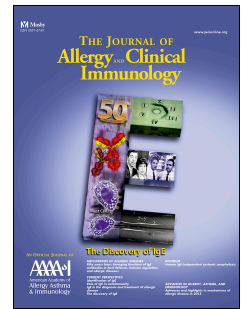


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Mepolizumab Efficacy in Patients with Severe Eosinophilic Asthma Receiving Different Controller Therapies

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1 **Mepolizumab Efficacy in Patients with Severe Eosinophilic Asthma**
2 **Receiving Different Controller Therapies**

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16 clinicaltrials.gov ID: NCT01691521)

17

18 **Clinical implications:** Add-on treatment with mepolizumab demonstrates benefits for
19 patients with severe eosinophilic asthma across a broad range of therapeutic backgrounds.

20 **Capsule summary:** This post hoc analysis of the MENSA study demonstrates that
21 mepolizumab reduced the annualized exacerbation rate relative to placebo in patients with
22 severe eosinophilic asthma irrespective of the number or type of background controller
23 therapies.

24 **Key words:** Mepolizumab, eosinophil, interleukin-5, asthma, tiotropium, exacerbation,
25 standard of care, background controller therapy

26 **Abbreviations:** GINA, Global Initiative for Asthma ; ICS, inhaled corticosteroids; IL,
27 interleukin; IV, intravenous; LABA, long-acting beta2 agonists; SC, subcutaneous

28

29 To the Editor

30 Severe asthma is a heterogeneous disease that can require multiple treatments to help
31 maintain control of symptoms and exacerbations.¹ Severe eosinophilic asthma is
32 characterized by increased eosinophilic inflammation, recurrent exacerbations, and poor
33 disease control.² Standard of care for patients with severe eosinophilic asthma includes the
34 use of inhaled corticosteroids (ICS) and long-acting beta2 agonists (LABA) with the option of
35 a number of further add-on treatments to maintain or improve asthma control.¹

36 Consequently, patients with severe asthma who are at Step 4 and 5 of treatment according
37 to the Global Initiative for Asthma (GINA) guidelines¹ may have a considerable treatment
38 burden, potentially requiring three or four controller therapies in the form of inhalers, oral
39 medications, or monthly injections. Mepolizumab is an anti-interleukin(IL)-5 monoclonal
40 antibody add-on therapy that has recently been added to Step 5 of the GINA guidelines for
41 patients with severe eosinophilic asthma.¹ Although, mepolizumab has been previously
42 shown to reduce exacerbation frequency and the corticosteroid dose in patients with severe
43 eosinophilic asthma compared with placebo when added to standard of care,³⁻⁵ the
44 influence of the background controller therapy has not been examined. Through this post
45 hoc analysis of the MENSA study (NCT01691521), we aimed to determine whether the
46 efficacy of mepolizumab was affected by the number or type of background controller
47 therapies taken by patients.

48 The MENSA study, a 32-week, randomized, double-blind study (N=576), assessed
49 mepolizumab efficacy in patients with severe eosinophilic asthma as an add-on therapy to
50 standard of care (ICS plus ≥ 1 controller therapy). In these patients, MENSA showed that
51 mepolizumab was efficacious at reducing exacerbation rates compared with placebo.⁴ In
52 MENSA, patients with severe eosinophilic asthma, aged ≥ 12 years old, with a history of ≥ 2
53 exacerbations in the previous year received 75 mg intravenous (IV) or 100 mg subcutaneous
54 (SC) mepolizumab or placebo every 4 weeks. Patients were allowed uninterrupted
55 concurrent use of a broad range of asthma treatments (background therapy), with the
56 exception of other biologics (e.g. omalizumab). Clinically significant exacerbations were
57 defined as those requiring administration of systemic corticosteroids for ≥ 3 days (needing a
58 ≥ 2 -fold increase in dose for those patients already on maintenance oral corticosteroids),
59 and/or an emergency room visit/hospitalization.⁴ In this post hoc analysis of MENSA, we
60 assessed the annualized rate of clinically significant exacerbations in patients receiving

mepolizumab or placebo according to the number (ICS plus 1, 2, or ≥ 3 controllers) and type (ICS, LABA, tiotropium, or other [leukotriene receptor antagonists, xanthine or nedocromil/cromolyn sodium]) of background controller therapies using negative binomial regression models with adjustment for covariates. Due to comparable bioequivalence and efficacy, mepolizumab doses (100 mg SC/75 mg IV) were pooled in this analysis. Data was available for 561 patients for this analysis. Analyses of exacerbation rates, lung function, and blood eosinophil counts by number and type of background therapy for the 100 mg SC dose only and the pooled mepolizumab doses are available in the supplementary appendix.

