

REVIEW

Comparison of anti-interleukin-5 therapies in patients with severe asthma: global and indirect meta-analyses of randomized placebo-controlled trials

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Summary

Inconsistent results have been reported regarding IL-5 blockade treatment in asthma. There were no direct between-treatment comparisons. Only differences between each drug and placebo were studied. We identified all RCTs with anti-IL5 treatments for patients with asthma over the 1990–September 2015 period. RCTs were searched on Medline, Cochrane and Embase. At least 50 patients were enrolled in each study. Outcomes considered were exacerbation rate reduction, FEV₁ changes, ACQ-5 improvement, adverse events and serious adverse events. A global meta-analysis was first conducted followed by an indirect comparison of each IL-5-targeting drug: benralizumab, reslizumab and mepolizumab. Further eosinophilic subgroup analysis and sensitivity analysis were also conducted in case of heterogeneity. Ten trials involving 3421 patients were eligible for meta-analysis. IL-5 blockade significantly reduced annual exacerbation rates vs. placebo by 40% [29–50] ($P < 0.01$, $I^2 = 0.61$). ACQ-5 was significantly improved vs. placebo but below the recognized MCID level (-0.31 [-0.41 , -0.21], $P < 0.01$, $I^2 = 0.11$). FEV₁ changes from baseline were improved vs. placebo by 0.09 L [0.05 – 0.12] ($P < 0.01$, $I^2 = 0.28$). The subgroup analysis identified a slight additional improvement in mean treatment effects in eosinophilic ($> 300 \text{ mm}^3/\text{L}$) patients with severe asthma. Similar patterns and rates of adverse events and severe adverse events were reported with the three drugs. The data interpretations were not affected by the sensitivity analysis. IL-5 blockade appears to be a relevant treatment strategy to improve severe asthma management, particularly for eosinophilic patients. No clear superiority appeared between the drugs when appropriate doses were compared.

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Introduction

Severe asthma is a challenging disease as poor levels of asthma control, frequent exacerbations and impaired lung function are associated with poor outcomes [1]. The role of eosinophils has yet to be clarified [2]. Twenty-five years ago, eosinophilic inflammation was reported to be a common inflammation pattern in asthmatic airways [3, 4], but uncertainties arose when negative results were reported with mepolizumab, a monoclonal antibody directed against IL-5 [2]. Concerns about the inclusion criteria used in these first studies were raised – patients included presented with asthma of mild severity and no prior phenotypic identification

was performed. Heterogeneity of severe asthma was then identified, and phenotypic and endotypic studies led to the idea that TH2/non-TH2 inflammation patterns are potential therapeutic targets [5, 6].

IL-5 is a critical cytokine for eosinophil maturation in bone marrow, with recruitment and activation taking place at the inflammation site through the IL-5 receptor [7]. Other TH2 cytokines, such as IL-13, IL-4, IL-9, TSLP, IL-33 and others, are targets currently under development [8]. IgE blockade downstream of these cytokines was an appealing strategy when there was evidence of IgE involvement. Omalizumab was developed and achieved impressive results in severe asthma [9, 10].

Overlaps between phenotypes were then explored, and IgE/eosinophils were seen as different TH2 surrogate markers [11]. Finally, IL-5 again became the focus of clinical trials, but only in eosinophilic patients.

Mepolizumab is a humanized mAb that was initially administered by monthly intravenous (i.v.) infusions [2], while subcutaneous (s.c.) infusion has also been developed and approved. Reslizumab is also a mAb directed against IL-5 tested on the basis of monthly i.v. infusions [12]. Benralizumab does not directly target IL-5, but rather the IL-5 receptor located mostly on eosinophils. Monthly s.c. administrations have also been designed [13, 14].

In evidence-based medicine, meta-analysis is the most effective way to demonstrate a treatment effect. The results are summarized in forest plots, with publication biases highlighted by funnel plots.

We then assessed whether IL-5 blockade was a relevant strategy through a meta-analysis of all anti-IL-5 mAbs tested in severe asthma. Direct face-to-face comparisons between these mAbs would be difficult to conduct as thousands of patients would probably be required in order to observe a significant difference.

Network meta-analysis offers the opportunity to compare treatment effects in the absence of direct comparison when there is a common comparator (usually a placebo arm).

We then compared these different mAbs at their different doses through an indirect network meta-analysis, which made it possible to address safety concerns.

Methods

A systematic literature review was conducted by two independent reviewers to identify relevant studies focused on asthma trials with mepolizumab, reslizumab and benralizumab treatments. The databases searched were MEDLINE, MEDLINE-IN-PROCESS, EMBASE, the Cochrane CENTRAL Register and PubMed from 1990 to September 2015. Only articles published in English were included. Data were extracted by the two independent reviewers, and the accordance was assessed by a third reviewer.

Of the 11 clinical trials identified, 10 were considered eligible for the meta-analysis, reported in six separate publications and two publications describing two different trials each [13, 15]. This method was applied to compare the three different anti-IL5 mAbs tested at different doses (Fig. 1). The eligible studies reported outcomes relevant for assessment in asthma therapeutic trials: annual exacerbation rates, FEV₁ change from baseline and variations in asthma symptoms assessed by changes in the ACQ-5. They involved 3421 patients [12, 13, 15–20].

A meta-analysis was first conducted to assess the efficacy of the IL-5 blockade strategy overall. Meta-analysis was used to aggregate individual study treatment effect estimates to achieve a single and more accurate treatment effect estimation. Summarized data from each of the included trials were used to conduct the meta-analysis according to Cochrane guidelines. In case of multi-arm studies, group combining methods were used to deal with treatment arm effects according to the Cochrane Handbook [21]. A random effect model was used in case of significant between-trial heterogeneity, as assessed by Cochran's Q and I². The meta-analysis results were expressed as mean differences, and corresponding 95% confidence intervals, for FEV₁ and ACQ-5 between aggregated treatments compared to placebo, and as an exacerbation rate risk ratio. *P*-values indicating significant differences and I² are also presented. Standard errors were selected for this meta-analysis to avoid population size weighting effects. Forest and funnels plots were drawn up. An additional sensitivity analysis was conducted to explore the source of heterogeneity.

An indirect network meta-analysis was then performed to compare each anti-IL5 mAb efficacy and safety result using the Bayesian framework according to Cochrane's collaboration guidelines [22]. The models included multi-arm correction. The network meta-analysis was conducted according to PRISMA guidelines, and R-AMSTAR criteria were assessed to check the overall data quality. We selected a random effect model to allow heterogeneity between indirect comparisons according to ISPOR guidelines [23]. Comparison and treatment rankings were assessed by the network.

A hierarchical model using uniform links was applied to normally distributed data (FEV₁ and ACQ-5) and log-normally distributed data (annual exacerbation rates). Adverse and serious adverse events were assessed using a Poisson discrete process with a logarithmic link function.

When studies did not report the effect variability, the corresponding outcomes were excluded from the analysis.

The results were presented as a median [95% credible interval] with respect to the posterior density (for FEV₁ and ACQ-5) or as an exponential of the median [95% credible interval] for exacerbation rates ratios and safety. The median rank probability (*P*_{rank} within the text) of the treatment was also provided. Specifically, *P*₁ indicates, for one treatment and one outcome, the probability of being the most effective.

The network meta-analysis was conducted using R 3.2.2 and Winbugs version 1.4.3 software [24]. Flat priors were used for estimate initialization. Estimates were analysed once convergence was assessed through at least 100 000 simulations.

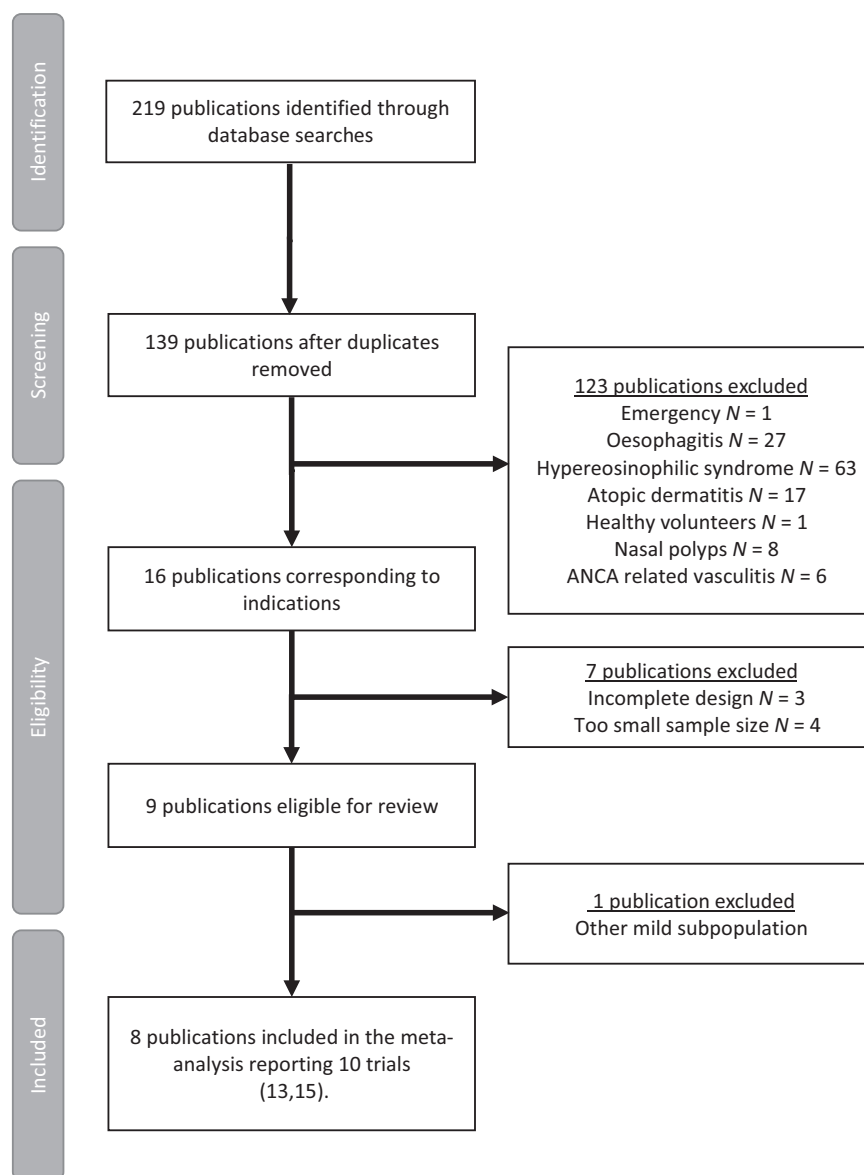


Fig. 1. Study selection flowchart.

The same analysis strategy was applied to the eosinophilic subgroup. The subgroup analysis of the eosinophilic patients was quite complex as the thresholds were defined slightly differently (in the mepolizumab trials, the eosinophilic population was defined by a threshold of 300 eosinophils/mm³/L, while a threshold of 400 eosinophils/mm³/L was used in the benralizumab and reslizumab trials, and other studies were based on induced sputum eosinophil percentages).

Results

The defined exacerbation and population characteristics were quite similar in the eight studies consisting of 10 trials, which involved a total of 3421 patients (59.6%

females, average age 47.3 years, average BMI 28.0 kg/m²; see details in the Supplementary Appendix). Only randomized, double-blinded, placebo-controlled trials were included. The reference trial numbers and main characteristics are listed in Table 1.

A meta-analysis was performed to assess the overall efficacy of the anti-IL5 strategy. The annual exacerbation rate ratio of the three aggregated anti-IL-5 mAbs vs. placebo was 0.60 [0.50, 0.71], $P < 0.01$ (Fig. 2). This effect was assessed by a random effect model due to heterogeneity ($I^2 = 0.61$). The FEV₁ change from baseline vs. placebo was 0.09 L [0.05; 0.12], $P < 0.01$, using a fixed effect model ($I^2 = 0.28$). The meta-analysis indicated an overall ACQ-5 change from baseline of -0.31 [$-0.41, -0.21$], $P < 0.01$, based on a fixed effect model

Table 1. Details of the studies included in the meta-analysis

Trial reference number (publication references)	Quality	Specific design*	Outcome available	Phase	Blood eosinophil count threshold (mm ³ /L)	Number of females (%)	Age (years)	Treatments involved in the studies (number of patients)			
								Treatment 1 (<i>comparator</i>)	Treatment 2	Treatment 3	Treatment 4
Halдар 2009 [20]	Moderate	Parallel group	ER, ACQ, FEV, AE, SAE	–	–	29 (48)	29.3	Plb (33)	Mep750 (29)	–	–
Pavord 2012 [18]	High	Multi-center	ER, ACQ, FEV, SAE	–	> 300	387 (63)	28.5	Plb (159)	Mep75 (153)	Mep250 (152)	Mep750 (156)
Ortega 2014 [17]	High	Double dummy	ER, ACQ, FEV, AE, SAE	III	> 300	329 (57)	27.8	Plb (191)	Mep75 (191)	Mep100 (194)	–
Flood-Page 2007 [19]	High	Parallel group	FEV, SAE	–	–	202 (56)	–	Plb (126)	Mep250 (120)	Mep750 (116)	–
Bel 2014 [16]	Moderate	Parallel group	ER, AE, SAE	–	> 300	74 (55)	28.6	Plb (66)	Mep100 (69)	–	–
Castro 2011 [12]	Moderate	–	ACQ, FEV, AE, SAE	–	–	63 (53)	–	Plb (53)	Res3 (53)	–	–
Castro 2014 [13]	High	Dose ranging, eosinophilic patients	ER, ACQ, FEV, AE [†] , SAE [†]	II b	> 300	219 (69)	28.5	Plb (80)	Ben2 (81)	Ben20 (81)	Ben100 (82)
Castro 2014 [13]	High	Dose ranging, non-eosinophilic patients	ER, ACQ, FEV, AE [†] , SAE [†]	II b	–	198 (70)	29.6	Plb (142)	Ben100 (140)	–	–
Castro 2015 study 1 [15]	High	Parallel group, 128 clinical research centres	ER, ACQ, FEV, AE, SAE	III	> 400	303 (62)	27.8	Plb (244)	Res3 (245)	–	–
Castro 2015 study 2 [15]	High	Multi-center, 104 centres	ER, FEV, AE, SAE	III	> 400	294 (63)	27	Plb (232)	Res3 (232)	–	–

ER, Exacerbation Rate, BMI and age were calculated as means over each arm study. The following abbreviations were used for treatments: Ben represents the benralizumab arm, Mep represents the mepolizumab arm, Plb represents the placebo arm and Res represents the reslizumab arm. Numbers after the abbreviation represent the corresponding dose (2, 20, 100, 75, 250 and 750 mg or 3 mg/kg for reslizumab).

*All included trials were randomized, double-blinded and placebo-controlled.

[†]AE and SAE were analysed for the overall study and not specifically by trial, as presented in the publications.

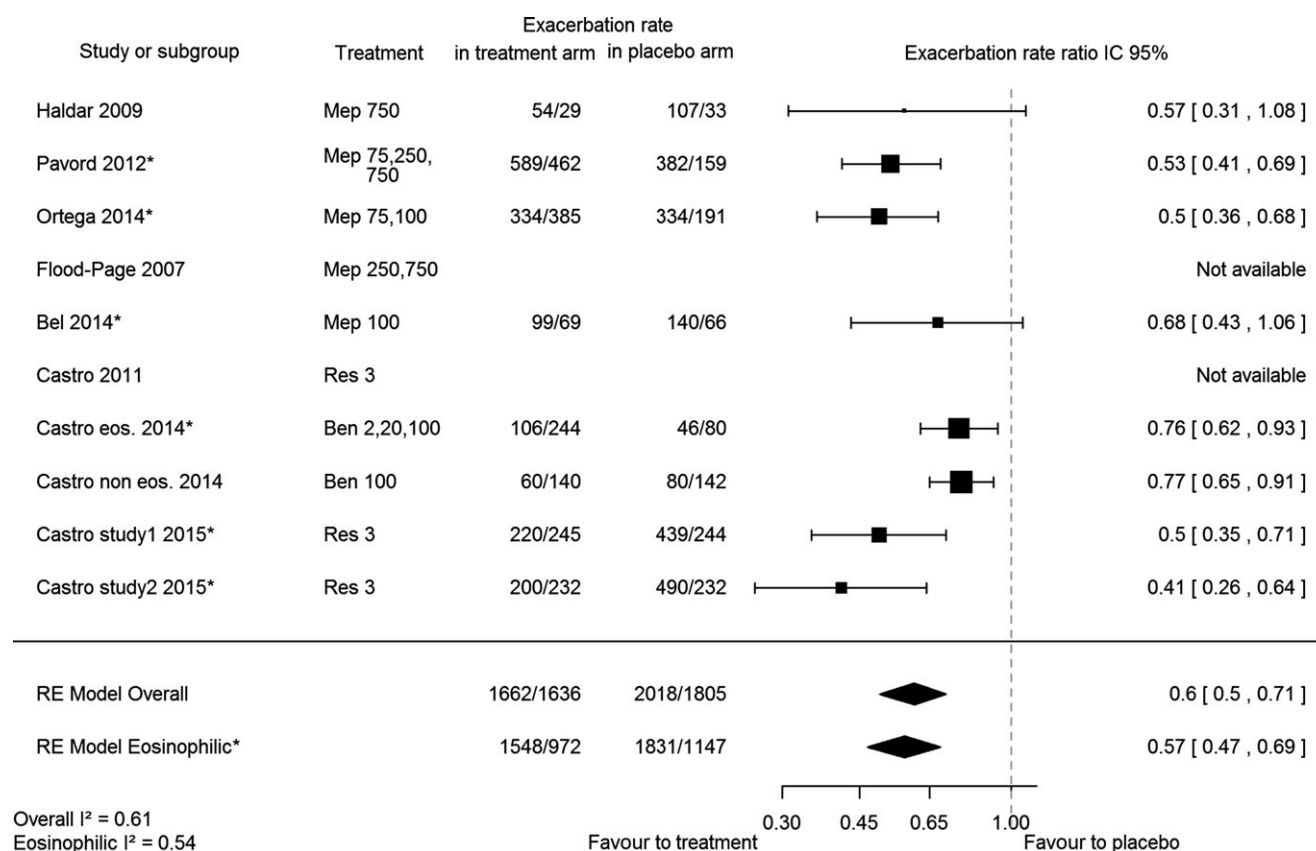


Fig. 2. Forest plot. The eosinophilic subgroup refers to patients enrolled with a blood eosinophilic count at entry $> 300 \text{ mm}^3/\text{L}$ and was represented by (*) on this figure.

($I^2 = 0.11$) involving seven studies only, because of missing values in three studies.

The heterogeneity noted in the exacerbation rate ratios was due to the combined rate reduction in eosinophilic and non-eosinophilic 2014 Castro's studies [13]. When these two trials were excluded, the exacerbation rate estimates based on the fixed effect model were 0.52 [0.45, 0.60] ($P < 0.01$, $I^2 = 0.0$).

A specific meta-analysis was performed in the eosinophilic patient subgroup ($> 300 \text{ mm}^3/\text{L}$). For this subgroup, including five studies, the annual exacerbation rate ratio was 0.57 [0.47, 0.69], $P < 0.01$, $I^2 = 0.54$ (Fig. 2). FEV₁ increased by 0.10 L [0.06, 0.14] ($P < 0.01$, $I^2 = 0$) in this subgroup. ACQ-5 changed by -0.33 [-0.45 , -0.21] ($P < 0.01$, $I^2 = 0.21$). The corresponding funnel and forest plots are provided in the Supplementary Appendix.

