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Dupilumab in chronic obstructive pulmonary disease: a pooled analysis of emergency department visits, hospital admissions, and systemic corticosteroid use

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Abstract

Rationale: **In chronic obstructive pulmonary disease (COPD), exacerbations drive morbidity, healthcare resource utilization, and mortality. Hospitalization and emergency department (ED) visits reflect acute clinical instability. Systemic corticosteroids are usually prescribed for exacerbations, but cumulative exposure is a concern.**

Objectives: **To evaluate the effect of dupilumab on ED visits/hospital admissions and systemic corticosteroid use in patients experiencing exacerbations.**

Methods: **BOREAS and NOTUS, two phase 3, randomized, double-blind, placebo-controlled trials, enrolled patients (40-85 years) with COPD, moderate-to-severe airflow limitation, and type 2 inflammation (screening blood eosinophil count ≥300 cells/μL). Patients received dupilumab 300 mg ($N=938$) or placebo ($N=936$) for 52 weeks. Systemic corticosteroid use and annualized rate and time to first ED visit/hospital admission were assessed.**

Measurements and Main Results: **Dupilumab versus placebo reduced ED visits/hospital admissions of any duration by 38% (rate ratio, 0.62 [95% CI, 0.43-0.90]; $P=.0121$), delayed time to first event, and reduced risk of a first event by 45% (hazard ratio, 0.55 [95% CI, 0.38-0.78]; $P=.0010$). Compared with placebo, systemic corticosteroid use was reduced in patients treated with dupilumab who experienced severe exacerbations by 42% (rate ratio, 0.58 [95% CI, 0.38-0.89]; $P=.0126$) and moderate exacerbations by 28% (rate ratio, 0.72 [95% CI, 0.60-0.87]; $P=.0005$).**

Conclusions: **Dupilumab reduced ED visits/hospital admissions of any duration. Patients who experienced moderate and/or severe exacerbations required fewer systemic corticosteroids with dupilumab compared with placebo.**

Clinical Trial Registration: **ClinicalTrials.gov (NCT03930732, NCT04456673).**

Keywords chronic obstructive pulmonary disease, dupilumab, exacerbations, severe exacerbations, systemic corticosteroids

Introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity, mortality, and healthcare resource utilization worldwide.[1] Despite advances in COPD management, severe exacerbations remain a major factor in poor clinical outcomes. They are associated with a higher risk of future exacerbations, accelerated lung function decline, greater cardiovascular risk, respiratory and all-cause mortality, reduced quality of life, and a significant cost burden on healthcare systems.[2-10] These risks are

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At a Glance Commentary

Scientific Knowledge on the Subject: In patients with chronic obstructive pulmonary disease (COPD), severe exacerbations drive morbidity, healthcare resource utilization, and mortality risk. Hospitalization and emergency department (ED) visits reflect acute clinical instability. Systemic corticosteroids are often prescribed for exacerbations, but cumulative exposure is a concern.

What This Study Adds to the Field: Results from the pooled BOREAS and NOTUS trials demonstrate that patients treated with dupilumab had fewer ED visits/hospitalizations due to COPD exacerbations, resulting in reduced healthcare resource utilization and cumulative exposure to systemic corticosteroids, indicating a meaningful reduction in exacerbation-related clinical and healthcare burden in COPD.

cumulative, with each additional exacerbation accelerating overall deterioration. Preventing and effectively managing exacerbations are therefore key to improving long-term prognosis in patients with COPD.[11]

Hospitalization rates for exacerbations have remained high over the last 2 decades.[12,13] COPD is the third leading cause of rehospitalization in the United States,[14] with 30-day and 90-day readmission rates of up to 26% and 39%, respectively.[2,6] Patients with COPD and type 2 inflammation have an increased risk of COPD-related readmission at 30, 60, and 90 days, and at 12 months, versus those without.[15]

Systemic corticosteroids are a mainstay of exacerbation management, administered in relatively short courses during acute exacerbations.[16] It has been well established that long-term corticosteroid use in patients with COPD is associated with a higher risk of multiple adverse outcomes, such as cardiovascular complications, osteoporosis and fractures, cataracts, hyperglycemia and diabetes, pneumonia, and all-cause mortality. The risks generally increase with greater cumulative doses.[17,18]

In the BOREAS and NOTUS pooled population, dupilumab, a human monoclonal antibody blocking interleukin-4/13 signaling, significantly reduced moderate exacerbations (defined as requiring systemic corticosteroid or antibiotic use) or severe exacerbations (defined as requiring hospitalization or an emergency department [ED] visit >24 hours, or resulting in death) by 31% (rate ratio [95% CI] vs placebo, 0.70 [0.58-0.86]; P <.001) in patients with COPD and type 2 inflammation. Severe exacerbations were nominally reduced by 32% (rate ratio [95% CI] vs placebo, 0.67 [0.44-1.04]; P = .073). Dupilumab also improved lung function and quality of life and reduced symptom burden.[19-21]

Definitions of severe exacerbations vary, with example definitions including events requiring hospitalization or ED visits,[16] hospitalization only,[22] or both hospitalization or death,[23-26] with some also including ED visits lasting >24 hours.[19,20,27,28] While hospitalizations and ED visits reflect acute clinical instability in COPD, often impacted by respiratory failure, comorbidities, and socioeconomic status,[29] some recent publications have called into question whether the use of treatment location and duration can adequately assess the clinical state of a patient.[30] Therefore, it is important to assess the overall healthcare utilization of a patient, which can be impacted by several factors, such as local healthcare systems, nonreporting by patients, and varied physician responses to patient reports.[16,30,31] Due to the heterogeneity of how exacerbations are managed, there is a need to assess the impact on healthcare resource utilization beyond the definitions used in clinical trials to better characterize and understand the impact of treatments.

