Meta-analysis of asthma-related hospitalization in mepolizumab studies of severe eosinophilic asthma

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Background: Studies show that mepolizumab can reduce the frequency of clinically significant exacerbations in patients with severe eosinophilic asthma, compared with placebo. However, important events such as hospitalizations and emergency room visits are rare and difficult to characterize in single studies.

Objective: We sought to compare hospitalization or hospitalization and/or emergency room visit rates in patients with severe eosinophilic asthma treated with mepolizumab or placebo in addition to standard of care for at least 24 weeks.

Methods: This study was conducted and reported in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses statement. PubMed and the GSK Clinical Study Register were searched for suitable studies. The primary end points were the rate of exacerbations requiring hospitalization and the rate of exacerbations requiring hospitalization/emergency room visit. The proportion of patients with 1 or more event was also assessed. All mepolizumab doses were combined and individual patient-level data were analyzed.

Results: Four studies (n = 1388) were eligible for inclusion. Mepolizumab significantly reduced the rate of exacerbations requiring hospitalization (relative rate, 0.49; 95% CI, 0.30-0.80; $P = .004$) and hospitalization/emergency room visit (relative rate, 0.49; 95% CI, 0.33-0.73; $P < .001$) versus placebo. Significant reductions of 45% and 38% were also observed for the proportion of patients experiencing 1 or more hospitalization and hospitalization and/or emergency room visit, respectively.

Conclusions: Mepolizumab approximately halved exacerbations requiring hospitalization and/or emergency room visits compared with placebo in patients with severe eosinophilic asthma. This treatment addresses a key outcome in a patient population with a high unmet need (GSK Study 204664). (J Allergy Clin Immunol 2016;■■■:■■■-■■■.)

Key words: *Antiasthmatic agents, exacerbation, emergency service, hospital, IL-5, mepolizumab, severe eosinophilic asthma, meta-analysis*

Severe asthma is a heterogeneous disease comprising several diverse phenotypic subgroups.[1,2] One subgroup is characterized by increased blood and sputum eosinophil counts.[3,4] Typically, these patients have frequent exacerbations and suboptimal asthma control despite intensive use of guideline-directed asthma therapies, including the use of maintenance systemic corticosteroids in many patients.[1] Asthma exacerbations are often of sufficient severity to require hospitalization or a visit to the emergency room,[5,6] accounting for a large proportion of asthma-related morbidity, mortality, and health care costs.[7-11] The prevention of severe asthma exacerbations is therefore a major goal of asthma management.[8]

Mepolizumab is a humanized mAb against IL-5, which primarily inhibits eosinophilic inflammation,[12,13] and has been shown to decrease sputum and blood eosinophil levels in patients with severe eosinophilic asthma.[3,14,15] To date, all the randomized, placebo-controlled studies of mepolizumab in this patient population have reported a reduction compared with placebo in the frequency of *clinically significant exacerbations*, defined as worsening of asthma that required use of/increased use of systemic corticosteroids.[3,15-18] Although this definition includes exacerbations that require hospitalization and/or a visit to the emergency room, the sample sizes of individual studies were insufficient for assessing these relatively infrequent events. The aim of this meta-analysis was therefore to assess the rate of exacerbations requiring hospitalization or an emergency room visit in clinical studies of mepolizumab compared with placebo in patients with severe eosinophilic asthma.

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The meta-analysis (study ID 204664) and studies in this meta-analysis (MEA112997 [NCT01000506], MEA115588 [NCT01691521], MEA115575 [NCT01691508], and CRT110184 [ISRCTN75169762]) were funded by GSK (study no. 204644). Medical writing support by Fishawack Indicia Ltd was also funded by GSK.

Disclosure of potential conflict of interest: S. W. Yancey, O. N. Keene, B. Mayer, and N. B. Gunsoy have received nonfinancial support for this work from GSK, are employed by GSK and receive stock/stock options from GSK. H. G. Ortega has received nonfinancial support for this work from GSK, was employed by GSK during the conduct of this study, and holds stock/stock options in GSK. C. E. Brightling has received consultancy and research income via his institution from GSK, AstraZeneca/MedImmune, Novartis, Genentech/Roche, Chiesi, and Boehringer Ingelheim. E. R. Bleecker has performed clinical trials administered by his employer, Wake Forest School of Medicine, for AstraZeneca, MedImmune, Boehringer Ingelheim, Pfizer, Cephalon/Teva, Forest, Genentech, GSK, Johnson & Johnson (Jansen), Novartis, and Sanofi and has also served as a paid consultant for AstraZeneca, MedImmune, Boehringer Ingelheim, Pfizer, GSK, Forest, Novartis, Regeneron, and Sanofi. P. Haldar has received nonfinancial support for this work from GSK. I. D. Pavord has received nonfinancial support for this work from GSK; honoraria for speaking at sponsored meetings from AstraZeneca, Boehringer Ingelheim, Aerocrine, Almirall, Novartis, and GSK; payment for organizing an educational event from AstraZeneca; advisory board honoraria from Almirall, Genentech, Regeneron, AstraZeneca, Boehringer Ingelheim, GSK, Merck & Co., Schering-Plough, Novartis, Mylan Specialty (Dey Pharma), Napp Pharmaceuticals, and Respivert; and sponsorship to attend international scientific meetings from Boehringer Ingelheim, GSK, AstraZeneca, and Napp Pharmaceuticals.

Received for publication February 8, 2016; revised July 25, 2016; accepted for publication August 9, 2016.

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0091-6749

http://dx.doi.org/10.1016/j.jaci.2016.08.008

Abbreviations used
IV: Intravenous
OCS: Oral corticosteroid
SC: Subcutaneous

METHODS

This meta-analysis was conducted according to Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement,[19] including search strategy, selection criteria, data extraction, and data analysis based on a defined review protocol (GSK etrack no. 204664[20]).

