Mepolizumab in Patients With Severe Asthma and Comorbidities: 1-Year REALITI-A Analysis

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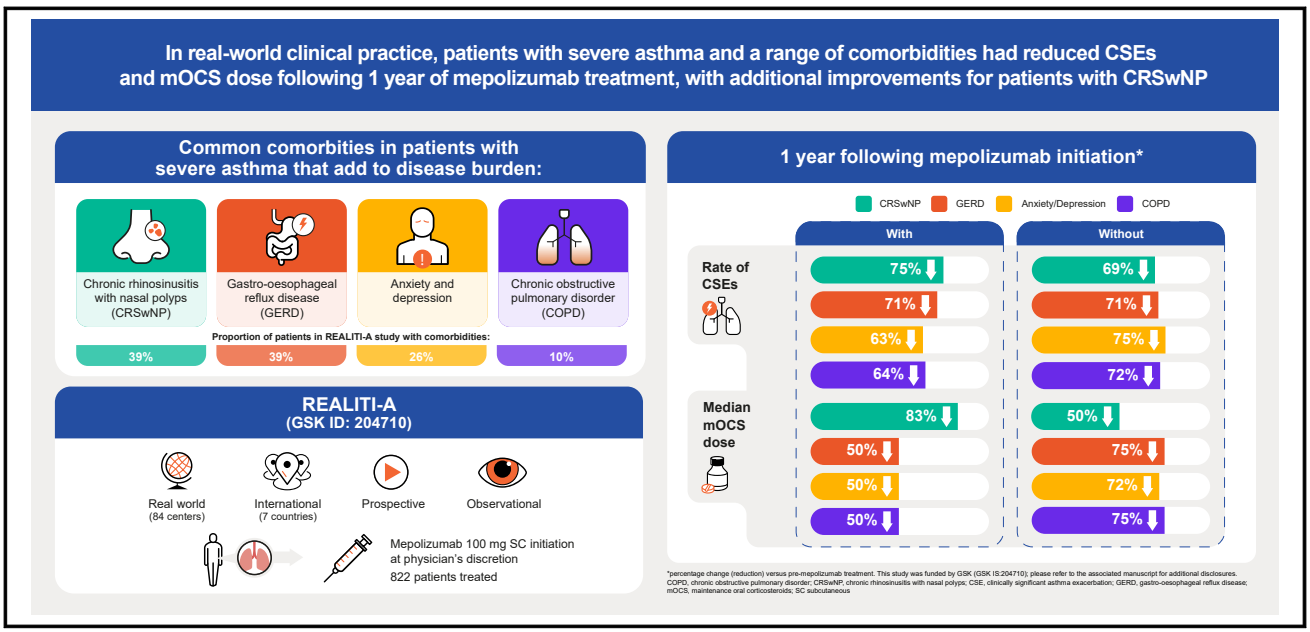
What is already known? Severe asthma is complex, and comorbidities such as chronic rhinosinusitis with nasal polyps, gastroesophageal reflux disease, depression/anxiety, and coexisting chronic obstructive pulmonary disease contribute to the disease burden.

What does this article add to our knowledge? In this *post hoc* analysis, mepolizumab improved real-world clinical outcomes in patients with severe asthma in both the presence and the absence of comorbidities; patients with comorbid chronic rhinosinusitis with nasal polyps showed a particularly favorable treatment response.

How does this study impact current management guidelines? A multidisciplinary approach to enable patients with severe asthma and comorbid conditions to receive timely targeted treatment should be pursued, with a range of clinical outcomes assessed to determine overall response/remission achievement as standard practice.

VISUAL SUMMARY



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Abbreviations used
ACQ-5- Asthma Control Questionnaire-5
ACO- Asthma—chronic obstructive pulmonary disease overlap
COPD- Chronic obstructive pulmonary disease
CRSwNP- Chronic rhinosinusitis with nasal polyps
CSE- Clinically significant asthma exacerbation
FEV_1- Forced expiratory volume in 1 second
GERD- Gastroesophageal reflux disease
IL- Interleukin
LS- Least squares
mOCS- Maintenance oral corticosteroid(s)
OCS- Oral corticosteroid(s)
SCS- Systemic corticosteroid(s)

BACKGROUND: Severe asthma is complex; comorbidities may influence disease outcomes.
OBJECTIVE: To assess mepolizumab effectiveness in patients with severe asthma and comorbidities.
METHODS: REALITI-A was a 2-year international, prospective study enrolling adults with asthma newly prescribed mepolizumab (100 mg subcutaneously) at physician's discretion. This *post hoc* analysis assessed 1-year outcomes stratified by comorbidities at enrollment: chronic rhinosinusitis with nasal polyps (CRSwNP), gastroesophageal reflux disease (GERD), depression/anxiety, and chronic obstructive pulmonary disease (COPD). Outcomes included the rate of clinically significant asthma exacerbations (CSEs; requiring systemic corticosteroids and/or hospital/emergency room admission) between the 12 months pre- and post-mepolizumab treatment and changes from baseline in daily maintenance oral corticosteroid dose (mo 12), Asthma Control Questionnaire-5 score (mo 12) and forced expiratory volume in 1 second (FEV_1; mo 9−12).
RESULTS: At enrollment (n = 822), 321 of 822 (39%), 309 of 801 (39%), 203 of 785 (26%), and 81 of 808 (10%) patients had comorbid CRSwNP, GERD, depression/anxiety, and COPD, respectively. Post- versus pre-treatment across all comorbidity subgroups: the rate of CSEs decreased by 63% or more; among 298 (39%) patients on maintenance oral corticosteroids at baseline, median dose decreased by 50% or more; Asthma Control Questionnaire-5 score decreased by 0.63 or more points; FEV_1 increased by 74 mL or more. Patients with versus without CRSwNP had the greatest improvements (eg, rate of CSEs decreased by 75%). Patients without GERD, depression/anxiety, or COPD had greater improvements than those with the respective comorbidities, except for FEV_1 in patients with COPD.
CONCLUSIONS: Mepolizumab improved disease outcomes in patients with severe asthma irrespective of comorbidities, with additional benefit for patients with CRSwNP. **(J Allergy Clin Immunol Pract 2023;11:3650-61)**

Key words: *Asthma; Mepolizumab; Comorbidities; Severe asthma; Chronic rhinosinusitis with nasal polyps; Gastroesophageal reflux disease; Depression; Anxiety; Chronic obstructive pulmonary disease*

INTRODUCTION

Severe asthma is a complex, heterogeneous disease with multiple phenotypes and endotypes.[1,2] Among patients with severe asthma, comorbidities such as chronic rhinosinusitis with nasal polyps (CRSwNP), gastroesophageal reflux disease (GERD), depression and anxiety as well as coexistent smoking-related disease, such as chronic obstructive pulmonary disease (COPD) can be present and add to disease burden.[3-9] Certain comorbidities, such as CRSwNP and GERD, may further increase risk of asthma exacerbations, and in addition, some comorbidities may also influence responses to or be influenced by asthma treatment.[3-16] Thus, comorbidities can act as confounding factors in the diagnosis or assessment of asthma control, potentially leading to inappropriate asthma therapy escalation.[5,15,16] In severe asthma, a multidisciplinary, treatable trait approach to disease management is advocated to holistically address all aspects of the disease and to optimize disease control.[17,18] It is recognized that some comorbidities, such as CRSwNP, share pathophysiological mechanisms with severe asthma, with interleukin-5 (IL-5) and eosinophilic-driven inflammation playing an important role.[19] Therefore, treatments targeting IL-5 could positively impact multiple components of disease burden faced by patients with severe eosinophilic asthma and certain comorbidities and, therefore, lead to better outcomes.[20]

Mepolizumab, a humanized monoclonal antibody that targets IL-5, represents a precision medicine approach for the treatment of

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severe eosinophilic asthma.[21,22] Mepolizumab is approved for the treatment of severe asthma, eosinophilic granulomatosis with polyangiitis, hypereosinophilic syndrome, and CRSwNP in multiple regions worldwide.[23-25] In clinical trials and real-world studies, including the REALITI-A study, mepolizumab significantly reduced exacerbation rates and oral corticosteroid (OCS) use while improving symptom control in patients with severe asthma.[13,26-38]

Analyses of randomized clinical trial data have demonstrated consistent benefits of mepolizumab in patients with asthma and comorbidities such as CRSwNP, psychopathologies, GERD, and cardiovascular disease.[20,39,40] Indeed, among patients with severe asthma, clinical improvements with mepolizumab were greater in patients with CRSwNP than in those without CRSwNP.[20,40] Unfortunately, owing to stringent eligibility criteria for patient enrollment in phase III clinical trials, there is limited generalizability of these data in real-world populations, with 1 study reporting that 4% to 18% of patients with severe asthma were eligible for trials assessing treatments.[41] One single-center real-world study demonstrated that patients with asthma and comorbid CRSwNP had an increased response to mepolizumab.[28] In addition, a U.S.-based retrospective analysis demonstrated that mepolizumab significantly reduced exacerbations in patients with severe asthma and comorbidities, including CRSwNP, COPD, and depression/anxiety.[39] Despite this, availability of data from real-world studies to assess the effectiveness of mepolizumab in patients with severe asthma and comorbidities is limited. Given the considerable impact of comorbidities on outcomes in patients with severe asthma,[3-12] supplementing data from robust phase III trials with real-world data assessing the effects of targeted treatments in a broader range of patients in clinical practice is essential. The REALITI-A study of 822 patients is sufficiently large enough to enable such an analysis.

This *post hoc* analysis from the full REALITI-A study population at 1 year assessed real-world outcomes with mepolizumab in patients with severe asthma and some of the most common comorbidities, including CRSwNP, GERD, depression/anxiety, and physician-labelled coexistent COPD.

METHODS

Study design

The REALITI-A (GSK ID: 204710) was a 2-year, international, prospective, single-arm, observational cohort study enrolling adults with asthma newly prescribed mepolizumab 100 mg subcutaneously. The study design has been described in full previously.[27,30] Briefly, patients were enrolled between December 2016 and October 2019. There was a variable length run-in period between enrollment and the first dose of mepolizumab (index date). This *post hoc* analysis used data from the full study population at 1 year: the pretreatment period was defined as 365 days prior to the enrollment plus the variable length run-in period and the follow-up period was defined as the 365 days post-index. All data were collected at patients' usual health care visits (routine or unscheduled).

