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Original Research

Dupilumab reduces acute exacerbations and improves lung function in patients with COPD with type 2 inflammation irrespective of body mass index, airflow obstruction, dyspnea, and exercise capacity index scores

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ABSTRACT

Background: The body mass index, airflow obstruction, dyspnea, and exercise capacity (BODE) index predicts 5-year mortality risk in chronic obstructive pulmonary disease (COPD); higher scores predict worse outcomes. Dupilumab, a fully human monoclonal antibody that blocks the shared receptor component for interleukin-4/13, reduced exacerbations and improved lung function in patients with COPD in the phase 3 BOREAS trial (NCT03930732). We assessed dupilumab efficacy in patients with COPD and type 2 inflammation by baseline BODE index.

Methods: Patients with COPD, moderate-to-severe airflow limitation, screening blood eosinophils ≥300 cells/μL, and high exacerbation risk, on triple therapy, received 300 mg add-on dupilumab or placebo every 2 weeks for 52 weeks. Annualized moderate or severe COPD exacerbation rate and change from baseline in pre-bronchodilator forced expiratory volume in 1 s (FEV_1) at Weeks 12 and 52 were assessed by baseline BODE index, categorized as low (≤4) or high (>4).

Results: Of 934 patients with reported baseline BODE index scores (dupilumab: 470; placebo: 464), 61.8 % had scores ≤4. Dupilumab reduced exacerbations versus placebo, regardless of baseline BODE index group. Exacerbation reductions were similar by BODE index group; relative risk (95 % confidence interval) for patients with BODE index >4 versus ≤4 was 0.656 (0.496–0.868) versus 0.718 (0.547–0.944). At Weeks 12 and 52, dupilumab consistently improved pre-bronchodilator FEV_1 versus placebo, regardless of baseline BODE index group.

Conclusion: Dupilumab reduced exacerbations and improved lung function in patients with COPD and type 2 inflammation irrespective of baseline BODE index score.

Clinical trial registration number: BOREAS trial NCT03930732.

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Abbreviations:

BMI	body mass index
BODE	body mass index, airflow obstruction, dyspnea, and exercise capacity
CI	confidence interval
COPD	chronic obstructive pulmonary disease
E-RS:COPD	Evaluating Respiratory Symptoms in Chronic Obstructive Pulmonary Disease
FEV_1	forced expiratory volume in 1 s
FVC	forced vital capacity
ICS	inhaled corticosteroid(s)
IL	interleukin
ITT	intention-to-treat
LABA	long-acting β2-agonist
LAMA	long-acting muscarinic antagonist
LS	least squares
pp	percent predicted
q2w	once every 2 weeks
SD	standard deviation
SGRQ	St. George's Respiratory Questionnaire

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a chronic, progressive, inflammatory disease characterized by poorly reversible airflow limitation with accompanying respiratory symptoms such as dyspnea, cough, wheezing, and increased mucus production [1,2]. COPD is a highly prevalent disease with a significant economic burden and risk of mortality [3,4]. Exacerbations of COPD are a frequent cause of deterioration of health in patients with COPD, contributing to morbidity, mortality, and diminished quality of life [2,4,5]. For a subset of patients with type 2 inflammation, indicated by elevated blood eosinophil counts, COPD, including exacerbation events, remains uncontrolled with available standard-of-care therapies [2], highlighting the need for more effective COPD therapies. The body mass index, airflow obstruction, dyspnea, and exercise capacity (BODE) index is a multidimensional grading system that predicts COPD severity and clinical outcomes [6]. The BODE index scores range from 0 to 10 points and are commonly grouped into quartiles for analysis (quartile 1: scores 0–2; quartile 2: scores 3–4; quartile 3: scores 5–6; quartile 4: scores 7–10) [6]. The BODE index quartiles representing higher scores are predictive of increased exacerbations, hospitalizations, mortality, and worse quality of life in COPD [6–9]. It is unknown whether patients with higher baseline BODE index scores (more severe COPD) will benefit from novel COPD medications like dupilumab in the same way as those with lower baseline BODE index scores.