This analysis of pooled data from BOREAS and NOTUS assesses the effect of dupilumab on ED visits/hospital admissions and time to first severe exacerbation, reflecting the overall burden on healthcare utilization, and systemic corticosteroid use in patients experiencing exacerbations. Together, these data provide comprehensive information on the effect of dupilumab on severe exacerbations. Some of the results of this analysis have been previously reported in the form of abstracts or poster presentations.[32-34]

Methods

Study design

Full study designs of BOREAS (NCT03930732) and NOTUS (NCT04456673), two phase 3, randomized, double-blind, placebo-controlled trials, have been previously described.[19-21] In brief, the intention-to-treat (ITT) population included patients aged 40 to 80 years (BOREAS) or 40 to 85 years (NOTUS) with COPD, moderate-to-severe airflow obstruction (post-bronchodilator forced expiratory volume in 1 second/forced vital capacity <0.7), and type 2 inflammation (blood eosinophil count ≥300 cells/μL at screening) on stable inhaled therapy (inhaled corticosteroids/long-acting muscarinic antagonist [LAMA]/long-acting beta-2 agonist [LABA], or LAMA/LABA if inhaled corticosteroids were contraindicated) for ≥3 months before randomization. Patients were randomized 1:1 to add-on dupilumab 300 mg or matched placebo every 2 weeks subcutaneously for up to 52 weeks.

Outcomes

In BOREAS and NOTUS, severe exacerbations were defined as exacerbations requiring hospitalization or an ED visit for >24 hours, or resulting in death. Moderate exacerbations were defined as exacerbations resulting in treatment with systemic corticosteroids, antibiotics, or both.

For this post hoc analysis, we analyzed exacerbations requiring hospitalizations and/or ED visits of any duration, hereafter referred to as "ED visits/hospital admissions". The analysis assessed the adjusted annualized event rate (including exacerbations, hospitalizations, or ED visits of any duration), cumulative number of events, and time to first event for severe exacerbations in the pooled ITT population.

The time to first severe exacerbation requiring hospitalization or an ED visit >24 hours or resulting in death in the overall ITT

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population was also assessed and is referred to as "severe exacerbation" in this analysis; the adjusted annualized event rate and cumulative number have been previously reported.[21] Additionally, total days hospitalized and number of patients with intensive care unit admission, systemic corticosteroid use, and adjusted annualized total systemic corticosteroid use in the overall ITT population were assessed.

Baseline characteristics are presented for the overall ITT population and subgroups of patients stratified by moderate or severe exacerbation events during the study (0: moderate only; ≥1: severe). Number of moderate or severe exacerbation events, number of patients with systemic corticosteroid use, adjusted annualized total systemic corticosteroid exposure and courses, and cumulative dose over the treatment period are reported for patients stratified by moderate or severe exacerbation events during the study (moderate only or ≥1 severe). Systemic corticosteroid use was annualized at the patient level by dividing the duration of systemic corticosteroid (days) and total courses for each patient by the number of patient-years followed in the treatment period for that patient. A course was considered continuous if treatment was separated by <7 days. The total intake duration or total courses were divided by the total number of patient-years followed in the 52-week treatment period. Consistent with the original study protocol, for moderate and severe exacerbation events to be counted separately, they had to be ≥14 days apart.

Statistical analysis

Statistical analyses were performed using SAS software (version 9.4 or higher, SAS Institute, Cary, NC, United States). Efficacy endpoints were analyzed according to the assigned treatment group. For the Cox model, there was no crossing of the Kaplan–Meier curves, and therefore no suspicion of a clear violation of the proportional hazards assumption. In addition, we performed a Kolmogorov-type supremum test for the proportional hazards assumption, which further confirmed this observation and did not reject the null hypothesis of proportional hazards ($P = .875$ and $P = .620$ for cumulative probability of having experienced a first ED visit/hospitalization or severe exacerbation, respectively, in the pooled ITT population over the 52-week treatment period). Hazard ratios (HRs) for time to first analyses were derived using the Cox proportional hazards model, including time to first event as a dependent variable, and treatment group, study, region, inhaled corticosteroid dose, smoking status at screening, baseline disease severity, and number of moderate or severe exacerbations within 1 year before the study as covariates. In NOTUS, all enrolled patients were included in the pre-specified early primary analysis, which was done after a positive interim analysis and included all available data. This is a post hoc analysis, and all reported P values are nominal, without adjustment to control for inflated type I error from testing multiple endpoints or subgroups.

Adjusted annualized event rates and systemic corticosteroid use, courses, and cumulative dose were derived using a negative binomial model with the total number of events over the 52-week treatment period as the response variable; treatment group, region, inhaled corticosteroid dose, smoking status at screening, baseline disease severity, and number of moderate or severe exacerbations within 1 year before the study as covariates; and log-transformed treatment duration as an offset variable. Negative binomial models accounted for potential overdispersion without the strong assumption of the Poisson model, where the mean is assumed to be always equal to the variance. A positive (non-negative) overdispersion parameter estimate supports the choice of negative binomial model over Poisson regression model, since it provides a more flexible, unified framework to analyze all the count outcomes consistently.

Results

Baseline demographics and disease characteristics

Baseline demographics and disease characteristics for the pooled ITT population (dupilumab: $N = 938$; placebo: $N = 936$), patients without an exacerbation event during the study (dupilumab: $n = 600$; placebo: $n = 542$), and patients with ≥1 severe exacerbation (dupilumab: $n = 41$; placebo: $n = 60$) or moderate exacerbation(s) only (dupilumab: $n = 297$; placebo: $n = 334$) during the study were similar across treatment arms and subgroups (Table 1 and Table S1).

