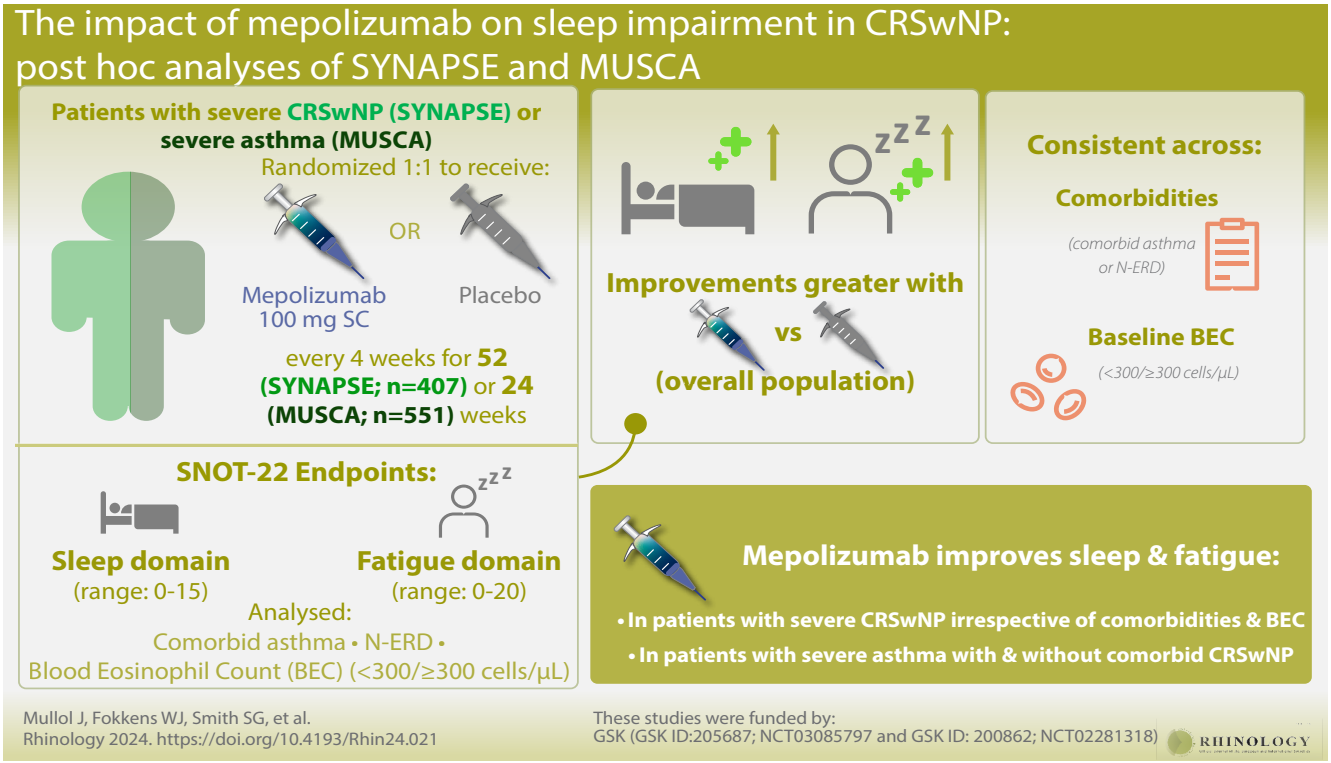
OPEN ACCESS

The impact of mepolizumab on sleep impairment in CRSwNP: post hoc analyses of SYNAPSE and MUSCA

Joaquim Mullol[1], Wytske J. Fokkens[2], Steven G. Smith[3], Tom Keeley[4], Lingjiao Zhang[5], Peter Howarth[6], Robert H. Chan[7], Claus Bachert[8,9]

Rhinology 62: 6, 669 - 680, 2024
https://doi.org/10.4193/Rhin24.021



Abstract

Background: The impact of mepolizumab on impaired sleep, one of the most bothersome symptoms in patients with chronic rhinosinusitis with nasal polyps (CRSwNP), is unknown. This study aimed to determine the effect of mepolizumab and impact of comorbid upper and lower airway disease and blood eosinophil count (BEC) on sleep-/fatigue-related outcomes in CRSwNP. **Methods**: This was an analysis of the Phase III SYNAPSE and MUSCA (NCT03085797/NCT02281318) trials of mepolizumab in patients with severe CRSwNP and severe asthma, respectively. Endpoints included change from baseline in 22-item Sino-Nasal Outcome Test (SNOT-22) sleep and fatigue domains (SYNAPSE: Weeks 24 and 52; MUSCA: Week 24) in the overall populations and post hoc subgroups (SYNAPSE: comorbid asthma, comorbid non-steroidal anti-inflammatory drug-exacerbated respiratory disease [N-ERD] and BEC [<300/≥300 cells/µL]; MUSCA: comorbid CRSwNP). **Results**: In SYNAPSE, 289/407 patients with severe CRSwNP had comorbid asthma, 108 had N-ERD, and 278 had BEC ≥300 cells/µL. In MUSCA, 105/551 patients with severe asthma had comorbid CRSwNP. Baseline sleep and fatigue scores were worse in patients with comorbid airway disease and higher BEC. Improvements from baseline in sleep and fatigue scores were greater with mepolizumab versus placebo at Week 52 in SYNAPSE (difference in least squares mean change: -2.7 [sleep], -3.4 [fatigue], and Week 24 in SYNAPSE (-1.6 and -2.2) and MUSCA (-0.8 and -1.2), with consistent results across comorbidity and BEC subgroups. **Conclusion**: Mepolizumab improves sleep and fatigue in severe CRSwNP, irrespective of comorbid airway disease and BEC, with consistent effects in severe asthma with and without comorbid CRSwNP.

Key words: CRSwNP, mepolizumab, sleep, fatigue, asthma

Introduction

Chronic rhinosinusitis with nasal polyps (CRSwNP) is characterised by chronic inflammation of the nasal cavities and paranasal sinuses, with sinonasal symptoms for >12 weeks and secondary outgrowths of sinonasal tissue into nasal polyps [1-3]. A large proportion of patients with CRSwNP exhibit an eosinophilic or type 2 inflammatory endotype [4-6]. The most common sinonasal symptoms of CRSwNP are nasal obstruction/congestion, reduction/loss of sense of smell, anterior/posterior nasal discharge, and facial pain/pressure [1]. Beyond the cardinal symptoms of CRSwNP, patients also have reduced physical and mental health, social functioning, and sleep, and impaired overall health-related quality of life (HRQoL) [1, 7-10]. In particular, previous studies have indicated that up to 90% of patients with severe CRSwNP have impaired sleep and up to approximately 80% experience negative impacts on their activities of daily living [11-13]. Sleep disruption increases with disease severity [12], and is a significant contributor to decreased HRQoL in CRSwNP [11], an increased risk of depression [11, 14, 15], and impaired cognitive function [15, 16], which can contribute to decreased work productivity [17].

In addition to conventional standard of care (SoC) treatments, Type 2 inflammation-targeting biologic therapies are now also available as add-on options for severe CRSwNP [1, 18-20]. One such biologic is mepolizumab, a first-in-class humanised monoclonal antibody that specifically inhibits interleukin (IL)-5, the primary cytokine responsible for the proliferation, activation and survival of eosinophils [21, 22]. In the Phase III SYNAPSE study in patients with severe, treatment-refractory CRSwNP, inhibition of IL-5 via treatment with mepolizumab 100 mg administered [20] subcutaneously (SC) reduced nasal polyp size and improved sinonasal symptoms. Additionally, patients treated with mepolizumab had a reduced requirement for systemic corticosteroids (SCS) and sinus surgery, compared with placebo [23]. Additionally, mepolizumab significantly reduced patients' 22-item Sino-Nasal Outcome Test (SNOT-22) total scores versus placebo, indicating improved disease-specific HRQoL [23]. However, the specific impact of mepolizumab on sleep and fatigue, as well as daily activity and work impairments in patients with CRSwNP have not been examined. In addition, the impact of comorbid upper and lower airway disease and blood eosinophil counts on these outcomes are still to be explored. This is of particular relevance given the body of evidence supporting the unified airway hypothesis, which proposes that diseases of the upper and lower airways represent a single pathological process, and therefore should be treated as such [24, 25].

The objective of this analysis was to investigate the impact of mepolizumab on sleep- and fatigue-related symptoms of severe CRSwNP, in addition to determining the impact of comorbid asthma, comorbid non-steroidal anti-inflammatory drug-exacerbated respiratory disease (N-ERD), and blood eosinophil counts on these outcomes using data from SYNAPSE in addition to the MUSCA trial of mepolizumab in patients with severe asthma [26], a proportion of whom had comorbid CRSwNP.