Higher blood eosinophil counts in COPD have been associated with type 2 inflammation and increased responsiveness to inhaled corticosteroids (ICS) [10–13]. Dupilumab, a fully human monoclonal antibody [14,15], blocks the shared receptor component for interleukin (IL)-4 and IL-13, which are key and central drivers of type 2 inflammation in multiple diseases [16–18]. Peripheral blood eosinophil counts are one of the most commonly used clinical tools for identifying type 2 inflammation [1]. In the phase 3 BOREAS trial (NCT03930732), which investigated the efficacy and safety of dupilumab 300 mg once every 2 weeks (q2w) versus placebo in patients with COPD and type 2 inflammation (screening blood eosinophil count ≥300 cells/μL) and high exacerbation risk, patients who received dupilumab had fewer exacerbations as well as improved lung function and quality of life compared with those on placebo [19].

The objective of this analysis of data from the phase 3 BOREAS trial was to evaluate dupilumab efficacy by baseline BODE index score in patients with moderate-to-severe COPD and type 2 inflammation (screening blood eosinophils ≥300 cells/μL) and high exacerbation risk.

2. Study design and methods

2.1. Study design

Details of the BOREAS trial have been published previously [19]. In summary, BOREAS was a phase 3, randomized, double-blind, placebo-controlled trial designed to assess the efficacy and safety of add-on dupilumab versus placebo in patients with COPD, moderate-to-severe airflow limitation, and type 2 inflammation, as evidenced by blood eosinophil counts ≥300 cells/μL at screening. Patients who met the entry criteria were randomized 1:1 to receive subcutaneous dupilumab 300 mg or placebo q2w for 52 weeks. Randomization was stratified according to country and ICS dose at baseline.

The study was conducted in accordance with the Declaration of Helsinki, the International Conference for Harmonisation Good Clinical Practice guidelines, and applicable regulatory requirements. An independent data and safety monitoring committee conducted blinded monitoring of patient safety data. The local institutional review board or ethics committee at each study center oversaw trial conduct and documentation. All patients provided written informed consent before participating in the trial.

2.2. Study population

The BOREAS trial enrolled patients aged 40–80 years with physician-diagnosed COPD ≥12 months before randomization and type 2 inflammation (defined as absolute blood eosinophil count ≥300 cells/μL at the screening visit) who were on background triple therapy with ICS, long-acting β2-agonists (LABA), and long-acting muscarinic antagonists (LAMA) (or LABA + LAMA if ICS was contraindicated). Patients were required to have ≥2 moderate or ≥1 severe exacerbation in the year before study inclusion, with at least 1 moderate exacerbation requiring use of systemic corticosteroids, and at least 1 exacerbation occurring while on ICS + LABA + LAMA (or LABA + LAMA if ICS was contraindicated). Other inclusion criteria were post-bronchodilator ratio of forced expiratory volume in 1 s (FEV_1) to forced vital capacity <0.70, post-bronchodilator percent predicted (pp)FEV_1 >30 % and ≤70 %, Medical Research Council dyspnea scale grade ≥2, and signs and symptoms of chronic bronchitis (chronic productive cough) for ≥3 months during the year before screening. Patients with a current diagnosis or prior history of asthma were excluded. A complete list of inclusion and exclusion criteria is published in Bhatt et al. [19]. The current analysis includes the intention-to-treat (ITT) population from the BOREAS trial. The BODE index, though not an inclusion requirement, was measured at baseline [6].

2.3. Endpoints

Endpoints assessed to evaluate the efficacy of dupilumab in the ITT population included the annualized rate of moderate or severe acute exacerbations of COPD over the 52-week treatment period and change from baseline in pre-bronchodilator FEV_1 at Weeks 12 and 52 stratified by baseline BODE index scores >4 or ≤4 points [6,8]. The BODE index was not an endpoint in the trial.

