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Dupilumab is effective in type 2-high asthma patients receiving high-dose inhaled corticosteroids at baseline

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Abstract

Background: Dupilumab blocks the shared receptor component for interleukin (IL)-4/IL-13, key drivers of type 2 inflammation. In phase 2b (NCT01854047) and phase 3 LIBERTY ASTHMA QUEST (NCT02414854), add-on dupilumab 200/300 mg every 2 weeks (q2w) reduced severe exacerbations, improved prebronchodilator (pre-BD) forced expiratory volume in 1 second (FEV_1) and quality of life measures, and it was generally well tolerated in patients with uncontrolled, persistent (phase 2b), or moderate-to-severe (phase 3) asthma.

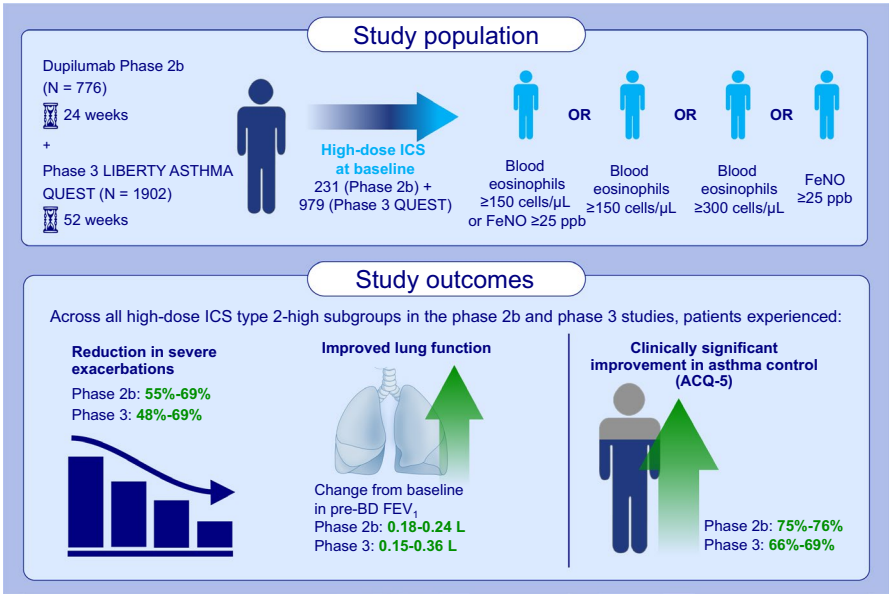
Methods: In patients on high-dose inhaled corticosteroids (ICS) with type 2-high asthma (subgroups including baseline blood eosinophils ≥150/300 cells/μL and/or fractional exhaled nitric oxide [FeNO] ≥25 ppb), annualized severe exacerbation rates over the treatment period, changes from baseline in pre-BD FEV_1 and asthma control (5-item asthma control questionnaire [ACQ-5]) were analyzed.

Results: In high-dose ICS type 2-high subgroups, dupilumab 200/300 mg q2w vs placebo in the phase 2b (24 weeks) and phase 3 (52 weeks) studies significantly reduced severe exacerbations by 55%-69%/57%-60% (all $P<.05$) and 53%-69%/48%-66% (all $P < .001$), respectively, except in patients with ≥ 300 eosinophils/μL in phase 2b study (24%/50% ($P = .52/0.15$). Across subgroups, pre-BD FEV_1 improved by 0.18-0.22 L/0.19-0.24 L (all $P < .05$) and 0.23-0.36 L/0.15-0.25 L (all $P < .01$) and ACQ-5 scores were reduced by 0.46-0.55/0.47-0.85 (all $P < .05$) and 0.38-0.50/0.24-0.30 (all $P < .05$), respectively, except dupilumab 200 mg q2w in phase 2b in patients with FeNO ≥ 25 ppb (0.41; $P = .09$). Dupilumab was also effective in patients taking medium-dose ICS.

Conclusion: Dupilumab significantly reduced severe exacerbations and improved lung function and asthma control in patients with type 2-high asthma on high-dose ICS at baseline.

KEYWORDS

asthma control, exacerbations, inhaled corticosteroids, moderate-to-severe asthma, prebronchodilator FEV_1



GRAPHICAL ABSTRACT

This study examines dupilumab efficacy in type 2-high asthma patients receiving high-dose ICS at baseline. Dupilumab reduces severe exacerbations, improves lung function and asthma control in patients on high-dose ICS with elevated baseline blood eosinophils or FeNO. Dupilumab efficacy is rapid and sustained throughout treatment and comparable across type 2-high asthma patients receiving high-dose ICS at baseline.