Identification of eligible studies

Studies eligible for inclusion were any randomized study comparing mepolizumab with placebo in patients with severe eosinophilic asthma of at least 24 weeks duration that involved at least 6 doses of the study drug. Studies were identified using a search strategy on PubMed of ("clinical trial"[Publication Type]) AND (mepolizumab[Title]) AND (asthma[Title]) and a search of completed studies on the GSK clinical trial register of "mepolizumab" and "asthma." Clinicaltrials.gov was also searched to find any completed, unpublished studies that met the inclusion criteria. These searches were carried out in May 2015.

Data extraction and outcome measures

Individual patient-level data were obtained from the GSK clinical trial databases and from the relevant investigating centers. Data used in these studies included study design, patient population, follow-up period for exacerbations, study drug and dose, number of hospitalizations, and number of emergency room visits. The intent-to-treat population was analyzed, and comprised all randomized patients who received 1 or more dose of study medication. Asthma exacerbations reported from the start of treatment until completion of the study or up to withdrawal (but less than 4 weeks after the last dose of study medication) were included in the analysis. Asthma exacerbations separated by less than 7 days were considered a continuation of the same exacerbation.[21] Hospitalization included intensive care unit admission and intubation.

The primary end points of this meta-analysis were (1) annual rate of exacerbations requiring hospitalization and (2) annual rate of exacerbations requiring a hospitalization and/or an emergency room visit. The proportion of patients with 1 or more exacerbation requiring hospitalization, the proportion of patients with 1 or more exacerbation requiring hospitalization/emergency room visit, and time to first exacerbation requiring hospitalization and hospitalization and/or emergency room visit were also assessed. Because previous studies have shown similar reductions in exacerbations based on a 10-fold dose range of mepolizumab or by a route of administration (intravenous [IV] vs subcutaneous [SC]),[3,17] all mepolizumab doses were combined for analysis and compared with placebo. In addition, a prespecified sensitivity analysis was carried out using only comparable doses of mepolizumab (75 mg IV and 100 mg SC).

Statistical analysis

The meta-analysis was conducted using SAS version 9.3 (SAS Institute, Cary, NC). The number of exacerbations requiring hospitalization/emergency room visit and the number of exacerbations requiring hospitalization were assumed to follow a negative binomial distribution.[22] Meta-analysis of relative rates of exacerbations was performed using the inverse variance fixed effects method to combine estimated rate ratios and standard errors from each individual study. Meta-analysis of relative risks for the proportion of patients with at least 1 exacerbation was performed using Mantel-Haenszel methods. Kaplan-Meier curves of time to first exacerbation were constructed using a weighted average of the curves for the individual studies, with Mantel-Haenszel weights for each study.[23] All outcomes were reported with 95% CIs. Statistical heterogeneity was tested with the I^2 statistic, with $I^2 \leq 50\%$ indicating no significant heterogeneity.[24]

RESULTS

Description of studies

A summary of the mepolizumab studies identified through the search strategy is provided in Fig 1 and in Table E1 in this article's Online Repository at www.jacionline.org. A total of 12 potentially eligible articles were identified after removal of duplicates.[3,15-18,25-31] Four studies were identified as meeting the inclusion criteria: DREAM (NCT01000506),[3] MENSA (NCT01691521),[17] SIRIUS (NCT01691508),[16] and the 2009 study by Haldar et al[15] (ISRCTN75169762). The study by Nair et al[18] was excluded because the treatment period was less than 24 weeks and included 5 administrations of the study drug rather than the 6 required to meet the prespecified inclusion criteria. Furthermore, there were no exacerbations requiring hospitalization or an emergency room visit reported in this study, and, therefore, inclusion of this study would not affect the results. SIRIUS could not be included in the analysis of rates of exacerbation requiring hospitalization because there were no exacerbations requiring hospitalization in the mepolizumab arm of the study, therefore no variability could be associated with the rate reduction for this study. Similarly, Haldar et al's 2009 study could not be included in the analysis of hospitalization/emergency room visit rates because data were not available for emergency room visits. The sensitivity analysis excluded the SIRIUS study because it was primarily an oral-sparing study and excluded Haldar et al's 2009 study because the study included only the 750 mg IV dose.

Most of the inclusion criteria for DREAM, MENSA, SIRIUS, and Haldar et al's 2009 study were similar (Table E1), with the following differences of note: Haldar et al[15] included only adults (18 years or older), whereas DREAM, MENSA, and SIRIUS included patients 12 years or older; DREAM, MENSA, and Haldar et al[15] included only those patients who had 2 or more exacerbations requiring corticosteroid treatment in the previous year, whereas SIRIUS required the use of maintenance oral corticosteroids (OCSs); definition of eosinophilic asthma in DREAM was not confined to peripheral blood eosinophil levels; Haldar et al[15] used sputum eosinophils to define eosinophilic asthma. Patients in all 4 studies met the American Thoracic Society definition of severe asthma,[4] requiring treatment with high-dose inhaled corticosteroids plus a second controller therapy to prevent it from becoming uncontrolled or which remains uncontrolled despite this therapy.

