American Journal of Respiratory and Critical Care Medicine, 2026, 212, 241–252
https://doi.org/10.1164/rccm.202410-1894OC
Published: October 28, 2025
Original Research | Asthma and Allergy

ATS American Thoracic Society
thoracic.org

Effect of dupilumab on mucus burden in patients with moderate-to-severe asthma: the VESTIGE trial

Celeste Porsbjerg[1,*], Eleanor M. Dunican[2,3], Njira L. Lugogo[4], Mario Castro[5], Alberto Papi[6], Vibeke Backer[7], Christopher E. Brightling[8], Arnaud Bourdin[9], J. Christian Virchow[10], Mei Zhang[11], Xavier Soler[12], Paul J. Rowe[11], Yamo Deniz[12], Lucía de Prado Gómez[13], Harry J. Sacks[12], Juby A. Jacob-Nara[11]

[1]Department of Respiratory Medicine and Infectious Diseases, Bispebjerg and Frederiksberg Hospital, Copenhagen, Denmark
[2]Education and Research Centre, St Vincent's Hospital Elm Park, Dublin, Ireland
[3]Department of Medicine, School of Medicine, University College Dublin, Dublin, Ireland
[4]Michigan Medicine Asthma Program, University of Michigan, Ann Arbor, MI, United States
[5]Department of Medicine, University of Kansas School of Medicine, Kansas City, KS, United States
[6]Department of Cardiorespiratory Medicine, Respiratory Unit, University of Ferrara, S. Anna University Hospital, Ferrara, Italy
[7]Department of Otorhinolaryngology, Head and Neck Surgery and Audiology, Rigshospitalet, Copenhagen University, Copenhagen, Denmark
[8]Institute for Lung Health, NIHR Leicester Biomedical Research Centre, Department of Respiratory Sciences, University of Leicester, Leicester, United Kingdom
[9]Department of Respiratory Diseases, PhyMedExp, University of Montpellier, INSERM CNRS, Montpellier, France
[10]Departments of Pneumology and Intensive Care Medicine, University of Rostock, Rostock, Germany
[11]Sanofi, Bridgewater, NJ, United States
[12]Regeneron Pharmaceuticals Inc, Tarrytown, NY, United States
[13]Sanofi, Madrid, Spain

*Corresponding author: Celeste Porsbjerg, M.D., Ph.D., Department of Respiratory Medicine and Infectious Diseases, Bispebjerg Hospital, Bispebjerg Bakke 23, Copenhagen NV DK-2400, Denmark (celeste.porsbjerg@regionh.dk).

Abstract

Rationale: **Chronic mucus hypersecretion contributes to airway obstruction in asthma.**

Objectives: **To assess dupilumab efficacy by baseline mucus plug score.**

Methods: **In VESTIGE (NCT04400318), adults with moderate-to-severe asthma, baseline blood eosinophils ≥300 cells/μL, and fractional exhaled nitric oxide (FeNO) ≥25 ppb received dupilumab 300 mg ($n = 72$) or placebo ($n = 37$) every 2 weeks for 24 weeks. Post hoc analyses included mucus plug score change from baseline, and patient proportion achieving FeNO <25 ppb, percent predicted FEV_1, and FVC stratified by baseline mucus plug score (high/low defined by score ≥4 or 0-3.5, respectively, derived from high-resolution computed tomography scans).**

Measurements and Main Results: **Fewer dupilumab-receiving patients had high mucus plug score at week 24 than at baseline (32.8% vs 67.2%); proportions remained similar in placebo-receiving patients (76.7% vs 73.3%). Dupilumab versus placebo recipients were more likely to achieve FeNO <25 ppb in high-/low-mucus-plug score subgroups (odds ratio, 6.64; $P = .003$/8.54; $P = .024$). Dupilumab versus placebo significantly increased pre-/post-bronchodilator percent predicted FEV_1 (least squares mean difference [LSMD], 16.77 percentage points [95% CI, 9.81-23.73]; $P < .0001$ [pre] and 12.70 [95% CI, 3.87-21.52]; $P = .0055$ [post]) and pre-bronchodilator FVC (LSMD, 0.42 mL [95% CI, 0.17-0.66]; $P = .001$), and numerically improved post-bronchodilator FVC (LSMD, 0.30 mL [95% CI, 0.01-0.59]; $P = .0399$) in the high-mucus-plug score subgroup.**

Conclusions: **Dupilumab reduced mucus plug scores and improved lung function in patients with moderate-to-severe asthma with high baseline mucus plug score, and increased the likelihood of achieving FeNO <25 ppb regardless of baseline mucus plug score.**

Keywords airway remodeling, forced expiratory volume, forced vital capacity, fractional exhaled nitric oxide, lung volume measurements

Received: October 2, 2024. **Accepted:** August 15, 2025

© The Author(s) 2025. Published by Oxford University Press on behalf of the American Thoracic Society.
This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs licence (https://creativecommons.org/licenses/by-nc-nd/4.0/), which permits non-commercial reproduction and distribution of the work, in any medium, provided the original work is not altered or transformed in any way, and that the work is properly cited. For commercial re-use, please contact reprints@oup.com for reprints and translation rights for reprints. All other permissions can be obtained through our RightsLink service via the Permissions link on the article page on our site—for further information please contact journals.permissions@oup.com.

Downloaded from https://academic.oup.com/ajrccm/article/212/2/241/8437460 by Dipartimento Economia Istituzioni user on 08 May 2026

At a Glance Commentary

Scientific Knowledge on the Subject

In patients with asthma, chronic airway inflammation contributes to increased mucus production, smooth muscle contraction and airway hyperresponsiveness, remodeling, and obstruction facilitated by airway occlusion by mucus plugs; high mucus plug score, which is often seen in patients with severe asthma despite maximal anti-inflammatory therapy, has an important role in chronic loss of lung function.

What This Study Adds to the Field

Dupilumab treatment reduced mucus plug score and mucus volume, and improved global and distal lung functions, in patients with moderate-to-severe asthma. Treatment effects on lung function were more pronounced in patients who had a high mucus plug score at study baseline, suggesting that dupilumab may offer a novel therapeutic option in patients with moderate-to-severe asthma, improving airflow obstruction and reducing airway occlusion by mucus plugs.

Introduction

Airway occlusion due to mucus plugging facilitates airway obstruction in acute and chronic asthma and is a contributory cause of death in patients with asthma.[1-5] Patients with severe asthma have an elevated mucus plug score, with occlusive airway mucus plugs that persist over time shown to impact the same airway for up to 3 years.[2,4] Studies show that mucus plug score has a strong negative association with spirometric measures such as FEV_1 and FVC, and that longitudinal changes in mucus plug score inversely correlate with lung function changes.[2,4] Currently, conventional asthma treatments, including bronchodilators, inhaled/oral steroids, or intramuscular triamcinolone, do not ameliorate the presence of persistent mucus plugs.

High levels of type 2 cytokines alongside elevated sputum eosinophil counts in patients with mucus plugs suggest an important role for type 2 inflammation in mucus plug formation.[2,3] In particular, interleukin 13 (IL-13) is thought to play a key role through its effects on goblet cells, cilia, and airway smooth muscle cells, which impacts mucus secretion, changes mucin viscosity, and increases fractional exhaled nitric oxide (FeNO), which in turn affects airway smooth muscle function and mucus production.[6-9] In patients with severe asthma, mucus plugging correlates with high FeNO levels, indicating an upregulated interleukin 4 (IL-4)/IL-13 pathway in these patients.[10]

Dupilumab, a fully human monoclonal antibody,[11,12] blocks the shared receptor component for IL-4 and IL-13, key and central drivers of type 2 inflammation in multiple diseases.[13,14] Treatment with dupilumab improves lung function, reduces the rate of severe exacerbations, and improves asthma control in adults and adolescents with moderate-to-severe asthma for up to 3 years.[15-18]

The phase-4 VESTIGE study used functional respiratory imaging to assess changes in airway structure in response to dupilumab treatment in adults and adolescents with moderate-to-severe type 2 asthma.[19] It reports that dupilumab versus placebo significantly reduced airway inflammation and mucus plug scores, and increased airway volumes over 24-week treatment in the intention-to-treat (ITT) population; the safety profile was consistent with the known dupilumab safety profile.[19]

This post hoc analysis of data from VESTIGE assessed the effect of dupilumab treatment on mucus plugging and mucus volume, and the impact of mucus plug scores on dupilumab treatment and lung function, including measurements reflecting air trapping and distal lung volume at total lung capacity (TLC) in patients with asthma.