Patients with ≥1 severe exacerbation had the highest rate of severe exacerbations in the year before the study. In contrast, those with moderate exacerbation(s) only had the highest rate of moderate exacerbations in the year before the study. Across all patient groups, baseline lung function was lower, and St. George's Respiratory Questionnaire total scores, Evaluating Respiratory Symptoms in COPD total scores, and body mass index, airflow obstruction, dyspnea, and exercise capacity index scores were higher in patients with increasing exacerbation severity; other disease characteristics were comparable (Table 1).

Emergency department visits/ hospitalizations

In the pooled ITT population, 5.3% (50 of 938) of patients receiving dupilumab and 8.5% (80 of 936) of patients receiving placebo had 65 and 96 ED visits/hospital admissions, respectively, during the 52-week treatment period. The number needed to treat to prevent 1 additional ED visit/hospital admission was 16 ($P = .0121$). Dupilumab reduced ED visits/hospital admissions by 38% (rate ratio [95% CI] vs placebo, 0.62 [0.43-0.90]; $P = .0121$) (Figure 1). Dupilumab also delayed the time to first ED visit/hospital admission, with a risk reduction of 45% (HR [95% CI] vs placebo, 0.55 [0.38-0.78]; $P = .0010$) (Figure 2). The Kaplan–Meier estimates for cumulative number and time to first ED visit/hospital admission demonstrate a separation between patients receiving dupilumab and placebo throughout the 52-week treatment period (Figures 1B and 2A).

Severe exacerbations

For severe exacerbations (requiring hospitalization, an ED visit >24 hours, or resulting in death), dupilumab versus placebo had a risk reduction of 39% (HR [95% CI], 0.61 [0.41-0.91]; $P = .0160$) (Figure 2). No deaths due to severe exacerbations were reported.

Overall, patients receiving dupilumab versus placebo who were hospitalized spent fewer days in hospital (mean [SD], 8.74 [5.39]

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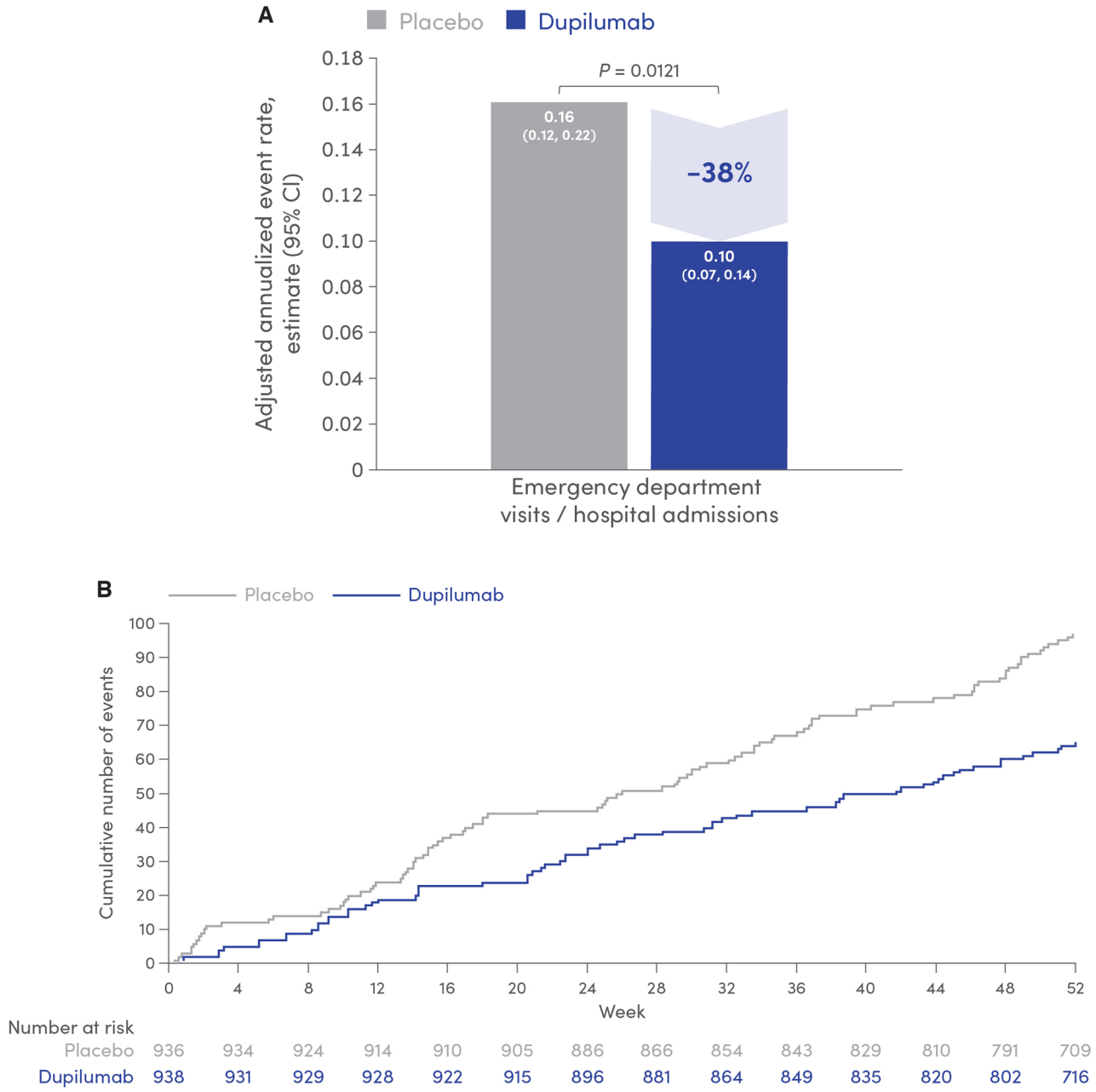