Across all studies, 1388 patients received either mepolizumab intravenously (75 mg, 250 mg, or 750 mg), mepolizumab subcutaneously (100 mg), or placebo approximately every 4 weeks in addition to their baseline standard of care (which included high-dose inhaled corticosteroids and additional asthma control medications). Baseline demographic characteristics of the patients in these studies are described in Table I. The mean age of the patients in each study was approximately 50 years, with a mean asthma duration of 17 to 24 years. Baseline blood eosinophil counts were similar across all studies (with geometric means ranging from 230 to 350 cells/μL), and the mean number of severe exacerbations in the previous year ranged between 2.9 and 5.5. Overall, 36% of patients were on maintenance OCS at the start of the studies. Lung function,

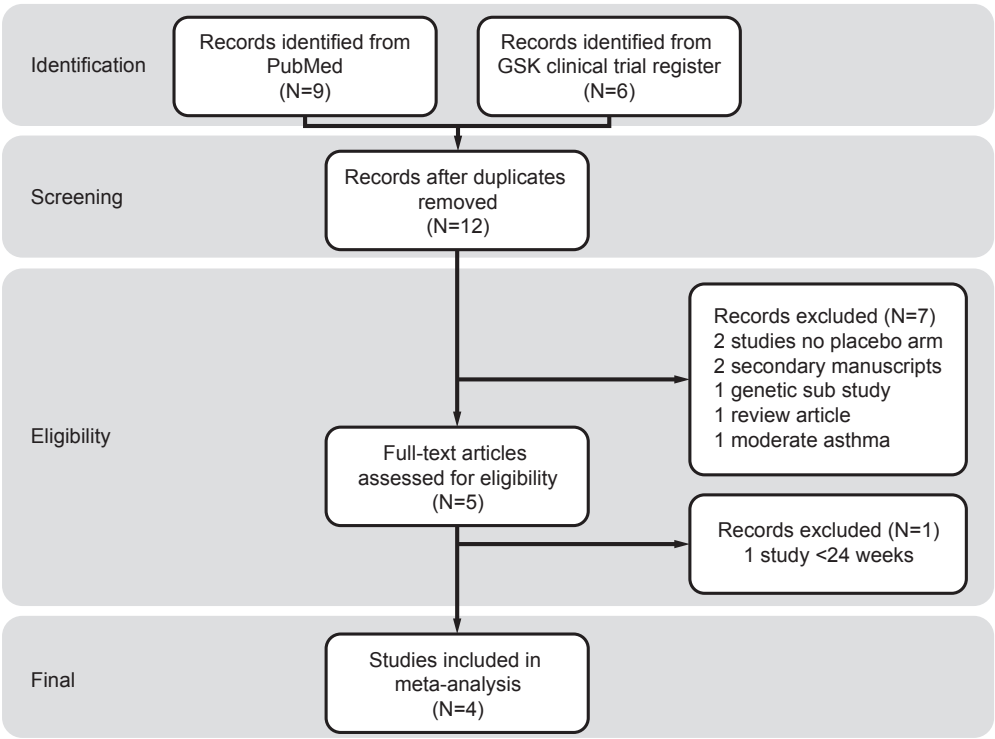

FIG 1. Flow of study identification, inclusion, and exclusion. Studies excluded: GSK Study 114092 (NCT01366521),[25] GSK Study 115661 (NCT01842607),[26] Prazma et al,[27] Haldar et al,[28] GSK study 201318 (genetic substudy),[29] Antoniu,[30] Flood-Page et al,[31] and Nair et al.[18]

characterized by baseline mean percent predicted prebronchodilator and postbronchodilator FEV_1, varied across studies from 58% to 75% and 68% to 78%, respectively.

Risk of bias in individual studies

All 4 studies were considered to have a low risk of bias. The study publications described appropriate methods for randomization, including sequence generation, allocation concealment, and blinding. In addition, the databases contained appropriate outcome data for exacerbations requiring hospitalization and/or an emergency room visit. There was no risk of publication bias because all studies with mepolizumab were known to the authors. In addition, clinicaltrials.gov did not reveal any completed, unpublished studies that met the inclusion criteria.

Exacerbations

When combining the results from the studies, 5.6% versus 9.5% of patients receiving mepolizumab (all doses, pooled) or placebo, respectively, experienced 1 or more exacerbation requiring hospitalization, increasing to 9.5% versus 14.1% for combined hospitalization/emergency room visits (Table II). Compared with placebo, there was a significant reduction of 45% in the proportion of patients experiencing an exacerbation requiring hospitalization (relative risk, 0.55; 95% CI, 0.36-0.83; $P = .004$) and a significant reduction of 38% in the proportion of patients experiencing an exacerbation requiring hospitalization/emergency room visits with mepolizumab (relative risk, 0.62; 95% CI, 0.45-0.86; $P = .004$) (Fig 2, *A*). Similar results were obtained in the sensitivity analysis for patients on the pooled 75 mg IV/100 mg SC doses of mepolizumab with a reduction of 38% ($P = .066$) for hospitalization and 43% ($P = .004$) for hospitalization/emergency room visits compared with placebo (Fig 2, *B*). Some patients experienced more than 1 exacerbation requiring hospitalization and/or an emergency room visit. For example, in DREAM, 11 of 155 (7%) patients on placebo had more than 1 exacerbation requiring hospitalization/emergency room visit and 6 of 155 (4%) had more than 1 exacerbation requiring hospitalization.

Kaplan-Meier curves of time to first exacerbation requiring hospitalization and of time to first exacerbation requiring hospitalization or an emergency room visit are provided in Fig 3.

Analysis of rate of exacerbations shows that exacerbations requiring hospitalization were significantly reduced by 51% (relative rate, 0.49; 95% CI, 0.30-0.80; $P = .004$) for patients on mepolizumab (all doses, pooled), compared with placebo (Fig 4). Similarly, exacerbations requiring hospitalization and/or an emergency room visit were significantly reduced by 51% (relative rate, 0.49; 95% CI, 0.33-0.73; $P < .001$). This effect was also observed in the sensitivity analysis for the mepolizumab 75 mg IV/100 mg SC pooled doses, with a significant reduction of 48% ($P = .027$) in hospitalization rates and 54% ($P = .001$) in hospitalization/emergency room visit rates, compared with placebo (Fig E1). In all analyses, the results were consistent between individual studies, with no heterogeneity shown for each outcome across the studies ($I^2 = 0\%$). Absolute rates per year of exacerbations requiring hospitalization and hospitalization and/or an emergency room visit after treatment with mepolizumab or placebo are also presented in Table III.

