Supplemental Content   1

Title: Adverse events of Benralizumab in moderate-to-severe eosinophilic asthma: A meta-analysis

Co-first authors: Wanshu Liu, Xuesu Ma

Supplemental content 1: The data and charts of death

In 8 trials, death was reported in 0.45% (11/2465) of patients treated with benralizumab and in 0.23% (3/1322) of patients treated with a placebo. No significant difference was noted between the benralizumab group and placebo group (RR 1.68, 95%CI 0.55—5.14, P=0.37, I²=0%; Figure 1s).

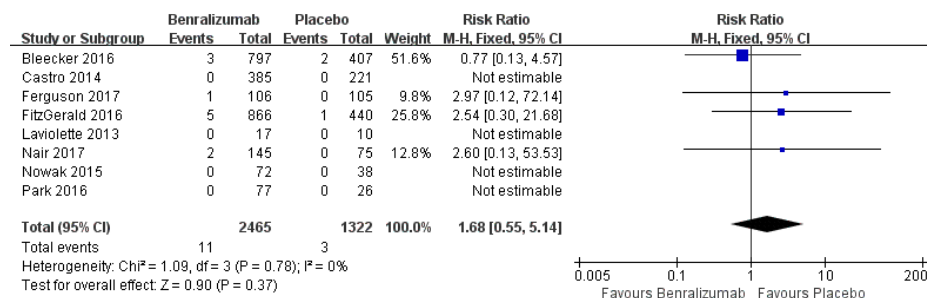|	Benralizumab		Placebo			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Bleecker 2016	3	797	2	407	51.6%	0.77 [0.13, 4.57]	
Castro 2014	0	385	0	221		Not estimable	
Ferguson 2017	1	106	0	105	9.8%	2.97 [0.12, 72.14]	
FitzGerald 2016	5	866	1	440	25.8%	2.54 [0.30, 21.68]	
Laviolette 2013	0	17	0	10		Not estimable	
Nair 2017	2	145	0	75	12.8%	2.60 [0.13, 53.53]	
Nowak 2015	0	72	0	38		Not estimable	
Park 2016	0	77	0	26		Not estimable	
Total (95% CI)		2465		1322	100.0%	1.68 [0.55, 5.14]	
Total events	11		3				
Heterogeneity: Chi² = 1.09, df = 3 (P = 0.78); I² = 0%							
Test for overall effect: Z = 0.90 (P = 0.37)							

Figure 1s. Meta-analysis of studies of the probability of the death was similar between the benralizumab group and placebo group; H-X, Fixed, fixed effect model. CI, confidence interval.

Supplemental Content　2

Title: Adverse events of Benralizumab in moderate-to-severe eosinophilic asthma: A meta-analysis

Co-first authors: Wanshu Liu, Xuesu Ma

Supplemental content 2: The data and charts of Hypersensitivity.

In 4 trials, hypersensitivity was reported in 2.87% (55/1914) of patients treated with benralizumab and in 2.92% (30/1027) of patients treated with placebo. There were no statistically significant differences between the benralizumab group and placebo group (RR 0.96, 95%CI 0.62—1.48, P=0.85, I^2=0%; Figure 2s).

Study or Subgroup	Benralizumab Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bleecker 2016	24	797	11	407	36.9%	1.11 [0.55, 2.25]
Ferguson 2017	2	106	1	105	2.5%	1.98 [0.18, 21.52]
FitzGerald 2016	26	866	17	440	57.2%	0.78 [0.43, 1.42]
Nair 2017	3	145	1	75	3.3%	1.55 [0.16, 14.66]
Total (95% CI)		1914		1027	100.0%	0.96 [0.62, 1.48]
Total events	55		30			

Heterogeneity: Chi² = 1.18, df = 3 (P = 0.76); I² = 0%
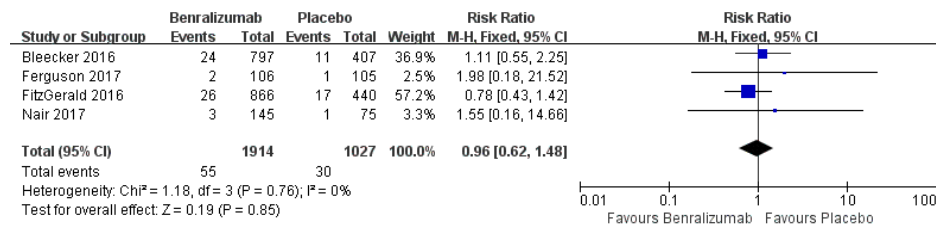Test for overall effect: Z = 0.19 (P = 0.85)

Figure 2s. Meta-analysis of studies of the probability of the hypersensitivity was similar between the benralizumab group and placebo group; H-X, Fixed, fixed effect model. CI, confidence interval.