The combined treatment effect from eosinophilic 2014 Castro's study [13] was a source of heterogeneity. When this study was excluded, the exacerbation rate estimates for the eosinophilic subgroup based on the fixed effect model were 0.52 [0.44, 0.60] ($P < 0.01$, $I^2 = 0.0$). A network meta-analysis was performed to assess indirect treatment comparisons (Fig. 3). The

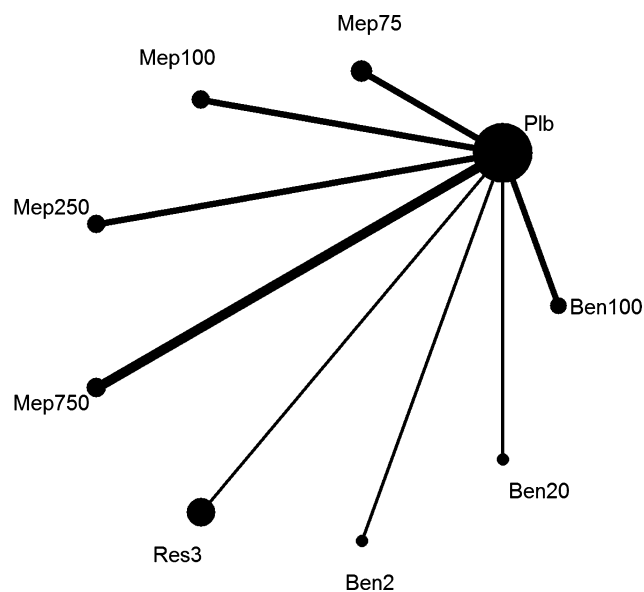


Fig. 3. Network. The line width shown is proportional to the number of comparisons between treatments. The circle size is proportional to the number of patients on the treatment arm.

network displayed all of the included trials vs. placebo, involving four doses of mepolizumab (75 mg i.v., 100 mg s.c., 250 and 750 mg s.c.), one dose of

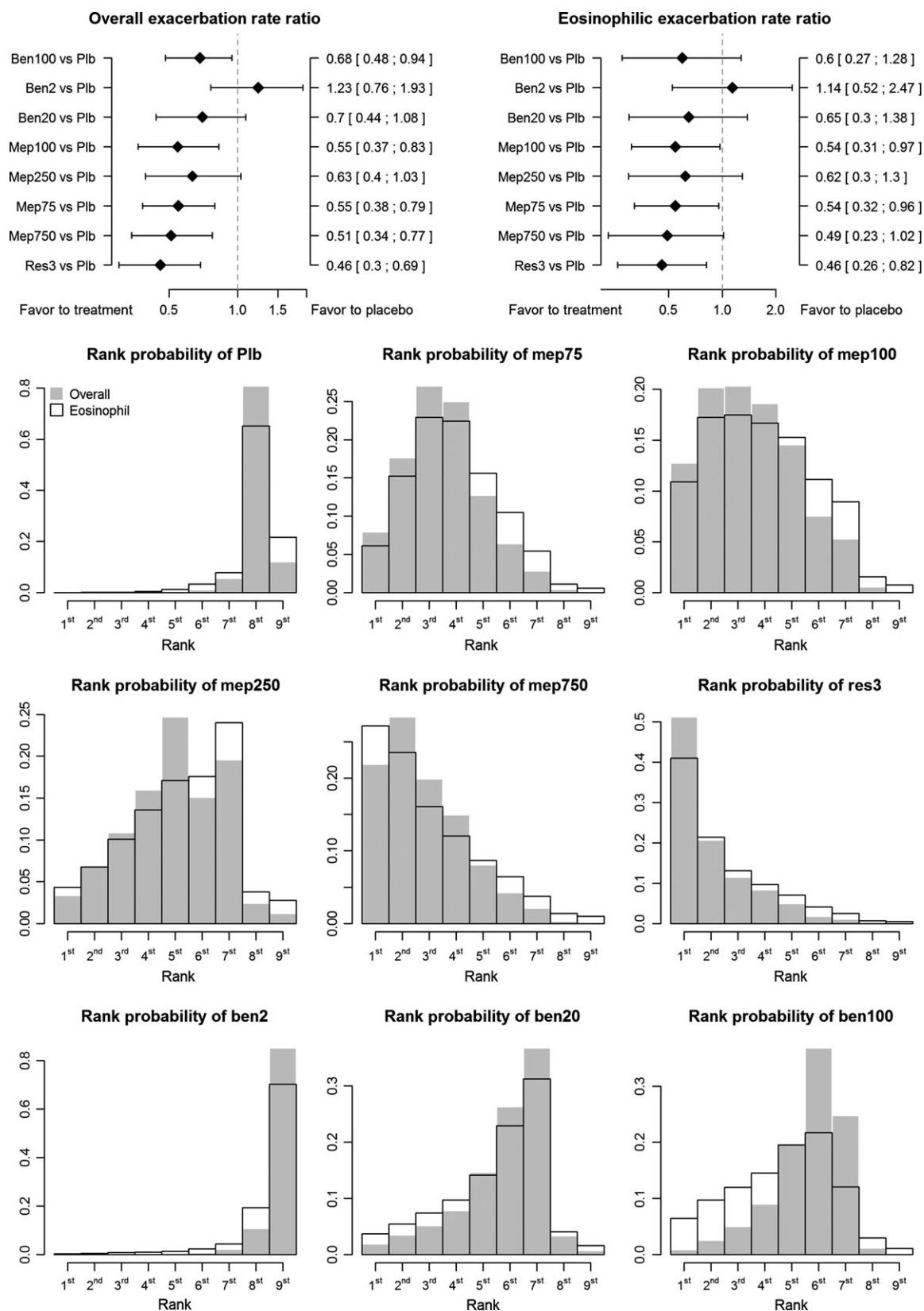


Fig. 4. MTC exacerbation results. The first two forest plots compare exacerbation rate treatment effect vs. placebo. Graphic bars display probabilities of ranking. Y axis is the level of probability of belonging to the class of ranking (given on the X axis), that is P_{rank} .

reslizumab (3 mg/kg i.v.) and three doses of benralizumab (2, 20 and 100 mg i.v.).

This network meta-analysis involved sorting all of these arms according to their probability of being ranked first, that is, to provide the greatest benefits (Fig. 4). Accordingly, the top three treatments with the greatest probability of being ranked first for reducing the exacerbation rate were reslizumab 3 mg/kg with $P_1 = 51\%$, followed by mepolizumab 750 mg ($P_1 = 22\%$) and mepolizumab 100 mg ($P_1 = 13\%$). Corresponding rate ratio reductions regarding the exacerbation rate vs. placebo were 0.46 [0.3, 0.69] for reslizumab 3 mg/kg, 0.51 [0.35, 0.77] for mepolizumab 750 mg and 0.55 [0.37, 0.83] for mepolizumab 100 mg. As expected, benralizumab 2 mg did not significantly differ from placebo (RR = 1.23 [0.76, 1.93]). Regarding the asthma control questionnaire (ACQ-5) findings, benralizumab 20 mg had the greatest probability of being ranked first (mean difference vs. placebo -0.38 [-0.97 , 0.18], $P_1 = 27\%$). Reslizumab 3 mg/kg (0.14 L [0.05 , 0.24], $P_1 = 37\%$) had the best likelihood of being ranked first for FEV₁ improvement. Regarding safety concerns (Fig. 5), we analysed non-severe adverse events first. Benralizumab 20 mg had the greatest probability of being ranked as the safest (RR = 0.94 [0.57, 1.54], $P_1 = 28\%$), which was also in favour of the treatment. For severe adverse events, reslizumab was ranked as the best SAE reducer compared to placebo (RR = 0.81 [0.22, 3.03], $P_1 = 37\%$), again in favour of the treatment (Table 2).

In the eosinophilic subgroup, the top three drugs for exacerbation rate reduction were reslizumab 3 mg/kg with a 0.46 [0.26, 0.81] rate ratio regarding the annual exacerbation rate vs. placebo, with a probability of being the best treatment $P_1 = 41\%$. This treatment was

followed by mepolizumab 750 mg with 0.49 [0.23, 1.02] ($P_1 = 27\%$) vs. placebo, and then mepolizumab 100 mg with a 0.54 [0.31, 0.97] ($P_1 = 11\%$) rate ratio regarding the annual exacerbation rate vs. placebo. On average, benralizumab 20 mg had the highest probability of being the best treatment for improving the FEV₁ value (0.15 L [-0.30 , 0.60], $P_1 = 29\%$) and decreasing the ACQ-5 score (-0.36 [-2.28 , 1.56], $P_1 = 18\%$). Additional results on treatment effect sizes, forest plots, other rank probabilities and heterogeneity assessments are provided in the Supplementary Appendix. Safety results are also provided in the Supplementary Appendix.

Discussion

Monoclonal antibodies targeting TH2 cytokines seem to be a good alternative in severe asthma management. In the present meta-analysis based on more than 3000 patients, aggregated anti-IL-5 studies showed a 40% decrease in exacerbation rate. Moreover, FEV₁ was slightly significantly improved by these mAbs, as also were the asthma control levels assessed by the ACQ-5-scores, with the improvement remaining below the minimal clinically important difference (MCID) level [25]. Identification of the high eosinophilic subgroup improved confidence in the overall anti-IL-5 strategy as it increased the homogeneity of population characteristics. Similar results were obtained in the sensitivity analyses. Reslizumab, at the monthly dose of 3 mg/kg, appeared to be the most likely effective treatment for reducing the exacerbation rate. The overall and specific safety profiles appeared to be similar to placebo. Higher AE rates were reported in the reslizumab study, which could potentially be attributed to the administration route.

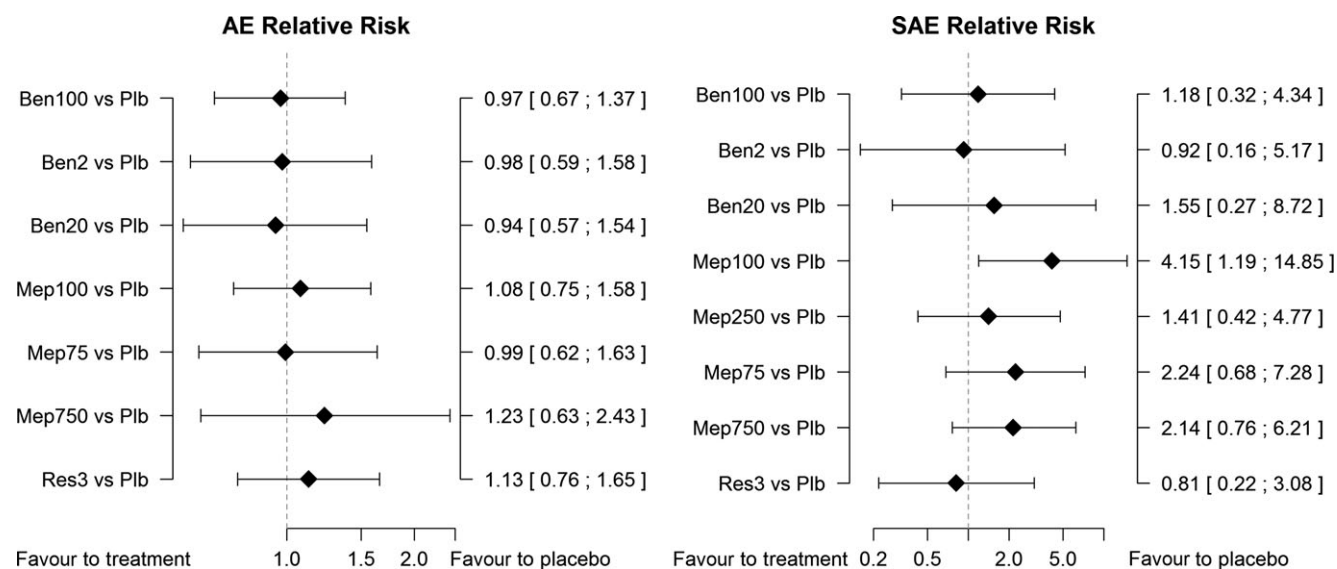


Fig. 5. Network meta-analysis: safety results.

Most of these results were expected [26, 27], but a global meta-analysis was lacking. Here, we selected significant studies and aggregated the results. This meta-analysis complied with PRISMA guidelines and fulfilled the R-AMSTAR criteria, with a total score of 41/44 (see online supplement).

We noticed some heterogeneity in the assessment of the outcome which could be attributed to 2014 Castro's studies [13]. For example, benralizumab had been tested at a very low dose and the results were nearly equivalent to those obtained for the placebo arm. We incorporated – for the sake of completeness, but at the risk of including the heterogeneity – the findings of all of the selected trials in our analysis. The relatively small number of studies including highly selected patients and the quite short drug exposure duration are other sources of concern regarding the direct transposability of these findings on a long-term basis in a real-life setting.

FDA's approval was published in November 2015 [28] regarding exacerbation rate reductions offered by the drug in 'eosinophilic asthma', especially with considerations for patients ineligible for omalizumab. Interestingly, mepolizumab was shown to be effective throughout the year, irrespective of the atopic status [29]. In the TH2 population, many patients eligible for mepolizumab may also have been eligible for omalizumab. It could potentially be expected that more dramatic IL5 blockade could have greater effects, but this was not observed with any of the three mAbs, as the highest doses never resulted in the best outcomes. The definition of eosinophilic patients was not always homogeneous across the different studies, and only five studies were thus involved in this subgroup analysis. Moreover, a single blood eosinophil threshold was used for the meta-analysis, whereas it differed in the studies. The benefits of anti-IL5 mAbs on FEV₁ were significant, but of moderate intensity, with a mean overall effect reaching 0.09 L in volume improvement in the overall meta-analysis, and 0.10 L in the eosinophilic subgroup. Interestingly, the level of asthma symptoms assessed via the ACQ-5 improved with anti-IL5 blockade, but only to a limited extent and usually below the MCID. It would therefore likely be difficult to identify responders.

We conducted an indirect network meta-analysis as it is unlikely that direct comparisons will ever be conducted, or only using a non-inferiority design. Only 10 trials in which multiple combinations of drugs and doses were tested could be compiled, and no reported head-to-head drug comparisons were available. Annual or annualized numbers of exacerbations were reported in most studies on the basis of a binomial negative model, or Poisson regression in others, and we opted to overlook these discrepancies. Accordingly, the rankings established in this network meta-analysis should be cautiously considered and uncertainties persisted. Our

overall feeling is that it would be nearly impossible to draw definitive conclusions on the superiority of one drug over others.

Phase III trials with benralizumab and reslizumab were not available at the moment of the study. The potential results of such trials could markedly differ from our findings, especially regarding indirect comparisons. Our results will thus require updating when phase III trial results are published. Furthermore, we did not address the issue of the oral steroid sparing effect in oral steroid-dependent patients, as the patients considered in reported studies devoted to oral steroids were pooled with the other patients.

The future will tell whether other strategies directed towards TH2 mediators are as efficient, such as IL-13 and IL-4/13 blockade. These mAbs are usually tested in milder asthma, but their potency should also be tested in severe asthma [30–32]. Promising results have been reported with non-mAbs TH2 inhibitors, and phase II studies are expected in the near future [33]. For non-eosinophilic patients, very few therapy options are currently available, or being developed, despite the fact that it represents a still unmet need in severe asthma.

In conclusion, anti-IL-5 treatment had significant effects in severe asthma patients with frequent exacerbations and evidence of eosinophilic inflammation. Reslizumab appeared to be the most effective mAb in reducing exacerbation rates and improving FEV₁. Nonetheless, mepolizumab 100 mg and benralizumab 20 mg appeared to be excellent alternatives. No clear significant differences between treatments in terms of efficacy and safety were found due to the limited number of studies available.

Long-term effects, best duration of treatment and the risk of relapse after withdrawal are important issues that should be addressed in further studies. A clear definition of the satisfactory clinical response and the ideal response time for its assessment would also be warranted.

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Conflict of interest

Pr Bourdin and Pr Chanez report advisory board membership and participation as an investigator in clinical trials sponsored by GlaxoSmithKline, Boehringer Ingelheim, Novartis, Astra Zeneca, Teva, Cephalon, Chiesi Pharmaceuticals and Sanofi.

References

- 1 Reddel HK, Bateman ED, Becker A *et al.* A summary of the new GINA strategy: a roadmap to asthma control. *Eur Respir J* 2015; **46**:622–39.
- 2 Flood-Page PT, Menzies-Gow AN, Kay AB, Robinson DS. Eosinophil's role remains uncertain as anti-interleukin-5 only partially depletes numbers in asthmatic airway. *Am J Respir Crit Care Med* 2003; **167**:199–204.
- 3 Bousquet J, Jeffery PK, Busse WW, Johnson M, Vignola AM. Asthma. From bronchoconstriction to airways inflammation and remodeling. *Am J Respir Crit Care Med* 2000; **161**:1720–45.
- 4 Bousquet J, Chanez P, Lacoste JY *et al.* Eosinophilic inflammation in asthma. *N Engl J Med* 1990; **323**:1033–9.
- 5 Lötvall J, Akdis CA, Bacharier LB *et al.* Asthma endotypes: a new approach to classification of disease entities within the asthma syndrome. *J Allergy Clin Immunol* 2011; **127**:355–60.
- 6 Wenzel SE. Asthma phenotypes: the evolution from clinical to molecular approaches. *Nat Med* 2012; **18**:716–25.
- 7 Rothenberg ME, Hogan SP. The eosinophil. *Annu Rev Immunol* 2006; **24**:147–74.
- 8 Bourdin A, Humbert M, Chanez P. Immunologic therapeutic interventions in asthma: impact on natural history. *Clin Chest Med* 2012; **33**:585–97.
- 9 Humbert M, Beasley R, Ayres J *et al.* Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. *Allergy* 2005; **60**:309–16.
- 10 Hanania NA, Wenzel S, Rosén K *et al.* Exploring the effects of omalizumab in allergic asthma: an analysis of biomarkers in the EXTRA study. *Am J Respir Crit Care Med* 2013; **187**:804–11.
- 11 Woodruff PG, Modrek B, Choy DF *et al.* T-helper type 2-driven inflammation defines major subphenotypes of asthma. *Am J Respir Crit Care Med* 2009; **180**:388–95.
- 12 Castro M, Mathur S, Hargreave F *et al.* Reslizumab for poorly controlled, eosinophilic asthma: a randomized, placebo-controlled study. *Am J Respir Crit Care Med* 2011; **184**:1125–32.
- 13 Castro M, Wenzel SE, Bleecker ER *et al.* Benralizumab, an anti-interleukin 5 receptor α monoclonal antibody, versus placebo for uncontrolled eosinophilic asthma: a phase 2b randomised dose-ranging study. *Lancet Respir Med* 2014; **2**:879–90.
- 14 Laviolette M, Gossage DL, Gauvreau G *et al.* Effects of benralizumab on airway eosinophils in asthmatic patients with sputum eosinophilia. *J Allergy Clin Immunol* 2013; **132**:1086–1096.e5.
- 15 Castro M, Zangrilli J, Wechsler ME *et al.* Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. *Lancet Respir Med* 2015; **3**:355–66.
- 16 Bel EH, Wenzel SE, Thompson PJ *et al.* Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. *N Engl J Med* 2014; **371**:1189–97.
- 17 Ortega HG, Liu MC, Pavord ID *et al.* Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med* 2014; **371**:1198–207.
- 18 Pavord ID, Korn S, Howarth P *et al.* Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet* 2012; **380**:651–9.
- 19 Flood-Page P, Swenson C, Faierman I *et al.* A study to evaluate safety and efficacy of mepolizumab in patients with moderate persistent asthma. *Am J Respir Crit Care Med* 2007; **176**:1062–71.
- 20 Haldar P, Brightling CE, Hargadon B *et al.* Mepolizumab and exacerbations of refractory eosinophilic asthma. *N Engl J Med* 2009; **360**:973–84.
- 21 Cochrane Handbook for Systematic Reviews of Interventions [Internet]. Disponible sur: <http://handbook.cochrane.org/> [cité 6 oct 2016].
- 22 Dias S, Welton NJ, Sutton AJ, Ades AE. NICE DSU Technical Support Document 2: a generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials. London, UK: National Institute for Health and Care Excellence (NICE)
- 23 Jansen JP, Fleurence R, Devine B *et al.* Interpreting indirect treatment comparisons and network meta-analysis for health-care decision making: report of the ISPOR task force on indirect treatment comparisons good research practices: Part 1. *Value Health* 2011; **14**:417–28.
- 24 Lunn D, Spiegelhalter D, Thomas A, Best N. The BUGS project: evolution, critique and future directions. *Stat Med* 2009; **28**:3049–67.
- 25 Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. *Eur Respir J* 1999; **14**:902–7.
- 26 Liu Y, Zhang S, Li D, Jiang S. Efficacy of anti-interleukin-5 therapy with mepolizumab in patients with asthma: a meta-analysis of randomized placebo-controlled trials. *PLoS ONE* 2013; **8**:e59872.
- 27 Powell C, Milan SJ, Dwan K, Bax L, Walters N. Mepolizumab versus placebo for asthma. *Cochrane Database Syst Rev* 2015; **7**:CD010834.
- 28 Keating GM. Mepolizumab: first global approval. *Drugs* 2015; **75**:2163–9.
- 29 Ortega H, Chupp G, Bardin P *et al.* The role of mepolizumab in atopic and nonatopic severe asthma with persistent eosinophilia. *Eur Respir J* 2014; **44**:239–41.
- 30 Corren J, Lemanske RF, Hanania NA *et al.* Lebrikizumab treatment in adults with asthma. *N Engl J Med* 2011; **365**:1088–98.
- 31 Wenzel S, Ford L, Pearlman D *et al.* Dupilumab in persistent asthma with elevated eosinophil levels. *N Engl J Med* 2013; **368**:2455–66.
- 32 Gauvreau GM, O'Byrne PM, Boulet L-P *et al.* Effects of an anti-TSLP antibody on allergen-induced asthmatic responses. *N Engl J Med* 2014; **370**:2102–10.
- 33 Krug N, Hohlfeld JM, Kirsten A-M *et al.* Allergen-induced asthmatic responses modified by a GATA3-specific DNase. *N Engl J Med* 2015; **372**:1987–95.

Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article:

Appendix

Appendix S1. Systematic review protocol.
Appendix S2. Study by study description.
Appendix S3. Additional results.

Appendix

Summary

Appendix 1: Systematic review protocol	3
PICO based question	3
Search strategy	3
Population size:.....	3
Conduct of the review.....	3
Data extraction	4
Data synthesis	4
Sensitivity analysis	4
Appendix 2: Study by study description	6
Appendix to main results	17
Meta-analysis results for overall group by criteria and there corresponding funnel plots.....	17
Funnel plot for Exacerbation Rate ratio.....	17
Sensitivity analysis for exacerbation rate ratio.....	18
Results for FEV1 change from baseline (expressed in Liters).	18
Results for ACQ-5 overall	20
Meta-analysis results for eosinophilic subgroup by criteria	21
Funnel plot for Exacerbation Rate ratio.....	21
Sensitivity analysis for exacerbation rate ratio.....	22
Results for FEV1 (L) change from baseline.....	23
Results for ACQ-5 on the subgroup eosinophilic.	24
Network meta-analysis results for overall population.	25
Exacerbation rate treatment comparison.	25
FEV1 (L) treatment comparison overall	26
ACQ-5 treatment comparison overall	28
AE treatment comparison overall	30
SAE treatment comparison overall	32
Network meta-analysis results on eosinophilic population.....	34
Exacerbation Rate treatment comparison for eosinophilic subgroup.....	34
FEV1 (L) treatment comparison for eosinophilic subgroup.	36
ACQ-5 treatment comparison for eosinophilic subgroup.....	39

AE treatment comparison for eosinophilic subgroup.....	41
SAE treatment comparison for eosinophilic subgroup.	43

Appendix 1: Systematic review protocol

The aim of this systematic review was to assess the efficacy of three new treatments in severe asthma, targeting anti-IL-5.

PICO based question

P = Patient, Problem, Population (How would you describe a group of patients similar to you? What are the most important characteristics of the patient?)

Only severe asthma patients were studied.

I = Intervention, Prognostic Factor, Exposure (What main intervention are you considering? What do you want to do with this patient? What is the main alternative being considered?)

Anti-IL-5 treatments were analyzed.

C = Comparison (Can be none or placebo.) (What is the main alternative to compare with the intervention? Are you trying to decide between two drugs, a drug and no medication or placebo, or two diagnostic tests?)

All Randomized controlled Clinical Trials of anti-IL5 treatments versus placebo or other active treatments were considered.

O= Outcome (What are you trying to accomplish, measure, improve or affect? Outcomes may be disease-oriented or patient-oriented.)

We assessed the efficacy of anti-IL-5 treatments and compared the three different anti-IL-5. Key outcomes recommended in current guidelines(1) for measuring interventions in severe asthma were assessed: Exacerbation rates, FEV1, ACQ changes. AE and SAE rates were also analyzed.

Search strategy

A systematic review was carried out for relevant articles in English using all available databases and information sources:

- MEDLINE, MEDLINE-IN-PROCESS
- EMBASE
- Cochrane CENTRAL Register

The key/mesh words used for the literature review were: *Asthma, Benralizumab, Mepolizumab, Reslizumab, IL-5.*

We searched articles published from 1990 to September 2015. There were no biases due to outdated publications (so there was little risk of differences between protocols).

Population size

Studies with less than 50 patients enrolled were excluded from the meta-analysis.

Conduct of the review

Due to the small number of publications relative to anti IL-5 treatment, we manually searched and evaluated the quality of each paper. Two methodologists reviewed the literature. A third reviewer dealt

with discordant information. The two reviewers were Y. Cabon and G. Marin. The third reviewer was A. Bourdin.

Data extraction

Data were extracted from each study by the primary reviewer and checked by the second one. The third one was consulted in case of discordance. For each publication, the following information was extracted:

- Study design
- Demographic data
- Inclusion/exclusion criteria
- Sample size
- Comparison group
- Eosinophilic subgroup
- Methodology: model used to assess exacerbation rate changes
- Results: Exacerbation rates, FEV1 values, ACQ-5 score, AE and SAE rates.

Exacerbation rates are currently seen as one of the most important asthma outcomes as they encompass current and future risks of asthma. FEV1 is an important marker of disability and long-term future risks of asthma; ACQ-5 is recommended in guidelines as a powerful tool for assessing current symptom levels and a good predictor for subsequent exacerbations.

Data synthesis

A meta-analysis model was carried out to assess the pooled treatment strategy effect for each criterion. Treatment arm have been combined according to Cochrane handbook (2) in case of multi-arm studies. A random model was applied in case of heterogeneity. Without heterogeneity, assessed by Q-Cochrane test, a fixed effect model was used.

An indirect Bayesian meta-analysis was carried out to estimate indirect treatment effects with multi-arm correction. We used a random effect model to avoid inconsistency limitations.

We did not investigate the meta-analysis heterogeneity. Indeed the pooled treatment effect strategy consisted of different treatments at different doses, while heterogeneity was inherent to this aggregate.

Inconsistency could not be assessed because of the structure of the indirect meta-analysis.

The quality of the evidence was assessed by Evidence Based Medicine levels.

Sensitivity analysis

- Meta-analysis: Sensitivity analysis was carried out on eosinophilic severe asthma patients due to the clinical relevance. Moreover, sources of the meta-analysis heterogeneity were also investigated. Indirect meta-analysis: no sensitive analysis was done due to the number of studies. The small sample size limited our interest in conducting a sensitivity analysis

Table: Included studies basic characteristics

Study reference	Arm		Age* (Year)	Follow up (weeks)
Haldar et al. 2009 (3)	Placebo		50 [24-72]	50
	Mepolizumab 750 mg		48 [21-63]	
Ian D Pavord et al. 2012 (4)	Placebo		46.4 (11.3)	52
	Mepolizumab 75 mg		50.2 (10.8)	
	Mepolizumab 250 mg		49.4 (11.6)	
	Mepolizumab 750 mg		48.6 (11.1)	
H G. Ortega 2014 (5)	Placebo		49 [12-76]	32
	Mepolizumab 75 mg i.v.		50 [13-82]	
	Mepolizumab 100 mg s.c.		51 [12-81]	
P Flood-Page 2007 (6)	Placebo		36.3 (10.4)	12
	Mepolizumab 250 mg		35.8 (40)	
	Mepolizumab 750 mg		36.8 (10)	
E H. Bel 2014 (7)	Placebo		50 [28-70]	20
	Mepolizumab 100 mg s.c.		50 [16-74]	
M Castro 2011 (8)	Placebo		44.9 (13.94)	15
	Reslizumab 3mg/kg		45.8 (11.74)	
M Castro 2014 (9)	Eosinophilic part of the study	Placebo	45.6 (11.7)	52
		Benralizumab 2 mg	47.1 (12.8)	
		Benralizumab 20 mg	46.6 (13.2)	
		Benralizumab 100 mg	47.8 (12.9)	
	Non-eosinophilic part of the study	Placebo	50.0 (12.3)	52
		Benralizumab 100 mg	50.0 (11.5)	
M Castro 2015 (10)	Study 1	Placebo	49 [38;-57]	52
		Reslizumab 3 mg/kg	48 [38-57]	
	Study 2	Placebo	48[39.5-57]	52
		Reslizumab 3 mg/kg	48[37-56.5]	

*Age was presented as Age [range] or (SD) as reported.

Appendix 2: Study by study description

Included studies

Study	Halder et al. 2009(3)
Population	Location: United Kingdom Study period: April 2006 to August 2008 Inclusion/exclusion criteria: >18 years old, positive diagnostic asthma, absence of exacerbation 6 weeks before enrollment Study population characteristics: N=62 with 29 females (48%) Treatment: mepolizumab 750 mg
Method	Study design: single center, randomized, double-blind, placebo-controlled, parallel-group Follow up: 50 weeks
Sponsor	GlaxoSmithKline
Outcomes	Exacerbation rate, ACQ, FEV, AE, SAE
Cochrane risk of bias assessment	Sequence generation? Randomised Allocation concealment? No Blinding? Double blind Incomplete outcome data addressed? No Free of selective reporting? Yes Free of other bias? Yes
Summary	Low risk of bias
Trial number	ISRCTN75169762

Study	Ian D Pavord et al. 2012(4)
Population	Location: 13 countries (Argentina, Australia, Canada, Chile, France, Germany, South Korea, Poland, Romania, Russia, Ukraine, UK, and USA) Study period: November 9, 2009 to December 5, 2011 Inclusion/exclusion criteria: 12-74 years old, history of recurrent severe asthma exacerbations, signs of eosinophilic inflammation, less than 10 pack-year past history of smoking. Perioral blood eosinophil count $>3.10^9$ per L Study population characteristics: N=621 with 387 females (63%) Treatment: mepolizumab 75 mg, 250 mg and 750 mg
Method	Study design: multicenter, double-blind, placebo-controlled Follow up: 52 weeks
Sponsor	GlaxoSmithKline
Outcomes	Exacerbation rate, ACQ, FEV, SAE
Cochrane risk of bias assessment	Sequence generation? Randomised Allocation concealment? No Blinding? Double blind Incomplete outcome data addressed? No Free of selective reporting? Yes Free of other bias? Yes
Summary	Low risk of bias
Trial number	NCT01000506

Study	H G. Ortega 2014(5)
Population	Location: Argentina, Australia, Belgium, Canada, Chile, France, Germany, Italy, Japan, Republic of Korea, Mexico, Russia, Spain, Ukraine, UK and USA Study period: October 2012 to January 2014 Inclusion/exclusion criteria: 12-82 years old, asthmatic patients, at least 2 exacerbations in the previous year, eosinophil count at least 150 mm³/L at screening or 300 mm/L at some time during the previous year Study population characteristics: N=576 with 329 females (57%) Treatment: mepolizumab 75 mg i.v. and 100 mg s.c.
Method	Study design: multicenter, randomized, double-blind, double dummy, placebo-controlled Follow up: 32 weeks
Sponsor	GlaxoSmithKline
Outcomes	Exacerbation rate, ACQ, FEV, AE, SAE
Cochrane risk of bias assessment	Sequence generation? Randomised Allocation concealment? No Blinding? Double blind Incomplete outcome data addressed? No Free of selective reporting? Yes Free of other bias? Yes
Summary	Low risk of bias
Trial number	NCT01691521

Study	P Flood-Page 2007(6)
Population	Location: France, Germany, Netherlands, UK and USA Study period: Not provided Inclusion/exclusion criteria: 18-55 years old, asthmatic patients managed with inhaled corticosteroids Study population characteristics: N=362 with 202 females (56%) Treatment: mepolizumab 250 mg and 750 mg
Method	Study design: multicenter, randomized, double-blind, placebo-controlled Follow up: 12 weeks
Sponsor	GlaxoSmithKline
Outcomes	FEV, SAE
Cochrane risk of bias assessment	Sequence generation? Randomised Allocation concealment? No Blinding? Double blind Incomplete outcome data addressed? No Free of selective reporting? Yes Free of other bias? Yes
Summary	Low risk of bias
Trial number	Not provided

Study	E H. Bel 2014(7)
Population	Location: Australia, Canada France, Czech Republic, Germany, Mexico, Netherlands, Poland, UK and USA Study period: October 2012 to December 2013 Inclusion/exclusion criteria: 6 month history of maintenance treatment with systemic glucocorticoids. Blood eosinophil level of 300 cells or more during Study population characteristics: N=135 with 74 females (55%) Treatment: mepolizumab 100 mg s.c.
Method	Study design: randomized, double-blind, placebo-controlled Follow up: 20 weeks
Sponsor	GlaxoSmithKline
Outcomes	FEV, SAE
Cochrane risk of bias assessment	Sequence generation? Randomised Allocation concealment? No Blinding? Double blind Incomplete outcome data addressed? No Free of selective reporting? Yes Free of other bias? Yes
Summary	Low risk of bias
Trial number	NCT01691508

Study	M Castro 2011(8)
Population	Location: Canada and USA Study period: February 2008 to January 2010 Inclusion/exclusion criteria: 18 to 75 years old with asthma ACQ > 1.5 Study population characteristics: N=106 with 63 females (53%) Treatment: reslizumab 3 mg/kg
Method	Study design: Randomized, double-blind, placebo-controlled Follow up: 15 weeks
Sponsor	Cepton Therapeutics
Outcomes	ACQ, FEV, AE, SAE
Cochrane risk of bias assessment	Sequence generation? Randomised Allocation concealment? No Blinding? Double blind Incomplete outcome data addressed? No Free of selective reporting? Yes Free of other bias? Yes
Summary	Low risk of bias
Trial number	Not provided

Study	M Castro 2014 (9)
Population	Location: Argentina, Bulgaria, Brazil, Canada, Colombia, Mexico, Peru, Poland, Russia and USA. Study period: January 2011 to August 2013 Inclusion/exclusion criteria: 18 to 75 years old with asthma Study population characteristics: - N=324 eosinophilic patients with 219 females (68%) - N=285 non-eosinophilic patients with 205 females (72%) Treatment: benralizumab 2 mg, 20 mg and 100 mg
Method	Study design: randomized, double-blind, placebo-controlled, dose-ranging study with eosinophilic groups Follow up: 52 weeks
Sponsor	MedImmune
Outcomes	Exacerbation Rate, ACQ, FEV, AE, SAE
Cochrane risk of bias assessment	Sequence generation? Randomised Allocation concealment? No Blinding? Double blind Incomplete outcome data addressed? No Free of selective reporting? Yes Free of other bias? Yes
Summary	Low risk of bias
Trial number	NCT01238861

Study	M Castro 2015(10)
Population	Location: Asia, Australia, South America, South Africa and Europe Studies period: April 2011 to April 2014 Inclusion/exclusion criteria: 12 to 75 years old with asthma Study population characteristics: - Study 1: N=477 with 303 females (62%) - Study 2: N=476 with 294 females (63%) Treatment: reslizumab 3 mg/kg
Method	Study design: randomized, double-blind, parallel-group, placebo-controlled with eosinophilic groups Follow up: 52 weeks
Sponsor	Teva Branded Pharmaceutical Product R&D
Outcomes	Exacerbation Rate, ACQ, FEV, AE, SAE
Cochrane risk of bias assessment	Sequence generation? Randomised Allocation concealment? No Blinding? Double blind Incomplete outcome data addressed? No Free of selective reporting? Yes Free of other bias? Yes
Summary	Low risk of bias
Trial number	NCT01287039 & NCT01285323

Excluded studies: incomplete design (N=3), too small sample size (N=4) and other subpopulation (N=1)

Title	Treatment	Sample Size	Reason for exclusion
Eosinophil's Role Remains Uncertain as Anti–Interleukin-5 only Partially Depletes Numbers in Asthmatic Airway(11)	Mepolizumab 750 mg versus placebo	N=24 (11 mepolizumab 750 mg 13 placebo)	Excluded due to sample size & mild asthma
Mepolizumab for difficult-to-control asthma with persistent sputum eosinophilia(12)	Mepolizumab	N=61 (32 placebo, 29 Mepo)	Study design
Mepolizumab for Prednisone-Dependent Asthma with Sputum Eosinophilia(13)	Mepolizumab 750 mg versus placebo	N=20 (9 mepolizumab 11 placebo)	Sample size
Lung involvement in hypereosinophilic syndromes(14)	Mepolizumab and others	N=49	Study design
A randomized trial of benralizumab, an antiinterleukin 5 receptor α monoclonal antibody, after acute asthma(15)	Benralizumab 0.3 mg/kg or 1 mg/kg versus placebo	N=110 (36/36/38)	Study design
Effects of an interleukin-5 blocking monoclonal antibody on eosinophils, airway hyper-responsiveness, and the late asthmatic response(16)	Mepolizumab 2.5 mg/kg or 10.0 mg/kg (IV)	N=16 treated patients	Sample size
Effects of benralizumab on airway eosinophils in asthmatic patients with sputum eosinophilia.(17)	Benralizumab 1 mg/kg & 100 mg or 200 mg benralizumab versus placebo	N=28	Sample size
Mepolizumab as a steroid-sparing treatment option in patients with Churg-Strauss syndrome(18)	Mepolizumab	N=7	Sample size

Bibliography:

1. GINA Reports [Internet]. Global Initiative for Asthma - GINA. [cité 5 sept 2016]. Disponible sur: <http://ginasthma.org/gina-reports/>
2. Cochrane Handbook for Systematic Reviews of Interventions [Internet]. [cité 6 oct 2016]. Disponible sur: <http://handbook.cochrane.org/>
3. Haldar P, Brightling CE, Hargadon B, Gupta S, Monteiro W, Sousa A, et al. Mepolizumab and exacerbations of refractory eosinophilic asthma. *N Engl J Med*. 5 mars 2009;360(10):973-84.
4. Pavord ID, Korn S, Howarth P, Bleecker ER, Buhl R, Keene ON, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet Lond Engl*. 18 août 2012;380(9842):651-9.
5. Ortega HG, Liu MC, Pavord ID, Brusselle GG, FitzGerald JM, Chetta A, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med*. 25 sept 2014;371(13):1198-207.
6. Flood-Page P, Swenson C, Faierman I, Matthews J, Williams M, Brannick L, et al. A study to evaluate safety and efficacy of mepolizumab in patients with moderate persistent asthma. *Am J Respir Crit Care Med*. 1 déc 2007;176(11):1062-71.
7. Bel EH, Wenzel SE, Thompson PJ, Prazma CM, Keene ON, Yancey SW, et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. *N Engl J Med*. 25 sept 2014;371(13):1189-97.
8. Castro M, Mathur S, Hargreave F, Boulet L-P, Xie F, Young J, et al. Reslizumab for poorly controlled, eosinophilic asthma: a randomized, placebo-controlled study. *Am J Respir Crit Care Med*. 15 nov 2011;184(10):1125-32.
9. Castro M, Wenzel SE, Bleecker ER, Pizzichini E, Kuna P, Busse WW, et al. Benralizumab, an anti-interleukin 5 receptor α monoclonal antibody, versus placebo for uncontrolled eosinophilic asthma: a phase 2b randomised dose-ranging study. *Lancet Respir Med*. nov 2014;2(11):879-90.
10. Castro M, Zangrilli J, Wechsler ME, Bateman ED, Brusselle GG, Bardin P, et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. *Lancet Respir Med*. mai 2015;3(5):355-66.
11. Flood-Page PT, Menzies-Gow AN, Kay AB, Robinson DS. Eosinophil's Role Remains Uncertain as Anti-Interleukin-5 only Partially Depletes Numbers in Asthmatic Airway. *Am J Respir Crit Care Med*. 15 janv 2003;167(2):199-204.
12. Antoniu SA. Mepolizumab for difficult-to-control asthma with persistent sputum eosinophilia. *Expert Opin Investig Drugs*. 1 juin 2009;18(6):869-71.
13. Nair P, Pizzichini MMM, Kjarsgaard M, Inman MD, Efthimiadis A, Pizzichini E, et al. Mepolizumab for Prednisone-Dependent Asthma with Sputum Eosinophilia. *N Engl J Med*. 5 mars 2009;360(10):985-93.