TABLE I. Patients' characteristics from studies of mepolizumab of at least 24-wk duration

	DREAM[3] (N = 616)				MENSA[17] (N = 576)			SIRIUS[16] (N = 135)		Haldar et al[15] (N = 61)	
	Mepo				Mepo			Mepo		Mepo	
Characteristic	75 IV (n = 153)	250 IV (n = 152)	750 IV (n = 156)	Placebo (n = 155)	75 IV (n = 191)	100 SC (n = 194)	Placebo (n = 191)	100 SC (n = 69)	Placebo (n = 66)	750 IV (n = 29)	Placebo (n = 32)
Age (y) (range)	50 (23-69)	49 (15-74)	49 (19-69)	46 (20-68)	50 (13-82)	51 (12-81)	49 (12-76)	50 (16-74)	50 (28-70)	48 (21-63)	50 (24-72)
Asthma duration (y), mean ± SD	19 ± 14	20 ± 14	19 ± 15	18 ± 14	20 ± 14	21 ± 13	20 ± 15	17 ± 12	20 ± 14	20 ± 16	22 ± 15
On maintenance OCS, n (%)	46 (30)	50 (33)	47 (30)	45 (29)	48 (25)	52 (27)	44 (23)	69 (100)	66 (100)	16 (57*)	17 (53)
Prebronchodilator FEV_1 (% predicted), mean ± SD	60 ± 16	59 ± 17	61 ± 16	59 ± 15	61 ± 18	59 ± 18	62 ± 18	60 ± 17	58 ± 19	75 ± 22	72 ± 20
Prebronchodilator FEV_1:FVC ratio (%), mean ± SD	64 ± 11	63 ± 13	63 ± 13	63 ± 12	64 ± 13	63 ± 13	64 ± 13	63 (12)	61 (12)	69 (11)	66 (12)
Postbronchodilator FEV_1 (% predicted), mean ± SD	71 ± 18	71 ± 17	70 ± 18	71 ± 18	71 ± 19	70 ± 18	72 ± 17	72 ± 20	68 ± 21	78 ± 21	78 ± 24
Postbronchodilator FEV_1:FVC ratio (%), mean ± SD	68 ± 12	66 ± 13	68 ± 20	67 ± 12	67 ± 13	66 ± 13	67 ± 12	67 ± 13	64 ± 13	72 ± 10	68 ± 14
Baseline blood eosinophil count ($\times 10^9$/L)	0.25 (0.95)†	0.23 (1.20)†	0.25 (0.93)†	0.28 (1.01)†	0.28 (0.99)†	0.29 (1.05)†	0.32 (0.94)†	0.25 (1.25)†	0.23 (1.00)†	0.32 (0.38)‡	0.35 (0.30)‡
Exacerbations in year before study start§	3.7 (3.1)	3.4 (2.4)	3.5 (2.8)	3.7 (3.8)	3.5 (2.2)	3.8 (2.7)	3.6 (2.8)	3.3 (3.4)	2.9 (2.8)	5.5	5.0
Exacerbations requiring admission in year before study start, n (%)	35 (23)	36 (24)	39 (25)	40 (26)	41 (21)	33 (17)	35 (18)	14 (20)	9 (14)	8 (28)‖	10 (31)‖

Unless specified, values are means.
FVC, Forced vital capacity; *Mepo*; mepolizumab.
*N = 28.
†Geometric mean ($\log_e$ SD).
‡Geometric mean (log10 SD).
§Rate per patient.
‖Based on any admissions to the intensive care unit before the study.

DISCUSSION

In this meta-analysis of 4 placebo-controlled studies ranging from 24- to 52-week duration, mepolizumab treatment resulted in an approximate halving of exacerbations requiring hospitalization or combined hospitalization and emergency room visit compared with placebo in patients with severe eosinophilic asthma already receiving maximal standard of care therapy.[4] This effect was observed in the pooled analysis of all doses of mepolizumab and in the sensitivity analysis for the 75 mg IV and 100 mg SC doses only, showing that the 100 mg SC dose and the comparable 75 mg IV dose achieved this same significant effect. Similarly, the proportion of patients experiencing these events was reduced by 45% for exacerbations requiring hospitalization and by 38% for exacerbations requiring hospitalization and/or emergency room visit for all doses of mepolizumab compared with placebo. In terms of absolute change, treatment with mepolizumab resulted in patients experiencing an exacerbation requiring hospitalization or hospitalization/emergency room visit every 14 and 7 years, respectively, compared with every 7 and 3 years, respectively, with placebo and standard of care. These results suggest an important clinical benefit for mepolizumab on a background of appropriate standard therapy in reducing major rare events such as hospitalizations and visits to the emergency room in severe eosinophilic asthma. This may also have economic benefits because patients with severe asthma place a high financial burden on health care systems, with hospitalizations and emergency room visits contributing a larger proportion of these costs compared with patients with nonsevere asthma.[32]

Meta-analyses are important tools for assessing treatment effects related to important, but infrequent end points. They have increased power to detect differences compared with individual studies and improve estimates of treatment effects. This study has several strengths. First, all the studies included were randomized, placebo-controlled studies. Second, the design of the meta-analysis meant that the authors had access to individual patient-level data. Third, there was low heterogeneity in the outcomes between the individual studies. Fourth, only those studies that included patients with severe eosinophilic asthma were included. A recent Cochrane review of the efficacy of