This study was conducted in accordance with the Declaration of Helsinki and local ethical approval was obtained per study site; written informed consent was obtained from each patient prior to commencing any study-related activities.

Patients

Inclusion and exclusion criteria for the study have been detailed previously.[27,30] In brief, eligible patients were 18 years of age or older, had a current clinical diagnosis of asthma, had received a physician decision to initiate mepolizumab treatment, and had relevant medical records for 12 months or longer prior to enrollment. Patients were excluded if they had received previous mepolizumab treatment or participated in an interventional clinical trial within 12 months of enrollment. The use of other biologics in the 12 months prior to enrollment was permitted.

Outcomes

The primary outcome was the rate of clinically significant asthma exacerbations (CSEs) between the pretreatment and the follow-up periods. The CSEs were defined as a deterioration in asthma requiring use of systemic corticosteroids (SCS) and/or an emergency department visit or hospitalization. The use of SCS was defined as OCS for 3 or more days or a single systemic administration (intravenous/intramuscular) of SCS owing to worsening of asthma symptoms; for patients on maintenance oral corticosteroids (mOCS), use of SCS was defined as 2-fold or greater increase in the existing maintenance dose for 3 or more days.

Secondary outcomes included changes from baseline in mOCS daily dose and total OCS daily dose and change from baseline in Asthma Control Questionnaire-5 (ACQ-5) score during the follow-up period. The total OCS dose included both maintenance doses and doses for rescue bursts; both mOCS and total OCS dose were expressed as prednisone-equivalent doses (mg/d). The baseline for the mOCS and total OCS dose analyses was defined as the 28 days preceding the index date. For ACQ-5 scores, baseline was defined as the value collected at the index date or the nearest historical value within 90 days prior to the index date; scores were collected on a voluntary basis at baseline and no more frequently than every 3 months at the usual asthma health care visits during the follow-up period.

An additional outcome assessed was the change from baseline in forced expiratory volume in 1 second (FEV_1) during the follow-up period. Baseline was defined as the value that was collected on the index date, or the nearest historical value within the 90 days prior to the index date, and values during follow-up were collected no more frequently than monthly at the usual asthma health care visits.

This *post hoc* analysis used data from the full study population at 1 year, stratified by CRSwNP status, GERD status, depression/anxiety status, and physician-labelled coexistent COPD at enrollment (with/without); comorbidity status was confirmed by the prescribing physician.

Statistical analysis

The difference in rate of CSEs between the pretreatment and the follow-up periods was analyzed using a generalized estimating equation regression model assuming a negative binomial distribution with the pretreatment or follow-up periods included as a covariate. Within the subset of patients providing baseline blood eosinophil results, annual rates of CSEs were compared between the pretreatment and the follow-up periods for patients stratified by thresholds of baseline blood eosinophil counts (as continuous variables) using the aforementioned model with covariates of period (pretreatment, follow-up), baseline eosinophils, and baseline eosinophils by period interaction. In both models, patients with and without each comorbidity were analyzed separately, and the logarithm of time on treatment was included as an offset variable. A prespecified log transformation was applied to blood eosinophil counts before analysis.

Median mOCS daily dose and total OCS daily dose (interquartile range [IQR]) were calculated and summarized at baseline and for each 4-week period during the follow-up period. The percentage

TABLE I. Patient demographics and clinical characteristics at enrollment

Demographics and clinical characteristics	Treated population (n = 822)[30]	CRSwNP status (n = 822)		GERD status (n = 801)		Depression/anxiety status (n = 785)		COPD status (n = 808)	
		With (n = 321)	Without (n = 501)	With (n = 309)	Without (n = 492)	With (n = 203)	Without (n = 582)	With (n = 81)	Without (n = 727)
Patients with/without respective comorbidity, %	-	39	61	39	61	26	74	10	90
Age (y), mean (SD)	54.0 (13.6)	53.7 (13.0)	54.2 (14.0)	55.8 (12.9)	53.1 (13.9)	54.5 (12.6)	54.0 (13.9)	61.9 (9.6)	53.2 (13.7)
Female, n (%)	521 (63)	169 (53)	352 (70)	212 (69)	295 (60)	154 (76)	344 (59)	39 (48)	473 (65)
Asthma duration (y), mean (SD)	n = 801 19.7 (15.7)	n = 316 20.7 (15.2)	n = 485 19.0 (16.0)	n = 305 21.7 (16.2)	n = 481 18.5 (15.4)	n = 198 22.3 (16.5)	n = 571 18.9 (15.4)	n = 77 19.5 (18.3)	n = 711 19.6 (15.4)
Smoking history, n (%)	n = 815	n = 319	n = 496	n = 305	n = 489	n = 201	n = 577	n = 79	n = 722
Never smoked	489 (60)	199 (62)	290 (58)	174 (57)	305 (62)	108 (54)	360 (62)	17 (22)	465 (64)
Former smoker	301 (37)	116 (36)	185 (37)	120 (39)	170 (35)	84 (42)	201 (35)	55 (70)	240 (33)
Current smoker	25 (3)	4 (1)	21 (4)	11 (4)	14 (3)	9 (4)	16 (3)	7 (9)	17 (2)
Pack-years,* mean (SD)	n = 217 17.8 (17.0)	n = 81 13.9 (13.3)	n = 136 20.2 (18.5)	n = 88 18.7 (16.5)	n = 121 17.5 (17.7)	n = 56 22.1 (20.6)	n = 150 16.6 (15.6)	n = 42 29.9 (21.2)	n = 171 15.1 (14.5)
Patients with mOCS use,† n (%)	319 (39)	134 (42)	185 (37)	127 (41)	181 (37)	84 (41)	216 (37)	32 (40)	281 (39)
mOCS daily dose, median (IQR)	n = 298 10.0 (5.0–15.0)	n = 129 7.5 (5.0–10.8)	n = 169 10.0 (5.0–17.5)	n = 119 10.0 (5.0–15.0)	n = 171 10.0 (5.0–12.5)	n = 78 10.0 (5.1–15.0)	n = 204 9.0 (5.0–12.5)	n = 29 10.0 (5.0–15.0)	n = 264 10.0 (5.0–13.9)
Blood eosinophil count,‡ cells/μL, geometric mean (SD log)	n = 614 353 (1.241)	n = 262 447 (1.184)	n = 352 297 (1.255)	n = 233 299 (1.359)	n = 366 394 (1.159)	n = 146 252 (1.407)	n = 443 402 (1.150)	n = 54 270 (1.334)	n = 551 361 (1.234)
$FEV_{1,}$ mean (SD) mL	n = 397 1,997.3 (810.1)	n = 185 2,163.7 (828.0)	n = 212 1,852.1 (767.0)	n = 150 1,920.0 (830.0)	n = 234 2,051.9 (805.0)	n = 80 1,797.3 (714.1)	n = 298 2,045.6 (822.2)	n = 33 1,624.1 (818.0)	n = 355 2,037.2 (805.7)
% predicted	67.7 (21.1)	70.0 (19.6)	65.6 (22.1)	68.8 (21.5)	67.2 (20.7)	66.5 (20.4)	68.0 (21.2)	58.1 (22.2)	68.8 (20.8)

IQR, Interquartile range.

*Smoking pack-year history was collected retrospectively; therefore, data were not available for all current or former smokers. Smoking pack-years were calculated for current/former smokers as (number of cigarettes smoked per day/20) × number of years smoked. 1 cigar equated to 4 cigarettes.

†Prednisone equivalent dose in the 28 d prior to and including the mepolizumab initiation date.

‡Baseline was defined as the value that was collected on the index date, or the nearest historical value within the 90 d prior to the index date.

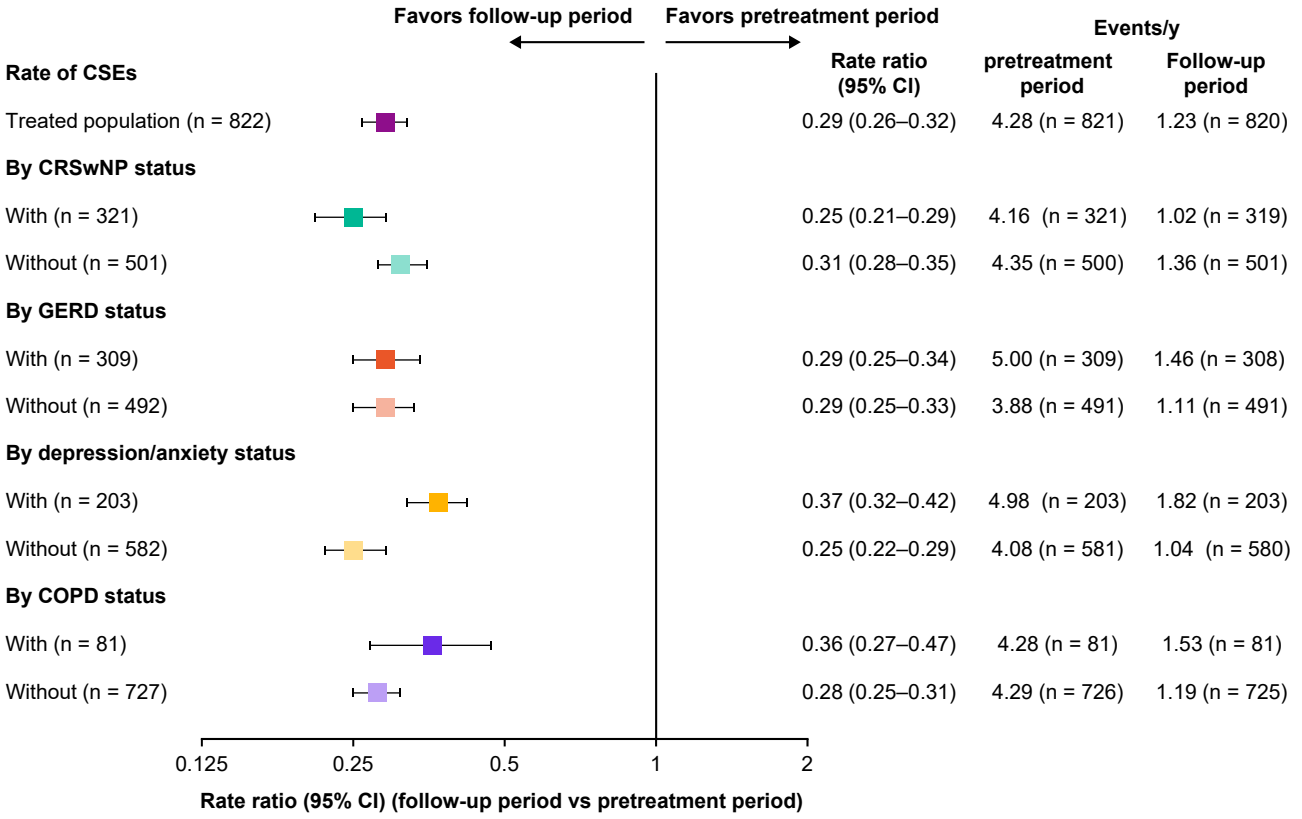

FIGURE 1. The rate of CSEs between the pretreatment and the follow-up periods for the treated population,[30] and stratified by CRSwNP, GERD, depression/anxiety and COPD status. The pretreatment period was defined as 365 d prior to enrollment and the variable length run-in period; the follow-up period was defined as 365 d following mepolizumab treatment initiation.

reduction from baseline in mOCS dose and total OCS dose was calculated at weeks 53 to 56 and were categorized as follows: 100% reduction, 75% to less than 100% reduction, 50% to less than 75% reduction, greater than 0% to less than 50% reduction, and 0% change or an increase in OCS dose.

