)
- Allopurinol 300 mg, febuxostat 40 mg, and febuxostat 80 mg are the most effective drugs for reducing the risk of gout flares up to 2 years. Probenecid 2g may also be among the most effective.
- Patients on placebo have the highest risk of gout flares up to 2 years of treatment.
- Febuxostat 240 mg has the greatest risk of gout flares during the first 3 months of ULT therapy. Febuxostat 120 mg may have higher risk of gout flares during the first 3 months of ULT therapy.
- Allopurinol 300 mg, Allopurinol 300mg + Lesinurad 200mg, Febuxostat 40 mg (including extended release), Febuxostat 80 mg (including extended release), Febuxostat 80 mg + Lesinurad 200 mg and placebo may have the lowest risk of gout flares during the first 3 months of ULT therapy
- We are uncertain about how biweekly and monthly Pegloticase 8 mg compares to other drugs for gout flares, because the trial assessing the effects of Pegloticase measured gout flares in a different way.

- There may not be differences among the non-placebo drugs analyzed regarding their efficacy for the outcome tophus up to 2 years
- Biweekly and monthly Pegloticase 8 mg may be more effective than placebo regarding their efficacy for the outcome tophus up to 6 months. Biweekly Pegloticase 8 mg may be more effective than monthly Pegloticase 8 mg for this outcome.
- Allopurinol 300mg and Febuxostat 80mg (extended release) are among the most effective for achieving serum urate levels <6 mg/d up to 2 years. Allopurinol 300mg + Lesinurad 200mg, Febuxostat 40mg (extended release), Febuxostat 30mg bid, Febuxostat 120mg, and Febuxostat 240mg may also be among the most effective. All the other drugs are less effective than the above mentioned, but all are more effective than placebo.
- Compared to placebo, Febuxostat 120mg increases the risk of serious adverse events. There may be no differences among any of the drugs in the risk of any serious adverse events when compared to placebo.
- There may be no differences among any of the drugs in the risk of cardiovascular-related serious adverse events when compared to Febuxostat 80mg.
- Most trials investigating allopurinol randomized patients to allopurinol 300 mg/d (or 200mg/d), in a fixed dose. Few studies reported on >300 mg dosages. No apparent differences existed between these trials, and therefore all studies were combined.

**The overall quality of the evidence is MODERATE**

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## Results

**Table 1: Most and least effective treatments for all outcomes.** For each outcome, interventions were grouped according to effectiveness. Interventions depicted with the same color belong to the same group. Green represents the most effective interventions, yellow represents intermediate effectiveness, and red represents the least effective. “Green” designates ‘good’ patient outcomes, while “red” designates ‘inferior’ patient outcomes (including for the SAEs).

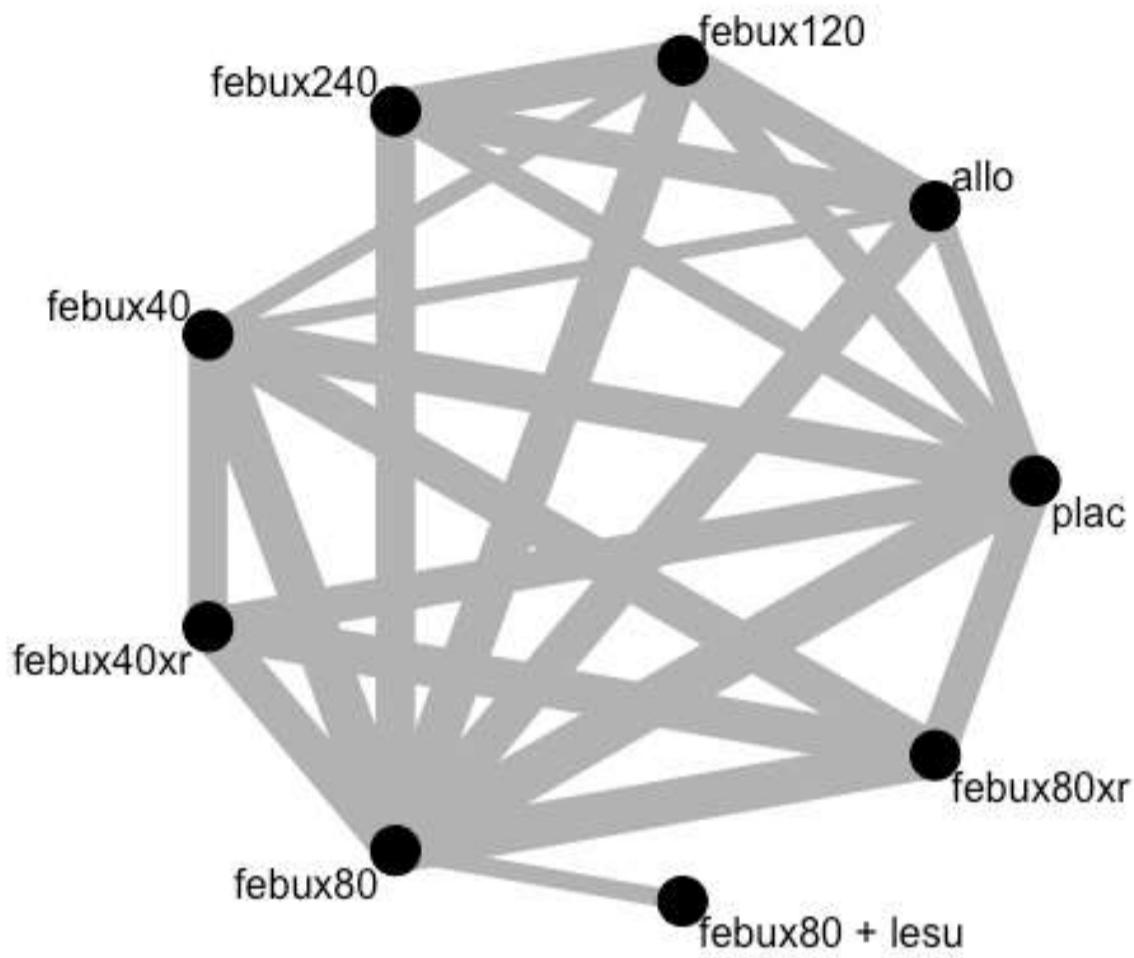
	gout flares <i>0 to 3 months</i>	gout flares <i>Flare assessed in final month of 5-13 month trials<sup>1</sup></i>	gout flares <i>Longest follow-up (up to 2 years)<sup>2</sup></i>	tophus	sUA	Serious adverse events (sAEs)	CV-related sAEs		
Reference for estimates & certainty	Table 2	Table 3	Table 4	Table 9	Table 5	Table 12	Table 13		
allopurinol 300mg <sup>3</sup>							NA		
allopurinol 300mg + lesinurad 200mg	NA		NA						
febuxostat 40mg				NA					
febuxostat 40mg XR		NA	NA	NA					
febuxostat 30mg bid	NA	NA	NA	NA					
febuxostat 80mg					NA				
febuxostat 80mg XR		NA	NA	NA					
febuxostat 80mg + lesinurad 200mg			NA						
febuxostat 120mg			NA	NA					
febuxostat 240mg		NA	NA	NA					
monthly pegloticase 8mg	NA	NA	NA	NA			NA		
biweekly pegloticase 8mg	NA	NA	NA	NA			NA		
probenecid 2g	NA	NA			NA		NA		
placebo		NA		NA					
Cell									
Category	Most effective, high or moderate quality	Most effective, low or very low quality	High or moderate quality	Low or very low quality	High or moderate quality	Low or very low quality	Least effective, high or moderate quality	Least effective, low or very low quality	Not studied for outcome

<sup>1</sup> Risk of gout flares in a 1-month period. Measured at the latest follow-up after ULT initiation (range: 5 to 13 months).

<sup>2</sup> Risk of gout flares at longest follow-up, where patients observed over a period of time greater than one month (e.g., baseline to 7 months or 2.25m to 24 months after ULT initiation; range: 0 to 24 months).

<sup>3</sup> The majority of trials report on this dose; there were too few trials that reported higher doses to analyze them separately, so all trials were combined.

**Figure 1:** Network plot for proportion of patients with at least 1 gout flare, 0 to 3 months follow-up (range: 28 days to 3 months).



**Table 2: Estimates and certainty for proportion of patients with at least 1 gout flare, 0 to 3 months follow-up (range: 28 days to 3 months).**

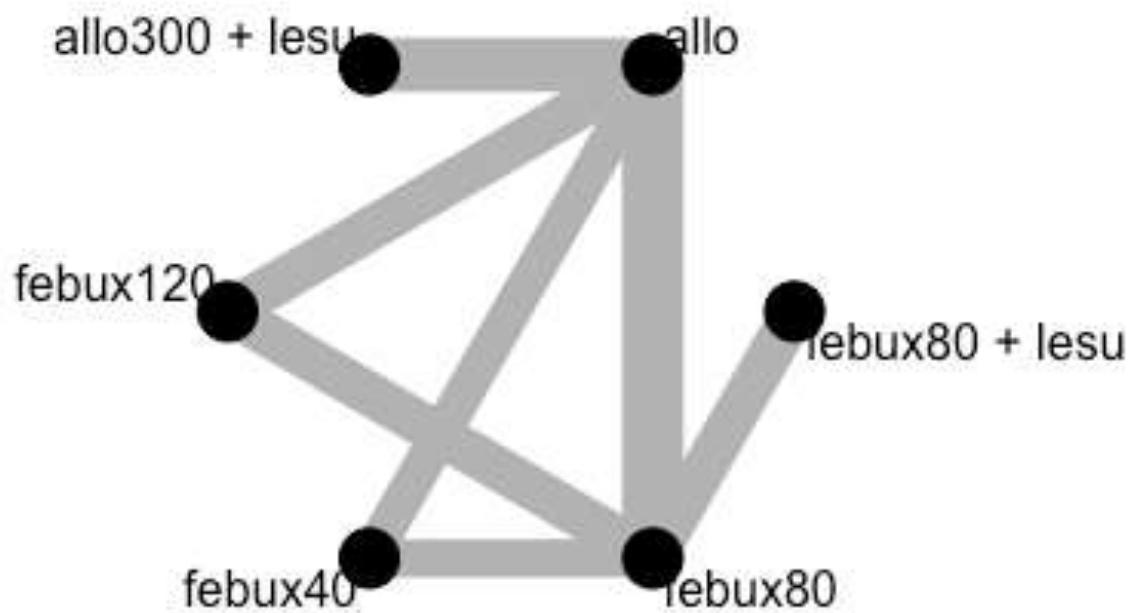
(Measured as proportion of patients with at least 1 gout flare – analyzed using relative risk)

Comparison			Direct estimate		Indirect estimate		Network estimates		
	Intervention	Comparator	Point estimate (95% CI)	Certainty	Point estimate (95% CI)	Certainty	Point estimate (95% CI)	Certainty	Reasons
1	Febuxostat 120mg	Allopurinol 300mg	1.58 (1.05, 2.37)	moderate	1.05 (0.59, 1.86)	low	1.41 (1.05, 1.9)	moderate	risk of bias
2	Febuxostat 240mg	Allopurinol 300mg	2.25 (1.49, 3.42)	moderate	1.22 (0.55, 2.73)	low	2.04 (1.47, 2.83)	moderate	risk of bias
3	Febuxostat 40mg	Allopurinol 300mg	0.56 (0.27, 1.18)	high	1.19 (0.74, 1.92)	low	0.93 (0.63, 1.36)	low	risk of bias, imprecision
4	Allopurinol 300mg	Febuxostat 40mg XR	NA	NA	1.56 (0.76, 3.21)	low	1.56 (0.76, 3.21)	low	risk of bias, imprecision
5	Febuxostat 80mg	Allopurinol 300mg	1 (0.67, 1.49)	moderate	0.97 (0.42, 2.28)	low	1.05 (0.8, 1.37)	low	risk of bias
6	Allopurinol 300mg	Febuxostat 80mg + Lesinurad 200mg	NA	NA	0.64 (0.34, 1.21)	low	0.64 (0.34, 1.21)	low	risk of bias, imprecision
7	Allopurinol 300mg	Febuxostat 80mg XR	NA	NA	0.86 (0.48, 1.52)	low	0.86 (0.48, 1.52)	low	risk of bias, imprecision
8	Allopurinol 300mg	Placebo	1.15 (0.77, 1.71)	low	1.62 (0.89, 2.95)	low	1.31 (0.91, 1.88)	low	risk of bias
9	Febuxostat 120mg	Febuxostat 240mg	0.7 (0.56, 0.88)	moderate	0.62 (0.24, 0.61)	low	0.69 (0.51, 0.94)	moderate	risk of bias
10	Febuxostat 120mg	Febuxostat 40mg	1.63 (0.98, 2.7)	low	1.44 (0.86, 2.42)	low	1.53 (1.05, 2.22)	moderate	risk of bias
11	Febuxostat 120mg	Febuxostat 40mg XR	NA	NA	2.21 (1.08, 4.51)	moderate	2.21 (1.08, 4.51)	moderate	risk of bias
12	Febuxostat 120mg	Febuxostat 80mg	1.31 (0.99, 1.73)	low	1.58 (0.76, 3.26)	low	1.35 (1.04, 1.76)	moderate	risk of bias
13	Febuxostat 120mg	Febuxostat 80mg + Lesinurad 200mg	NA	NA	0.9 (0.47, 1.7)	low	0.9 (0.47, 1.7)	low	risk of bias, imprecision
14	Febuxostat 120mg	Febuxostat 80mg XR	NA	NA	1.21 (0.69, 2.13)	low	1.21 (0.69, 2.13)	low	risk of bias, imprecision
15	Febuxostat 120mg	Placebo	1.72 (1.07, 2.76)	moderate	8.78 (2.09, 36.88)	moderate	1.85 (1.33, 2.57)	moderate	risk of bias
16	Febuxostat 240mg	Febuxostat 40mg	NA	NA	2.21 (1.44, 3.37)	moderate	2.21 (1.44, 3.37)	moderate	risk of bias
17	Febuxostat 240mg	Febuxostat 40mg XR	NA	NA	3.19 (1.53, 6.67)	moderate	3.19 (1.53, 6.67)	moderate	risk of bias

18	Febuxostat 240mg	Febuxostat 80mg	1.85 (1.34, 2.55)	moderate	2.42 (1.21, 4.86)	moderate	1.95 (1.43, 2.66)	moderate	risk of bias
19	Febuxostat 240mg	Febuxostat 80mg + Lesinurad 200mg	NA	NA	1.3 (0.67, 2.51)	low	1.3 (0.67, 2.51)	low	risk of bias, imprecision
20	Febuxostat 240mg	Febuxostat 80mg XR	NA	NA	1.75 (0.96, 3.17)	low	1.75 (0.96, 3.17)	low	risk of bias, imprecision
21	Febuxostat 240mg	Placebo	2.57 (1.4, 4.72)	moderate	2.98 (1.47, 6.02)	moderate	2.67 (1.84, 3.88)	moderate	risk of bias
22	Febuxostat 40mg XR	Febuxostat 40mg	0.86 (0.47, 1.57)	moderate	2.91 (0.4, 21.37)	low	0.69 (0.35, 1.37)	moderate	imprecision
23	Febuxostat 40mg	Febuxostat 80mg	0.84 (0.64, 1.1)	low	0.56 (0.24, 1.32)	low	0.88 (0.63, 1.25)	low	risk of bias
24	Febuxostat 40mg	Febuxostat 80mg + Lesinurad 200mg	NA	NA	0.59 (0.3, 1.16)	low	0.59 (0.3, 1.16)	low	risk of bias, imprecision
25	Febuxostat 80mg XR	Febuxostat 40mg	1.2 (0.86, 1.68)	moderate	2.98 (0.86, 10.29)	low	1.26 (0.74, 2.14)	moderate	imprecision
26	Febuxostat 40mg	Placebo	1.06 (0.72, 1.57)	moderate	0.98 (0.51, 1.88)	low	1.21 (0.8, 1.83)	moderate	imprecision
27	Febuxostat 40mg XR	Febuxostat 80mg	0.8 (0.58, 1.11)	moderate	0.62 (0.1, 3.63)	low	0.61 (0.31, 1.21)	low	risk of bias
28	Febuxostat 40mg XR	Febuxostat 80mg + Lesinurad 200mg	NA	NA	0.41 (0.17, 1)	low	0.41 (0.17, 1)	moderate	risk of bias
29	Febuxostat 80mg XR	Febuxostat 40mg XR	1.3 (0.9, 1.87)	moderate	NA	NA	1.82 (0.89, 3.76)	low	risk of bias
30	Febuxostat 40mg XR	Placebo	1.13 (0.73, 1.75)	moderate	0.41 (0.16, 1.07)	low	0.84 (0.4, 1.73)	low	risk of bias
31	Febuxostat 80mg + Lesinurad 200mg	Febuxostat 80mg	1.5 (0.88, 2.55)	low	NA	NA	1.5 (0.84, 2.68)	low	risk of bias
32	Febuxostat 80mg XR	Febuxostat 80mg	0.99 (0.73, 1.36)	moderate	1.12 (0.37, 3.41)	low	1.11 (0.66, 1.89)	low	risk of bias
33	Febuxostat 80mg	Placebo	1.33 (0.96, 1.83)	low	0.83 (0.24, 2.87)	low	1.37 (0.99, 1.9)	low	risk of bias
34	Febuxostat 80mg + Lesinurad 200mg	Febuxostat 80mg XR	NA	NA	1.35 (0.61, 2.96)	low	1.35 (0.61, 2.96)	low	risk of bias, imprecision
35	Febuxostat 80mg + Lesinurad 200mg	Placebo	NA	NA	2.05 (1.05, 4)	moderate	2.05 (1.05, 4)	moderate	risk of bias
36	Febuxostat 80mg XR	Placebo	1.62 (0.63, 4.17)	moderate	0.96 (0.47, 1.95)	low	1.53 (0.85, 2.74)	low	risk of bias

Estimates presented correspond to Treatment 1 (intervention) compared with Treatment 2 (comparison). Number above 1 indicate a larger risk of gout flares with Treatment 1 (favors Treatment 2); while numbers below 1 indicate a larger risk of gout flares with Treatment 2 (favors treatment 1).

**Figure 2:** Network plot for proportion of patients with at least 1 gout flare, at latest follow-up (range: 5 to 13 months). Patients were observed for 1 month period only.



**Table 3: Estimates and certainty for proportion of patients with at least 1 gout flare, at latest follow-up (range: 5 to 13 months). Patients were observed for 1 month period only.**

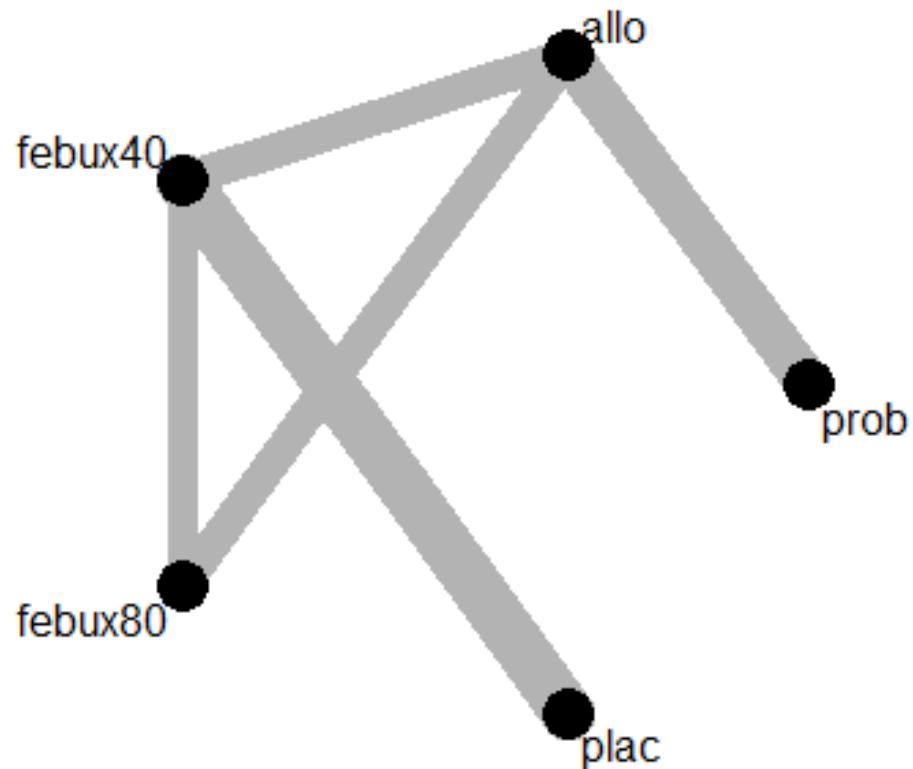
(Measured as proportion of patients with at least 1 gout flare – analyzed using relative risk)

Comparison			Direct estimate		Indirect estimate		Network estimate		
	Intervention	Comparator	Point estimate (95% CI)	Certainty	Point estimate (95% CI)	Certainty	Point estimate (95% CI)	Certainty	Reasons
1	Allopurinol 300mg + Lesinurad 200mg	Allopurinol 300mg	0.79 (0.4, 1.54)	moderate	NA	NA	0.81 (0.42, 1.6)	moderate	imprecision
2	Febuxostat 120mg	Allopurinol 300mg	0.83 (0.31, 2.21)	low	0.4 (0.02, 7.4)	very low	0.79 (0.36, 1.75)	low	risk of bias, imprecision
3	Febuxostat 40mg	Allopurinol 300mg	1.03 (0.33, 3.23)	moderate	1.82 (0.22, 15.43)	very low	1.13 (0.48, 2.63)	moderate	imprecision
4	Febuxostat 80mg	Allopurinol 300mg	0.99 (0.48, 2.03)	low	NA	NA	0.99 (0.55, 1.8)	low	risk of bias, imprecision
5	Febuxostat 80mg + Lesinurad 200mg	Allopurinol 300mg	NA	NA	1.09 (0.4, 2.99)	low	1.09 (0.4, 2.99)	low	risk of bias, imprecision
6	Allopurinol 300mg + Lesinurad 200mg	Febuxostat 120mg	NA	NA	1.03 (0.36, 2.9)	low	1.03 (0.36, 2.9)	low	risk of bias, imprecision
7	Allopurinol 300mg + Lesinurad 200mg	Febuxostat 40mg	NA	NA	0.72 (0.25, 2.13)	low	0.72 (0.25, 2.13)	low	risk of bias, imprecision
8	Allopurinol 300mg + Lesinurad 200mg	Febuxostat 80mg	NA	NA	0.82 (0.33, 2.01)	low	0.82 (0.33, 2.01)	low	risk of bias, imprecision
9	Allopurinol 300mg + Lesinurad 200mg	Febuxostat 80mg + Lesinurad 200mg	NA	NA	0.75 (0.22, 2.5)	low	0.75 (0.22, 2.5)	low	risk of bias, imprecision
10	Febuxostat 120mg	Febuxostat 40mg	NA	NA	0.7 (0.24, 2.08)	low	0.7 (0.24, 2.08)	low	risk of bias, imprecision
11	Febuxostat 120mg	Febuxostat 80mg	1.26 (0.48, 3.29)	low	1.59 (0.08, 30.1)	low	0.8 (0.36, 1.76)	low	risk of bias, imprecision
12	Febuxostat 120mg	Febuxostat 80mg + Lesinurad 200mg	NA	NA	0.73 (0.23, 2.25)	very low	0.73 (0.23, 2.25)	low	risk of bias, imprecision

13	Febuxostat 40mg	Febuxostat 80mg	0.76 (0.33, 1.72)	moderate	0.74 (0.1, 5.22)	low	1.14 (0.48, 2.69)	moderate	imprecision
14	Febuxostat 40mg	Febuxostat 80mg + Lesinurad 200mg	NA	NA	1.03 (0.32, 3.37)	low	1.03 (0.32, 3.37)	low	risk of bias, imprecision
15	Febuxostat 80mg + Lesinurad 200mg	Febuxostat 80mg	1.1 (0.49, 2.48)	low	NA	NA	1.1 (0.49, 2.48)	low	risk of bias, imprecision

Estimates presented correspond to Treatment 1 (intervention) compared with Treatment 2 (comparison). Number above 1 indicate a larger risk of gout flares with Treatment 1 (favors Treatment 2); while numbers below 1 indicate a larger risk of gout flares with Treatment 2 (favors treatment 1).

**Figure 3:** Network plot for proportion of patients with at least 1 gout flare, at longest follow-up (range: from baseline or 2.25 months up to 7 or 24 months). Patients were observed for >1 month period.



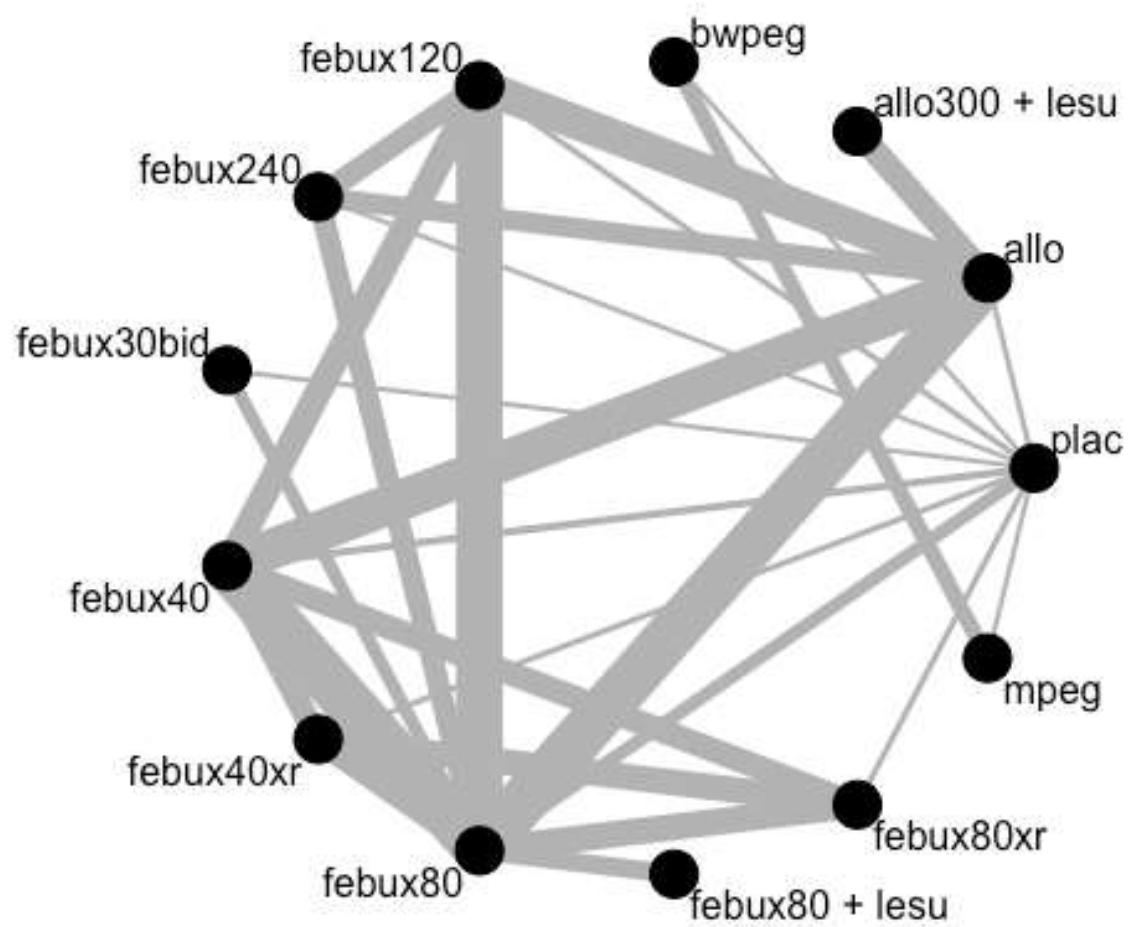
**Table 4: Estimates and certainty for proportion of patients with at least 1 gout flare, at longest follow-up (range: from baseline or 2.25 months up to 7 or 24 months). Patients were observed for >1 month period.**

(Measured as proportion of patients with at least 1 gout flare – analyzed using relative risk)

Comparison		Direct estimate		Indirect estimate		Network estimate			
	Intervention	Comparator	Point estimate (95% CI)	Certainty	Point estimate (95% CI)	Certainty	Point estimate (95% CI)	Certainty	Reasons
1	Febuxostat 40mg	Allopurinol 300mg	0.56 (0.22, 1.41)	moderate	NA	NA	0.56 (0.22, 1.41)	moderate	imprecision
2	Febuxostat 80mg	Allopurinol 300mg	0.44 (0.16, 1.17)	moderate	NA	NA	0.44 (0.16, 1.17)	moderate	imprecision
3	Allopurinol 300mg	Placebo	NA	NA	1.26 (0.54, 2.93)	low	1.26 (0.54, 2.93)	low	risk of bias, imprecision
4	Allopurinol 300mg	Probenecid 2g	1.04 (0.57, 1.89)	very low	NA	NA	1.04 (0.57, 1.89)	very low	risk of bias, imprecision
5	Febuxostat 40mg	Febuxostat 80mg	1.29 (0.49, 3.37)	moderate	NA	NA	1.29 (0.49, 3.37)	moderate	imprecision
6	Febuxostat 40mg	Placebo	0.71 (0.52, 0.96)	moderate	NA	NA	0.71 (0.52, 0.96)	moderate	risk of bias
7	Febuxostat 40mg	Probenecid 2g	NA	NA	0.58 (0.22, 1.57)	very low	0.58 (0.22, 1.57)	very low	risk of bias, imprecision
8	Febuxostat 80mg	Placebo	NA	NA	0.55 (0.2, 1.51)	low	0.55 (0.2, 1.51)	low	risk of bias, imprecision
9	Febuxostat 80mg	Probenecid 2g	NA	NA	0.45 (0.16, 1.3)	very low	0.45 (0.16, 1.3)	very low	risk of bias, imprecision
10	Probenecid 2g	Placebo	NA	NA	1.21 (0.43, 3.41)	very low	1.21 (0.43, 3.41)	very low	risk of bias, imprecision

Estimates presented correspond to Treatment 1 (intervention) compared with Treatment 2 (comparison). Number above 1 indicate a larger risk of gout flares with Treatment 1 (favors Treatment 2); while numbers below 1 indicate a larger risk of gout flares with Treatment 2 (favors treatment 1).