Supplemental Content　3

Title: Adverse events of Benralizumab in moderate-to-severe eosinophilic asthma: A meta-analysis

Co-first authors: Wanshu Liu, Xuesu Ma

Supplemental content 3: The data and charts of nasopharyngitis.

Nasopharyngitis was one of the most frequently reported AEs in all the trials included in this analysis. The nasopharyngitis data revealed that 15.36% (365/2377) of patients receiving benralizumab developed nasopharyngitis, and 14.67% (194/1322) of patients receiving placebo developed nasopharyngitis. There was no significant difference in the incidence of nasopharyngitis between the benralizumab group and the placebo group (RR 1.03, 95%CI 0.88—1.21, P=0.71, I^2=40%; Figure 3s).

Study or Subgroup	Benralizumab Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bleecker 2016	93	797	47	407	24.9%	1.01 [0.73, 1.41]
Castro 2014	44	385	13	221	6.6%	1.94 [1.07, 3.53]
Ferguson 2017	8	106	8	105	3.2%	0.99 [0.39, 2.54]
FitzGerald 2016	169	758	92	440	46.5%	1.07 [0.85, 1.34]
Laviolette 2013	4	17	4	10	2.0%	0.59 [0.19, 1.85]
Nair 2017	22	145	15	75	7.9%	0.76 [0.42, 1.37]
Nowak 2015	2	92	2	38	1.1%	0.41 [0.06, 2.83]
Park 2016	23	77	13	26	7.8%	0.60 [0.36, 1.00]
Total (95% CI)		2377		1322	100.0%	1.03 [0.88, 1.21]
Total events	365		194			

Heterogeneity: Chi² = 11.57, df = 7 (P = 0.12); I² = 40%
Test for overall effect: Z = 0.37 (P = 0.71)

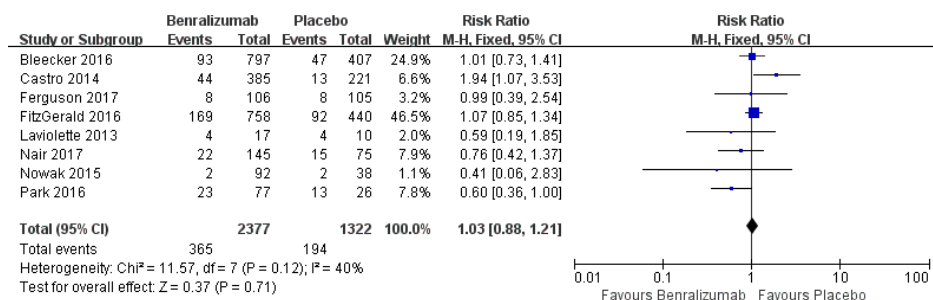Risk Ratio M-H, Fixed, 95% CI — Favours Benralizumab　Favours Placebo

Figure 3s. Meta-analysis of studies of the probability of the nasopharyngitis was similar between the benralizumab group and placebo group; H-X, Fixed, fixed effect model. CI, confidence interval.

Supplemental Content   4

Title: Adverse events of Benralizumab in moderate-to-severe eosinophilic asthma: A meta-analysis

Co-first authors: Wanshu Liu, Xuesu Ma

Supplemental content 4: The data and charts of Rhinitis.

Four trials included in this analysis reported rhinitis. 3.55% (67/1885) of patients receiving benralizumab developed rhinitis as compared to 2.68% (34/948) of patients receiving placebo. No statistically significant difference in the incidence of rhinitis was observed between the benralizumab group and placebo group (RR 0.98, 95%CI 0.65—1.47, P=0.92, I²=0%; Figure 4s).