Some of the results of these studies have been previously reported in the form of abstracts.[20-25]

Methods

Study design

VESTIGE (NCT04400318) was a multinational, randomized, double-blind, placebo-controlled, phase 4 study in patients (aged 18-70 years) with physician-diagnosed uncontrolled moderate-to-severe type 2 asthma (baseline blood eosinophils ≥300 cells/μL and FeNO ≥25 parts per billion [ppb]). Full details have been described previously.[19] The trial design is shown in Figure E1. Eligible patients had ≥1 severe asthma exacerbations in the previous year, Asthma Control Questionnaire-5 score ≥1.5, pre-bronchodilator percent predicted FEV_1 ($ppFEV_1$) ≤80%, and bronchodilator reversibility before randomization; and were receiving stable treatment with medium- or high-dose inhaled corticosteroids (ICS) with a second or third controller. Patients who received chronic oral corticosteroids for >2 weeks before visit 1 were excluded. Patients were randomized (2:1) to receive add-on 300 mg dupilumab subcutaneously, or volume-matched placebo, every 2 weeks for 24 weeks. High-resolution computed tomography (HRCT) scans were taken at weeks 0 (baseline), 4, and 24.

The trial adhered to the Declaration of Helsinki and International Council for Harmonisation Good Clinical Practice guidelines with approval from institutional review boards and ethics committees. All patients provided written informed consent.

Endpoints

Efficacy endpoints included proportion of patients with mucus plug score categories 0, 0.5-3.5, and 4-20 at baseline, week 4, and week 24, and change from baseline to weeks 4 and 24 in global lung mucus plug score and global lung mucus volume. Mucus plug scores were derived from HRCT scans using a validated scoring system to quantify number of bronchopulmonary segments completely occluded with mucus, resulting in an average mucus plug score of 0-20 in 0.5 increments; 4-20 corresponds to a high mucus plug score and 0-3.5 to a low mucus plug score, based on definitions from Dunican et al.[4] The scoring system and its limitations are detailed in the Supplementary Materials.

Mucus volume was calculated by quantification of voxels per mucus plug following the protocol described by Castro et al.[19]

Downloaded from https://academic.oup.com/ajrccm/article/212/2/241/8437460 by Dipartimento Economia Istituzioni user on 08 May 2026

Changes in mucus plug score and volume were stratified by baseline ICS dose (high/medium).

Other efficacy endpoints assessed according to baseline mucus plug score included FeNO responders (defined as achieving FeNO <25 ppb at week 24), and change from baseline in pre-/post-bronchodilator FEV_1, pre-/post-bronchodilator $ppFEV_1$, pre-/post-bronchodilator FEV_1/FVC ratio, peripheral airway resistance measured by the forced oscillometry parameter difference in resistance at 5 Hz and 20 Hz (R5-R20), peripheral compliance measured by forced oscillometry reactance area, and specific untrimmed distal airway volumes corrected for lung volume [$(s)iV_{aw}$] at TLC derived from HRCT scans. $(s)iV_{aw}$ methodology is detailed in the Supplementary Materials. Exploratory correlation analysis assessed the relation of mucus plug score to mucus volume and lung function (pre- and post-bronchodilator FEV_1 and $ppFEV_1$) to mucus plug score.

Statistical analysis

Statistical analyses were performed using SAS for Windows (version 9.4 or higher, SAS Institute, Cary, NC, USA).

The ITT population, which includes all randomized patients, was analyzed. Efficacy outcomes used a mixed-effects model with repeated measures; covariates used are detailed in the Supplementary Materials. Least squares (LS) mean of each treatment group, LS mean difference (LSMD) between the treatment arms, and corresponding 95% CI of the differences and *P* values were calculated. Correlations were evaluated using Pearson correlation analysis.

Results

In total, 109 patients were randomized (2:1) to receive either dupilumab 300 mg every 2 weeks ($n = 72$) or volume-matching placebo ($n = 37$). All randomized patients received intervention (Figure 1). A total of 71 patients had high baseline mucus plug score, comprising 63.9% of the patients randomized to dupilumab and 67.6% of the patients randomized to placebo. Low mucus plug score at baseline was present in 33 patients, which corresponded to 31.9% of the patients randomized to dupilumab and 27.0% of the patients randomized to placebo.

Baseline characteristics of patients with high or low mucus plug score at baseline who received dupilumab or placebo are shown in Tables 1 and 2. Patients from the high-mucus-plug score subgroup had mean (SD) mucus plug scores of 9.93 (3.96)

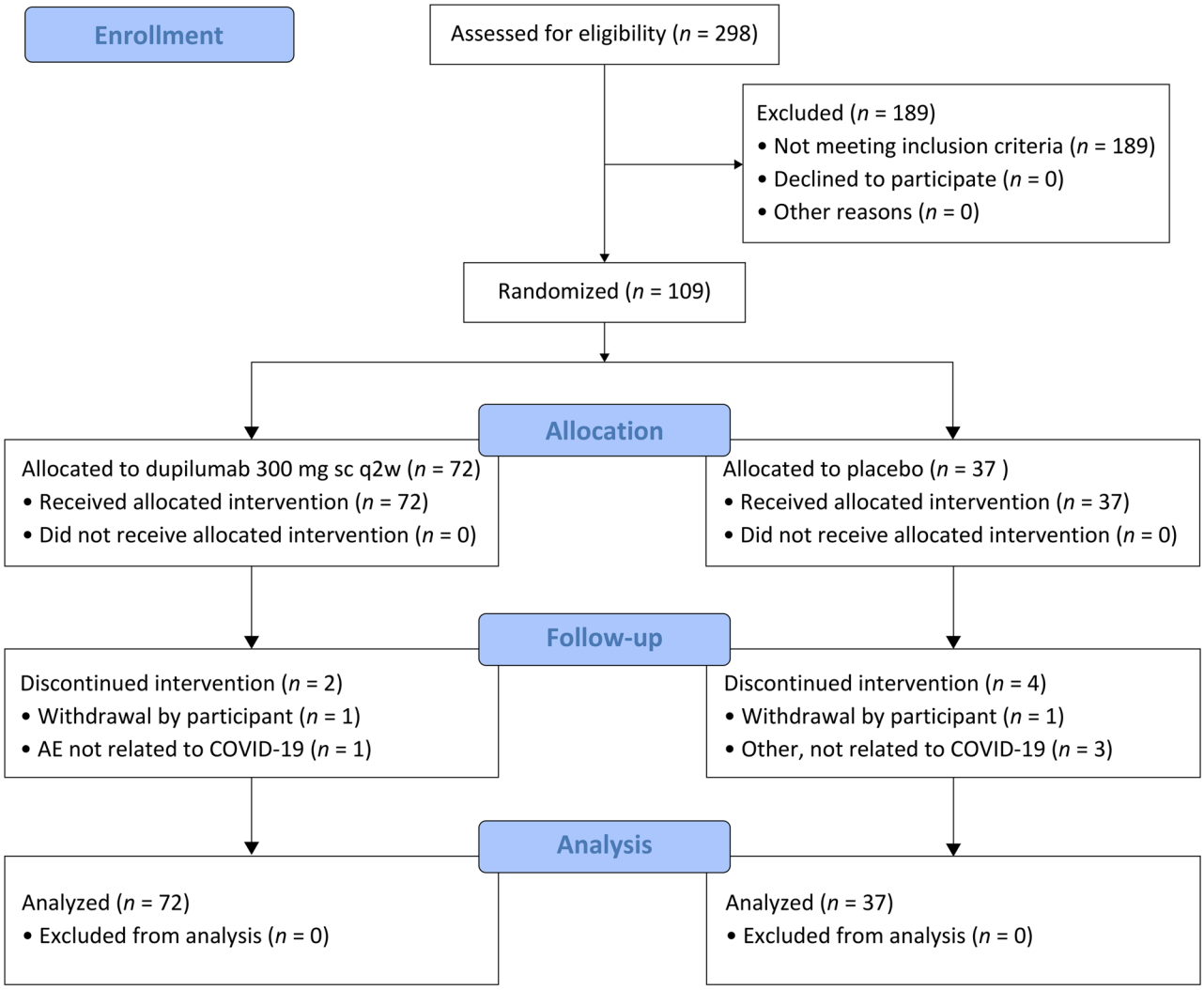


Figure 1 Consolidated Standards of Reporting Trials (CONSORT) flow diagram. Abbreviations: AE, adverse event; q2w, every 2 weeks; sc, subcutaneous.

Downloaded from https://academic.oup.com/ajrccm/article/212/2/241/8437460 by Dipartimento Economia Istituzioni user on 08 May 2026

Table 1 Demographic characteristics of the intention-to-treat population stratified by mucus plug score at baseline.