Abbreviations: ACQ-5, 5-item Asthma Control Questionnaire; FeNO, fractional exhaled nitric oxide; FEV 1 , forced expiratory volume in 1 second; ICS, inhaled corticosteroids; ppb, parts per billion; pre-BD, prebronchodilator

1 | INTRODUCTION

Inhaled corticosteroids (ICS) have been the mainstay treatment of persistent asthma for more than 40 years. By targeting the glucocorticoid receptor, ICS inhibit the release of cytokines and other proinflammatory mediators, decrease eosinophil and mast cell recruitment, and inhibit nuclear transcription factors, thus suppressing adhesion molecule function and inducible nitric oxide synthase.[1-4] However, the largest clinical benefits are seen at low-dose ICS, with diminishing returns due to increased systemic adverse events at higher doses.[5]

Uncontrolled, moderate-to-severe asthma accounts for approximately 20% of all asthma cases[6,7] and includes patients who have persistent symptoms and/or exacerbations despite the use of high-dose ICS and controller medicines. This population is at an increased risk of exacerbations, with many patients having substantially reduced lung function and impaired quality of life, all of which culminate in considerable healthcare resource use and associated costs.[8] Type 2-high asthma, characterized by type 2 inflammation, occurs in approximately 50% of patients with asthma.[9] It includes the allergic phenotype, characterized by increased expression of specific immunoglobulin E (IgE) to aeroallergens; eosinophilic phenotype, characterized by eosinophilia evident in the blood, airways, and/or tissue[9-11]; and nonallergic, adult-onset, intrinsic phenotype. In recent years, add-on biologic treatments for use in patients with uncontrolled moderate-to-severe or persistent asthma have been developed that specifically target elements of type 2 inflammation such as interleukin (IL)-4, IL-5, and IL-13, which play crucial roles in the pathogenesis of asthma.[12,13] One such agent, dupilumab, is a fully human VelocImmune®-derived monoclonal antibody that blocks the shared receptor component for IL-4 and IL-13, key and central drivers of type 2 inflammation in multiple diseases.[14-17]

In the phase 2 studies (NCT01312961 and NCT01854047), dupilumab- vs placebo-treated patients with uncontrolled persistent asthma had a significantly reduced severe exacerbation rate and improved prebronchodilator (pre-BD) forced expiratory volume in 1 second (FEV_1).[18,19] Of importance, these findings were consistent irrespective of baseline blood eosinophil count, a biomarker for type 2 inflammation.[19] In the subsequent phase 3 LIBERTY ASTHMA QUEST study (NCT02414854), add-on dupilumab significantly reduced severe asthma exacerbations and improved pre-BD FEV_1 in the overall intention-to-treat (ITT) population of patients with uncontrolled, moderate-to-severe asthma.[20] Treatment effects were of greater magnitude in subgroups of patients with elevated baseline levels of the type 2 biomarkers (blood eosinophils ≥150 cells/μL or fractional exhaled nitric oxide [FeNO] ≥25 ppb). Dupilumab was generally well tolerated by patients in each of the studies.

This analysis across the dupilumab phase 2b and phase 3 QUEST studies further assessed the effect of dupilumab on severe exacerbations, pre-BD FEV_1, and asthma control in subgroups of patients with different characteristics of type 2-high disease who were taking high-dose ICS at baseline. Given the evidence from previous studies and in other biologics, we expected dupilumab to also be effective in this patient population. For completeness and transparency, we also repeated the analysis in patients with elevated type 2 biomarkers

taking medium-dose ICS at baseline and have included the findings in Appendix S1.

2 | METHODS

2.1 | Study design and patients

The phase 2b study (NCT01854047) was a randomized, double-blind, placebo-controlled, parallel-group study conducted in adults (aged ≥18 years) with an asthma diagnosis for at least 12 months based on the Global Initiative for Asthma 2009 guidelines[21] and receiving treatment with high- (>1000 μg/day) or medium- (500-1000 μg/day) dose ICS plus long-acting β_2-agonists. Patients were randomly assigned (1:1:1:1:1) to receive subcutaneous dupilumab 200 or 300 mg every 2 weeks (q2w) or every 4 weeks or placebo, over a 24-week period. Full details of the study design and conduct, including inclusion and exclusion criteria, have been published previously.[19] For this post hoc analysis, only the data from patients randomized to dupilumab q2w regimens (the approved dosing regimen) and placebo were included.

LIBERTY ASTHMA QUEST was a phase 3 multinational, multicenter, randomized, double-blind, placebo-controlled, parallel-group study that assessed the efficacy and safety of dupilumab in patients with uncontrolled asthma treated with high- (>1000 μg/day) or medium- (500-1000 μg/day) dose ICS (Table S1). Patients ≥12 years were randomized in a 2:2:1:1 ratio to receive add-on subcutaneous dupilumab 200 or 300 mg q2w or volume-matched placebo for 52 weeks. The study was open to all patients irrespective of eosinophilic status or any other biomarker requirement. Full details of study design, methodology, and eligibility criteria have been reported previously.[20,22]

In both the phase 2b study and LIBERTY ASTHMA QUEST, atopy was self-reported by patients; no further clinical assessments were conducted to verify.

Both studies were conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines of the International Conference on Harmonisation and with applicable regulatory requirements. An independent data and safety monitoring committee conducted blinded monitoring of patient safety data. Study conduct and documentation were monitored by local institutional review boards or ethics committees, and all the patients provided written informed consent before participating in the trial. Adolescent patients provided assent according to the ethics committee and approved standard practice for pediatric patients at each participating center.