Study or Subgroup	Benralizumab Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bleecker 2016	26	797	15	407	43.4%	0.89 [0.47, 1.65]
FitzGerald 2016	29	866	17	440	49.2%	0.87 [0.48, 1.56]
Nair 2017	8	145	2	75	5.8%	2.07 [0.45, 9.50]
Park 2016	4	77	0	26	1.6%	3.12 [0.17, 55.99]
Total (95% CI)		1885		948	100.0%	0.98 [0.65, 1.47]
Total events	67		34			

Heterogeneity: Chi² = 1.81, df = 3 (P = 0.61); I² = 0%
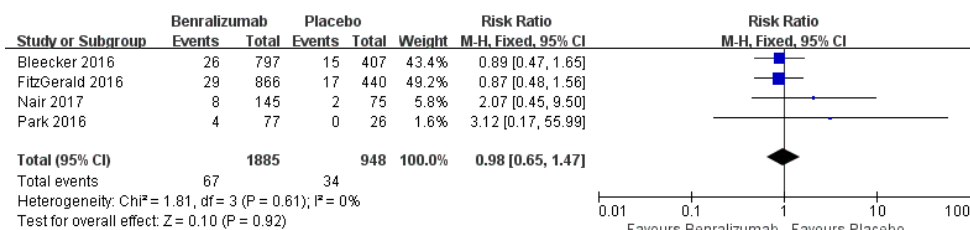Test for overall effect: Z = 0.10 (P = 0.92)

Figure 4s. Meta-analysis of studies of the probability of the rhinitis was similar between the benralizumab group and placebo group; H-X, Fixed, fixed effect model. CI, confidence interval.

Supplemental Content 5

Title: Adverse events of Benralizumab in moderate-to-severe eosinophilic asthma: A meta-analysis

Co-first authors: Wanshu Liu, Xuesu Ma

Supplemental content 5: The data and charts of Pharyngitis.

Three trials included in this analysis reported the incidence of pharyngitis. 3.33% (58/1740) of patients in the benralizumab group developed pharyngitis compared with 2.75% (24/873)of patients in the placebo group. No statistically significant difference was observed between the benralizumab group and the placebo group (RR 1.19, 95%CI 0.74—1.90, P=0.47, I²=5%; Figure 5s).
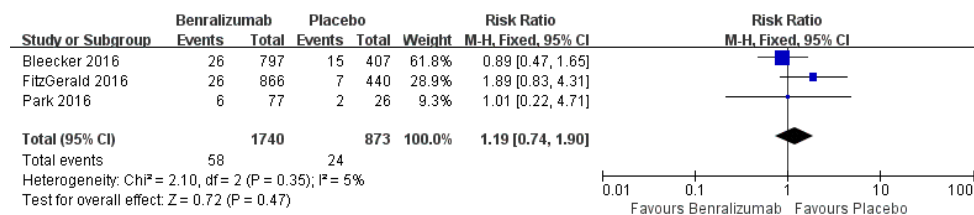

Figure 5s. Meta-analysis of studies of the probability of the pharyngitis was similar between the benralizumab group and placebo group; H-X, Fixed, fixed effect model. CI, confidence interval.

Supplemental Content 6

Title: Adverse events of Benralizumab in moderate-to-severe eosinophilic asthma: A meta-analysis

Co-first authors: Wanshu Liu, Xuesu Ma

Supplemental content 6: The data and charts of Upper respiratory tract infection.

Six trials included in this analysis reported upper respiratory tract infection. 8.58% (177/2063) of patients in the benralizumab group developed upper respiratory tract infection as compared to 8.98% (98/1091) of patients in the placebo group. No statistically significant difference was observed between the two groups (RR 0.91 95%CI 0.72—1.15, P=0.42, I²=0%; Figure 6s).