Characteristic	High mucus plug score[a] at baseline		Low mucus plug score[a] at baseline	
	Placebo (*n* = 25)	Dupilumab 300 mg q2w (*n* = 46)	Placebo (*n* = 10)	Dupilumab 300 mg q2w (*n* = 23)
Age, y, mean (SD)	51.4 (11.5)	48.6 (13.7)	43.6 (13.2)	55.5 (10.2)
Sex				
Female	16 (64.0)	28 (60.9)	5 (50.0)	16 (69.6)
Male	9 (36.0)	18 (39.1)	5 (50.0)	7 (30.4)
Race				
White	22 (88.0)	39 (84.8)	10 (100.0)	23 (100.0)
Black/African American	1 (4.0)	0	0	0
Asian	2 (8.0)	7 (15.2)	0	0
Ethnicity				
Hispanic	1 (4.0)	3 (6.5)	0	0
Not Hispanic	24 (96.0)	43 (93.5)	10 (100.0)	22 (95.7)
Not reported	0	0	0	1 (4.3)
Region				
Eastern Europe[b]	15 (60.0)	27 (58.7)	7 (70.0)	17 (73.9)
Rest of the world[c]	10 (40.0)	19 (41.3)	3 (30.0)	6 (26.1)
BMI, kg/m^2, mean (SD)	29.4 (9.0)	26.8 (4.2)	26.8 (4.5)	30.3 (5.2)

Data are presented as No. (%) unless otherwise specified.
Abbreviations: BMI, body mass index; q2w, every 2 weeks; SD, standard deviation.
[a]Low: mucus plug score 0-3.5; high: mucus plug score 4-20.
[b]Bulgaria, Romania, and Ukraine.
[c]Denmark, France, Italy, Portugal, Saudi Arabia, Spain, Sweden, Taiwan, United Kingdom, and United States.

and 9.24 (3.76) in the dupilumab versus placebo treatment arms, respectively, while those from the low-mucus-plug score subgroup had mean (standard deviation [SD]) scores of 1.61 (1.03) and 1.00 (1.05), respectively. Baseline mucus plug scores showed moderate-to-strong correlations with baseline mucus volume in both subgroups. A majority of study participants were female, non-Hispanic White, and from Eastern Europe, with no history of smoking. Within subgroups of patients with high or low mucus plug score at study baseline, baseline demographics were similar between the 2 treatment arms. Biomarkers of type 2 inflammation were similar between subgroups and treatment arms. As may be expected, patients with a high mucus plug score at baseline had numerically lower baseline spirometric values and distal airway volume than patients with a low mucus plug score at baseline. Table E1 shows additional respiratory characteristics from spirometry, functional and conventional imaging, and forced oscillometry.

Dupilumab treatment reduced the proportion of patients with high mucus plug score from 67.2% at baseline to 50.8% by week 4, with continuing reduction to week 24 (32.8%). Meanwhile, similar proportions of patients on placebo maintained a high mucus plug score at baseline, week 4, and week 24 (73.3%, 73.3%, and 76.7%, respectively) (Figure 2).

Representative HRCT images of mucus plugs at baseline and week 24 by treatment arm and ICS dose are shown in Figure E2. At week 24, dupilumab versus placebo significantly reduced global lung mucus plug scores in patients on high- and medium-dose ICS at baseline (LSMD [95% CI] vs placebo: -5.26 [-7.70 to -2.82]; *P*<.0001, and -3.79 [-5.94 to -1.64]; *P*<.001, in the high- and medium-dose ICS groups, respectively) (Figure E3). Similar significant reductions at week 24 were observed with dupilumab versus placebo in global lung mucus volume in both ICS-dose groups (Figure E3, Videos E1 and E2).

A significantly higher proportion of patients achieved FeNO <25 ppb by week 24 in the dupilumab versus placebo arms in both the high (50.0% vs 12.0%, respectively; odds ratio [OR], 6.64; *P* = .003) and low (65.2% vs 10.0%, respectively; OR, 8.54; *P* = .024) baseline mucus plug score subgroups (Figure 3).

Evaluation of the change from baseline in FEV_1 (Figure 4) showed that in patients with a high mucus plug score at baseline, dupilumab versus placebo led to significant improvements from baseline in both pre- and post-bronchodilator FEV_1 (LSMD [95% CI] vs placebo at week 24: pre-bronchodilator FEV_1: 0.48 L [0.23-0.72], *P* = .0002; post-bronchodilator FEV_1: 0.39 L [0.12-0.66], *P* = .0059). In patients with a low mucus plug score at baseline, small numerical increases in pre- and post-bronchodilator FEV_1 were observed with dupilumab (LSMD [95% CI] vs placebo at week 24: pre-bronchodilator FEV_1: 0.05 L [-0.52 to 0.62], *P* = .8561; post-bronchodilator FEV_1: 0.28 L [-0.24 to 0.80], *P* = .2826).

Similarly, dupilumab versus placebo also led to significant improvements from baseline in both pre- and post-bronchodilator $ppFEV_1$ (LSMD [95% CI] vs placebo at week 24: pre-bronchodilator $ppFEV_1$: 16.77 percentage points [9.81-23.73], *P*<.0001; post-bronchodilator $ppFEV_1$: 12.70 percentage points [3.87-21.52], *P* = .0055) in patients with a high mucus plug score at baseline (Figure 5). Changes were not significant in patients with low mucus plug score at baseline (LSMD [95% CI] vs placebo at week 24: pre-bronchodilator $ppFEV_1$: 2.88 percentage points [-13.68 to 19.43], *P* = .7251; post-bronchodilator $ppFEV_1$: 7.38 percentage points [-8.20 to 22.96], *P* = .3407) (Figure 5). Comparable patterns of improvement were observed in patients with a high mucus plug score at baseline for dupilumab versus placebo in pre- and post-bronchodilator FVC; changes were significant at most timepoints (Figure E4).

In patients with high mucus plug score at baseline, dupilumab versus placebo significantly improved the pre- and

Downloaded from https://academic.oup.com/ajrccm/article/212/2/241/8437460 by Dipartimento Economia Istituzioni user on 08 May 2026

Table 2 Disease characteristics and biomarkers of the intention-to-treat population stratified by mucus plug score at baseline.

Characteristic	High mucus plug score[a] at baseline		Low mucus plug score[a] at baseline	
	Placebo (*n* = 25)	Dupilumab 300 mg q2w (*n* = 46)	Placebo (*n* = 10)	Dupilumab 300 mg q2w (*n* = 23)
ICS dose, No. (%)				
High	13 (52.0)	25 (54.3)	7 (70.0)	6 (26.1)
Medium	12 (48.0)	21 (45.7)	3 (30.0)	17 (73.9)
Smoking history, No. (%)				
Former	2 (8.0)	7 (15.2)	1 (10.0)	4 (17.4)
Never	23 (92.0)	39 (84.8)	9 (90.0)	19 (82.6)
Age at onset of asthma, y, mean (SD)	29.2 (16.9)	33.3 (18.2)	30.8 (17.7)	37.1 (16.0)
Time since last severe exacerbation, mo, mean (SD)	5.8 (3.3)	4.9 (3.4)	6.1 (3.7)	4.5 (2.8)
Severe asthma exacerbations in the past year, mean (SD)	1.5 (1.0)	1.4 (1.2)	1.2 (0.4)	1.7 (1.7)
Pre-bronchodilator FEV_1, L, mean (SD)	1.80 (0.60)	1.77 (0.61)	2.16 (0.62)	1.98 (0.83)
Post-bronchodilator FEV_1, L, mean (SD)	2.11 (0.74)	2.16 (0.67)	2.57 (0.76)	2.32 (0.80)
Pre-bronchodilator $ppFEV_1$, %, mean (SD)	58.2 (12.5)	55.3 (13.4)	60.4 (13.9)	64.1 (13.8)
Post-bronchodilator $ppFEV_1$, %, mean (SD)	68.1 (15.5)	67.4 (14.3)	70.6 (12.1)	76.1 (13.7)
Pre-bronchodilator FVC, L, mean (SD)	3.03 (1.05)	3.12 (1.05)	3.50 (1.19)	3.02 (1.12)
Post-bronchodilator FVC, L, mean (SD)	3.32 (1.08)	3.47 (1.09)	3.83 (1.26)	3.30 (1.05)
(s)iV_{aw} at TLC, mL, mean (SD)	1.80 (1.30)	1.75 (0.81)	2.16 (0.69)	2.21 (1.15)
Airway resistance R5-R20, kPa*s/L, mean (SD)	0.13 (0.12)	0.17 (0.13)	0.10 (0.09)	0.17 (0.12)
Mucus plug score, mean (SD)	9.24 (3.76)	9.93 (3.96)	1.00 (1.05)	1.61 (1.03)
Baseline mucus plug score correlation with mucus volume, Pearson coefficient	*r* = 0.7519 *P* < .0001	*r* = 0.7454 *P* < .0001	*r* = 0.7635 *P* = .0102	*r* = 0.4677 *P* = .0244
Biomarkers				
Blood eosinophil count, cells/μL				
Median (IQR)	440.0 (350.0-790.0)	500.0 (310.0-790.0)	500.0 (350.0-900.0)	440.0 (260.0-592.0)
Mean (SD)	631.0 (426.4)	647.8 (473.7)	561.0 (338.7)	460.1 (231.4)
FeNO, ppb				
Median (IQR)	45.0 (36.0-63.0)	49.0 (36.0-87.0)	47.0 (31.0-59.0)	45.0 (34.0-70.0)
Mean (SD)	55.4 (28.8)	65.9 (41.4)	45.7 (15.6)	58.5 (37.8)
Baseline FeNO correlation with mucus plug score, Pearson coefficient	*r* = 0.0804 *P* = .7025	*r* = 0.1527 *P* = .3109	*r* = 0.1752 *P* = .6283	*r* = 0.1160 *P* = .5981
Baseline FeNO correlation with mucus volume, Pearson coefficient	*r* = 0.0082 *P* = .9691	*r* = -0.0030 *P* = .9844	*r* = 0.1379 *P* = .7041	*r* = 0.2348 *P* = .2808