14. Duloherly MM, Patel RR, Schneider F, Ryu JH. Lung involvement in hypereosinophilic syndromes. *Respir Med.* 1 janv 2011;105(1):114–21.
15. Nowak RM, Parker JM, Silverman RA, Rowe BH, Smithline H, Khan F, et al. A randomized trial of benralizumab, an antiinterleukin 5 receptor α monoclonal antibody, after acute asthma. *Am J Emerg Med.* 1 janv 2015;33(1):14–20.
16. Leckie MJ, ten Brinke A, Khan J, Diamant Z, O'Connor BJ, Walls CM, et al. Effects of an interleukin-5 blocking monoclonal antibody on eosinophils, airway hyper-responsiveness, and the late asthmatic response. *Lancet Lond Engl.* 23 déc 2000;356(9248):2144–8.
17. Laviolette M, Gossage DL, Gauvreau G, Leigh R, Olivenstein R, Katial R, et al. Effects of benralizumab on airway eosinophils in asthma with sputum eosinophilia. *J Allergy Clin Immunol.* nov 2013;132(5):1086–1096.e5.
18. Kim S, Marigowda G, Oren E, Israel E, Wechsler ME. Mepolizumab as a steroid-sparing treatment option in patients with Churg-Strauss syndrome. *J Allergy Clin Immunol.* 1 juin 2010;125(6):1336–43.

Appendix 3: Additional results

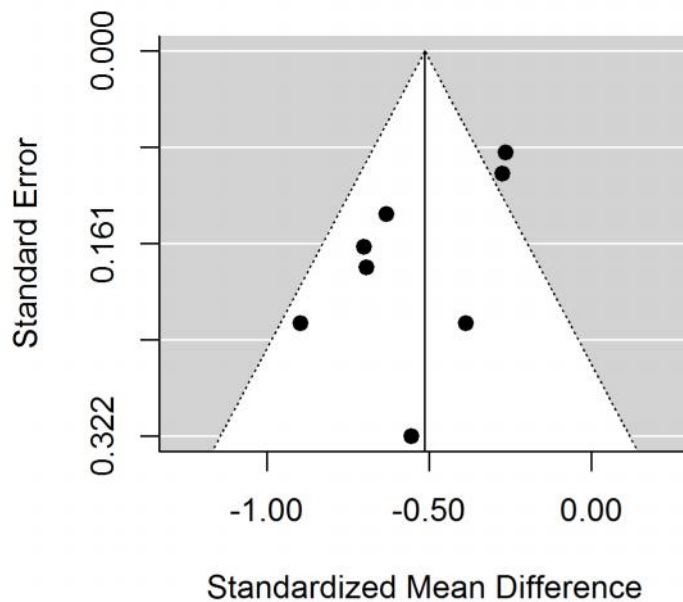
This appendix summarizes results not presented in the main document. Only studies including criteria are presented in the forest plot.

As presented in the main papers RR under 1 are in favor of treatment. Treatment effect have been combined in case of multi-arm studies.

Meta-analysis results for overall group by criteria and the corresponding funnel plots.

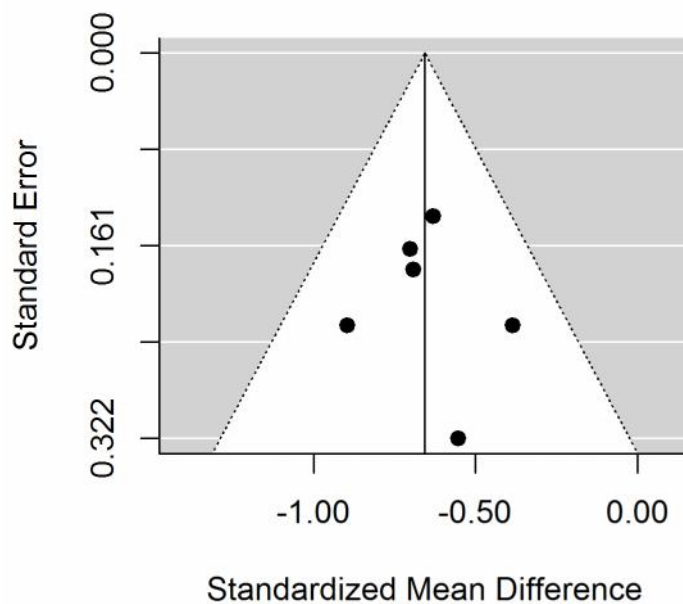
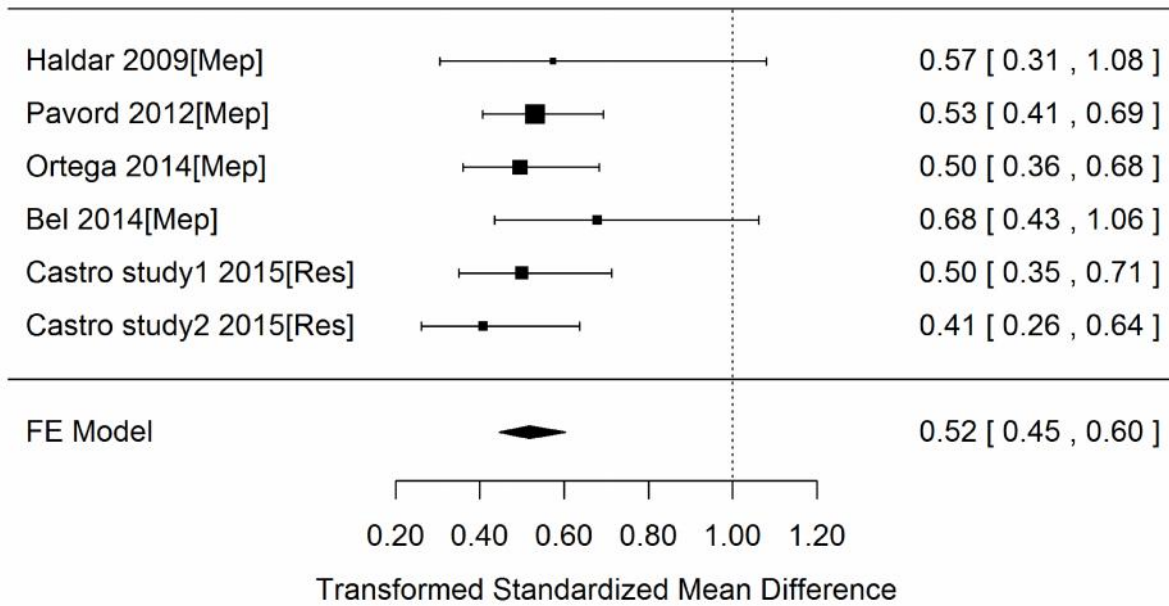
Funnel plot for the exacerbation rate ratio

Cochran's $Q < 0.01$



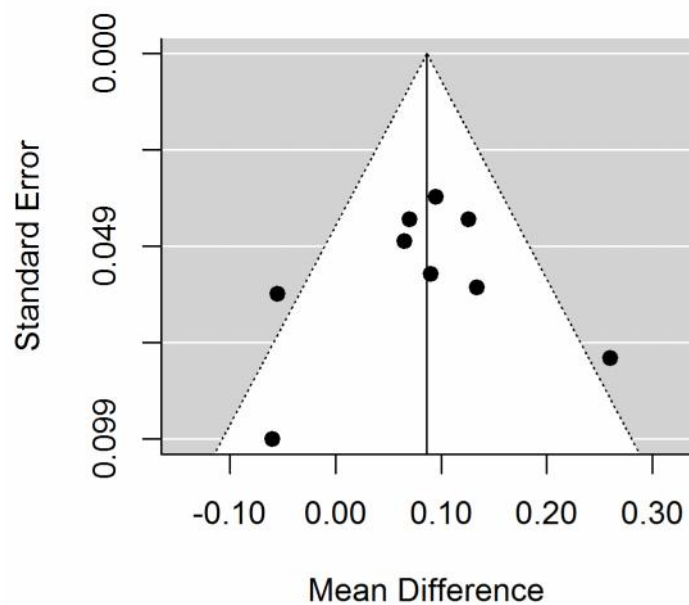
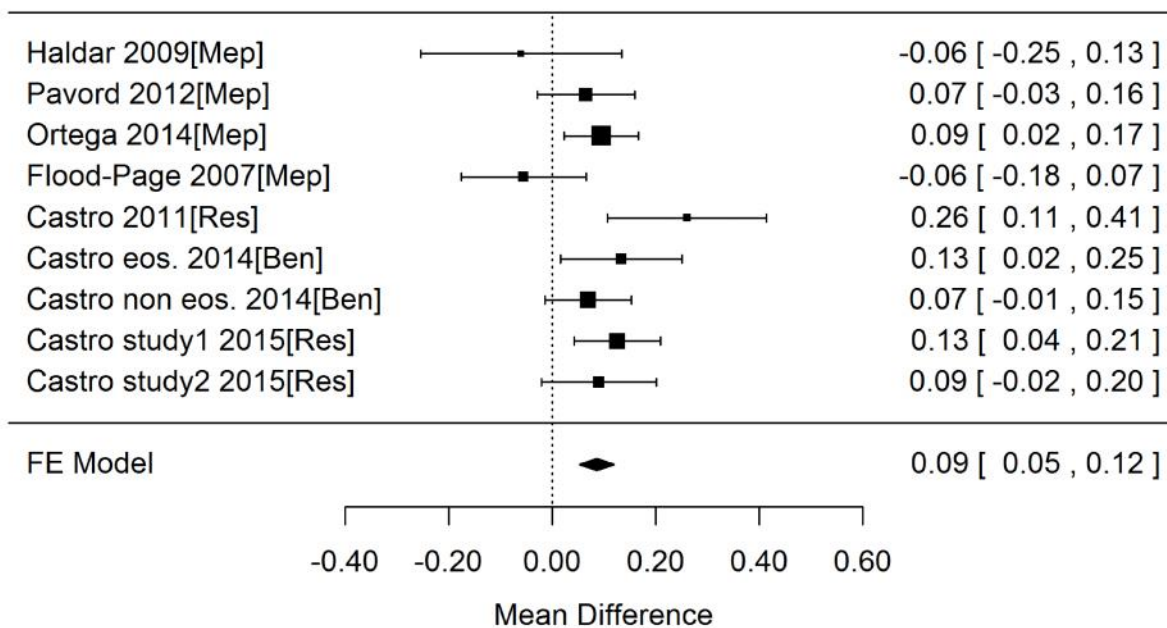
Sensitivity analysis for the exacerbation rate ratio

Cochran's Q = 0.73



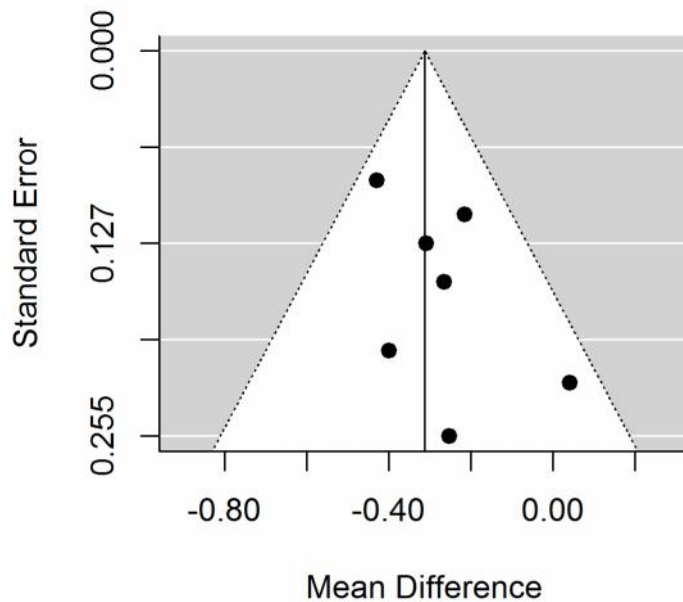
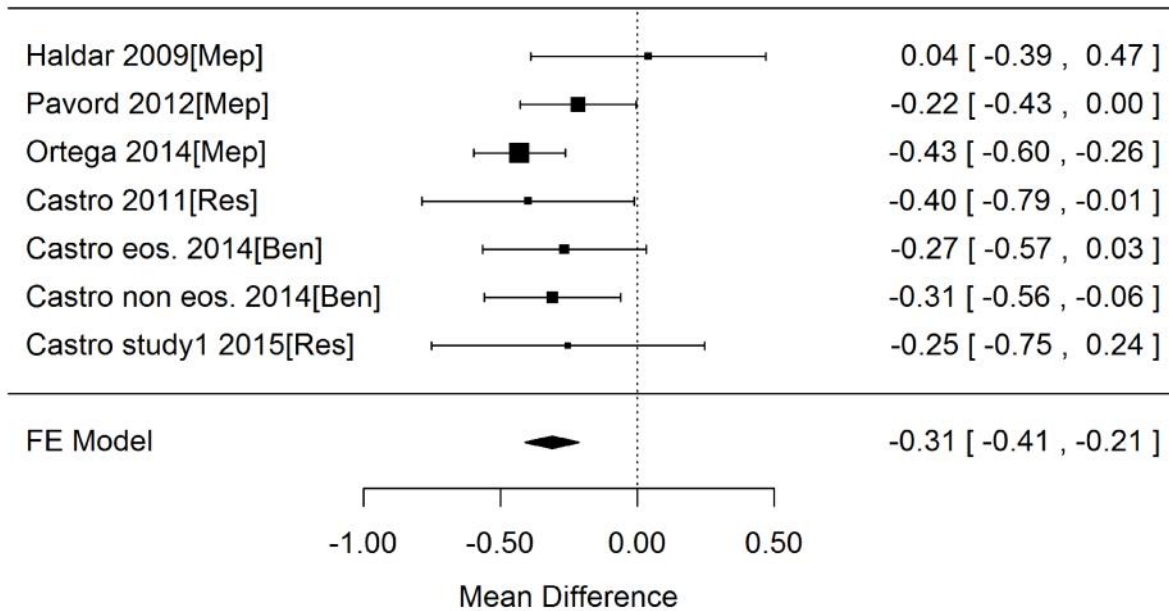
Results for the FEV1 change from baseline (expressed in liters).

This meta-analysis was not heterogeneous, Cochran's Q=0.07 and $I^2=0.28$. Results were significantly different from zero, 0.09 [0.05,0.12], $p < 0.01$.



Results for ACQ-5 overall

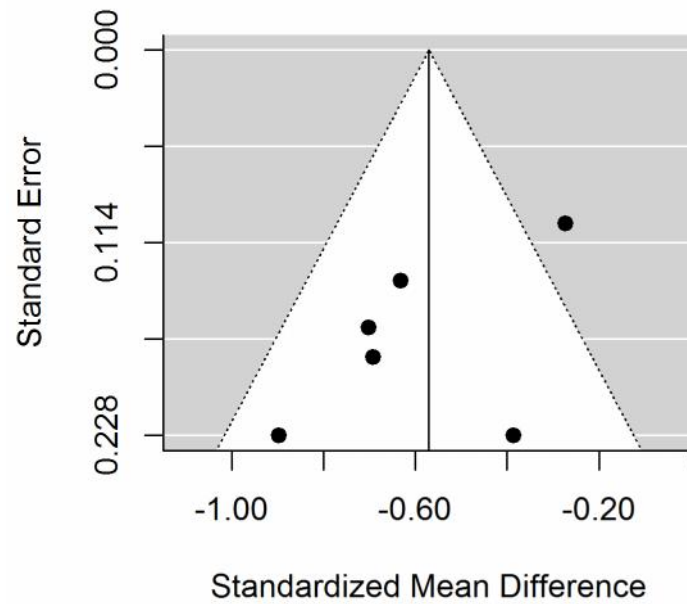
This meta-analysis was not heterogeneous, Cochran's $Q=0.47$ and $I^2=0.11$. Results were significantly different from zero, $-0.31 [-0.41, -0.21]$, $p < 0.01$.



Meta-analysis results for the eosinophilic subgroup by criteria

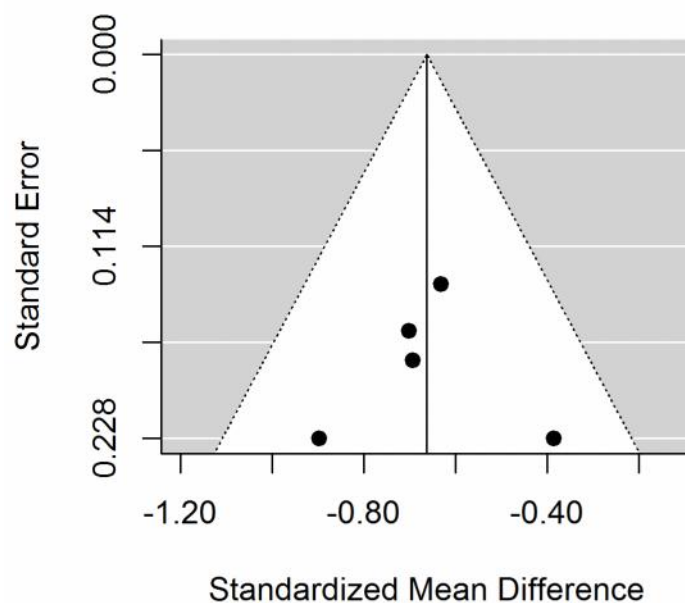
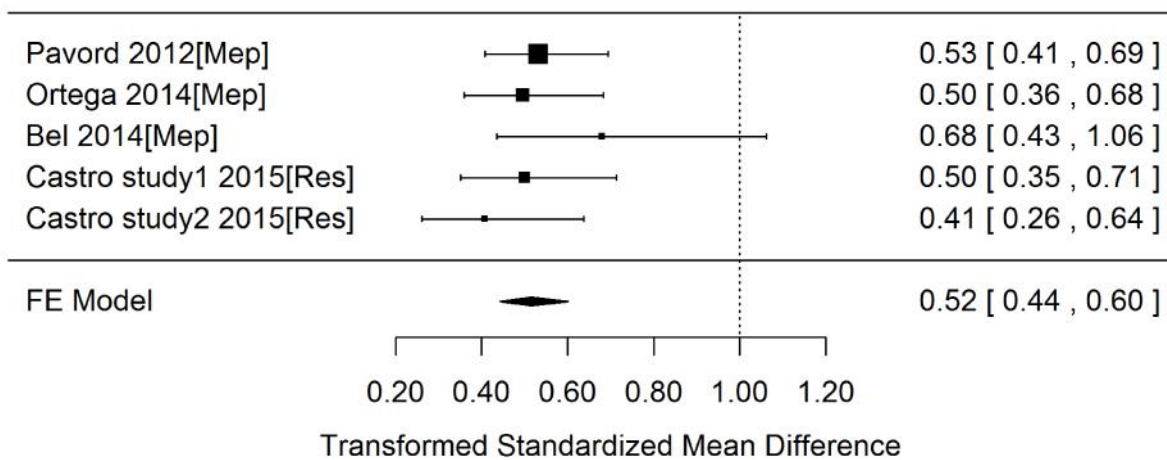
Funnel plot for the exacerbation rate ratio

Cochran's $Q < 0.01$



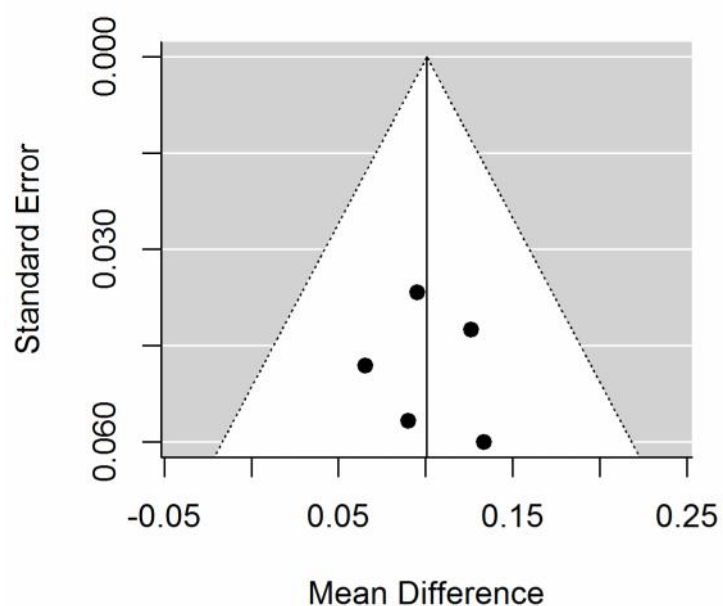
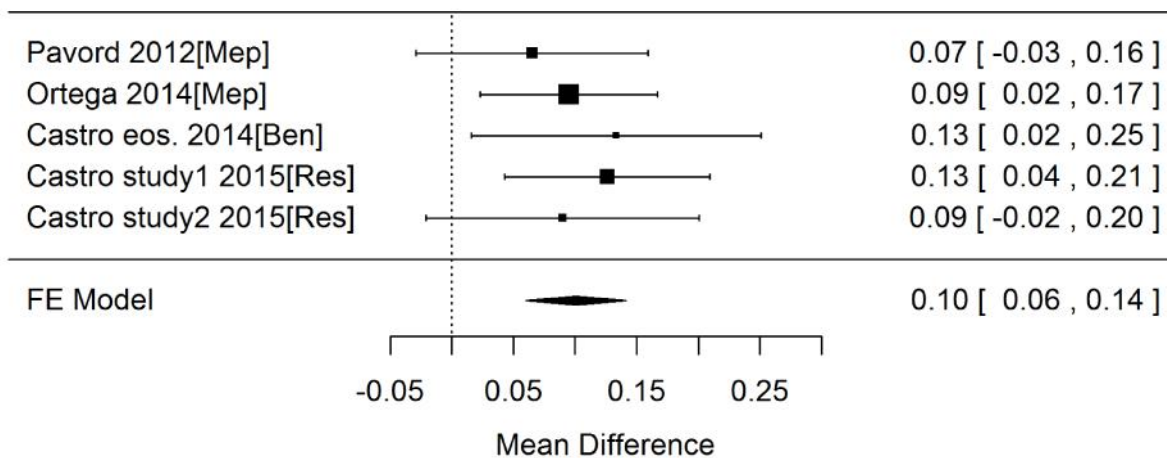
Sensitivity analysis for the exacerbation rate ratio