Materials and methods

Study designs

The study designs of SYNAPSE and MUSCA have previously been described [23, 26]. Briefly, SYNAPSE and MUSCA were Phase III, randomised, double-blind, placebo-controlled, parallel-group trials including patients with severe CRSwNP and severe asthma, respectively (205687 [NCT03085797]; 200862 [NCT02281318]).

In SYNAPSE, patients with severe CRSwNP were randomised (1:1) to receive mepolizumab 100 mg SC or placebo every 4 weeks, in addition to SoC, for 52 weeks. SoC included daily mometasone furoate nasal spray throughout the study period, in addition to saline nasal irrigations, and courses of SCS and/or antibiotics, as required. In MUSCA, patients with severe asthma were randomised (1:1) to receive mepolizumab 100 mg SC or placebo every 4 weeks, in addition to SoC, for 24 weeks. SoC included inhaled corticosteroid (ICS) and ≥1 additional controller medication such as a long-acting β_2-agonist, leukotriene receptor antagonist or theophylline.

Both studies were conducted in accordance with the ethical principles of the Declaration of Helsinki, Good Clinical Practice guidelines from the International Conference on Harmonisation, and applicable country-specific regulatory requirements. All patients provided written informed consent before initiation and the studies were approved by local ethics review boards at the participating sites.

Patient eligibility

Key patient eligibility criteria for SYNAPSE [23] included being ≥18 years of age with recurrent, severe bilateral sinonasal symptoms (according to the 2012 European Position Paper on Rhinosinusitis and Nasal Polyps) [27] that were refractory to SoC, having ≥1 endoscopic sinus surgery (a procedure involving incision and removal of nasal polyp tissue from the nasal cavity) in the prior 10 years, and being in need of further sinus surgery (defined as an overall symptoms visual analogue scale score >7 [severe disease] and endoscopic nasal polyp score of ≥5 [maximum 8], with a score ≥2 in each nasal cavity). Patients with comorbid asthma were eligible for inclusion, except for those who had an asthma exacerbation requiring hospitalisation within 4 weeks of the screening visit, those who used SCS during the 4-week pre-screening period, or those who planned to use maintenance SCS during the double-blind study period of SYNAPSE.

Key patient eligibility criteria for MUSCA [26] included being ≥12 years of age with severe asthma and having ≥2 exacerbations requiring SCS in the previous 12 months and a pre-bronchodilator forced expiratory volume in 1 second (FEV_1) <80% predicted (for patients ≥18 years) or <90% predicted (for patients 12–17 years), as per European Respiratory Society/American Thoracic Society

Table 1. Patient baseline demographics and clinical characteristics in SYNAPSE and MUSCA.

	SYNAPSE		MUSCA	
	Placebo (n=201)	**Mepolizumab 100 mg (n=206)**	**Placebo (n=277)**	**Mepolizumab 100 mg (n=274)**
Age, years, mean (SD)	48.9 (12.5)	48.6 (13.6)	52.1 (12.9)	49.8 (14.0)
Female, n (%)	76 (38)	67 (33)	176 (64)	149 (54)
Total endoscopic nasal polyp score (0-8), mean (SD)	5.6 (1.4)	5.4 (1.2)	N/A	N/A
Overall VAS score (0-10), mean (SD)	9.1 (0.7)	9.0 (0.8)	N/A	N/A
Nasal obstruction VAS score (0-10), mean (SD)	9.0 (0.8)	8.9 (0.8)	N/A	N/A
SNOT-22 scores, mean (SD)	(n=198)	(n=205)	(n=212)	(n=210)
Total score (0-110)	64.4 (19.0)	63.7 (17.6)	33.4 (21.8)	33.5 (20.5)
Sleep domain score (0-15)	8.9 (3.9)	8.7 (3.8)	5.3 (4.3)	5.0 (3.9)
Difficulty falling asleep	2.8 (1.5)	2.7 (1.4)	1.5 (1.6)	1.5 (1.4)
Wake up at night	3.0 (1.5)	2.9 (1.4)	1.9 (1.6)	1.8 (1.4)
Lack of good night's sleep	3.2 (1.4)	3.1 (1.4)	1.9 (1.6)	1.8 (1.5)
Fatigue domain score (0-20)	11.3 (5.1)	11.2 (4.8)	7.7 (5.6)	7.5 (5.4)
Wake up tired	3.2 (1.4)	3.1 (1.3)	2.0 (1.6)	1.9 (1.5)
Fatigue	3.0 (1.4)	2.9 (1.3)	2.1 (1.7)	2.0 (1.5)
Reduced productivity	2.7 (1.4)	2.8 (1.3)	2.0 (1.5)	2.0 (1.5)
Reduced concentration	2.4 (1.5)	2.5 (1.4)	1.5 (1.5)	1.5 (1.5)
Comorbidities, n (%)				
CRSwNP	201 (100)	206 (100)	47 (17)	58 (21)
Asthma	149 (74)	140 (68)	277 (100)	274 (100)
N-ERD	63 (31)	45 (22)	17 (6)	15 (6)
Blood eosinophil count, cells/μL, geometric mean (SD*)	400 (0.8)	390 (0.8)	350 (0.9)	300 (1.1)
ACQ-5 score, mean (SD)	2.2 (1.4)	2.4 (1.4)	2.2 (1.2)	2.2 (1.1)
WPAI scores (%), mean (SD)			-	-
Work time missed	n=151, 5.0 (12.88)	n=153, 4.9 (12.91)		
Impairment while working	n=148, 50.1 (30.77)	n=151, 48.1 (28.95)		
Overall work impairment	n=151, 50.8 (31.82)	n=153, 49.5 (29.76)		
Activity impairment	n=198, 53.2 (29.07)	n=204, 53.4 (27.99)		

*SD of log-transformed eosinophil count. ACQ-5, Asthma Control Questionnaire; CRSwNP, chronic rhinosinusitis with nasal polyps; N-ERD, non-steroidal anti-inflammatory drug-exacerbated respiratory disease; SC, subcutaneous; SD, standard deviation; SNOT-22, mean 22-item Sino-Nasal Outcome Test; VAS, visual analog scale; WPAI, Work Productivity and Activity Impact questionnaire.

criteria for severe uncontrolled asthma [28]. Excluded patients were current or former smokers (≥10 pack years), those with concurrent respiratory disease, and those and who had received omalizumab ≤130 days prior to screening. Patients with comorbid CRSwNP were eligible for inclusion.

Endpoints and assessments

This analysis focused on sleep-related endpoints from the SYNAPSE and MUSCA studies. SYNAPSE endpoints included changes from baseline to Week 52 in: SNOT-22 sleep domain and item scores, SNOT-22 fatigue domain and item scores, Asthma Control Questionnaire (ACQ-5) score (in patients with comorbid asthma only), and Work Productivity and Activity Impairment (WPAI) questionnaire scores. These endpoints were assessed in the overall SYNAPSE patient population receiving mepolizumab or placebo; to investigate the impact of comorbid upper and lower airway disease and blood eosinophil counts on these outcomes, post hoc subgroup analyses of patients stratified by comorbid asthma (yes/no), N-ERD (yes/no), and blood eosinophil count threshold (<300 or ≥300 cells/μL) were also performed.

Endpoints were also assessed at Week 24 in the overall populations of SYNAPSE and MUSCA, and post hoc in subgroups of patients with comorbid asthma and comorbid CRSwNP, respectively; endpoints included change from baseline at Week 24 in the SNOT-22 sleep domain and item scores, SNOT-22 fatigue domain and item scores, and ACQ-5 scores (for all MUSCA patients and SYNAPSE patients with comorbid asthma only).