Abbreviations: FeNO, fractional exhaled nitric oxide; ICS, inhaled corticosteroid; IQR, interquartile range; ppb, parts per billion; $ppFEV_1$, percent predicted FEV_1; q2w, every 2 weeks; R5-R20, difference in resistance at 5 Hz and 20 Hz; SD, standard deviation; (s)iV_{aw}, untrimmed distal airway volumes corrected for lung volume; TLC, total lung capacity.
[a]Low: mucus plug score 0-3.5; high: mucus plug score 4-20.

post-bronchodilator FEV_1/FVC ratio as early as week 4 and sustained this improvement to week 24 (LSMD [95% CI]: pre-bronchodilator FEV_1/FVC: 7.52 [3.37-11.68], *P* = .0006; post-bronchodilator FEV_1/FVC: 6.08 [2.56-9.61], *P* = .0010) (Figure E5). Changes were not significant in patients with low mucus plug score at baseline (LSMD [95% CI] vs placebo at week 24: pre-bronchodilator FEV_1/FVC: 2.03 [-5.85 to 9.91], *P* = .6051; post-bronchodilator FEV_1/FVC: 5.33 [-1.57 to 12.24], *P* = .1261) (Figure E5).

In patients with high mucus plug score who received dupilumab, correlation analyses demonstrated moderate to strong relationships between changes in pre- and post-bronchodilator FEV_1 and mucus plug score (*r* = -0.6087 [*P* < .0001] and *r* = -0.5603 [*P* = .0001], respectively) (Figure E6). Correlations between mucus plug score and pre-bronchodilator $ppFEV_1$ changes were also moderate to strong (*r* = -0.6055 [*P* < .0001]) (Figure E6). In contrast, in the low-mucus-plug score subgroup, correlations between improvements in lung function and mucus plug score were weak and not significant (Figure E6).

With regard to peripheral airway dynamics, numerical but not statistically significant improvements from baseline in distal airway volumes, represented by the functional imaging parameter (s)iV_{aw} at TLC, were observed at week 24 with dupilumab versus placebo in both high- and low-mucus-plug score subgroups. These improvements were variable and more pronounced in the high-mucus-plug score subgroup (LSMD [95% CI] vs placebo: high-mucus-plug score subgroup: 28.85% [-13.35% to 71.05%], *P* = .1596; low-mucus-plug score subgroup: 7.79% [-11.70% to 27.28%], *P* = .4216) (Table 3).

Numerical improvements from baseline to week 24 in peripheral airway resistance as assessed by the forced oscillometry pa-

Downloaded from https://academic.oup.com/ajrccm/article/212/2/241/8437460 by Dipartimento Economia Istituzioni user on 08 May 2026

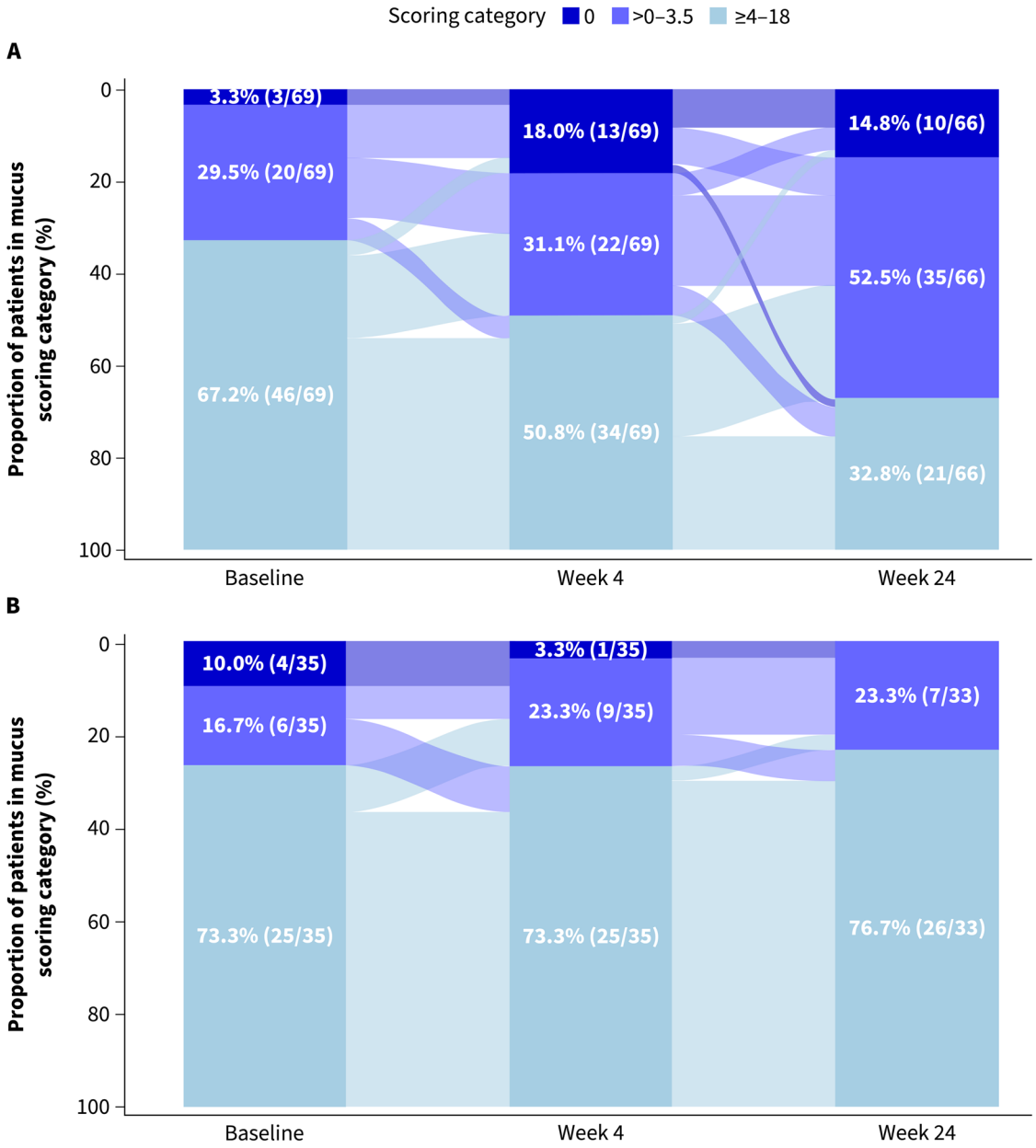


Figure 2 Proportion of patients in mucus scoring categories at baseline, week 4, and week 24 in (A) dupilumab and (B) placebo groups. Patients with missing mucus plug scores at baseline, week 4, or week 24 were excluded from the Sankey plots.

rameter R5-R20 were observed with dupilumab versus placebo in patients with high mucus plug score at baseline (LSMD [95% CI] vs placebo at week 24: -0.06 kPa*s/L [-0.12 to -0.01]; $P = .0183$) (Figure E7). A nominally significant improvement in reactance area was observed from baseline to week 24 (LSMD [95% CI] vs placebo at week 24: -1.96 [-3.31 to -0.60]; $P = .0054$) (Table E2).

Improvements in these parameters were less pronounced or absent in the low-mucus-plug score group at the same timepoint, with an LSMD (95% CI) versus placebo of 0.01 kPa*s/L (-0.04 to 0.07; $P = .6007$) in peripheral airway resistance, and 1.23 kPa/L (-0.08 to 2.54; $P = .0640$) in reactance area.