**Figure 4: Network plot for proportion of patients with serum urate <6.0mg/dL at longest follow-up (range: 28 days to 24 months)**



**Table 5: Estimates and certainty for proportion of patients with serum urate <6.0mg/dL at longest follow-up (range: 28 days to 24 months)**

(Measured as proportion of patients with serum urate &lt;6.0mg/dL – analyzed using relative risk)

Comparison			Direct estimate		Indirect estimate		Network estimate		
	Intervention	Comparator	Point estimate (95% CI)	Certainty	Point estimate (95% CI)	Certainty	Point estimate (95% CI)	Certainty	Reasons
1	Allopurinol 300mg + Lesinurad 200mg	Allopurinol 300mg	1.98 (1.64, 2.4)	high	NA	NA	1.98 (1.47, 2.66)	high	NA
2	Biweekly Pegloticase 8mg	Allopurinol 300mg	NA	NA	0.83 (0.11, 6.4)	low	0.83 (0.11, 6.4)	low	RoB, imprecision
3	Febuxostat 120mg	Allopurinol 300mg	1.5 (0.92, 2.45)	low	2.11 (1.59, 2.8)	low	1.7 (1.43, 2.02)	moderate	RoB
4	Febuxostat 240mg	Allopurinol 300mg	2.29 (1.72, 3.05)	moderate	1.54 (0.94, 2.53)	very low	2 (1.48, 2.68)	moderate	RoB
5	Febuxostat 30mg bid	Allopurinol 300mg	NA	NA	0.43 (0.24, 0.75)	low	0.43 (0.24, 0.75)	low	RoB, inconsistency
6	Febuxostat 40mg	Allopurinol 300mg	1.04 (0.89, 1.21)	very low	1.04 (0.77, 1.4)	very low	1.03 (0.88, 1.21)	very low	RoB, inconsistency, imprecision
7	Febuxostat 40mg XR	Allopurinol 300mg	NA	NA	0.74 (0.55, 0.99)	low	0.74 (0.55, 0.99)	low	RoB, inconsistency, imprecision
8	Febuxostat 80mg	Allopurinol 300mg	1.68 (1.31, 2.14)	low	1.27 (0.88, 1.84)	low	1.55 (1.34, 1.79)	low	RoB, inconsistency
9	Febuxostat 80mg + Lesinurad 200mg	Allopurinol 300mg	NA	NA	0.51 (0.34, 0.79)	low	0.51 (0.34, 0.79)	low	RoB, inconsistency
10	Febuxostat 80mg XR	Allopurinol 300mg	NA	NA	0.62 (0.47, 0.83)	low	0.62 (0.47, 0.83)	moderate	RoB, inconsistency, imprecision
11	Monthly Pegloticase 8mg	Allopurinol 300mg	NA	NA	0.97 (0.13, 7.57)	low	0.97 (0.13, 7.57)	low	RoB, imprecision
12	Allopurinol 300mg	Placebo	36.11 (9.06, 143.87)	moderate	13.42 (7.35, 24.49)	low	15.99 (9.2, 27.78)	moderate	RoB
13	Allopurinol 300mg + Lesinurad 200mg	Biweekly Pegloticase 8mg	NA	NA	1.64 (0.21, 12.93)	low	1.64 (0.21, 12.93)	low	RoB, imprecision

14	Allopurinol 300mg + Lesinurad 200mg	Febuxostat 120mg	NA	NA	1.16 (0.82, 1.64)	low	1.16 (0.82, 1.64)	low	RoB, imprecision
15	Allopurinol 300mg + Lesinurad 200mg	Febuxostat 240mg	NA	NA	0.99 (0.65, 1.51)	low	0.99 (0.65, 1.51)	low	RoB, imprecision
16	Allopurinol 300mg + Lesinurad 200mg	Febuxostat 30mg bid	NA	NA	0.85 (0.45, 1.6)	low	0.85 (0.45, 1.6)	low	RoB, imprecision
17	Allopurinol 300mg + Lesinurad 200mg	Febuxostat 40mg	NA	NA	1.91 (1.36, 2.68)	low	1.91 (1.36, 2.68)	low	RoB, inconsistency
18	Allopurinol 300mg + Lesinurad 200mg	Febuxostat 40mg XR	NA	NA	1.46 (0.97, 2.22)	low	1.46 (0.97, 2.22)	low	RoB, imprecision
19	Allopurinol 300mg + Lesinurad 200mg	Febuxostat 80mg	NA	NA	1.28 (0.92, 1.78)	very low	1.28 (0.92, 1.78)	very low	RoB, inconsistency, imprecision
20	Allopurinol 300mg + Lesinurad 200mg	Febuxostat 80mg + Lesinurad 200mg	NA	NA	1.02 (0.6, 1.71)	low	1.02 (0.6, 1.71)	low	RoB, imprecision
21	Allopurinol 300mg + Lesinurad 200mg	Febuxostat 80mg XR	NA	NA	1.23 (0.81, 1.86)	low	1.23 (0.81, 1.86)	low	RoB, imprecision
22	Allopurinol 300mg + Lesinurad 200mg	Monthly Pegloticase 8mg	NA	NA	1.93 (0.24, 15.3)	low	1.93 (0.24, 15.3)	low	RoB, imprecision
23	Allopurinol 300mg + Lesinurad 200mg	Placebo	NA	NA	31.61 (16.87, 59.23)	moderate	31.61 (16.87, 59.23)	moderate	RoB
24	Biweekly Pegloticase 8mg	Febuxostat 120mg	NA	NA	0.71 (0.09, 5.46)	low	0.71 (0.09, 5.46)	low	RoB, imprecision
25	Biweekly Pegloticase 8mg	Febuxostat 240mg	NA	NA	0.6 (0.08, 4.72)	low	0.6 (0.08, 4.72)	low	RoB, imprecision
26	Biweekly Pegloticase 8mg	Febuxostat 30mg bid	NA	NA	0.52 (0.06, 4.24)	low	0.52 (0.06, 4.24)	low	RoB, imprecision
27	Biweekly Pegloticase 8mg	Febuxostat 40mg	NA	NA	1.16 (0.15, 8.97)	low	1.16 (0.15, 8.97)	low	RoB, imprecision
28	Biweekly Pegloticase 8mg	Febuxostat 40mg XR	NA	NA	0.89 (0.11, 6.95)	low	0.89 (0.11, 6.95)	low	RoB, imprecision
29	Biweekly Pegloticase 8mg	Febuxostat 80mg	NA	NA	0.78 (0.1, 5.98)	low	0.78 (0.1, 5.98)	low	RoB, imprecision

30	Biweekly Pegloticase 8mg	Febuxostat 80mg + Lesinurad 200mg	NA	NA	0.62 (0.08, 4.95)	low	0.62 (0.08, 4.95)	low	RoB, imprecision
31	Biweekly Pegloticase 8mg	Febuxostat 80mg XR	NA	NA	0.75 (0.1, 5.84)	low	0.75 (0.1, 5.84)	low	RoB, imprecision
32	Biweekly Pegloticase 8mg	Monthly Pegloticase 8mg	1.32 (0.44, 3.95)	low	0.37 (0, 123434.1)	very low	1.17 (0.74, 1.86)	low	RoB, imprecision
33	Biweekly Pegloticase 8mg	Placebo	9.6 (1.39, 66.26)	low	NA	NA	19.26 (2.7, 137.57)	moderate	RoB
34	Febuxostat 120mg	Febuxostat 240mg	0.92 (0.85, 1)	moderate	0.66 (0.37, 1.21)	low	0.85 (0.64, 1.14)	low	RoB, imprecision
35	Febuxostat 120mg	Febuxostat 30mg bid	NA	NA	0.73 (0.41, 1.28)	low	0.73 (0.41, 1.28)	low	RoB, imprecision
36	Febuxostat 120mg	Febuxostat 40mg	1.94 (1.38, 2.73)	moderate	1.5 (1.19, 1.9)	low	1.64 (1.37, 1.97)	moderate	RoB
37	Febuxostat 120mg	Febuxostat 40mg XR	NA	NA	1.26 (0.94, 1.7)	low	1.26 (0.94, 1.7)	low	RoB, imprecision
38	Febuxostat 120mg	Febuxostat 80mg	1.08 (1.01, 1.17)	moderate	0.96 (0.63, 1.46)	very low	1.1 (0.95, 1.28)	very low	RoB, incoherence, imprecision
39	Febuxostat 120mg	Febuxostat 80mg + Lesinurad 200mg	NA	NA	0.87 (0.57, 1.34)	low	0.87 (0.57, 1.34)	low	RoB, imprecision
40	Febuxostat 120mg	Febuxostat 80mg XR	NA	NA	1.06 (0.79, 1.42)	low	1.06 (0.79, 1.42)	low	RoB, imprecision
41	Febuxostat 120mg	Monthly Pegloticase 8mg	NA	NA	1.66 (0.21, 12.89)	low	1.66 (0.21, 12.89)	low	RoB, imprecision
42	Febuxostat 120mg	Placebo	28.66 (6.9, 119.11)	moderate	21.31 (11.47, 39.61)	moderate	27.21 (15.62, 47.39)	moderate	RoB
43	Febuxostat 30mg bid	Febuxostat 240mg	NA	NA	0.85 (0.46, 1.58)	low	0.85 (0.46, 1.58)	low	RoB, imprecision
44	Febuxostat 240mg	Febuxostat 40mg	NA	NA	1.93 (1.42, 2.63)	moderate	1.93 (1.42, 2.63)	moderate	RoB
45	Febuxostat 240mg	Febuxostat 40mg XR	NA	NA	1.48 (1, 2.17)	low	1.48 (1, 2.17)	low	RoB, imprecision
46	Febuxostat 240mg	Febuxostat 80mg	1.23 (1.08, 1.41)	moderate	1.42 (0.83, 2.45)	low	1.29 (0.97, 1.72)	very low	RoB, incoherence, imprecision

47	Febuxostat 240mg	Febuxostat 80mg + Lesinurad 200mg	NA	NA	1.03 (0.63, 1.68)	low	1.03 (0.63, 1.68)	low	RoB, imprecision
48	Febuxostat 80mg XR	Febuxostat 240mg	NA	NA	1.24 (0.85, 1.82)	low	1.24 (0.85, 1.82)	low	RoB, imprecision
49	Febuxostat 240mg	Monthly Pegloticase 8mg	NA	NA	1.94 (0.25, 15.34)	low	1.94 (0.25, 15.34)	low	RoB, imprecision
50	Febuxostat 240mg	Placebo	93.98 (3.15, 2802.4)	moderate	28.56 (15.12, 53.95)	moderate	31.91 (17.41, 58.45)	moderate	RoB, imprecision
51	Febuxostat 30mg bid	Febuxostat 40mg	NA	NA	2.26 (1.29, 3.97)	moderate	2.26 (1.29, 3.97)	moderate	RoB
52	Febuxostat 30mg bid	Febuxostat 40mg XR	NA	NA	1.73 (0.94, 3.17)	low	1.73 (0.94, 3.17)	low	RoB, imprecision
53	Febuxostat 30mg bid	Febuxostat 80mg	1.52 (0.97, 2.39)	low	2.04 (0.03, 157.47)	very low	1.51 (0.88, 2.6)	low	RoB, imprecision
54	Febuxostat 30mg bid	Febuxostat 80mg + Lesinurad 200mg	NA	NA	1.2 (0.61, 2.36)	low	1.2 (0.61, 2.36)	low	RoB, imprecision
55	Febuxostat 30mg bid	Febuxostat 80mg XR	NA	NA	1.45 (0.8, 2.66)	low	1.45 (0.8, 2.66)	low	RoB, imprecision
56	Febuxostat 30mg bid	Monthly Pegloticase 8mg	NA	NA	2.28 (0.27, 18.87)	very low	2.28 (0.27, 18.87)	low	RoB, imprecision
57	Febuxostat 30mg bid	Placebo	22.85 (1.48, 353.5)	low	36.82 (16.78, 80.81)	moderate	37.37 (17.54, 79.62)	moderate	RoB
58	Febuxostat 40mg XR	Febuxostat 40mg	1.23 (0.97, 1.54)	moderate	1.36 (0.8, 2.31)	low	1.31 (1, 1.71)	low	RoB
59	Febuxostat 40mg	Febuxostat 80mg	0.68 (0.62, 0.74)	moderate	0.72 (0.49, 1.05)	very low	0.67 (0.58, 0.77)	moderate	RoB
60	Febuxostat 40mg	Febuxostat 80mg + Lesinurad 200mg	NA	NA	0.53 (0.35, 0.81)	low	0.53 (0.35, 0.81)	moderate	RoB
61	Febuxostat 80mg XR	Febuxostat 40mg	1.53 (1.22, 1.91)	high	1.55 (0.93, 2.6)	low	1.55 (1.19, 2.03)	moderate	RoB, imprecision
62	Febuxostat 40mg	Monthly Pegloticase 8mg	NA	NA	1.01 (0.13, 7.83)	low	1.01 (0.13, 7.83)	low	RoB, imprecision
63	Febuxostat 40mg	Placebo	11.69 (6.6, 20.71)	moderate	10.52 (5.42, 20.4)	low	16.54 (9.53, 28.73)	moderate	RoB

64	Febuxostat 40mg XR	Febuxostat 80mg	0.84 (0.7, 1)	moderate	0.98 (0.51, 1.87)	low	0.87 (0.67, 1.14)	low	RoB, imprecision
65	Febuxostat 40mg XR	Febuxostat 80mg + Lesinurad 200mg	NA	NA	0.69 (0.43, 1.12)	low	0.69 (0.43, 1.12)	low	RoB, imprecision
66	Febuxostat 80mg XR	Febuxostat 40mg XR	1.25 (1.1, 1.42)	high	NA	NA	1.19 (0.89, 1.59)	low	RoB, imprecision
67	Febuxostat 40mg XR	Monthly Pegloticase 8mg	NA	NA	1.32 (0.17, 10.34)	low	1.32 (0.17, 10.34)	low	RoB, imprecision
68	Febuxostat 40mg XR	Placebo	30.8 (3.51, 269.91)	moderate	15.36 (7.87, 29.96)	moderate	21.6 (11.96, 39.02)	moderate	RoB
69	Febuxostat 80mg + Lesinurad 200mg	Febuxostat 80mg	1.26 (0.99, 1.59)	moderate	NA	NA	1.26 (0.84, 1.88)	low	RoB, imprecision
70	Febuxostat 80mg XR	Febuxostat 80mg	1.04 (0.88, 1.23)	moderate	1.16 (0.62, 2.18)	low	1.04 (0.8, 1.35)	low	RoB, imprecision
71	Febuxostat 80mg	Monthly Pegloticase 8mg	NA	NA	1.51 (0.19, 11.67)	low	1.51 (0.19, 11.67)	low	RoB, imprecision
72	Febuxostat 80mg	Placebo	25.61 (8.87, 73.93)	moderate	68.11 (4.51, 1028.69)	low	24.73 (14.43, 42.38)	moderate	RoB
73	Febuxostat 80mg + Lesinurad 200mg	Febuxostat 80mg XR	NA	NA	1.21 (0.75, 1.95)	low	1.21 (0.75, 1.95)	low	RoB, imprecision
74	Febuxostat 80mg + Lesinurad 200mg	Monthly Pegloticase 8mg	NA	NA	1.9 (0.24, 15.26)	low	1.9 (0.24, 15.26)	low	RoB, imprecision
75	Febuxostat 80mg + Lesinurad 200mg	Placebo	NA	NA	31.11 (15.88, 60.91)	moderate	31.11 (15.88, 60.91)	moderate	RoB
76	Febuxostat 80mg XR	Monthly Pegloticase 8mg	NA	NA	1.57 (0.2, 12.29)	low	1.57 (0.2, 12.29)	low	RoB, imprecision
77	Febuxostat 80mg XR	Placebo	35.29 (3.08, 403.99)	moderate	18.18 (9.35, 35.37)	moderate	25.69 (14.26, 46.3)	moderate	RoB
78	Monthly Pegloticase 8mg	Placebo	7.2 (1.03, 50.31)	low	$5.33 \times 10^{14} (2.98 \times 10^2, 9.54 \times 10^{26})$	moderate	16.41 (2.28, 118.2)	moderate	RoB

Estimates presented correspond to Treatment 1 (intervention) compared with Treatment 2 (comparison). Number above 1 indicate a greater number of patients with serum urate <6.0mg/dL with Treatment 1 (favors Treatment 1); while numbers below 1 indicate a greater number of patients with serum urate <6.0mg/dL with Treatment 2 (favors treatment 2).

**Table 6: Estimates and certainty for proportion of patients with pain closest to 3 months (follow up: 28 days).**

(Measured as proportion of patients with subjective adverse event of pain – analyzed as relative risk)

Comparison			Direct estimate		Indirect estimate		Network estimate		
	Intervention	Comparator	Point estimate (95% CI)	Certainty	Point estimate (95% CI)	Certainty	Point estimate (95% CI)	Certainty	Reasons
1	Febuxostat 40mg	Placebo	1.59 (0.27, 9.3)	low	NA	NA	NA	NA	risk of bias, imprecision
2	Febuxostat 80mg	Placebo	0.73 (0.11, 5.12)	low	NA	NA	NA	NA	NA
3	Febuxostat 120mg	Placebo	0.51 (0.06, 4.2)	very low	NA	NA	NA	NA	risk of bias, imprecision
4	Febuxostat 120mg	Febuxostat 40mg	0.32 (0.07, 1.51)	low	NA	NA	NA	NA	NA
5	Febuxostat 40mg	Febuxostat 80mg	2.16 (0.39, 11.89)	very low	NA	NA	NA	NA	risk of bias, imprecision
6	Febuxostat 120mg	Febuxostat 80mg	0.7 (0.09, 5.43)	very low	NA	NA	NA	NA	risk of bias, imprecision

Estimates presented correspond to Treatment 1 (intervention) compared with Treatment 2 (comparison). Number above 1 indicate a larger risk of pain with Treatment 1 (favors Treatment 2); while numbers below 1 indicate a larger risk of pain with Treatment 2 (favors treatment 1).

**Table 7: Estimates and certainty for change in pain score at longest follow-up (0 to 6.25 months).**

(Measured using 0 to 100mm visual analogue scale, where higher scores are worse – analyzed using mean difference)

Comparison		Direct estimate		Indirect estimate		Network estimate			
	Intervention	Comparator	Point estimate (95% CI)	Certainty	Point estimate (95% CI)	Certainty	Point estimate (95% CI)	Certainty	Reasons
1	Biweekly pegloticase 8 mg	Placebo	-12.80 (-27.53, 1.93)	very low	NA	NA	NA	NA	risk of bias, imprecision
2	Monthly pegloticase 8 mg	Placebo	-8.30 (-22.33, 5.73)	very low	NA	NA	NA	NA	risk of bias, imprecision
3	Biweekly pegloticase 8 mg	Monthly pegloticase 8 mg	-4.50 (-14.10, 5.10)	very low	NA	NA	NA	NA	risk of bias, imprecision

Estimates presented correspond to Treatment 1 (intervention) compared with Treatment 2 (comparison). Positive numbers indicate a larger reduction of pain levels with Treatment 2 (favors Treatment 2); while negative numbers indicate a larger reduction of pain levels with Treatment 1 (favors treatment 1).

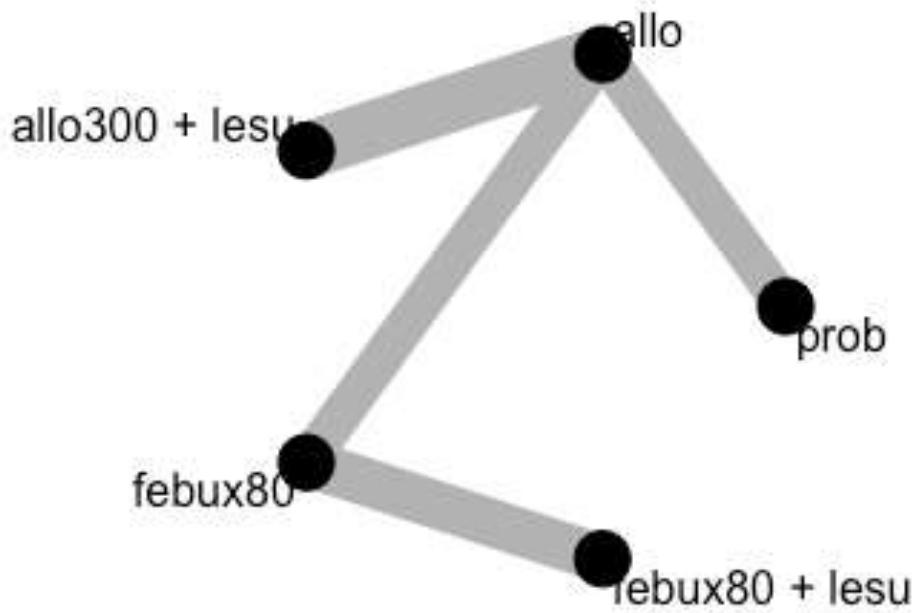
**Table 8: Estimates and certainty for change patient global assessment as measured on 100mm visual analogue scale at longest follow-up (0 to 6.25 months)**

(Measured using 0 to 100mm visual analogue scale, where higher scores are better – analyzed using mean difference)

Comparison		Direct estimate		Indirect estimate		Network estimate			
	Intervention	Comparator	Point estimate (95% CI)	Certainty	Point estimate (95% CI)	Certainty	Point estimate (95% CI)	Certainty	Reasons
1	Biweekly pegloticase 8 mg	Placebo	12.69 (0.36, 25.02)	moderate	NA	NA	NA	NA	risk of bias
2	Monthly pegloticase 8 mg	Placebo	13.48 (0.31, 26.65)	moderate	NA	NA	NA	NA	risk of bias
3	Biweekly pegloticase 8 mg	Monthly pegloticase 8 mg	-4.5 (-14.1, 5.1)	low	NA	NA	NA	NA	risk of bias, imprecision

Estimates presented correspond to Treatment 1 (intervention) compared with Treatment 2 (comparison). Positive numbers indicate a larger improvement in patient global assessment with Treatment 1 (favors Treatment 1); while negative numbers indicate a larger improvement in patient global assessment with Treatment 2 (favors treatment 2).

**Figure 5: Network plot for proportion of patients with tophus resolution at longest follow-up (range: 0 to 24 months)**



**Table 9: Estimates and certainty for proportion of patients with tophus resolution at longest follow-up (range: 0 to 24 months)**

(Measured as proportion of patients with resolution of at least 1 tophus – analyzed using relative risk)

Comparison			Direct estimate		Indirect estimate		Network estimate		
	Intervention	Comparator	Point estimate (95% CI)	Certainty	Point estimate (95% CI)	Certainty	Point estimate (95% CI)	Certainty	Reasons
<b>DIRECT COMPARISON ONLY</b>									
1	Biweekly pegloticase 8 mg	Placebo	5.45 (0.80, 36.99)	very low	NA	NA	NA	NA	risk of bias, imprecision
2	Monthly pegloticase 8 mg	Placebo	2.86 (0.40, 20.26)	low	NA	NA	NA	NA	risk of bias, imprecision
3	Biweekly pegloticase 8 mg	Monthly pegloticase 8 mg	1.91 (1.01, 3.55)	moderate	NA	NA	NA	NA	risk of bias,
<b>NETWORK COMPARISONS</b>									
1	Allopurinol 300mg + Lesinurad 200mg	Allopurinol 300mg	0.43 (0.05, 3.89)	moderate	NA	NA	0.43 (0.05, 3.89)	low	imprecision
2	Febuxostat 80mg	Allopurinol 300mg	2.04 (0.39, 10.66)	very low	NA	NA	2.04 (0.09, 44.64)	very low	risk of bias, imprecision
3	Allopurinol 300mg	Febuxostat 80mg + Lesinurad 200mg	NA	NA	0.45 (0.01, 26.07)	very low	0.45 (0.01, 26.07)	very low	risk of bias, imprecision
4	Allopurinol 300mg	Probenecid 2g	1.33 (0.27, 6.61)	very low	NA	NA	1.33 (0.06, 28.43)	very low	risk of bias, imprecision
5	Allopurinol 300mg + Lesinurad 200mg	Febuxostat 80mg	NA	NA	0.21 (0, 9.35)	very low	0.21 (0, 9.35)	very low	risk of bias, imprecision
6	Allopurinol 300mg + Lesinurad 200mg	Febuxostat 80mg + Lesinurad 200mg	NA	NA	0.19 (0, 19.56)	very low	0.19 (0, 19.56)	very low	risk of bias, imprecision
7	Allopurinol 300mg + Lesinurad 200mg	Probenecid 2g	NA	NA	0.57 (0.01, 24.8)	very low	0.57 (0.01, 24.8)	very low	risk of bias, imprecision
8	Febuxostat 80mg + Lesinurad 200mg	Febuxostat 80mg	1.08 (0.81, 1.45)	low	NA	NA	1.08 (0.08, 14.95)	very low	risk of bias, imprecision

9	Febuxostat 80mg	Probenecid 2g	NA	NA	2.72 (0.04, 209.97)	very low	2.72 (0.04, 209.97)	very low	risk of bias, imprecision
10	Febuxostat 80mg + Lesinurad 200mg	Probenecid 2g	NA	NA	2.94 (0.02, 472.67)	very low	2.94 (0.02, 472.67)	very low	risk of bias, imprecision

Estimates presented correspond to Treatment 1 (intervention) compared with Treatment 2 (comparison). Number above 1 indicate a greater number of patients with tophus resolution with Treatment 1 (favors Treatment 1); while numbers below 1 indicate a greater number of patients tophus resolution with Treatment 2 (favors treatment 2).

**Table 10: Estimates and certainty for change in health-related quality of life at longest follow-up (0 to 6.25 months)**

(Measured using physical component summary (PCS) score of 36-Item Short Form Health Survey (SF-36), where higher scores are better – analyzed using mean difference)

Comparison		Direct estimate		Indirect estimate		Network estimate			
	Intervention	Comparator	Point estimate (95% CI)	Certainty	Point estimate (95% CI)	Certainty	Point estimate (95% CI)	Certainty	Reasons
1	Biweekly pegloticase 8 mg	Placebo	4.70 (0.35, 9.05)	moderate	NA	NA	NA	NA	risk of bias
2	Monthly pegloticase 8 mg	Placebo	5.20 (0.95, 9.45)	moderate	NA	NA	NA	NA	risk of bias
3	Biweekly pegloticase 8 mg	Monthly pegloticase 8 mg	-0.5 (-3.33, 2.33)	low	NA	NA	NA	NA	risk of bias, imprecision

Estimates presented correspond to Treatment 1 (intervention) compared with Treatment 2 (comparison). Positive numbers indicate a larger improvement in health-related quality of life with Treatment 1 (favors Treatment 1); while negative numbers indicate a larger improvement in health-related quality of life with Treatment 2 (favors treatment 2).

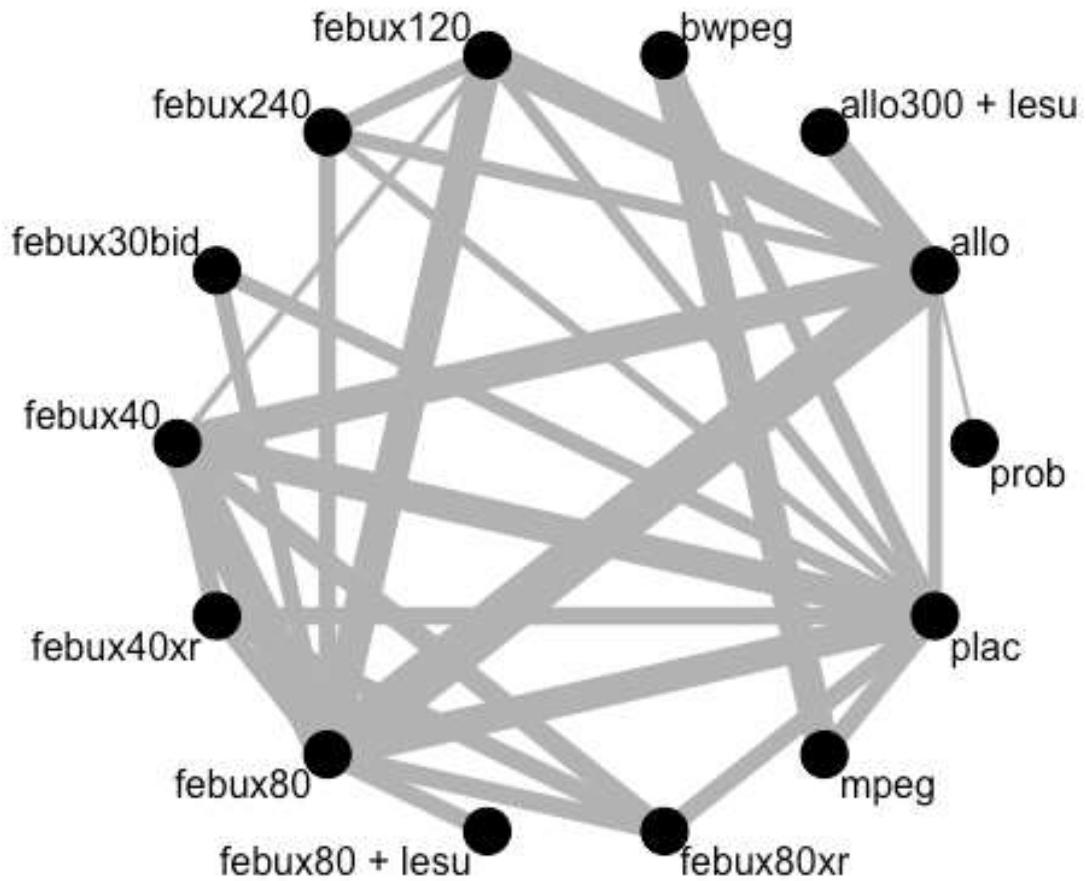
**Table 11: Estimates and certainty for change in activity limitation at longest follow-up (0 to 6.25 months).**

(Measured using Health Assessment Questionnaire-Disability Index score (HAQ-DI), where lower scores are better – analyzed using mean difference)

Comparison		Direct estimate		Indirect estimate		Network estimate			
	Intervention	Comparator	Point estimate (95% CI)	Certainty	Point estimate (95% CI)	Certainty	Point estimate (95% CI)	Certainty	Reasons
1	Biweekly pegloticase 8 mg	Placebo	-0.24 (-0.46, -0.02)	moderate	NA	NA	NA	NA	risk of bias
2	Monthly pegloticase 8 mg	Placebo	-0.22 (-0.43, -0.01)	moderate	NA	NA	NA	NA	risk of bias
3	Biweekly pegloticase 8 mg	Monthly pegloticase 8 mg	-0.02 (-0.21, 0.17)	low	NA	NA	NA	NA	risk of bias, imprecision

Estimates presented correspond to Treatment 1 (intervention) compared with Treatment 2 (comparison). Negative numbers indicate a larger improvement in activity limitation with Treatment 1 (favors Treatment 1); while positive numbers indicate a larger improvement in activity limitation with Treatment 2 (favors treatment 2).