Study or Subgroup	Benralizumab Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bleecker 2016	76	797	36	407	36.8%	1.08 [0.74, 1.57]
Ferguson 2017	5	106	5	105	3.9%	0.99 [0.30, 3.32]
FitzGerald 2016	65	866	41	440	42.0%	0.81 [0.55, 1.17]
Nair 2017	9	145	5	75	5.1%	0.93 [0.32, 2.68]
Nowak 2015	1	72	3	38	3.0%	0.18 [0.02, 1.63]
Park 2016	21	77	8	26	9.2%	0.89 [0.45, 1.75]
Total (95% CI)		2063		1091	100.0%	0.91 [0.72, 1.15]
Total events	177		98			

Heterogeneity: Chi² = 3.30, df = 5 (P = 0.65); I² = 0%
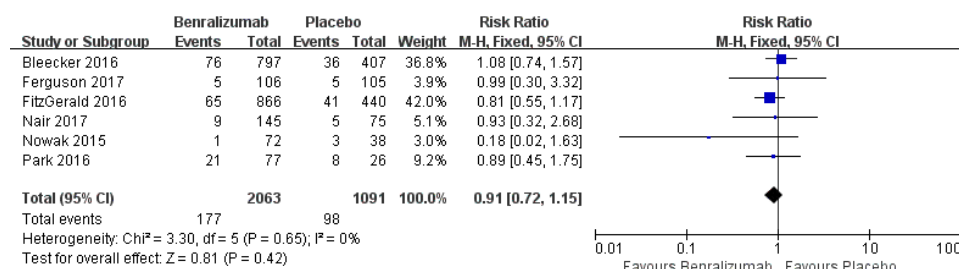Test for overall effect: Z = 0.81 (P = 0.42)

Figure 6s. Meta-analysis of studies of the probability of the upper respiratory tract infection was similar between the benralizumab group and placebo group; H-X, Fixed, fixed effect model. CI, confidence interval.

Supplemental Content　7

Title: Adverse events of Benralizumab in moderate-to-severe eosinophilic asthma: A meta-analysis

Co-first authors: Wanshu Liu, Xuesu Ma

Supplemental content 7: The data and charts of Influenza

In these trials, 4.62% (87/1885) of patients receiving benralizumab experienced influenza as compared to 5.60% (53/948) of patients receiving placebo. No statistically significant difference was observed between the benralizumab group and the placebo group (RR 0.81,95%CI 0.58—1.13, P=0.21, I^2=10%; Figure 7s).
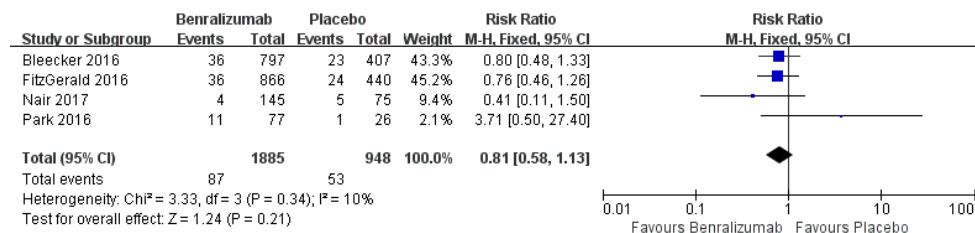

Figure 7s. Meta-analysis of studies of the probability of the influenza was similar between the benralizumab group and placebo group; H-X, Fixed, fixed effect model. CI, confidence interval.

Supplemental Content 8

Title: Adverse events of Benralizumab in moderate-to-severe eosinophilic asthma: A meta-analysis

Co-first authors: Wanshu Liu, Xuesu Ma

Supplemental content 8: The data and charts of Nausea.

Four trials included in this analysis reported nausea. 3.12% (8/251) of patients in the benralizumab group experienced nausea as compared to 4.51% (6/133) of patients in the placebo group. No statistically significant difference was observed between the benralizumab group and the placebo group (RR 1.04, 95%CI 0.54—2.00, P=0.91, I²=0%; Figure 8s).