TABLE II. Proportion of patients with more than 1 exacerbation requiring hospitalization or hospitalization/ER visit

	Placebo					Mepolizumab (all doses, pooled)					Mepolizumab (75 mg IV/100 mg SC)				
		Hospitalization		Hospitalization/ ER visit			Hospitalization		Hospitalization/ ER visit			Hospitalization		Hospitalization/ ER visit	
Study	N	n	%	n	%	N	n	%	n	%	N	n	%	n	%
DREAM	155	17	11.0	27	17.4	461	37	8.0	56	12.1	153	12	7.8	15	9.8
MENSA	191	13	6.8	24	12.6	385	14	3.6	28	7.3	385	14	3.6	28	7.3
SIRIUS	66	7	10.6	7	10.6	69	0	0	3	4.3	—	—	—	—	—
Haldar et al[15]	32	5	15.6	—	—	29	2	6.9	—	—	—	—	—	—	—
Combined	444	42	9.5	58	14.1*	944	53	5.6	87	9.5†	538	26	4.8	43	8.0

ER, Emergency room.
*N = 412.
†N = 915.

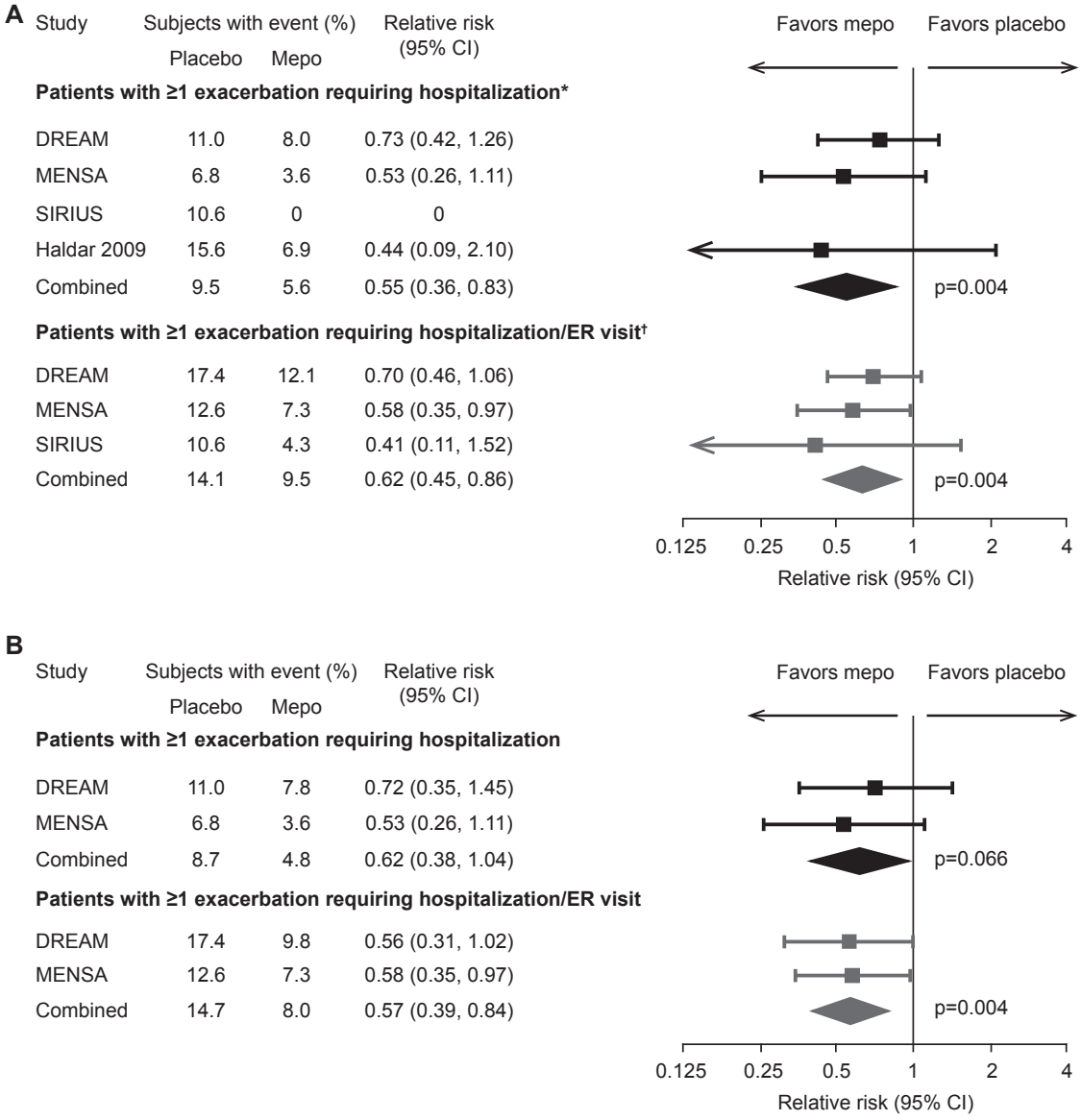

FIG 2. Meta-analysis of proportion of patients with 1 or more exacerbation requiring hospitalization or hospitalization/ER visit for all doses **(A)** and 75 mg IV/100 mg SC (pooled) doses of mepolizumab **(B)** versus placebo. Heterogeneity in hospitalization data: I^2 = (*A*) 0% (95% CI, 0-69), (*B*) 0% (95% CI, 0-0); heterogeneity in hospitalization/ER visit data: I^2 = (*A*) 0% (95% CI, 0-72), (*B*) 0% (95% CI, 0-0). *ER*, Emergency room; *Mepo*, mepolizumab. *Relative risk not calculated for SIRIUS, but data included in the meta-analysis. †Data not available for Haldar et al.[15]