Discussion

Mucus plugging is a significant contributory factor to airway obstruction and death in acute asthma, and to exacerbations, airflow obstruction, and inflammation in chronic asthma.[2-4,26] It has been suggested that mucus plugging may represent a persistent asthma phenotype, and changes in the burden of mucus plugs over time correlate with fluctuations in the severity of airflow obstruction and air trapping.[2] The mucus plug score serves as a validated metric to quantify airway occlusions caused by mucus plugs, offering an indirect yet robust representation of mucus burden in the airways.[4] The mucus plug score cutoff of ≥4 was initially defined by Dunican et al., where it demonstrated a strong association with severe airflow obstruction and elevated eosinophilic inflammation.[4] This cutoff was subsequently validated in a larger cohort of 165 participants, where its persistence and correlation with longitudinal changes in lung function was confirmed.[2] A recent study further supported the utility of this score in assessing airway-specific resistance and air trapping.[27]

Higher mucus plug scores reflect a greater number of airway segments fully obstructed by mucus.[4] Previous studies have

Downloaded from https://academic.oup.com/ajrccm/article/212/2/241/8437460 by Dipartimento Economia Istituzioni user on 08 May 2026

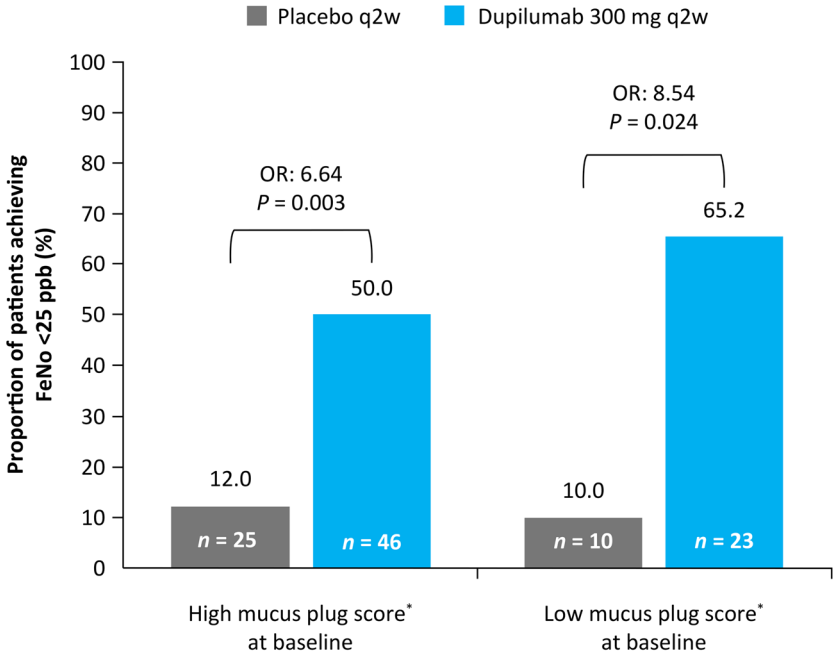


Figure 3 Proportion of patients achieving FeNO <25 ppb at week 24 stratified by mucus plug score at baseline. *High: mucus plug score 4-20; low: mucus plug score: 0-3.5. Abbreviations: FeNO, fractional exhaled nitric oxide; OR, odds ratio; ppb, parts per billion; q2w, every 2 weeks.

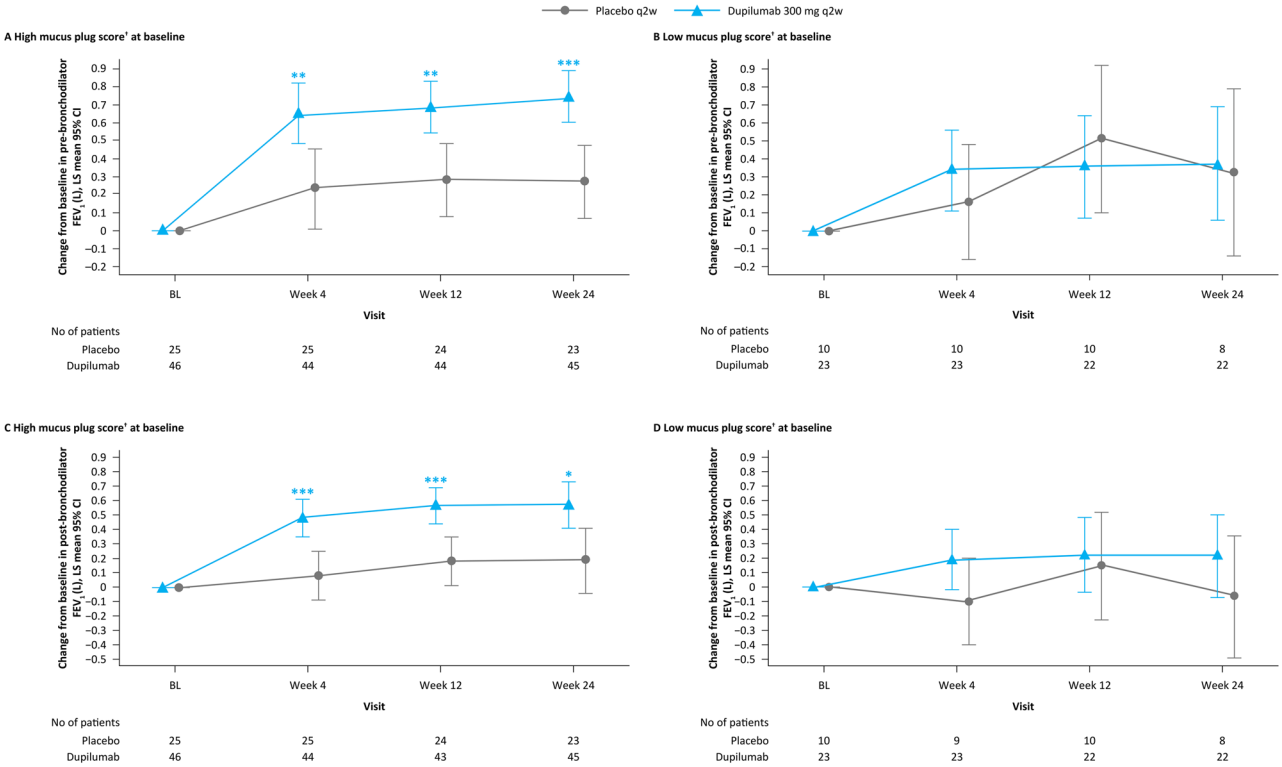


Figure 4 Change from baseline at weeks 4, 12, and 24 in pre-bronchodilator FEV_1 (A and B) and post-bronchodilator FEV_1 (C and D) stratified by mucus plug score at baseline. *P<.01; **P<.005; ***P<.001. †High: mucus plug score 4-20; low: mucus plug score 0-3.5. Abbreviations: BL, baseline; LS, least squares; q2w, every 2 weeks.

shown that elevated mucus plug scores are associated with markers of airway inflammation, such as elevated eosinophils and FeNO, and worsened lung function parameters,[2,4] linking mucus plug scores to the physiological and pathological impacts of high mucus burden. In this study, mucus plug score showed a moderate to strong correlation with mucus volume at baseline. By providing a standardized framework for assessing mucus pathology, the mucus plug score complements other exploratory measures, such as mucus volume, in elucidating the role of mucus in airway obstruction.

Downloaded from https://academic.oup.com/ajrccm/article/212/2/241/8437460 by Dipartimento Economia Istituzioni user on 08 May 2026