Figure 1 (A) Annualized event rate and (B) cumulative number of ED visits/hospital admissions* in the pooled ITT population during the 52-week treatment period. Abbreviations: CI, confidence interval; ED, emergency department; ITT, intention-to-treat. *ED visits/hospital admissions are defined as exacerbations requiring hospitalization or an ED visit of any duration.

vs 9.65 [20.85] days; $P = .7544$). Of patients receiving dupilumab, 0.3% (3 of 938) had 3 COPD-related admissions to an intensive care unit; of patients receiving placebo, 0.7% (7 of 936) reported 7 admissions to an intensive care unit.

Systemic corticosteroid use

Overall, 33.6% (315 of 938) of patients receiving dupilumab and 39.1% (366 of 936) receiving placebo reported systemic corticosteroid use during the treatment period. Patients receiving dupilumab versus placebo required systemic corticosteroids for fewer days (adjusted annualized total SCS intake duration, estimate [95% CI]: 6.36 [4.82–8.39] vs 9.58 [7.33–12.52] days), with dupilumab significantly reducing annualized total time that patients required systemic corticosteroids by 34% (incidence rate ratio [IRR] [95% CI] vs placebo: 0.66 [0.51-0.86] days; $P = .0018$). Patients receiving dupilumab versus placebo also required fewer systemic corticosteroid courses (adjusted annualized total SCS courses, estimate [95% CI]: 0.76 [0.65–0.90] vs 1.09 [0.94–1.26]; −30%, IRR [95% CI] vs placebo, 0.70 [0.60-0.82]; $P < .0001$) and had a lower cumulative systemic corticosteroid dose (adjusted annualized total SCS dose, estimate [95% CI]: 174.46 [118.47–256.93] vs 272.98 [185.94–400.79] mg; −36%, IRR [95% CI] vs placebo, 0.64 [0.44-0.92]; $P = .0162$).

In the pooled ITT population for patients who experienced ≥1 severe exacerbation (hospitalization, ED visit >24 hours, or death)

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Table 1 Baseline characteristics of patients without exacerbation, with moderate exacerbation(s) only, or with ≥1 severe exacerbation during the study.

Characteristic	Without exacerbation		Moderate exacerbation(s) only[a]		≥1 severe exacerbation[b]	
	Placebo	Dupilumab	Placebo	Dupilumab	Placebo	Dupilumab
	n = 542	*n* = 600	*n* = 334	*n* = 297	*n* = 60	*n* = 41
Age, y, mean (SD)	65.1 (8.2)	65.3 (8.0)	64.4 (8.6)	64.5 (8.0)	68.1 (7.0)	66.1 (8.7)
Female, No. (%)	178 (32.8)	196 (32.7)	106 (31.7)	111 (37.4)	18 (30.0)	13 (31.7)
Race, No. (%)						
White	464 (85.6)	510 (85.0)	297 (88.9)	271 (91.2)	52 (86.7)	34 (82.9)
Asian	45 (8.3)	51 (8.5)	18 (5.4)	17 (5.7)	7 (11.7)	6 (14.6)
Black/of African descent	6 (1.1)	6 (1.0)	4 (1.2)	0	0	1 (2.4)
Moderate exacerbations[c] in the year before the study, mean (SD)	1.8 (0.9)	1.8 (1.2)	2.1 (1.2)	2.1 (1.2)	1.7 (1.3)	1.7 (1.8)
Severe exacerbations[d] in the year before the study, mean (SD)	0.3 (0.5)	0.3 (0.6)	0.2 (0.5)	0.3 (0.6)	0.8 (1.1)	1.0 (1.3)
Pre-BD FEV_1, L, mean (SD)	1.38 (0.49)	1.37 (0.47)	1.33 (0.48)	1.24 (0.47)	1.14 (0.36)	1.10 (0.32)
Post-BD FEV_1, L, mean (SD)	1.47 (0.50)	1.45 (0.47)	1.43 (0.49)	1.35 (0.49)	1.25 (0.33)	1.17 (0.35)
Post-BD ppFEV_1, %, mean (SD)	51.9 (13.1)	51.4 (12.8)	49.4 (12.3)	48.2 (13.1)	46.0 (10.7)	43.0 (10.4)
Post-BD FVC, L, mean (SD)	2.95 (0.91)	2.89 (0.80)	3.04 (0.90)	2.95 (0.88)	2.84 (0.79)	2.71 (0.79)
Post-BD FEV_1/FVC ratio, mean (SD)	0.51 (0.11)	0.51 (0.11)	0.48 (0.11)	0.46 (0.12)	0.45 (0.11)	0.45 (0.11)
Post-BD $FEF_{25\%–75\%}$, L/s, mean (SD)	0.59 (0.33)	0.59 (0.33)	0.54 (0.35)	0.50 (0.31)	0.45 (0.20)	0.40 (0.21)
SGRQ total score[e], mean (SD)	48.5 (17.4)	48.9 (17.5)	50.5 (16.6)	51.8 (16.9)	56.6 (17.6)	56.9 (16.5)
E-RS:COPD total score[f], mean (SD)	12.6 (7.0)	12.7 (7.0)	13.5 (6.9)	13.8 (6.8)	16.2 (7.5)	15.3 (7.0)
BODE index total score, mean (SD)	3.9 (1.7)	4.0 (1.6)	4.0 (1.6)	4.3 (1.7)	4.7 (1.5)	4.8 (1.7)
High-dose ICS medication history, No. (%)	148 (27.3)	165 (27.5)	89 (26.6)	85 (28.6)	23 (38.3)	8 (19.5)
Biomarkers						
BEC, cells/μL, median (Q1, Q3)	330 (230, 470)	330 (230, 470)	340 (230, 460)	340 (250, 440)	300 (230, 440)	370 (280, 500)
FeNO, ppb, median (Q1, Q3)	16.0 (10.0, 29.0)	17.0 (10.0, 31.0)	17.0 (10.0, 30.0)	16.0 (10.0, 27.0)	17.0 (10.0, 34.0)	15.5 (12.0, 24.0)