2.4. Statistical analysis

Primary and key secondary endpoints for this analysis were evaluated in the BOREAS ITT population and stratified by BODE high (>4; quartiles 3 and 4) and low (≤4; quartiles 1 and 2) categories [6,8]. Patients who underwent randomization were analyzed according to the trial group to which they were randomly assigned. The unadjusted annualized rate of exacerbations consisted of the total number of events

that occurred during the 52-week treatment period divided by the total number of patient-years of follow-up in the treatment period. The adjusted annualized rate of exacerbations was derived using a negative binomial model, with the total number of events occurring during the 52-week treatment period as the response variable; treatment group, region (pooled country), ICS dose, smoking status at screening, baseline disease severity, and number of moderate or severe COPD exacerbation events within 1 year before the study as covariates (except where index group was of interest); and log-transformed treatment duration as an offset variable. The interaction p value for exacerbation rate was derived using a negative binomial model, with total number of events occurring during the 52-week treatment period as the response variable; treatment group, region (pooled country), ICS dose, smoking status at screening, baseline disease severity, number of moderate or severe exacerbation events within 1 year before the study, baseline BODE index score (≤4 or >4) category, and treatment-by-baseline BODE index score interaction as covariates; and log-transformed treatment duration as an offset variable. Change in pre-bronchodilator FEV_1 was derived using a mixed-effects model with repeated measures, with change in FEV_1 from baseline to Week 12 as the response variable and factors for treatment group, age, sex, height, region (pooled country), ICS dose at baseline, smoking status at screening, visit, treatment-by-visit interaction, baseline pre-bronchodilator FEV_1, and FEV_1 baseline-by-visit interaction as covariates. The interaction p value for change in pre-bronchodilator FEV_1 was derived from a mixed-effects model with repeated measures, with change in pre-bronchodilator FEV_1 from baseline to Week 12 as the response variable and treatment group, age, sex, height, region (pooled country), ICS dose, smoking status at screening, visit, treatment by visit interaction, baseline pre-bronchodilator FEV_1, FEV_1 baseline by visit interaction, baseline BODE index score (≤4 or >4) category, baseline BODE score by treatment interaction, and baseline BODE score by treatment by visit interaction as covariates.

3. Results

3.1. Patient demographics

The BOREAS trial enrolled 939 patients (dupilumab 300 mg q2w: n = 468; placebo: n = 471). Baseline demographics and disease characteristics were similar between treatment groups (Table 1). Most patients in the study were male and White. Of the overall study population, 70 % were former smokers, with a smoking history of ~40 pack-years in both dupilumab and placebo treatment arms. On average, the patients experienced 2.3 (standard deviation [SD] 1.0) moderate or severe COPD exacerbations in the year prior to the study in both the dupilumab and placebo treatment arms. Baseline values for pre-bronchodilator FEV_1 and BODE index in the overall study population were similar between dupilumab and placebo treatment arms.

3.2. BODE index scores at baseline

A total of 934 patients from the ITT population had BODE index measurements at baseline, with 464 randomized to dupilumab and 470 to placebo (Fig. 1); 41.4 % of patients receiving dupilumab and 43.4 % receiving placebo had BODE index scores of 3 or 4 (category 2). Approximately 60 % of patients in both treatment arms had a low BODE index (score ≤4; dupilumab: 59.9 % and placebo: 63.6 %) at baseline, while 40.1 % (dupilumab) and 36.4 % (placebo) had a high BODE index (score >4) at baseline.

3.3. Annualized rate of moderate or severe exacerbations by baseline BODE category

Dupilumab reduced exacerbations versus placebo at a similar rate across baseline BODE index groups (Fig. 2). In the low baseline BODE index group, dupilumab reduced exacerbations by 28.2 %, with an adjusted relative risk versus placebo (95 % confidence interval [CI]) of 0.718 (0.547–0.944) and an adjusted annualized rate (95 % CI) of 0.631 (0.482–0.827) for dupilumab versus 0.879 (0.684–1.129) for placebo. In patients with a high baseline BODE index score, dupilumab reduced exacerbations by 34.4 %, with an adjusted relative risk versus placebo (95 % CI) of 0.656 (0.496–0.868) and an adjusted annualized rate (95 % CI) of 0.960 (0.746–1.234) for dupilumab versus 1.464 (1.172–1.828) for placebo. There was no treatment-by-index-group interaction effect

Table 1
Baseline demographics and disease characteristics: ITT population.[a]