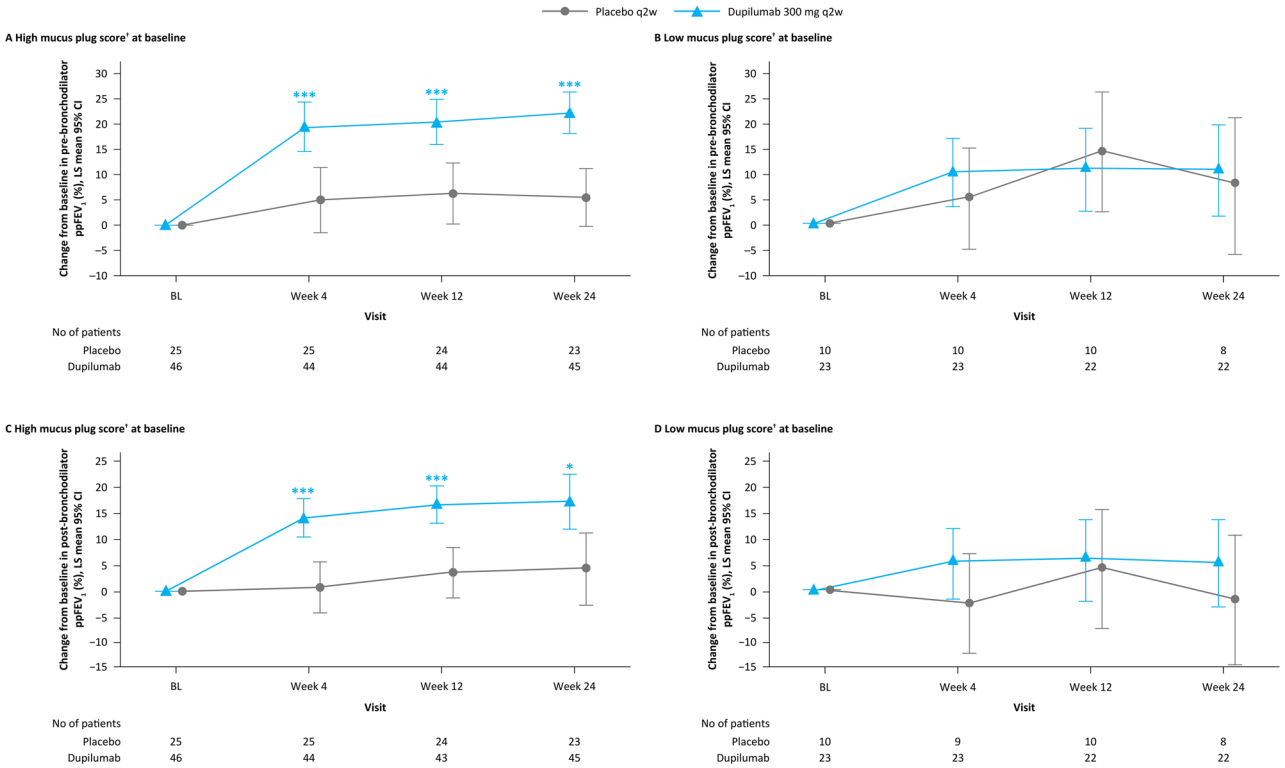


Figure 5 Change from baseline at weeks 4, 12, and 24 in pre-bronchodilator percent predicted FEV_1 (A and B) and post-bronchodilator percent predicted FEV_1 (C and D) stratified by mucus plug score at baseline. *P <.01; ***P <.001. †High: mucus plug score 4-20; low: mucus plug score 0-3.5. Abbreviations: BL, baseline; LS, least squares; pp, percent predicted; q2w, every 2 weeks.

Table 3 Percent change from baseline in distal airway volume as represented by (s)iV_{aw} at TLC stratified by mucus plug score at baseline.

(s)iV_{aw} at TLC, mL	High mucus plug score[a] at baseline		Low mucus plug score[a] at baseline	
	Placebo (n = 25)	Dupilumab 300 mg q2w (n = 46)	Placebo (n = 10)	Dupilumab 300 mg q2w (n = 23)
Baseline, mean (SD)	1.80 (1.30)	1.75 (0.81)	2.16 (0.69)	2.21 (1.15)
Percent change from baseline at week 4, %				
LS mean (SE)	18.48 (34.21)	49.74 (24.85)	-7.28 (6.53)	-4.02 (4.53)
LSMD (95% CI) vs placebo		31.26 (-52.98 to 115.50)		3.26 (-13.13 to 19.66)
Percent change from baseline at week 24, %				
LS mean (SE)	2.73 (15.52)	31.59 (11.32)	-8.77 (7.96)	-0.98 (5.13)
LSMD (95% CI) vs placebo		28.85 (-13.35 to 71.05)		7.79 (-11.70 to 27.28)
***P* value vs placebo**		.1596		.4216

Abbreviations: LS, least squares; LSMD, least squares mean difference; q2w, every 2 weeks; SD, standard deviation; SE, standard error; (s)iV_{aw}, untrimmed distal airway volumes corrected for lung volume; TLC, total lung capacity.
[a]High: mucus plug score 4-20; low: mucus plug score 0-3.5.

Currently, long-term treatment with conventional asthma therapy (inhaled or systemic steroids) does not ameliorate the presence of mucus plugs in patients with asthma.[2] Reductions in mucus plugging, and associated improvements in lung function, observed with dupilumab treatment reported here, and comparative stability observed in the placebo group, suggest that targeting type 2 inflammation with dupilumab may offer a novel therapeutic option complementing existing treatment options to address asthma pathology, including mucus plugging, in patients with moderate-to-severe asthma.

While the mechanisms behind mucus hypersecretion and plugging in asthma are not fully elucidated, mucus plug pathophysiology appears to be driven, at least in part, by type 2 inflammation.[2-4] Markers of the IL-4/IL-13 pathway are significantly upregulated in patients with asthma where mucus is the dominant cause of airway obstruction[9] and is thought to play a key role in mucus cell hyperplasia, mucin gene induction, mucin storage and release, and changes in mucin viscosity.[6,7] Although blocking IL-13 signaling has been suggested to be beneficial in patients with poorly controlled asthma and more severe airway hyperresponsiveness with significant mucus hypersecretion, some studies report that blocking IL-13 alone is insufficient to improve asthma outcomes.[28] Nevertheless, the effect of dupilumab on mucus plugging and mucus volume may be attributable, at least partially, to the fact that

Downloaded from https://academic.oup.com/ajrccm/article/212/2/241/8437460 by Dipartimento Economia Istituzioni user on 08 May 2026

it targets IL4-Rα, common to both type 1 (IL-4–specific) and type 2 (IL-4– and IL-13–specific) IL4-R complexes.[29]

In VESTIGE, more than half of all patients had a high mucus plug score at study baseline, defined as having a score of at least 4 and up to 20 bronchopulmonary segments occluded by mucus plugs as determined by HRCT.[4] Treatment with dupilumab versus placebo significantly reduced mucus plugging and mucus volume over 24 weeks in these patients. Dupilumab efficacy in reducing mucus plugging has been observed in other single-center, placebo-controlled, randomized clinical trials.[30] In the present study, significant reductions in mucus plug score and mucus volume were observed as early as week 4, suggesting that mucus plugging may be modified earlier in the disease process than previously thought;[2] these reductions were sustained to week 24. Elevated levels of FeNO have been associated with increased risk of exacerbations, loss of lung function,[31,32] and higher mucus plug scores.[26] While FeNO directly reflects IL-13 activity rather than airway inflammation, it is widely accepted as an indirect marker of type 2 inflammation.[33,34] The present results from VESTIGE suggest potential reductions in airway inflammation, as indicated by a greater proportion of patients achieving FeNO <25 ppb at week 24 in patients receiving dupilumab versus placebo, a trend that was observed in both the high- and low-mucus-plug score subgroups. Compared with patients receiving placebo, patients receiving dupilumab in the high-mucus-plug score subgroup were almost 10 times as likely to achieve FeNO levels <25 ppb at the end of the study; those with low baseline mucus plug score were almost 7 times as likely to achieve reduced FeNO levels with dupilumab treatment.

In keeping with other clinical studies of dupilumab in patients with asthma,[15-18] dupilumab improved global airway volume and lung function parameters over 24 weeks in VESTIGE. In patients with high mucus plug score at baseline, dupilumab treatment resulted in significant improvements as early as week 4 of treatment in absolute and percent predicted FEV_1 and the FEV_1/FVC ratio. Dupilumab also reduced air trapping, as indicated by improvements in FVC and reduced resistance, and, to a lesser degree, improved volume in smaller, distal airways as measured by the forced oscillometry parameter R5-R20, reactance area, and functional imaging parameter (s)iV_{aw} at TLC. Treatment effects were consistently more pronounced in patients with high mucus plug score at baseline than in patients with low mucus plug score.

Correlation analysis suggested significant moderate-to-strong associations between improvements in mucus plug scoring and lung function (measured by FEV_1) in patients with high mucus plug score at baseline. In contrast, there were no significant correlations between mucus plug score and lung function improvements among patients with low mucus plug score. These data suggest that dupilumab may improve distal and global lung function by addressing type 2 inflammation–related symptoms and by reducing mucus plug score.

Our findings add to existing evidence that mucus plugs in asthma may be associated with type 2 inflammation, and their resolution with dupilumab treatment could reflect effective therapeutic targeting. The observed resolution of mucus plugs within 4 weeks of dupilumab treatment likely reflected the rapid anti-inflammatory effects of targeting IL-4/IL-13 pathways,[13,14] which were associated with improved lung function metrics. However, interestingly, levels of type 2 biomarkers, and blood eosinophils and FeNO levels, were similar between patients with high or low mucus plug score at baseline. In patients who received dupilumab treatment, baseline FeNO showed only weak positive correlations with mucus plug score ($r = 0.1527$, $P = .3109$ in patients with high mucus plug scores; $r = 0.1160$, $P = .5981$ in patients with low mucus plug scores). These findings suggest that although FeNO is widely accepted as an indirect marker of type 2 inflammation, it may not fully capture the complexity of biological processes underlying mucus plug formation and treatment responses with regard to type 2–driven mucus plug burden. While not a strict boundary of asthma severity, a mucus plug score of ≥4 has demonstrated utility in identifying patients with more severe airflow obstruction and higher mucus-associated inflammation.[4] As was then expected, baseline lung function was lower in patients with high compared with low mucus plug scores. However improvements in FEV_1 that were evident in these patients by week 24 varied in the degree of FEV_1 reversibility, indicating that mechanisms beyond bronchodilator responsiveness, such as the reduction of mucus plugs, contributed to lung function improvements. Our results support the added value of HRCT imaging in stratifying asthma phenotypes and predicting treatment outcomes.