The least squares (LS) mean change (95% confidence interval) from baseline in ACQ-5 score and FEV_1 were each analyzed using a mixed model repeated measures approach, with covariates of time point, country, exacerbations during the pretreatment period, and use of mOCS at enrollment. The mean change from baseline in ACQ-5 score was determined at month 12 and the mean change from baseline in FEV_1 determined at months 9 to 12.

RESULTS

Patient population

In total, 822 patients were treated with mepolizumab; the demographics and characteristics of these patients at enrollment, as well as safety results, have been reported previously.[30] Based on physician diagnosis, 321 of 822 patients (39%) had comorbid CRSwNP, 309 of 801 (39%) had GERD, 203 of 785 (26%) had depression/anxiety, and 81 of 808 (10%) were listed as having coexistent COPD.

The patient baseline demographics and clinical characteristics, shown in Table I, were generally similar across the comorbid subgroups, with some exceptions. In a comparison between the with and without subgroups for each comorbidity, patients with GERD and with COPD had a higher mean age; those with GERD and with depression/anxiety subgroups had a greater proportion of females, whereas those with CRSwNP subgroup and with COPD subgroup had a lower proportion of females. Patients with GERD and those with depression/anxiety had a longer duration of asthma than patients without GERD or depression/anxiety, respectively. A greater proportion of patients reported mOCS use in each with comorbid subgroup than those without each respective comorbidity. Similarly, except for the with CRSwNP subgroup, a lower geometric mean blood eosinophil count was reported across each comorbid subgroup versus the without comorbid group, respectively. Comparing across all comorbid subgroups, patients with depression/anxiety had the longest mean duration of asthma, whereas patients with COPD had the highest mean age and the greatest proportions of current and former smokers and the highest number of smoking pack-years.

Rate of CSEs

During the pretreatment period, the rate of CSEs was generally similar in the treated population and in patients with/without CRSwNP and COPD, whereas patients with GERD and those with depression/anxiety had a higher rate of CSEs than patients without GERD and depression/anxiety, respectively (Figure 1). Following mepolizumab treatment, the rate of CSEs reduced in the treated population[30] and across all comorbidity subgroups compared with the pretreatment period. A numerically greater reduction in the rate of CSEs was reported for patients with versus without CRSwNP, whereas the reverse was reported for patients with versus without COPD and depression/anxiety, although the confidence intervals were large for the with COPD subgroup.

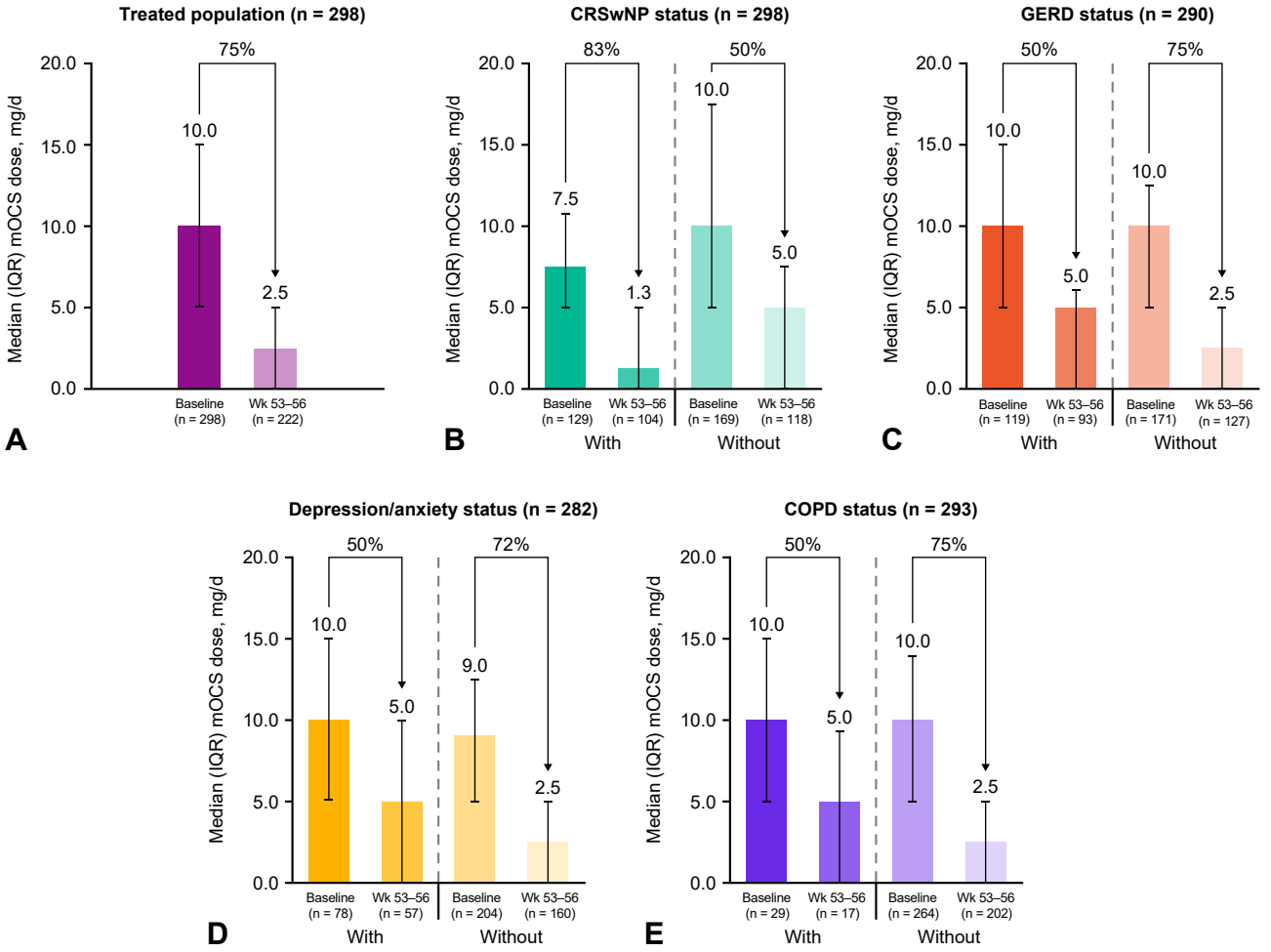

FIGURE 2. Change from baseline* in median mOCS daily dose at wk 53−56, (**A**) in the treated population[30] and stratified by (**B**) CRSwNP, (**C**) GERD, (**D**) depression/anxiety, and (**E**) COPD status. Relative percentage reductions from baseline in median mOCS daily dose at wk 53−56 are shown. Prednisone equivalent OCS dose (mg/d). *Baseline was defined as the 28 d preceding mepolizumab treatment initiation.

When analyzed by baseline blood eosinophil count, there was a small trend for a greater reduction in rate of CSE with increasing blood eosinophil counts in the treated population (Figure E1; available in this article's Online Repository at www.jaci-inpractice.org). When analyzed by comorbidity subgroup, patients with CRSwNP or with COPD had a small trend of greater reductions in rate of CSEs with increased blood eosinophil count at baseline compared with patients without the respective comorbidity. There was no increase in effect size with increasing blood eosinophil levels in patients with GERD or with depression/anxiety (Figure E1).

Change from baseline in mOCS and total OCS dose and use

At baseline, the median mOCS daily dose was generally similar in the treated population[30] and across the comorbid subgroups, except for patients with comorbid CRSwNP who had a marginally lower baseline median mOCS dose (Figure 2). At weeks 53 to 56 following mepolizumab treatment, median mOCS daily dose reduced by at least 50% in the treated population[30] and across all comorbidity subgroups; patients with CRSwNP had the greatest reduction from baseline (83%), whereas patients with comorbid GERD, depression/anxiety, and COPD had smaller reductions than patients in the respective without comorbid subgroups. Similar results were observed for total median OCS daily dose (Figure E2; available in this article's Online Repository at www.jaci-inpractice.org).

At weeks 53 to 56, mOCS was discontinued in 32% to 47% of patients across the treated population[30] and the comorbid subgroups (Figure 3). Comparing within each comorbid subgroup, a greater proportion of patients with CRSwNP and COPD discontinued mOCS, whereas a smaller proportion of patients with GERD and with depression/anxiety discontinued mOCS; the greatest difference in patients discontinuing mOCS was reported within the depression/anxiety subgroup, with the smallest proportion of patients discontinuing mOCS being those with depression/anxiety. Generally, results were similar for total OCS use (Figure E3; available in this article's Online Repository at www.jaci-inpractice.org).