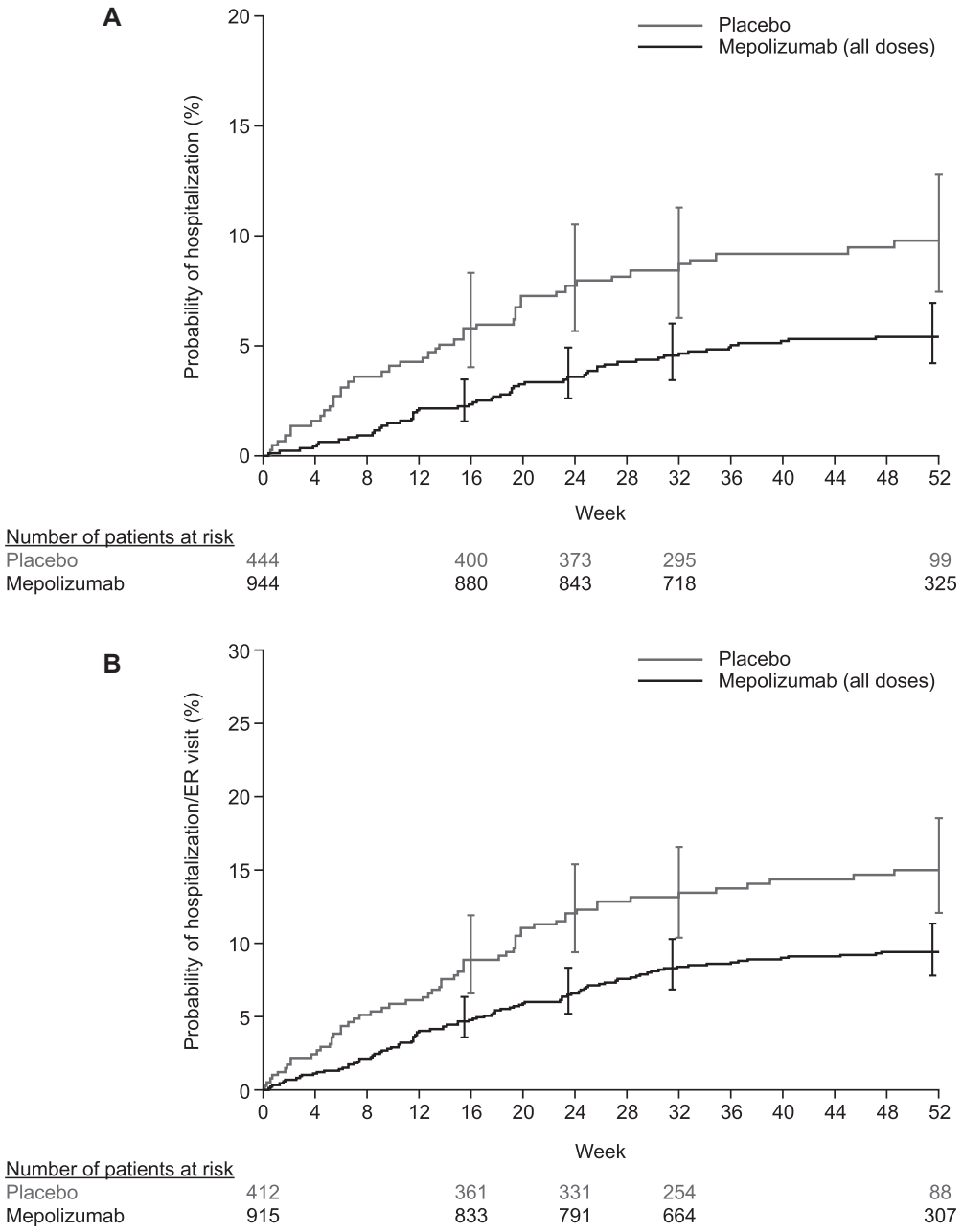

FIG 3. Kaplan-Meier cumulative incidence curve for time to first exacerbation requiring hospitalization **(A)** and hospitalization and/or ER visit **(B)**. *ER,* Emergency room.

mepolizumab assessed efficacy in a wider asthma phenotype.[33] In addition, a previous meta-analysis of the efficacy of mepolizumab by Liu et al,[14] which did not include the most recent phase III studies, MENSA and SIRIUS, also assessed efficacy across a wider asthma phenotype.[14] Conversely, the current analysis composed of only patients with severe eosinophilic asthma and a history of frequent exacerbations includes the most recent phase III study data in this patient population.[14] Thus, this meta-analysis constitutes a robust analysis of exacerbation rates requiring hospitalization and/or emergency room visits for mepolizumab therapy in patients with severe eosinophilic asthma.