There are some limitations associated with this post hoc analysis, and the results should be interpreted with these in mind. The VESTIGE study was not powered to show statistical significance in patient subgroups stratified by their mucus plug score at baseline, and this stratification resulted in low patient numbers in some subgroups. The study population is patients enrolled in VESTIGE with high FeNO levels (≥25 ppb) and high blood eosinophils (≥300 cells/μL) beyond the thresholds often utilized in clinics to categorize type 2 asthma. There was also limited diversity across subgroups that reflected the lack of diversity in the overall study population, which may limit the wider applicability of these findings to more diverse populations of people with asthma. While these results support an association between mucus plug resolution and improved lung function, co-localization of resolved mucus plugs and specific areas of lung function recovery was not performed. This may make for an interesting area of future HRCT image analysis important in understanding localized air trapping around mucus plugs. The capacity of the HRCT-based mucus plug scoring system to distinguish mucus and airway walls is limited without contrast and it is important to be aware of this when interpreting the associations observed in this study. Moreover, while the cutoff of ≥4 for high mucus plug scores has been validated to represent high mucus burden in multiple studies, its definition was based on empirical data and requires further refinement to optimize its predictive accuracy across diverse patient populations.

In summary, these outcomes show that dupilumab reduces mucus plugging and airway inflammation in patients with moderate-to-severe asthma as early as 4 weeks after treatment initiation. Reduced mucus plugging may contribute to the clinically meaningful improvements in global and distal lung function, with more pronounced effects in patients with higher mucus plug score at baseline compared with those with lower scores.

Acknowledgments

We thank Colin Mitchell and Ranjini Prithviraj for their contributions to the development of this manuscript. Medical writing and editorial assistance in the development of this manuscript was provided by Akshi Sudan, M.Sc., and Jo Mooij, Ph.D., of Excerpta Medica, and

Downloaded from https://academic.oup.com/ajrccm/article/212/2/241/8437460 by Dipartimento Economia Istituzioni user on 08 May 2026

was funded by Sanofi and Regeneron Pharmaceuticals Inc., according to Good Publication Practice guidelines.

Author contributions

M.C., X.S., P.J.R., Y.D., L.d.P.G., H.J.S., and J.A.J.-N. contributed to study concept and design and conceived the post hoc analyses described in this manuscript. C.P., E.M.D., N.L.L., A.P., V.B., C.E.B., and A.B. acquired data. M.Z. conducted the statistical analyses on the data. J.C.V. interpreted the data for the work. All authors provided critical feedback on the manuscript, approved the final manuscript for submission, and are accountable for the accuracy and integrity of the manuscript.

Supplementary material

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

Conflicts of interest

Please see the ICMJE disclosure forms, which have been provided as supplementary material. Celeste Porsbjerg: grants, consultancy, and speaker fees from ALK, AstraZeneca, Chiesi, GSK, Novartis, Sanofi, and Teva; advisory board member for ALK, AstraZeneca, Novartis, Sanofi, and Teva. Eleanor M. Dunican: advisory board member for Aer Therapeutics and Sanofi. Njira L. Lugogo: research support paid to institution from Amgen, AstraZeneca, Avillion, Genentech, Gossamer Bio, GSK, Regeneron Pharmaceuticals Inc., Sanofi, and Teva Pharmaceuticals; advisory board member and consultant for Amgen, AstraZeneca, Genentech, GSK, Novartis, Regeneron Pharmaceuticals Inc., Sanofi, and Teva Pharmaceuticals; travel support from AstraZeneca; honoraria for non–speaker's bureau presentations from AstraZeneca and GSK. Mario Castro: research support from American Lung Association, AstraZeneca, Gala Therapeutics, Genentech, GSK, National Institutes of Health (NIH), Novartis, Patient-Centered Outcomes Research Institute (PCORI), Pulmatrix, Sanofi, Shionogi, and Theravance Biopharma; consultant for Allakos, Amgen, Arrowhead Pharmaceuticals, Genentech, GSK, Merck & Co, Novartis, OM Pharma, Pfizer, Pioneering Medicines, Sanofi, and Teva; speaker's fees from Amgen, AstraZeneca, Genentech, Regeneron Pharmaceuticals Inc., Sanofi, and Teva; royalties from Aer Therapeutics. Alberto Papi: consultant/advisory board membership for AstraZeneca, Avillion, Chiesi Farmaceutici, Edmond Pharma, GSK, Mundipharma, Roche, and Sanofi; advisory board membership for IQVIA; speaker for Mundipharma; lectures fees from Sandoz and Zambon. Vibeke Backer: grants from ALK-Abelló, Birk, Chiesi, GSK, MSD, Novartis, and Sanofi; other from AstraZeneca, Pharmaxis, Regeneron Pharmaceuticals Inc., and Teva. Christopher E. Brightling: grants and consultancy paid to institution from 4D Pharma, Areteia, AstraZeneca, Chiesi, Genentech, GSK, Mologic, Novartis, Regeneron Pharmaceuticals Inc., Roche, and Sanofi. Arnaud Bourdin: nonfinancial support during the conduct of the study from GSK; other from Acceleron Pharma, Actelion, Galapagos, MSD, Nuvaira, Pulmonx, United Therapeutics, and Vertex Pharmaceuticals; grants and personal fees from Boehringer Ingelheim; personal fees from AstraZeneca, Chiesi, GSK, Regeneron Pharmaceuticals Inc., and Sanofi. J. Christian Virchow: lectures and honoraria from AstraZeneca, Avontec, Bayer, Bencard Allergie, Bionorica, Boehringer Ingelheim, Chiesi, Essex/Schering-Plough, GSK, Janssen-Cilag, Leti Pharma, Meda Pharmaceuticals, Merck, MSD, Mundipharma, Novartis, Nycomed/Altana, Pfizer, Revotar, Sandoz-Hexal, Stallergenes Greer, Teva Pharmaceuticals, UCB/Schwarz Pharma, and Zydus/Cadila; advisory board membership for Avontec, Boehringer Ingelheim, Chiesi, Essex/Schering-Plough, GSK, Janssen-Cilag, Meda, MSD, Mundipharma, Novartis, Regeneron Pharmaceuticals Inc., Revotar, Roche, Sanofi-Aventis, Sandoz-Hexal, Teva Pharmaceuticals, and UCB/Schwarz Pharma; research grants from Deutsche Forschungsgesellschaft, GSK, Land Mecklenburg-Vorpommern, and MSD. Mei Zhang, Paul J. Rowe, Lucía de Prado Gómez, and Juby A. Jacob-Nara: employees of Sanofi and may hold stock and/or stock options in the company. Xavier Soler and Yamo Deniz: employees and shareholders of Regeneron Pharmaceuticals Inc. Harry J. Sacks: employee of Regeneron Pharmaceuticals Inc. and shareholder of Optinose.

Funding

The study was sponsored by Sanofi and Regeneron Pharmaceuticals Inc. Trial data were collected by the study investigators and analyzed by the sponsors.

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 specifications. 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: https://www.vivli.org/. This article has an online data supplement, which is accessible at the Supplements tab.

Artificial intelligence disclaimer

No artificial intelligence tools were used in writing this manuscript.

References

1. Kuyper LM, Paré PD, Hogg JC, et al. Characterization of airway plugging in fatal asthma. *Am J Med*. 2003;115:6-11. https://doi.org/10.1016/s0002-9343(03)00241-9
2. Tang M, Elicker BM, Henry T, 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;205:1036-1045. https://doi.org/10.1164/rccm.202110-2265OC
3. Dunican EM, Watchorn DC, Fahy JV. Autopsy and imaging studies of mucus in asthma. Lessons learned about disease mechanisms and the role of mucus in airflow obstruction. *Ann Am Thorac Soc*. 2018;15:S184-S191. https://doi.org/10.1513/AnnalsATS.201807-485AW
4. Dunican EM, Elicker BM, Gierada DS, et al.; National Heart Lung and Blood Institute (NHLBI) Severe Asthma Research Program (SARP). Mucus plugs in patients with asthma