Abbreviations: BD, bronchodilator; BEC, blood eosinophil count; BODE, body mass index, airflow obstruction, dyspnea, and exercise capacity; ED, emergency department; E-RS:COPD, Evaluating Respiratory Symptoms in Chronic Obstructive Pulmonary Disease; $FEF_{25\%-75\%}$, forced expiratory flow between 25% and 75% of forced vital capacity; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroid(s); pp, percent predicted; ppb, parts per billion; Q, quartile; SD, standard deviation; SGRQ, St. George's Respiratory Questionnaire.
[a]Patients with moderate exacerbation(s) only were defined as those experiencing ≥1 moderate exacerbation event but no severe exacerbation events.
[b]Patients with ≥1 severe exacerbation event were defined as those experiencing ≥1 severe exacerbation event. These patients may have also experienced moderate exacerbations.
[c]Moderate exacerbations are defined as exacerbations resulting in treatment with systemic corticosteroid(s), antibiotics, or both.
[d]Severe exacerbations are defined as exacerbations requiring hospitalization or an ED visit >24 hours, or resulting in death.
[e]SGRQ score ranges from 0 to 100, with lower scores indicating better quality of life.
[f]ERS:COPD total score ranges from 0 to 40, with a lower score indicating less severe symptoms.

during the study, patients receiving dupilumab (*n* = 41) had 21 moderate and 54 severe exacerbations, compared with 82 moderate and 76 severe exacerbations for those receiving placebo (*n* = 60) (Table 2). In the same population, patients receiving dupilumab versus placebo required systemic corticosteroids for fewer days (adjusted annualized total SCS intake duration, estimate [95% CI]: 19.82 [13.25–29.66] vs 34.31 [24.67–47.72] days; −42%, IRR [95% CI] vs placebo, 0.58 [0.38-0.89] days; *P* = .0126), required fewer systemic corticosteroid courses (adjusted annualized total SCS courses, estimate [95% CI]: 2.56 [1.91–3.43] vs 3.43 [2.76–4.27]; −25%, IRR [95% CI] vs placebo, 0.75 [0.55-1.01]; *P* = .0605), and had a lower cumulative systemic corticosteroid dose (adjusted

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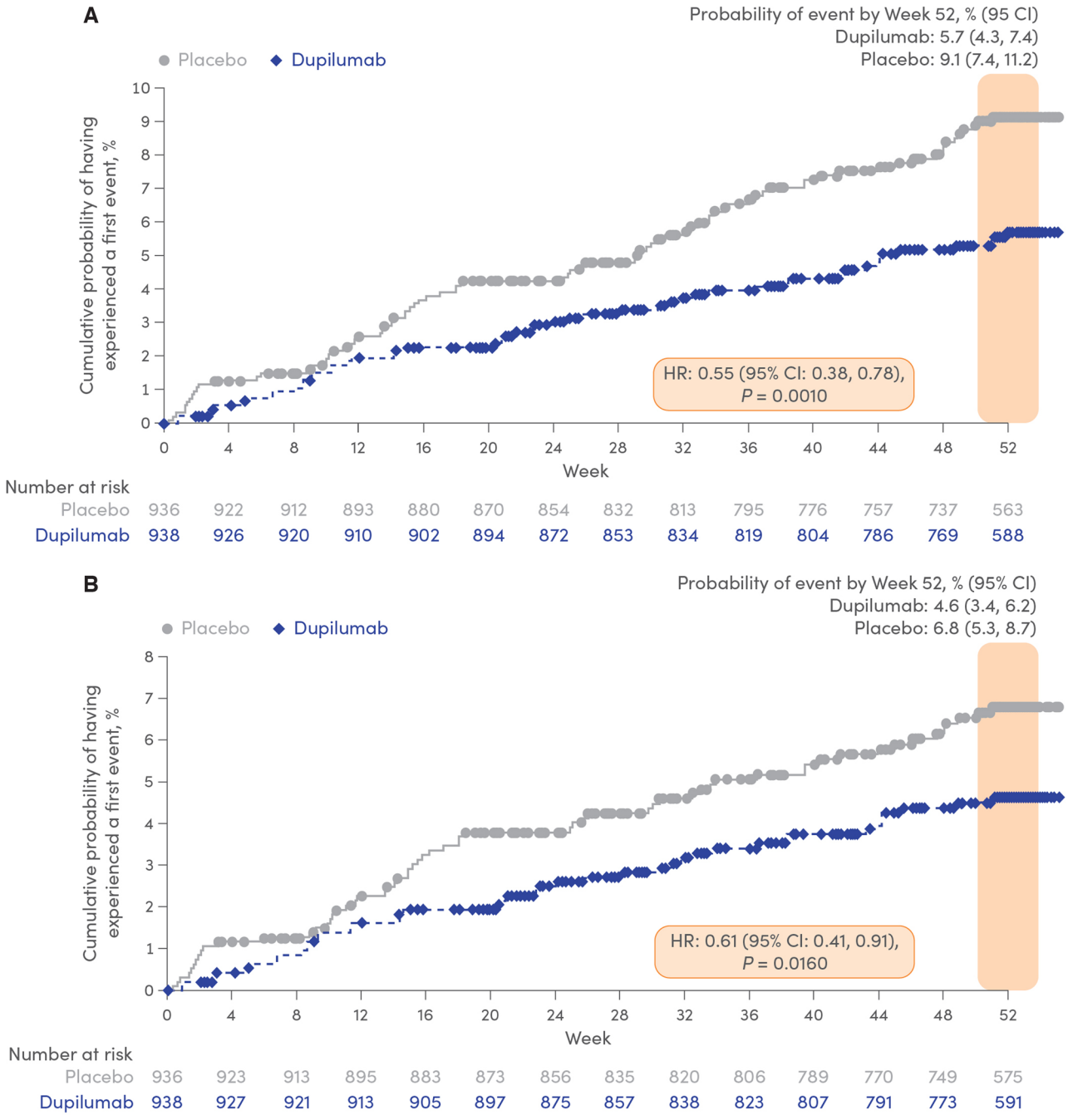