Characteristic	BODE score ≤4		BODE score >4	
	Placebo (n = 299)	Dupilumab (n = 278)	Placebo (n = 171)	Dupilumab (n = 186)
Age, mean (SD), years	64.4 (8.3)	64.5 (8.2)	66.4 (7.7)	65.9 (7.5)
Sex, n (%)				
Female	89 (29.8)	98 (35.3)	60 (35.1)	69 (37.1)
Male	210 (70.2)	180 (64.7)	111 (64.9)	117 (62.9)
Race/ethnicity, n (%)				
White	249 (83.3)	232 (83.5)	147 (86.0)	157 (84.4)
Black	0	2 (0.7)	2 (1.2)	1 (0.5)
Asian	46 (15.4)	40 (14.4)	21 (12.3)	27 (14.5)
American Indian/ Alaska Native	3 (1.0)	2 (0.7)	1 (0.6)	1 (0.5)
Native Hawaiian/ Pacific Islander	1 (0.3)	0	0	0
Multiple	0	2 (0.7)	0	0
BMI, mean (SD), kg/ m^2	27.51 (5.27)	27.79 (5.05)	27.92 (6.48)	27.14 (6.00)
High-dose ICS history, n (%)	65 (21.7)	76 (27.3)	61 (35.7)	53 (28.5)
Smoking status at screening, n (%)				
Former	210 (70.2)	200 (71.9)	113 (66.1)	131 (70.4)
Current	89 (29.8)	78 (28.1)	58 (33.9)	55 (29.6)
Smoking history, pack-years, mean (SD)	40.8 (22.6)	37.9 (21.8)	42.3 (27.3)	42.4 (23.0)
Number of moderate or severe exacerbations in the previous year, mean (SD)	2.2 (0.8)	2.2 (1.0)	2.4 (1.1)	2.3 (1.3)
Pre-bronchodilator FEV_1, mean (SD), L	1.5 (0.5)	1.4 (0.5)	1.1 (0.3)	1.1 (0.3)
Post-bronchodilator FEV_1, mean (SD), L	1.6 (0.5)	1.6 (0.5)	1.2 (0.3)	1.2 (0.4)
Pre-bronchodilator $ppFEV_1$, mean (SD), %	51.7 (12.8)	52.1 (13.5)	39.7 (10.0)	39.2 (9.6)
Post-bronchodilator $ppFEV_1$, mean (SD), %	55.1 (12.5)	55.8 (12.8)	42.9 (9.6)	42.8 (9.7)
Pre-bronchodilator FEV_1/FVC, mean (SD)[a]	0.5 (0.1)	0.5 (0.1)	0.5 (0.1)	0.4 (0.1)
Post-bronchodilator FEV_1/FVC, mean (SD)	0.5 (0.1)	0.5 (0.1)	0.5 (0.1)	0.5 (0.1)
BODE index score, mean (SD)	3.0 (1.0)	3.0 (0.9)	5.8 (0.9)	5.8 (1.0)
E-RS:COPD total score, mean (SD)	12.2 (6.7)	12.0 (7.1)	14.3 (7.1)	14.3 (7.2)
SGRQ total score, mean (SD)	45.8 (17.3)	45.8 (16.8)	53.0 (18.0)	52.3 (16.9)

Percentages may not total 100 because of rounding.
Abbreviations: BMI, body mass index; BODE, body mass index, airway obstruction, dyspnea, and exercise capacity; E-RS:COPD, Evaluating Respiratory Symptoms in Chronic Obstructive Pulmonary Disease; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; ICS, inhaled corticosteroid(s); ITT, intention-to-treat; pp, percent predicted; SD, standard deviation; SGRQ, St. George's Respiratory Questionnaire.
[a] The ITT population includes all patients who were randomized.