The established minimal clinically important difference (MCID) for total SNOT-22 score is 8.9 [29]. The MCID for ACQ-5 is a 0.5

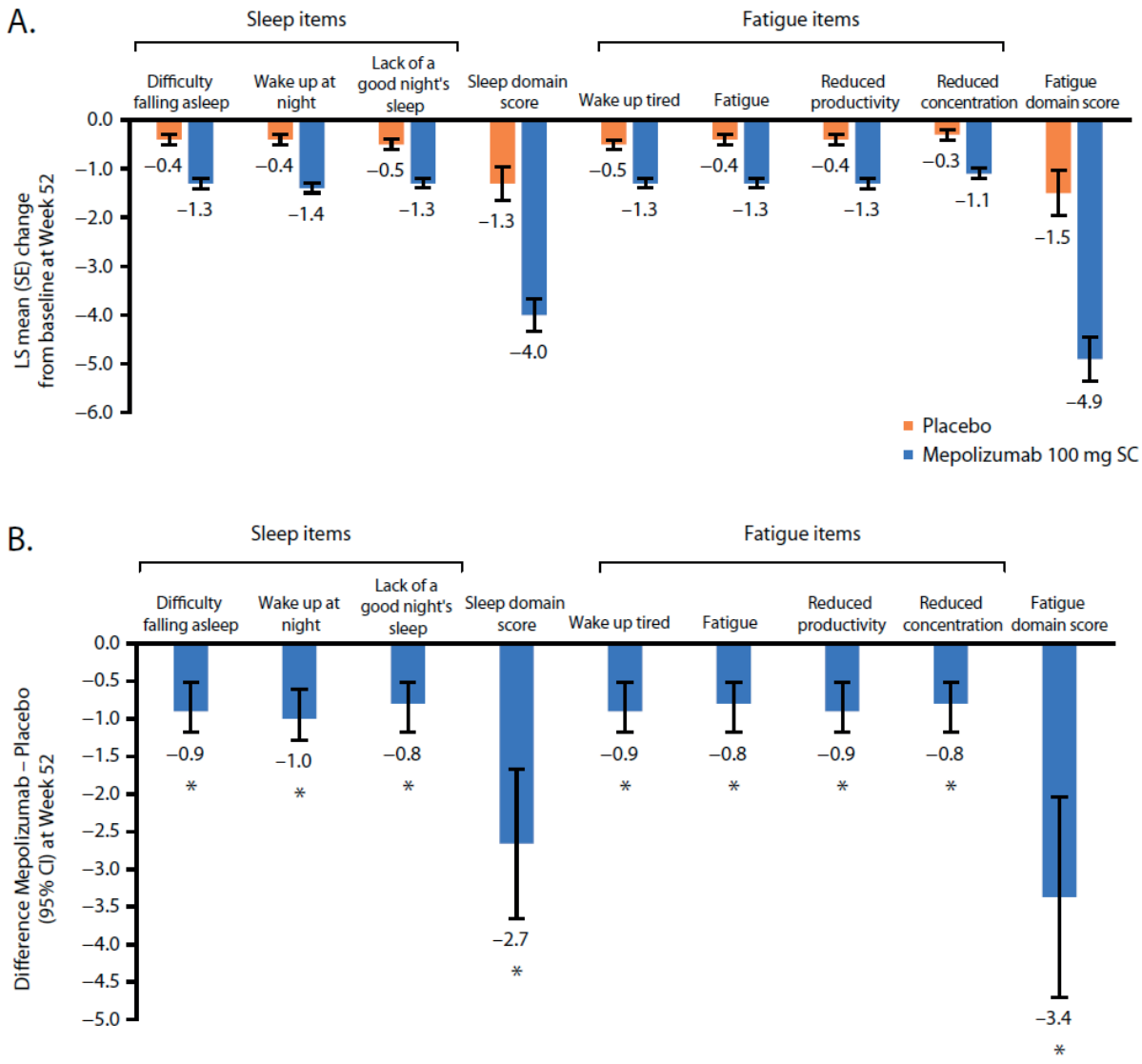


Figure 1. A) Change from baseline and B) treatment difference in SNOT-22 sleep and fatigue domains and items at Week 52 for mepolizumab versus placebo (SYNAPSE population). *p<0.001; Data available for 403 patients at Week 52 (placebo n=198, mepolizumab n=205); One patient in the mepolizumab group and three patients in the placebo group with missing baseline data were excluded from the analysis. Note: p-values have not been adjusted for multiple testing. CI, confidence interval; LS, least squares; SNOT-22, mean 22-item Sino-Nasal Outcome Test; SC, subcutaneous; SE, standard error.

change in total score [30]. For WPAI, a study in patients receiving surgery for chronic rhinosinusitis reported an MCID of ≥15.2% for improvement in impairment while working and ≥14.5% for activity impairment [31].

Statistical analysis

Change from baseline in SNOT-22 sleep and fatigue domain and individual item scores were reported as least squares (LS) mean (standard error). Treatment differences between mepolizumab and placebo were analysed using a mixed model repeated measures model adjusted for covariates and reported as mean 95% confidence interval [CI]). For the SYNAPSE population, covariates included treatment group, geographic region, baseline, log(e) baseline blood eosinophil count, visit and interaction terms for visit by baseline and visit by treatment group. Estimates were based on weighting applied to each level of class variable determined from observed proportions. Patients who had sinus surgery before Week 52, withdrew from the study early, or had missing data were assigned their worst observed score before the event for all subsequent visits. For the MUSCA population, covariates included baseline, region, baseline maintenance oral corticosteroid (OCS) therapy (OCS vs no OCS), exacerbations in the year prior to the study (as an ordinal variable), baseline % predicted FEV_1, treatment and visit, plus interaction terms for visit by baseline and visit by treatment group.

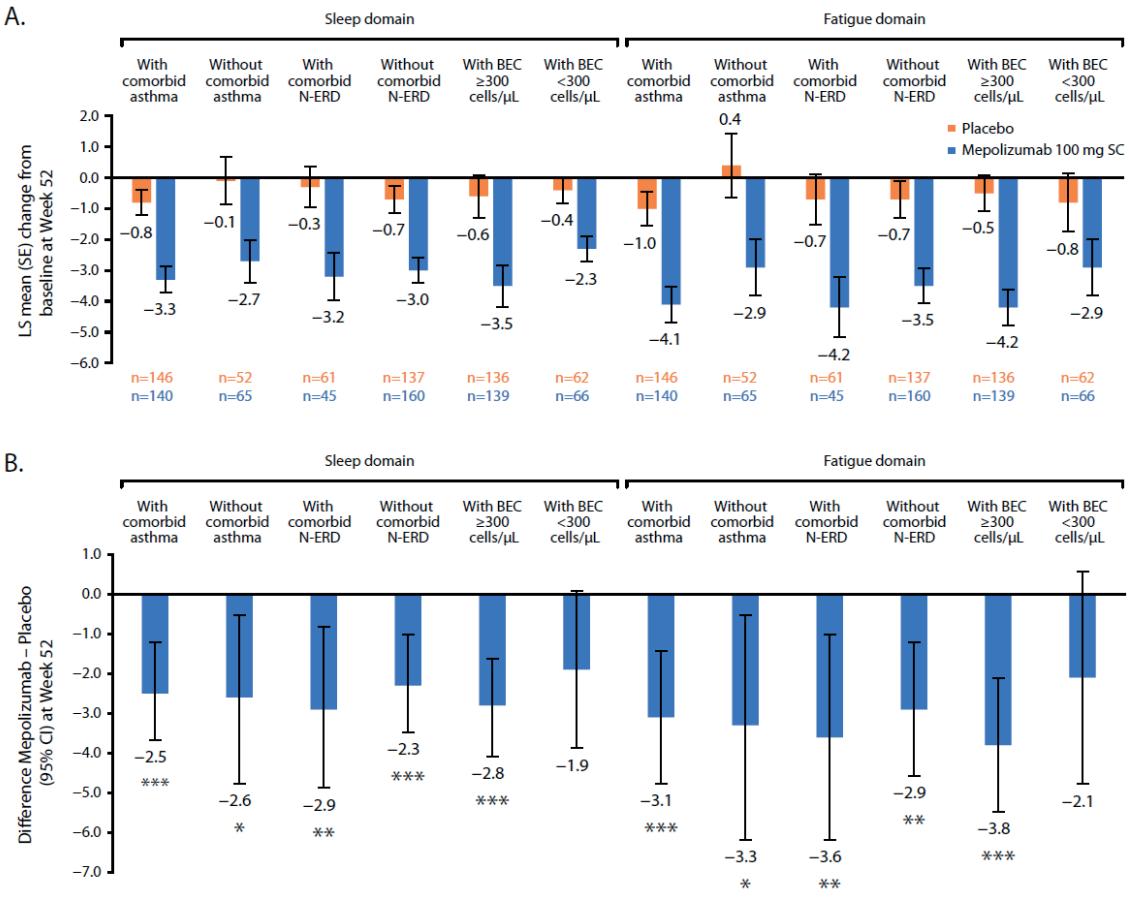


Figure 2. Impact of comorbidities and blood eosinophil count on A) change from baseline and B) treatment difference in SNOT-22 sleep and fatigue domains at Week 52 for mepolizumab versus placebo (SYNAPSE population). P-values: ***<0.001; **0.001–<0.01; *0.01–≤0.05. Note: p-values have not been adjusted for multiple testing. BEC, blood eosinophil count; CI, confidence interval; LS, least squares; N-ERD, non-steroidal anti-inflammatory drug-exacerbated respiratory disease; SNOT-22, mean 22-item Sino-Nasal Outcome Test; SC, subcutaneous; SE, standard error.