Figure 2 Cumulative probability of having experienced a first (A) ED visit/hospital admission and (B) severe exacerbation in the pooled ITT population over the 52-week treatment period. ED visits/hospital admissions are defined as exacerbations requiring hospitalization or an ED visit of any duration. Severe exacerbations are defined as exacerbations requiring hospitalization or an ED visit >24 hours, or resulting in death. Abbreviations: CI, confidence interval; ED, emergency department; HR, hazard ratio; ITT, intention-to-treat.

annualized total SCS use, estimate [95% CI]: 599.65 [376.42–955.29] vs 1066.77 [707.81–1607.77] mg; −44%, IRR [95% CI] vs placebo, 0.56 [0.33-0.95]; *P* = .0317) (Figure 3).

In patients who experienced only moderate exacerbation(s) during the study, those receiving dupilumab reported 484 moderate exacerbations, compared with 616 receiving placebo (Table 2). Similarly, although not to the same magnitude, patients receiving dupilumab versus placebo required systemic corticosteroids for fewer days (adjusted annualized total SCS intake duration, estimate [95% CI]: 10.46 [8.59–12.73] vs 14.49 [12.03–17.47] days; −28%, IRR [95% CI] vs placebo, 0.72 [0.60-0.87] days; *P* = .0005), required fewer systemic corticosteroid courses (adjusted annualized total SCS courses, estimate [95%CI]: 1.55 [1.35–1.78] vs 1.87 [1.63–2.14]; −17%, IRR [95% CI] vs placebo, 0.83 [0.73-0.95]; *P* = .0060), and had a lower cumulative systemic corticosteroid dose (adjusted annualized SCS use, estimate [95% CI]: 258.70 [197.05–339.66] vs 381.18 [294.56–493.28] mg; −32%, IRR [95% CI] vs placebo, 0.68 [0.53-0.87]; *P* = .0025) (Figure 3).

Dupilumab also showed numerical reductions in antibiotic use of 8% in patients with moderate exacerbations and 21% in those

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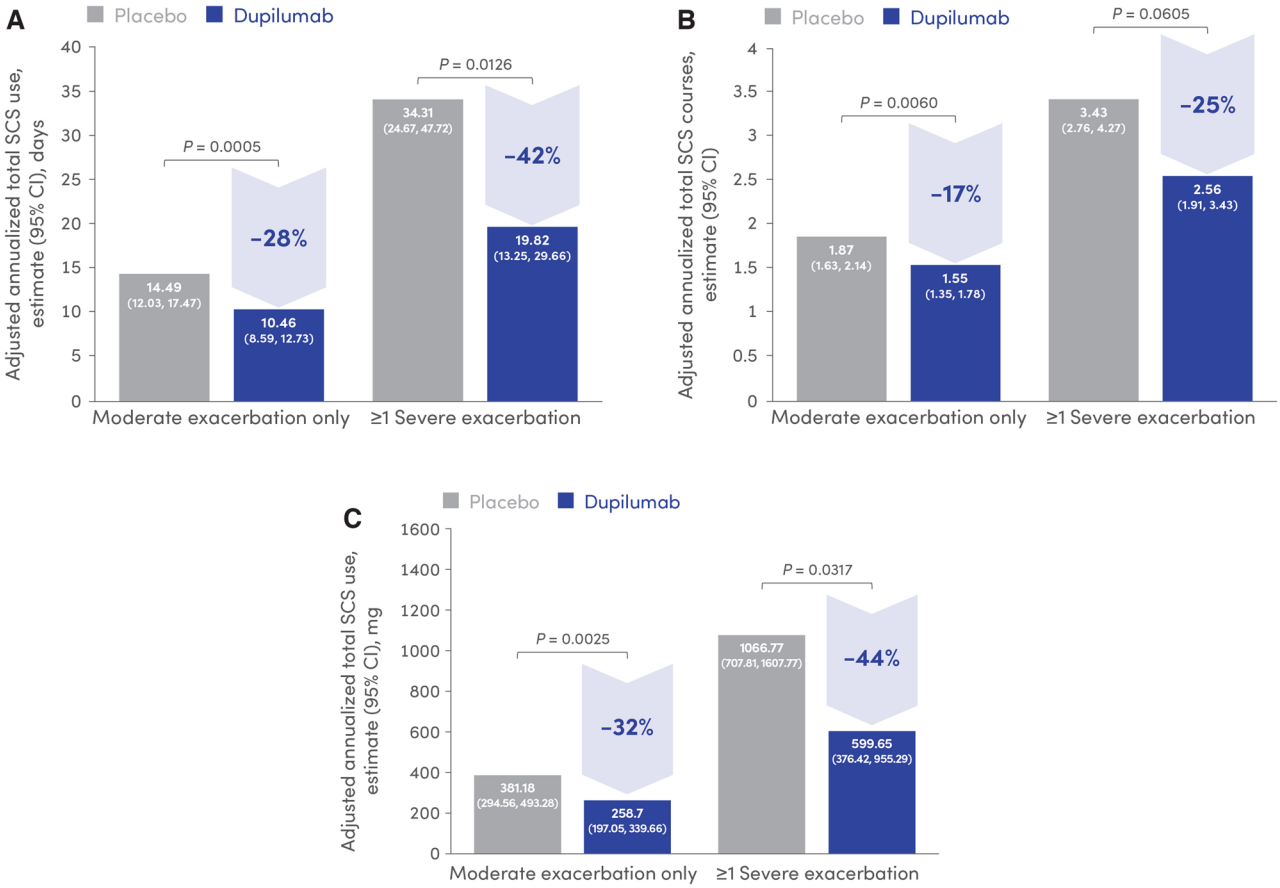