Cochran's Q = 0.61



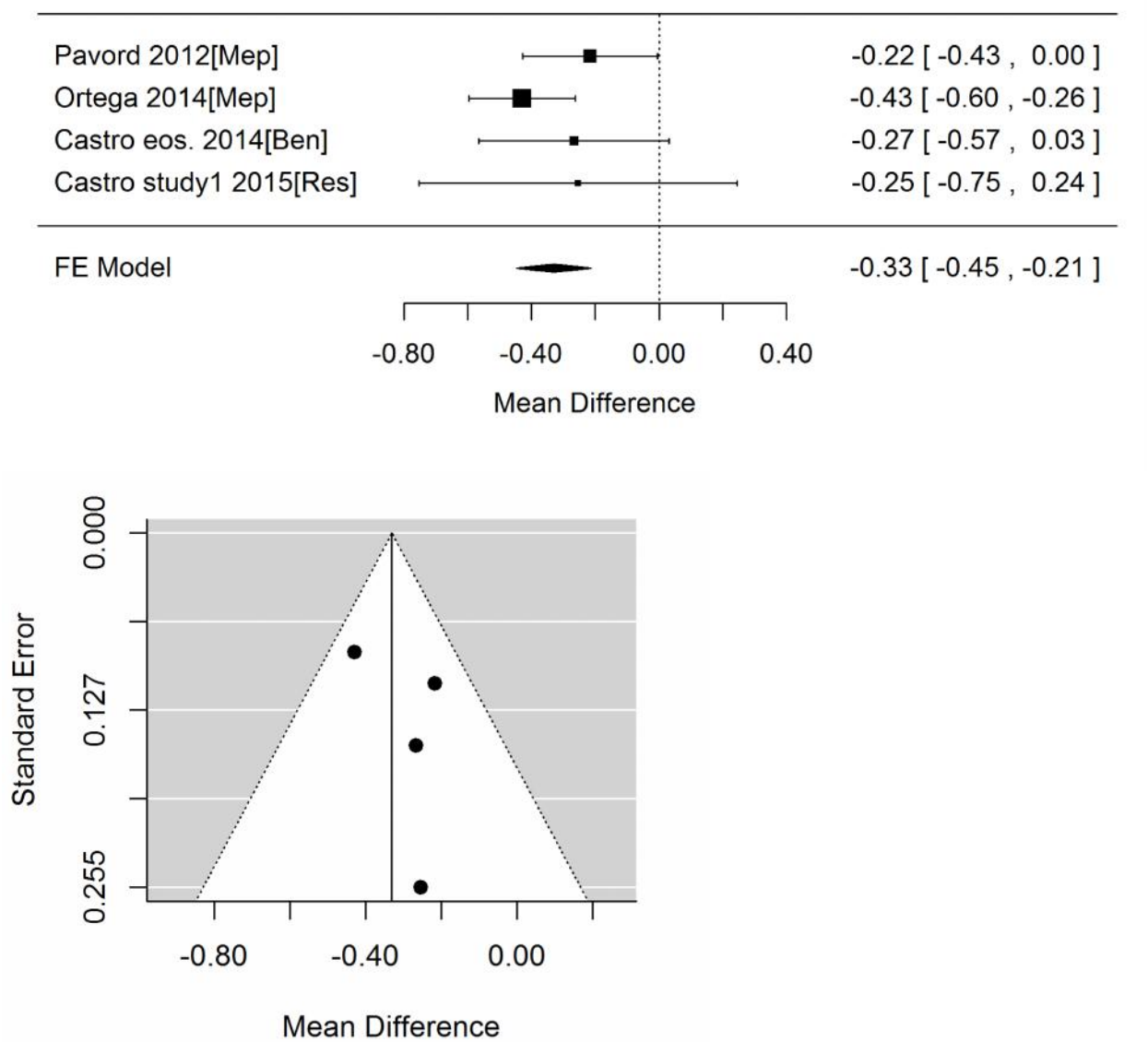
Results for FEV1 (L) change from baseline

This meta-analysis was not heterogeneous, Cochran's $Q=0.87$ and $I^2<0.01$. Results were significantly different from zero, $0.1 [0.06,0.14]$, $p < 0.01$.



Results for ACQ-5 in the eosinophilic subgroup

This meta-analysis was not heterogeneous, Cochran’s Q=0.43 and I²=0.21. Results were significantly different from zero, -0.33 [-0.45,-0.21], p <0.01.



Network meta-analysis results for the overall population

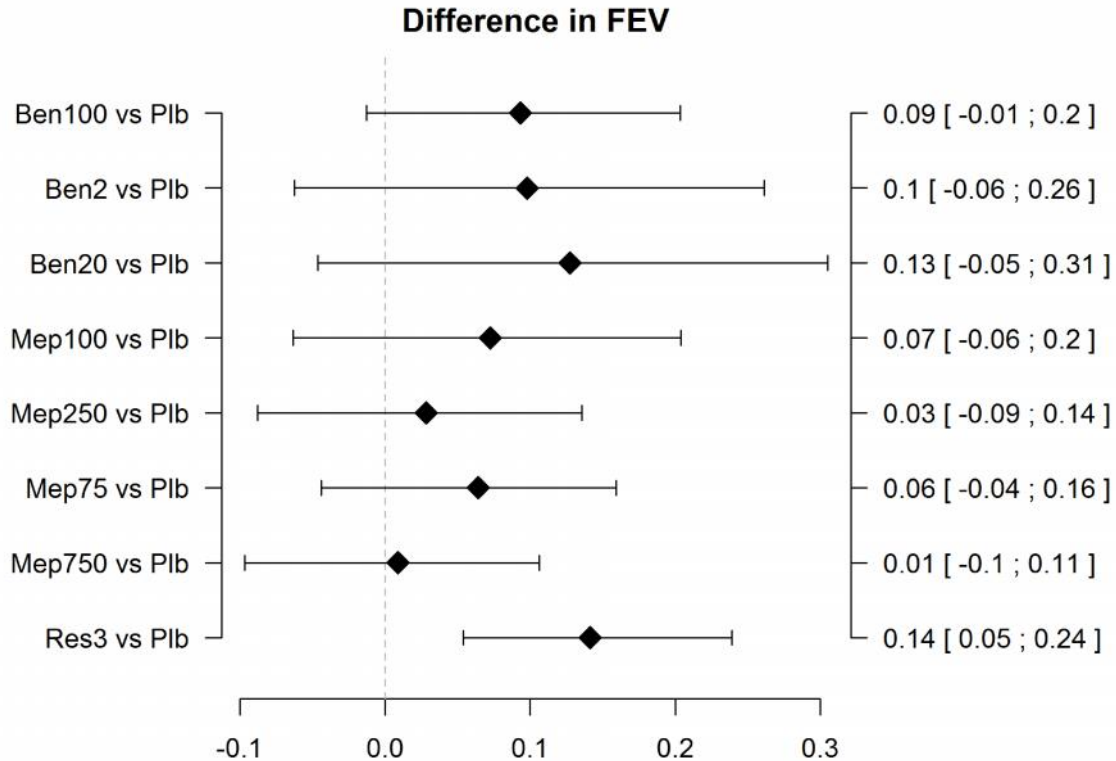
Exacerbation rate treatment comparison

Median of the random effect was 0.14 [0.01 , 0.53] and DIC:-12.914.

Treatment effect table was:

	Plb	Mep75	Mep100	Mep250	Mep750	Res3	Ben2	Ben20	Ben100
Plb		1.82 [2.63,1.27]	1.82 [2.7,1.2]	1.59[2.5,0 .97]	1.96[2.94, 1.3]	2.17[3.33, 1.45]	0.81[1.32, 0.52]	1.43[2.27, 0.93]	1.47[2.08, 1.06]
Mep75	0.55[0.38, 0.79]		1.01[1.59, 0.63]	0.87[1.43, 0.52]	1.08[1.69, 0.68]	1.19[2.13, 0.7]	0.45[0.83, 0.25]	0.79[1.43, 0.45]	0.81[1.35, 0.5]
Mep100	0.55[0.37, 0.83]	0.99[0.63, 1.58]		0.86[1.56, 0.47]	1.08[1.85, 0.61]	1.19[2.13, 0.68]	0.44[0.84, 0.24]	0.78[1.45, 0.44]	0.8[1.37,0 .48]
Mep250	0.63[0.4,1 .03]	1.15[0.7,1 .91]	1.16[0.64, 2.12]		1.23[2.04, 0.74]	1.37[2.63, 0.75]	0.51[1.04, 0.27]	0.91[1.79, 0.48]	0.93[1.69, 0.53]
Mep750	0.51[0.34, 0.77]	0.93[0.59, 1.47]	0.93[0.54, 1.63]	0.81[0.49, 1.35]		1.11[2,0.6 3]	0.41[0.79, 0.23]	0.73[1.39, 0.41]	0.75[1.3,0 .46]
Res3	0.46[0.3,0 .69]	0.84[0.47, 1.43]	0.84[0.47, 1.47]	0.73[0.38, 1.34]	0.9[0.5,1.5 8]		0.37[0.69, 0.2]	0.66[1.22, 0.36]	0.67[1.15, 0.4]
Ben2	1.23[0.76, 1.93]	2.24[1.21, 3.96]	2.25[1.19, 4.09]	1.95[0.96, 3.69]	2.42[1.27, 4.35]	2.67[1.45, 4.95]		1.75[2.86, 1.09]	1.82[2.86, 1.14]
Ben20	0.7[0.44,1 .08]	1.27[0.7,2 .21]	1.28[0.69, 2.29]	1.1[0.56,2 .09]	1.37[0.72, 2.43]	1.52[0.82, 2.81]	0.57[0.35, 0.92]		1.02[1.59, 0.66]
Ben100	0.68[0.48, 0.94]	1.24[0.74, 2]	1.25[0.73, 2.07]	1.08[0.59, 1.89]	1.34[0.77, 2.19]	1.49[0.87, 2.49]	0.55[0.35, 0.88]	0.98[0.63, 1.51]	

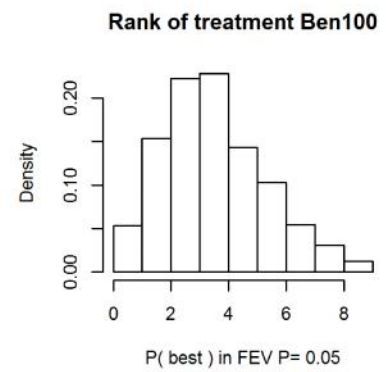
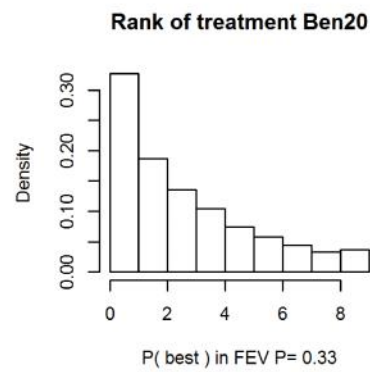
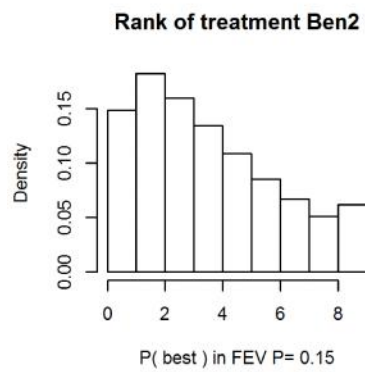
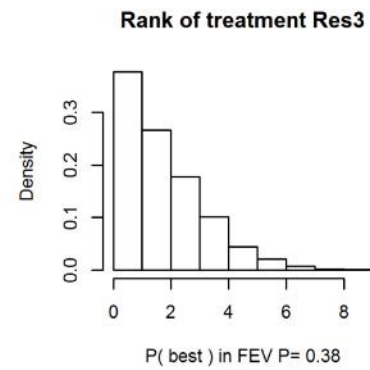
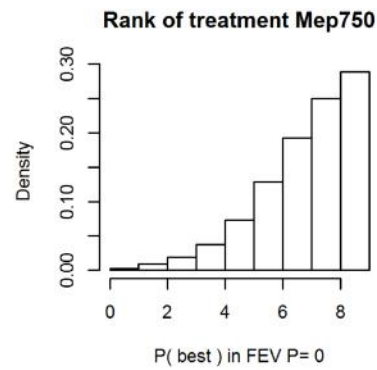
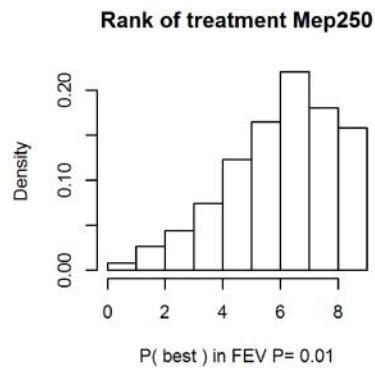
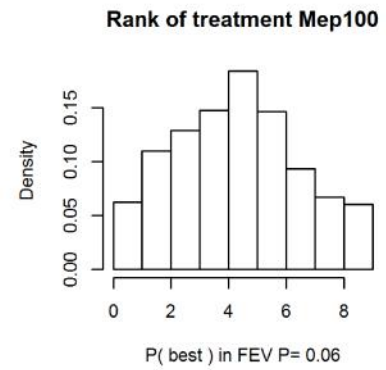
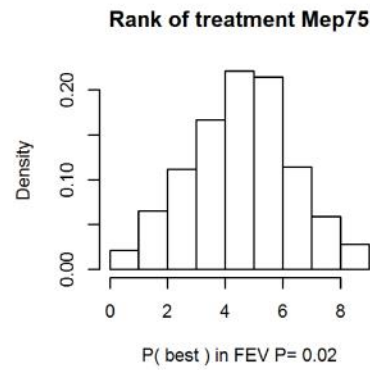
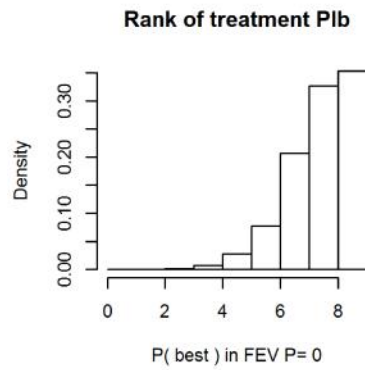
FEV1 (L) treatment comparison overall



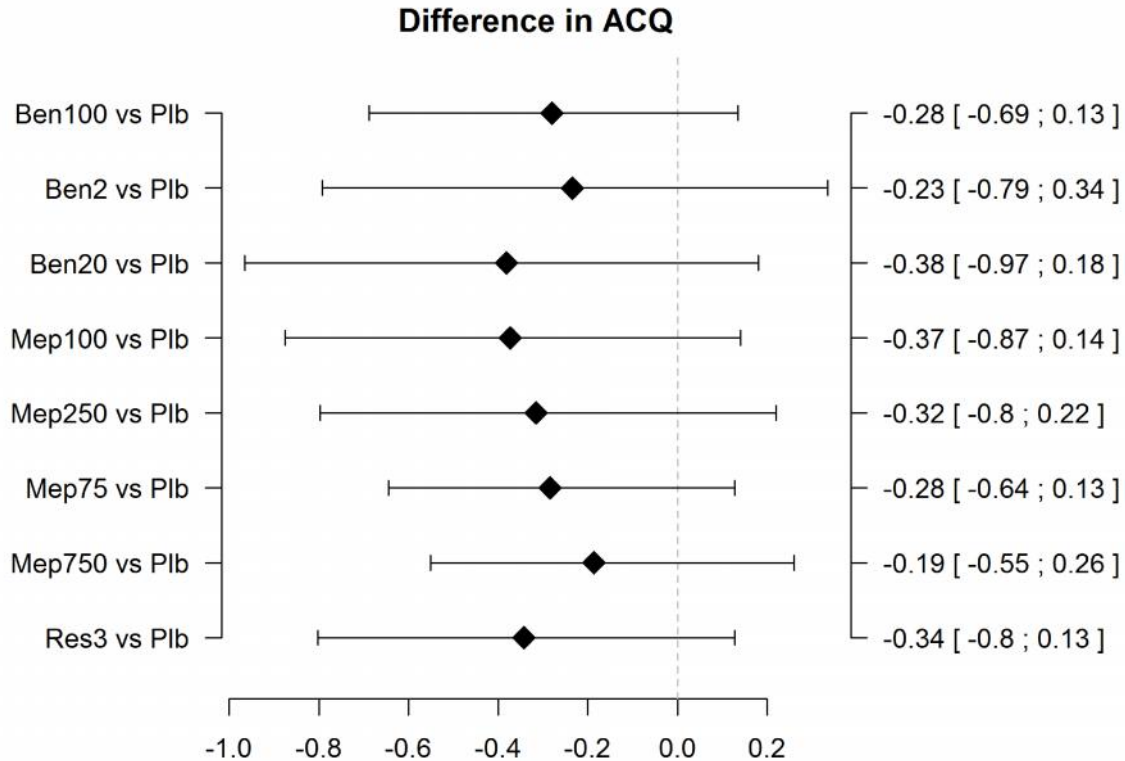
Median of the random effect was 0.04 [0 , 0.13] and DIC:-64.504.