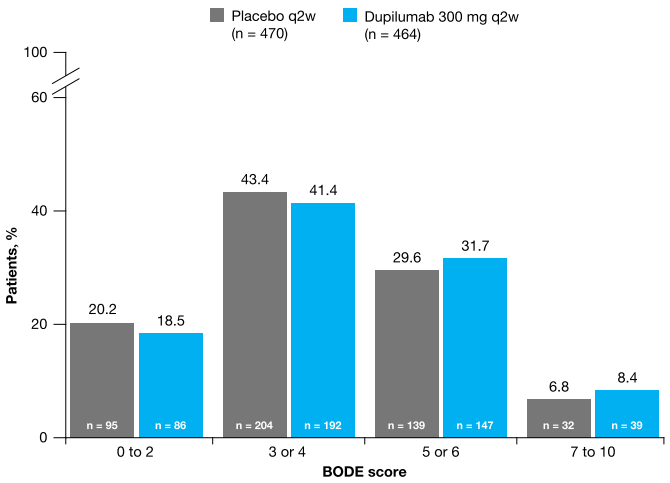

Fig. 1. Distribution of BODE index score categories at baseline: ITT population.[a] Abbreviations: BODE, body mass index, airway obstruction, dyspnea, and exercise capacity; ITT, intention-to-treat; q2w, once every 2 weeks.
[a]The ITT population includes all patients who were randomized.

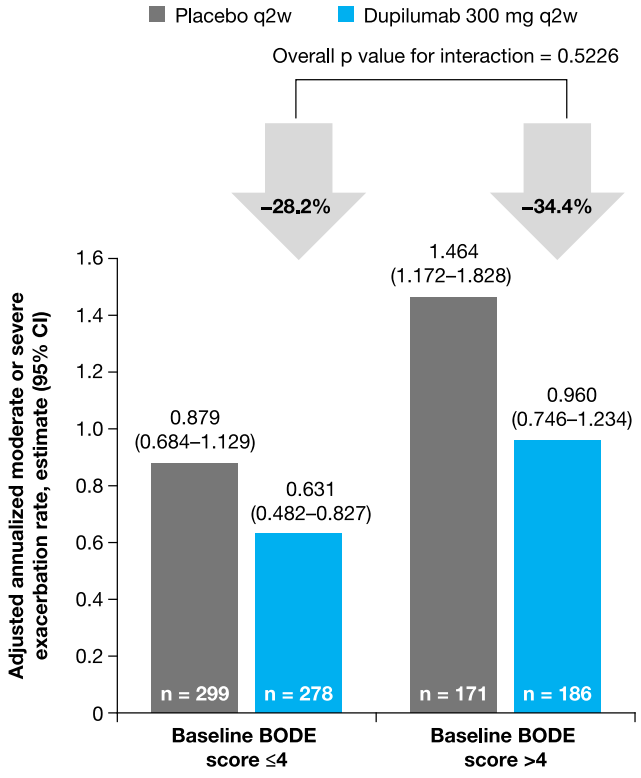

Fig. 2. R'Annualized moderate or severe exacerbation rates by BODE subgroup (≤4 or >4): ITT population.[a] Abbreviations: BODE, body mass index, airway obstruction, dyspnea, and exercise capacity; CI, confidence interval; ITT, intention-to-treat; q2w, once every 2 weeks.
[a]The ITT population includes all patients who were randomized.

on the annualized rate of moderate or severe exacerbations over the 52-week treatment period by baseline BODE index scores (p value for interaction = 0.5226).

3.4. Change in pre-bronchodilator FEV_1 by baseline BODE category at weeks 12 and 52

At Week 12, treatment with dupilumab led to similar improvements in pre-bronchodilator FEV_1 regardless of baseline BODE group versus placebo (Fig. 3). The least squares (LS) mean difference in pre-bronchodilator FEV_1 (95 % CI) was 0.101 L (0.053–0.150) and 0.064 L (−0.013–0.141) in patients with low and high baseline BODE index categories, respectively. There was no treatment-by-index-group interaction effect on pre-bronchodilator FEV_1 at Week 12 for baseline BODE index scores (p value for interaction = 0.4677).

At Week 52, treatment with dupilumab continued to demonstrate similar improvements in pre-bronchodilator FEV_1 in both baseline BODE groups versus placebo (Fig. 3). At Week 52, the LS mean difference in pre-bronchodilator FEV_1 (95 % CI) was 0.104 L (0.051–0.157) and 0.058 L (−0.024–0.139) in patients with low and high baseline BODE index groups, respectively. No treatment-by-index-group interaction effect was observed on pre-bronchodilator FEV_1 at Week 52 for baseline BODE index scores (p value for interaction = 0.3944).