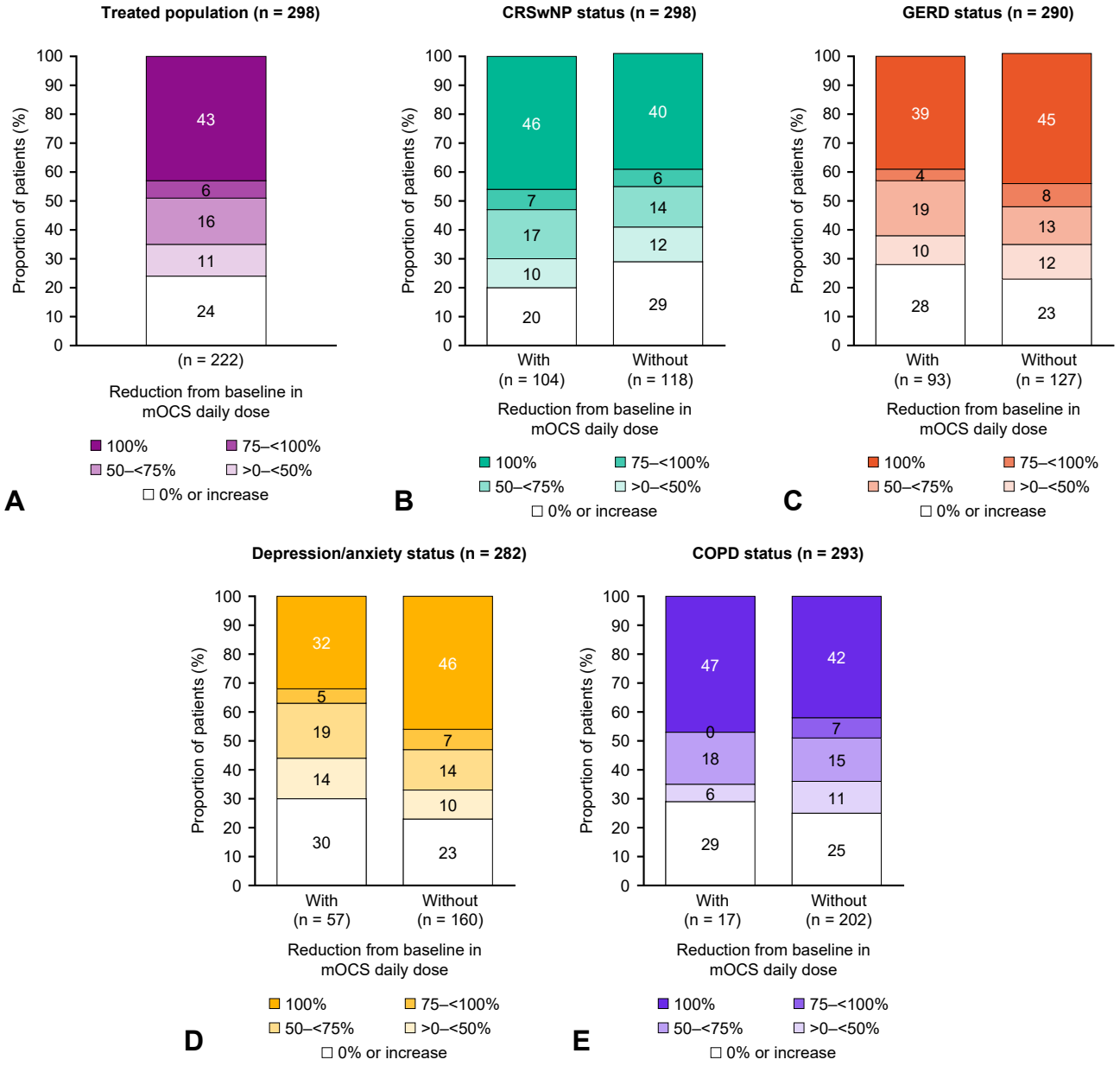

FIGURE 3. Proportion of patients with a reduction from baseline* in mOCS daily dose at wk 53–56, (**A**) in the treated population[30] and stratified by (**B**) CRSwNP, (**C**) GERD, (**D**) depression/anxiety, and (**E**) COPD status. Prednisone equivalent OCS dose (mg/d). *Baseline was defined as the 28 d preceding mepolizumab treatment initiation.

Change from baseline in ACQ-5 score

Patients with versus without CRSwNP had a marginally lower baseline LS mean ACQ-5 score, whereas patients with versus without COPD, GERD, and depression/anxiety had a marginally higher baseline LS mean ACQ-5 score; patients with depression/anxiety had the highest baseline LS mean ACQ-5 score across the comorbidity subgroups (Figure 4). At month 12, a reduction from baseline in LS mean ACQ-5 score was observed in the treated population and across all comorbidity subgroups; the greatest reduction was observed in patients with CRSwNP, whereas the smallest reduction was in patients with COPD, although the confidence intervals were large. All reductions exceeded the ACQ-5 minimum clinically important difference of 0.5 points.[42] It should be noted that ACQ-5 scores were only available/collected when performed as per local clinical practice. As a result, data were only available within a subset of the overall study population.

Change from baseline in FEV_1

Patients with versus without comorbid CRSwNP had higher baseline LS mean FEV_1 values, whereas patients with versus without COPD and depression/anxiety had lower baseline LS mean FEV_1 values; patients with COPD had the lowest LS mean FEV_1 value across all subgroups (Figure 5). Following

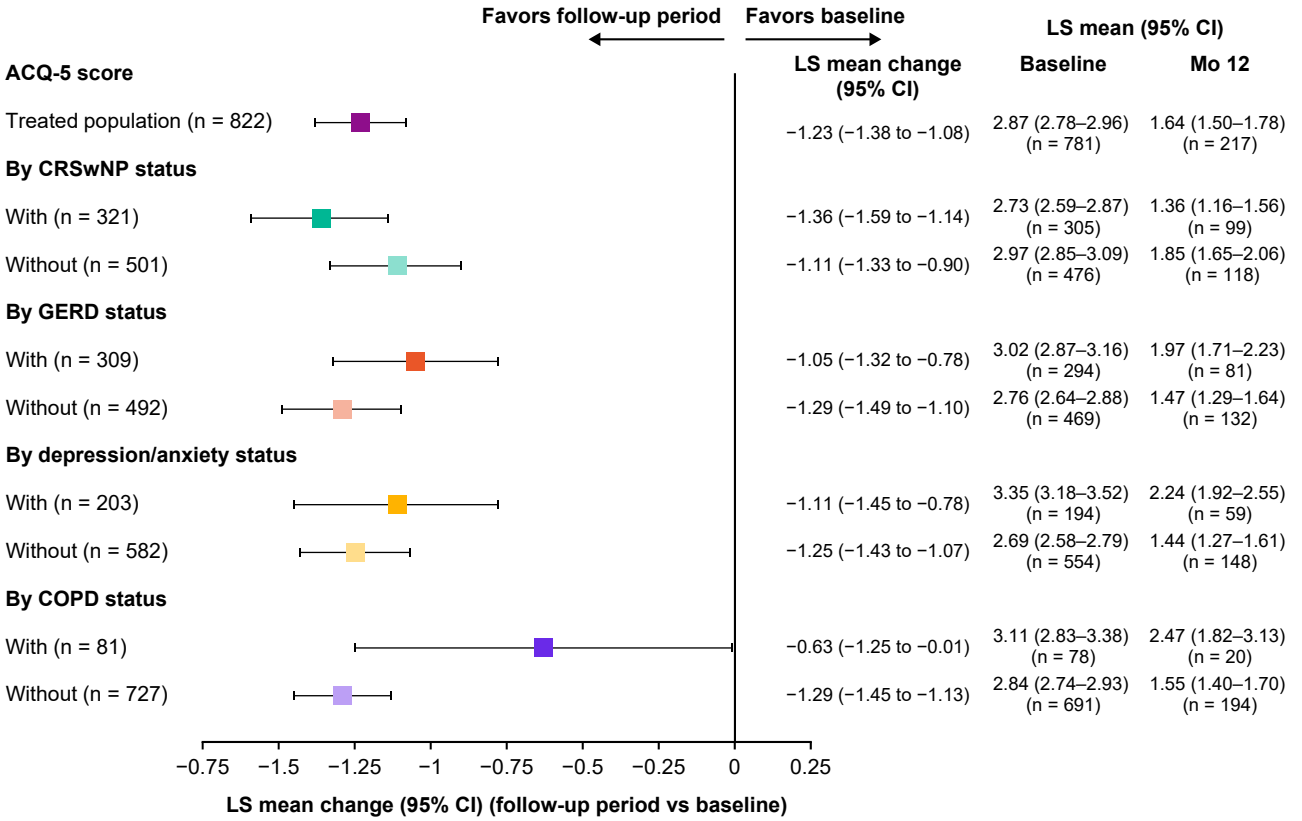

FIGURE 4. Change in asthma control from baseline* to mo 12 as measured by LS mean ACQ-5 score in the treated population[30] and stratified by CRSwNP, GERD, depression/anxiety and COPD status. Analysis performed using mixed model repeated measures with covariates of time point, country, baseline OCS therapy (yes/no), and ordinal exacerbation pretreatment (0, 1, 2, 3, and ≥4). *Baseline was defined as the value that was collected on the date of mepolizumab treatment initiation, or the nearest historical value within the 90 ds prior to mepolizumab treatment initiation.

mepolizumab treatment (mo 9−12), an increase from baseline in LS mean FEV_1 was observed for the treated population and for all comorbidity subgroups. Greater numerical increases from baseline in LS mean FEV_1 were observed for patients with CRSwNP, COPD, and depression/anxiety than patients without the respective comorbidity; patients with COPD had the greatest increase across all subgroups but confidence intervals were large. It should be noted that FEV_1 data were only available/collected when performed as per local clinical practice. As a result, data were only available within a subset of the overall study population.

DISCUSSION

In this *post hoc* analysis of the full REALITI-A patient population at 1 year, mepolizumab reduced exacerbations and OCS use, while improving asthma control and lung function in patients with severe asthma, irrespective of comorbid CRSwNP, GERD, depression/anxiety, and physician-labelled coexistent COPD. These data highlight that real-world mepolizumab treatment provides clinical benefit to patients with severe asthma with a range of comorbidities, despite the increased disease burden and difficulties in achieving asthma control that these patients typically face.[3-9,12] It was notable that baseline blood eosinophil counts were higher for patients with CRSwNP versus those without, and for patients without GERD, without depression/anxiety, or without COPD versus those with each respective comorbidity. Based on the more favorable responses across CSE, mOCS, total OCS, and ACQ-5 outcomes in the with CRSwNP subgroup, and the without GERD, depression/anxiety, or COPD subgroups compared with their respective counterparts, this may suggest a greater clinical benefit for mepolizumab in patients with higher versus lower baseline eosinophil counts. This is in line with previous studies, which analyzed outcomes by baseline blood eosinophil counts.[27,36-38] However, further analysis would be required to confirm these suggestions in REALITI-A and it should be noted that this potential association was less apparent for the FEV_1 outcome.