Treatment effect table was:

	Plb	Mep75	Mep100	Mep250	Mep750	Res3	Ben2	Ben20	Ben100
Plb		-0.06[0.04,-0.16]	-0.07[0.06,-0.2]	-0.03[0.09,-0.14]	-0.01[0.1,-0.11]	-0.14[-0.05,-0.24]	-0.1[0.06,-0.26]	-0.13[0.05,-0.31]	-0.09[0.01,-0.2]
Mep75	0.06[-0.04,0.16]		-0.01[0.12,-0.15]	0.04[0.16,-0.09]	0.05[0.18,-0.07]	-0.08[0.05,-0.23]	-0.03[0.15,-0.23]	-0.06[0.13,-0.27]	-0.03[0.11,-0.19]
Mep100	0.07[-0.06,0.2]	0.01[-0.12,0.15]		0.04[0.21,-0.12]	0.06[0.23,-0.09]	-0.07[0.09,-0.24]	-0.03[0.18,-0.24]	-0.06[0.16,-0.28]	-0.02[0.15,-0.2]
Mep250	0.03[-0.09,0.14]	-0.04[-0.16,0.09]	-0.04[-0.21,0.12]		0.02[0.13,-0.1]	-0.11[0.02,-0.27]	-0.07[0.12,-0.28]	-0.1[0.1,-0.32]	-0.06[0.08,-0.23]
Mep750	0.01[-0.1,0.11]	-0.05[-0.18,0.07]	-0.06[-0.23,0.09]	-0.02[-0.13,0.1]		-0.13[0,-0.28]	-0.09[0.1,-0.29]	-0.12[0.08,-0.33]	-0.08[0.06,-0.24]
Res3	0.14[0.05,0.24]	0.08[-0.05,0.23]	0.07[-0.09,0.24]	0.11[-0.02,0.27]	0.13[0,0.28]		0.04[0.23,-0.14]	0.01[0.21,-0.18]	0.05[0.2,-0.09]
Ben2	0.1[-0.06,0.26]	0.03[-0.15,0.23]	0.03[-0.18,0.24]	0.07[-0.12,0.28]	0.09[-0.1,0.29]	-0.04[-0.23,0.14]		-0.03[0.16,-0.22]	0[0.17,-0.16]
Ben20	0.13[-0.05,0.31]	0.06[-0.13,0.27]	0.06[-0.16,0.28]	0.1[-0.1,0.32]	0.12[-0.08,0.33]	-0.01[-0.21,0.18]	0.03[-0.16,0.22]		0.03[0.21,-0.14]
Ben100	0.09[-0.01,0.2]	0.03[-0.11,0.19]	0.02[-0.15,0.2]	0.06[-0.08,0.23]	0.08[-0.06,0.24]	-0.05[-0.2,0.09]	0[-0.17,0.16]	-0.03[-0.21,0.14]	



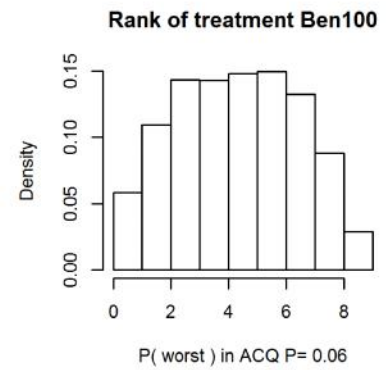
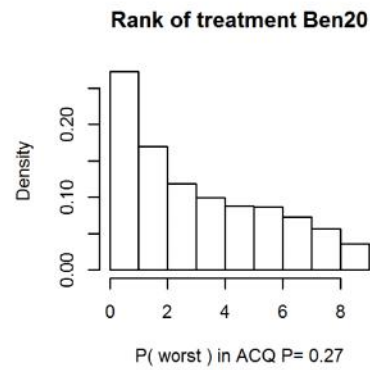
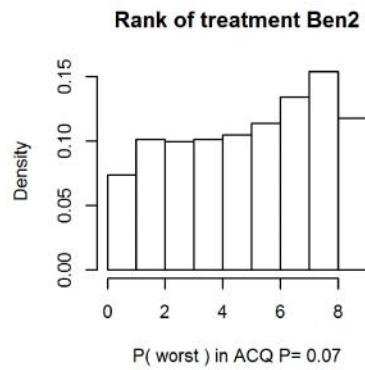
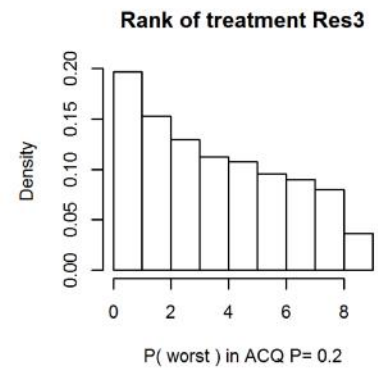
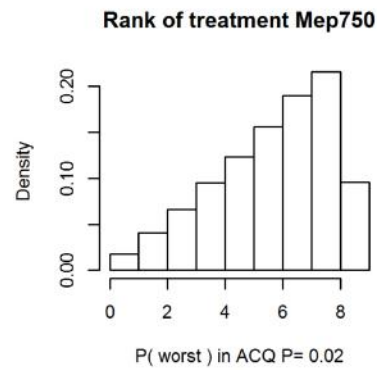
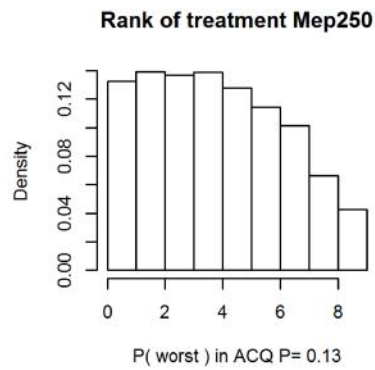
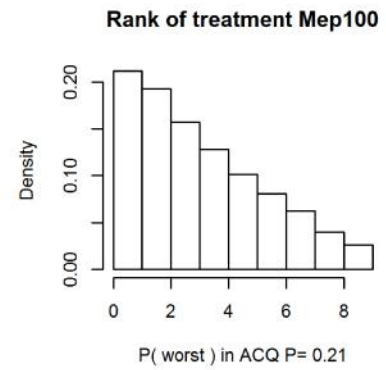
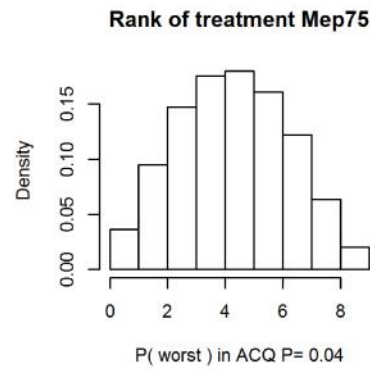
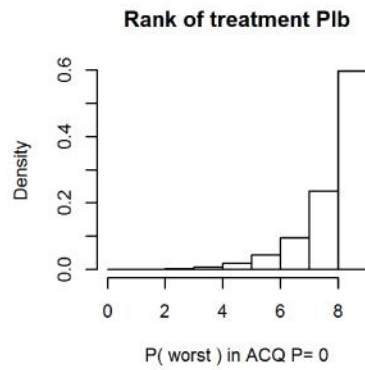
ACQ-5 treatment comparison overall



Median of the random effect was 0.15 [0.01 , 0.66] and DIC:-12.675.

Treatment effect table was:

	Plb	Mep75	Mep100	Mep250	Mep750	Res3	Ben2	Ben20	Ben100
Plb		0.28[0.64,-0.13]	0.37[0.87,-0.14]	0.32[0.8,-0.22]	0.19[0.55,-0.26]	0.34[0.8,-0.13]	0.23[0.79,-0.34]	0.38[0.97,-0.18]	0.28[0.69,-0.13]
Mep75	-0.28[-0.64,0.13]		0.09[0.62,-0.41]	0.03[0.56,-0.5]	-0.1[0.36,-0.59]	0.06[0.67,-0.51]	-	0.1[0.83,-0.55]	0[0.57,-0.56]
Mep100	-0.37[-0.87,0.14]	-0.09[-0.62,0.41]		-	-	-	-	0.01[0.78,-0.73]	-
Mep250	-0.32[-0.8,0.22]	-0.03[-0.56,0.5]	0.06[-0.59,0.74]		-	0.03[0.73,-0.63]	-0.08[0.7,-0.81]	0.07[0.87,-0.67]	-
Mep750	-0.19[-0.55,0.26]	0.1[-0.36,0.59]	0.18[-0.39,0.84]	0.13[-0.39,0.69]		0.16[0.82,-0.42]	0.05[0.77,-0.61]	0.2[0.93,-0.46]	0.09[0.71,-0.46]
Res3	-0.34[-0.8,0.13]	-0.06[-0.67,0.51]	0.03[-0.65,0.72]	-0.03[-0.73,0.63]	-0.16[-0.82,0.42]		-	0.04[0.8,-0.67]	-
Ben2	-0.23[-0.79,0.34]	0.05[-0.65,0.7]	0.14[-0.62,0.88]	0.08[-0.7,0.81]	-0.05[-0.77,0.61]	0.11[-0.62,0.83]		0.15[0.76,-0.45]	0.05[0.61,-0.52]
Ben20	-0.38[-0.97,0.18]	-0.1[-0.83,0.55]	-0.01[-0.78,0.73]	-0.07[-0.87,0.67]	-0.2[-0.93,0.46]	-0.04[-0.8,0.67]	-0.15[-0.76,0.45]		-
Ben100	-0.28[-0.69,0.13]	0[-0.57,0.56]	0.09[-0.57,0.74]	0.03[-0.64,0.67]	-0.09[-0.71,0.46]	0.06[-0.55,0.69]	-0.05[-0.61,0.52]	0.11[-0.46,0.69]	

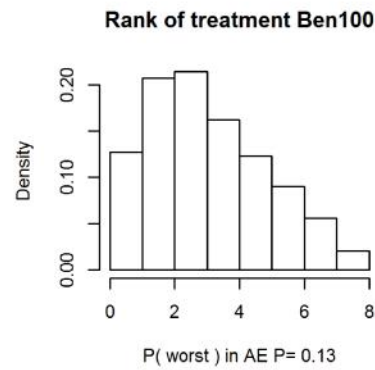
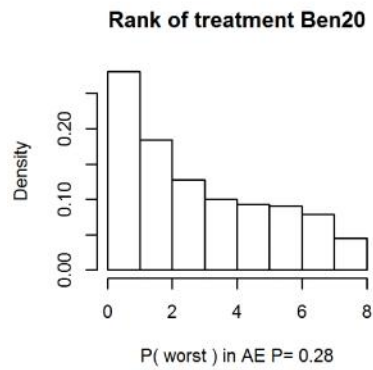
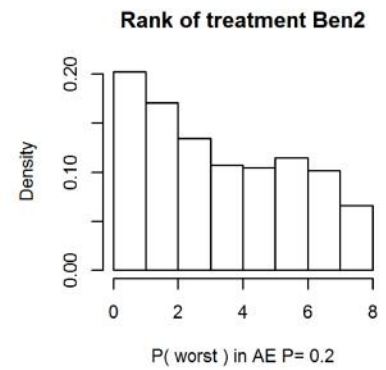
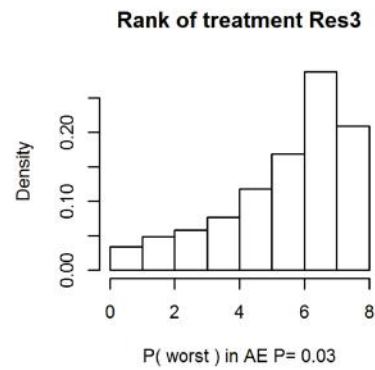
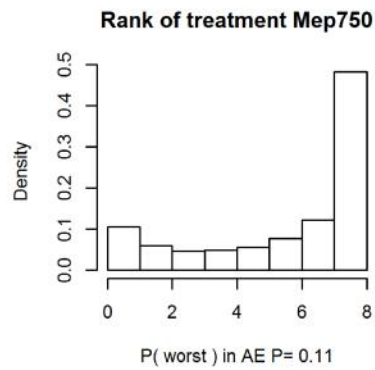
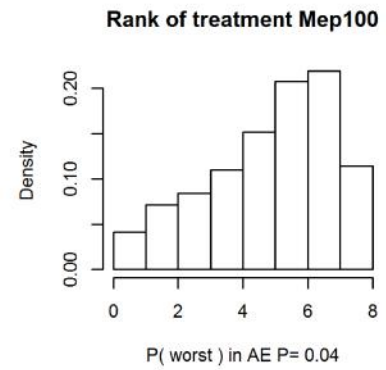
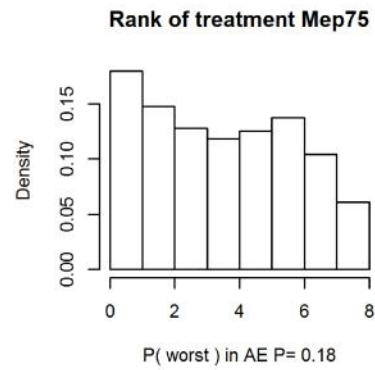
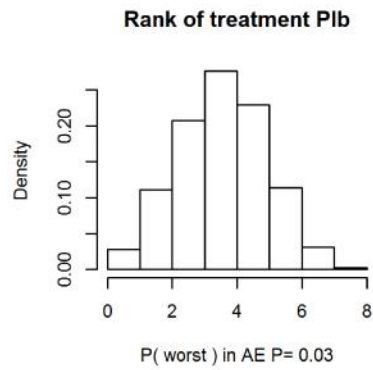


AE treatment comparison overall

Median of the random effect was 0.11 [0.01 , 0.73] and DIC:143.252.

Treatment effect table was:

	Plb	Mep75	Mep100	Mep250	Mep750	Res3	Ben2	Ben20
Plb		1.01[1.61,0 .61]	0.93[1.33,0 .63]	0.81[1.59,0 .41]	0.88[1.32,0 .6]	1.02[1.69,0 .63]	1.06[1.75,0 .65]	1.03[1.49,0 .73]
Mep75	0.99[0.62,1 .63]		0.93[1.49,0 .56]	0.81[1.85,0 .36]	0.88[1.64,0 .48]	1.02[2.04,0 .52]	1.05[2.13,0 .53]	1.02[1.89,0 .57]
Mep100	1.08[0.75,1 .58]	1.08[0.67,1 .77]		0.88[1.92,0 .4]	0.95[1.67,0 .56]	1.1[2.08,0 .61]	1.15[2.17,0 .63]	1.11[1.89,0 .67]
Mep250	1.23[0.63,2 .43]	1.24[0.54,2 .81]	1.14[0.52,2 .47]		1.09[2.38,0 .51]	1.27[2.94,0 .55]	1.32[3.03,0 .57]	1.27[2.78,0 .6]
Mep750	1.13[0.76,1 .66]	1.13[0.61,2 .1]	1.05[0.6,1. 79]	0.92[0.42,1 .98]		1.16[2.17,0 .63]	1.19[2.27,0 .64]	1.16[1.96,0 .69]
Res3	0.98[0.59,1 .58]	0.98[0.49,1 .94]	0.91[0.48,1 .65]	0.79[0.34,1 .83]	0.86[0.46,1 .59]		1.03[1.82,0 .6]	1.01[1.67,0 .61]
Ben2	0.94[0.57,1 .54]	0.95[0.47,1 .87]	0.87[0.46,1 .59]	0.76[0.33,1 .76]	0.84[0.44,1 .56]	0.97[0.55,1 .66]		0.97[1.61,0 .59]
Ben20	0.97[0.67,1 .37]	0.98[0.53,1 .75]	0.9[0.53,1. 5]	0.79[0.36,1 .67]	0.86[0.51,1 .44]	0.99[0.6,1. 63]	1.03[0.62,1 .7]	

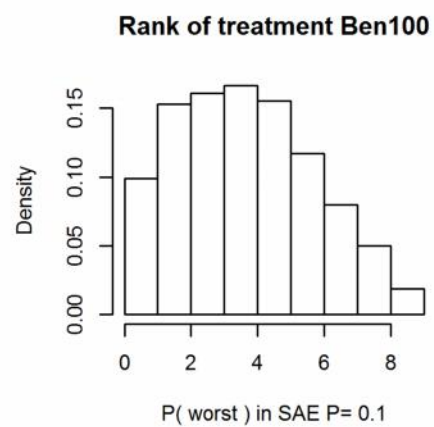
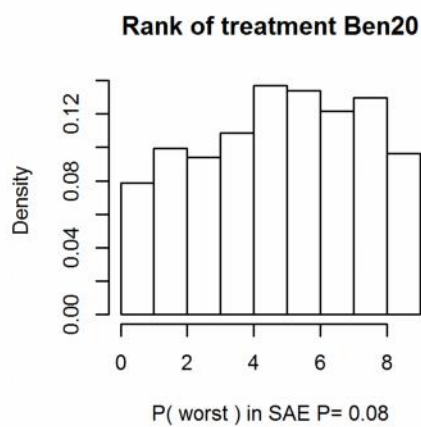
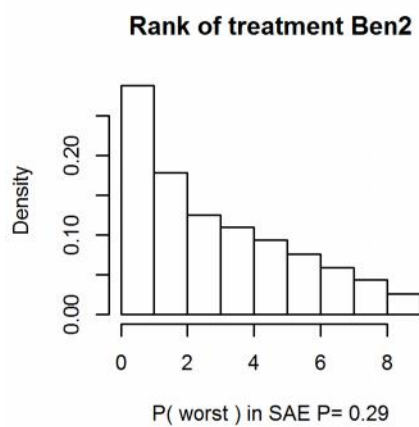
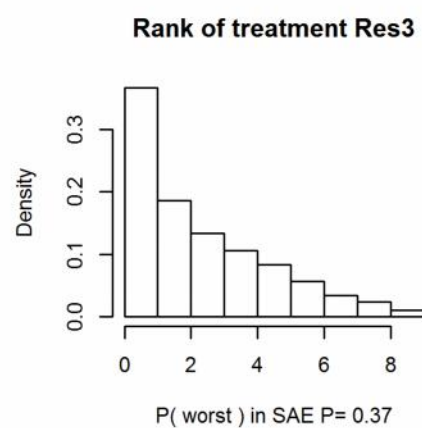
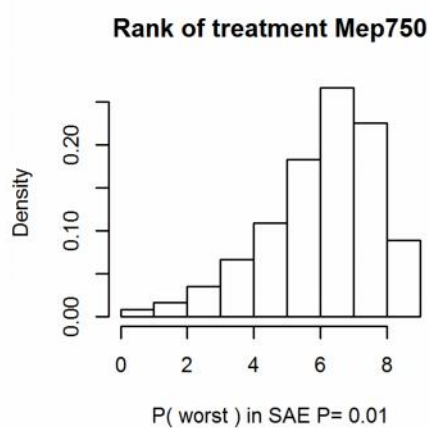
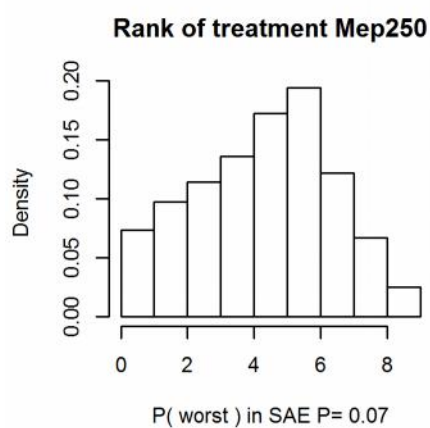
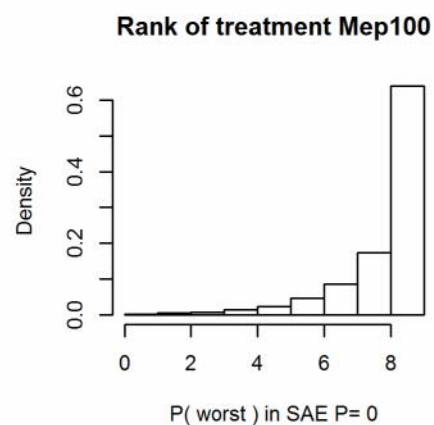
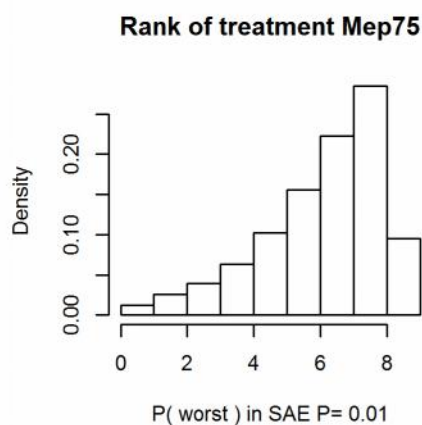
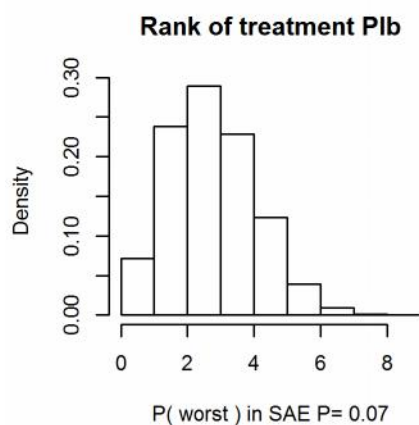


SAE treatment comparison overall

Median of the random effect was 0.79 [0.47 , 1.66] and DIC:206.965.