4. Discussion

The phase 3 BOREAS trial included patients with symptomatic COPD and evidence of type 2 inflammation and a high risk of COPD exacerbation despite the use of maximal standard-of-care triple therapy. This analysis showed that treatment of these patients with dupilumab led to greater reductions in moderate or severe exacerbations and improvements in lung function compared with placebo, regardless of high or low baseline BODE index score. BOREAS was not powered to detect differences in the efficacy of dupilumab versus placebo by high or low baseline BODE index score. This post hoc analysis therefore focuses on numerical differences in exacerbation rates and lung function when evaluating the effect of dupilumab treatment in these patients.

The BODE index assesses four components that are independently associated with increased mortality in COPD [6]. Thus, assessing treatment response among participants with different BODE scores is of clinical importance. In this post hoc analysis of BOREAS, at baseline, patients with a BODE score of >4 had higher unadjusted and adjusted annualized moderate or severe exacerbation event rates lung function than patients with BODE scores ≤4, demonstrating an increased risk of exacerbations in these patients. Improvements seen in patients irrespective of baseline BODE index demonstrate that dupilumab reduces exacerbations and improves lung function, even in those with greater risk of mortality.

Two of the key components of the BODE index are airflow obstruction and dyspnea. Here, we showed that dupilumab improved airflow obstruction in patients with COPD regardless of baseline BODE index scores. Dupilumab is known to reduce downstream effects of IL-4 and IL-13 by blocking their signaling, potentially leading to improvements in airway smooth muscle contractility and decreased airway remodeling, mucus secretion, and airway inflammation [16,17]. IL-4 and IL-13 mediate structural changes to the airway and fibrosis through alternatively activating macrophages (ie, M2 polarization) [20] and inducing matrix metalloproteases involved in extracellular matrix remodeling [21,22]. Mouse models of asthma have shown that IL-13 promotes mucus production through increased of MUC5 gene expression, leading to goblet cell hyperplasia and mucus hypersecretion [16,23]. Aberrant IL-13 activity may therefore result in airway narrowing and dysfunction, thereby increasing airway resistance and impairing lung function in patients with COPD. Finally, as key and central drivers of type 2 inflammation, IL-4 and IL-13 recruit proinflammatory cells (eg, eosinophils, basophils, mast cells) to the lung by inducing the production of chemokines [24,25]. IL-4 also promotes class switching of antibodies to IgE during the B cell maturation process and induces naïve T cells to differentiate into T helper type 2 cells, which in turn produce type 2 cytokines that potentiate the immune response [16]. As the collective