Results

Patients

Of the 407 patients with severe CRSwNP in the overall SYNAPSE population, 289 (71%) had comorbid asthma, 108 (27%) had comorbid N-ERD and 278 (68%) had blood eosinophil counts ≥300 cells/µL. Of the 551 patients with severe asthma in the overall MUSCA population, 105 (19%) had comorbid CRSwNP. Baseline SNOT-22 sleep and fatigue domain scores for SYNAPSE and MUSCA, patient demographics and baseline characteristics for SYNAPSE and patient demographics and nasal polyp status for MUSCA are included in Table 1. In the SYNAPSE population, patients with comorbid airway disease and higher blood eosinophil counts had numerically higher baseline SNOT-22 sleep and fatigue domain scores, indicating higher impact on sleep and fatigue; baseline WPAI scores were similar between subgroups with no noticeable trends observed (Supplementary Table 1). In the MUSCA population, baseline SNOT-22 sleep domain scores, and to a lesser extent baseline SNOT-22 fatigue domain scores were higher in patients with comorbid CRSwNP versus without CRSwNP (Supplementary Table 1).

Change from baseline in SNOT-22 sleep and fatigue domain and item scores at Week 52 (SYNAPSE)

Improvements from baseline to Week 52 in sleep and fatigue domain scores, in addition to individual items from these domains, were larger with mepolizumab compared with placebo (Figure 1A). These treatment differences were significantly greater ($p<0.001$) for sleep and fatigue domain scores (difference in LS mean change: -2.7 and -3.4, respectively) and all sleep- and fatigue-related SNOT-22 item scores (Figure 1B). Improvements from baseline at Week 52 in SNOT-22 sleep and fatigue domain scores were numerically larger with mepolizumab versus placebo, irrespective of comorbid asthma, comorbid N-ERD, and blood eosinophil count (Figures 2A and B).

Change from baseline in ACQ-5 score and WPAI score at Week 52 (SYNAPSE)

Patients with comorbid asthma treated with mepolizumab versus placebo had a greater reduction from baseline in ACQ-5 score at Week 52 (LS mean change: -1.12 vs -0.46 points), indicating improved disease control with mepolizumab (treatment

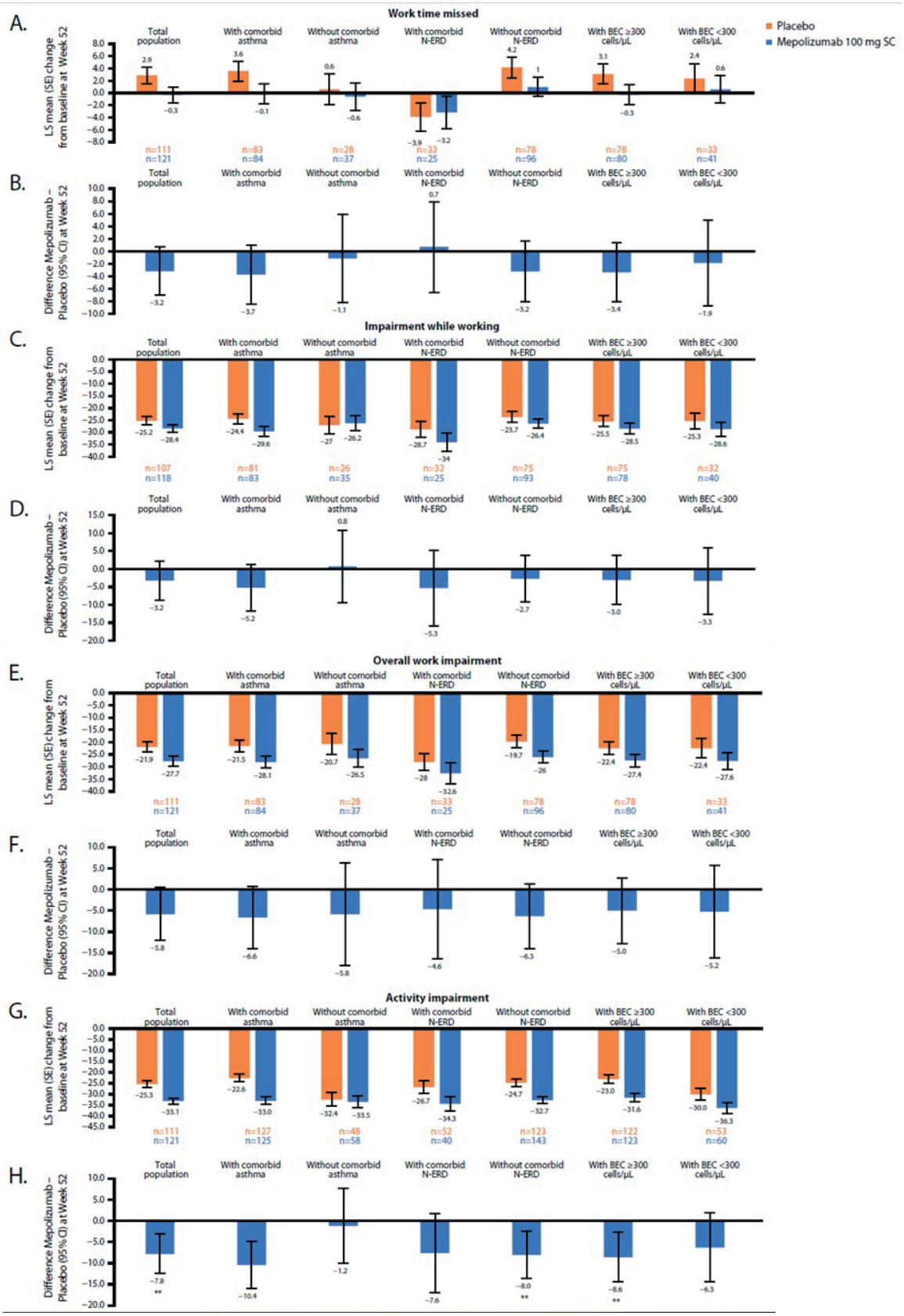


Figure 3. Impact of comorbidities on change from baseline in LS mean (SE) and treatment difference in WPAI scores at Week 52 (SYNAPSE population) on A&B) Work time missed; C&D) Impairment while working; E&F) Overall work impairment and; G&H) Activity impairment. P-values: ***<0.001; **0.001–<0.01; *0.01–≤0.05. BEC, blood eosinophil count; CI, confidence interval; LS, least squares; N-ERD, non-steroidal anti-inflammatory drug-exacerbated respiratory disease; WPAI, Work Productivity and Activity Impact questionnaire; SC, subcutaneous; SE, standard error.