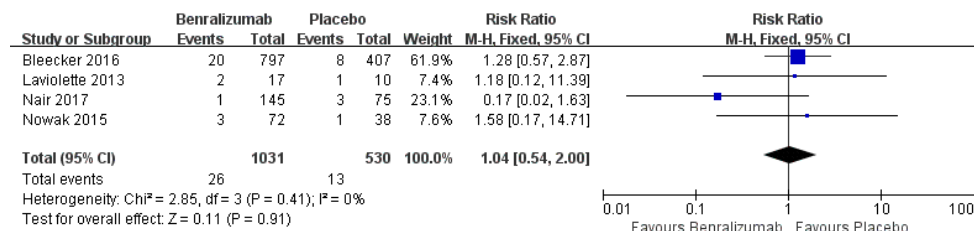|	Benralizumab		Placebo			Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	
Bleecker 2016	20	797	8	407	61.9%	1.28 [0.57, 2.87]	
Laviolette 2013	2	17	1	10	7.4%	1.18 [0.12, 11.39]	
Nair 2017	1	145	3	75	23.1%	0.17 [0.02, 1.63]	
Nowak 2015	3	72	1	38	7.6%	1.58 [0.17, 14.71]	
Total (95% CI)		1031		530	100.0%	1.04 [0.54, 2.00]	
Total events	26		13				
Heterogeneity: Chi² = 2.85, df = 3 (P = 0.41); I² = 0%							
Test for overall effect: Z = 0.11 (P = 0.91)							

Figure 8s. Meta-analysis of studies of the probability of the nausea was similar between the benralizumab group and placebo group; H-X, Fixed, fixed effect model. CI, confidence interval.

Supplemental Content   9

Title: Adverse events of Benralizumab in moderate-to-severe eosinophilic asthma: A meta-analysis

Co-first authors: Wanshu Liu, Xuesu Ma

Supplemental content 9: The data and charts of cough.

Five trials included in this analysis reported cough. 3.32% (63/1897) of patients in the benralizumab group developed cough as compared to 2.68% (26/970) of patients in the placebo group. No statistically significant difference was observed between the benralizumab group and the placebo group (RR 1.25, 95%CI 0.79—1.95, P=0.34, I^2=0%; Figure 9s).

Study or Subgroup	Benralizumab Events	Total	Place Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bleecker 2016	28	797	10	407	38.6%	1.43 [0.70, 2.91]
FitzGerald 2016	24	866	8	440	30.9%	1.52 [0.69, 3.36]
Laviolette 2013	1	17	1	10	3.7%	0.59 [0.04, 8.41]
Nair 2017	3	145	4	75	15.4%	0.39 [0.09, 1.69]
Nowak 2015	7	72	3	38	11.4%	1.23 [0.34, 4.49]
Total (95% CI)		1897		970	100.0%	1.25 [0.79, 1.95]
Total events	63		26			

Heterogeneity: Chi² = 3.12, df = 4 (P = 0.54); I^2 = 0%
Test for overall effect: Z = 0.96 (P = 0.34)
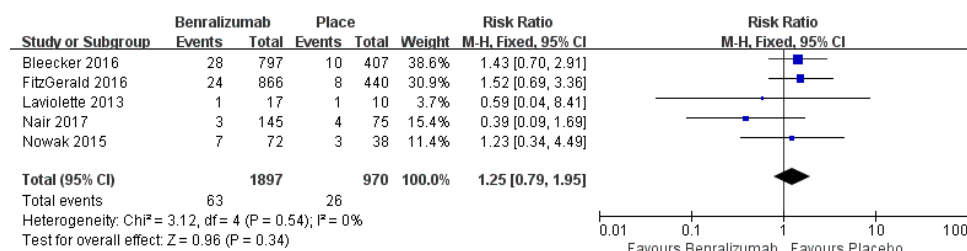
Favours Benralizumab   Favours Placebo

Figure 9s. Meta-analysis of studies of the probability of the cough was similar between the benralizumab group and placebo group; H-X, Fixed, fixed effect model. CI, confidence interval.

Supplemental Content　10

Title: Adverse events of Benralizumab in moderate-to-severe eosinophilic asthma: A meta-analysis

Co-first authors: Wanshu Liu, Xuesu Ma

Supplemental content 10: The data and charts of back pain.

Five trials included in this analysis reported back pain. 2.86% (56/1957) of patients treated with benralizumab developed back pain as compared to 3.85% (38/986) of patients treated with placebo. No statistically significant difference was observed between the benralizumab group and the placebo group (RR 0.73, 95%CI 0.49—1.10, P=0.13, I²=0%; Figure 10s).