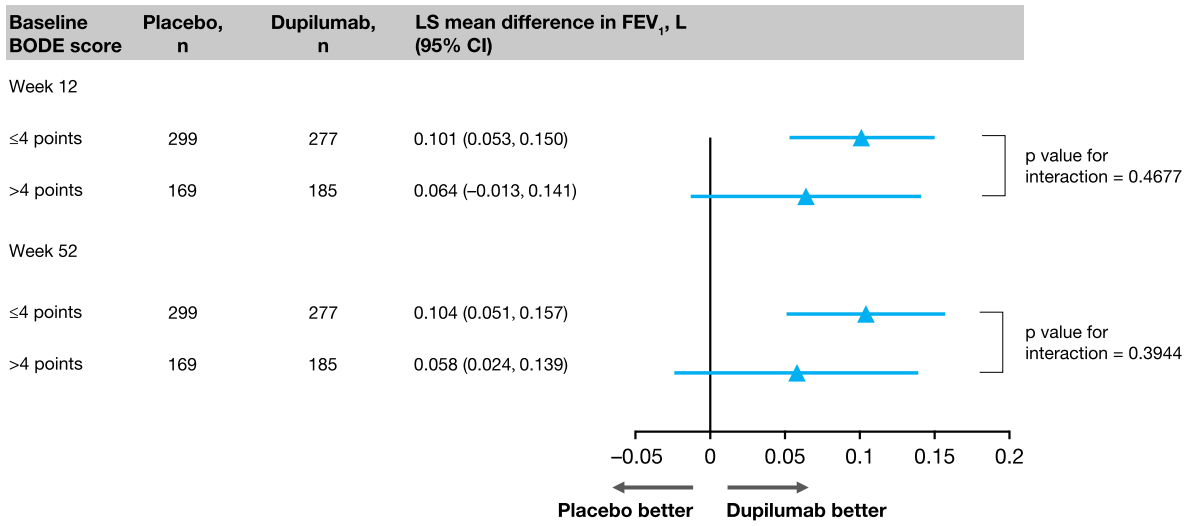

Fig. 3. Forest plot of LS mean difference (dupilumab versus placebo) in the change from baseline in pre-bronchodilator FEV_1 (L) at Week 12 and Week 52 by low or high baseline BODE score index group (≤4 or >4): ITT population.[a] Abbreviations: BODE, body mass index, airway obstruction, dyspnea, and exercise capacity; CI, confidence interval; FEV_1, forced expiratory volume in 1 s; ITT, intention-to-treat; LS, least squares.
[a]The ITT population includes all patients who were randomized.

effects of IL-4 and IL-13 impact multiple facets of COPD pathogenesis, it is reasonable to expect that disrupting pathogenic IL-4/IL-13 signaling with dupilumab may result in the improvement of COPD outcomes as observed in BOREAS. However, as the mechanism of dupilumab in COPD was not evaluated in BOREAS, future studies will be required to conclusively link improvements in clinical outcomes to the BODE index score and potential reductions in the risk of morbidity and mortality with dupilumab treatment.

This trial had several strengths and limitations. Strengths of this trial include strict exclusion of patients with a current or previous diagnosis of asthma, as well as a low dropout rate. However, the trial was conducted during the COVID-19 pandemic, during which changes in patient behavior may have affected enrollment, exposures, and outcomes. Moreover, the trial population was predominantly White, limiting its ability to generalize the results reported here to patient populations underrepresented in the study. Specific to this post hoc analysis, a limitation of the original study design is that BODE index scores were only obtained at baseline and not reassessed after the 52-week treatment period.

Nevertheless, our results show that dupilumab added on to standard triple therapy with ICS + LABA + LAMA reduces exacerbations and improves lung function in patients with COPD and type 2 inflammation across BODE index groups, supporting the role of dupilumab in the management of COPD.

5. Conclusion

Treatment with add-on dupilumab 300 mg q2w resulted in greater reductions in exacerbations and improvements in lung function, compared with placebo, in patients with COPD and type 2 inflammation at high exacerbation risk, regardless of the baseline BODE index score (>4 or ≤4) for up to 52 weeks.

CRediT authorship contribution statement

Claus F. Vogelmeier: Writing – review & editing, Methodology, Investigation. **Klaus F. Rabe:** Writing – review & editing, Methodology, Investigation. **Surya P. Bhatt:** Writing – review & editing, Methodology, Investigation. **Nicola A. Hanania:** Writing – review & editing, Methodology, Investigation. **Mona Bafadhel:** Writing – review & editing, Methodology, Investigation. **Stephanie A. Christenson:** Writing – review & editing, Methodology, Investigation. **Alberto Papi:** Writing – review & editing, Methodology, Investigation. **Dave Singh:** Writing – review & editing, Methodology, Investigation. **Elizabeth Laws:** Writing – review & editing, Methodology, Investigation. **Jennifer Maloney:** Writing – review & editing, Methodology, Investigation. **Paula Dakin:** Writing – review & editing, Methodology, Investigation. **Xin Lu:** Writing – review & editing, Methodology, Investigation, Formal analysis. **Deborah Bauer:** Writing – review & editing, Methodology, Investigation, Formal analysis. **Ashish Bansal:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Lacey B. Robinson:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Raolat M. Abdulai:** Writing – review & editing, Methodology, Investigation.