Mepolizumab reduced the rate of CSEs for patients with and without comorbid CRSwNP, GERD, depression/anxiety, and COPD, supporting findings from previous clinical trials and real-world studies[13,39,40,43] that have assessed the impact of comorbidities on a limited number of end points and in clinical populations. Building on these previous studies, the current data from the REALITI-A study provide further real-world evidence of the impact of mepolizumab across comorbidity subgroups in a large (n = 822) prospective, international population of patients across a range of outcomes (CSE, mOCS use, ACQ-5, and FEV_1). Mepolizumab reduced the rate of CSEs for patients across baseline blood eosinophil counts, with a small increase in

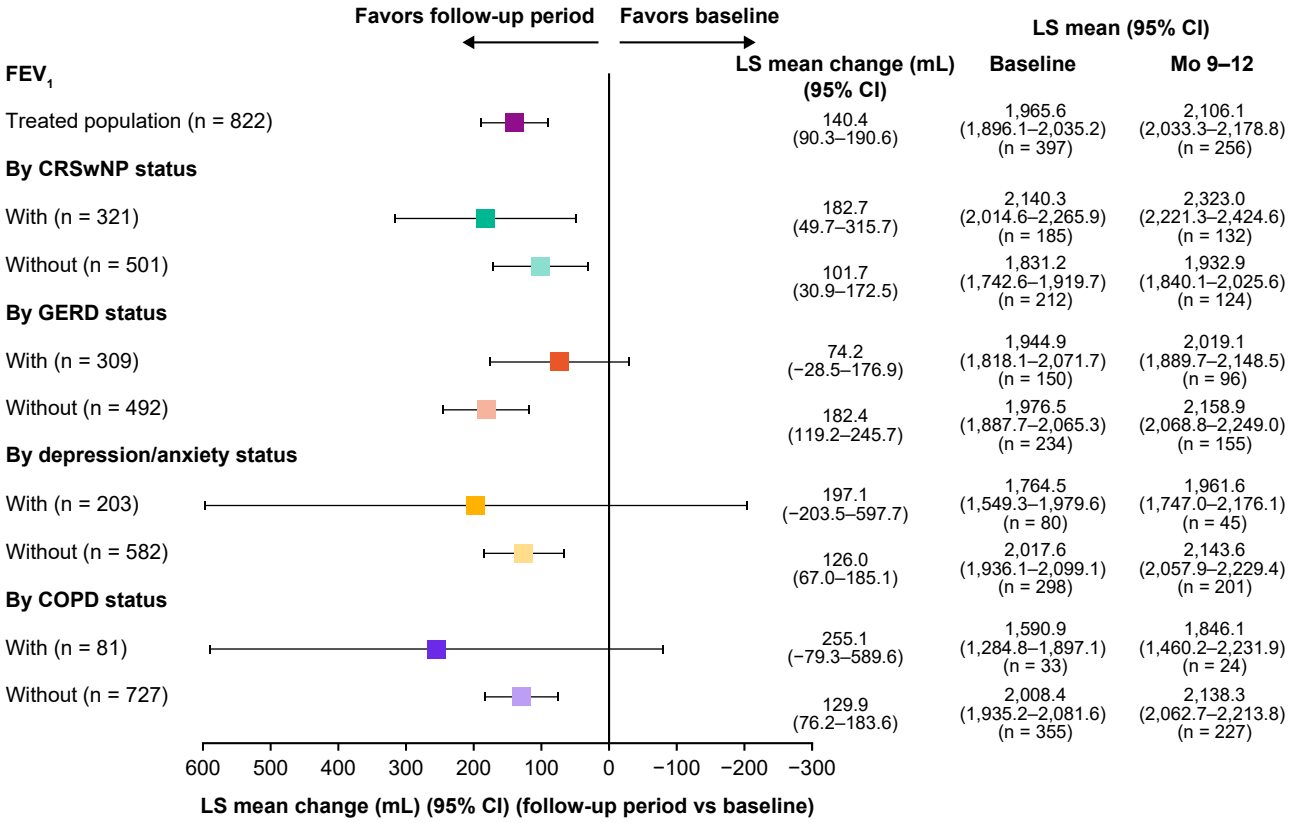

FIGURE 5. Change from baseline* in LS mean FEV_1 at mo 9–12, in the treated population[30] and stratified by CRSwNP, GERD, depression/anxiety, and COPD status. Analysis performed using mixed model repeated measures with covariates of time point, country, baseline OCS therapy (yes/no), and ordinal exacerbation pretreatment (0, 1, 2, 3, and ≥4). *Baseline was defined as the value that was collected on the date of mepolizumab treatment initiation, or the nearest historical value within the 90 d prior to mepolizumab treatment initiation.

effect size seen with increasing blood eosinophil counts. This trend was also seen in some comorbidity subgroups (such as those patients with CRSwNP and COPD) but not in others (such as patients with GERD and with depression/anxiety) suggesting that these improvements are not solely linked to baseline blood eosinophil count.

In this study, mepolizumab also effectively reduced mOCS use and dose regardless of comorbid CRSwNP, GERD, depression/anxiety, and COPD status. Of note, a greater proportion of patients with versus without these comorbidities used mOCS prior to mepolizumab treatment, indicating previous treatment escalation, potentially due to persistent inadequate asthma control. Alternatively, escalation to mOCS may contribute to the development and progression of comorbidities such as GERD and anxiety/depression, which has considerable population level implications.[14-16] It is more probable that the comorbidities are impacting asthma control instead of treatment addressing poor asthma control accounting for the comorbidities observed, although both situations are possible. Undoubtedly, it is a complex interaction because obesity and GERD are well-recognized consequences of OCS therapy.[14,16,44] Mepolizumab helps to reduce this vicious circle by reducing mOCS use and dose across all subgroups of patients with these comorbidities. This not only reduces the associated side effects of OCS use but may also help alleviate the severity of the comorbidities. Indeed, mepolizumab has been reported to reduce the hospital anxiety and depression scale score[45] and improve CRSwNP outcomes[46] during real-world use for severe asthma.[5,15,16]

Overall, this analysis highlights that patients had improvements from baseline in ACQ-5 score and FEV_1 following mepolizumab treatment, across the comorbidities assessed, with group differences exceeding the minimum clinically important difference for ACQ-5 score in all instances. However, some patient groups had greater responses in some outcomes over others. For example, the with COPD group had the highest mean age, the worst baseline FEV_1, and lesser improvements in ACQ-5 score compared with patients without COPD; however, those patients with COPD also had the largest improvements from baseline in FEV_1. The presence of comorbid COPD in this analysis is based on a label given by patients' health care professionals as a secondary condition, alongside their primary diagnosis of severe asthma and the reason for mepolizumab initiation. Chronic obstructive pulmonary disease is commonly considered a smoking-related lung disease and, indeed, both the proportions of former and current smokers and the number of smoking pack-years were higher in the with versus the without COPD subgroups. However, it is recognized that the physiological basis of COPD, namely, an obstructive pattern that is not or only partially reversible, is not confined to those with a smoking history and that longstanding asthma can also lead to

this physiological situation.[47,48] This condition has been termed asthma–chronic obstructive pulmonary disease overlap (ACO); there are specific ACO criteria and because the basis for the label of COPD was not described, we cannot determine whether patients in the current study had ACO. The finding that the largest improvements in lung function were seen in the with COPD subgroup raises the potential that these were patients whose lung function may have been bronchodilator-irreversible owing to mucus plugging,[49] and because eosinophilic inflammation has been identified as a prominent risk factor for this feature,[49,50] the improvement may be related to mepolizumab effecting clearance of mucus plugging. In the pivotal trial of mepolizumab in patients with COPD,[51] change from baseline in FEV_1 did not differ between placebo versus mepolizumab treatment arms. The contrast between these findings and our results may be due to exclusion of patients with ACO from the COPD study based on strict clinical trial criteria. Notably, our analysis is limited owing to the potential that the diagnosis of COPD from health care professionals as a secondary condition may be inaccurate and that there were a small number of patients in the with COPD subgroup. In addition the large confidence intervals for the change in lung function suggest a potential heterogeneity of response, a finding that would be commensurate with the diversity of potential underlying pathology in those with this disease label.[52]

Patients with CRSwNP had a numerically greater reduction in the rate of CSEs and mOCS dose, paralleled with greater improvement in symptom control and lung function with mepolizumab treatment compared with those patients without CRSwNP. These results are in agreement with findings from clinical trials and previous real-world studies.[20,28,40] Patients with severe asthma and comorbid CRSwNP are recognized as having a high disease burden as demonstrated by more frequent exacerbations and may, therefore, have an increased reliance on OCS,[5,53] as also observed in our analysis. Mepolizumab may serve to reduce the disease burden of this high-risk group by targeting the common pathophysiological pathway of IL-5 and eosinophilic-driven inflammation because it has proven clinical benefits in treating asthma and CRSwNP separately and together, including OCS-sparing effects.[27,30,34-38,54] These findings provide direct evidence supporting that mepolizumab should be the first-line biologic therapy for patients with severe eosinophilic asthma and comorbid CRSwNP. Of note, during the pretreatment period, patients with and without CRSwNP or with and without COPD had similar CSE rates. This would not necessarily be expected because patients with CRSwNP and COPD typically have higher rates of CSEs than patients without these comorbidities. This finding may be due to the difference in the proportion of females in the different subgroups (53% with and 70% without CRSwNP; 48% with and 65% without COPD). It has been noted previously that women are more likely to have severe asthma and higher rates of exacerbations than men, which may reflect physiological differences, differences in symptom perception and reporting, exposure to triggers, and/or lifestyle differences.[55] In addition, for the COPD subgroups, these data may also have been impacted by the relatively small size of the with COPD subgroup and/or the limitations related to the diagnosis of COPD as a secondary condition.