**Figure 6: Network plot for proportion of patients with serious adverse events at longest follow-up (range: 28 days to 24 months)**



**Table 12: Estimates and certainty for proportion of patients with serious adverse events at longest follow-up (range: 28 days to 24 months)**

(Measured as proportion of patients with serious adverse events – analyzed with relative risk)

Comparison		Direct estimate		Indirect estimate		Network estimate			
	Intervention	Comparator	Point estimate (95% CI)	Certainty	Point estimate (95% CI)	Certainty	Point estimate (95% CI)	Certainty	Reasons
1	Allopurinol 300mg + Lesinurad 200mg	Allopurinol 300mg	0.95 (0.51, 1.79)	moderate	NA	NA	0.95 (0.5, 1.78)	moderate	imprecision
2	Allopurinol 300mg	Biweekly pegloticase 8 mg	NA	NA	0.76 (0.26, 2.19)	low	0.76 (0.26, 2.19)	low	risk of bias, imprecision
3	Febuxostat 120mg	Allopurinol 300mg	1.54 (0.73, 3.26)	low	1.22 (3.21, 0.46)	very low	1.48 (2.42, 0.91)	very low	risk of bias, imprecision
4	Febuxostat 240mg	Allopurinol 300mg	1.43 (0.31, 6.59)	low	0.84 (5.52, 0.13)	low	1.24 (3.27, 0.47)	low	risk of bias, imprecision
5	Allopurinol 300mg	Febuxostat 30mg bid	NA	NA	1.88 (0.7, 5.1)	low	1.88 (0.7, 5.1)	low	risk of bias, imprecision
6	Febuxostat 40mg	Allopurinol 300mg	1.3 (0.02, 68.22)	very low	1.29 (2.92, 0.57)	low	0.77 (1.21, 0.5)	very low	risk of bias, inconsistency, imprecision
7	Allopurinol 300mg	Febuxostat 40mg XR	NA	NA	1.91 (0.79, 4.6)	very low	1.91 (0.79, 4.6)	very low	risk of bias, imprecision
8	Febuxostat 80mg	Allopurinol 300mg	1 (0.62, 1.59)	low	0.4 (1.52, 0.11)	very low	0.95 (1.36, 0.66)	low	risk of bias, imprecision
9	Febuxostat 80mg XR	Febuxostat 80mg + Lesinurad 200mg	1 (0.62, 1.59)	low	1.71 (0.6, 4.83)	very low	1.71 (0.6, 4.83)	low	risk of bias, imprecision
10	Allopurinol 300mg	Febuxostat 80mg XR	NA	NA	1.06 (0.49, 2.31)	low	1.06 (0.49, 2.31)	low	risk of bias, imprecision
11	Febuxostat 80mg + Lesinurad 200mg	Monthly pegloticase 8 mg	NA	NA	0.79 (0.27, 2.28)	low	0.79 (0.27, 2.28)	low	risk of bias, imprecision
12	Allopurinol 300mg	Placebo	2.03 (0.58, 7.14)	moderate	1.44 (0.79, 2.62)	very low	1.54 (0.89, 2.64)	low	risk of bias, imprecision
13	Allopurinol 300mg	Probenecid 2g	0.85 (0.02, 40.83)	very low	NA	NA	0.85 (0.02, 40.83)	very low	risk of bias, imprecision x2

14	Allopurinol 300mg + Lesinurad 200mg	Biweekly pegloticase 8 mg	NA	NA	0.72 (0.21, 2.47)	low	0.72 (0.21, 2.47)	low	risk of bias, imprecision
15	Allopurinol 300mg + Lesinurad 200mg	Febuxostat 120mg	NA	NA	0.64 (0.29, 1.42)	low	0.64 (0.29, 1.42)	low	risk of bias, imprecision
16	Allopurinol 300mg + Lesinurad 200mg	Febuxostat 240mg	NA	NA	0.76 (0.24, 2.42)	low	0.76 (0.24, 2.42)	low	risk of bias, imprecision
17	Allopurinol 300mg + Lesinurad 200mg	Febuxostat 30mg bid	NA	NA	1.79 (0.55, 5.81)	low	1.79 (0.55, 5.81)	low	risk of bias, imprecision
18	Allopurinol 300mg + Lesinurad 200mg	Febuxostat 40mg	NA	NA	1.22 (0.57, 2.65)	very low	1.22 (0.57, 2.65)	very low	risk of bias, imprecision x2
19	Allopurinol 300mg + Lesinurad 200mg	Febuxostat 40mg XR	NA	NA	1.81 (0.61, 5.34)	low	1.81 (0.61, 5.34)	low	risk of bias, imprecision
20	Allopurinol 300mg + Lesinurad 200mg	Febuxostat 80mg	NA	NA	1 (0.48, 2.07)	low	1 (0.48, 2.07)	low	risk of bias, imprecision
21	Allopurinol 300mg + Lesinurad 200mg	Febuxostat 80mg + Lesinurad 200mg	NA	NA	1.62 (0.48, 5.47)	low	1.62 (0.48, 5.47)	low	risk of bias, imprecision
22	Allopurinol 300mg + Lesinurad 200mg	Febuxostat 80mg XR	NA	NA	1.01 (0.37, 2.74)	low	1.01 (0.37, 2.74)	low	risk of bias, imprecision
23	Allopurinol 300mg + Lesinurad 200mg	Monthly pegloticase 8 mg	NA	NA	0.75 (0.22, 2.58)	low	0.75 (0.22, 2.58)	low	risk of bias, imprecision
24	Allopurinol 300mg + Lesinurad 200mg	Placebo	NA	NA	1.46 (0.63, 3.35)	low	1.46 (0.63, 3.35)	low	risk of bias, imprecision

25	Allopurinol 300mg + Lesinurad 200mg	Probenecid 2g	NA	NA	0.81 (0.02, 40.76)	very low	0.81 (0.02, 40.76)	very low	risk of bias, imprecision x2
26	Biweekly pegloticase 8 mg	Febuxostat 120mg	NA	NA	0.89 (0.29, 2.68)	low	0.89 (0.29, 2.68)	low	risk of bias, imprecision
27	Biweekly pegloticase 8 mg	Febuxostat 240mg	NA	NA	1.06 (0.27, 4.21)	low	1.06 (0.27, 4.21)	low	risk of bias, imprecision
28	Biweekly pegloticase 8 mg	Febuxostat 30mg bid	NA	NA	2.48 (0.66, 9.28)	low	2.48 (0.66, 9.28)	low	risk of bias, imprecision
29	Biweekly pegloticase 8 mg	Febuxostat 40mg	NA	NA	1.7 (0.61, 4.74)	low	1.7 (0.61, 4.74)	low	risk of bias, imprecision
30	Biweekly pegloticase 8 mg	Febuxostat 40mg XR	NA	NA	2.52 (0.72, 8.76)	low	2.52 (0.72, 8.76)	low	risk of bias, imprecision
31	Biweekly pegloticase 8 mg	Febuxostat 80mg	NA	NA	1.39 (0.5, 3.88)	low	1.39 (0.5, 3.88)	low	risk of bias, imprecision
32	Biweekly pegloticase 8 mg	Febuxostat 80mg + Lesinurad 200mg	NA	NA	2.25 (0.55, 9.29)	low	2.25 (0.55, 9.29)	low	risk of bias, imprecision
33	Biweekly pegloticase 8 mg	Febuxostat 80mg XR	NA	NA	1.4 (0.43, 4.54)	low	1.4 (0.43, 4.54)	low	risk of bias, imprecision
34	Biweekly pegloticase 8 mg	Monthly pegloticase 8 mg	1.04 (0.6, 1.8)	low	NA	NA	1.04 (0.6, 1.8)	low	risk of bias, imprecision
35	Biweekly pegloticase 8 mg	Placebo	1.98 (0.83, 4.73)	low	NA	NA	2.02 (0.82, 5.02)	low	risk of bias, imprecision
36	Biweekly pegloticase 8 mg	Probenecid 2g	NA	NA	1.12 (0.02, 62)	very low	1.12 (0.02, 62)	very low	risk of bias, imprecision x2
37	Febuxostat 120mg	Febuxostat 240mg	NA	NA	5.06 (0.46, 56.2)	very low	1.2 (0.45, 3.19)	very low	risk of bias, imprecision x2
38	Febuxostat 120mg	Febuxostat 30mg bid	NA	NA	2.8 (0.99, 7.94)	very low	2.8 (0.99, 7.94)	very low	risk of bias, imprecision x2
39	Febuxostat 120mg	Febuxostat 40mg	4.87 (0.24, 98.1)	very low	1.88 (1.04, 3.4)	very low	1.92 (1.08, 3.41)	very low	risk of bias, inconsistency, imprecision
40	Febuxostat 120mg	Febuxostat 40mg XR	NA	NA	2.83 (1.11, 7.27)	very low	2.83 (1.11, 7.27)	very low	risk of bias, imprecision x2

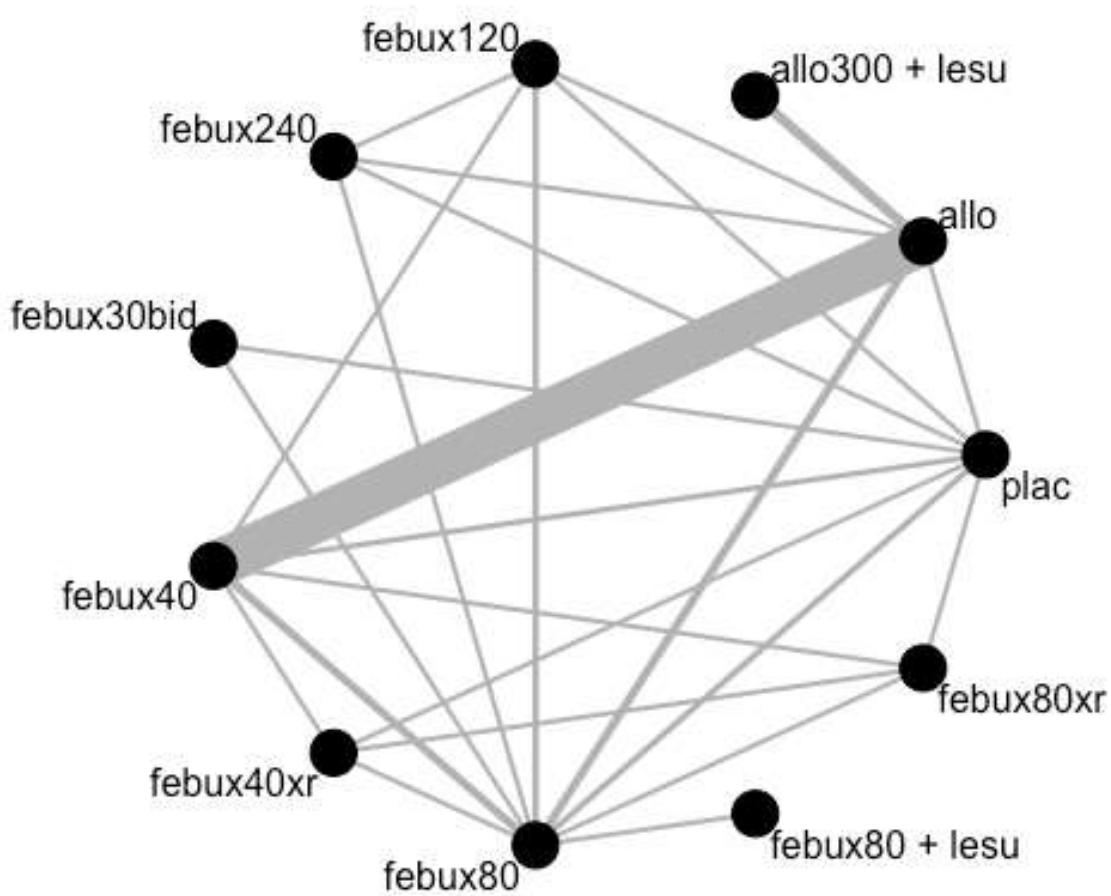
41	Febuxostat 120mg	Febuxostat 80mg	1.42 (0.81, 2.51)	very low	3.04 (1.03, 8.96)	low	1.56 (0.98, 2.5)	very low	risk of bias, inconsistency, imprecision
42	Febuxostat 120mg	Febuxostat 80mg + Lesinurad 200mg	NA	NA	2.54 (0.86, 7.49)	very low	2.54 (0.86, 7.49)	very low	risk of bias, imprecision x2
43	Febuxostat 120mg	Febuxostat 80mg XR	NA	NA	1.57 (0.67, 3.68)	very low	1.57 (0.67, 3.68)	very low	risk of bias, imprecision x2
44	Febuxostat 120mg	Monthly pegloticase 8 mg	NA	NA	1.17 (0.39, 3.56)	low	1.17 (0.39, 3.56)	low	risk of bias, imprecision
45	Febuxostat 120mg	Placebo	2.03 (0.31, 13.53)	very low	2.25 (1.09, 4.64)	very low	2.28 (1.21, 4.29)	very low	risk of bias, imprecision x2
46	Febuxostat 120mg	Probenecid 2g	NA	NA	1.27 (0.03, 62.5)	very low	1.27 (0.03, 62.5)	very low	risk of bias, imprecision x2
47	Febuxostat 240mg	Febuxostat 30mg bid	NA	NA	2.34 (0.62, 8.86)	low	2.34 (0.62, 8.86)	low	risk of bias, imprecision
48	Febuxostat 240mg	Febuxostat 40mg	NA	NA	1.6 (0.58, 4.41)	low	1.6 (0.58, 4.41)	low	risk of bias, imprecision
49	Febuxostat 240mg	Febuxostat 40mg XR	NA	NA	2.37 (0.68, 8.31)	low	2.37 (0.68, 8.31)	low	risk of bias, imprecision
50	Febuxostat 240mg	Febuxostat 80mg	0.91 (0.28, 2.98)	low	9.74 (0.87, 109.43)	low	1.31 (0.5, 3.39)	low	risk of bias, imprecision
51	Febuxostat 240mg	Febuxostat 80mg + Lesinurad 200mg	NA	NA	2.12 (0.54, 8.3)	low	2.12 (0.54, 8.3)	low	risk of bias, imprecision
52	Febuxostat 240mg	Febuxostat 80mg XR	NA	NA	1.32 (0.4, 4.31)	low	1.32 (0.4, 4.31)	low	risk of bias, imprecision
53	Febuxostat 240mg	Monthly pegloticase 8 mg	NA	NA	0.98 (0.25, 3.91)	low	0.98 (0.25, 3.91)	low	risk of bias, imprecision
54	Febuxostat 240mg	Placebo	2.51 (0.2, 31.38)	very low	1.58 (0.41, 6.1)	very low	1.91 (0.68, 5.38)	low	risk of bias, imprecision
55	Febuxostat 240mg	Probenecid 2g	NA	NA	1.06 (0.02, 57.15)	very low	1.06 (0.02, 57.15)	very low	risk of bias, imprecision x2
56	Febuxostat 30mg bid	Febuxostat 40mg	NA	NA	0.69 (0.25, 1.84)	low	0.69 (0.25, 1.84)	low	risk of bias, imprecision
57	Febuxostat 30mg bid	Febuxostat 40mg XR	NA	NA	1.01 (0.3, 3.45)	very low	1.01 (0.3, 3.45)	low	risk of bias, imprecision
58	Febuxostat 30mg bid	Febuxostat 80mg	0.63 (0.23, 1.71)	low	0.24 (0.01, 3.85)	low	0.56 (0.22, 1.44)	low	risk of bias, imprecision

59	Febuxostat 30mg bid	Febuxostat 80mg + Lesinurad 200mg	NA	NA	0.91 (0.23, 3.53)	low	0.91 (0.23, 3.53)	low	risk of bias, imprecision
60	Febuxostat 30mg bid	Febuxostat 80mg XR	NA	NA	0.56 (0.18, 1.79)	low	0.56 (0.18, 1.79)	low	risk of bias, imprecision
61	Febuxostat 30mg bid	Monthly pegloticase 8 mg	NA	NA	0.42 (0.11, 1.57)	low	0.42 (0.11, 1.57)	low	risk of bias, imprecision
62	Febuxostat 30mg bid	Placebo	0.71 (0.21, 2.44)	low	1.69 (0.15, 19.45)	low	0.82 (0.31, 2.12)	low	risk of bias, imprecision
63	Febuxostat 30mg bid	Probenecid 2g	NA	NA	0.45 (0.01, 24.58)	very low	0.45 (0.01, 24.58)	very low	risk of bias, imprecision x2
64	Febuxostat 40mg XR	Febuxostat 40mg	0.54 (0.17, 1.74)	low	2.08 (0.24, 17.83)	very low	0.68 (0.3, 1.54)	low	risk of bias, imprecision
65	Febuxostat 40mg	Febuxostat 80mg	0.77 (0.47, 1.26)	moderate	0.62 (0.25, 1.54)	low	0.82 (0.54, 1.23)	moderate	imprecision
66	Febuxostat 40mg	Febuxostat 80mg + Lesinurad 200mg	NA	NA	1.32 (0.46, 3.81)	very low	1.32 (0.46, 3.81)	very low	risk of bias, imprecision x2
67	Febuxostat 80mg XR	Febuxostat 40mg	0.97 (0.23, 4.09)	low	4.31 (0.87, 21.23)	very low	1.22 (0.6, 2.47)	low	risk of bias, imprecision
68	Febuxostat 40mg	Monthly pegloticase 8 mg	NA	NA	0.61 (0.22, 1.71)	low	0.61 (0.22, 1.71)	low	risk of bias, imprecision
69	Febuxostat 40mg	Placebo	1.14 (0.59, 2.18)	moderate	0.9 (0.37, 2.18)	very low	1.19 (0.74, 1.91)	moderate	imprecision
70	Febuxostat 40mg	Probenecid 2g	NA	NA	0.66 (0.01, 32.45)	very low	0.66 (0.01, 32.45)	very low	risk of bias, imprecision x2
71	Febuxostat 40mg XR	Febuxostat 80mg	0.78 (0.21, 2.87)	low	0.18 (0.04, 0.88)	low	0.55 (0.24, 1.28)	low	risk of bias, imprecision
72	Febuxostat 40mg XR	Febuxostat 80mg + Lesinurad 200mg	NA	NA	0.89 (0.25, 3.24)	low	0.89 (0.25, 3.24)	low	risk of bias, imprecision
73	Febuxostat 80mg XR	Febuxostat 40mg XR	1.65 (0.64, 4.23)	low	3333.33 (0.55, $\infty$ )	very low	1.8 (0.73, 4.42)	low	risk of bias, imprecision
74	Febuxostat 40mg XR	Monthly pegloticase 8 mg	NA	NA	0.41 (0.12, 1.45)	low	0.41 (0.12, 1.45)	low	risk of bias, imprecision
75	Febuxostat 40mg XR	Placebo	0.76 (0.19, 3.13)	low	0.67 (0.13, 3.54)	low	0.8 (0.34, 1.89)	low	risk of bias, imprecision

76	Febuxostat 40mg XR	Probenecid 2g	NA	NA	0.45 (0.01, 23.6)	very low	0.45 (0.01, 23.6)	very low	risk of bias, imprecision x2
77	Febuxostat 80mg + Lesinurad 200mg	Febuxostat 80mg	0.62 (0.23, 1.64)	low	NA	NA	0.62 (0.23, 1.64)	low	risk of bias, imprecision
78	Febuxostat 80mg XR	Febuxostat 80mg	1.22 (0.36, 4.2)	low	0.67 (0.2, 2.25)	low	0.99 (0.48, 2.07)	low	risk of bias, imprecision
79	Febuxostat 80mg	Monthly pegloticase 8 mg	NA	NA	0.75 (0.27, 2.1)	low	0.75 (0.27, 2.1)	low	risk of bias, imprecision
80	Febuxostat 80mg	Placebo	1.13 (0.52, 2.43)	low	1.85 (0.77, 4.45)	low	1.46 (0.9, 2.36)	low	risk of bias, imprecision
81	Febuxostat 80mg	Probenecid 2g	NA	NA	0.81 (0.02, 39.4)	very low	0.81 (0.02, 39.4)	very low	risk of bias, imprecision x2
82	Febuxostat 80mg + Lesinurad 200mg	Febuxostat 80mg XR	NA	NA	0.62 (0.18, 2.11)	low	0.62 (0.18, 2.11)	low	risk of bias, imprecision
83	Febuxostat 80mg + Lesinurad 200mg	Monthly pegloticase 8 mg	NA	NA	0.46 (0.11, 1.91)	low	0.46 (0.11, 1.91)	low	risk of bias, imprecision
84	Febuxostat 80mg + Lesinurad 200mg	Placebo	NA	NA	0.9 (0.3, 2.67)	low	0.9 (0.3, 2.67)	low	risk of bias, imprecision
85	Febuxostat 80mg + Lesinurad 200mg	Probenecid 2g	NA	NA	0.5 (0.01, 27.43)	very low	0.5 (0.01, 27.43)	very low	risk of bias, imprecision x2
86	Febuxostat 80mg XR	Monthly pegloticase 8 mg	NA	NA	0.74 (0.23, 2.43)	low	0.74 (0.23, 2.43)	low	risk of bias, imprecision
87	Febuxostat 80mg XR	Placebo	1.22 (0.32, 4.7)	low	1.96 (0.53, 7.22)	low	1.45 (0.68, 3.07)	low	risk of bias, imprecision
88	Febuxostat 80mg XR	Probenecid 2g	NA	NA	0.8 (0.02, 41.59)	very low	0.8 (0.02, 41.59)	very low	risk of bias, imprecision x2
89	Monthly pegloticase 8 mg	Placebo	1.95 (0.57, 6.66)	low	NA	NA	1.95 (0.78, 4.85)	low	risk of bias, imprecision
90	Monthly pegloticase 8 mg	Probenecid 2g	NA	NA	1.08 (0.02, 59.68)	very low	1.08 (0.02, 59.68)	very low	risk of bias, imprecision x2
91	Probenecid 2g	Placebo	NA	NA	1.8 (0.04, 89.29)	very low	1.8 (0.04, 89.29)	very low	risk of bias, imprecision x2

Estimates presented correspond to Treatment 1 (intervention) compared with Treatment 2 (comparison). Number above 1 indicate a larger risk of serious adverse events with Treatment 1 (favors Treatment 2); while numbers below 1 indicate a larger risk of serious adverse events with Treatment 2 (favors treatment 1).

**Figure 7: Network plot for proportion of patients with cardiovascular-related serious, Longest follow-up (range: 28 day to median of 32 months)**



**Table 13: Estimates and certainty for proportion of patients with cardiovascular-related serious, longest follow-up (range: 28 day to median of 32 months)**

Comparison			Direct estimate		Indirect estimate		Network estimate		
	Intervention	Comparator	Point estimate (95% CI)	Certainty	Point estimate (95% CI)	Certainty	Point estimate (95% CI)	Certainty	Reasons
1	Allopurinol 300mg + Lesinurad 200mg	Allopurinol 300mg	0.95 (0.49, 1.83)	moderate	NA	NA	0.95 (0.49, 1.83)	moderate	imprecision
2	Febuxostat 120mg	Allopurinol 300mg	2.18 (0.19, 24.97)	very low	1.01 (0.23, 4.51)	low	1.51 (0.51, 4.44)	low	Risk of bias, imprecision
3	Febuxostat 240mg	Allopurinol 300mg	2.01 (0.04, 102.01)	very low	0.14 (0, 3.85)	very low	0.67 (0.08, 5.65)	very low	Risk of bias, imprecisionX2
4	Febuxostat 30mg bid	Allopurinol 300mg	NA	NA	4.03 (0.21, 78.34)	very low	4.03 (0.21, 78.34)	very low	Risk of bias, imprecisionX2
5	Febuxostat 40mg	Allopurinol 300mg	1.04 (0.9, 1.2)	moderate	1.32 (0.16, 10.92)	very low	1.05 (0.91, 1.21)	low	Risk of bias, imprecision
6	Febuxostat 40mg XR	Allopurinol 300mg	NA	NA	0.37 (0.09, 1.57)	very low	0.37 (0.09, 1.57)	very low	Risk of bias, imprecisionX2
7	Febuxostat 80mg	Allopurinol 300mg	1.19 (0.44, 3.22)	low	1.06 (0.38, 2.97)	low	1.3 (0.7, 2.45)	low	Risk of bias, imprecision
8	Febuxostat 80mg + Lesinurad 200mg	Allopurinol 300mg	NA	NA	0.25 (0.02, 2.56)	very low	0.25 (0.02, 2.56)	very low	Risk of bias, imprecisionX2
9	Febuxostat 80mg XR	Allopurinol 300mg	NA	NA	0.65 (0.11, 3.92)	low	0.65 (0.11, 3.92)	low	Risk of bias, imprecision
10	Allopurinol 300mg	Placebo	0.5 (0.03, 7.93)	low	0.74 (0.27, 2.01)	low	0.72 (0.29, 1.8)	low	Risk of bias, imprecision
11	Allopurinol 300mg + Lesinurad 200mg	Febuxostat 120mg	NA	NA	0.63 (0.18, 2.22)	low	0.63 (0.18, 2.22)	low	Risk of bias, imprecision
12	Allopurinol 300mg + Lesinurad 200mg	Febuxostat 240mg	NA	NA	1.41 (0.15, 13.12)	very low	1.41 (0.15, 13.12)	very low	Risk of bias, imprecisionX2
13	Allopurinol 300mg + Lesinurad 200mg	Febuxostat 30mg bid	NA	NA	3.82 (0.18, 79.86)	very low	3.82 (0.18, 79.86)	very low	Risk of bias, imprecisionX2

14	Allopurinol 300mg + Lesinurad 200mg	Febuxostat 40mg	NA	NA	0.91 (0.46, 1.77)	low	0.91 (0.46, 1.77)	low	Risk of bias, imprecision
15	Allopurinol 300mg + Lesinurad 200mg	Febuxostat 40mg XR	NA	NA	0.35 (0.07, 1.72)	low	0.35 (0.07, 1.72)	very low	Risk of bias, imprecisionX2
16	Allopurinol 300mg + Lesinurad 200mg	Febuxostat 80mg	NA	NA	0.73 (0.29, 1.8)	low	0.73 (0.29, 1.8)	low	Risk of bias, imprecision
17	Allopurinol 300mg + Lesinurad 200mg	Febuxostat 80mg + Lesinurad 200mg	NA	NA	0.24 (0.02, 2.66)	very low	0.24 (0.02, 2.66)	very low	Risk of bias, imprecisionX2
18	Allopurinol 300mg + Lesinurad 200mg	Febuxostat 80mg XR	NA	NA	0.62 (0.09, 4.17)	very low	0.62 (0.09, 4.17)	very low	Risk of bias, imprecisionX2
19	Allopurinol 300mg + Lesinurad 200mg	Placebo	NA	NA	0.68 (0.22, 2.11)	low	0.68 (0.22, 2.11)	low	Risk of bias, imprecision
20	Febuxostat 120mg	Febuxostat 240mg	0.9 (0.31, 2.62)	low	0.05 (0, 23582.8)	very low	2.25 (0.27, 18.53)	very low	Risk of bias, imprecisionX2
21	Febuxostat 120mg	Febuxostat 30mg bid	NA	NA	6.08 (0.28, 131.74)	very low	6.08 (0.28, 131.74)	very low	Risk of bias, imprecisionX2
22	Febuxostat 120mg	Febuxostat 40mg	0.97 (0.02, 47.7)	very low	1.49 (0.48, 4.58)	low	1.44 (0.49, 4.24)	low	Risk of bias, imprecision
23	Febuxostat 120mg	Febuxostat 40mg XR	NA	NA	0.55 (0.1, 3.02)	low	0.55 (0.1, 3.02)	low	Risk of bias, imprecision
24	Febuxostat 120mg	Febuxostat 80mg	0.83 (0.24, 2.84)	low	8.52 (0.49, 147.11)	very low	1.16 (0.43, 3.12)	low	Risk of bias, imprecision
25	Febuxostat 120mg	Febuxostat 80mg + Lesinurad 200mg	NA	NA	0.38 (0.03, 4.38)	very low	0.38 (0.03, 4.38)	very low	Risk of bias, imprecisionX2
26	Febuxostat 120mg	Febuxostat 80mg XR	NA	NA	0.99 (0.14, 7.22)	low	0.99 (0.14, 7.22)	low	Risk of bias, imprecision
27	Febuxostat 120mg	Placebo	2.53 (0.08, 84.65)	very low	0.68 (0.13, 3.46)	low	1.09 (0.32, 3.71)	low	Risk of bias, imprecision
28	Febuxostat 240mg	Febuxostat 30mg bid	NA	NA	2.7 (0.08, 96.79)	very low	2.7 (0.08, 96.79)	very low	Risk of bias, imprecisionX2

29	Febuxostat 240mg	Febuxostat 40mg	NA	NA	0.64 (0.08, 5.4)	very low	0.64 (0.08, 5.4)	low	Risk of bias, imprecision
30	Febuxostat 240mg	Febuxostat 40mg XR	NA	NA	0.25 (0.02, 2.98)	very low	0.25 (0.02, 2.98)	very low	Risk of bias, imprecisionX2
31	Febuxostat 240mg	Febuxostat 80mg	0.4 (0.04, 4.02)	very low	52.11 (0.01, 4.52 x 10 <sup>5</sup> )	very low	0.52 (0.06, 4.12)	very low	Risk of bias, imprecisionX2
32	Febuxostat 240mg	Febuxostat 80mg + Lesinurad 200mg	NA	NA	0.17 (0.01, 3.57)	very low	0.17 (0.01, 3.57)	very low	Risk of bias, imprecisionX2
33	Febuxostat 240mg	Febuxostat 80mg XR	NA	NA	0.44 (0.03, 6.55)	very low	0.44 (0.03, 6.55)	very low	Risk of bias, imprecisionX2
34	Febuxostat 240mg	Placebo	1.02 (0.02, 51.3)	very low	0.14 (0, 5.23)	very low	0.48 (0.05, 4.37)	very low	Risk of bias, imprecisionX2
35	Febuxostat 30mg bid	Febuxostat 40mg	NA	NA	0.24 (0.01, 4.61)	very low	0.24 (0.01, 4.61)	very low	Risk of bias, imprecisionX2
36	Febuxostat 30mg bid	Febuxostat 40mg XR	NA	NA	0.09 (0, 2.23)	very low	0.09 (0, 2.23)	very low	Risk of bias, imprecisionX2
37	Febuxostat 30mg bid	Febuxostat 80mg	0.33 (0.01, 7.88)	very low	0.01 (0, 15.92)	very low	0.19 (0.01, 3.62)	very low	Risk of bias, imprecisionX2
38	Febuxostat 30mg bid	Febuxostat 80mg + Lesinurad 200mg	NA	NA	0.06 (0, 2.51)	very low	0.06 (0, 2.51)	very low	Risk of bias, imprecisionX2
39	Febuxostat 30mg bid	Febuxostat 80mg XR	NA	NA	0.16 (0.01, 4.68)	very low	0.16 (0.01, 4.68)	very low	Risk of bias, imprecisionX2
40	Febuxostat 30mg bid	Placebo	0.13 (0.01, 2.66)	very low	1.07 x 10 <sup>3</sup> (0, 8.52 x 10 <sup>10</sup> )	very low	0.18 (0.01, 3.2)	very low	Risk of bias, imprecisionX2
41	Febuxostat 40mg XR	Febuxostat 40mg	2.34 (0.12, 46.37)	very low	1.91 (0.27, 13.32)	very low	2.6 (0.61, 11.11)	very low	Risk of bias, imprecisionX2
42	Febuxostat 40mg	Febuxostat 80mg	1.01 (0.42, 2.39)	moderate	0.61 (0.22, 1.7)	low	0.8 (0.43, 1.5)	low	Risk of bias, imprecision
43	Febuxostat 40mg	Febuxostat 80mg + Lesinurad 200mg	NA	NA	0.26 (0.03, 2.68)	very low	0.26 (0.03, 2.68)	very low	Risk of bias, imprecisionX2

44	Febuxostat 80mg XR	Febuxostat 40mg	1.44 (0.06, 33.71)	very low	1.08 (0.08, 14.53)	very low	1.46 (0.24, 8.73)	low	Risk of bias, imprecision
45	Febuxostat 40mg	Placebo	0.6 (0.15, 2.36)	low	0.81 (0.2, 3.26)	low	0.75 (0.3, 1.87)	low	Risk of bias, imprecision
46	Febuxostat 40mg XR	Febuxostat 80mg	1.58 (0.08, 30.81)	very low	2.77 (0.27, 28.48)	very low	2.09 (0.5, 8.7)	low	Risk of bias, imprecision
47	Febuxostat 40mg XR	Febuxostat 80mg + Lesinurad 200mg	NA	NA	0.68 (0.05, 9.7)	very low	0.68 (0.05, 9.7)	very low	Risk of bias, imprecisionX2
48	Febuxostat 80mg XR	Febuxostat 40mg XR	0.51 (0.05, 5.43)	very low	NA	NA	0.56 (0.11, 3)	low	Risk of bias, imprecision
49	Febuxostat 40mg XR	Placebo	1.22 (0.1, 14.12)	very low	2.37 (0.2, 28.54)	very low	1.96 (0.45, 8.45)	low	Risk of bias, imprecision
50	Febuxostat 80mg + Lesinurad 200mg	Febuxostat 80mg	3.08 (0.33, 29.19)	very low	NA	NA	3.08 (0.33, 29.15)	very low	Risk of bias, imprecisionX2
51	Febuxostat 80mg XR	Febuxostat 80mg	0.97 (0.04, 22.42)	very low	1.53 (0.09, 26.67)	very low	1.17 (0.2, 6.88)	low	Risk of bias, imprecision
52	Febuxostat 80mg	Placebo	0.78 (0.16, 3.78)	low	0.68 (0.13, 3.42)	low	0.94 (0.38, 2.29)	low	Risk of bias, imprecision
53	Febuxostat 80mg + Lesinurad 200mg	Febuxostat 80mg XR	NA	NA	2.63 (0.15, 45.91)	very low	2.63 (0.15, 45.91)	very low	Risk of bias, imprecisionX2
54	Febuxostat 80mg + Lesinurad 200mg	Placebo	NA	NA	2.9 (0.26, 32.51)	very low	2.9 (0.26, 32.51)	very low	Risk of bias, imprecisionX2
55	Febuxostat 80mg XR	Placebo	0.41 (0.04, 4.31)	very low	1.29 (0.06, 25.55)	very low	1.1 (0.18, 6.65)	low	Risk of bias, imprecision

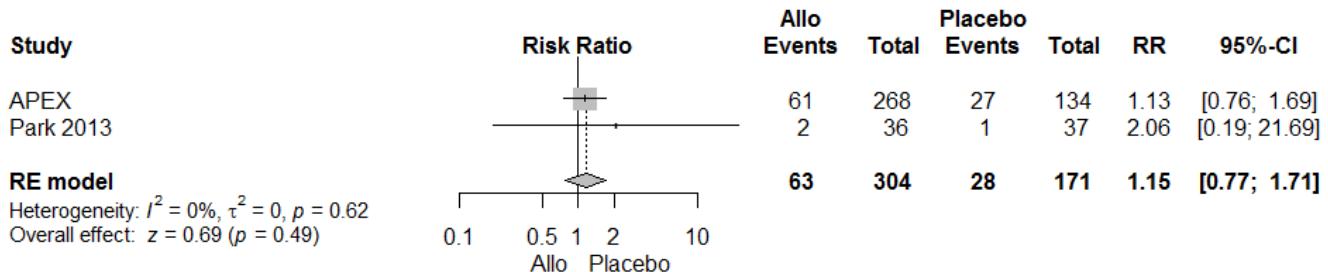
Estimates presented correspond to Treatment 1 (intervention) compared with Treatment 2 (comparison). Number above 1 indicate a larger risk of serious adverse events with Treatment 1 (favors Treatment 2); while numbers below 1 indicate a larger risk of serious adverse events with Treatment 2 (favors treatment 1).