As might be expected, exacerbation rates in the placebo group were highest in patients on the greatest number of controller therapies (Figure 1 and Figure E1), potentially reflecting the higher disease burden and more severe asthma symptoms in these patients. Clinically relevant reductions in exacerbation rates were seen with mepolizumab relative to placebo in patients with severe eosinophilic asthma irrespective of the number of controller therapies (Figure 1 and Figure E1). Furthermore, whilst reductions in exacerbation rates with mepolizumab versus placebo were identified in all groups, the largest reduction was seen in the ICS+ ≥ 3 controller therapy subgroup, in which patients were likely to have the greatest burden of disease. This highlights that mepolizumab may be an effective treatment option for even the most difficult to treat patients with severe eosinophilic asthma.

In addition to the number of controller therapies, we also assessed whether the type of background controller therapy (ICS, LABA, tiotropium, or other) affected the efficacy of mepolizumab. Since tiotropium, a long-acting anti-cholinergic bronchodilator add-on therapy, has been recently added to Step 4 and 5 of the GINA guidelines for patients with a history of asthma exacerbations, it was included in the analysis.⁶ In all assessed combinations of concomitant controller medication types, we observed clinically relevant reductions in exacerbation rates with mepolizumab added to standard of care relative to placebo. For patients receiving ICS, LABA and tiotropium in combination (inhaled triple therapy), mepolizumab reduced exacerbation rates by 65–70% relative to placebo and by 56–62% if an additional controller was taken (Figure 2 and Figure E2). One limitation of this analysis is that the number of patients in each subgroup was low; however, reductions in exacerbation rates reported for patients receiving other therapy combinations were comparable, ranging 47–52% and 47–60% (Figure 2 and Figure E2, respectively). This demonstrates that mepolizumab was effective in reducing exacerbation rates compared

with placebo in patients with severe eosinophilic asthma, irrespective of the type of controller therapies taken by these patients, whether they are ICS, LABA, tiotropium, other controllers, or a combination of these therapies.

Overall, our analysis has shown that mepolizumab reduced exacerbation rates compared with placebo in patients with severe eosinophilic asthma on low or high numbers of controller therapies. This suggests that mepolizumab can be a beneficial add-on therapy to reduce the rate of exacerbations even if a combination of numerous other therapies has not been effective in these patients. Furthermore, results for those receiving the licensed 100 mg SC dose were consistent with the results found when pooling the mepolizumab doses (Figures E1 and E2). Results presented here demonstrate that mepolizumab was effective even in patients who are currently receiving maximal therapy with combinations of ICS, LABA, tiotropium, and other controllers. This may be due to the targeted mechanism of action of mepolizumab, which reduces blood and sputum eosinophil counts through the neutralization of IL-5,³⁻⁵ specifically addressing the eosinophilic inflammation in the target population of patients with severe eosinophilic asthma and a history of 2 or more exacerbations in the past year despite maximal therapy. Of note, baseline blood eosinophil counts were comparable across all the subgroups studied and were reduced and remained low at Week 32 irrespective of the number and type of controllers used (Table E2).

The results from this post hoc analysis indicate that add-on treatment with mepolizumab demonstrates benefits for patients with severe eosinophilic asthma across a broad range of therapeutic backgrounds.

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editing and referencing) was provided by Elizabeth Hutchinson PhD, CMPP, at Fishawack Indicia Ltd, UK, and was funded by GSK.

Conflicts of interests

FCA, RGP, SGS, and SWY are all employees of GSK and FCA, RGP, and SWY own stock in GSK.

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Figure legends

Figure 1. Reductions in exacerbation rate according to the number of standard of care asthma controller therapies taken in addition to mepolizumab or placebo

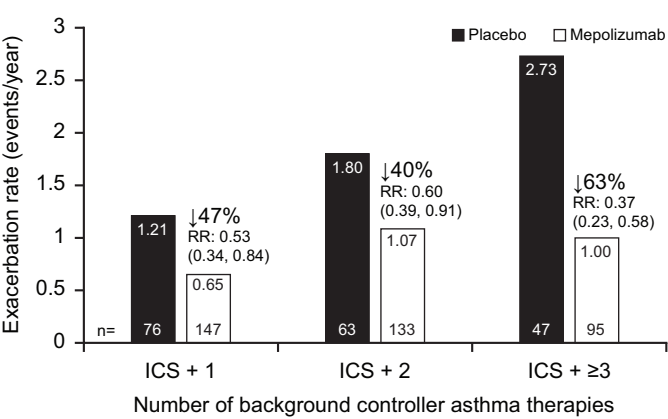
ICS, inhaled corticosteroid; RR, rate ratio.