Whereas mOCS use (and dose) was reduced across all patients following mepolizumab treatment, reductions in OCS use were greater and OCS discontinuation more common in patients without GERD than in those with GERD. This may be related to the positive feedback cycle of asthma and high-dose mOCS contributing to the induction and progression of GERD, leading to worsening of asthma control and outcomes and then a persistent need for high-dose mOCS use.[5,14-16,53,56] Bronchial epithelial cells in severe asthma are more susceptible to exposure to reflux components (pepsin, acid, and bile acids) than those from healthy subjects,[57] potentially due to loss of tight junction proteins related to IL-5 exposure.[57,58] In severe asthma, reflux-simulated exposure leads to bronchial epithelial structural disruption, increased permeability, and increased expression of IL-33, a cytokine that would drive type 2 innate lymphoid cell development, promoting production of IL-5, thus worsening asthma. Accordingly, in severe asthma with GERD, there is increased IL-33 immunoreactivity in airway biopsies compared with severe asthma without GERD.[57]

Similar to the impact of comorbid GERD, patients without depression/anxiety had a greater reduction in OCS use and greater improvement in ACQ-5 score than patients with depression/anxiety. These findings support a previous study in which patients with depression were less likely to be considered super-responders to mepolizumab treatment than those without depression.[45] Our findings also support previous reports of greater asthma disease burden in patients with depression and/or anxiety, possibly as a result of the asthma and/or OCS use contributing to depression/anxiety symptoms.[5,15,59] Factors contributing to poorer outcomes may include depression/anxiety worsening asthma symptoms and outcomes; symptom overlap between asthma and anxiety leading to overuse of OCS; and depression/anxiety negatively impacting treatment adherence and engagement with healthy lifestyle changes.[5,59-62] In addition, similarly to GERD, depression/anxiety can be induced and/or exacerbated by OCS use further worsening asthma outcomes and perpetuating the requirement for OCS.[5,15,44,60] Nevertheless, mepolizumab treatment provided improvements across these subgroups and represents a treatment that can help improve clinical outcomes in patients with high disease burden.

The limitations of the REALITI-A study have been previously discussed.[27,30] Because data were collected during standard routine or unscheduled clinical care, there may be missing information, particularly where assessments were voluntary, such as for the patient-reported ACQ-5. This may also be particularly pertinent for lung function data, in which patients with comorbid depression/anxiety appeared to have a lower uptake of FEV_1 testing, potentially impacting confidence intervals for the outcome in this subgroup. Limitations of this analysis include its *post hoc* nature, which led to the relatively small numbers of patients in the subgroups for analysis, particularly for the COPD subgroup. In addition, there is potential for inaccuracy in the diagnosis of COPD as a secondary condition by health care professionals. Nevertheless, because the amount of improvement in each outcome following mepolizumab treatment differed depending on the comorbidity in question, our findings highlight the impact that comorbidities and their prevalence and severity have on outcomes. This is particularly relevant when considering an integrated and holistic assessment of treatment benefit, such as the emerging concept of a clinical remission target for severe asthma management.[63] The complexity of the asthma population studied in any assessment of remission outcome will be a factor to consider when evaluating outcomes.

In conclusion, these results show that mepolizumab improved real-life clinical outcomes in patients with severe asthma and comorbid CRSwNP, GERD, depression/anxiety, and COPD. Patients with comorbid CRSwNP showed a particularly favorable treatment response in all areas, whereas those with lower respiratory disease (COPD) showed favorable lung function outcomes than those without COPD. Our findings build on results from clinical trials showing mepolizumab reduced the rate of CSEs across a range of clinical characteristics and comorbidities and support the generalizability of these results to the real-world population of patients with severe asthma.[20,39,40,43]

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www.clinicalstudydatarequest.com To access data supporting this study and related study documents, please submit a request via https://www.gsk-studyregister.com/en/.

REFERENCES

1. Hinks TSC, Brown T, Lau LCK, Rupani H, Barber C, Elliott S, et al. Multidimensional endotyping in patients with severe asthma reveals inflammatory heterogeneity in matrix metalloproteinases and chitinase 3-like protein 1. J Allergy Clin Immunol 2016;138:61-75.
2. Kuo CS, Pavlidis S, Loza M, Baribaud F, Rowe A, Pandis I, et al. T-helper cell type 2 (Th2) and non-Th2 molecular phenotypes of asthma using sputum transcriptomics in U-BIOPRED. Eur Respir J 2017;49:1602135.
3. Hekking PP, Amelink M, Wener RR, Bouvy ML, Bel EH. Comorbidities in difficult-to-control asthma. J Allergy Clin Immunol Pract 2018;6:108-13.
4. Novelli F, Bacci E, Latorre M, Seccia V, Bartoli ML, Cianchetti S, et al. Comorbidities are associated with different features of severe asthma. Clin Mol Allergy 2018;16:25.
5. Porsbjerg C, Menzies-Gow A. Co-morbidities in severe asthma: clinical impact and management. Respirology 2017;22:651-61.
6. Tay TR, Hew M. Comorbid "treatable traits" in difficult asthma: current evidence and clinical evaluation. Allergy 2018;73:1369-82.
7. Laidlaw TM, Mullol J, Woessner KM, Amin N, Mannent LP. Chronic rhinosinusitis with nasal polyps and asthma. J Allergy Clin Immunol Pract 2021;9:1133-41.
8. Marcon A, Locatelli F, Dharmage SC, Svanes C, Heinrich J, Leynaert B, et al. The coexistence of asthma and COPD: risk factors, clinical history and lung function trajectories. Eur Respir J 2021;58:2004656.
9. Shaw DE, Sousa AR, Fowler SJ, Fleming LJ, Roberts G, Corfield J, et al. Clinical and inflammatory characteristics of the European U-BIOPRED adult severe asthma cohort. Eur Respir J 2015;46:1308-21.
10. Jones TL, Neville DM, Chauhan AJ. Diagnosis and treatment of severe asthma: a phenotype-based approach. Clin Med (Lond) 2018;18:s36-40.
11. Boulet LP. Influence of comorbid conditions on asthma. Eur Respir J 2009;33:897-906.
12. Denlinger LC, Phillips BR, Ramratnam S, Ross K, Bhakta NR, Cardet JC, et al. Inflammatory and comorbid features of patients with severe asthma and frequent exacerbations. Am J Respir Crit Care Med 2017;195:302-13.
13. Harvey ES, Langton D, Katelaris C, Stevens S, Farah CS, Gillman A, et al. Mepolizumab effectiveness and identification of super-responders in severe asthma. Eur Respir J 2020;55:1902420.
14. Aziz R, Saralaya D, Regan K, Walker L. Effect of oral corticosteroids on symptomatuc reflux in severe allergic asthma: is there a link? Eur Respir J 2014;44:P973.
15. Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J 2014;43:343-73.
16. Lazenby JP, Guzzo MR, Harding SM, Patterson PE, Johnson LF, Bradley LA. Oral corticosteroids increase esophageal acid contact times in patients with stable asthma. Chest 2002;121:625-34.
17. Burke H, Davis J, Evans S, Flower L, Tan A, Kurukulaaratchy RJ. A multidisciplinary team case management approach reduces the burden of frequent asthma admissions. ERJ Open Res 2016;2:00039-2016.
18. McDonald VM, Harrington J, Clark VL, Gibson PG. Multidisciplinary care in chronic airway diseases: the Newcastle model. ERJ Open Res 2022;8:00215-2022.
19. Bachert C, Han JK, Wagenmann M, Hosemann W, Lee SE, Backer V, et al. EUFOREA expert board meeting on uncontrolled severe chronic rhinosinusitis with nasal polyps (CRSwNP) and biologics: definitions and management. J Allergy Clin Immunol 2021;147:29-36.
20. Howarth P, Chupp G, Nelsen LM, Bradford ES, Bratton DJ, Smith SG, et al. Severe eosinophilic asthma with nasal polyposis: a phenotype for improved sinonasal and asthma outcomes with mepolizumab therapy. J Allergy Clin Immunol 2020;145:1713-5.
21. Yamaguchi Y, Suda T, Ohta S, Tominaga K, Miura Y, Kasahara T. Analysis of the survival of mature human eosinophils: interleukin-5 prevents apoptosis in mature human eosinophils. Blood 1991;78:2542-7.
22. Pavord ID, Menzies-Gow A, Buhl R, Chanez P, Dransfield M, Lugogo N, et al. Clinical development of mepolizumab for the treatment of severe eosinophilic asthma: on the path to personalized medicine. J Allergy Clin Immunol Pract 2021;9:1121-1132.e7.
23. Mepolizumab (Nucala) Summary of Product Characteristics; 2021. Accessed July 3, 2023. https://www.ema.europa.eu/en/documents/product-information/nucala-epar-product-information_en.pdf
24. Mepolizumab (Nucala) Prescribing Information. March 2023. Accessed July 3, 2023. https://gskpro.com/content/dam/global/hcpportal/en_US/Prescribing_Information/Nucala/pdf/NUCALA-PI-PIL-IFU-COMBINED.PDF
25. Mepolizumab (Nucala) Prescribing Information (Japan); 2020. Accessed July 3, 2023. https://gskpro.com/ja-jp/products-info/nucala/index/
26. Domingo Ribas C, Carrillo Diaz T, Blanco Aparicio M, Martinez Moragon E, Banas Conejero D, Sanchez Herrero MG, et al. REal worlD Effectiveness and Safety of mepolizumab in a multicentric spanish cohort of asthma patients stratified by eosinophils: the REDES Study. Drugs 2021;81:1763-74.
27. Harrison T, Canonica GW, Chupp G, Lee J, Schleich F, Welte T, et al. Real-world mepolizumab in the prospective severe asthma REALITI-A study: initial analysis. Eur Respir J 2020;56:2000151.
28. Kavanagh JE, d'Ancona G, Elstad M, Green L, Fernandes M, Thomson L, et al. Real-world effectiveness and the characteristics of a "super-responder" to mepolizumab in severe eosinophilic asthma. Chest 2020;158:491-500.
29. Llanos JP, Ortega H, Bogart M, Packnett ER, Manjelievskaia J, Bell CF, et al. Real-world effectiveness of mepolizumab in patients with severe asthma: an examination of exacerbations and costs. J Asthma Allergy 2020;13:77-87.
30. Pilette C, Canonica GW, Chaudhuri R, Chupp G, Lee FE, Lee JK, et al. REALITI-A study: real-world oral corticosteroid−sparing effect of mepolizumab in severe asthma. J Allergy Clin Immunol Pract 2022;10:2646-56.
31. Pini L, Caruso C, Colantuono S, Bagnasco D, Maxwell A, Price RG, et al. Prospective Italian real-world study of mepolizumab in severe eosinophilic asthma validates retrospective outcome reports. Clin Transl Allergy 2021;11:e12067.
32. Silver J, Bogart M, Packnett E, Wu J, McMorrow D, Hahn B. Real-world reductions in oral corticosteroid use in the USA following mepolizumab therapy for severe asthma. J Asthma Allergy 2020;13:689-99.
33. Taille C, Chanez P, Devouassoux G, Didier A, Pison C, Garcia G, et al. Mepolizumab in a population with severe eosinophilic asthma and corticosteroid dependence: results from a French early access programme. Eur Respir J 2020;55:1902345.
34. Menzella F, Lusuardi M, Galeone C, Taddei S, Zucchi L. Profile of anti-IL-5 mAb mepolizumab in the treatment of severe refractory asthma and hypereosinophilic diseases. J Asthma Allergy 2015;8:105-14.