**Figure 8: Risk of bias assessment.**

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias) – Objective outcomes	Blinding of outcome assessment (detection bias) – Objective outcomes	Blinding of participants and personnel (performance bias) – Subjective outcomes	Blinding of outcome assessment (detection bias) – Subjective outcomes	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
APEX	?	?	+	+	+	?	?	?	+
Bardin 2017	+	+	+	+	+	+	+	+	+
Becker 2005	+	?	+	+	+	+	+	+	+
CONFIRMS	+	+	+	+	+	+	+	+	+
Dalbeth 2017a	+	+	+	+	?	?	+	+	+
Dalbeth 2017b	?	?	+	+	+	+	+	+	+
FACT	+	+	?	+	?	?	?	+	+
Gibson 1979	?	?	?	?			+	+	+
Goldfarb 2011	?	?	+	+	+	+	+	+	+
Gunawardhana 2018	+	+	+	+	+	+	+	+	+
Huang 2014	+	+	+	+	+	+	+	+	+
Park 2013	?	?	?	+			+	+	+
Polley 2016	?	?	+	+	+	+	+	+	+
Saag 2016	+	?	+	+	+	+	+	+	+
Saag 2017	+	+	+	+	+	+	+	+	+
Saag 2019	+	+	+	+	+	+	+	+	+
Scott 1966	+	+	?	+	?	?	+	+	+
Sundy 2011	+	+	+	+	+	+	+	+	+
White 2018	?	?	+	+	+	+	+	+	+
Xu 2015	+	+	+	+	+	+	+	+	+
Yu 2016	?	?	+	+	+	+	+	+	+

**Figures 9a-l: Forest plots for proportion of patients with at least 1 gout flare, 0 to 3 months follow-up (range: 28 days to 3 months).**

*Figure 9a: Allopurinol 300 mg vs. placebo.*



*Figure 9b: Any dose of febuxostat vs. placebo.*

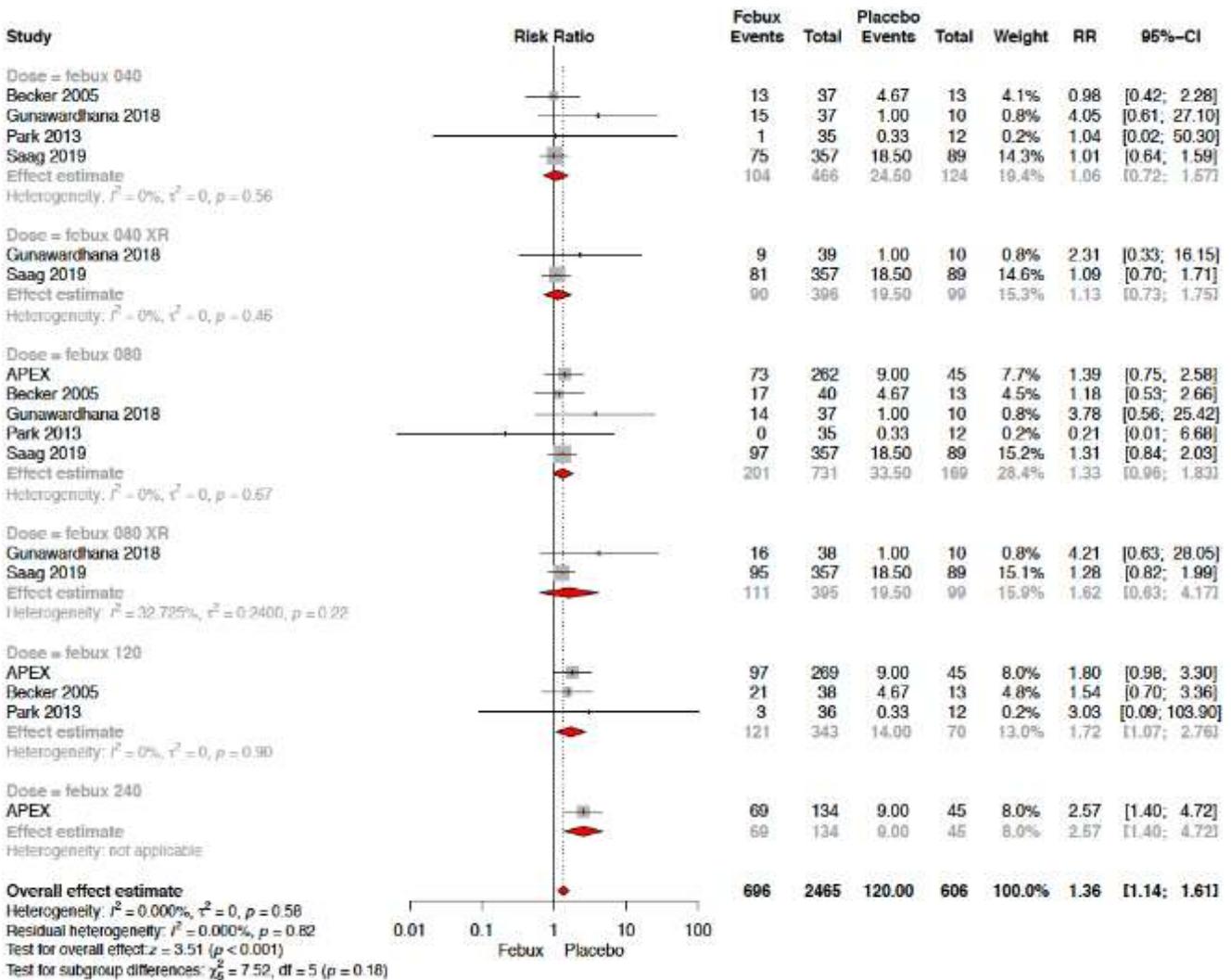


Figure 9c: Any dose of febuxostat vs. allopurinol 300mg.

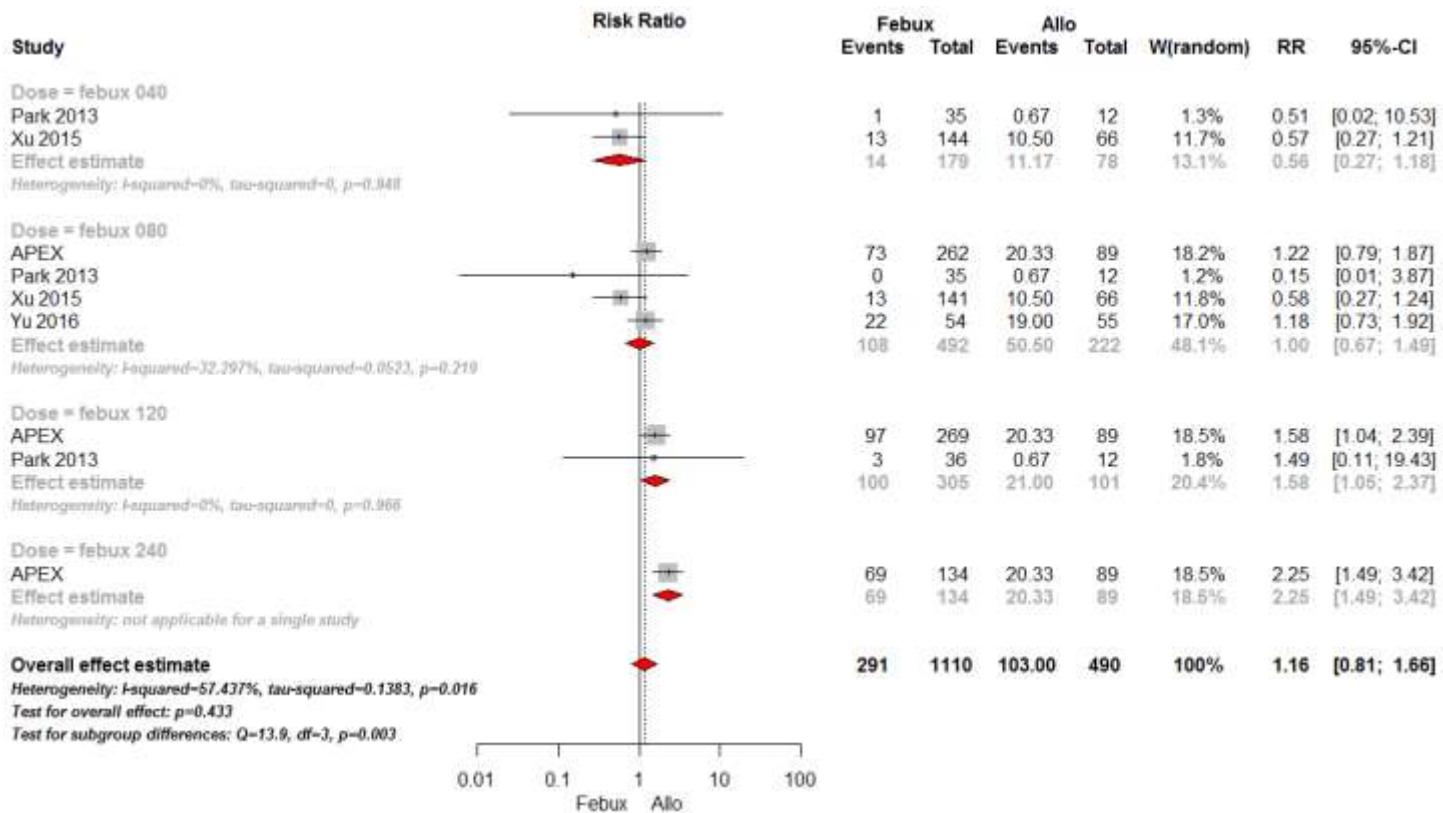


Figure 9d: Any dose of febuxostat vs. febuxostat 40mg.

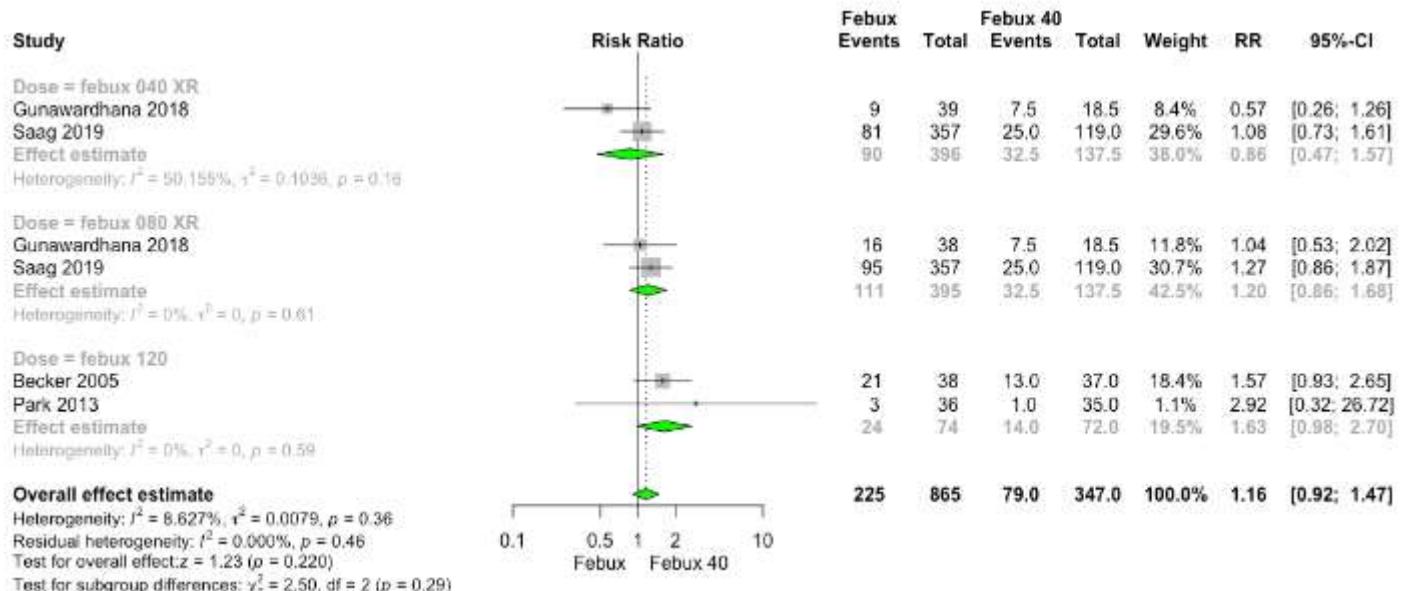


Figure 9e: Any dose of febuxostat vs. febuxostat 80mg.

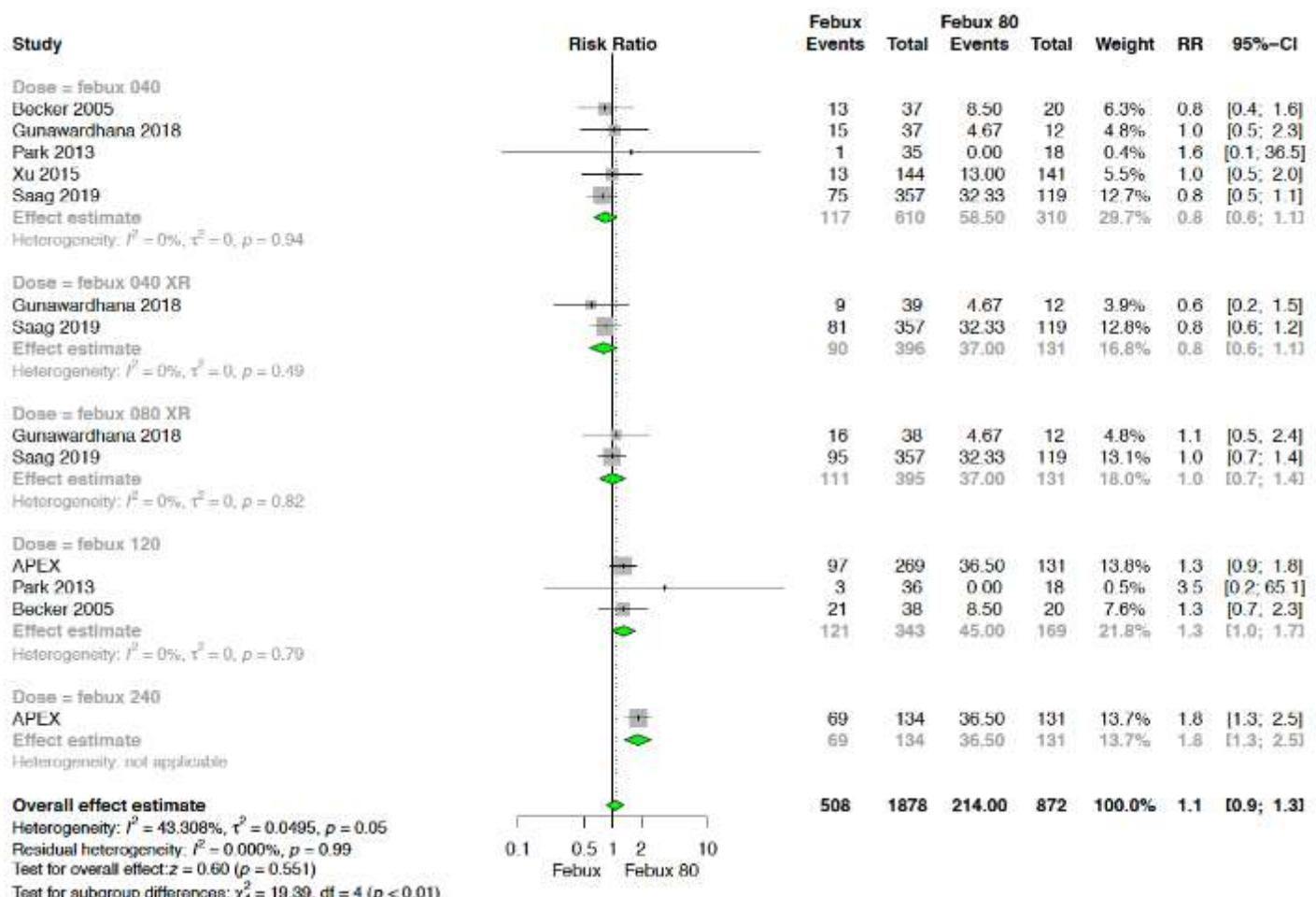


Figure 9f: Any dose of febuxostat vs. febuxostat 240mg.

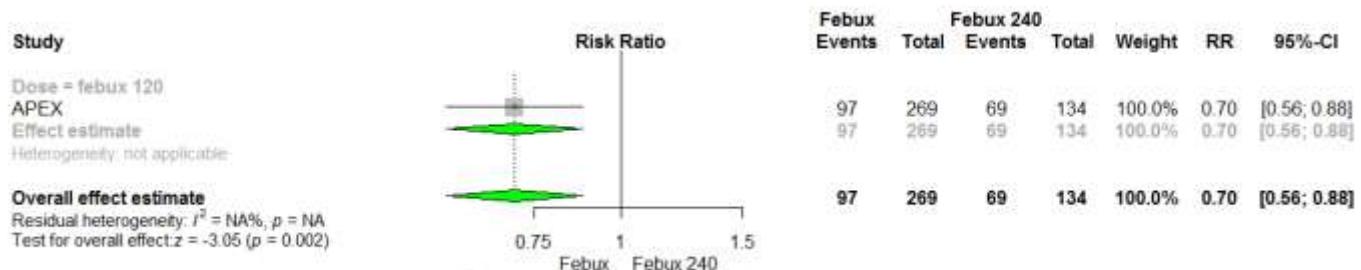


Figure 9g: Febuxostat 80mg XR vs. febuxostat 40mg XR.

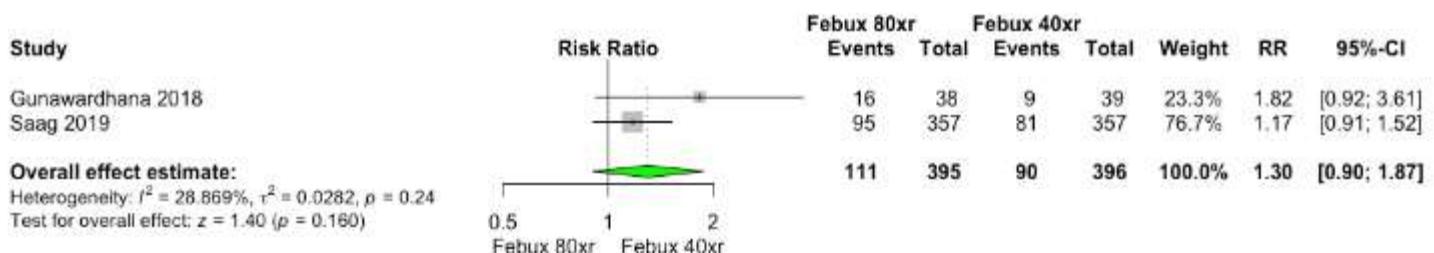


Figure 9h: Lesinurad 200mg + febuxostat 80mg vs. febuxostat 80mg

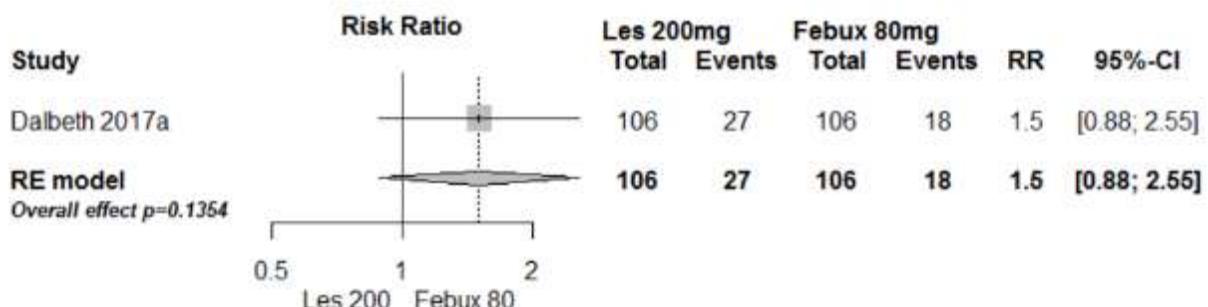


Figure 9k: Network forest plot with placebo as comparator.

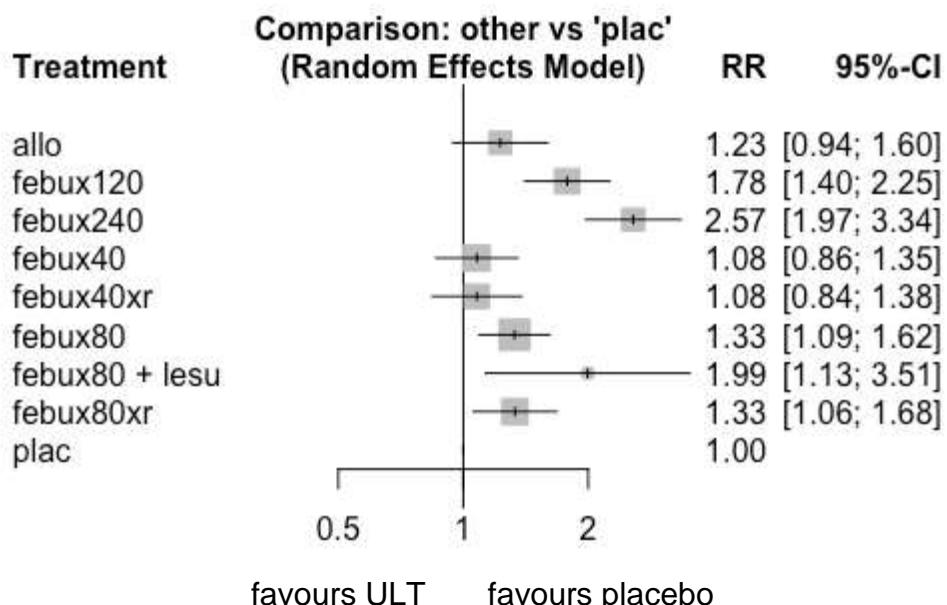
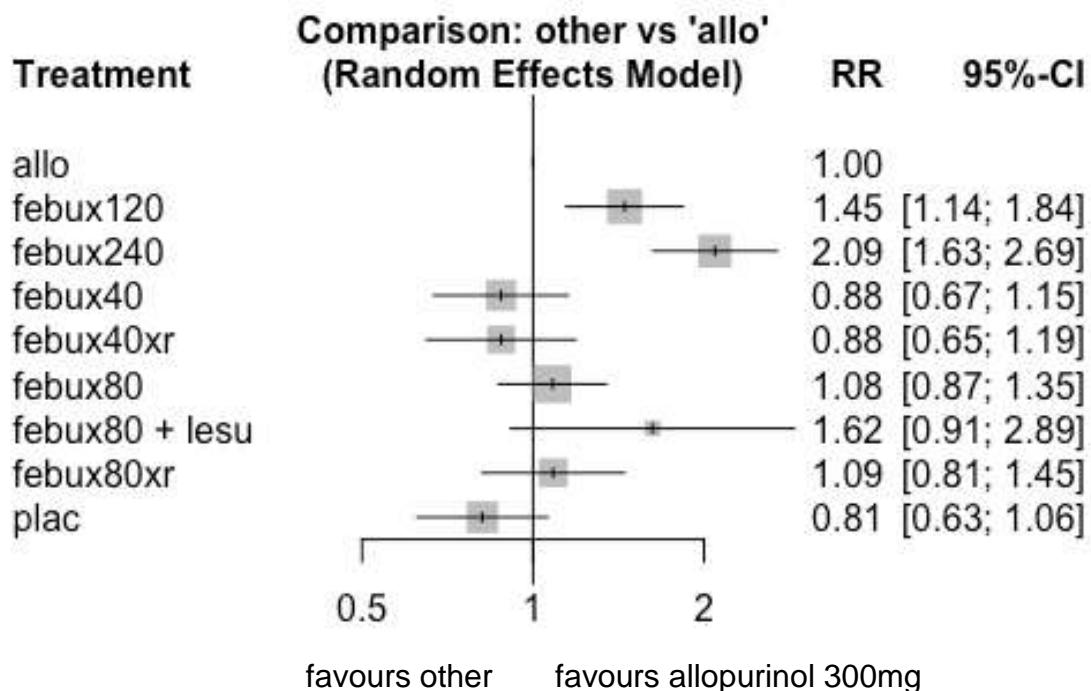
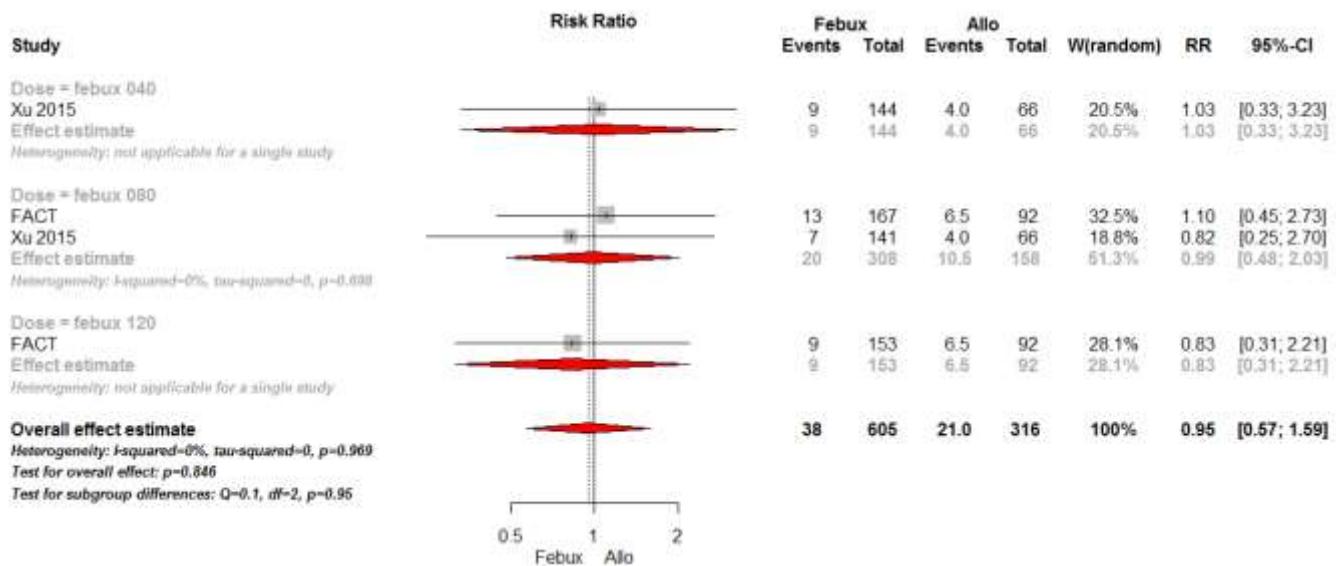


Figure 9l: Network forest plot with allopurinol 300mg as comparator.

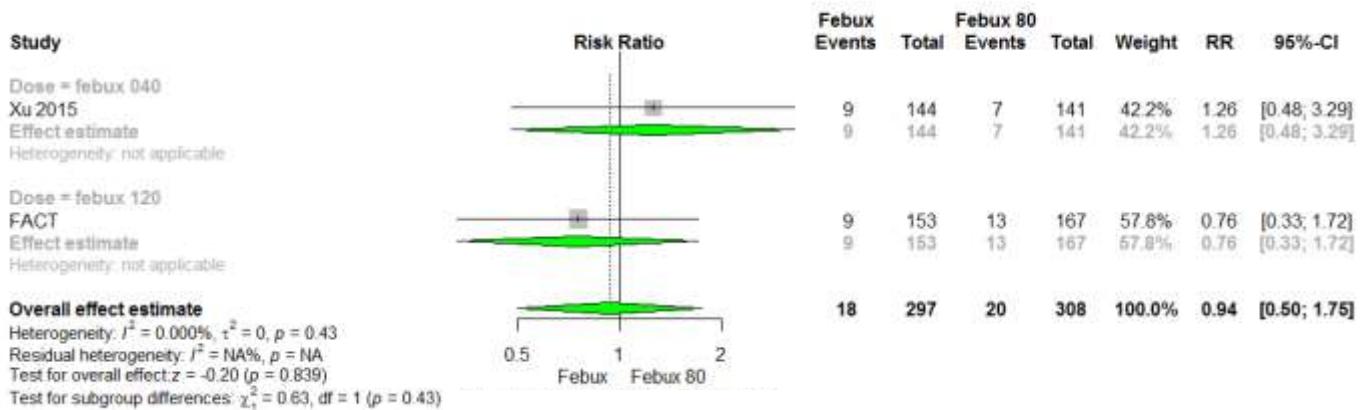


**Figures 10a-c: Forest plots for proportion of patients with at least 1 gout flare, at latest follow-up (range: 5 to 13 months). Patients were observed for 1 month period only.**

*Figure 10a: Any dose of febuxostat vs. allopurinol 300mg.*



*Figure 10b: Any dose of febuxostat vs. febuxostat 80mg.*



*Figure 10c: Lesinurad 200mg + allopurinol 300mg vs. allopurinol 300mg.*

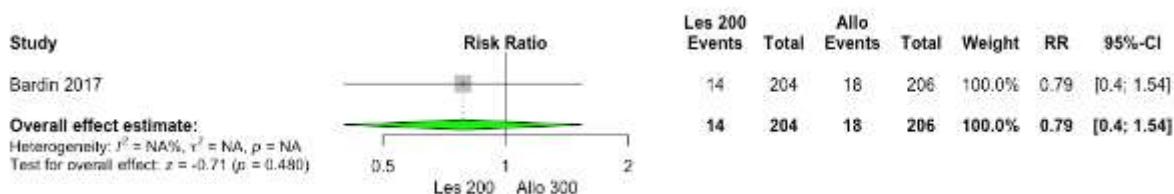
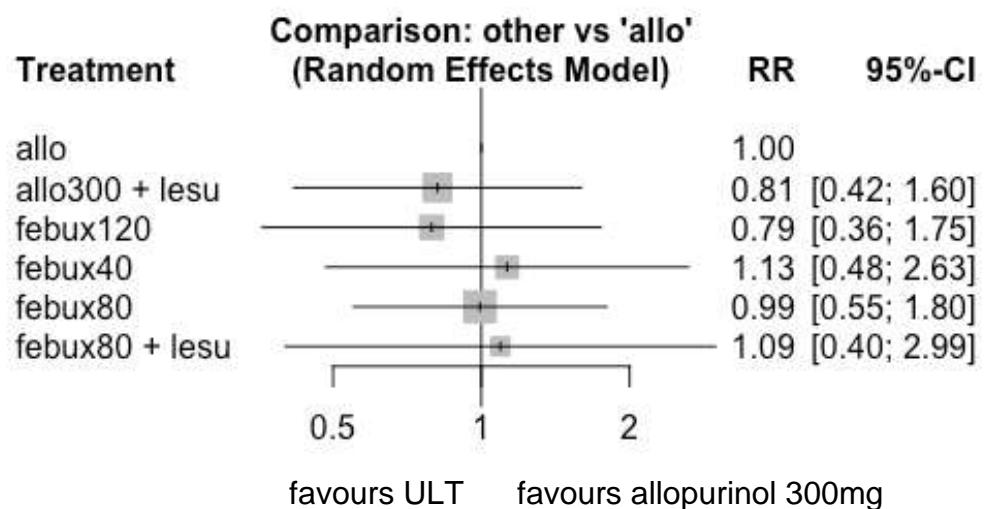
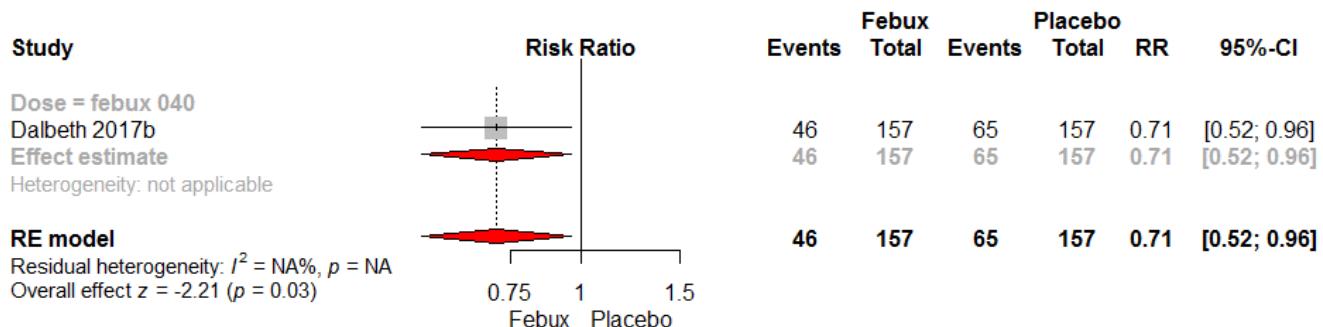


Figure 10d: Network forest plot with allopurinol 300mg as comparator.