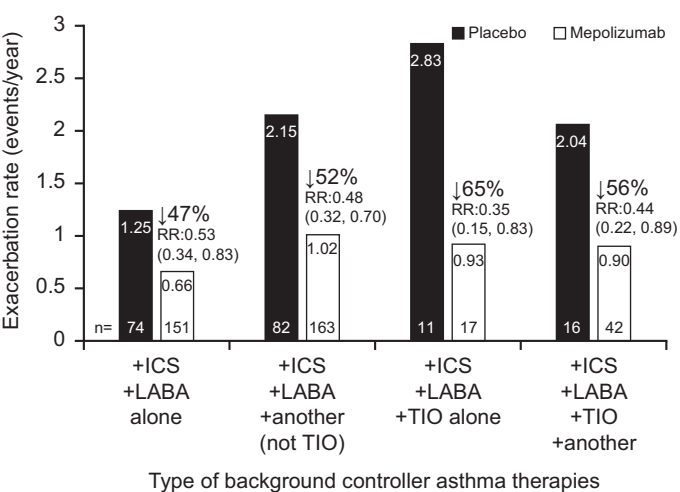
95% confidence intervals shown in brackets after RR; number of patients presented at the bottom of each bar.

Figure 2. Reductions in exacerbation rate according to the type of standard of care asthma controller therapies taken in addition to mepolizumab or placebo

ICS, Inhaled Corticosteroid; LABA, long-acting beta2 agonist; TIO, tiotropium; RR, rate ratio.

95% confidence intervals shown in brackets after RR; number of patients presented at the bottom of each bar; other could be one or more of leukotriene receptor antagonists, xanthine or nedocromil/cromolyn sodium; five patients did not report a LABA controller and therefore are not included in Figure 2



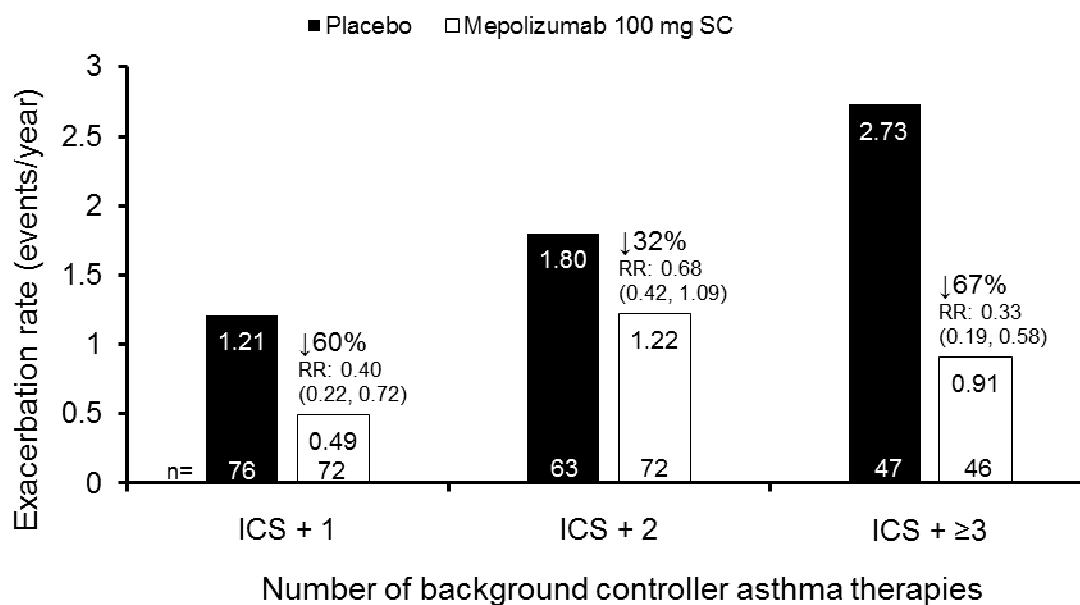


Supplement for Albers *et al.* – Mepolizumab Efficacy in Patients with Severe Eosinophilic Asthma Receiving Different Controller Therapies