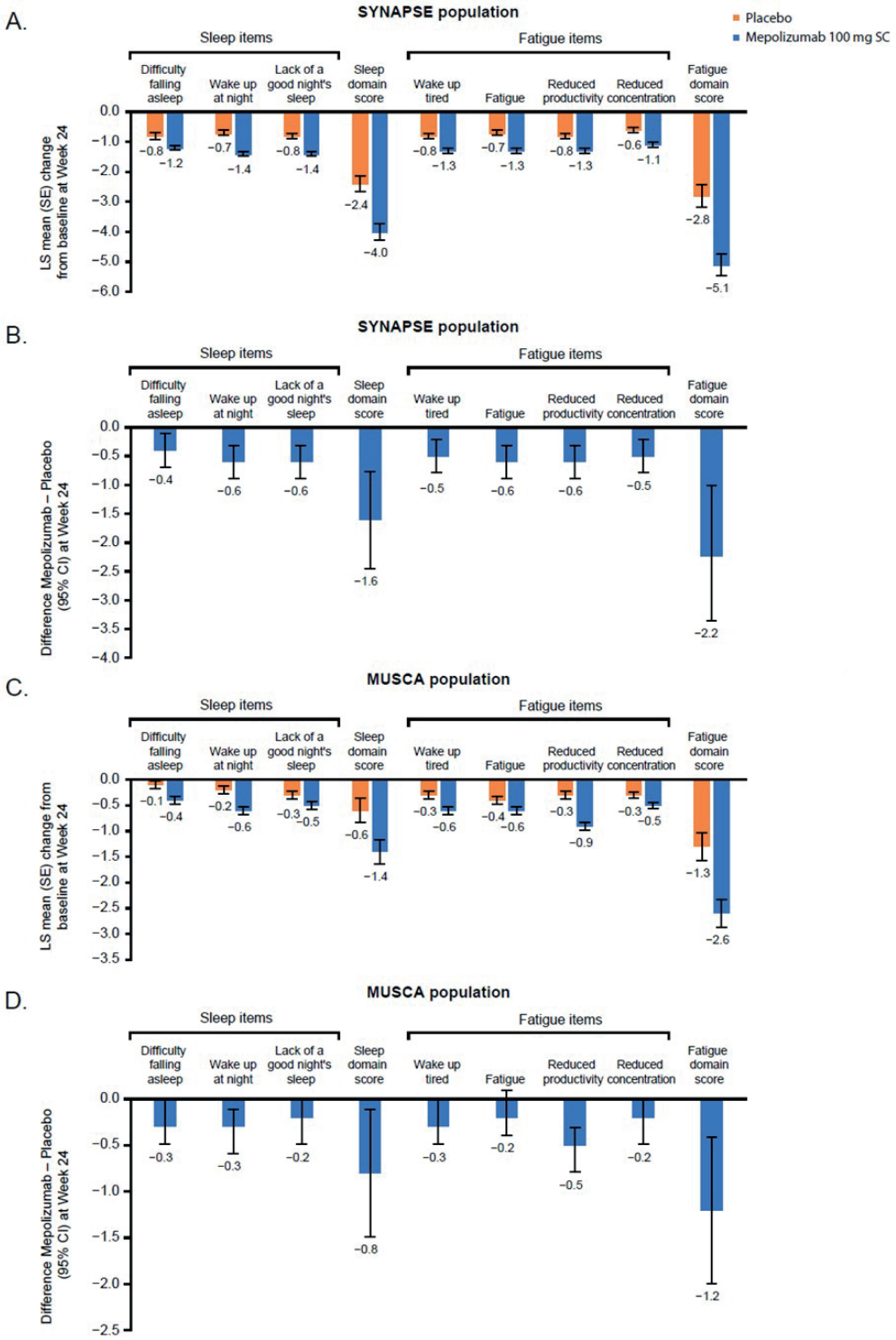


Figure 4. A) Change from baseline and B) treatment difference for SYNAPSE population and C) change from baseline and D) treatment difference for MUSCA population in SNOT-22 sleep and fatigue domain and item scores at Week 24 for mepolizumab (SYNAPSE: N=194; MUCSA: N=204) versus placebo (SYNAPSE: N=189; MUCSA N=201). Analysis was performed separately for each item using mixed model repeated measures with covariates of treatment group, geographic region, baseline, log(e) baseline blood eosinophil count, visit plus interaction terms for visit by baseline and visit by treatment group. Estimates are based on weighting applied to each level of class variable determined from observed proportions. Patients with nasal surgery/sinuplasty prior to visit were assigned the worst possible score across all patients. CI, confidence interval; LS, least squares; SNOT-22, mean 22-item Sino-Nasal Outcome Test; SC, subcutaneous; SE, standard error.

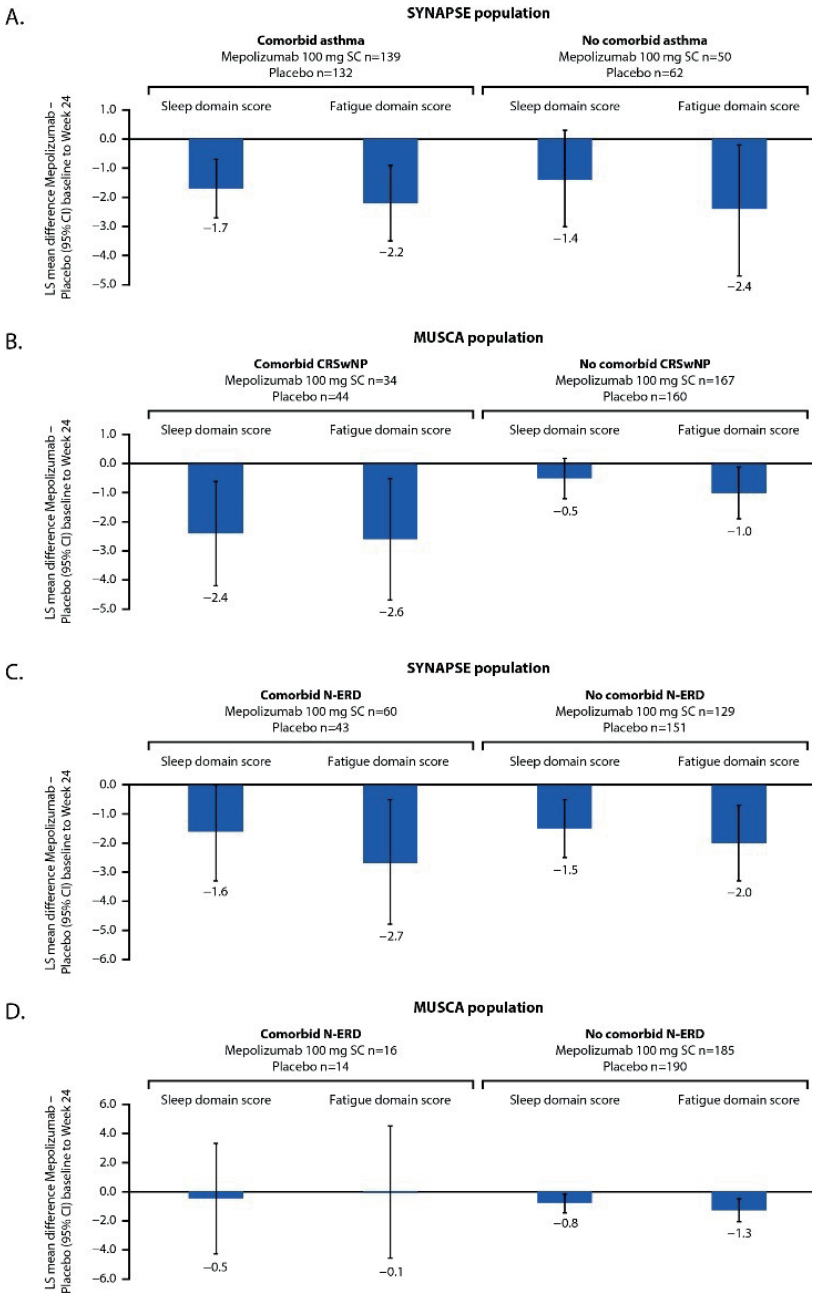


Figure 5. Impact of comorbidities on change from baseline at Week 24 on SNOT-22 sleep and fatigue domain and item scores (A. SYNAPSE and B. MUSCA; C. SYNAPSE with/without N-ERD; D. MUSCA with/without N-ERD). CI, confidence interval; CRSwNP, chronic rhinosinusitis with nasal polyps; LS, least squares; N-ERD, non-steroidal anti-inflammatory drug-exacerbated respiratory disease; SC, subcutaneous; SE, standard error; SNOT-22, mean 22-item Sino-Nasal Outcome Test.

difference: -0.66 [95% CI: -0.92, -0.40]; p<0.001).

In the total SYNAPSE population, WPAI scores were lower with mepolizumab compared with placebo, indicating less impairment on work and daily activities (Figure 3A–H). Results for the airway comorbidity and blood eosinophil count subgroups were similar to the total population, although patients with a blood eosinophil count ≥300 cells/μL tended to have higher WPAI domain scores, indicating more impairment than patients with counts <300 cells/μL.

Change from baseline in SNOT-22 sleep and fatigue domain and item scores, and ACQ-5 score at Week 24 (SYNAPSE and MUSCA populations)

At Week 24, patients in the SYNAPSE and MUSCA populations treated with mepolizumab had larger reductions in sleep and fatigue domain scores and items compared with placebo (Figure 4A–D); these treatment differences were generally larger in the SYNAPSE versus the MUSCA population, including sleep domain scores (-1.6 vs -0.8) and fatigue domain scores (-2.2 vs -1.2).

When assessed by subgroups, patients with a primary diagnosis of severe CRSwNP (SYNAPSE) and patients with a primary diagnosis of severe asthma (MUSCA) had numerically larger improvements from baseline to Week 24 in SNOT-22 sleep and fatigue domain scores with mepolizumab versus placebo, irrespective of comorbid asthma (SYNAPSE) or CRSwNP (MUSCA) (Figure 5A and 5B). Treatment differences in SNOT-22 sleep and fatigue scores were similar for SYNAPSE patients with and without comorbid asthma but MUSCA patients with comorbid CRSwNP had numerically greater differences than those without CRSwNP (Figure 5A and 5B).

At Week 24, SYNAPSE patients with comorbid asthma treated with mepolizumab versus placebo had a larger LS mean reduction from baseline in ACQ-5 score (-0.71 vs -1.22 points), indicating improved asthma control with mepolizumab (treatment difference: -0.51 [95% CI: -0.76, -0.26]; p<0.001). The change from baseline reported here for both placebo and mepolizumab exceeds the commonly accepted MCID for ACQ-5 (30). For patients in MUSCA with comorbid CRSwNP, LS mean reductions from baseline in SNOT-22 scores were also greater with mepolizumab versus placebo for sleep (-2.5 vs -0.1 points; treatment difference: -2.4 [95% CI: -4.2, -0.6]) and fatigue (-2.9 vs -0.3 points; treatment difference: -2.6 [95% CI: -4.7, -0.5]).