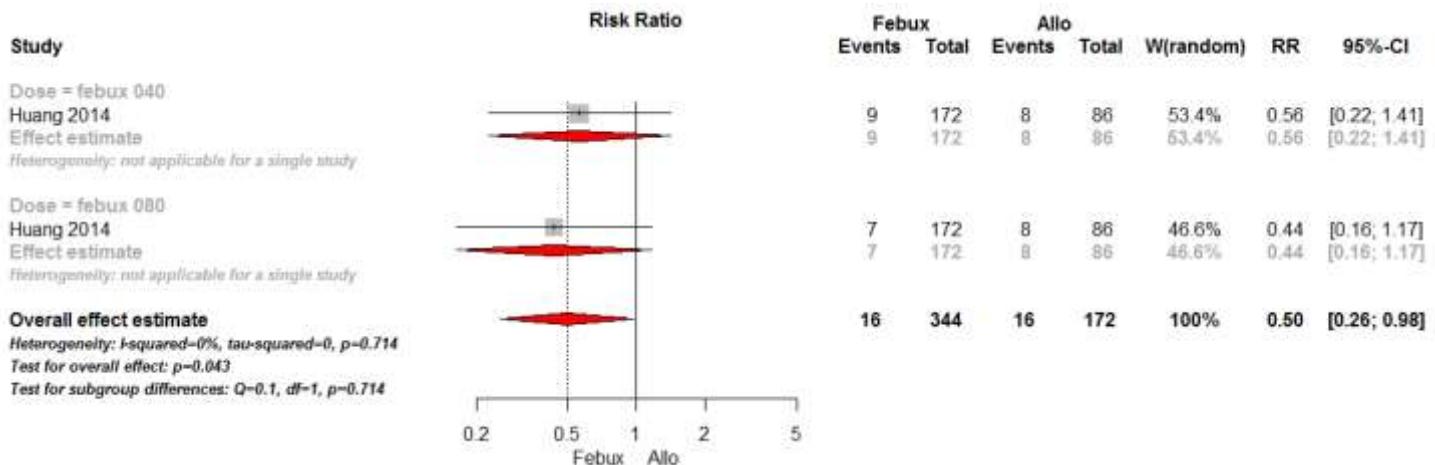


**Figures 11a-g: Forest plots for proportion of patients with at least 1 gout flare, at longest follow-up (range: from baseline or 2.25 months up to 7 or 24 months). Patients were observed for >1 month period.**

*Figure 11a: Any dose of febuxostat 40mg vs. placebo.*



*Figure 11b: Any dose of febuxostat vs. allopurinol 300mg.*



*Figure 11c: Any dose of febuxostat vs. febuxostat 80mg.*

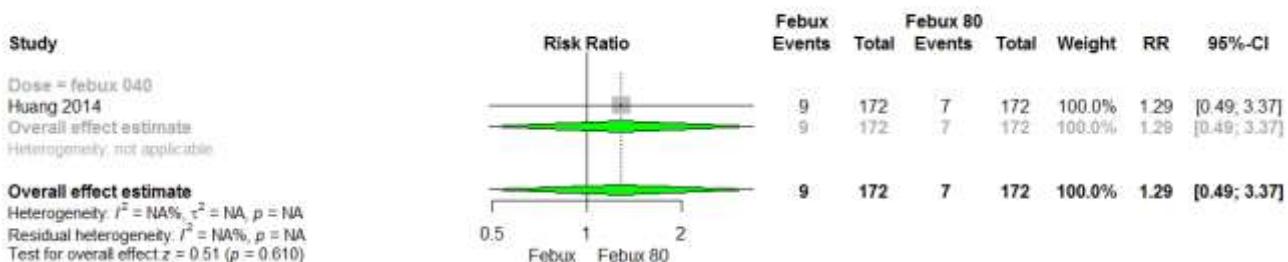


Figure 11d: Allopurinol 300mg vs. probenecid 2g.

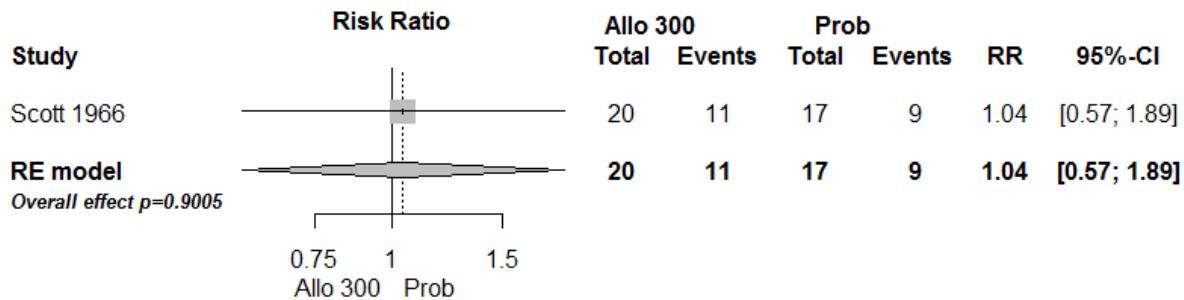


Figure 11e: Lesinurad 200mg + febuxostat 80mg vs. febuxostat 80mg.

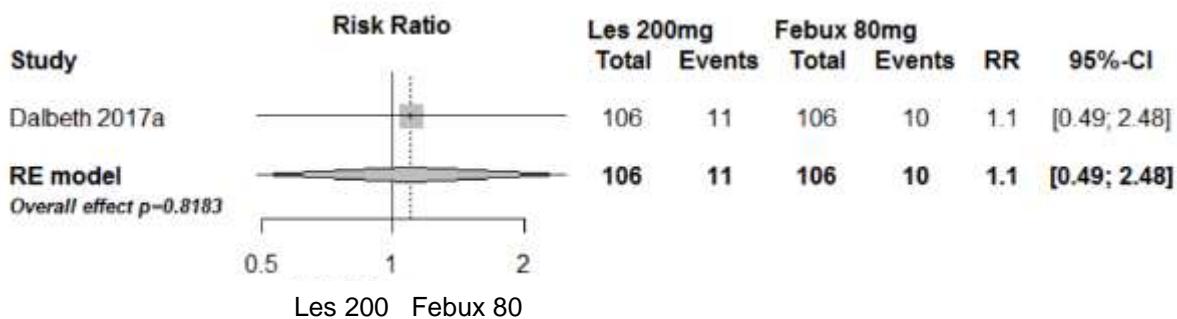


Figure 11f: Network forest plot with allopurinol 300mg as comparator.

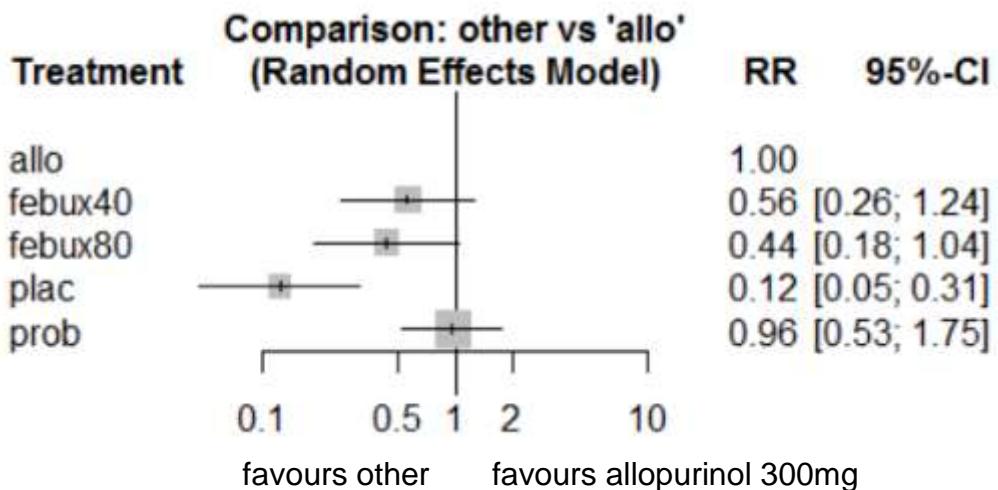
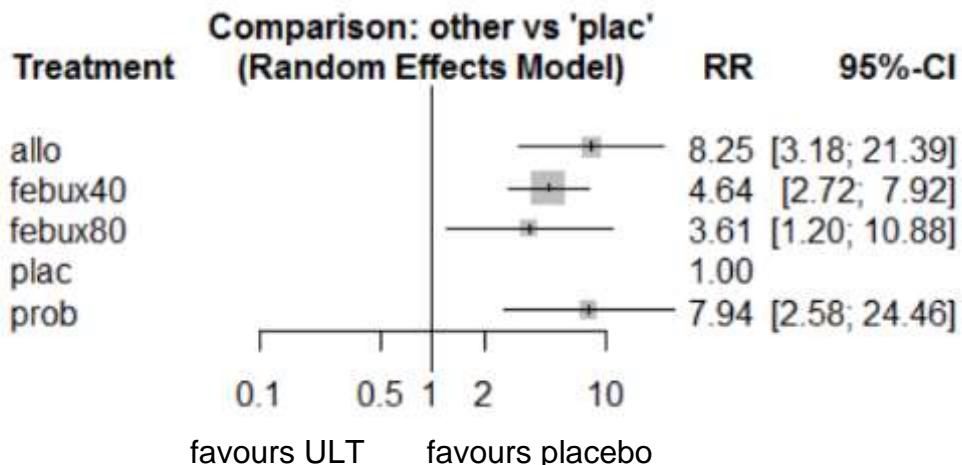


Figure 11g: Network forest plot with placebo as comparator.



Figures 12a-m: Forest plots for proportion of patients with serum urate <6.0mg/dL at longest follow-up (range: 28 days to 24 months)

Figure 12a: Allopurinol 300mg vs. placebo.

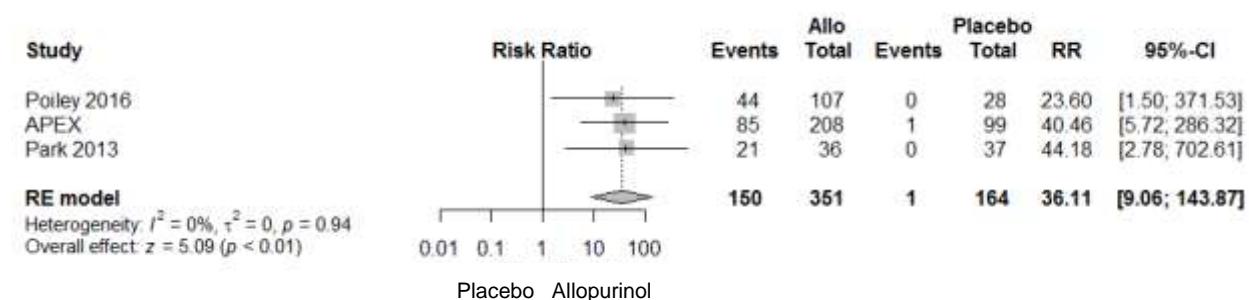
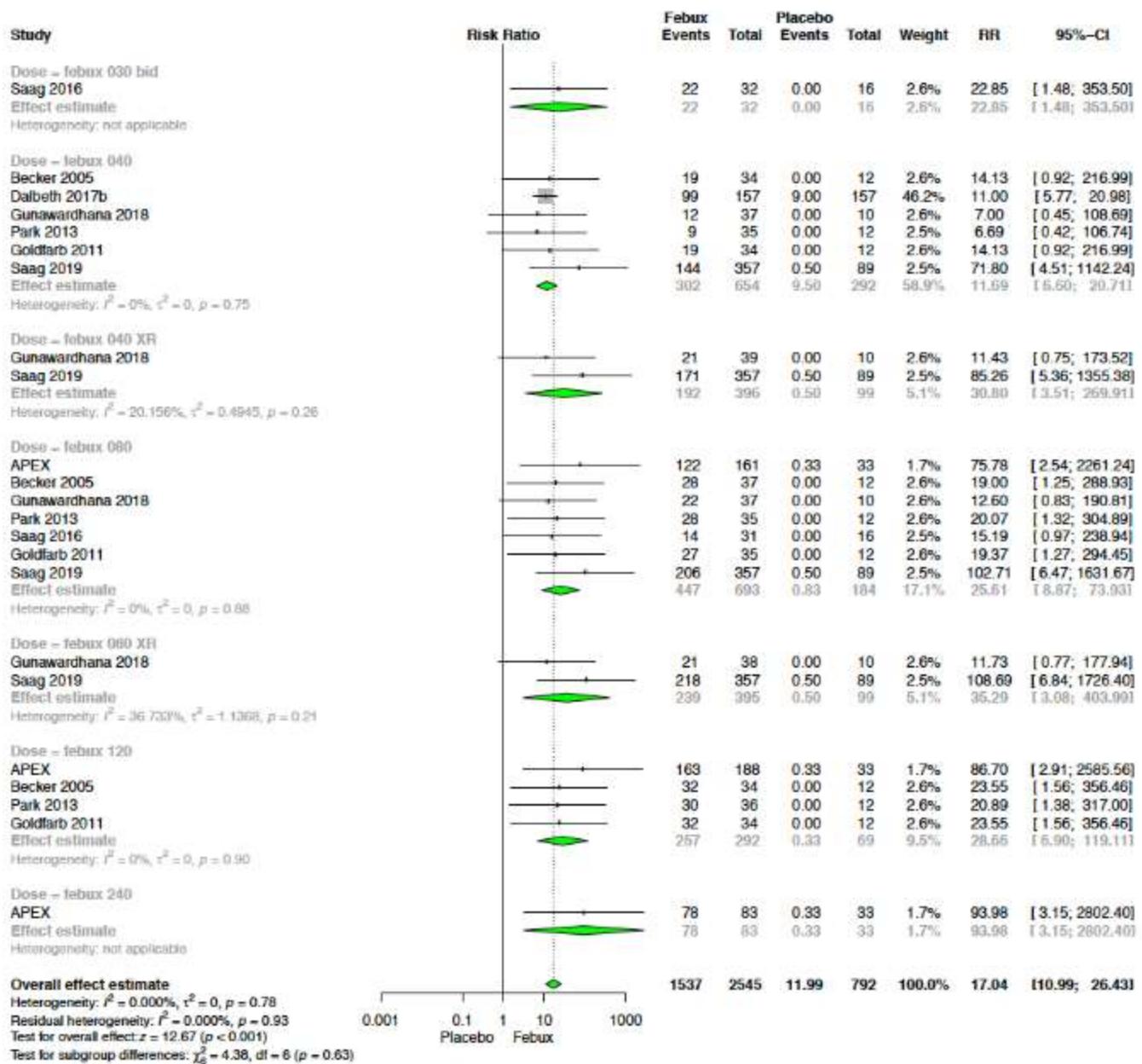


Figure 12b: Any dose of febuxostat vs. placebo.



*Figure 12c: Any dose of febuxostat vs. allopurinol 300mg.*

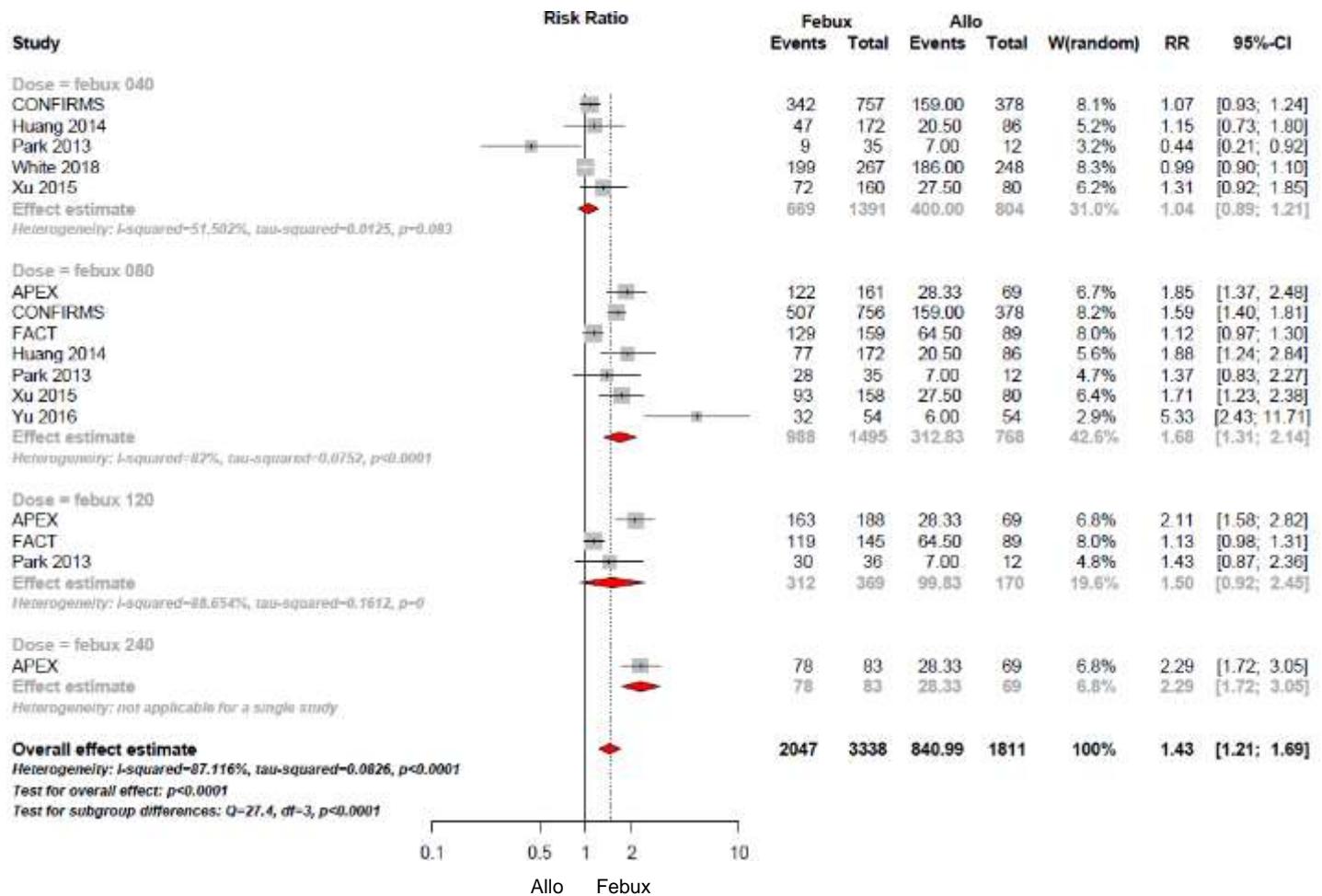


Figure 12d: Any dose of febuxostat vs. febuxostat 40mg.

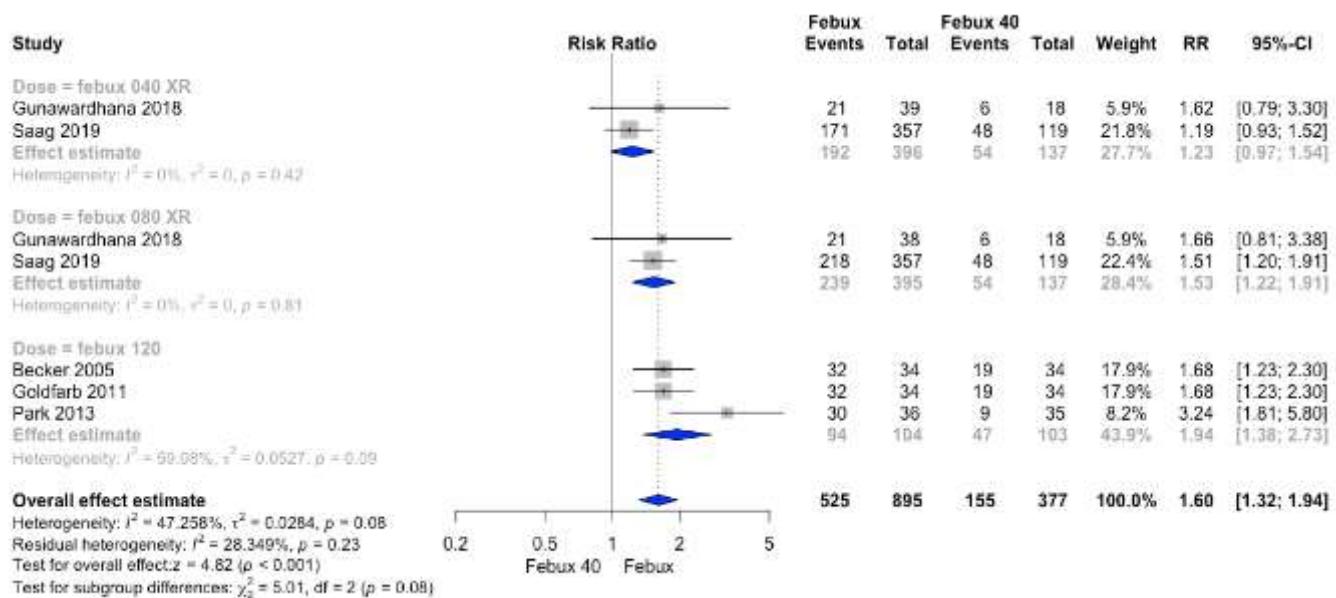


Figure 12e: Any dose of febuxostat vs. febuxostat 80mg.

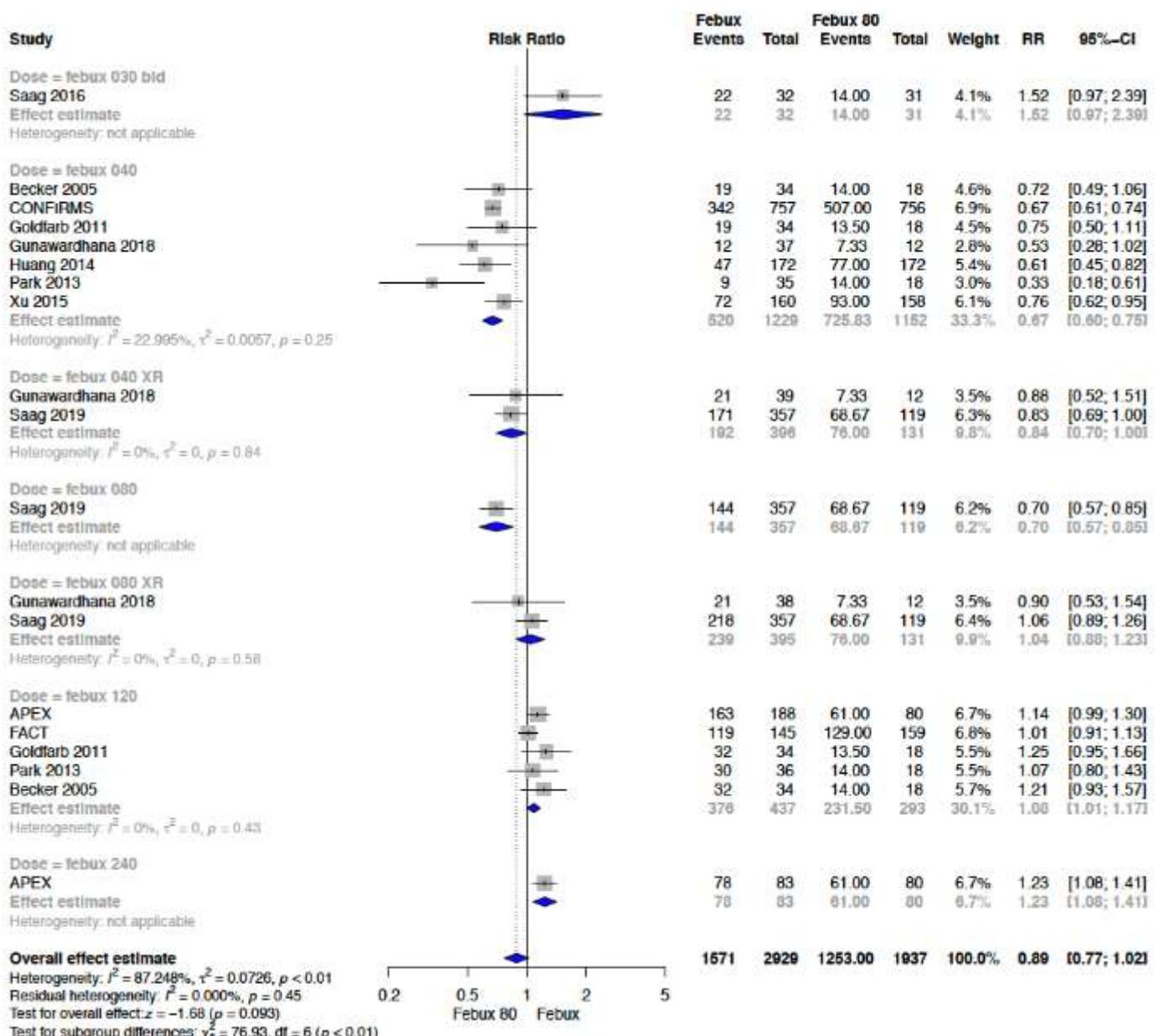


Figure 12f: Any dose of febuxostat vs. febuxostat 240mg.

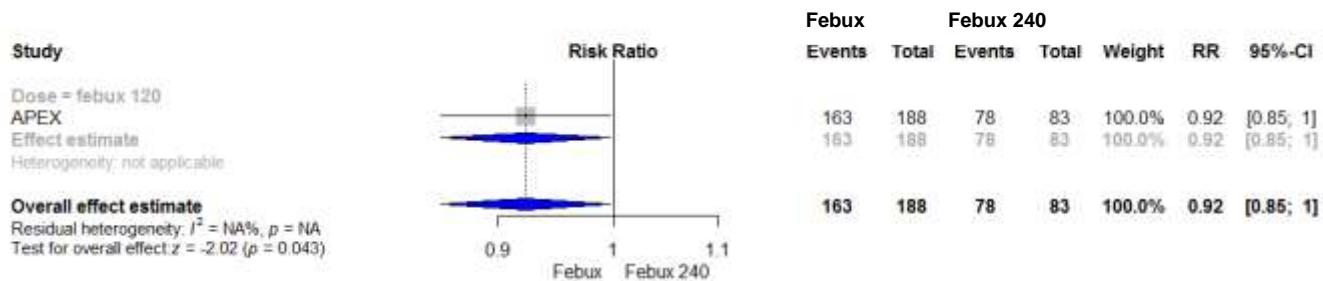


Figure 12g: Febuxostat 80mg XR vs. febuxostat 40mg XR.

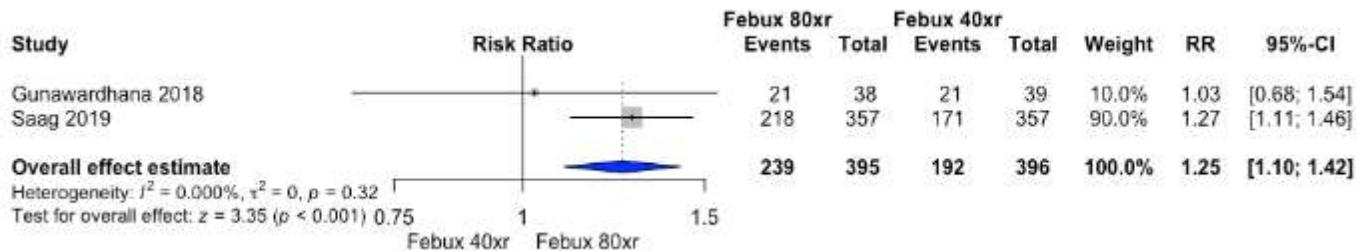


Figure 12h: Pegloticase 8mg vs. placebo.