Downloaded from https://academic.oup.com/ajrccm/article/212/2/241/8437460 by Dipartimento Economia Istituzioni user on 08 May 2026

linked to eosinophilia and airflow obstruction. *J Clin Invest*. 2018;128:997-1009. https://doi.org/10.1172/JCI95693
5. Dunnill MS. The pathology of asthma, with special reference to changes in the bronchial mucosa. *J Clin Pathol*. 1960;13:27-33. https://doi.org/10.1136/jcp.13.1.27
6. Whittaker L, Niu N, Temann U-A, et al. Interleukin-13 mediates a fundamental pathway for airway epithelial mucus induced by CD4 T cells and interleukin-9. *Am J Respir Cell Mol Biol*. 2002;27:593-602. https://doi.org/10.1165/rcmb.4838
7. Gour N, Wills-Karp M. IL-4 and IL-13 signaling in allergic airway disease. *Cytokine*. 2015;75:68-78. https://doi.org/10.1016/j.cyto.2015.05.014
8. Pelaia C, Heffler E, Crimi C, et al. Interleukins 4 and 13 in asthma: key pathophysiologic cytokines and druggable molecular targets. *Front Pharmacol*. 2022;13:851940. https://doi.org/10.3389/fphar.2022.851940
9. Boomer J, Choi J, Alsup A, et al. Increased Muc5AC and decreased ciliated cells in severe asthma partially restored by inhibition of IL-4Rα receptor. *Am J Respir Crit Care Med*. 2024;210:1409-1420. https://doi.org/10.1164/rccm.202307-1266OC
10. Svenningsen S, Haider E, Boylan C, et al. CT and functional MRI to evaluate airway mucus in severe asthma. *Chest*. 2019;155:1178-1189. https://doi.org/10.1016/j.chest.2019.02.403
11. Macdonald LE, Karow M, Stevens S, et al. Precise and in situ genetic humanization of 6 Mb of mouse immunoglobulin genes. *Proc Natl Acad Sci U S A.* 2014;111:5147-5152. https://doi.org/10.1073/pnas.1323896111
12. Murphy AJ, Macdonald LE, Stevens S, et al. Mice with megabase humanization of their immunoglobulin genes generate antibodies as efficiently as normal mice. *Proc Natl Acad Sci U S A.* 2014;111:5153-5158. https://doi.org/10.1073/pnas.1324022111
13. Gandhi NA, Pirozzi G, Graham NMH. Commonality of the IL-4/IL-13 pathway in atopic diseases. *Expert Rev Clin Immunol*. 2017;13:425-437. https://doi.org/10.1080/1744666X.2017.1298443
14. Le Floc'h A, Allinne J, Nagashima K, et al. Dual blockade of IL-4 and IL-13 with dupilumab, an IL-4Rα antibody, is required to broadly inhibit type 2 inflammation. *Allergy*. 2020;75:1188-1204. https://doi.org/10.1111/all.14151
15. Wenzel S, Castro M, Corren J, et al. Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting β2 agonist: a randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial. *Lancet*. 2016;388:31-44. https://doi.org/10.1016/S0140-6736(16)30307-5
16. Castro M, Corren J, Pavord ID, et al. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. *N Engl J Med*. 2018;378:2486-2496. https://doi.org/10.1056/NEJMoa1804092
17. Rabe KF, FitzGerald JM, Bateman ED, et al. Dupilumab is effective in patients with moderate-to-severe uncontrolled GINA-defined type 2 asthma irrespective of an allergic asthma phenotype. *J Allergy Clin Immunol Pract*. 2022;10:2916-2924.e4. https://doi.org/10.1016/j.jaip.2022.06.036
18. Wechsler ME, Ford LB, Maspero JF, et al. Long-term safety and efficacy of dupilumab in patients with moderate-to-severe asthma (TRAVERSE): an open-label extension study. *Lancet Respir Med*. 2022;10:11-25. https://doi.org/10.1016/S2213-2600(21)00322-2
19. Castro M, Papi A, Porsbjerg C, et al. Effect of dupilumab on exhaled nitric oxide, mucus plugs, and functional respiratory imaging in patients with type 2 asthma (VESTIGE): a randomised, double-blind, placebo-controlled, phase 4 trial. *Lancet Respir Med*. 2025;13:208-220. https://doi.org/10.1016/S2213-2600(24)00362-X
20. Porsbjerg C, Dunican E, Lugogo NL, et al. Effect of dupilumab treatment on mucus plugging and mucus volume in type 2 asthma: the phase 4 VESTIGE trial [abstract]. *Am J Respir Crit Care Med.* 2024;209:A1385. https://doi.org/10.1164/ajrccm-conference.2024.209.1_MeetingAbstracts.A1385
21. Porsbjerg CM, Dunican E, Lugogo NL, et al. Dupilumab reduces mucus plugging and volume: phase 4 VESTIGE trial [abstract]. *Eur Respir J*. 2024;64:OA3649. https://doi.org/10.1183/13993003.congress-2024.OA3649
22. Porsbjerg C, DuAmérigo DA, Dunican E, Soler X, de Prado Gómez L. Reducción en tapones de moco y su volumen mediante dupilumab [abstract]. *J Investig Allergol Clin Immunol*. 2024;34(Suppl 1):87-357.
23. Porsbjerg C, Dunican E, Lugogo NL, et al. S95 Effect of dupilumab treatment on mucus plugging and mucus volume in type 2 asthma: the phase 4 VESTIGE trial [abstract]. *Thorax*. 2024;79(Suppl 2):A69-A70.
24. Porsbjerg C, Dunican E, Lugogo NL, et al. Effect of dupilumab treatment on mucus plugging and mucus volume in type 2 asthma: the phase 4 VESTIGE trial [abstract]. In: Eastern Allergy Conference 2024, Palm Beach, FL, United States. 6.1 F 2024 EAC abstracts Friday 5.31.24 1-xx.pdf
25. Papi A, Dunican E, Lugogo NL, et al. Impact of dupilumab on mucus plugging and volume: results from the phase 4 VESTIGE study [abstract]. In: Congresso Nazionale Della Pneumologia 2024, Milan, Italy. V19-INTERATTIVO-COMPLETO-15-11-2024-.pdf
26. Chan R, Duraikannu C, Lipworth B. Clinical associations of mucus plugging in moderate to severe asthma. *J Allergy Clin Immunol Pract*. 2023;11:195-199.e2. https://doi.org/10.1016/j.jaip.2022.09.008
27. Huang BK, Elicker BM, Henry TS, et al. Persistent mucus plugs in proximal airways are consequential for airflow limitation in asthma. *JCI Insight*. 2024;9:e174124. https://doi.org/10.1172/jci.insight.174124
28. Nair P, O'Byrne PM. The interleukin-13 paradox in asthma: effectivebiology,ineffectivebiologicals.*EurRespirJ*.2019;53:1802250. https://doi.org/10.1183/13993003.02250-2018
29. Harb H, Chatila TA. Mechanisms of dupilumab. *Clin Exp Allergy*. 2020;50:5-14. https://doi.org/10.1111/cea.13491
30. Svenningsen S, Kjarsgaard M, Haider E, et al. Effects of dupilumab on mucus plugging and ventilation defects in patients with moderate-to-severe asthma: a randomized, double-blind, placebo-controlled trial. *Am J Respir Crit Care Med*. 2023;208:995-997. https://doi.org/10.1164/rccm.202306-1102LE
31. Kuruvilla ME, Lee FE-H, Lee GB. Understanding asthma phenotypes, endotypes, and mechanisms of disease. *Clin Rev Allergy Immunol*. 2019;56:219-233. https://doi.org/10.1007/s12016-018-8712-1

Downloaded from https://academic.oup.com/ajrccm/article/212/2/241/8437460 by Dipartimento Economia Istituzioni user on 08 May 2026

32. Pavord ID, de Prado Gómez L, Brusselle G, et al.; QUEST Lung Function Decline Study Group. Biomarkers associated with lung function decline and dupilumab response in patients with asthma. *Am J Respir Crit Care Med*. 2024;209:1031-1033. https://doi.org/10.1164/rccm.202310-1751LE
33. Escamilla-Gil JM, Fernandez-Nieto M, Acevedo N. Understanding the cellular sources of the fractional exhaled nitric oxide (FeNO) and its role as a biomarker of type 2 inflammation in asthma. *Biomed Res Int*. 2022;2022:5753524. https://doi.org/10.1155/2022/5753524
34. Lipworth B, Kuo CR, Chan R. 2020 updated asthma guidelines: clinical utility of fractional exhaled nitric oxide (FeNO) in asthma management. *J Allergy Clin Immunol*. 2020;146:1281-1282. https://doi.org/10.1016/j.jaci.2020.03.006

Downloaded from https://academic.oup.com/ajrccm/article/212/2/241/8437460 by Dipartimento Economia Istituzioni user on 08 May 2026

© The Author(s) 2025. Published by Oxford University Press on behalf of the American Thoracic Society.
This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs licence (https://creativecommons.org/licenses/by-nc-nd/4.0/), which permits non-commercial reproduction and distribution of the work, in any medium, provided the original work is not altered or transformed in any way, and that the work is properly cited. For commercial re-use, please contact reprints@oup.com for reprints and translation rights for reprints. All other permissions can be obtained through our RightsLink service via the Permissions link on the article page on our site—for further information please contact journals.permissions@oup.com. American Journal of Respiratory and Critical Care Medicine 2026 212(2) 241–252
https://doi.org/10.1164/rccm.202410-1894OC
Original Research | Asthma and Allergy Asthma and Allergy