Discussion

This is the first analysis to examine the effect of mepolizumab on sleep- and fatigue-related symptoms in patients with CRSwNP, including how comorbid upper and lower airway disease impacts these outcomes. The results indicated that mepolizumab reduced sleep disturbances and fatigue in patients with CRSwNP, the former being one of the most common and bothersome patient-reported symptoms of the disease [7, 11, 13, 32], and that reductions in these disease impacts in these patients were irrespective of the presence of comorbid asthma/N-ERD or baseline blood eosinophil count. Additionally, in patients with a primary diagnosis of severe asthma treated with mepolizumab in MUSCA, reductions in sleep impairment were observed in those with comorbid CRSwNP. Similarly, reductions in fatigue were observed in patients with and without comorbid CRSwNP. Together, these findings suggest that mepolizumab provides sleep benefits across patients with severe CRSwNP and severe asthma, supporting the united airways disease hypothesis.

This corresponds with the results of two previous studies, which found that the severity of CRSwNP, and presence and severity of allergic rhinitis, are both predictors of increased risk of sleep impairment [33, 34]. However, it should be noted that other studies have not shown an association between nasal polyp scores and sleep impairment when analysing Lund–Mackay computed tomography score and endoscopy grading [11, 35].

The basis on which comorbid airway disease increases sleep impairment may be due to several factors, including a direct impact from an increased burden of respiratory symptoms and/or further inflammatory changes [36]. This is supported by a previous questionnaire study, which found that the prevalence of sleep problems increase with the number of sinonasal symptoms patients experience [12]. Similarly, a prospective study found an association between daytime sleepiness and nasal blockage, in addition to a correlation between daytime sleepiness and disease severity, as indicated by SNOT-22 score [35]. Furthermore, individual CRSwNP symptoms including nasal obstruction, anterior nasal drainage, facial pain/pressure, headache, and cough, and characteristic symptoms of asthma such as wheezing and chest tightness are all significantly associated with increased risk of sleep impairment [33, 37]. The relationship to the impact of chronic inflammation on sleep may be bidirectional, with Type 2 inflammation (as reflected by the altered expression of cytokines IL-4 and IL-13), resulting in disturbed sleep [38], and sleep deprivation in turn inducing changes in inflammatory marker expression [39]. In mice, alteration in the circadian rhythm regulator, brain and muscle aryl hydrocarbon receptor nuclear translocator-like 1 increased IL-5 levels and eosinophil counts [40]. In the current study, higher blood eosinophil counts were associated with worse SNOT-22 sleep domain scores at baseline, although whether this was due to a direct impact of the inflammation associated with blood eosinophil counts or an increased severity of symptoms due to inflammation is unknown. Overall, further research is required to establish the relationship between sleep disturbance, symptoms, and inflammation in CRSwNP and asthma.

Mepolizumab-treated SYNAPSE patients slept better and were less fatigued than those receiving placebo irrespective of comorbid asthma/N-ERD, as indicated by greater improvements in SNOT-22 sleep and fatigue domain scores, both of which have previously been validated for patients with moderate-to-severe CRSwNP [41]. Although numerical improvements with mepolizumab versus placebo were clear for patients irrespective of baseline blood eosinophil count, only the improvement for patients with baseline blood eosinophil count ≥300 reached statistical significance; in those with baseline blood eosinophil count <300 cells/μL the benefit of mepolizumab was not statistically significant for either domain. Additionally, improvements in sleep and fatigue were also seen for patients with a primary diagnosis of severe asthma in MUSCA after 24 weeks of mepolizumab treatment, although treatment differences were approximately half those seen for patients with a primary diagnosis of CRSwNP in SYNAPSE at the same timepoint. This difference is likely a reflection of the severity of the CRSwNP population in SYNAPSE, as indicated by criteria such as a need of further sinus surgery. Interestingly, improvements in SNOT-22 sleep and fatigue domain scores with mepolizumab versus placebo were larger in patients from MUSCA with severe asthma

and comorbid CRSwNP, compared with those without CRSwNP. Together, these results suggest that the symptoms and pathology of CRSwNP have a greater impact on sleep and fatigue than those of asthma, and that sleep impairment and fatigue, as measured by SNOT-22 domains, are constructs that better score the impact of CRSwNP severity than asthma severity. Nevertheless, the improvement in sleep and fatigue domain scores in patients with severe asthma without comorbid CRSwNP suggest that mepolizumab provides sleep and fatigue benefits across both severe CRSwNP and severe asthma. These results also provide support for the united airways disease hypothesis, and suggest that eosinophils and IL-5 have pathological roles in both diseases [24, 25].

Patients with severe CRSwNP from the SYNAPSE study treated with mepolizumab had lower WPAI scores at study end than those receiving placebo, suggesting mepolizumab reduces work impairment, with generally similar results in the comorbidity and blood eosinophil subgroups. This may be a result of improved sleep and reduced fatigue, particularly given that the SNOT-22 fatigue domain items for reduced productivity and reduced concentration were significantly improved with mepolizumab treatment. However, despite this, for patients without comorbid asthma there was not any significant difference between treatments for work time missed, impairment while working, or activity impairment.

The treatment benefits of mepolizumab may also contribute to the previously demonstrated meaningful improvements in HRQoL [42], particularly given the association between HRQoL and sleep [11]. HRQoL in patients with severe CRSwNP, including those with coexisting asthma/N-ERD, is as severely affected as for patients with diseases including type 2 diabetes, rheumatoid arthritis, and asthma [43]. It remains to be established whether mepolizumab also improves disease-associated depression and impaired cognition, both of which are increased in CRSwNP [14-16]. Overall, these results suggest that in addition to reducing nasal polyp size, symptoms, quality of life, and the need for SCS and sinus surgery over SoC treatment alone [23], mepolizumab reduces the impact of CRSwNP on sleep and fatigue, across patients with comorbid upper and lower airway disease and across baseline blood eosinophil count thresholds. These benefits are also further to the consistent improvements in nasal polyp size and nasal obstruction with mepolizumab versus placebo demonstrated across comorbidity and blood eosinophil count subgroups in a previous analysis of SYNAPSE [44]. Similarly, the results also suggest that mepolizumab versus placebo provides sleep and fatigue benefits in patients with severe asthma both with and without comorbid CRSwNP, further to the previously demonstrated reductions in exacerbation frequency and improvements in symptoms, HRQoL and lung function across comorbidity subgroups (including CRSwNP, sinusitis and allergic rhinitis) [45].

The limitations of this study should be considered when interpreting results. First, comorbid asthma and N-ERD in patients from SYNAPSE and comorbid CRSwNP in patients from MUSCA were determined using medical history. Therefore, not all patients may have met a more formal definition of either comorbidity. Second, the number of patients in some subgroups was small, particularly those with comorbid N-ERD in SYNAPSE and those with comorbid CRSwNP in MUSCA; moreover, the post hoc assessment of outcomes in subgroups precluded statistical testing to determine differences between subgroups. Additionally, SNOT-22 is validated for use as a composite score; however, for the purposes of this study the sleep-relevant components have been analysed separately, and the tailored subdomain used requires cautious interpretation in relation to findings from other studies using the standard definition. This bespoke approach reflects the specific clinical framework of our study but may limit the comparability of our findings with those studies using a broader, established metric. Finally, it should be noted that SYNAPSE was a 52-week study and was therefore not designed to compare endpoints at Week 24; as such, the SYNAPSE results should be interpreted with caution.

Conclusion

These results suggest that mepolizumab improves sleep disturbances and reduces fatigue in patients with severe CRSwNP, irrespective of comorbid asthma, N-ERD, and baseline blood eosinophil count. Improvements in these symptoms were also observed in patients with severe asthma both with and without comorbid CRSwNP, suggesting inhibition of IL-5 by mepolizumab treatment provides improvements in sleep impairment and fatigue across both patients with severe CRSwNP and severe asthma.

Acknowledgement

Editorial support (in the form of writing assistance, including preparation of the draft manuscript under the direction and guidance of the authors, collating, and incorporating authors' comments for each draft, assembling tables and figures, grammatical editing and referencing) was provided by Laura Murch, PhD, at Fishawack Indicia Ltd, UK, part of Avalere Health, and was funded by GSK.

Authors' contributions

WJF and CB contributed to the acquisition of data, RHC contributed to conception and design, and all authors contributed to the data analysis and interpretation, development of the manuscript, and approval of the final draft to be published. All authors reviewed and revised the manuscript critically for important intellectual content, agreed to submit to the current journal, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work. All authors had access to the study data.