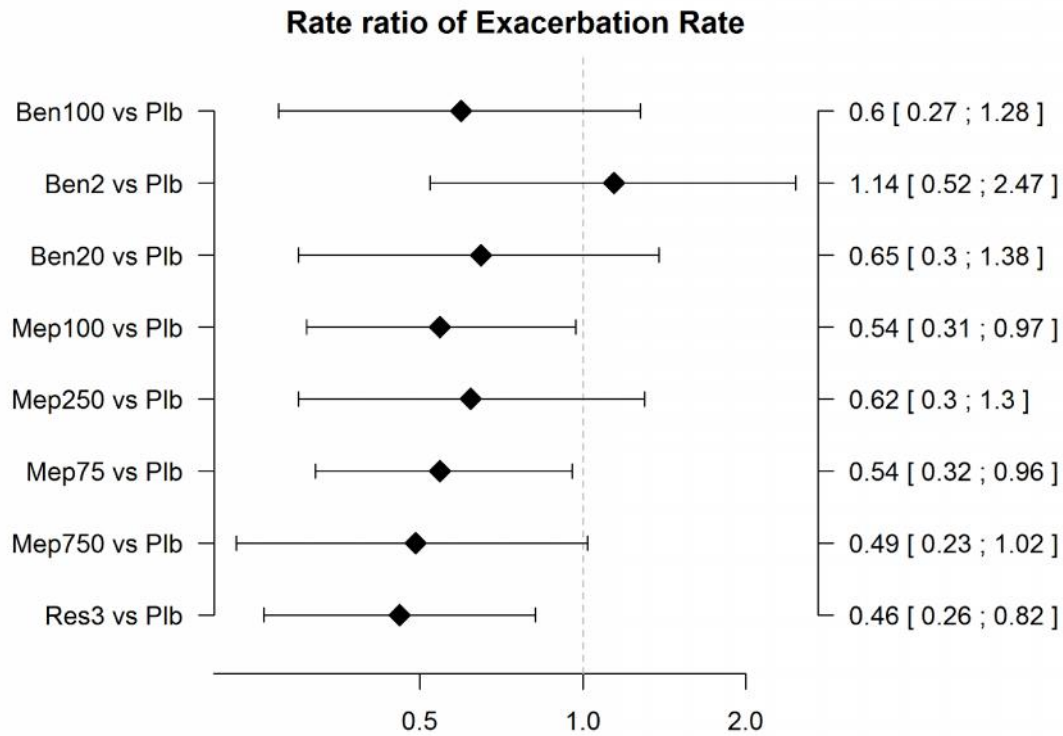
Treatment effect table was:

	Plb	Mep75	Mep100	Mep250	Mep750	Res3	Ben2	Ben20	Ben100
Plb		0.45[1.47, 0.14]	0.24[0.84, 0.07]	0.71[2.38, 0.21]	0.47[1.32, 0.16]	1.23[4.55, 0.32]	1.09[6.25, 0.19]	0.65[3.7, 0.11]	0.85[3.12, 0.23]
Mep75	2.24[0.68, 7.28]		0.54[2.33, 0.12]	1.56[6.67, 0.36]	1.04[4, 0.26]	2.78[14.29, 0.47]	2.38[20, 0.3]	1.45[12.5, 0.18]	1.89[11.11, 0.33]
Mep100	4.15[1.19, 14.86]	1.86[0.43, 8.12]		2.94[16.67, 0.55]	1.96[9.09, 0.41]	5.26[33.33, 0.81]	4.55[33.33, 0.53]	2.7[25, 0.3]	3.57[20, 0.58]
Mep250	1.41[0.42, 4.77]	0.64[0.15, 2.74]	0.34[0.06, 1.81]		0.66[2.27, 0.19]	1.72[10, 0.29]	1.54[12.5, 0.19]	0.91[7.69, 0.11]	1.19[7.14, 0.21]
Mep750	2.14[0.76, 6.21]	0.96[0.25, 3.87]	0.51[0.11, 2.46]	1.51[0.44, 5.26]		2.63[14.29, 0.49]	2.33[20, 0.31]	1.39[11.11, 0.19]	1.79[10, 0.34]
Res3	0.81[0.22, 3.08]	0.36[0.07, 2.13]	0.19[0.03, 1.23]	0.58[0.1, 3.48]	0.38[0.07, 2.05]		0.88[7.69, 0.1]	0.53[4.76, 0.06]	0.69[4.35, 0.11]
Ben2	0.92[0.16, 5.17]	0.42[0.05, 3.33]	0.22[0.03, 1.9]	0.65[0.08, 5.17]	0.43[0.05, 3.23]	1.14[0.13, 10.02]		0.6[3.85, 0.09]	0.79[4.35, 0.13]
Ben20	1.55[0.27, 8.72]	0.69[0.08, 5.44]	0.37[0.04, 3.06]	1.1[0.13, 8.9]	0.72[0.09, 5.27]	1.89[0.21, 16.75]	1.67[0.26, 10.56]		1.32[7.14, 0.23]
Ben100	1.18[0.32, 4.34]	0.53[0.09, 3.04]	0.28[0.05, 1.71]	0.84[0.14, 4.83]	0.56[0.1, 2.9]	1.45[0.23, 8.94]	1.27[0.23, 7.47]	0.76[0.14, 4.31]	



Network meta-analysis results on the eosinophilic population

Exacerbation rate treatment comparison for the eosinophilic subgroup

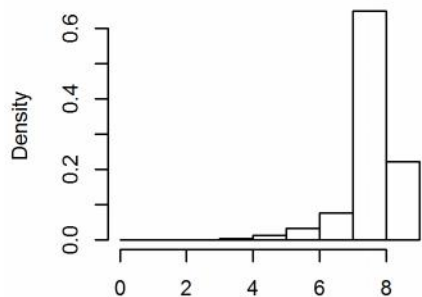


Median of the random effect was 0.17 [0.01 , 1.05] and DIC:-9.84.

Treatment effect table was:

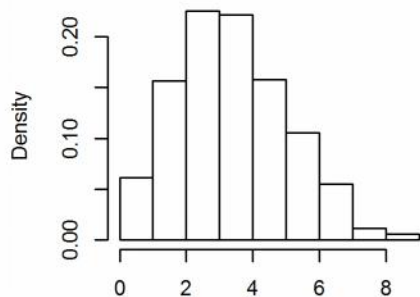
	Plb	Mep75	Mep100	Mep250	Mep750	Res3	Ben2	Ben20	Ben100
Plb		1.85[3.12,1.04]	1.85[3.23,1.03]	1.61[3.33,0.77]	2.04[4.35,0.98]	2.17[3.85,1.22]	0.88[1.92,0.4]	1.54[3.33,0.72]	1.67[3.7,0.78]
Mep75	0.54[0.32,0.96]		1[1.96,0.51]	0.88[1.85,0.41]	1.11[2.38,0.53]	1.19[2.63,0.55]	0.48[1.25,0.19]	0.84[2.27,0.33]	0.92[2.38,0.37]
Mep100	0.54[0.31,0.97]	1[0.51,1.96]		0.88[2.17,0.37]	1.11[2.78,0.46]	1.19[2.7,0.53]	0.48[1.28,0.19]	0.83[2.22,0.33]	0.91[2.44,0.36]
Mep250	0.62[0.3,1.3]	1.14[0.54,2.41]	1.14[0.46,2.72]		1.27[2.86,0.58]	1.35[3.45,0.53]	0.55[1.59,0.19]	0.96[2.78,0.34]	1.04[3.03,0.36]
Mep750	0.49[0.23,1.02]	0.9[0.42,1.87]	0.9[0.36,2.19]	0.79[0.35,1.72]		1.06[2.7,0.42]	0.43[1.25,0.15]	0.76[2.17,0.25]	0.83[2.44,0.29]
Res3	0.46[0.26,0.82]	0.84[0.38,1.83]	0.84[0.37,1.88]	0.74[0.29,1.87]	0.94[0.37,2.4]		0.4[1.06,0.15]	0.71[1.85,0.27]	0.77[2,0.29]
Ben2	1.14[0.52,2.47]	2.1[0.8,5.24]	2.1[0.78,5.37]	1.83[0.63,5.23]	2.33[0.8,6.89]	2.49[0.94,6.53]		1.75[3.85,0.81]	1.92[4.17,0.89]
Ben20	0.65[0.3,1.38]	1.19[0.44,3.02]	1.2[0.45,3.05]	1.04[0.36,2.96]	1.32[0.46,3.95]	1.41[0.54,3.67]	0.57[0.26,1.24]		1.09[2.38,0.5]
Ben100	0.6[0.27,1.28]	1.09[0.42,2.73]	1.1[0.41,2.81]	0.96[0.33,2.79]	1.21[0.41,3.48]	1.3[0.5,3.43]	0.52[0.24,1.12]	0.92[0.42,1.99]	

Rank of treatment Plb



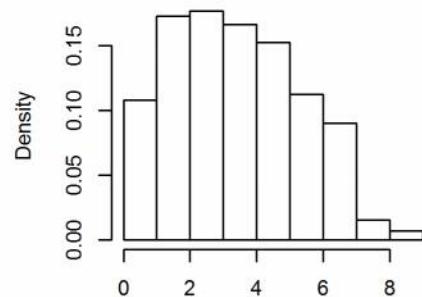
P(worst) in Exacerbation Rate $P=0$

Rank of treatment Mep75



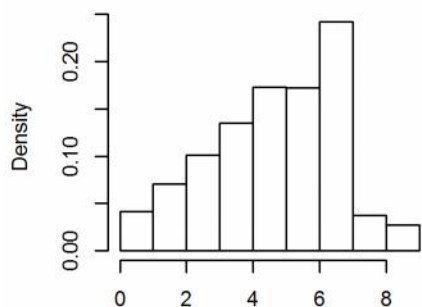
P(worst) in Exacerbation Rate $P=0.06$

Rank of treatment Mep100



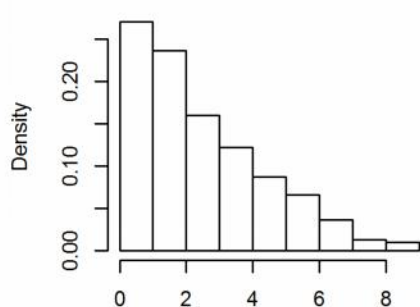
P(worst) in Exacerbation Rate $P=0.11$

Rank of treatment Mep250



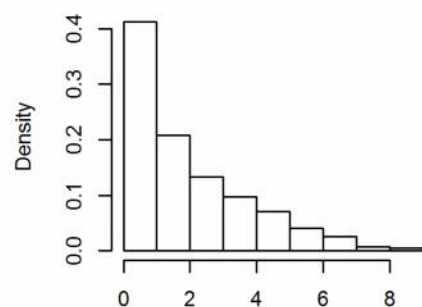
P(worst) in Exacerbation Rate $P=0.04$

Rank of treatment Mep750



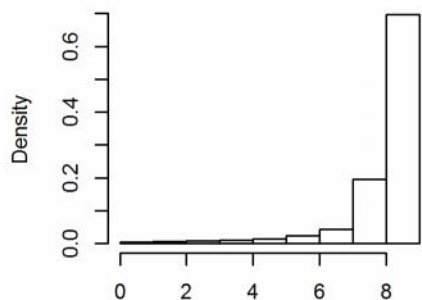
P(worst) in Exacerbation Rate $P=0.27$

Rank of treatment Res3



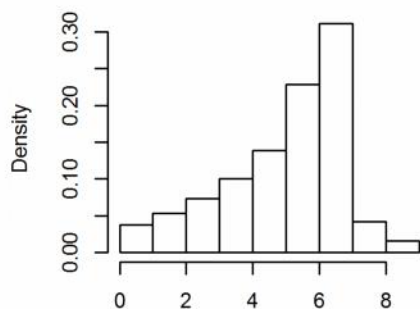
P(worst) in Exacerbation Rate $P=0.41$

Rank of treatment Ben2



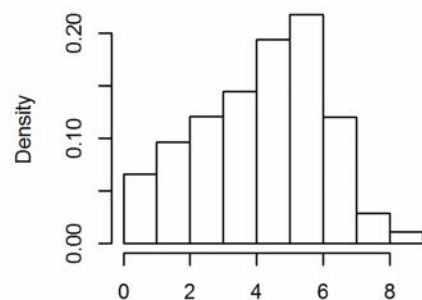
P(worst) in Exacerbation Rate $P=0$

Rank of treatment Ben20



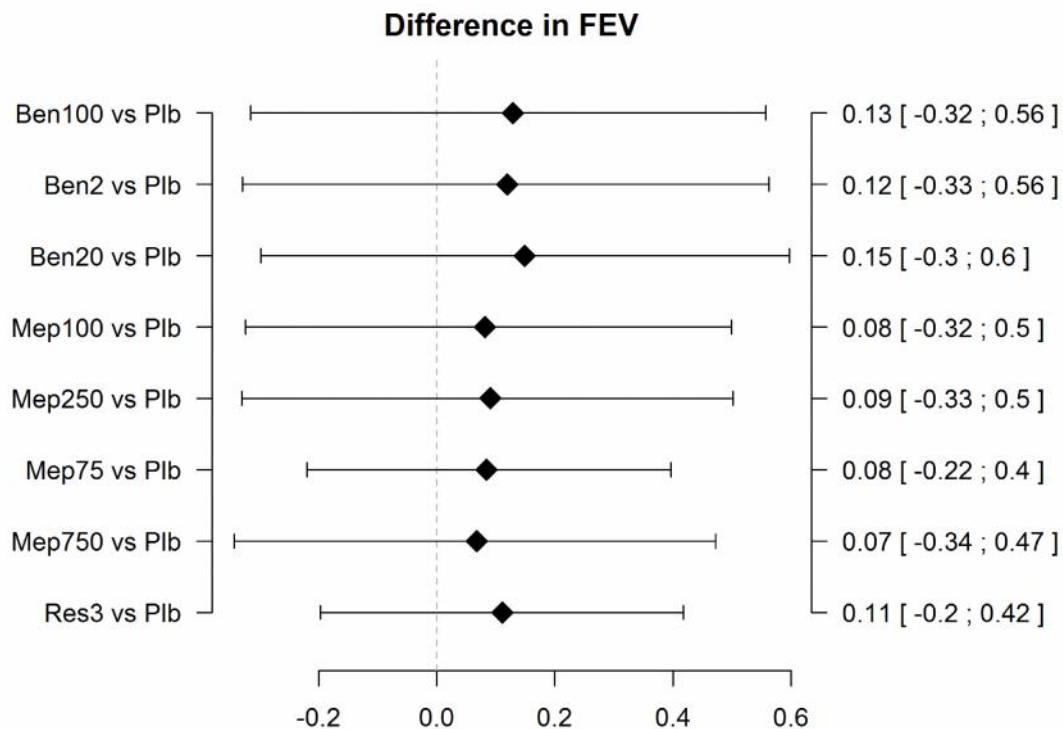
P(worst) in Exacerbation Rate $P=0.04$

Rank of treatment Ben100



P(worst) in Exacerbation Rate $P=0.07$

FEV1 (L) treatment comparison for the eosinophilic subgroup



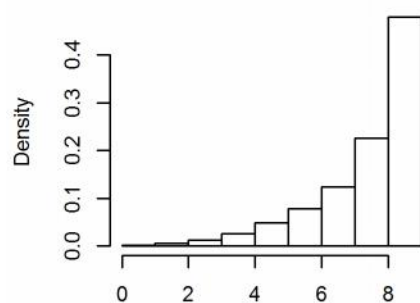
Median of the random effect was 0.06 [0 , 0.85] and DIC:-41.911.

Treatment effect table was:

	Plb	Mep75	Mep100	Mep250	Mep750	Res3	Ben2	Ben20	Ben100
Plb		-0.08[0.22,-0.4]	-0.08[0.32,-0.5]	-0.09[0.33,-0.5]	-0.07[0.34,-0.47]	-0.11[0.2,-0.42]	-0.12[0.33,-0.56]	-0.15[0.3,-0.6]	-0.13[0.32,-0.56]
Mep75	0.08[-0.22,0.4]		0[0.41,-0.41]	-0.01[0.42,-0.43]	0.02[0.42,-0.39]	-0.03[0.42,-0.47]	-0.04[0.52,-0.58]	-0.06[0.49,-0.61]	-0.04[0.51,-0.59]

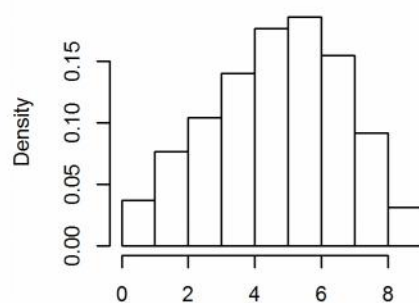
Mep100	0.08[- 0.32,0.5]	0[- 0.41,0.41]		-0.01[0.53,- 0.55]	0.01[0.56,- 0.54]	-0.03[0.48,- 0.54]	-0.04[0.58,- 0.64]	-0.07[0.56,- 0.68]	-0.05[0.58,- 0.64]
Mep250	0.09[- 0.33,0.5]	0.01[- 0.42,0.43]	0.01[- 0.53,0.55]		0.02[0.45,- 0.43]	-0.02[0.51,- 0.53]	-0.03[0.58,- 0.65]	-0.06[0.56,- 0.66]	-0.04[0.57,- 0.65]
Mep750	0.07[- 0.34,0.47]	-0.02[- 0.42,0.39]	-0.01[- 0.56,0.54]	-0.02[- 0.45,0.43]		-0.04[0.48,- 0.57]	-0.05[0.56,- 0.65]	-0.08[0.52,- 0.69]	-0.06[0.55,- 0.64]
Res3	0.11[- 0.2,0.42]	0.03[- 0.42,0.47]	0.03[- 0.48,0.54]	0.02[- 0.51,0.53]	0.04[- 0.48,0.57]		-0.01[0.54,- 0.53]	-0.04[0.52,- 0.58]	-0.02[0.54,- 0.56]
Ben2	0.12[- 0.33,0.56]	0.04[- 0.52,0.58]	0.04[- 0.58,0.64]	0.03[- 0.58,0.65]	0.05[- 0.56,0.65]	0.01[- 0.54,0.53]		-0.03[0.41,- 0.48]	-0.01[0.44,- 0.45]
Ben20	0.15[- 0.3,0.6]	0.06[- 0.49,0.61]	0.07[- 0.56,0.68]	0.06[- 0.56,0.66]	0.08[- 0.52,0.69]	0.04[- 0.52,0.58]	0.03[- 0.41,0.48]		0.02[0.47,- 0.41]
Ben100	0.13[- 0.32,0.56]	0.04[- 0.51,0.59]	0.05[- 0.58,0.64]	0.04[- 0.57,0.65]	0.06[- 0.55,0.64]	0.02[- 0.54,0.56]	0.01[- 0.44,0.45]	-0.02[- 0.47,0.41]	