Study or Subgroup	Benralizumab Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bleecker 2016	19	797	15	407	38.9%	0.65 [0.33, 1.26]
FitzGerald 2016	27	866	16	440	41.6%	0.86 [0.47, 1.57]
Nair 2017	4	145	4	75	10.3%	0.52 [0.13, 2.01]
Nowak 2015	2	72	3	38	7.7%	0.35 [0.06, 2.02]
Park 2016	4	77	0	26	1.5%	3.12 [0.17, 55.99]
Total (95% CI)		**1957**		**986**	**100.0%**	**0.73 [0.49, 1.10]**
Total events	56		38			

Heterogeneity: Chi² = 2.29, df = 4 (P = 0.68); I² = 0%
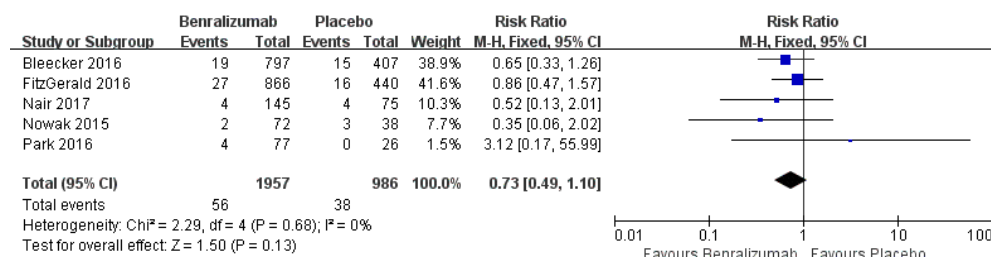Test for overall effect: Z = 1.50 (P = 0.13)

Figure 10s. Meta-analysis of studies of the probability of the back pain was similar between the benralizumab group and placebo group; H-X, Fixed, fixed effect model. CI, confidence interval.

Supplemental Content   11

Title: Adverse events of Benralizumab in moderate-to-severe eosinophilic asthma: A meta-analysis

Co-first authors: Wanshu Liu, Xuesu Ma

Supplemental content 11: The data and charts of Arthralgia.

Arthralgia

Four trials included in this analysis reported arthralgia.3.20% (58/1812) of patients treated with benralizumab developed arthralgia as compared to 2.41% (22/911) of patients treated with placebo. No statistically significant difference was observed between patients receiving benralizumab and those receiving placebo (RR 1.30, 95%CI 0.80—2.12, P=0.29, I²=0%; Figure 11s)

Study or Subgroup	Benralizumab Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bleecker 2016	29	797	10	407	45.2%	1.48 [0.73, 3.01]
FitzGerald 2016	22	866	9	440	40.8%	1.24 [0.58, 2.67]
Nowak 2015	1	72	2	38	8.9%	0.26 [0.02, 2.82]
Park 2016	6	77	1	26	5.1%	2.03 [0.26, 16.05]
Total (95% CI)		1812		911	100.0%	1.30 [0.80, 2.12]
Total events	58		22			

Heterogeneity: Chi² = 2.06, df = 3 (P = 0.56); I² = 0%
Test for overall effect: Z = 1.07 (P = 0.29)
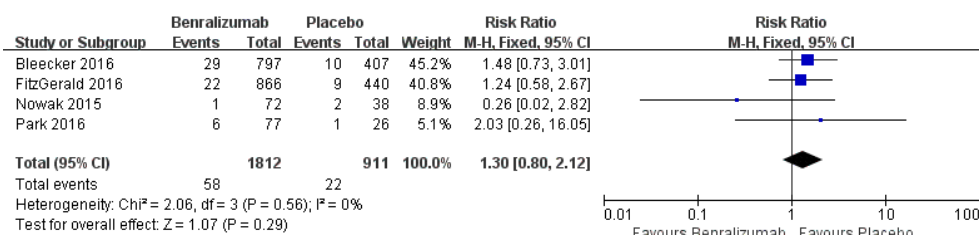
Favours Benralizumab Favours Placebo

Figure 11s. Meta-analysis of studies of the probability of the arthralgia was similar between the benralizumab group and placebo group; H-X, Fixed, fixed effect model. CI, confidence interval.