Figure 3 Annualized (A) total SCS days, (B) total SCS courses, and (C) cumulative SCS dose over the 52-week treatment period in patients with moderate exacerbation(s) only or severe exacerbation(s) during the study period. Moderate exacerbations are defined as exacerbations resulting in treatment with SCS, antibiotics, or both. Patients with moderate exacerbation(s) only were defined as those experiencing ≥1 moderate exacerbation event but no severe exacerbation events. Severe exacerbations are defined as exacerbations requiring hospitalization or an ED visit >24 hours, or resulting in death. Patients with ≥1 severe exacerbation event were defined as those experiencing ≥1 severe exacerbation event. These patients may have also experienced moderate exacerbations. Abbreviations: CI, confidence interval; ED, emergency department; SCS, systemic corticosteroid(s).

with ≥1 severe exacerbation (Figure S1). When measuring systemic corticosteroid and/or antibiotic use combined, significantly fewer courses were reported among those with moderate exacerbations (12% reduction; $P = .0138$) or ≥1 severe exacerbation (25% reduction; $P = .0349$) (Figure S2). Similarly, dupilumab showed significant reductions in the number of days of systemic corticosteroid and/or antibiotic use for those with moderate exacerbations (19% reduction; $P = .0034$) or ≥1 severe exacerbation (33% reduction; $P = .0351$) during the treatment period (Figure S3).

Discussion

This post hoc analysis of pooled data from the phase 3 BOREAS and NOTUS trials demonstrated that add-on dupilumab versus placebo reduced ED visits/hospital admissions by 38%, reduced the risk of ED visits/hospital admissions by 45%, and delayed time to first ED visits/hospital admissions in patients with COPD, moderate-to-severe airflow limitation, and type 2 inflammation on a background of inhaled triple therapy.

Patients with COPD represent a sizable portion of ED visits; one study estimated that up to 24% of ED visits were by patients with COPD and that they were 85% more likely to visit an ED than the general population.[35] Exacerbations that result in an ED visit, even without admission, are likely to result in healthcare utilization for subsequent exacerbations. For example, in a Canadian study, while approximately 70% of patients visiting an ED for a COPD exacerbation were discharged without admission, 25% revisited the ED within the next year.[36]

While hospitalization is a key element of the clinical trial definition of a "severe" exacerbation, the decision of whether to admit a patient to hospital is influenced by a number of factors other than true exacerbation severity, such as availability of support/care at home (eg, living alone), patient mobility,[37,38] or even the day of the week,[39] and varies geographically. For example, in the United States, the Hospital Readmission Reduction Program captures excess days in acute care, which includes ED visits/hospital admissions of any duration.[40] In contrast, the United Kingdom's National Health Service accounts for ED visits of >4 hours within its readmission metrics, which better captures the true extent of impact on healthcare utilization in acute care. While no direct comparisons were made with previously published data on severe exacerbation rates from the pooled BOREAS and NOTUS trials,[19-21] our analysis provides valuable insights into the impact of dupilumab on a broader scope of emergency care than previously reported, by including ED visits/hospitalizations of any length,

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Table 2 Exacerbations and systemic corticosteroid use in patients with moderate exacerbation(s) only or severe exacerbation(s) during the study.

Characteristic	Moderate exacerbation(s) only[a]		≥1 severe exacerbation[b]	
	Placebo	Dupilumab	Placebo	Dupilumab
	n = 334	*n* = 297	*n* = 60	*n* = 41
Moderate exacerbation events[c], No.	616	484	82	21
Requiring SCS use only, No. (%)	206 (33.4)	150 (31.0)	31 (37.8)	4 (19.0)
Requiring antibiotic use only, No. (%)	116 (18.8)	91 (18.8)	8 (9.8)	1 (4.8)
Requiring SCS and antibiotic use, No. (%)	294 (47.7)	243 (50.2)	43 (52.4)	16 (76.2)
Severe exacerbation events[d], No.	0	0	76	54
Requiring hospitalization, No. (%)	0	0	75 (98.7)	53 (98.1)
Requiring ED visit, No. (%)	0	0	1 (1.3)	1 (1.9)
Resulting in death, No. (%)	0	0	0	0
Patients with SCS use, No. (%)	282 (84.4)	246 (82.8)	58 (96.7)	39 (95.1)

Abbreviations: ED, emergency department; SCS, systemic corticosteroid(s); SD, standard deviation.
[a]Patients with moderate exacerbation(s) only were defined as those experiencing ≥1 moderate exacerbation event but no severe exacerbation events.
[b]Patients with ≥1 severe exacerbation event were defined as those experiencing ≥1 severe exacerbation event. These patients may have also experienced moderate exacerbations.
[c]Moderate exacerbations are defined as exacerbations resulting in treatment with SCS, antibiotics, or both.
[d]Severe exacerbations are defined as exacerbations requiring hospitalization or an ED visit >24 hours, or resulting in death.

rather than excluding ED visits ≤24 hours from the definition of a severe exacerbation.