35. 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 2014;371:1189-97.
36. 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 2014;371:1198-207.
37. 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 2012;380:651-9.
38. Chupp GL, Bradford ES, Albers FC, Bratton DJ, Wang-Jairaj J, Nelsen LM, et al. Efficacy of mepolizumab add-on therapy on health-related quality of life and markers of asthma control in severe eosinophilic asthma (MUSCA): a randomised, double-blind, placebo-controlled, parallel-group, multicentre, phase 3b trial. Lancet Respir Med 2017;5:390-400.
39. Casale T, Molfino NA, Silver J, Bogart M, Packnett E, McMorrow D, et al. Real-world effectiveness of mepolizumab in patients with severe asthma and associated comorbidities. Ann Allergy Asthma Immunol 2021;127:354-62.e2.
40. Gibson PG, Prazma CM, Chupp GL, Bradford ES, Forshag M, Mallett SA, et al. Mepolizumab improves clinical outcomes in patients with severe asthma and comorbid conditions. Respir Res 2021;22:171.
41. Brown T, Jones T, Gove K, Barber C, Elliott S, Chauhan A, et al. Randomised controlled trials in severe asthma: selection by phenotype or stereotype. Eur Respir J 2018;52:1801444.
42. Bonini M, Di Paolo M, Bagnasco D, Baiardini I, Braido F, Caminati M, et al. Minimal clinically important difference for asthma endpoints: an expert consensus report. Eur Respir Rev 2020;29:190137.
43. Ortega H, Li H, Suruki R, Albers F, Gordon D, Yancey S. Cluster analysis and characterization of response to mepolizumab. A step closer to personalized medicine for patients with severe asthma. Ann Am Thorac Soc 2014;11:1011-7.
44. Volmer T, Effenberger T, Trautner C, Buhl R. Consequences of long-term oral corticosteroid therapy and its side-effects in severe asthma in adults: a focused review of the impact data in the literature. Eur Respir J 2018: 521800703.
45. Fong WCG, Azim A, Knight D, Mistry H, Freeman A, Felongco M, et al. Real-world omalizumab and mepolizumab treated difficult asthma phenotypes and their clinical outcomes. Clin Exp Allergy 2021;51:1019-32.
46. Detoraki A, Tremante E, D'Amato M, Calabrese C, Casella C, Maniscalco M, et al. Mepolizumab improves sino-nasal symptoms and asthma control in severe eosinophilic asthma patients with chronic rhinosinusitis and nasal polyps: a 12-month real-life study. Ther Adv Respir Dis 2021;15: 17534666211009398.
47. Silva GE, Sherrill DL, Guerra S, Barbee RA. Asthma as a risk factor for COPD in a longitudinal study. Chest 2004;126:59-65.
48. Vonk JM, Jongepier H, Panhuysen CI, Schouten JP, Bleecker ER, Postma DS. Risk factors associated with the presence of irreversible airflow limitation and reduced transfer coefficient in patients with asthma after 26 years of follow up. Thorax 2003;58:322-7.
49. Dunican EM, Elicker BM, Gierada DS, Nagle SK, Schiebler ML, Newell JD, et al. Mucus plugs in patients with asthma linked to eosinophilia and airflow obstruction. J Clin Invest 2018;128:997-1009.
50. Tang M, Elicker BM, Henry T, Gierada DS, Schiebler ML, Huang BK, et al. Mucus plugs persist in asthma, and changes in mucus plugs associate with changes in airflow over time. Am J Respir Crit Care Med 2022;205:1036-45.
51. Pavord ID, Chanez P, Criner GJ, Kerstjens HAM, Korn S, Lugogo N, et al. Mepolizumab for eosinophilic chronic obstructive pulmonary disease. N Engl J Med 2017;377:1613-29.
52. Kitaguchi Y, Yasuo M, Hanaoka M. Comparison of pulmonary function in patients with COPD, asthma-COPD overlap syndrome, and asthma with airflow limitation. Int J Chron Obstruct Pulmon Dis 2016;11:991-7.
53. Denlinger LC, Phillips BR, Ramratnam S, Ross K, Bhakta NR, Cardet JC, et al. Inflammatory and comorbid features of patients with severe asthma and frequent exacerbations. Am J Respir Crit Care Med 2017;195:302-13.
54. Han JK, Bachert C, Fokkens W, Desrosiers M, Wagenmann M, Lee SE, et al. Mepolizumab for chronic rhinosinusitis with nasal polyps (SYNAPSE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Respir Med 2021;9:1141-53.
55. Boulet LP, Lavoie KL, Raherison-Semjen C, Kaplan A, Singh D, Jenkins CR. Addressing sex and gender to improve asthma management. NPJ Prim Care Respir Med 2022;32:56.
56. Liang B, Yi Q, Feng Y. Association of gastroesophageal reflux disease with asthma control. Dis Esophagus 2013;26:794-8.
57. Perotin JM, Wheway G, Tariq K, Azim A, Ridley RA, Ward JA, et al. Vulnerability to acid reflux of the airway epithelium in severe asthma. Eur Respir J 2022;60:2101634.
58. Barretto KT, Brockman-Schneider RA, Kuipers I, Basnet S, Bochkov YA, Altman MC, et al. Human airway epithelial cells express a functional IL-5 receptor. Allergy 2020;75:2127-30.
59. Amelink M, Hashimoto S, Spinhoven P, Pasma HR, Sterk PJ, Bel EH, et al. Anxiety, depression and personality traits in severe, prednisone-dependent asthma. Respir Med 2014;108:438-44.
60. McLoughlin RF, McDonald VM. The management of extrapulmonary comorbidities and treatable traits; obesity, physical inactivity, anxiety, and depression, in adults with asthma. Front Allergy 2021;2:735030.
61. Goodwin RD, Bandiera FC, Steinberg D, Ortega AN, Feldman JM. Asthma and mental health among youth: etiology, current knowledge and future directions. Expert Rev Respir Med 2012;6:397-406.
62. Cluley S, Cochrane GM. Psychological disorder in asthma is associated with poor control and poor adherence to inhaled steroids. Respir Med 2001;95:37-9.
63. Menzies-Gow A, Bafadhel M, Busse WW, Casale TB, Kocks JWH, Pavord ID, et al. An expert consensus framework for asthma remission as a treatment goal. J Allergy Clin Immunol 2020;145:757-65.

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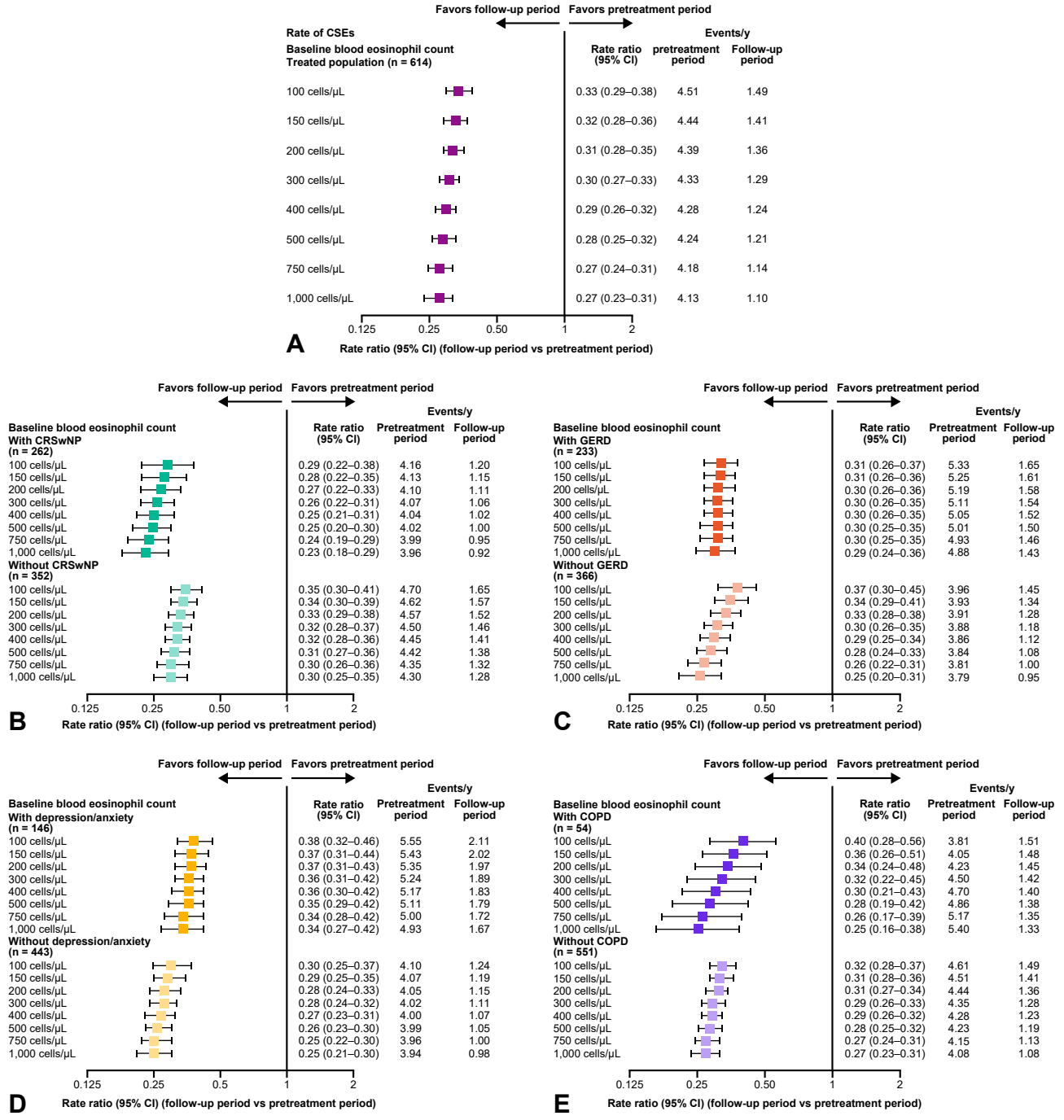

FIGURE E1. The rate of CSEs (**A**) between the pretreatment and the follow-up periods for the treated population[30] and stratified by comorbidity status ([**B**] (CRSwNP, [**C**] GERD, [**D**] depression/anxiety, [**E**] COPD) and baseline blood eosinophil counts. *COPD,* Chronic obstructive pulmonary disease; *CRSwNP,* chronic rhinosinusitis with nasal polyps; *CSE,* clinically significant asthma exacerbation; *GERD,* gastroesophageal reflux disease.