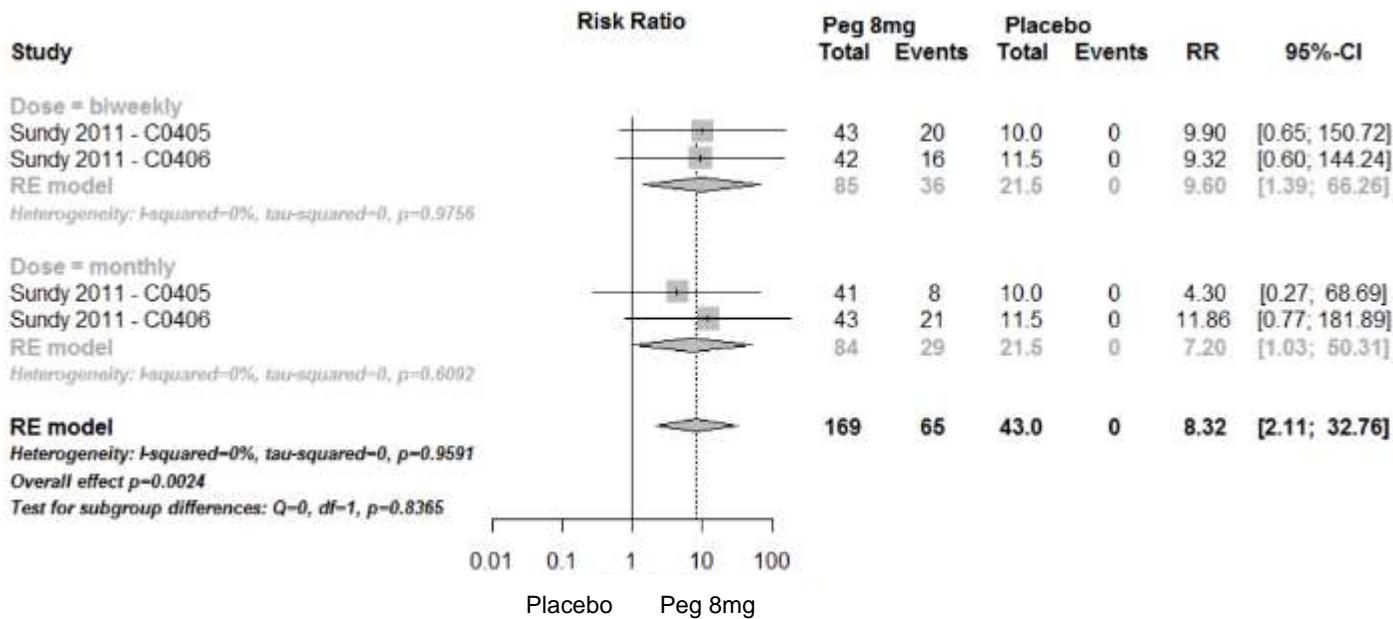


Figure 12i: Monthly vs. biweekly pegloticase 8mg.

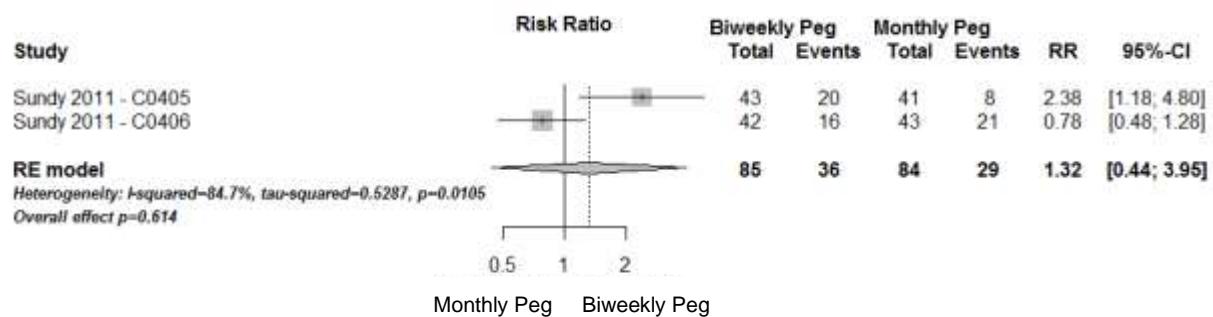


Figure 12j: Lesinurad 200mg + allopurinol 300mg vs. allopurinol 300mg.

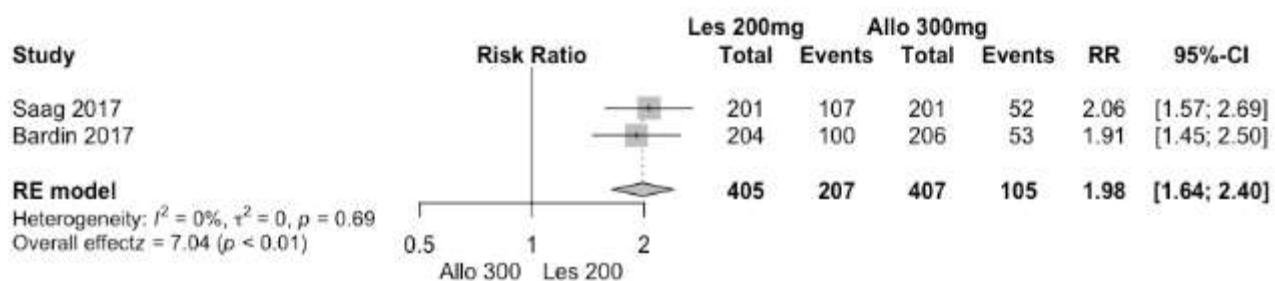


Figure 12k: Lesinurad 200mg + febuxostat 80mg vs. febuxostat 80mg

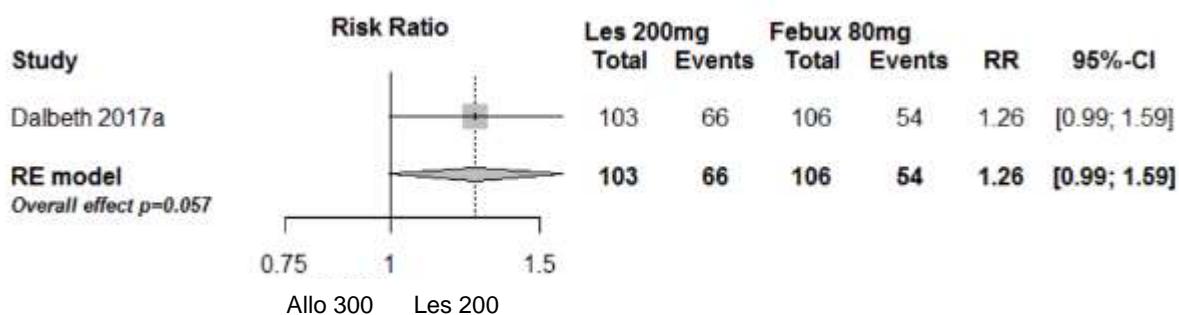


Figure 12l: Network forest plot with allopurinol 300mg.

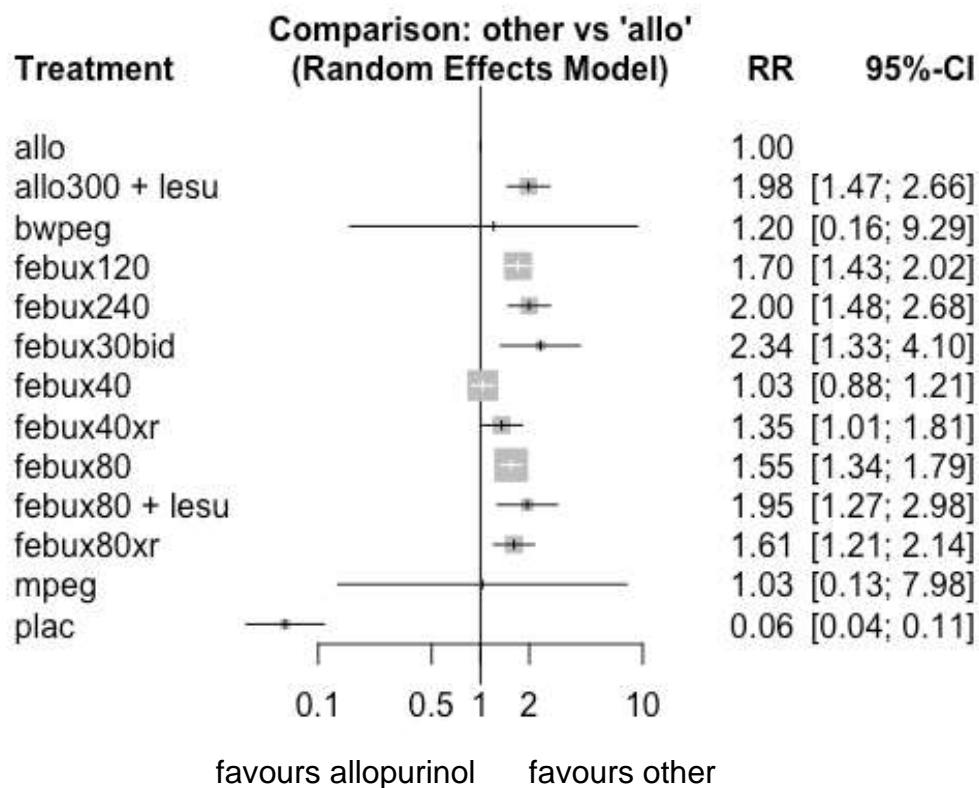
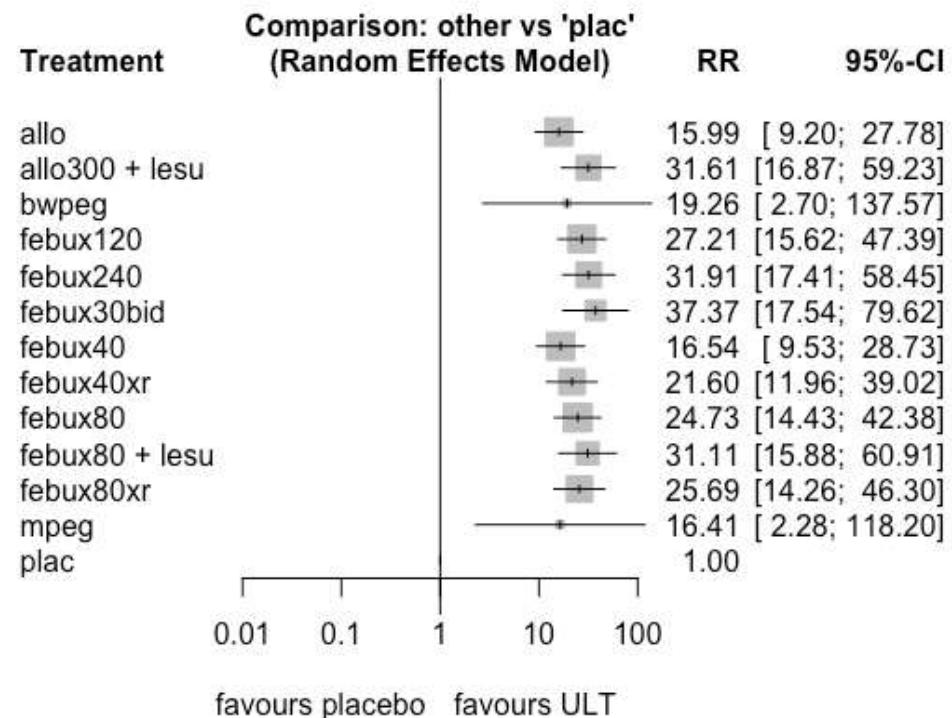
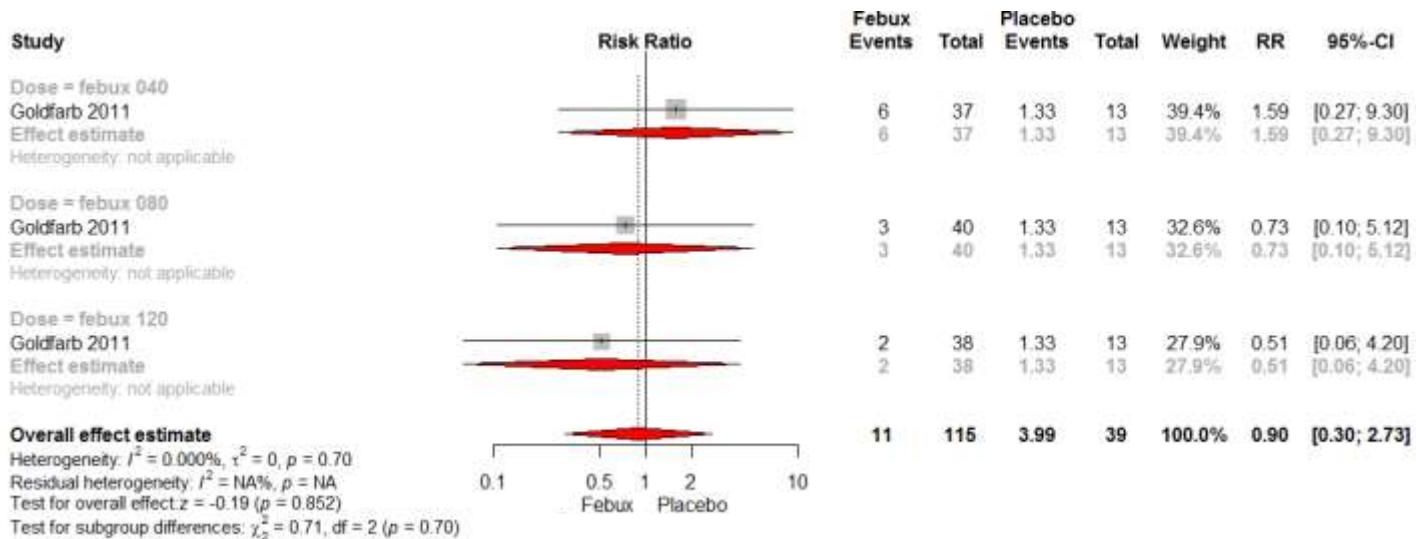


Figure 12m: Network forest plot with placebo as comparator.

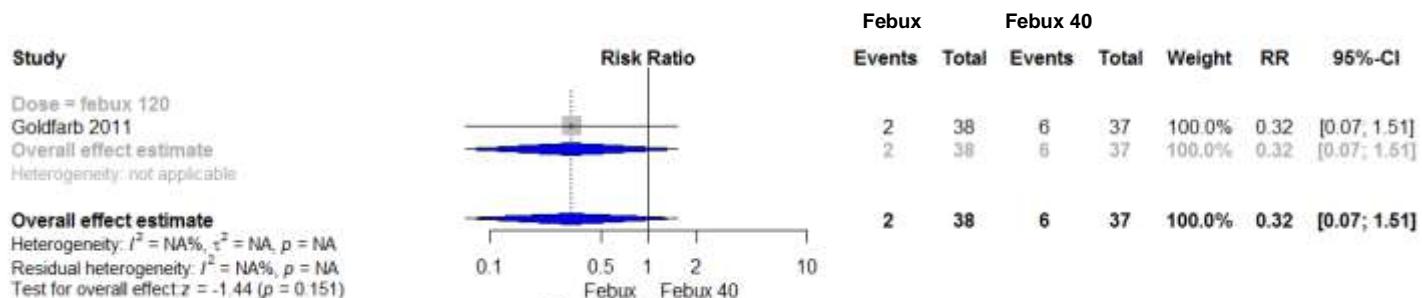


**Figures 13a-c: Forest plots for proportion of patients with subjective adverse event of pain; closest to 3 months (follow up: 28 days)**

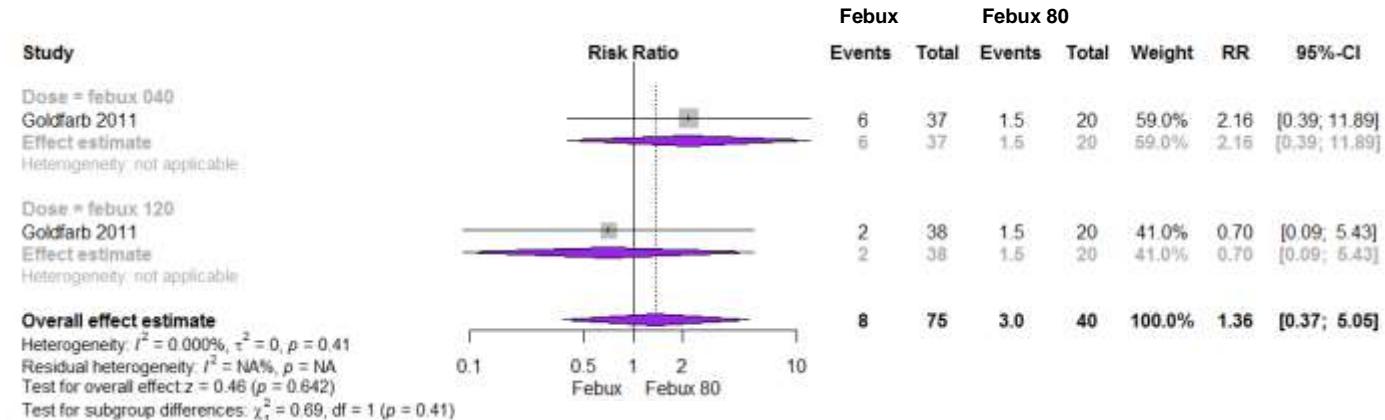
*Figure 13a: Any dose of febuxostat vs. placebo.*



*Figure 13b: Any dose of febuxostat vs. febuxostat 40mg.*

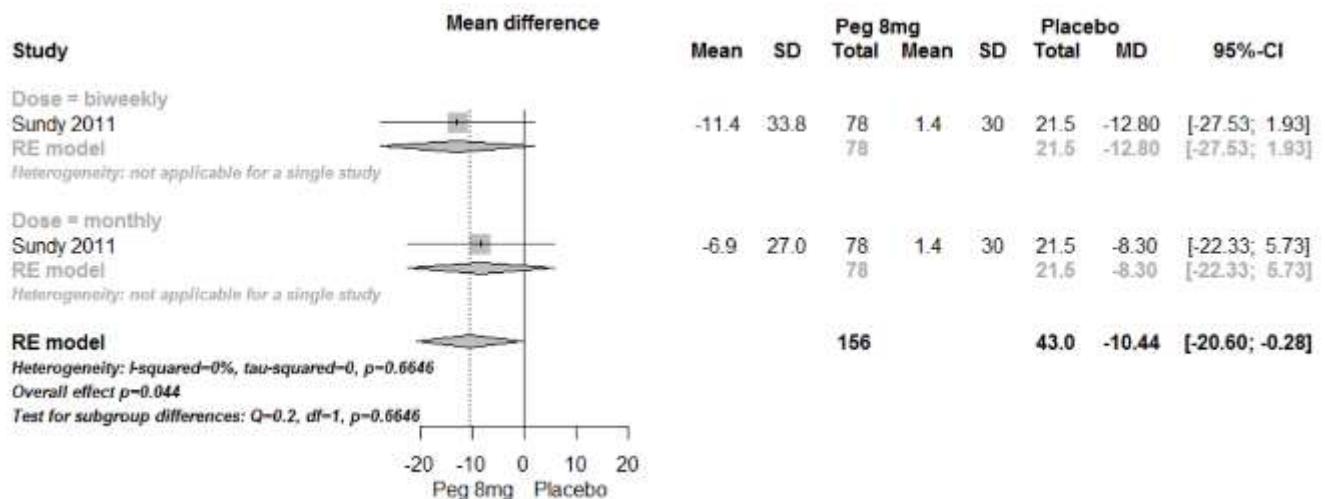


*Figure 13c: Any dose of febuxostat vs. febuxostat 80mg.*

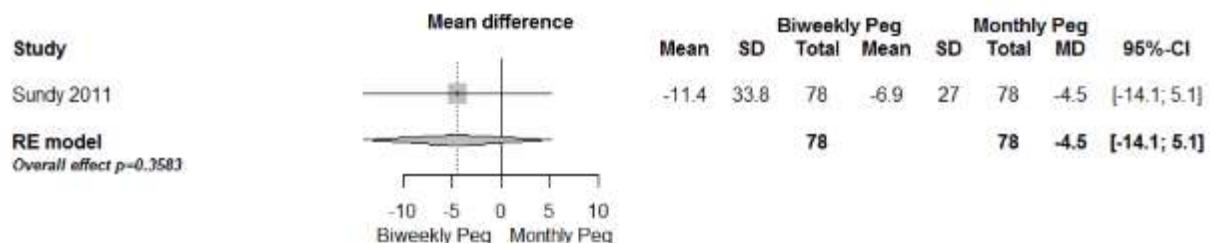


**Figures 14a-b: Forest plots for change in pain score using 0 to 100 mm visual analogue scale, at longest follow-up (0 to 6.25 months)**

*Figure 14a: Pegloticase 8mg vs. placebo.*

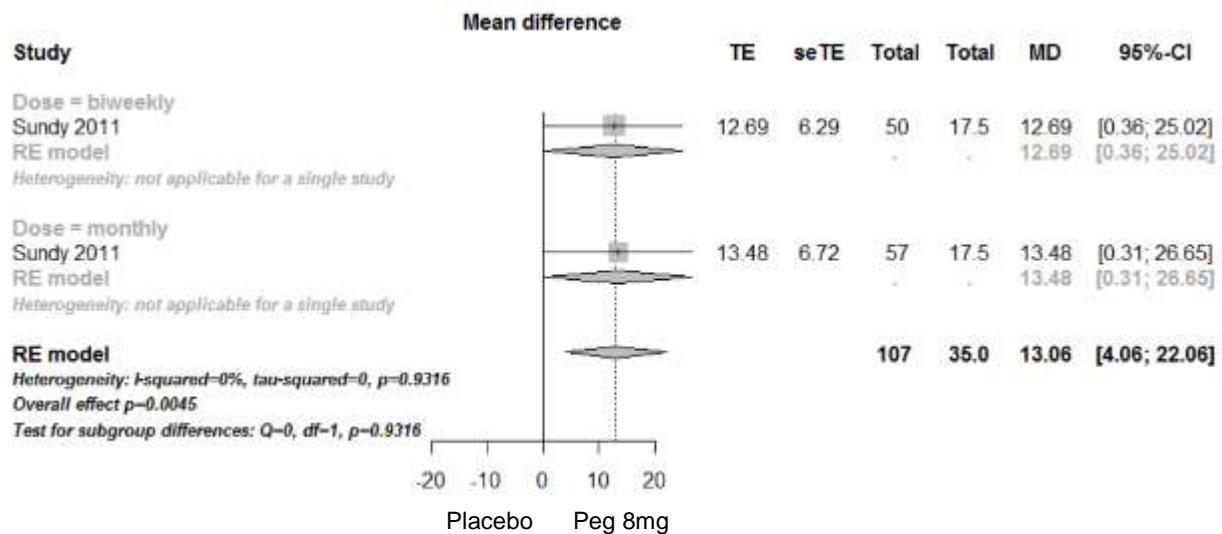


*Figure 14b: Biweekly vs. monthly pegloticase 8mg.*

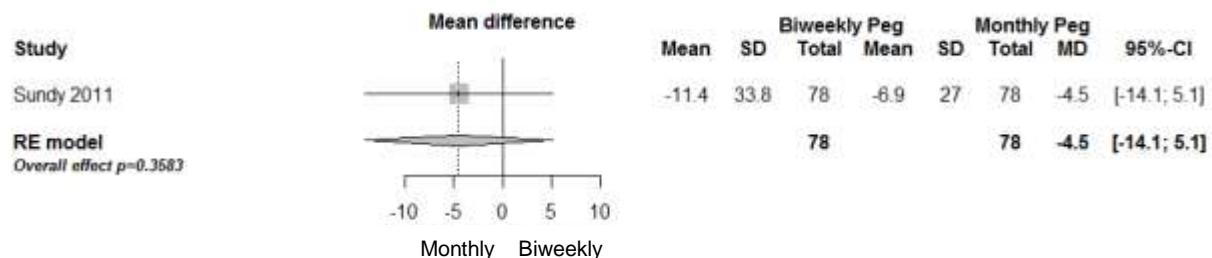


**Figures 15a-b: Forest plots for change patient global assessment as measured on 100mm visual analogue scale at longest follow-up (0 to 6.25 months)**

*Figure 15a: Pegloticase 8mg vs. placebo.*



*Figure 15b: Biweekly vs. monthly pegloticase 8mg.*



**Figures 16a-f: Forest plots for proportion of patients with tophus resolution at longest follow-up (range: 0 to 24 months)**

Figure 16a: Allopurinol 300mg vs. probenecid 2g.

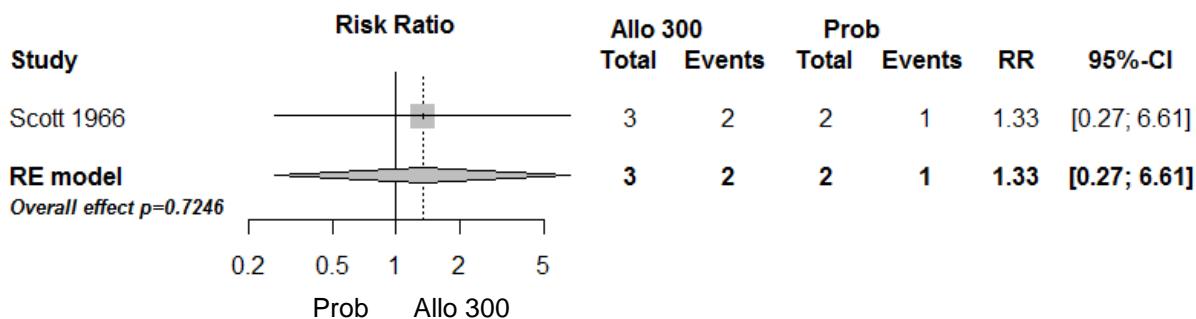


Figure 16b: Pegloticase 8mg vs. placebo.

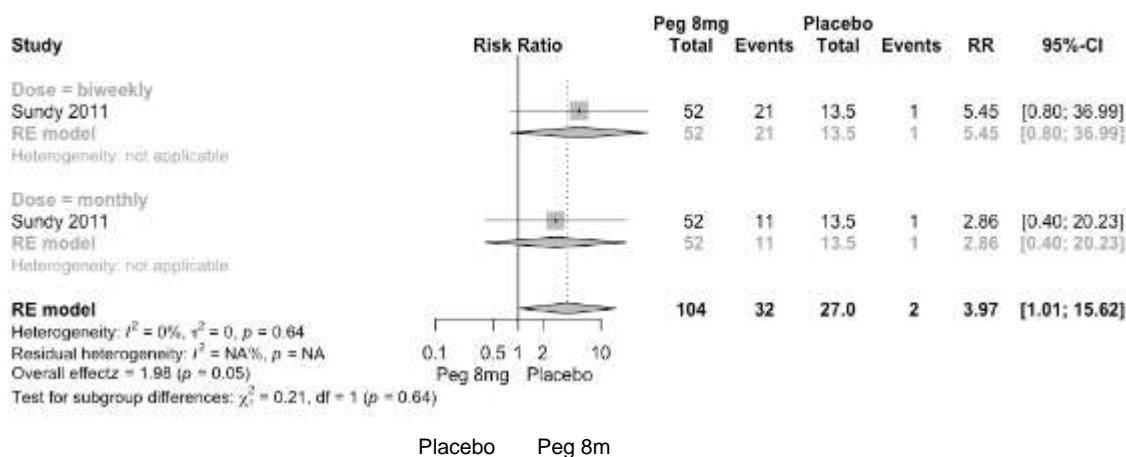


Figure 16c: Biweekly vs. monthly pegloticase 8mg.

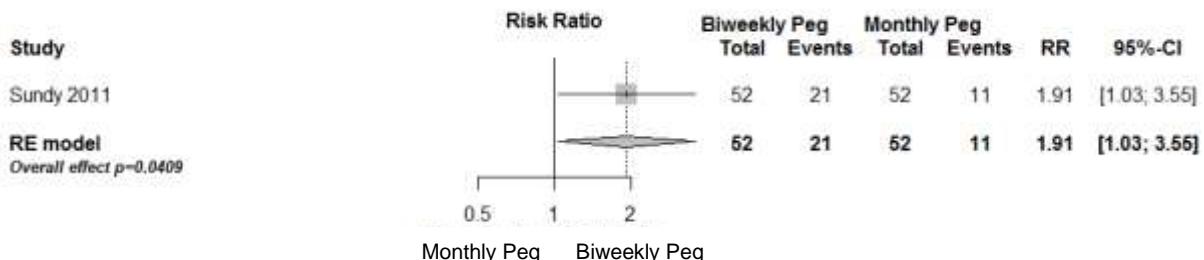


Figure 16d: Lesinurad 200mg + allopurinol 300mg vs. allopurinol 300mg

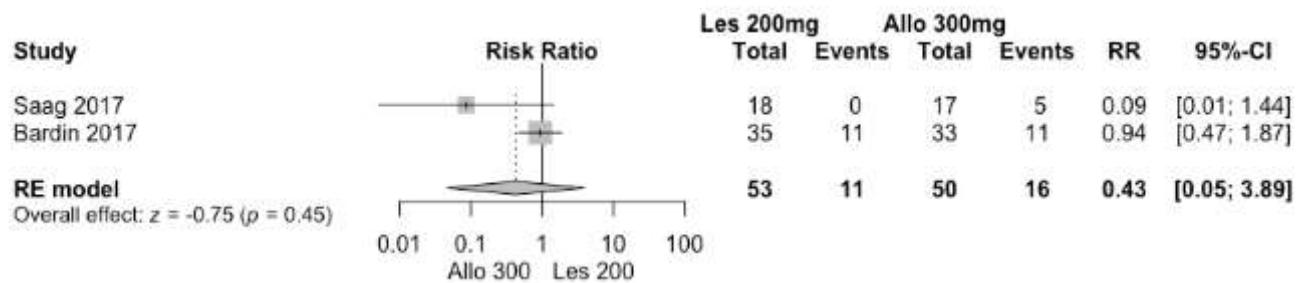


Figure 16e: Lesinurad 200mg + febuxostat 80mg vs. febuxostat 80mg

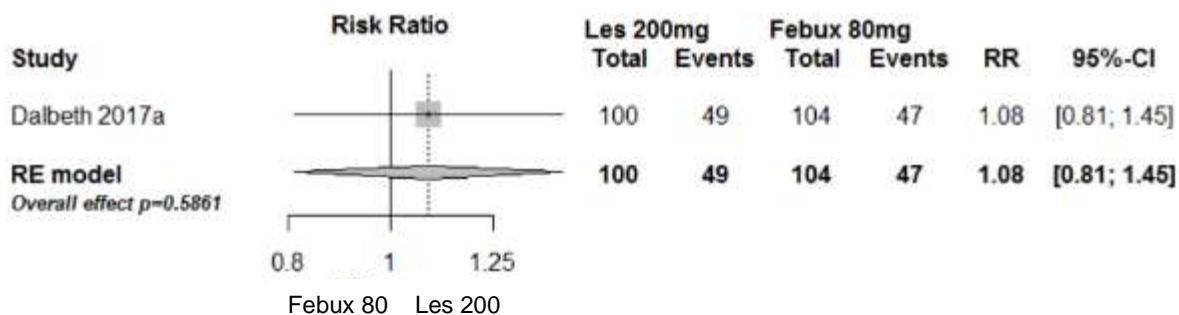
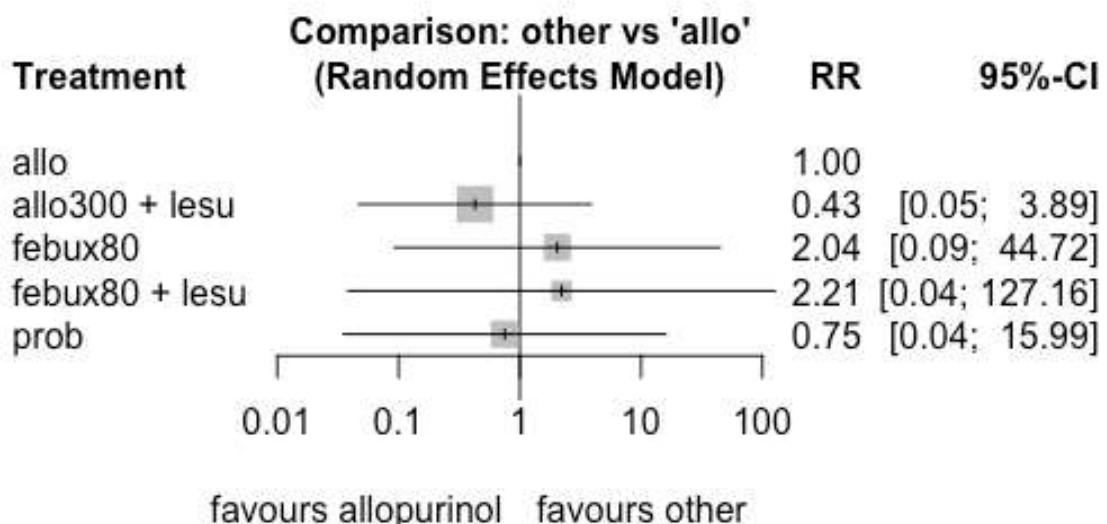
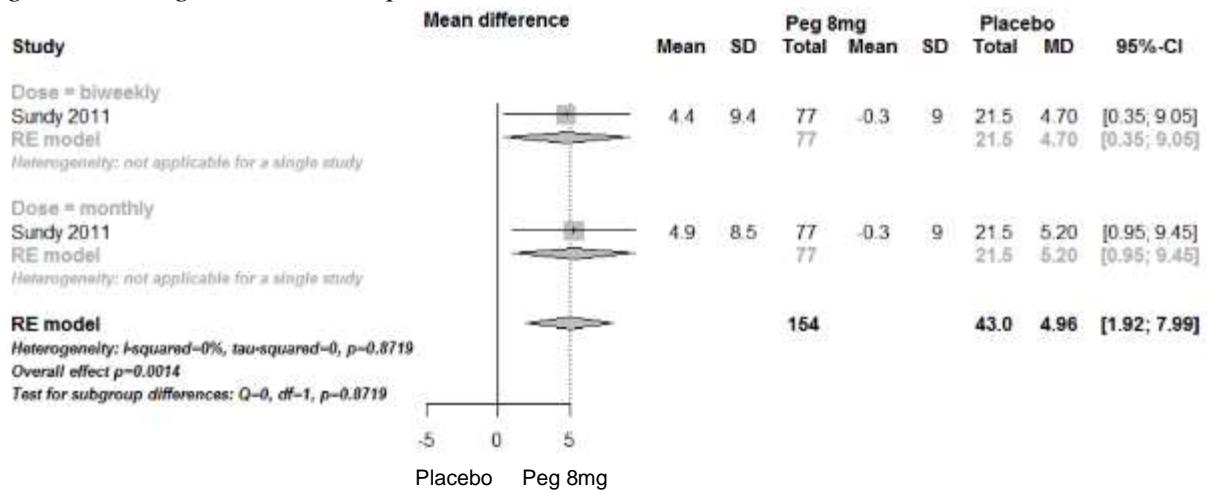


Figure 16f: Network forest plot with allopurinol 300mg as comparator.