Funding

These studies were funded by GSK (GSK ID: 205687/NCT03085797; 200862 NCT02281318). Medical writing and editorial support (in the form of writing assistance, including development of the initial draft based on author direction, assembling tables and figures, collating, and incorporating authors' comments on the drafts, grammatical editing, and referencing) was funded by GSK. Authors had roles in the conception, design, and acquisition of data for the study. All authors participated in the development of the manuscript and had access to the study data. The decision to submit for publication was that of the authors alone. The sponsor did not place any restrictions on access to the data or on the statements made in the manuscript. The corresponding author had final responsibility for the decision to submit for publication.

Conflicts of interest

JM has received research grants from AstraZeneca, Genentech, GSK, Viatris, Novartis, Regeneron, Sanofi-Genzyme and Noucor/Uriach Group, consulting fees from Sanofi-Genzyme and Noucor/Uriach Group and attended speaker bureaus and/or advisory boards for AstraZeneca, Genentech, GSK, Glenmark, Lilly, Menarini, Mitsubishi-Tanabe Pharma, MSD, Viatris, Novartis, Proctor & Gamble, Regeneron, Pharmaceuticals Inc., Sanofi Genzyme, UCB Pharma and Noucor/Uriach Group. WJF declares advisory board attendance and participation as a trial investigator for GSK, clinical trial funding from GSK, Sanofi, Mylan, ALK, Allergy Therapeutics, Novartis and Chordate, and personal fees from GSK and Sanofi. SGS, TK, LZ, PH and RHC are employees of GSK and hold financial equities in GSK. CB has participated in advisory boards and received speaker fees from ALK-Abello, AstraZeneca, Sanofi, Novartis, GSK, and Meda Pharmaceuticals.

Data availability

Anonymised individual participant data and study documents can be requested for further research from https://www.GSK-studyregister.com/en/

References

1. Fokkens WJ, Lund VJ, Hopkins C, et al. Executive summary of EPOS 2020 including integrated care pathways. Rhinology. 2020;58(2):82-111.
2. Schleimer RP. Immunopathogenesis of chronic rhinosinusitis and nasal polyposis. Annu Rev Pathol. 2017;12:331-357.
3. Stevens WW, Schleimer RP, Kern RC. Chronic rhinosinusitis with nasal polyps. J Allergy Clin Immunol Pract. 2016;4(4):565-572.
4. Bachert C, Han JK, Desrosiers MY, et al. Efficacy and safety of benralizumab in chronic rhinosinusitis with nasal polyps: A randomized, placebo-controlled trial. J Allergy Clin Immunol. 2022;149(4):1309-1317 e12.
5. Gitomer SA, Fountain CR, Kingdom TT, et al. Clinical examination of tissue eosinophilia in patients with chronic rhinosinusitis and nasal polyposis. Otolaryngol Head Neck Surg. 2016;155(1):173-178.
6. Wang K, Deng J, Yang M, Chen Y, Chen F, Gao WX, et al. Concordant systemic and local eosinophilia relates to poorer disease control in patients with nasal polyps. World Allergy Organ J. 2019;12(8):100052.
7. Bengtsson C, Jonsson L, Holmström M, et al. Incident chronic rhinosinusitis is associated with impaired sleep quality: results of the RHINE study. J Clin Sleep Med. 2019;15(6):899-905.
8. Khan A, Huynh TMT, Vandeplas G, et al. The GALEN rhinosinusitis cohort: chronic rhinosinusitis with nasal polyps affects health-related quality of life. Rhinology. 2019;57(5):343-351.
9. Mullol J, Azar A, Buchheit KM, Hopkins C, Bernstein JA. Chronic rhinosinusitis with nasal polyps: quality of life in the biologics Era. J Allergy Clin Immunol Pract. 2022;10(6):1434-1453.e9.
10. Värendh M, Johannisson A, Hrubos-Strøm H, Andersson M. Sleep quality improves with endoscopic sinus surgery in patients with chronic rhinosinusitis and nasal polyposis. Rhinology. 2017;55(1):45-52.
11. Alt JA, Smith TL, Mace JC, Soler ZM. Sleep quality and disease severity in patients with chronic rhinosinusitis. Laryngoscope. 2013;123(10):2364-2370.
12. Bengtsson C, Lindberg E, Jonsson L, et al. Chronic rhinosinusitis impairs sleep quality: results of the GA2LEN study. Sleep. 2017;40(1).
13. Hall R, Trennery C, Chan R, et al. Understanding the patient experience of severe, recurrent, bilateral nasal polyps: a qualitative interview study in the United States and Germany. Value Health. 2020;23(5):632-641.
14. Schlosser RJ, Storck K, Cortese BM, Uhde TW, Rudmik L, Soler ZM. Depression in chronic rhinosinusitis: a controlled cohort study. Am J Rhinol Allergy. 2016;30(2):128-133.
15. Soler ZM, Eckert MA, Storck K, Schlosser RJ. Cognitive function in chronic rhinosinusitis: a controlled clinical study. Int Forum Allergy Rhinol. 2015;5(11):1010-1017.
16. Alt JA, Mace JC, Smith TL, Soler ZM. Endoscopic sinus surgery improves cognitive dysfunction in patients with chronic rhinosinusitis. Int Forum Allergy Rhinol. 2016;6(12):1264-1272.
17. Claeys N, Teeling MT, Legrand P, et al. patients unmet needs in chronic rhinosinusitis with nasal polyps care: a patient advisory board statement of EUFOREA. Front Allergy. 2021;2:761388.
18. Bachert C, Han JK, Wagenmann M, 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(1):29-36.
19. Klimek L, Förster-Ruhrmann U, Beule AG, et al. Indicating biologics for chronic rhinosinusitis with nasal polyps (CRSwNP). Allergo J Int. 2022:1-12.
20. Kolkhir P, Akdis CA, Akdis M, et al. Type 2 chronic inflammatory diseases: targets, therapies and unmet needs. Nat Rev Drug Discov. 2023;22:743-767.
21. GSK. NUCALA Prescribing Information. Available from https://gskpro.com/content/dam/global/hcpportal/en_US/Prescribing_Information/Nucala/pdf/NUCALA-PI-PIL-IFU-COMBINED.PDF (accessed July 2022). 2022.
22. Quirce S, Cosío BG, España A, et al. Management of eosinophil-associated inflammatory diseases: the importance of a multidisciplinary approach. Front Immunol. 2023;14:1192284.
23. Han JK, Bachert C, Fokkens W, et al. Mepolizumab for chronic rhinosinusitis with nasal polyps (SYNAPSE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Respir Med. 2021;9(10):1141-1153.
24. Bachert C, Luong AU, Gevaert P, et al. The

unified airway hypothesis: evidence from specific intervention with anti-IL-5 biologic therapy. J Allergy Clin Immunol Pract. 2023; 11(9):2630-2641.
25. Mullol J, Maldonado M, Castillo JA, et al. Management of united airway disease focused on patients with asthma and chronic rhinosinusitis with nasal polyps: a systematic review. J Allergy Clin Immunol Pract. 2022;10(9):2438-2447.e9.
26. Chupp GL, Bradford ES, Albers FC, 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(5):390-400.
27. Fokkens WJ, Lund VJ, Mullol J, et al. European position paper on rhinosinusitis and nasal polyps 2012. Rhinol Suppl. 2012;23:3 p preceding table of contents, 1-298.
28. Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J. 2014;43(2):343-373.
29. Hopkins C, Gillett S, Slack R, Lund V, Browne J. Psychometric validity of the 22-item Sinonasal Outcome Test. Clin Otolaryngol. 2009;34(5):447-454.
30. Juniper EF, Svensson K, Mörk A-C, Ståhl E. Measurement properties and interpretation of three shortened versions of the asthma control questionnaire. Respir Med. 2005;99(5):553-558.
31. Pandrangi VC, Mace JC, Kim JH, et al. Work productivity and activity impairment in patients with chronic rhinosinusitis undergoing endoscopic sinus surgery - a prospective, multi-institutional study. Int Forum Allergy Rhinol. 2023;13(3):216-229.
32. O'Quinn S, Shih VH, Martin UJ, et al. Measuring the patient experience of chronic rhinosinusitis with nasal polyposis: qualitative development of a novel symptom diary. Int Forum Allergy Rhinol. 2022;12(8):996-1005.
33. Ando Y, Chiba S, Capasso R, et al. Risk factors for sleep impairment in adult patients with chronic rhinosinusitis. Auris Nasus Larynx. 2016;43(4):418-421.
34. Colás C, Galera H, Añibarro B, Soler R, Navarro A, Jáuregui I, et al. Disease severity impairs sleep quality in allergic rhinitis (The SOMNIAAR study). Clin Exp Allergy. 2012;42(7):1080-1087.
35. Jiang RS, Liang KL, Hsin CH, Su MC. The impact of chronic rhinosinusitis on sleep-disordered breathing. Rhinology. 2016;54(1):75-79.
36. Mahdavinia M, Schleimer RP, Keshavarzian A. Sleep disruption in chronic rhinosinusitis. Expert Rev Anti Infect Ther. 2017;15(5):457-465.
37. Janson C, De Backer W, Gislason T, et al. Increased prevalence of sleep disturbances and daytime sleepiness in subjects with bronchial asthma: a population study of young adults in three European countries. Eur Respir J. 1996;9(10):2132-2138.
38. Alt JA, Sautter NB, Mace JC, Detwiller KY, Smith TL. Antisomnogenic cytokines, quality of life, and chronic rhinosinusitis: a pilot study. Laryngoscope. 2014;124(4):E107-114.
39. Irwin MR, Olmstead R, Carroll JE. Sleep disturbance, sleep duration, and inflammation: a systematic review and meta-analysis of cohort studies and experimental sleep deprivation. Biol Psychiatry. 2016;80(1):40-52.
40. Zasłona Z, Case S, Early JO, et al. The circadian protein BMAL1 in myeloid cells is a negative regulator of allergic asthma. Am J Physiol Lung Cell Mol Physiol. 2017;312(6):L855-l860.
41. Khan AH, Reaney M, Guillemin I, et al. Development of sinonasal outcome test (snot-22) domains in chronic rhinosinusitis with nasal polyps. Laryngoscope. 2022;132(5):933-941.
42. Fokkens W, Trigg A, Lee SE, et al. Mepolizumab improvements in health-related quality of life and disease symptoms in a patient population with very severe chronic rhinosinusitis with nasal polyps: psychometric and efficacy analyses from the SYNAPSE study. J Patient Rep Outcomes. 2023;7(1):4.
43. Maspero JF, Khan AH, Philpott C, et al. health-related quality of life impairment among patients with severe chronic rhinosinusitis with nasal polyps in the SINUS-24 trial. J Asthma Allergy. 2023;16:323-332.
44. Bachert C, Sousa AR, Han JK, al. Mepolizumab for chronic rhinosinusitis with nasal polyps: treatment efficacy by comorbidity and blood eosinophil count. J Allergy Clin Immunol. 2022;149(5):1711-1721.e6.
45. Gibson PG, Prazma CM, Chupp GL, et al. Mepolizumab improves clinical outcomes in patients with severe asthma and comorbid conditions. Respir Res. 2021;22(1):171.