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Exacerbation rate results

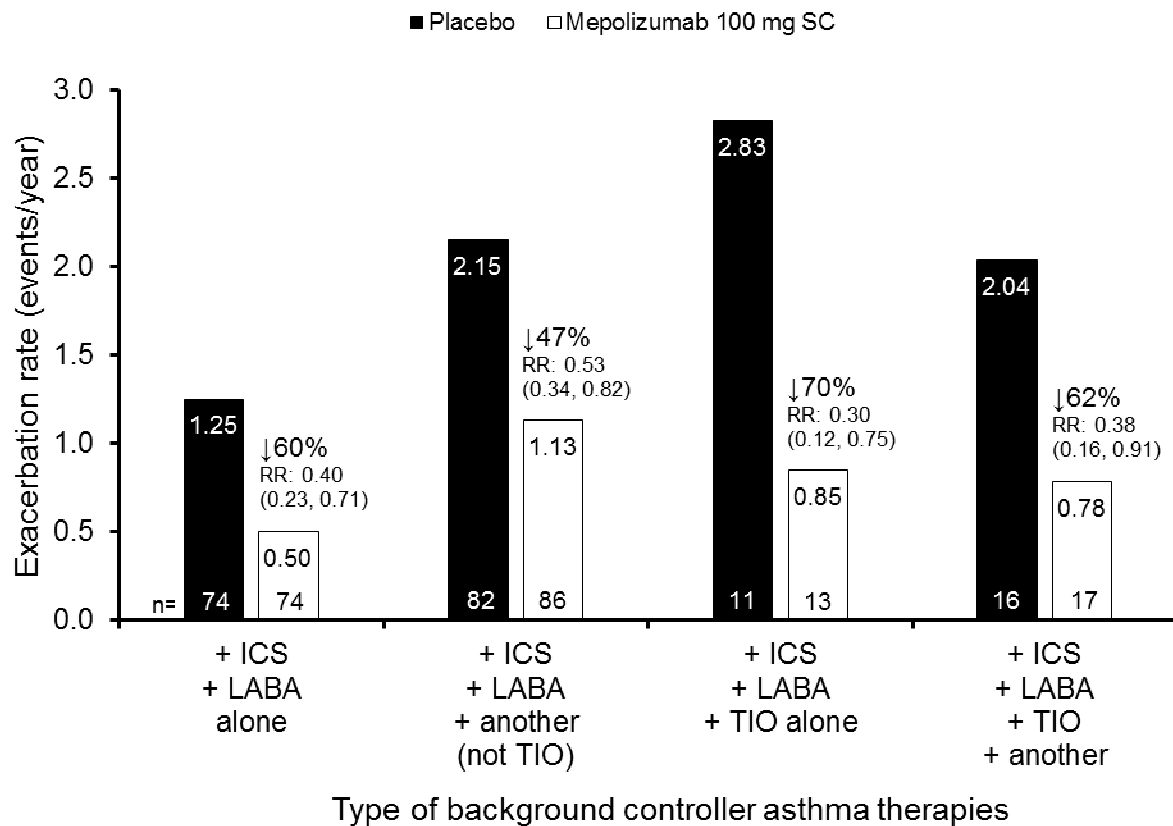
Supplementary Figure E1. Reductions in exacerbation rate according to the number of standard of care asthma controller therapies taken in addition to 100 mg SC mepolizumab or placebo.



ICS, inhaled corticosteroids; RR, rate ratio; SC, subcutaneous

Reductions presented as RR (95% confidence interval); patient numbers are presented at the bottom of each bar.

Supplementary Figure E2. Reductions in exacerbation rate according to the type of standard of care asthma controller therapies taken in addition to 100 mg SC mepolizumab or placebo.



ICS, inhaled corticosteroids; LABA, long-acting beta2 agonists; RR, rate ratio; SC, subcutaneous; TIO, tiotropium

Reductions presented as RR (95% confidence interval); patient numbers are presented at the bottom of each bar; other could be one or more of leukotriene receptor antagonists, xanthine or nedocromil/cromolyn sodium; five patients did not report a LABA controller and, therefore, are not included in Figure E2.

FEV₁ results

Supplementary Table E1. Pre-bronchodilator FEV₁ (mL) at baseline and Week 32 in patients on different numbers and types of background standard of care asthma controller therapies taken in addition to placebo or mepolizumab.