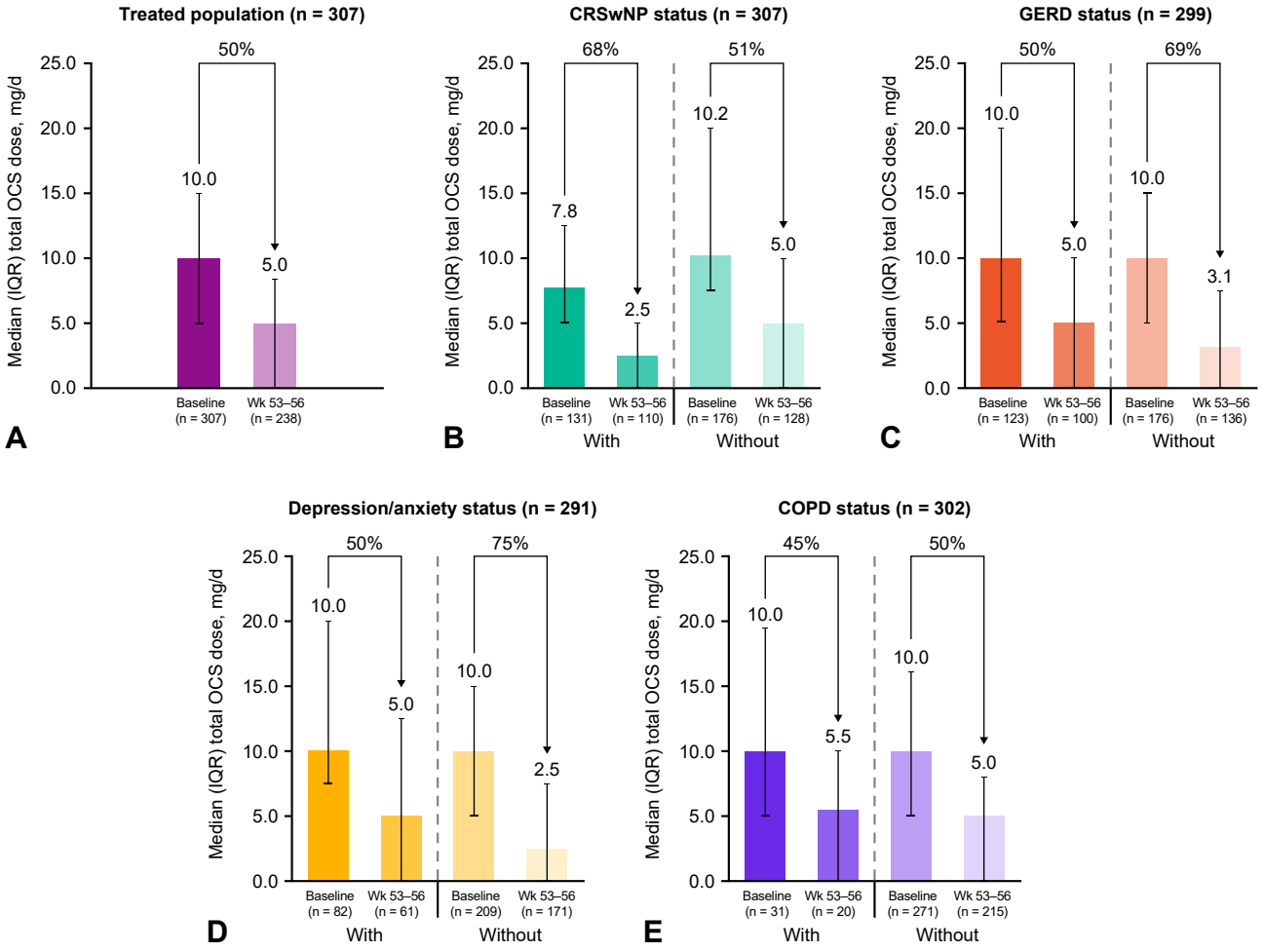

FIGURE E2. Change from baseline* in median total OCS daily dose at wk 53–56, (**A**) in the treated population[30] and stratified by (**B**) CRSwNP, (**C**) GERD, (**D**) depression/anxiety, (**E**) and COPD status. Relative percentage reductions from baseline in median total OCS daily dose at wk 53–56 are shown. Prednisone equivalent OCS dose (mg/d). *Baseline was defined as the 28 d preceding mepolizumab treatment initiation; total OCS dose was inclusive of OCS taken for both maintenance and rescue burst reasons. *COPD,* Chronic obstructive pulmonary disease; *CRSwNP,* chronic rhinosinusitis with nasal polyps; *GERD,* gastroesophageal reflux disease; *IQR,* interquartile range; *OCS,* oral corticosteroids.

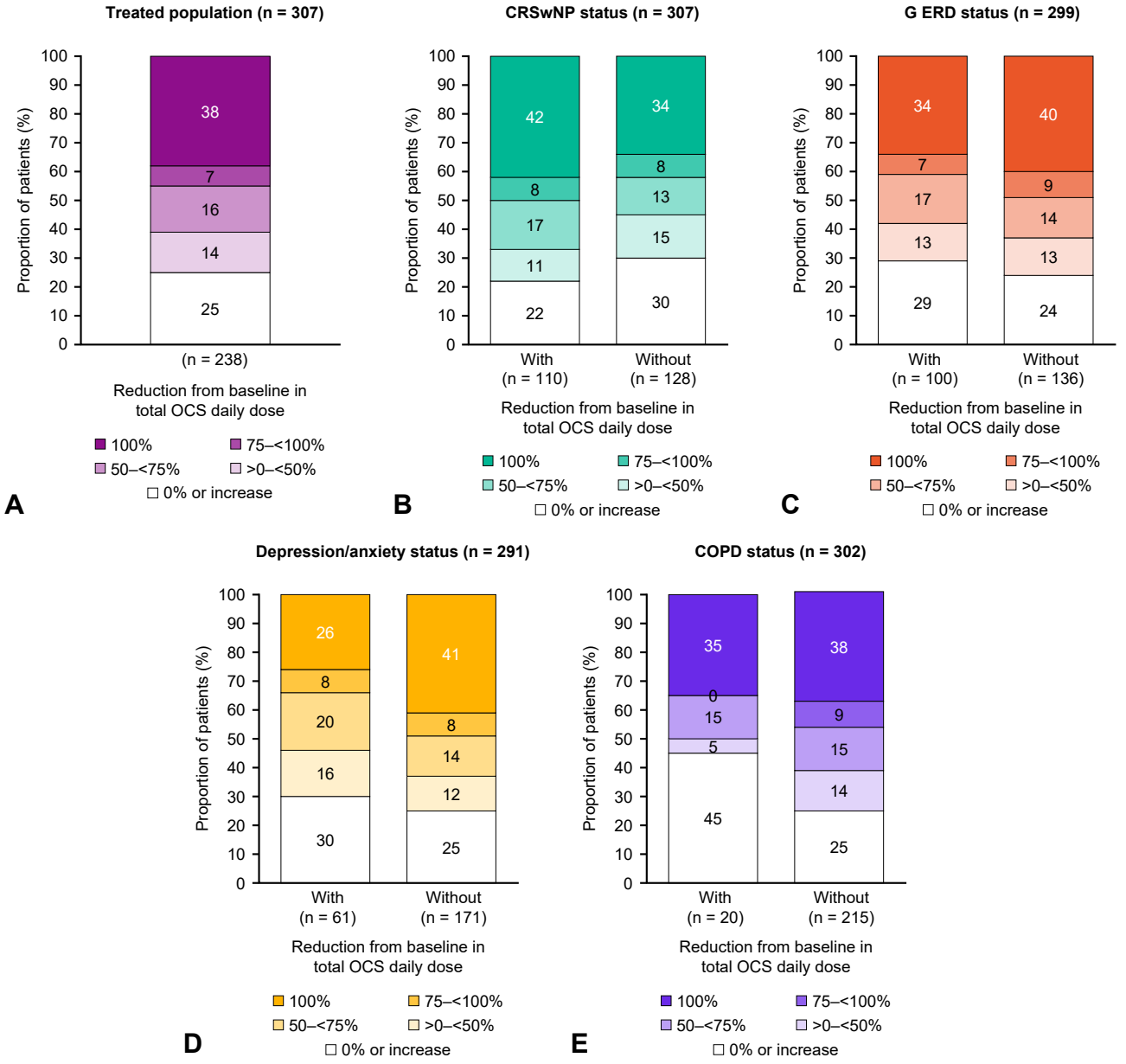

FIGURE E3. Proportion of patients with a reduction from baseline* in total OCS daily dose at Week 53–56, (**A**) in the treated population[30] and stratified by (**B**) CRSwNP, (**C**) GERD, (**D**) depression/anxiety, and (**E**) COPD status. Prednisone equivalent OCS dose (mg/day). *Baseline was defined as the 28 days preceding mepolizumab treatment initiation; total OCS dose was inclusive of OCS taken for both maintenance and rescue burst reasons. *COPD,* Chronic obstructive pulmonary disease; *CRSwNP,* chronic rhinosinusitis with nasal polyps; *GERD,* gastroesophageal reflux disease; *OCS,* oral corticosteroids.