Rank of treatment Plb



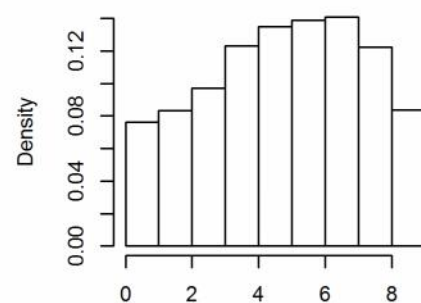
P(best) in FEV P= 0

Rank of treatment Mep75



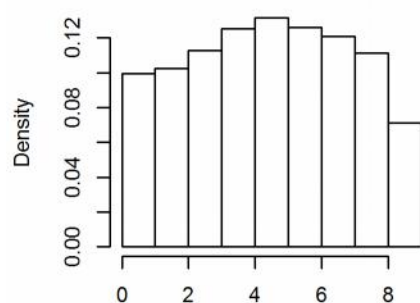
P(best) in FEV P= 0.04

Rank of treatment Mep100



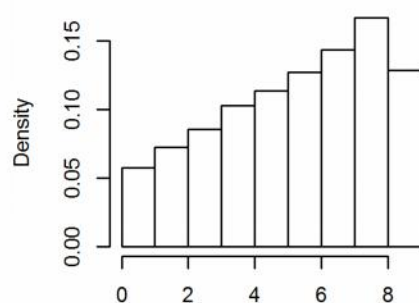
P(best) in FEV P= 0.08

Rank of treatment Mep250



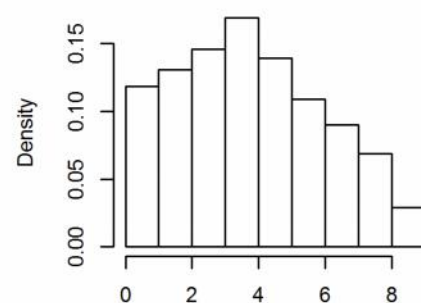
P(best) in FEV P= 0.1

Rank of treatment Mep750



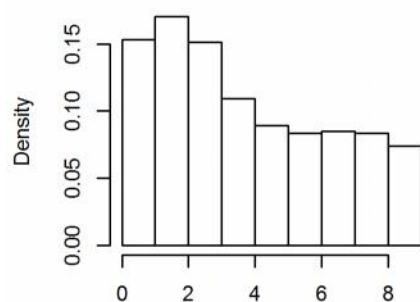
P(best) in FEV P= 0.06

Rank of treatment Res3



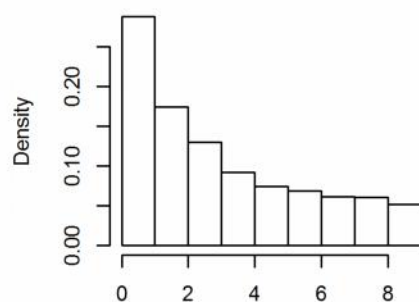
P(best) in FEV P= 0.12

Rank of treatment Ben2



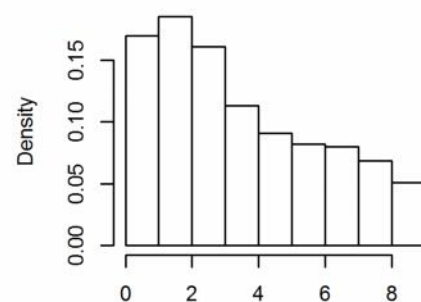
P(best) in FEV P= 0.15

Rank of treatment Ben20



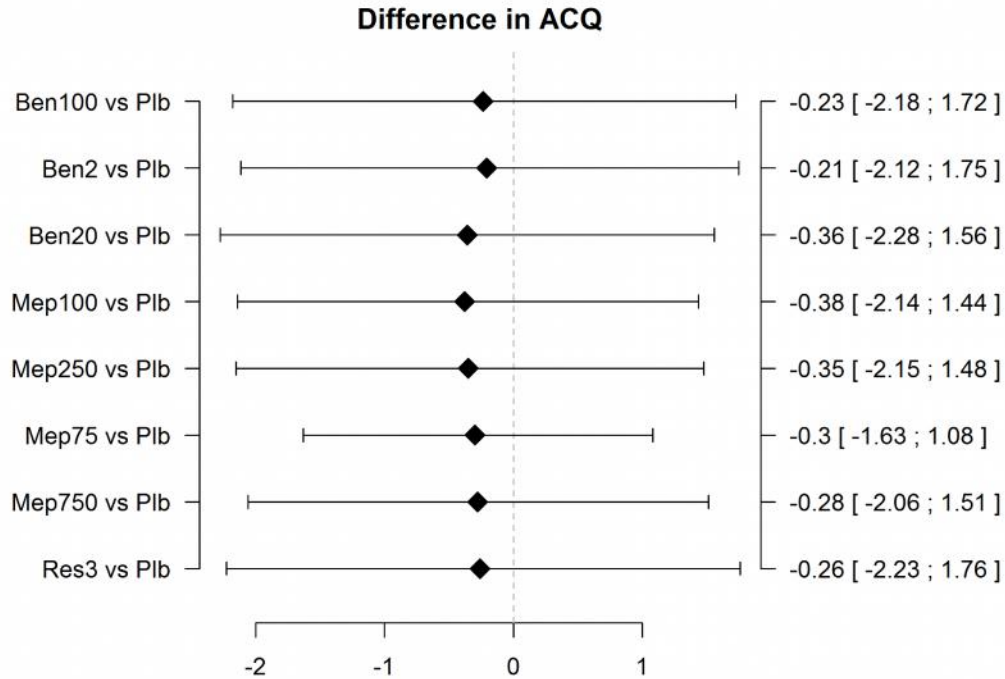
P(best) in FEV P= 0.29

Rank of treatment Ben100



P(best) in FEV P= 0.17

ACQ-5 treatment comparison for the eosinophilic subgroup

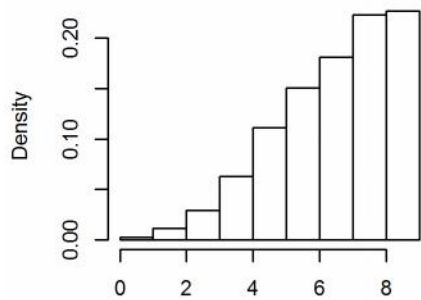


Median of the random effect was 0.51 [0.03 , 1.87] and DIC:-8.282.

Treatment effect table was:

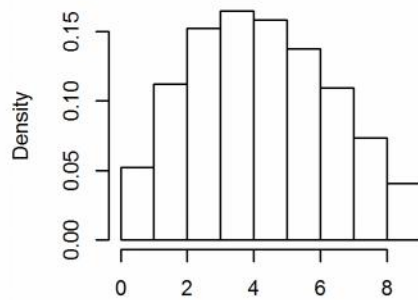
	Plb	Mep75	Mep100	Mep250	Mep750	Res3	Ben2	Ben20	Ben100
Plb		0.3[1.63,-1.08]	0.38[2.14,-1.44]	0.35[2.15,-1.48]	0.28[2.06,-1.51]	0.26[2.23,-1.76]	0.21[2.12,-1.75]	0.36[2.28,-1.56]	0.23[2.18,-1.72]
Mep75	-0.3[-1.63,1.08]		0.08[1.88,-1.71]	0.05[1.84,-1.78]	-0.02[1.78,-1.8]	-0.04[2.36,-2.43]	-0.09[2.3,-2.44]	0.06[2.45,-2.27]	-0.06[2.37,-2.42]
Mep100	-0.38[-2.14,1.44]	-0.08[-1.88,1.71]		-0.03[2.31,-2.37]	-0.1[2.26,-2.46]	-0.12[2.57,-2.82]	-0.17[2.5,-2.75]	-0.02[2.63,-2.62]	-0.14[2.5,-2.78]
Mep250	-0.35[-2.15,1.48]	-0.05[-1.84,1.78]	0.03[-2.31,2.37]		-0.07[1.86,-2]	-0.09[2.56,-2.77]	-0.14[2.55,-2.79]	0[2.71,-2.6]	-0.12[2.6,-2.75]
Mep750	-0.28[-2.06,1.51]	0.02[-1.78,1.8]	0.1[-2.26,2.46]	0.07[-1.86,2]		-0.02[2.63,-2.69]	-0.07[2.58,-2.74]	0.08[2.7,-2.59]	-0.05[2.64,-2.71]
Res3	-0.26[-2.23,1.76]	0.04[-2.36,2.43]	0.12[-2.57,2.82]	0.09[-2.56,2.77]	0.02[-2.63,2.69]		-0.05[2.75,-2.76]	0.1[2.9,-2.69]	-0.02[2.73,-2.77]
Ben2	-0.21[-2.12,1.75]	0.09[-2.3,2.44]	0.17[-2.5,2.75]	0.14[-2.55,2.79]	0.07[-2.58,2.74]	0.05[-2.75,2.76]		0.15[2.12,-1.8]	0.02[1.98,-1.93]
Ben20	-0.36[-2.28,1.56]	-0.06[-2.45,2.27]	0.02[-2.63,2.62]	0[-2.71,2.6]	-0.08[-2.7,2.59]	-0.1[-2.9,2.69]	-0.15[-2.12,1.8]		-0.12[1.83,-2.06]
Ben100	-0.23[-2.18,1.72]	0.06[-2.37,2.42]	0.14[-2.5,2.78]	0.12[-2.6,2.75]	0.05[-2.64,2.71]	0.02[-2.73,2.77]	-0.02[-2.75,2.76]	0.12[-1.83,2.06]	

Rank of treatment Plb



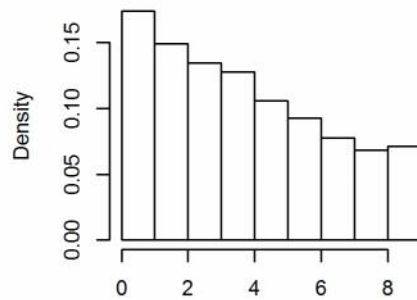
P(worst) in ACQ P= 0

Rank of treatment Mep75



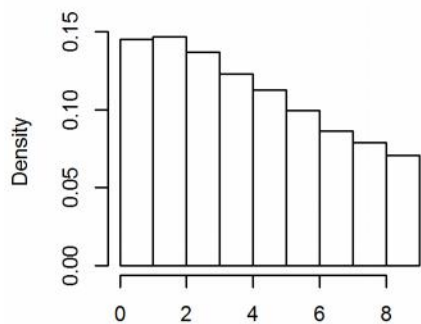
P(worst) in ACQ P= 0.05

Rank of treatment Mep100



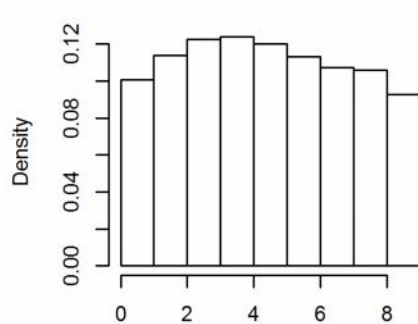
P(worst) in ACQ P= 0.17

Rank of treatment Mep250



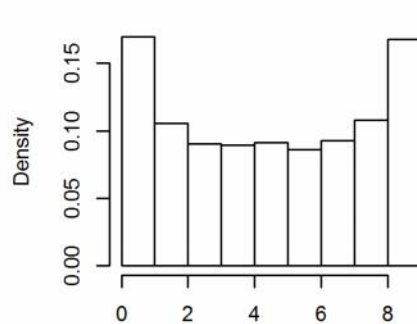
P(worst) in ACQ P= 0.15

Rank of treatment Mep750



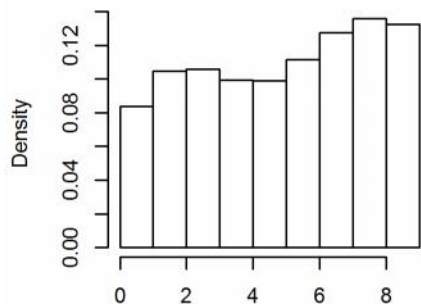
P(worst) in ACQ P= 0.1

Rank of treatment Res3



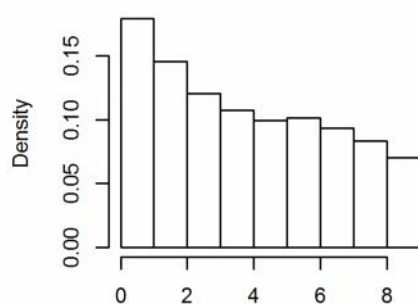
P(worst) in ACQ P= 0.17

Rank of treatment Ben2



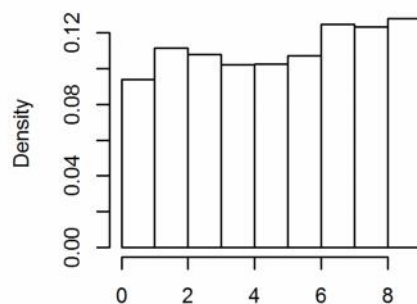
P(worst) in ACQ P= 0.08

Rank of treatment Ben20



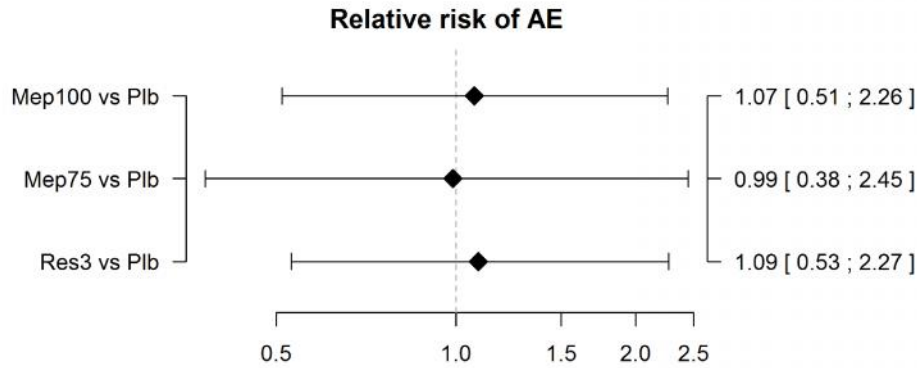
P(worst) in ACQ P= 0.18

Rank of treatment Ben100



P(worst) in ACQ P= 0.09

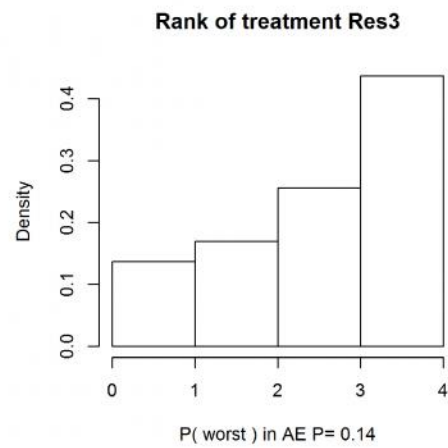
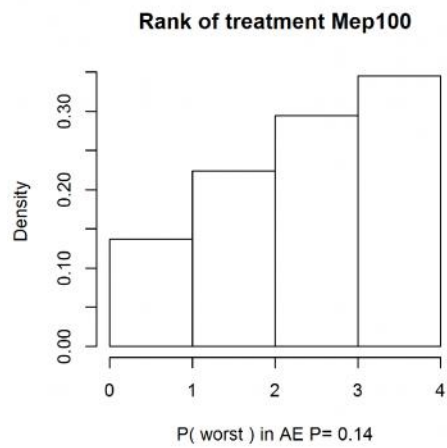
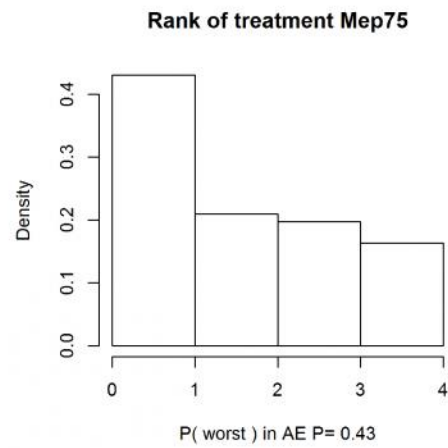
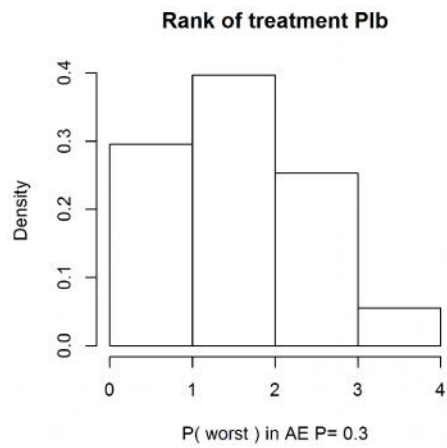
AE treatment comparison for the eosinophilic subgroup



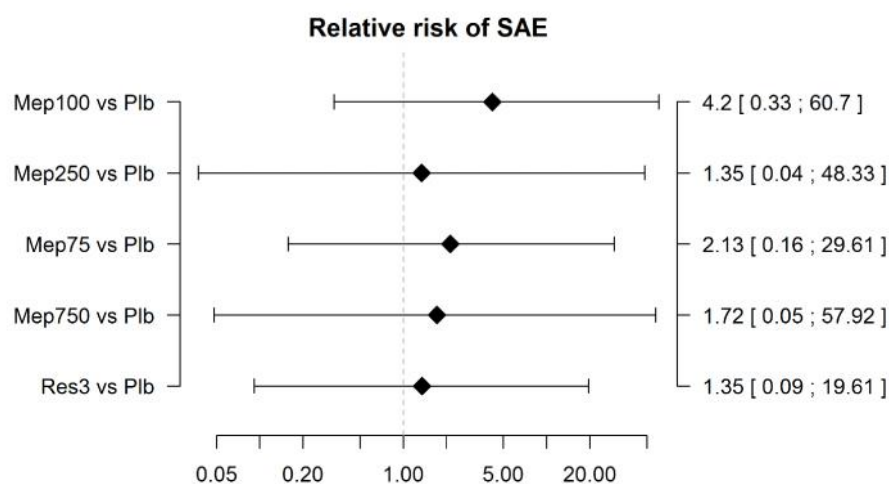
Median of the random effect was 0.12 [0 , 2] and DIC:78.859.

Treatment effect table was:

	Plb	Mep75	Mep100	Mep250
Plb		1.01[2.63,0.41]	0.93[1.96,0.44]	0.92[1.89,0.44]
Mep75	0.99[0.38,2.45]		0.93[2.27,0.35]	0.91[2.94,0.26]
Mep100	1.07[0.51,2.26]	1.08[0.44,2.86]		0.98[2.86,0.35]
Mep250	1.09[0.53,2.27]	1.1[0.34,3.82]	1.02[0.35,2.85]	



SAE treatment comparison for the eosinophilic subgroup

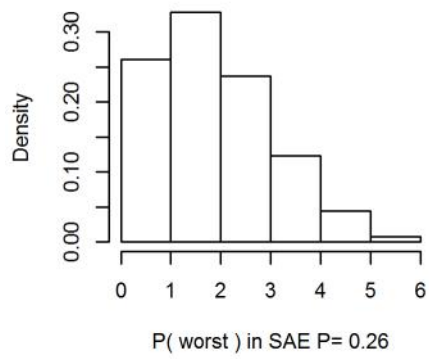


Median of the random effect was 1.32 [0.58 , 4.09] and DIC:116.147.

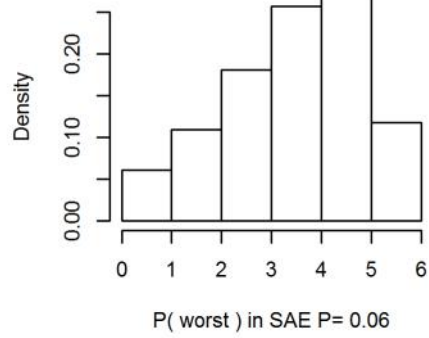
Treatment effect table was:

	Plb	Mep75	Mep100	Mep250	Mep750	Res3
Plb		0.47[6.25,0.03]	0.24[3.03,0.02]	0.74[25,0.02]	0.58[20,0.02]	0.74[11.11,0.05]
Mep 75	2.13[0.16,29.6]		0.5[11.11,0.02]	1.59[50,0.05]	1.23[50,0.04]	1.59[100,0.04]
Mep 100	4.2[0.33,60.73]	1.99[0.09,44.38]		3.12[Inf,0.05]	2.44[100,0.04]	3.03[100,0.08]
Mep 250	1.35[0.04,48.35]	0.63[0.02,20.43]	0.32[0,18.26]		0.78[33.33,0.02]	1.01[100,0.01]
Mep 750	1.72[0.05,57.9]	0.81[0.02,26.18]	0.41[0.01,23.56]	1.28[0.03,59.59]		1.28[100,0.01]
Res3	1.36[0.09,19.62]	0.63[0.01,26.66]	0.33[0.01,13.24]	0.99[0.01,91.7]	0.78[0.01,72.12]	

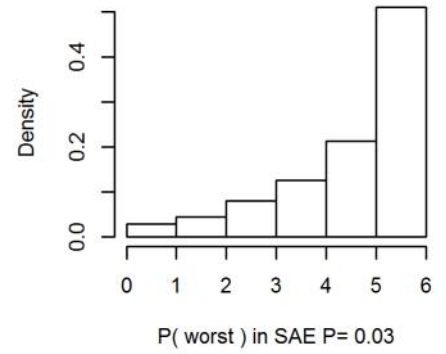
Rank of treatment Plb



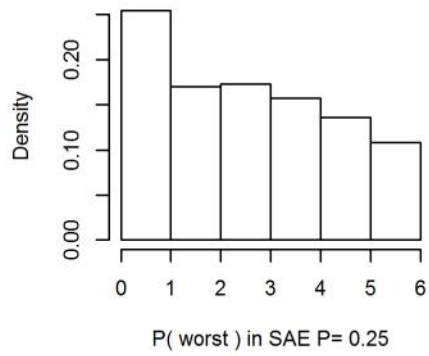
Rank of treatment Mep75



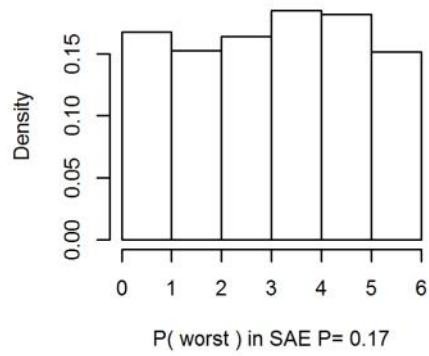
Rank of treatment Mep100



Rank of treatment Mep250



Rank of treatment Mep750



Rank of treatment Res3