Data sharing statement

Qualified researchers may request access to study documents (including the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan) that support the methods and findings reported in this manuscript. Individual anonymized participant data will be considered for sharing: 1) once the product and indication has been approved by major health authorities (e.g., FDA, EMA, PMDA) or development of the product has been discontinued globally for all indications on or after April 2020 and there are no plans for future development; 2) if there is legal authority to share the data; and 3) there is not a reasonable likelihood of participant reidentification. Submit requests to https://vivli.org/.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships, which may be considered as potential competing interests: **CFV** has given presentations at symposia and/or served on scientific advisory boards for Aerogen, AstraZeneca, Boehringer Ingelheim, Chiesi, CSL Behring, Grifols, GSK, Insmed, Menarini, Novartis, Nuvaira, Roche, and Sanofi. **KFR** reports being a consultant and advisory board

member for and reports receiving speaker fees from AstraZeneca, Boehringer Ingelheim, Chiesi, Gilead, GSK, Novartis, Pearl Pharmaceuticals, Sanofi, and Teva, and is a co-founder of rnatics, Germany. **SPB** has acted as a consultant for Apreo, AstraZeneca, Boehringer Ingelheim, Chiesi, Genentech, GSK, Merck, Regeneron Pharmaceuticals Inc., Sanofi, and Verona Pharma; reports receiving grant support to his institution from Genentech, Nuvaira, and Sanofi; and honoraria from Horizon CME, Integritas Communications, Integrity CE, and Medscape. **NAH** has acted as a consultant for Amgen, AstraZeneca, Boehringer Ingelheim, Genentech, and GSK; reports receiving institutional grant support from AstraZeneca, Genentech, GSK, Sanofi, and Teva Pharmaceuticals; is an advisory board member for Sanofi and Teva Pharmaceuticals; and is an editor in chief, Respiratory Medicine, for Elsevier Publishing. **MB** reports being a Research Professor NIHR304263, is funded by the National Institute for Health and Care Research (NIHR). The views expressed in this publication are those of the author(s) and not necessarily those of the NIHR, NHS, or the UK Department of Health and Social Care; reports receiving grant support to her institution from Asthma + Lung UK, AstraZeneca, NIHR, and Roche; has received consulting fees to her institution from Areteia, AstraZeneca, GSK, and Sanofi; has received honoraria paid to her institution from AstraZeneca and GSK; has been supported to attend conference meetings by Chiesi; has been a scientific advisor for Albus Health and Areteia; and is a chair for the British Thoracic Society (BTS) research and scientific committee. **SAC** reports personal fees for advisory board participation/consulting on asthma/COPD therapeutics and non-branded COPD talks for AstraZeneca, Regeneron Pharmaceuticals Inc., and Sanofi; personal fees for consulting on asthma/COPD therapeutics for Apogee Therapeutics, Axon Advisors, and Genentech; personal fees for advisory board participation on asthma/COPD therapeutics for Amgen, DevPro Biopharma, Kymera Therapeutics, and Verona Pharma; and personal fees for advisory board participation for Glenmark Pharmaceuticals. **AP** reports institutional payments from AstraZeneca, Chiesi, GSK, and Sanofi; consultancy fees from AstraZeneca, Avillion, Chiesi, GSK, Moderna, Roche, and Sanofi; and payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from AstraZeneca, Avillion, Chiesi, GSK, IQVIA, Moderna, Roche, Sanofi, and Zambon. **DS** has acted as a consultant for Aerogen, AstraZeneca, BIAL, Boehringer Ingelheim, Chiesi Farmaceutici, Cipla USA, CSL Behring, EpiEndo, Glenmark, GSK, Kinaset, Menarini, Novartis Pharma, Orion Corporation, PULMATRiX, Sanofi, Theravance, and Verona Pharma; and research grants paid to his institution from NIHR Manchester Biomedical Research Centre. **EL**, **XL**, **DB**, and **LBR** are employees of Sanofi and may hold stock and/or stock options in the company. **RMA** is a former employee of Sanofi and may hold stock and/or stock options in the company. **JM**, **PD**, and **AB** are employees and shareholders of Regeneron Pharmaceuticals Inc.

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