Joaquim Mullol
Department of Otorhinolaryngology
Hospital Clínic Barcelona
FRCB-IDIBAPS
Villarroel 170
08036, Barcelona
Catalonia
Spain

Tel: +34-932-279 872
E-mail: JMULLOL@clinic.cat

Joaquim Mullol[1], Wytske J. Fokkens[2], Steven G. Smith[3], Tom Keeley[4], Lingjiao Zhang[5], Peter Howarth[6], Robert H. Chan[7], Claus Bachert[8,9]

[1] Department of Otorhinolaryngology, Hospital Clínic Barcelona, FRCB-IDIBAPS, Universitat de Barcelona, CIBERES, Barcelona, Catalonia, Spain
[2] Department of Otorhinolaryngology, Academic Medical Centre, Amsterdam, the Netherlands
[3] Clinical Sciences - Respiratory, GSK, Durham, NC, USA
[4] Respiratory Patient Centered Outcomes, Value Evidence and Outcomes, GSK, GSK House, Brentford, Middlesex, UK
[5] Respiratory Marketed Products Statistics, GSK, Warren, NJ, USA
[6] Global Medical Affairs, GSK, Brentford, Middlesex, UK
[7] Respiratory Patient Centered Outcomes, Value Evidence and Outcomes, GSK, GSK House, Brentford, Middlesex, UK
[8] Department of Otorhinolaryngology - Head and Neck Surgery, University Hospital of Münster, Münster, Germany
[9] Department of Otorhinolaryngology, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, Guangdong, China

Rhinology 62: 6, 669 - 680, 2024
https://doi.org/10.4193/Rhin24.021

Received for publication:
January 12, 2024
Accepted: August 14, 2024

Assocociate Editor:
Sietze Reitsma

This manuscript contains online supplementary material

SUPPLEMENTARY MATERIAL

Supplementary Table 1. Baseline clinical characteristics by subgroup in SYNAPSE and MUSCA.

	SYNAPSE			
	Comorbid asthma (n=289)		No comorbid asthma (n=118)	
	Placebo (n=149)	Mepolizumab (n=140)	Placebo (n=52)	Mepolizumab (n=66)
SNOT-22 sleep domain score (0-15), mean (SD)	9.4 (3.7)	9.0 (3.9)	7.6 (4.2)	8.1 (3.6)
SNOT-22 fatigue domain score (0-20), mean (SD)	11.9 (4.78)	12.1 (4.63)	9.5 (5.65)	9.4 (4.70)
WPAI scores (%), mean (SD)				
Work time missed	n=114, 5.0 (13.60)	n=107, 5.3 (13.98)	n=37, 5.0 (10.49)	n=46 ,4.1 (10.04)
Impairment while working	n=112, 52.8 (29.45)	n=105. 48.1 (29.16)	n=36, 41.9 (33.71)	n=46, 48.0 (28.80)
Overall work impairment	n=114, 53.7 (30.34)	n=107, 49.6 (29.99)	n=37, 41.8 (34.91)	n=46, 49.2 (29.52)
Activity impairment	n=146, 54.5 (28.31)	n=139, 52.0 (28.01)	n=52, 49.4 (31.09)	n=65, 56.5 (27.92)
	Comorbid N-ERD (n=108)		No comorbid N-ERD (n=299)	
	Placebo (n=63)	Mepolizumab (n=45)	Placebo (n=138)	Mepolizumab (n=161)
SNOT-22 sleep domain score (0-15), mean (SD)	9.8 (3.8)	9.3 (3.8)	8.6 (3.9)	8.5 (3.8)
SNOT-22 fatigue domain score (0-20), mean (SD)	12.9 (4.66)	12.9 (4.51)	10.6 (5.17)	10.8 (4.80)
WPAI scores, mean (SD)				
Work time missed	n=48, 8.5 (19.15)	n=34, 7.1 (15.85)	n=103, 3.3 (8.14)	n=119, 4.3 (11.94)
Impairment while working	n=46, 58.7 (26.47)	n=34, 46.2 (28.50)	n=102, 46.3 (31.90)	n=117, 48.6 (29.18)
Overall work impairment	n=48, 59.5 (28.59)	n=34, 48.4 (29.69)	n=103, 46.8 (32.56)	n=119, 49.8 (29.89)
Activity impairment	n=61, 57.5 (28.32)	n=45, 50.4 (27.63)	n=137, 51.2 (29.29)	n=159, 54.3 (28.12)
	Blood eosinophil count <300 cells/µL (n=129)		Blood eosinophil count ≥300 cells/µL (n=278)	
	Placebo (n=62)	Mepolizumab (n=67)	Placebo (n=139)	Mepolizumab (n=139)
SNOT-22 sleep domain score (0-15), mean (SD)	8.5 (4.2)	7.7 (4.0)	9.1 (3.8)	9.1 (3.7)
SNOT-22 fatigue domain score (0-20), mean (SD)	10.8 (5.09)	10.1 (5.11)	11.5 (5.14)	11.8 (4.57)
WPAI scores (%), mean (SD)				
Work time missed	n=44, 2.1 (5.91)	n=50, 5.4 (15.97)	n=107, 6.1 (14.69)	n=103, 4.7 (11.20)
Impairment while working	n=44, 45.2 (28.89)	n=49, 49.8 (31.66)	n=104, 52.2 (31.44)	n=102, 47.3 (27.69)
Overall work impairment	n=44, 45.9 (29.38)	n=50, 51.8 (32.44)	n=107, 52.8 (32.69)	n=103, 48.4 (28.46)
Activity impairment	n=62, 52.1 (25.93)	n=66, 57.1 (29.13)	n=136, 53.7 (30.47)	n=138. 51.7 (27.36)
	MUSCA			
	Comorbid CRSwNP (n=82)		No comorbid CRSwNP (n=352)	
	Placebo (n=37)	Mepolizumab (n=45)	Placebo (n=181)	Mepolizumab (n=171)
SNOT-22 sleep domain score (0-15), mean (SD)	n=36, 6.8 (4.82)	n=44, 5.9 (3.96)	n=176, 4.9 (4.18)	n=166, 4.8 (3.84)
SNOT-22 fatigue domain score (0-20), mean (SD)	n=36, 8.2 (5.51)	n=44, 7.7 (5.62)	n=176, 7.6 (5.58)	n=166, 7.5 (5.30)

N-ERD, non-steroidal anti-inflammatory drug-exacerbated respiratory disease; SD, standard deviation; SNOT-22, mean 22-item Sino-Nasal Outcome Test; WPAI, Work Productivity and Activity Impact questionnaire.