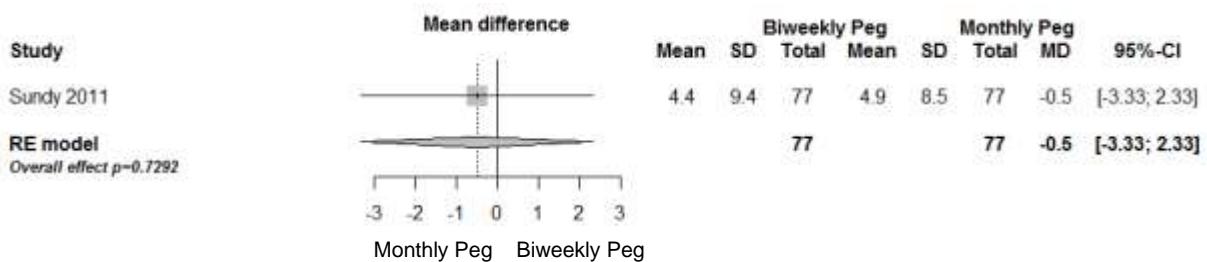


**Figures 17a-b: Forest plot for change in physical component summary (PCS) score of 36-Item Short Form Health Survey (SF-36) at longest follow-up (0 to 6.25 months)**

*Figure 17a: Pegloticase 8m vs. placebo.*

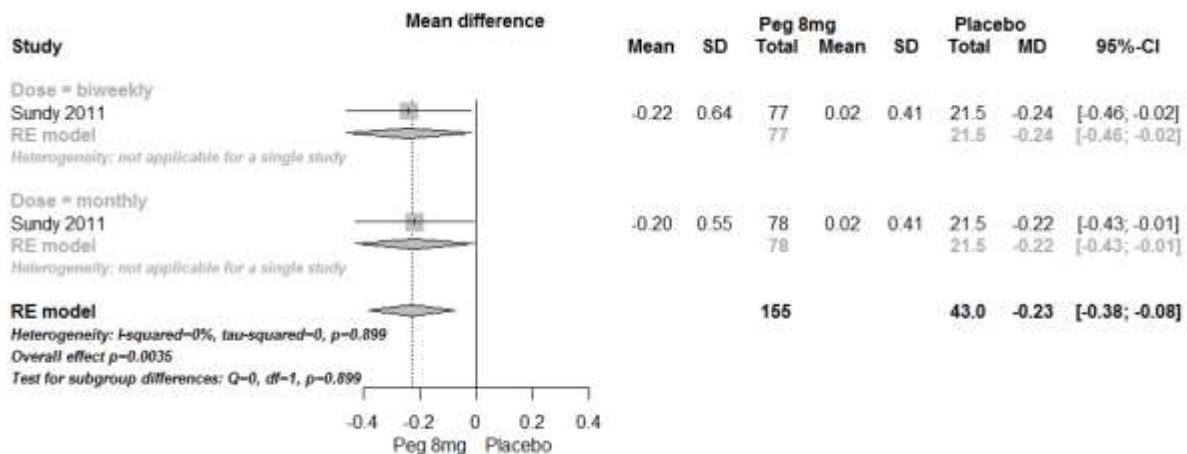


*Figure 17b: Biweekly vs. monthly pegloticase 8mg.*

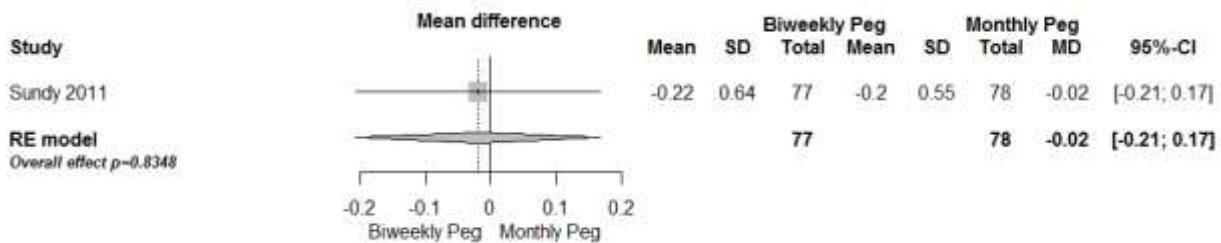


**Figures 18a-b: Forest plots for change in Health Assessment Questionnaire-Disability Index score (HAQ-DI) at longest follow-up (0 to 6.25 months)**

*Figure 18a: Pegloticase 8mg vs. placebo.*



*Figure 18b: Monthly vs. biweekly pegloticase 8mg.*



**Figures 19a-n: Forest plots for proportion of patients with serious adverse events at longest follow-up (range: 28 days to 24 months)**

Figure 19a: Allopurinol 300mg vs. placebo.

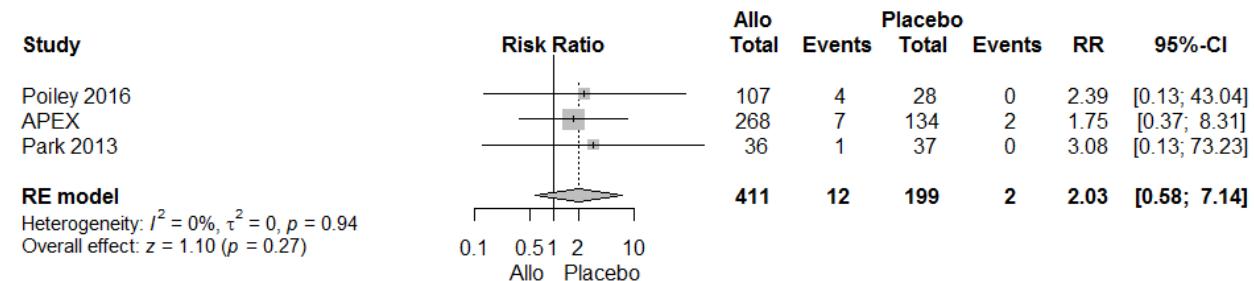


Figure 19b: Any dose of febuxostat vs. placebo.

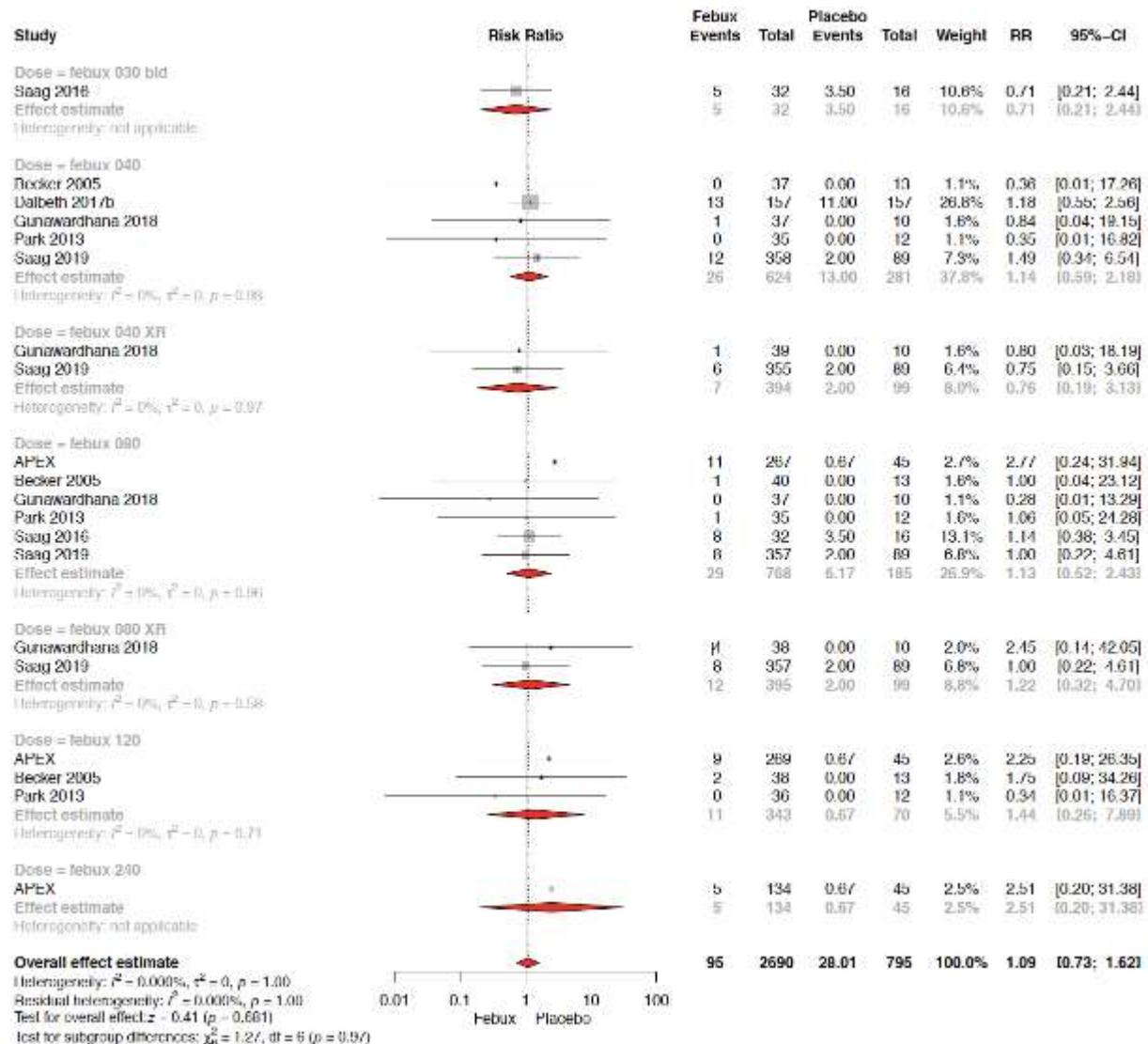


Figure 19c: Any dose of febuxostat vs. allopurinol 300mg.

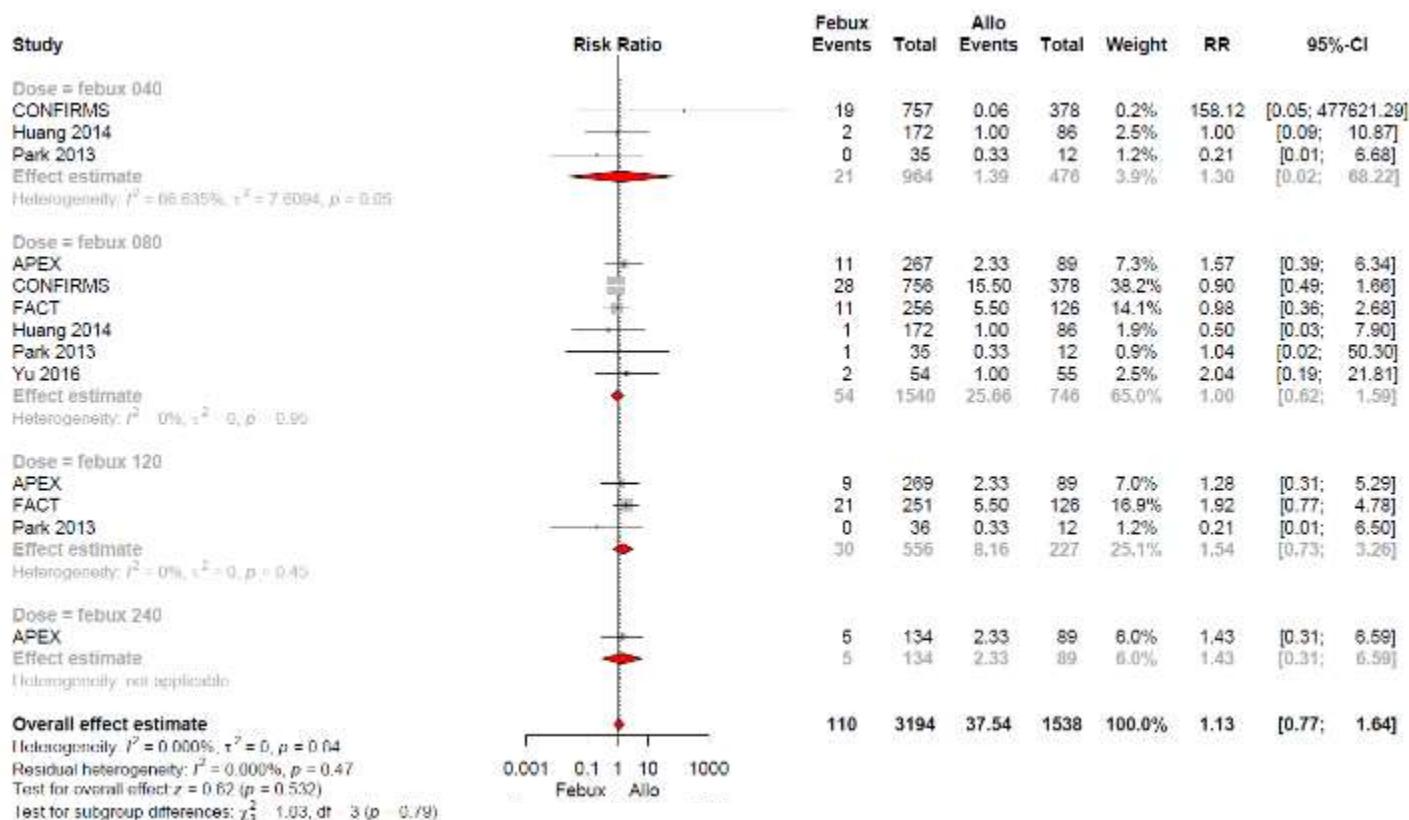


Figure 19d: Any dose of febuxostat vs. febuxostat 40mg.

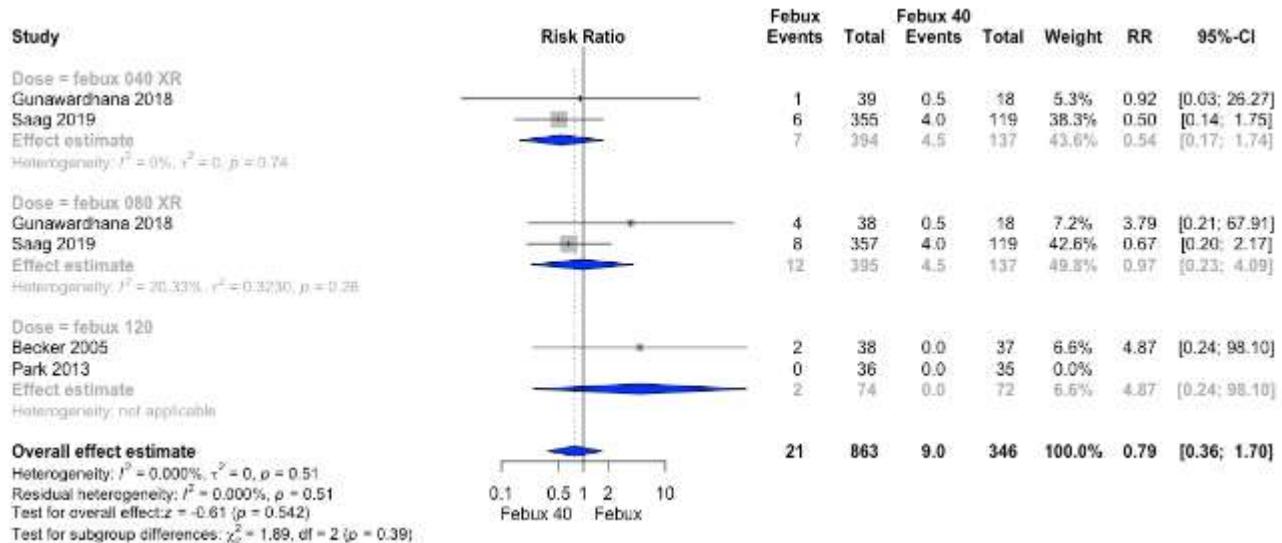


Figure 19e: Any dose of febuxostat vs. febuxostat 80mg.

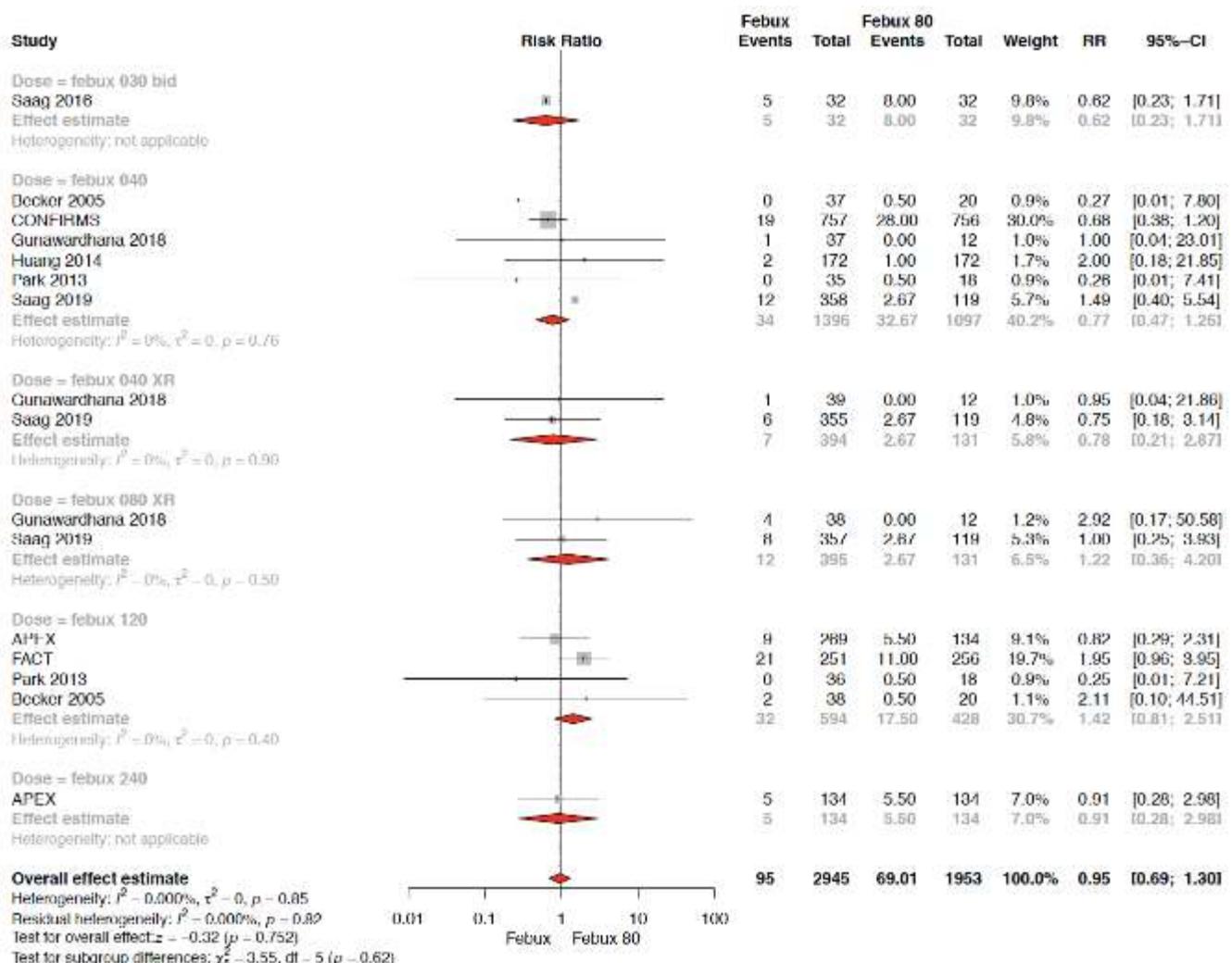


Figure 19f: Any dose of febuxostat vs. febuxostat 240mg.

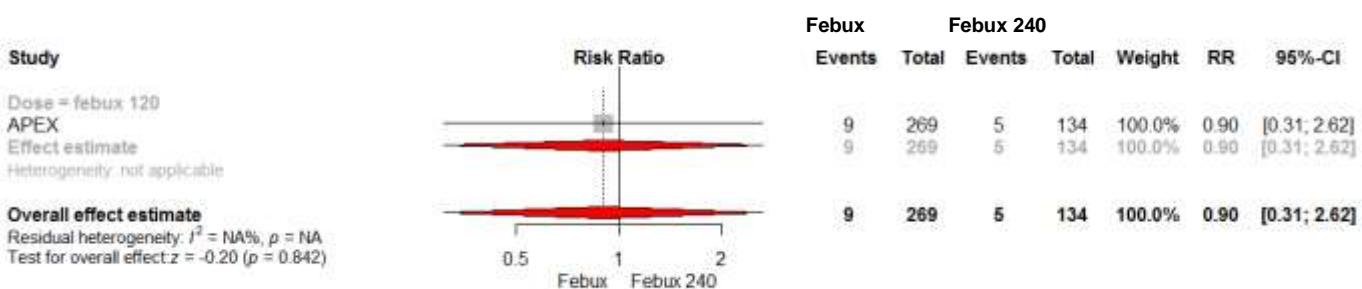


Figure 19g: Febuxostat 80mg XR vs. febuxostat 40mg XR.

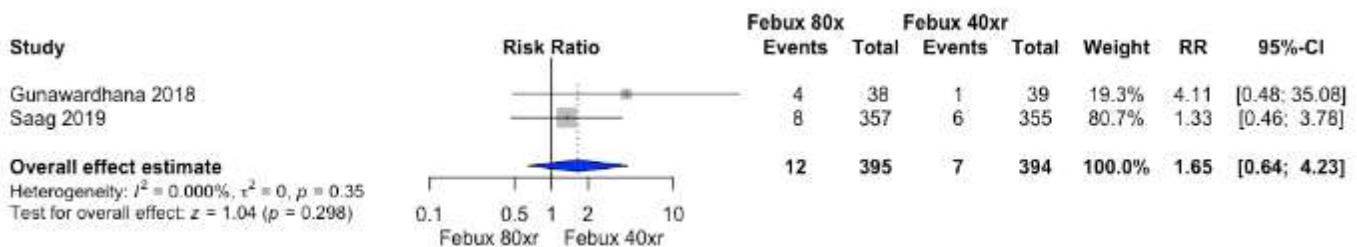


Figure 19h: Allopurinol 300mg vs. probenecid 2g.

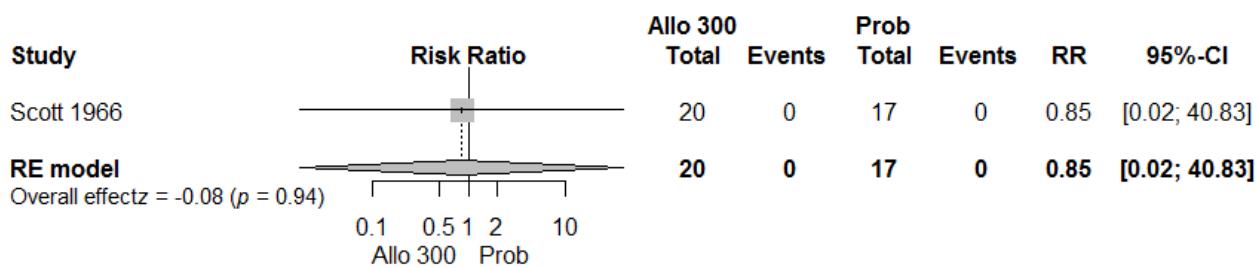


Figure 19i: Pegloticase 8mg vs. placebo.

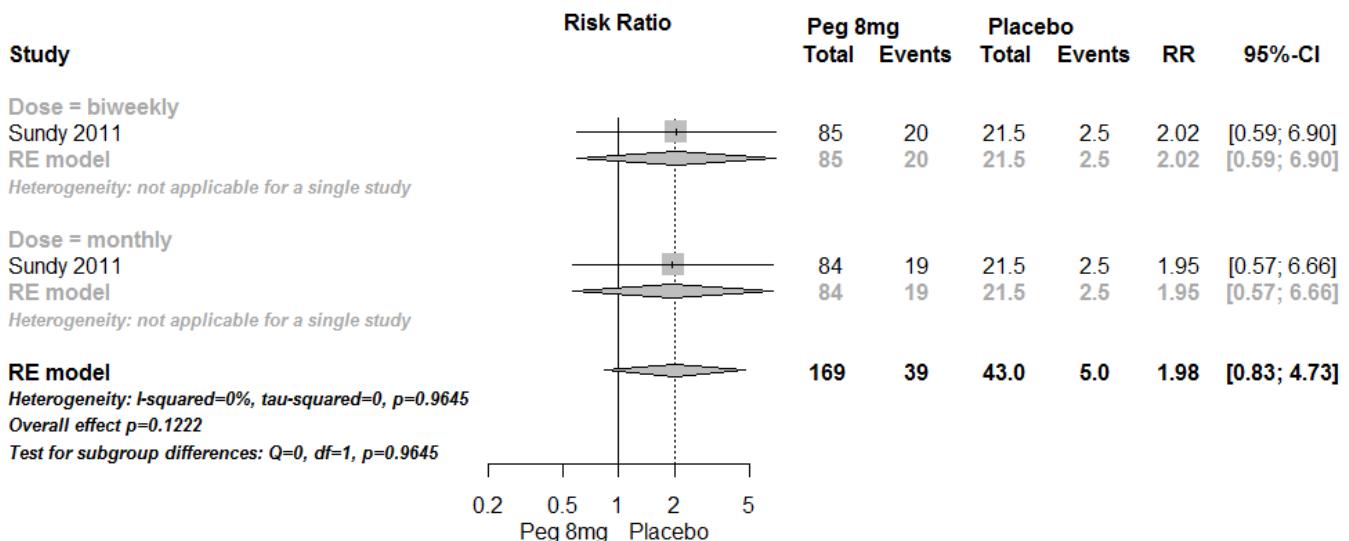


Figure 19j: Monthly vs. biweekly pegloticase 8mg.

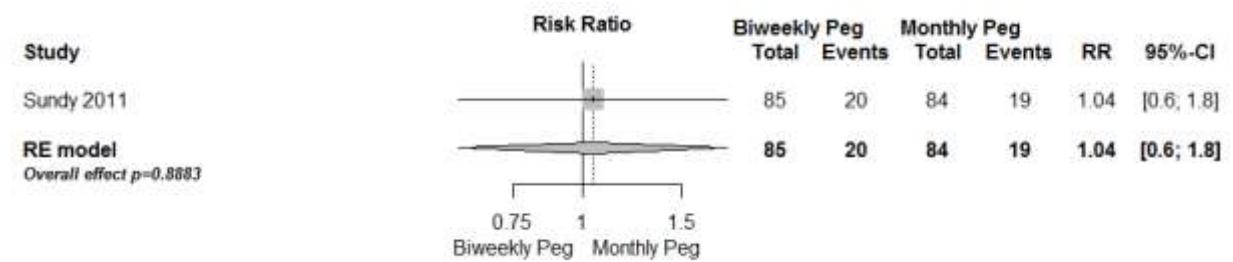


Figure 19k: Lesinurad 200mg + allopurinol 300mg vs. allopurinol 300mg.

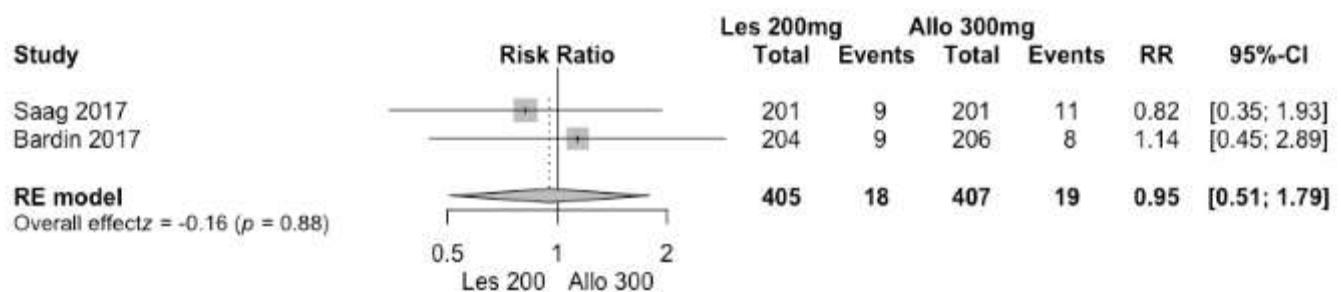


Figure 19l: Lesinurad 200mg + febuxostat 80mg vs. febuxostat 80mg.

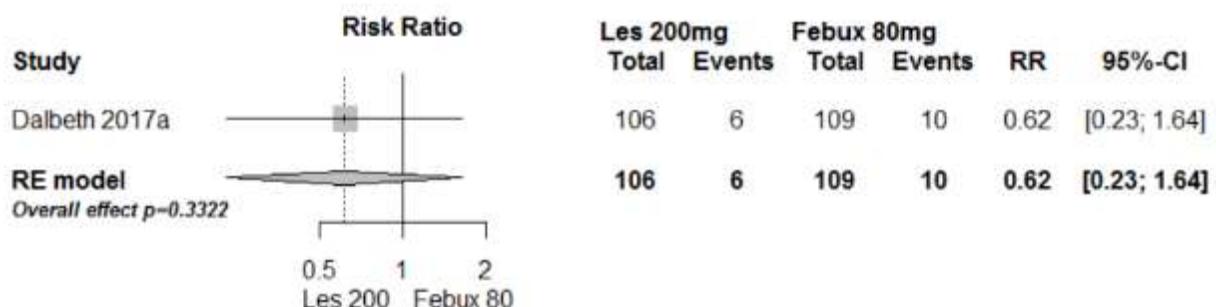


Figure 19m: Network forest plot with placebo as comparator.