This analysis had some limitations. The analysis included SIRIUS, which was a steroid-sparing study, and hence, exacerbation events may have been induced by a reduction in steroid dose, rather than being spontaneous, as they were in MENSA, DREAM, and Haldar et al.[3,15-17] However, the sensitivity analysis, which excluded SIRIUS, showed similar results. The maximum duration of treatment with mepolizumab was 1 year. However, despite this short duration, the number of patients with 1 or more exacerbation requiring hospitalization and/or emergency room visit each year was reduced by 38% to 45%. Any reduction in exacerbations is a major benefit to patients and health care services; exacerbations associated with

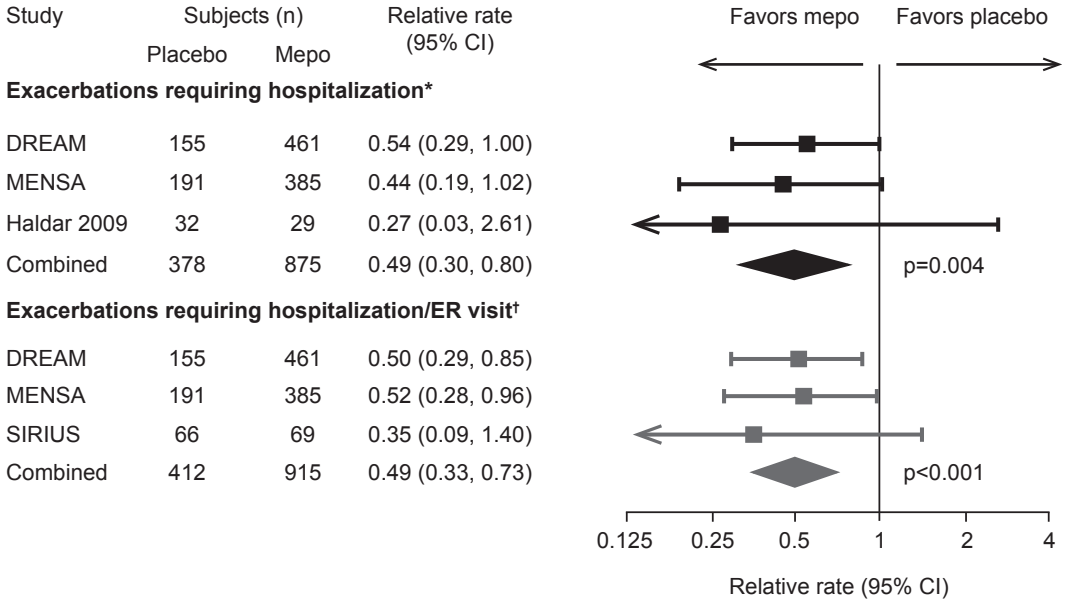

FIG 4. Meta-analysis of rate of exacerbations requiring hospitalization or hospitalization/ER visit for all doses of mepolizumab versus placebo. Heterogeneity in hospitalization data: $I^2 = 0\%$ (95% CI, 0-53); heterogeneity in hospitalization/ER visit data: $I^2 = 0\%$ (95% CI, 0-22). *ER*, Emergency room; *Mepo*, mepolizumab. *SIRIUS not included because there were no hospitalizations in the Mepo arm. †Haldar et al[15] not included because data were not available for ER visits.

TABLE III. Absolute rates of hospitalization or hospitalization/ER visit per year for combined analysis

			Mean rate per year (no. of years before experiencing 1 exacerbation)	
Analysis	**End point**	**Studies**	**Placebo**	**Mepolizumab**
Meta-analysis on all mepolizumab doses	Exacerbations requiring hospitalization*	DREAM MENSA Haldar et al[15]	0.15 (6.7)	0.07 (14.3)
	Exacerbations requiring hospitalization and/or ER visit†	DREAM MENSA SIRIUS	0.31 (3.2)	0.15 (6.7)
Sensitivity analysis on 75 mg IV/100 mg SC (pooled) mepolizumab doses	Exacerbations requiring hospitalization	DREAM MENSA	0.14 (7.1)	0.07 (14.3)
	Exacerbations requiring hospitalization and/or ER visit	DREAM MENSA	0.28 (3.6)	0.13 (7.7)

ER, Emergency room.
*SIRIUS not included because there were no hospitalizations in the mepolizumab arm.
†Haldar et al[15] not included because data were not available for ER visits.

hospitalization are the most severe form of these events, and are associated with considerable morbidity and mortality as well as a long-term risk of accelerated lung function decline.[5,6,34] Furthermore, hospital admissions are expensive and contribute disproportionately to asthma health care costs, particularly for severe asthma.[7,8] Therefore, the beneficial effect of mepolizumab on this end point may result in significant long-term cost savings.

In this meta-analysis, approximately 36% of patients were on daily OCS; previous studies have shown that baseline blood eosinophil levels are similar in OCS-dependent and non–OCS-dependent patients.[27] In addition, in a subanalysis of the DREAM study, mepolizumab was shown to have similar efficacy in reducing exacerbation rates in these 2 groups of patients.[27] Furthermore, in the SIRIUS study, where all patients were treated with daily OCS, there were reductions in the OCS dose and the frequency of exacerbations in patients who received mepolizumab.[16] This is important because daily use of OCS is associated with significant systemic adverse effects, which are cumulative and dose dependent.[35,36] Taken together, this suggests that mepolizumab may have similar efficacy in reducing exacerbations requiring hospitalization or a visit to the emergency room in OCS-dependent and non–OCS-dependent patients with severe eosinophilic asthma.

The importance of appropriate patient selection has been demonstrated by the fact that mepolizumab has only minimal efficacy in patients who were not selected by using specific biomarkers and clinical features relevant to the target population.[12,31,37] A recent post hoc analysis of the DREAM and MENSA studies has shown that baseline blood eosinophil counts are biomarkers that predict increasing baseline morbidity

in patients with severe eosinophilic asthma.[38] In addition, measurement of blood eosinophil counts at baseline is a good biomarker to identify patients for mepolizumab treatment. The exacerbation rate reduction with mepolizumab versus placebo increased progressively from 52% in patients with a baseline eosinophil count of 150 cells/μL or more to 70% in patients with a baseline count of 500 cells/μL or more.[38] It would be reasonable to assume that reductions in rates of hospitalizations and hospitalization/emergency room visits stratified by baseline eosinophil count would follow a similar pattern to exacerbation rates; however, these events were too infrequent for meaningful stratification in the current meta-analysis.