In this analysis, dupilumab reduced the need for systemic corticosteroid use, which was amplified in patients who continued experiencing exacerbations during the treatment period. By reducing exacerbations and the need for systemic corticosteroids, dupilumab may help reduce the burden of systemic corticosteroid exposure, as well as the probability of adverse events that are more likely to occur with increasing cumulative systemic corticosteroid exposure.[3,17,41] The reported outcomes are highly relevant, given the known risks of systemic corticosteroid exposure. For example, an additional 5 to 7 days of exposure to steroids may significantly increase the risk of pneumonia and all-cause mortality,[41] as well as osteoporosis (80% increased risk), type 2 diabetes (44% increased risk), and heart disease (26% increased risk).[18]

This study also highlighted important differences in patient baseline characteristics across exacerbation categories. At baseline, patients who experienced severe exacerbations while on treatment had reduced lung function, worse quality of life, a higher symptom burden, and more severe disease, with a worse prognosis compared with patients who did not exacerbate and those who experienced only moderate exacerbation(s) during the study. Early treatment intervention can significantly reduce the risk of future exacerbations, slow lung function decline, and prevent symptoms from worsening.[42] While longer-term studies are needed, these results lead us to theorize that starting treatment with dupilumab early in the progression of the disease could positively change the trajectory for patients with more severe disease.

The findings of this analysis are consistent with those of other trials,[25,43,44] demonstrating the benefit of biologic therapies targeting type 2 inflammation in reducing severe exacerbations in patients with COPD and evidence of type 2 inflammation. While no reductions in annualized exacerbation rates leading to ED visits/hospital admissions were observed with mepolizumab versus placebo in patients with COPD and an eosinophilic phenotype in the phase 3 METREX trial, phase 3 METREO did show reductions in severe exacerbation rates.[25] Similarly, in the recent phase 3 MATINEE trial, mepolizumab reduced severe exacerbation rates (resulting in hospitalization or ED visits of any duration or death) by 34% (relative risk vs placebo [95% CI], 0.66 [0.43-1.01]).[28]

Our analysis must be interpreted with consideration of the limitations of the trials and their design. Although pooled data from two trials were included, the post hoc nature of the analyses may have resulted in subgroup analyses that are not adequately powered for statistical comparison. Additionally, the overall exacerbation rates and ED visits in these trials were low, which has led to small patient numbers in the subgroups used for analysis, particularly at later timepoints; therefore, these outcomes need to be interpreted with caution. It should also be noted that NOTUS ended early due to a positive interim analysis, which further reduced the number of patients completing the 52-week treatment period. The BOREAS and NOTUS trials were conducted during the COVID-19 pandemic, when COPD hospitalization rates were reduced and patient behavior became more exposure avoidant.[45] Furthermore, together with the restrictions in place during the trials (ie, masking, social isolation), these factors may have resulted in fewer exacerbations and decreased hospital admissions compared with pre- and post-pandemic times. Further studies are required to confirm whether the effect of dupilumab on severe exacerbations and healthcare resource utilization observed in this analysis is greater post-pandemic, and whether dupilumab may help to reduce the overall risk of all-cause mortality associated with hospitalization due to exacerbations, as well as COPD-related costs to the healthcare system. Finally, as previously discussed, the use of "hospitalization" may be seen as a weak endpoint as it can be influenced by nonclinical factors. While not collected in these trials, other endpoints, such as days alive out of hospital/hospital-free days or composite endpoints (including clinically important deterioration or COPDCompEx), could provide additional insight into the impact of dupilumab on severe exacerbations and healthcare resource utilization.[46-48]

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Conclusions

Compared with placebo, dupilumab treatment reduced the rate of ED visits/hospital admissions and delayed the time to first event over the 52-week treatment period when added to background triple inhaled therapy in patients with COPD and type 2 inflammation. Patients who experienced moderate or severe exacerbations required fewer systemic corticosteroids on dupilumab compared with those on placebo. Together, these data demonstrate the positive effects of dupilumab in reducing exacerbations, healthcare resource utilization, and cumulative exposure to systemic corticosteroids, and suggest a potentially positive impact on the burden of healthcare costs driven by exacerbations in patients with COPD.

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Author contributions

J.H. and M.S. contributed to the study design, data analysis, data interpretation, and writing of this manuscript. C.X. accessed and verified the data and did statistical analyses. S.P.B., F.J.M., I.S., A.A., J.B., A.P., S.K., G.D., and M.B. contributed to the data collection, data interpretation, and writing of this manuscript. All authors had full access to all of the data. All authors participated in the interpretation of the data, provided critical feedback, and took responsibility for the accuracy, completeness, and protocol adherence of data and analyses; all authors took final responsibility to submit for publication.

Supplementary material

Supplementary material is available at *American Journal of Respiratory and Critical Care Medicine* online.

Conflicts of interest

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Data availability

Qualified researchers may request access to patient level data and related study documents including the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan, and dataset specficications. Patient-level data will be anonymized, and study documents will be redacted to protect the privacy of our trial participants. Further details on Sanofi's data-sharing criteria, eligible studies, and process for requesting access can be found at: http://www.clinicalstudydatarequest.com/.

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