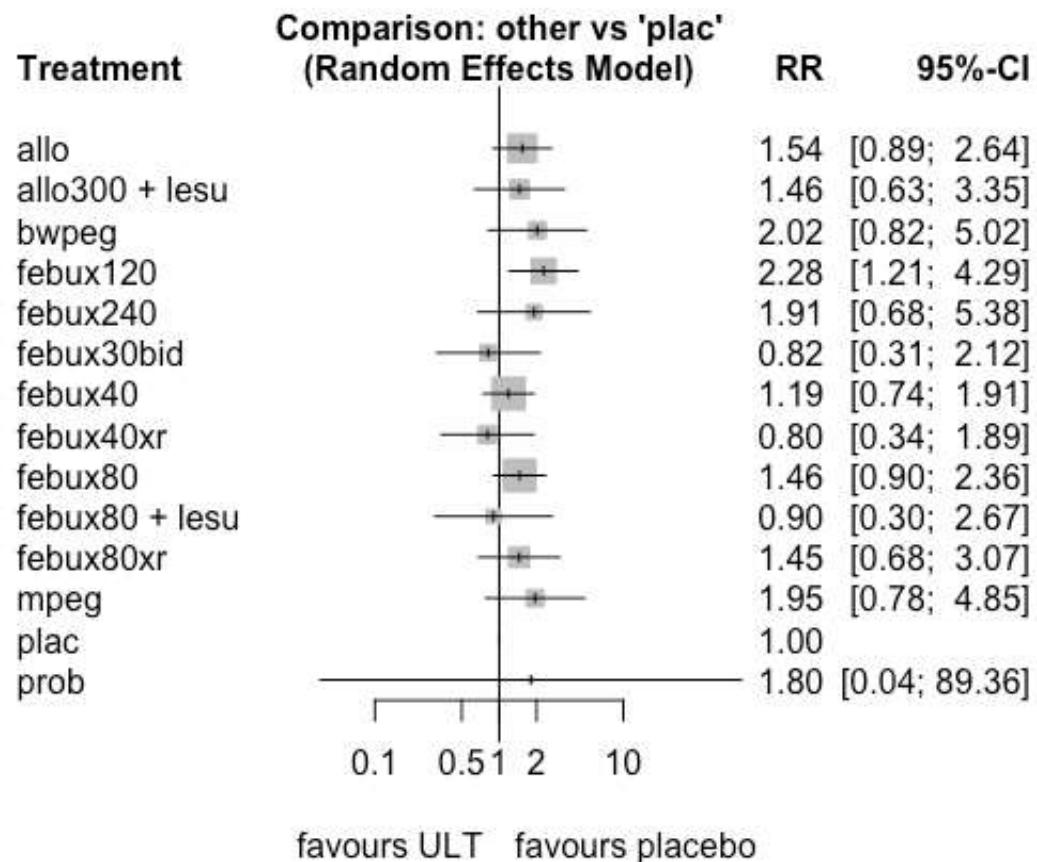
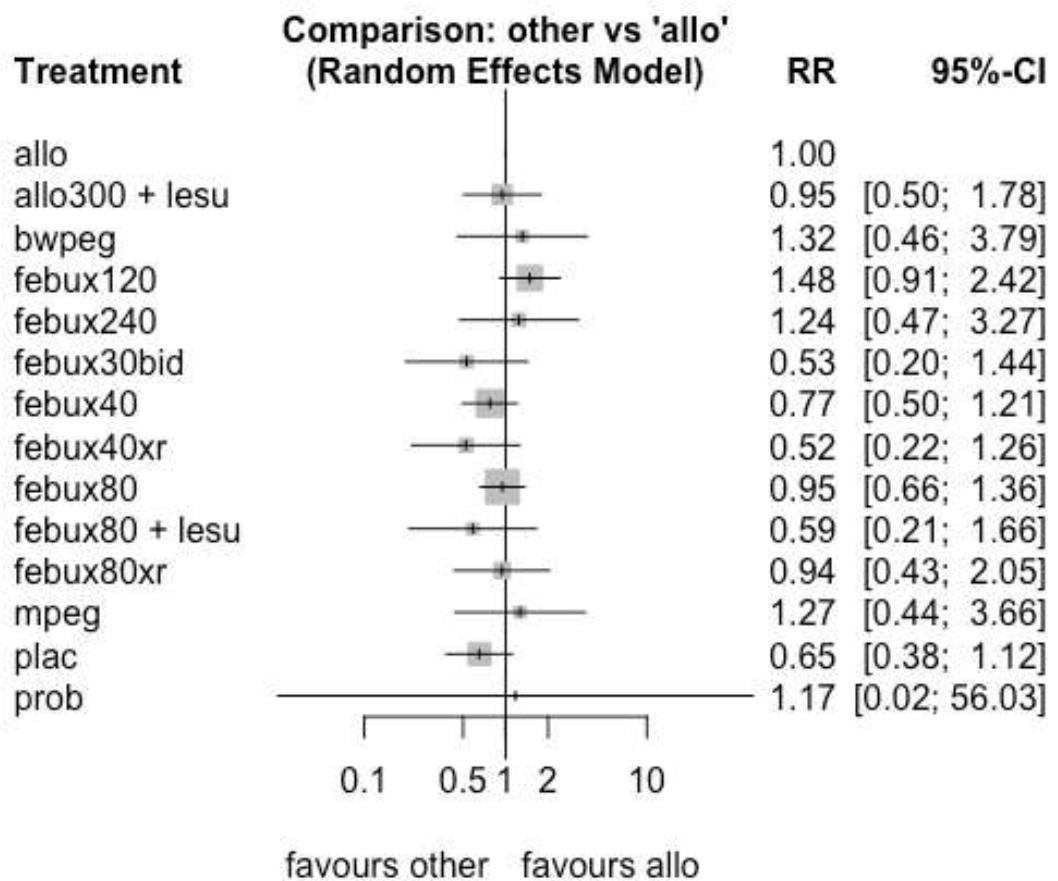
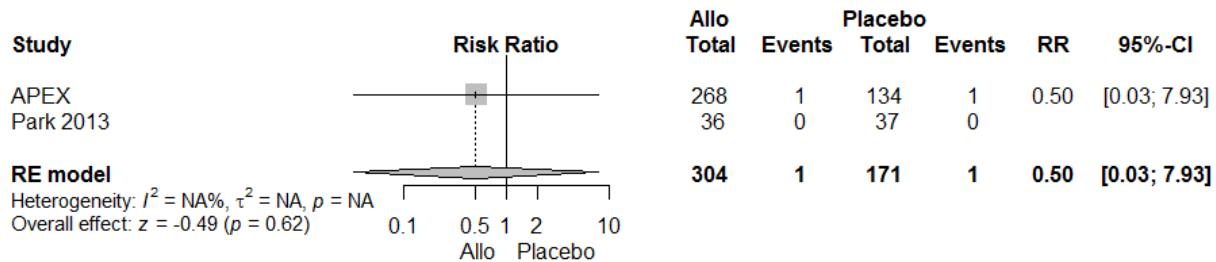


Figure 19n: Network forest plot with allopurinol 300mg as comparator.



**Figures 20a-l: Forest plots for proportion of patients with cardiovascular-related serious, Longest follow-up (range: 28 day to median of 32 months)**

*Figure 20a: Allopurinol 300mg vs. placebo.*



*Figure 20b: Any dose of febuxostat vs. placebo.*

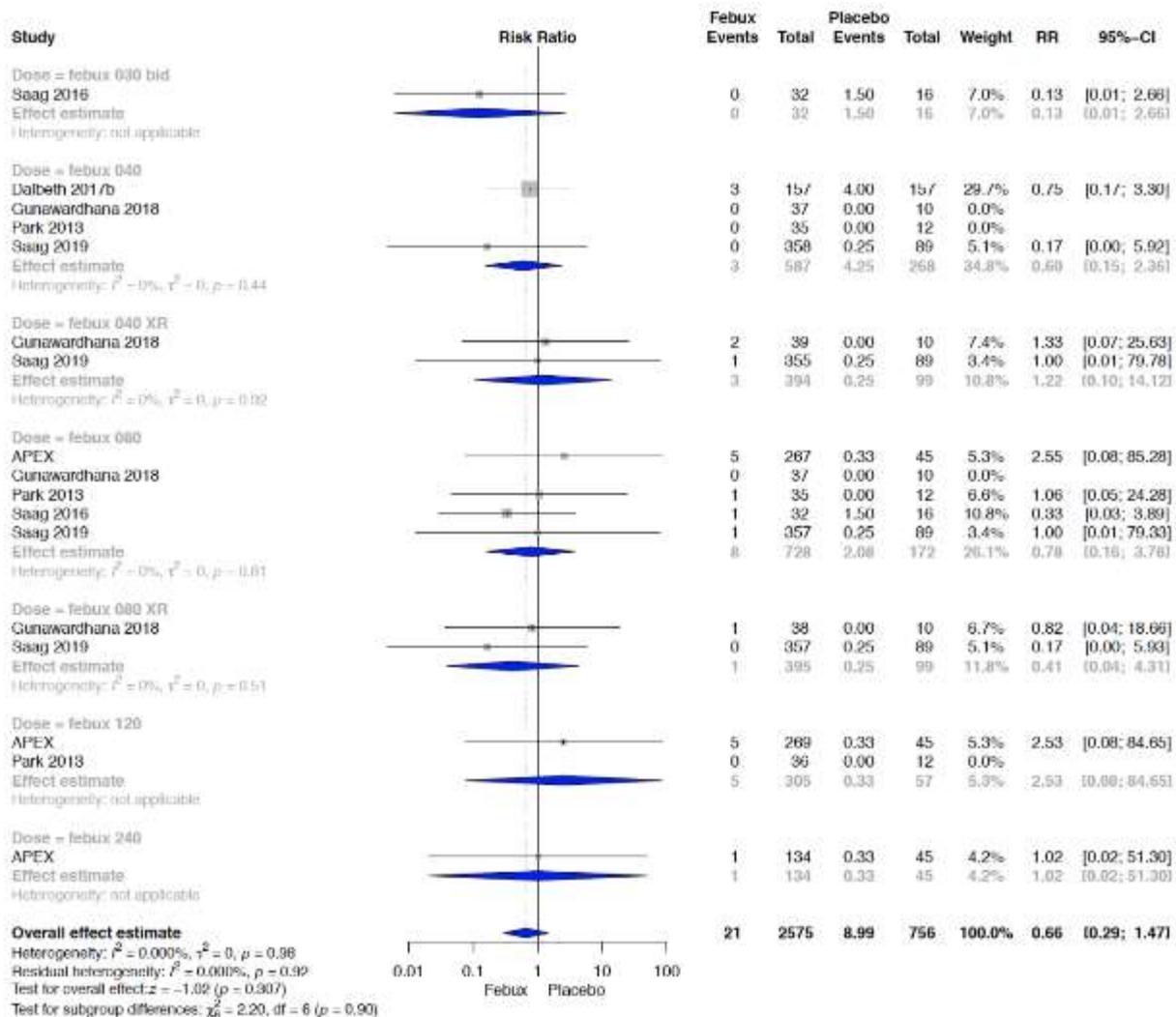


Figure 20c: Any dose of febuxostat vs. allopurinol 300mg.

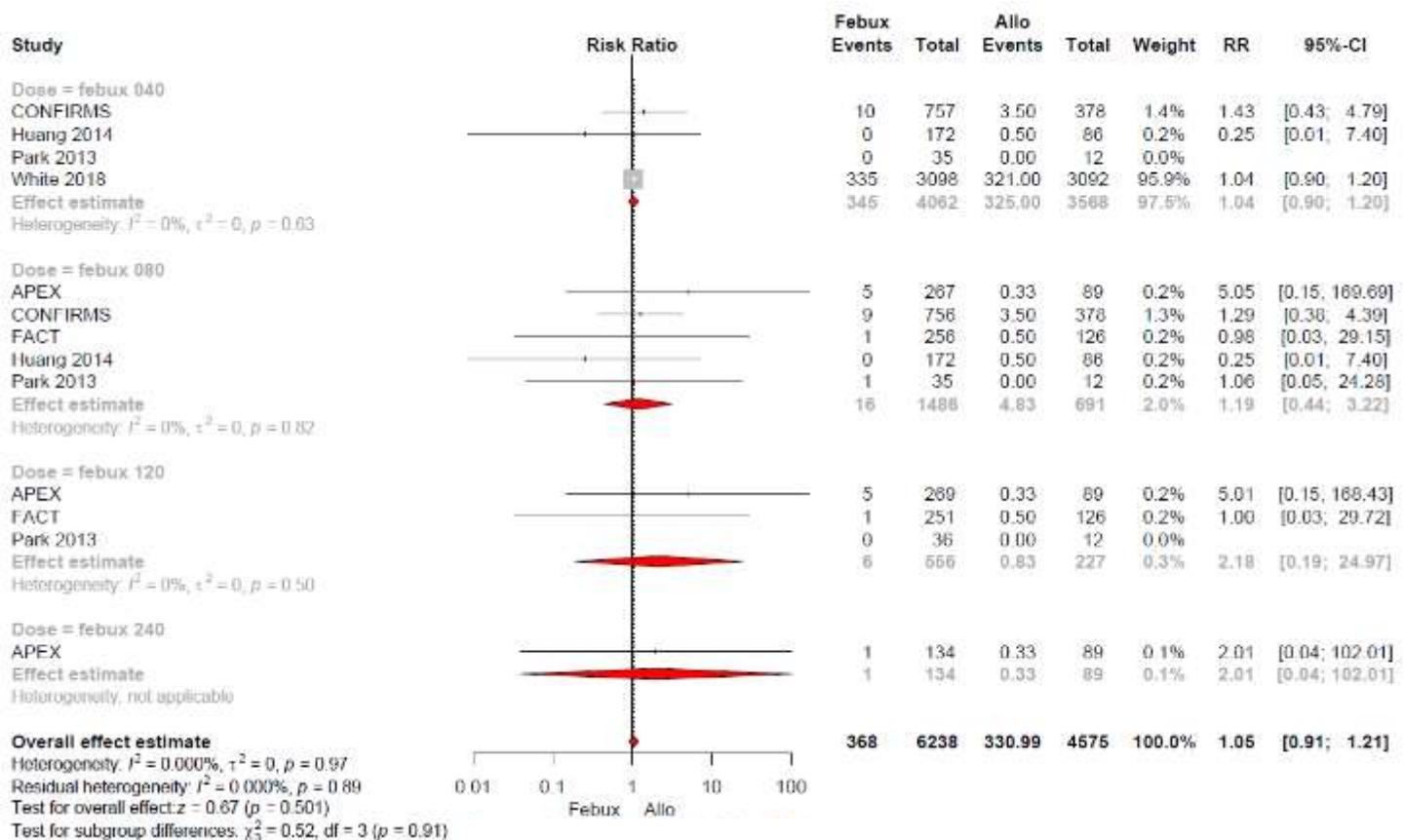


Figure 20d: Any dose of febuxostat vs. febuxostat 40mg.

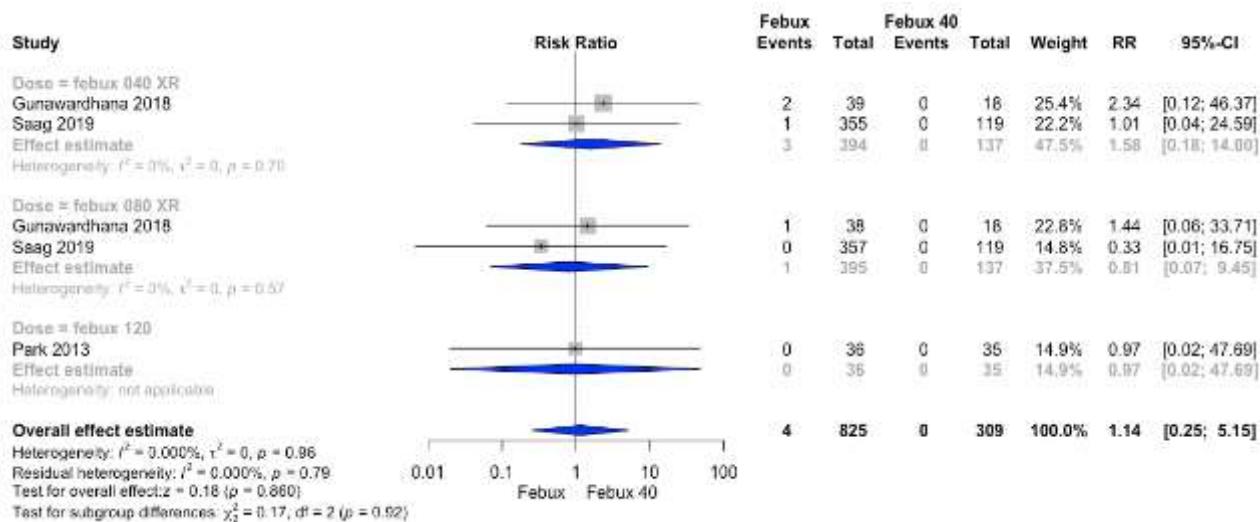


Figure 20e: Any dose of febuxostat vs. febuxostat 80mg.

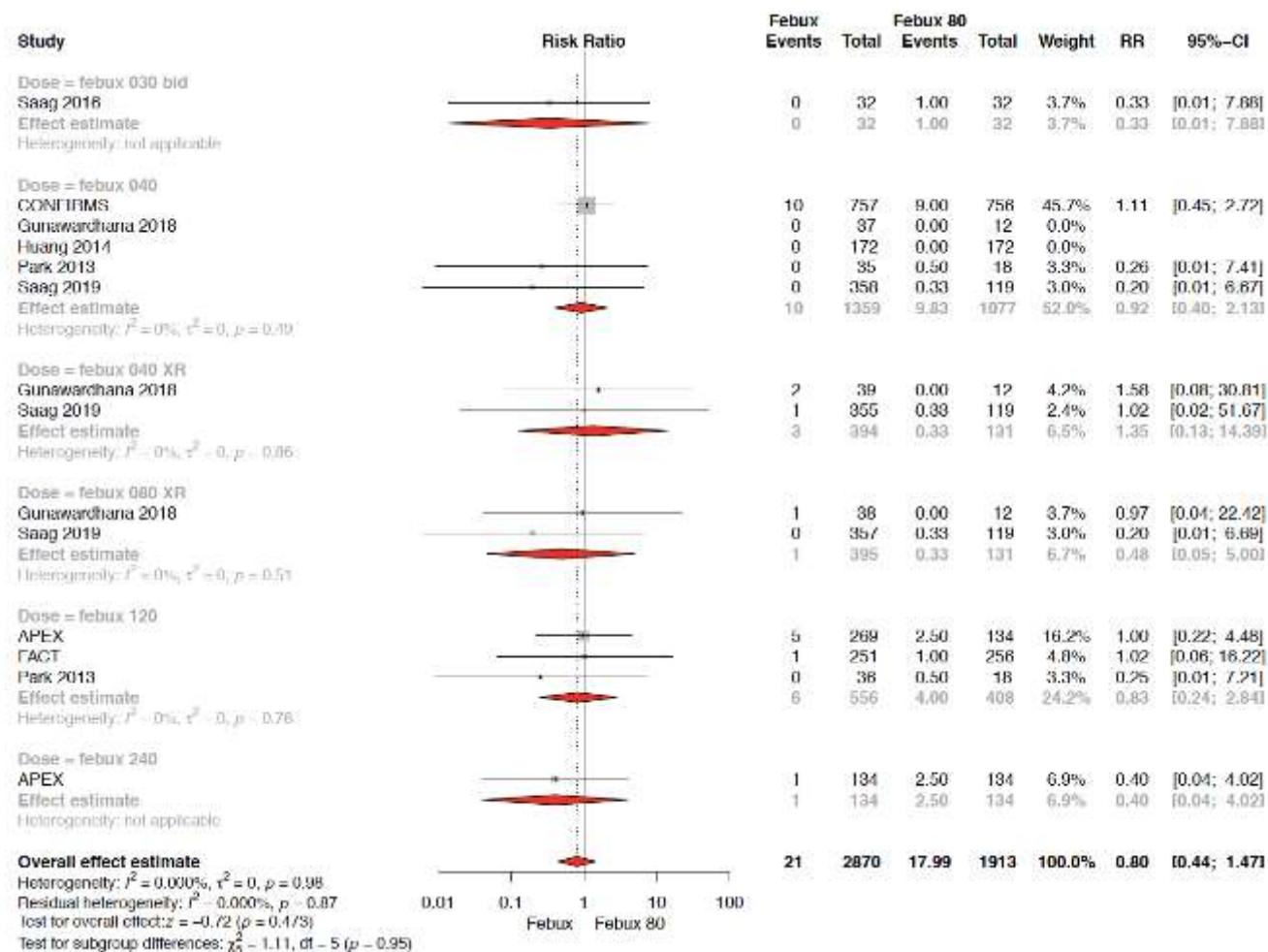


Figure 20f: Any dose of febuxostat vs. Febuxostat 240mg.

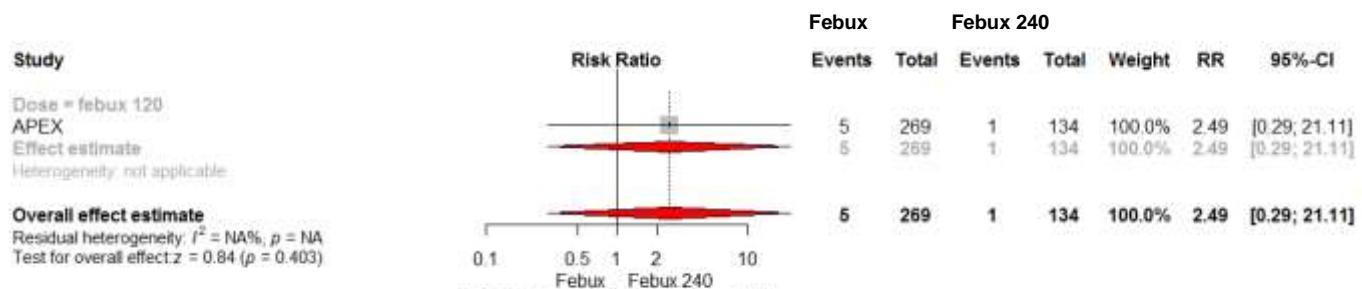


Figure 20g: Febuxostat 80mg XR vs. Febuxostat 40mg XR.

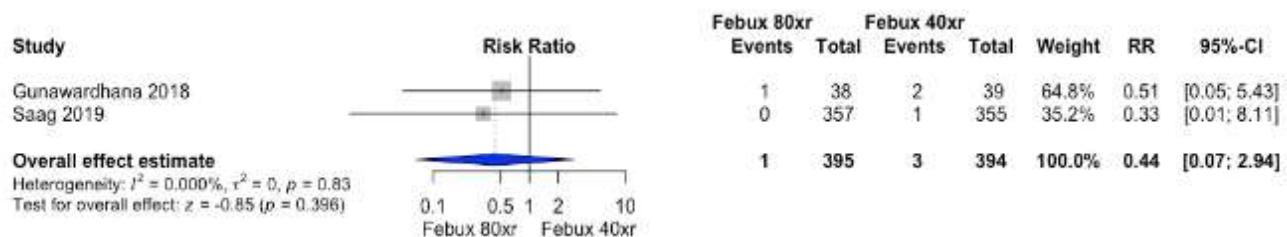


Figure 20h: Monthly vs. Biweekly pegloticase 8mg.

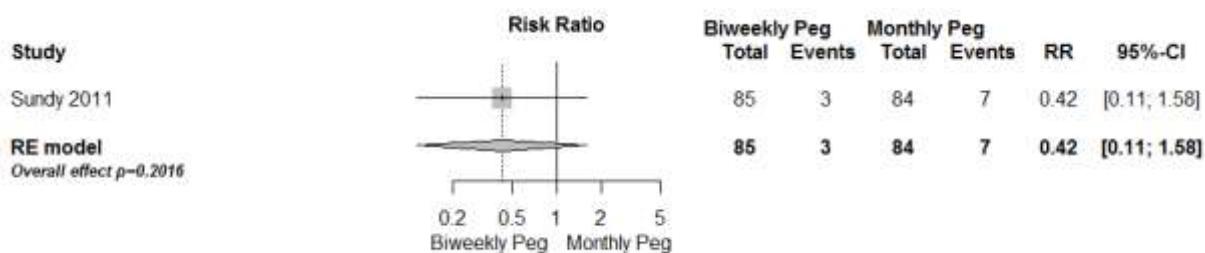


Figure 20i: Lesinurad 200mg + allopurinol 300mg vs. allopurinol 300mg

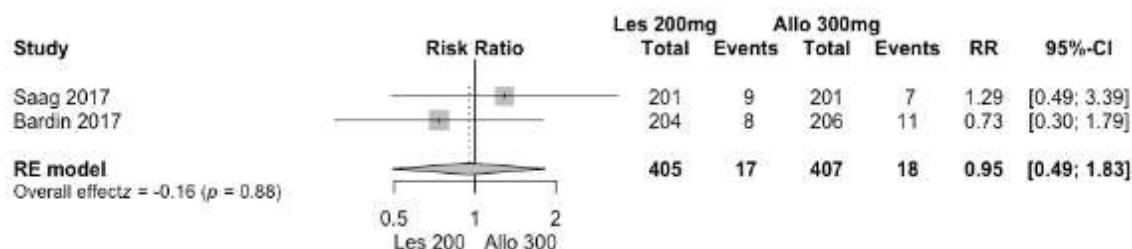


Figure 20j: Lesinurad 200mg + febuxostat 80mg vs. febuxostat 80mg.

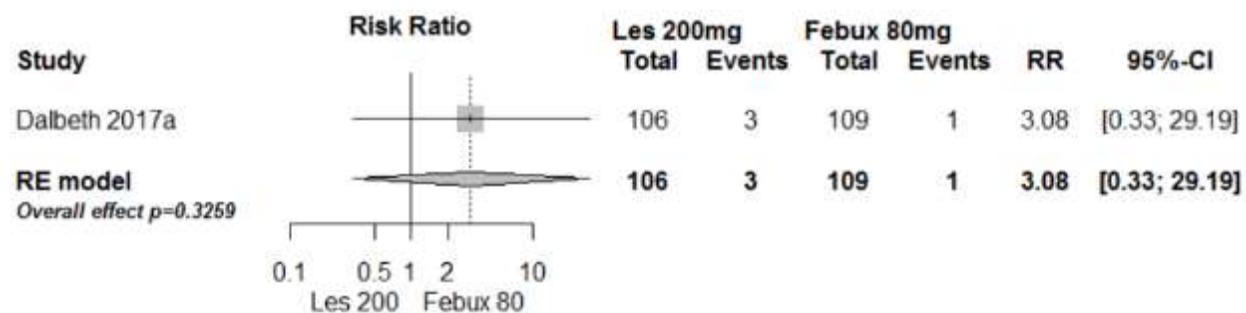


Figure 20k: Network forest plot with placebo as comparator.

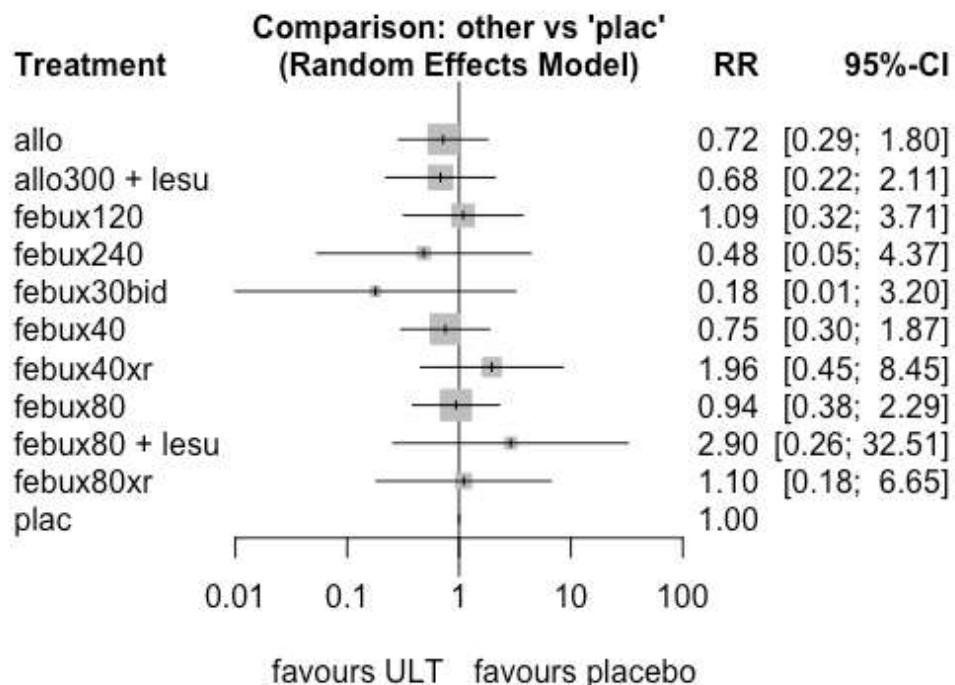
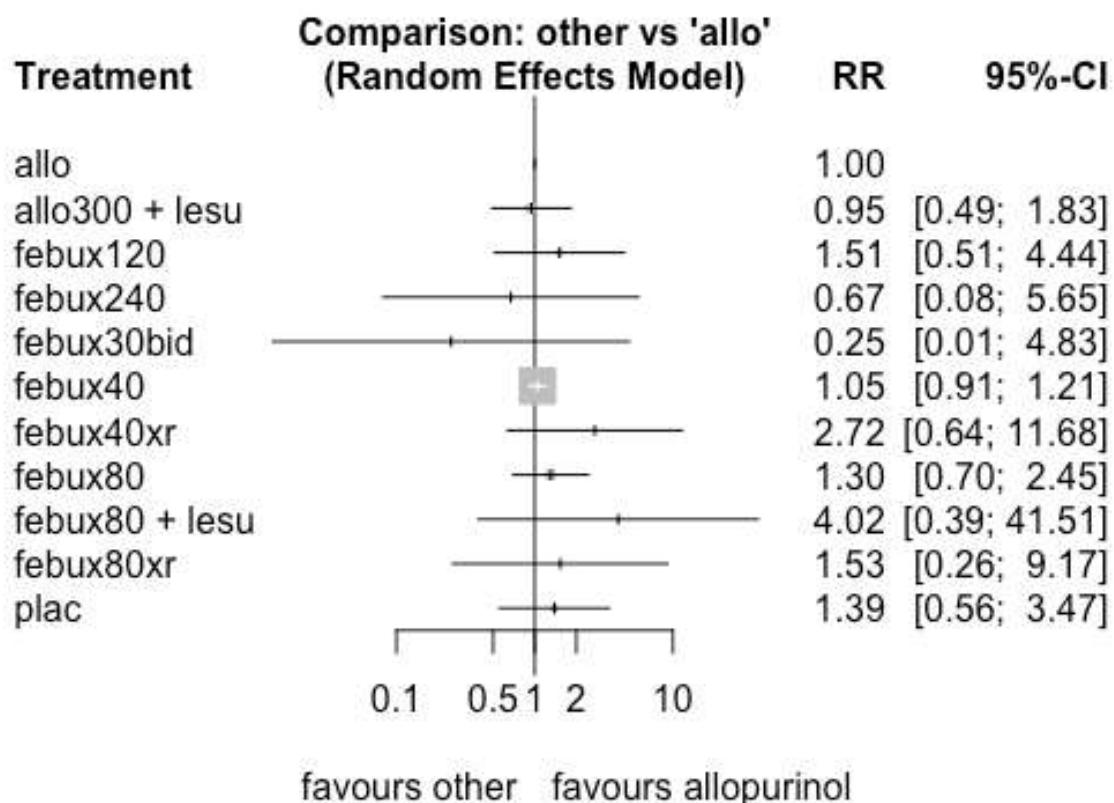


Figure 20l: Network forest plot with allopurinol 300mg as comparator.



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