In summary, the results of this meta-analysis show that mepolizumab significantly reduces the risk of exacerbations requiring hospitalization or a visit to the emergency room. This reduction is similar to the reductions achieved for all severe exacerbations experienced in the pivotal trials, indicating that mepolizumab retains therapeutic efficacy across the spectrum of exacerbation severity. Previous studies have shown that mepolizumab is associated with a clinically acceptable safety profile across a number of conditions.[3,15-17,31,39,40] Mepolizumab therefore represents an important treatment option for patients with severe eosinophilic asthma, and addresses a patient population that currently has a high unmet need and limited treatment options.

Editorial support (in the form of writing assistance, including the development of the initial draft on the basis of author feedback on an initial outline developed by the first author, collating and incorporating author comments on all drafts, grammatical editing, and referencing) was provided by Elizabeth Hutchinson, PhD, of Fishawack Indicia Ltd, funded by GSK.

Clinical implications: Mepolizumab represents a targeted treatment option for patients with severe eosinophilic asthma, and impacts significantly on key exacerbation-related outcomes. This confers benefit to a population with high unmet need.

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Study	Subjects (n)		Relative rate (95% CI)
	Placebo	Mepo	
Exacerbations requiring hospitalization			
DREAM	155	153	0.61 (0.28, 1.33)
MENSA	191	385	0.44 (0.19, 1.02)
Combined	346	538	0.52 (0.29, 0.93)
Exacerbations requiring hospitalization/ER visit			
DREAM	155	153	0.40 (0.19, 0.81)
MENSA	191	385	0.52 (0.28, 0.96)
Combined	346	538	0.46 (0.29, 0.74)

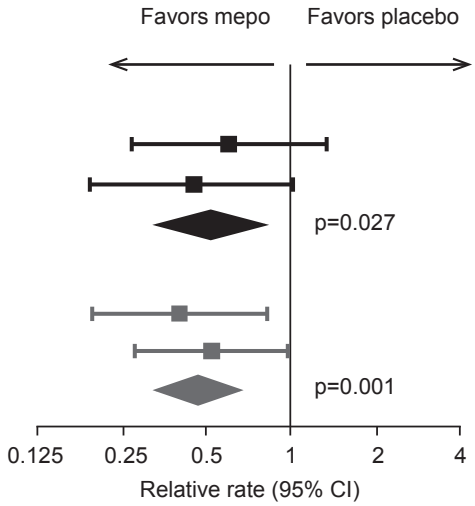

FIG E1. Meta-analysis of rate of exacerbations requiring hospitalization or hospitalization/ER visit for 75 mg IV/100 mg SC (pooled) doses of mepolizumab versus placebo. Heterogeneity in hospitalization data: $I^2 = 0\%$ (95% CI, 0-0); heterogeneity in hospitalization/ER visit data: $I^2 = 0\%$ (95% CI, 0-0). *ER*, Emergency room; *Mepo*, mepolizumab.

TABLE E1. Summary of studies included in the meta-analysis

Parameter	DREAM (Pavord et al[3])	MENSA (Ortega et al[17])	SIRIUS (Bel et al[16])	Haldar et al[15]
Study design				
Design	Multicenter, randomized, placebo-controlled, double-blind, parallel-group	Multicenter, randomized, placebo-controlled, double-blind, double-dummy, parallel-group	Multicenter, randomized, placebo-controlled, double-blind, parallel-group	Single-center, randomized, placebo-controlled, double-blind, parallel-group
Drugs and regimen	75 mg IV, 250 mg IV, 750 mg IV, or placebo every 4 wk for 52 wk (13 doses)	75 mg IV, 100 mg SC, or placebo every 4 wk for 32 wk (8 doses)	100 mg SC or placebo every 4 wk for 24 wk (6 doses)	750 mg IV or placebo every month for 12 mo (12 doses)
Primary end point	Annual rate of clinically significant exacerbations, defined as worsening of asthma requiring systemic glucocorticoids for ≥3 d, ER visit, or hospitalization	Annual rate of clinically significant exacerbations, defined as worsening of asthma requiring systemic glucocorticoids for ≥3 d, ER visit, or hospitalization	Percent reduction in daily oral glucocorticoid dose during weeks 20 to 24 compared with the run-in period	Number of severe exacerbations of asthma per subject, defined as period of deterioration in asthma control in subjects who had been treated with high-dose oral prednisolone for ≥5 d
Inclusion criteria				
Age group	≥12 y	≥12 y	≥12 y	≥18 y
Exacerbation history	≥2 exacerbations requiring corticosteroid treatment in previous year	≥2 exacerbations requiring corticosteroid treatment in previous year	Not required	≥2 exacerbations requiring corticosteroid treatment in previous year
Sputum eosinophil count	Historical or baseline 3%*	Not required	Not required	Historical or baseline 3%
Peripheral blood eosinophil count	Historical count (12 mo) ≥300 cells/μL*	Historical count (12 mo) ≥300 cells/μL OR Baseline count ≥150 cells/μL	Historical count (12 mo) ≥300 cells/μL OR Baseline count ≥150 cells/μL	Not required
Baseline treatments†	± OCS High-dose ICS + controller	± OCS High-dose ICS + controller	+ OCS ≥6 mo High-dose ICS + controller	± OCS High-dose ICS + controller

ER, Emergency room; *ICS*, inhaled corticosteroid; *LABA*, long-acting beta$_2$ agonist; *LTRA*, leukotriene receptor antagonist.
*Eosinophilic inflammation was defined by 1 of several criteria, of which sputum eosinophil and peripheral blood cell count were 2 possibilities. Patients were required to meet 1 of these criteria to be included in the study.
†Controller medication: LABA, LTRA, or theophylline.