Analysis according to:		Placebo FEV ₁ , mL, mean (SD)		Mepolizumab 100 mg SC FEV ₁ , mL, mean (SD)		Mepolizumab (all doses) FEV ₁ , mL, mean (SD)	
		Baseline	Week 32	Baseline	Week 32	Baseline	Week 32
Background controller number	ICS + 1	n=76 1819 (573.5)	n=69 1888 (617.5)	n=72 1809 (640.1)	n=71 2015 (689.3)	n=147 1864 (676.8)	n=143 2027 (718.3)
	ICS + 2	n=63 1953 (683.8)	n=60 2004 (611.9)	n=72 1743 (674.5)	n=65 1977 (794.8)	n=133 1772 (659.5)	n=120 2025 (757.7)
	ICS + ≥3	n=47 1740 (588.7)	n=45 1908 (619.8)	n=46 1625 (675.4)	n=45 1838 (701.0)	n=95 1703 (714.2)	n=88 1894 (738.6)
Background controller type	ICS + LABA alone	n=74 1818 (581.3)	n=67 1889 (626.4)	n=74 1812 (640.8)	n=73 2049 (712.8)	n=151 1888 (700.0)	n=148 2069 (748.3)
	ICS + LABA + another (not TIO)	n=82 1945 (685.2)	n=78 2007 (618.7)	n=86 1762 (691.6)	n=80 1937 (750.3)	n=163 1757 (651.5)	n=147 1975 (749.2)
	ICS + LABA + TIO alone	n=11 1547 (511.5)	n=11 1672 (434.0)	n=13 1621 (607.3)	n=12 1779 (582.0)	n=17 1580 (641.6)	n=16 1848 (621.6)
	ICS + LABA + TIO + another	n=16 1654 (459.3)	n=15 1955 (694.9)	n=17 1402 (573.3)	n=16 1774 (811.5)	n=42 1662 (729.6)	n=39 1839 (686.1)

FEV₁, Forced Expiratory Volume in the first second; ICS, inhaled corticosteroids; LABA, long-acting beta2 agonists; SC, subcutaneous; SD, standard deviation; TIO, tiotropium

Other could be one or more of leukotriene receptor antagonists, xanthine or nedocromil/cromolyn sodium; five patients did not report a LABA controller and, therefore, are not included when summarizing by background controller type.

Blood eosinophil count results

Supplementary Table E2. Blood eosinophil count (cells/ μ L) at baseline and Week 32 in patients on different numbers and types of background standard of care asthma controller therapies taken in addition to placebo or mepolizumab.

Analysis according to:		Placebo Eosinophil count, cells/ μ L, geometric mean (SD logs)		Mepolizumab 100 mg SC Eosinophil count, cells/ μ L, geometric mean (SD logs)		Mepolizumab (all doses) Eosinophil count, cells/ μ L, geometric mean (SD logs)	
		Baseline	Week 32	Baseline	Week 32	Baseline	Week 32
Background controller number	ICS + 1	n=76 320 (0.849)	n=66 290 (0.871)	n=71 270 (0.920)	n=71 50 (0.865)	n=145 290 (0.885)	n=139 50 (0.918)
	ICS + 2	n=63 290 (0.851)	n=60 290 (0.880)	n=71 280 (1.071)	n=64 40 (0.917)	n=131 270 (1.071)	n=119 50 (0.928)
	ICS + ≥ 3	n=46 350 (1.026)	n=42 200 (1.091)	n=46 360 (1.144)	n=45 30 (1.043)	n=94 310 (1.104)	n=88 30 (0.945)
Background controller type	ICS + LABA alone	n=74 320 (0.854)	n=65 290 (0.877)	n=73 280 (0.915)	n=72 50 (0.859)	n=149 290 (0.886)	n=143 50 (0.902)
	ICS + LABA + another (not TIO)	n=81 290 (0.931)	n=76 260 (1.021)	n=86 310 (0.941)	n=80 40 (0.884)	n=161 290 (1.028)	n=147 40 (0.943)
	ICS + LABA + TIO alone	n=11 320 (0.836)	n=11 240 (0.737)	n=12 190 (1.454)	n=12 60 (1.089)	n=16 200 (1.279)	n=16 50 (0.982)
	ICS + LABA + TIO + another	n=16 460 (0.966)	n=14 250 (1.046)	n=17 390 (1.538)	n=16 40 (1.306)	n=42 310 (1.243)	n=39 40 (0.988)

ICS, inhaled corticosteroids; LABA, long-acting beta2 agonists; SC, subcutaneous; SD, standard deviation; TIO, tiotropium

Other could be one or more of leukotriene receptor antagonists, xanthine or nedocromil/cromolyn sodium; five patients did not report a LABA controller and therefore are not included when summarizing by background controller type.