2.2 | Study endpoints

Annualized severe exacerbation rates (defined as number of severe exacerbations per patient-year), change from baseline in pre-BD FEV_1 (L), and asthma control (using the patient-reported 5-item Asthma Control Questionnaire [ACQ-5][23]) were assessed over the 24-week (phase 2b study) and 52-week (QUEST) treatment periods. A responder analysis of ACQ-5 scores was conducted in which the proportion of patients with a response to treatment (responders) was defined as those with an improvement from baseline in ACQ-5 score that reached or exceeded the threshold of the minimum clinically important difference (MCID) of 0.5.[24] In line with the primary analyses for these studies, patients with improvement from baseline of <0.5 or with a missing value were considered as nonresponders for that time point.

2.3 | Statistical analysis

Prespecified efficacy analyses were performed on subgroups of patients in the overall ITT population categorized by ICS controller requirement at baseline (adapted from GINA 2014[25]; Table S1), and post hoc analyses, which further stratified the groups by baseline levels of blood eosinophils or FeNO. The subgroups examined were high-dose ICS and eosinophils ≥150 cells/μL, high-dose ICS and eosinophils ≥300 cells/μL, high-dose ICS and FeNO ≥25 ppb, high-dose ICS and eosinophils ≥150 cells/μL or FeNO ≥25 ppb, and high-dose ICS ITT subgroups. The same analyses were also performed on equivalent subgroups for completeness and transparency in patients taking medium-dose ICS. The ITT population was defined as all patients who were randomized, and data were analyzed according to the assigned intervention and whether an intervention was received. Results are presented separately for each study.

In both studies, the annualized rate of severe asthma exacerbations was analyzed using a negative binomial regression model.[19,20,22] Change from baseline in FEV_1 (L) and ACQ-5 was analyzed using mixed-effects models with repeated measures. Additional model details are provided in Appendix S1.

Descriptive statistics have been employed to present the data; a P value of <.05 for the comparison between each dupilumab dose and placebo (within each subgroup) was considered statistically significant.

3 | RESULTS

3.1 | Baseline characteristics

In the phase 2b study, 307 patients were randomized to dupilumab q2w regimens, and 158 patients were randomized to placebo (Figure S1A). Of these 465 patients, 231 (49.6%) received high-dose ICS, and 221 (47.5%) received medium-dose ICS at baseline. In QUEST, a total of 1902 patients were randomized (placebo: n = 638, dupilumab: n = 1264; Figure S1B). Fifteen (0.8%) patients were on low-dose ICS at study entry (in violation of the protocol) and are not included in this analysis, resulting in an analysis population of 1887. Of these, 979 (51.9%) were on high-dose ICS at baseline, and 908 (48.1%) patients received medium-dose ICS (Table 1). In each study, the

TABLE 1 Baseline demographic and disease characteristics in phase 2b and phase 3 QUEST studies by baseline ICS dose

	Dupilumab phase 2b			Dupilumab phase 3 QUEST			
	Placebo[a]	Dupilumab 200 mg q2w	Dupilumab 300 mg q2w	Matching placebo to dupilumab 200 mg q2w	Dupilumab 200 mg q2w	Matching placebo to dupilumab 300 mg q2w	Dupilumab 300 mg q2w
High-dose ICS at baseline, n	77	75	79	172	317	167	323
Age, mean (SD), years	50.3 (10.9)	54.0 (11.6)	48.3 (12.4)	48.9 (14.1)	49.5 (13.8)	49.5 (13.9)	49.1 (14.9)
Age <18 y, n (%)	0	0	0	6 (3.5)	6 (1.9)	3 (1.8)	11 (3.4)
Female sex, n (%)	54.0 (70.1)	43 (57.3)	52 (65.8)	110 (64.0)	199 (62.8)	119 (71.3)	203 (62.8)
Ongoing atopic medical condition, n (%)	57 (75.0)	52 (69.3)	59 (74.7)	147 (85.5)	257 (81.1)	136 (81.4)	262 (81.1)
Prebronchodilator FEV_1, mean (SD), L	1.70 (0.50)	1.73 (0.54)	1.80 (0.53)	1.74 (0.55)	1.69 (0.56)	1.65 (0.50)	1.70 (0.60)
Percent predicted, mean (SD)	58.97 (10.79)	59.45 (11.45)	60.14 (10.79)	58.10 (12.77)	56.38 (13.48)	56.43 (13.33)	56.37 (14.40)
Postbronchodilator FEV_1, mean (SD), L	NA	NA	NA	2.11 (0.62)	2.06 (0.69)	2.03 (0.61)	2.11 (0.71)
FEV_1 reversibility[b], mean (SD), %	25.79 (12.12)	25.61 (19.02)	27.59 (17.25)	23.57 (15.65)	28.23 (23.58)	27.04 (16.43)	28.20 (26.72)
Severe asthma exacerbations in past year, mean (SD), n	2.57 (2.72)	2.19 (1.75)	2.77 (2.77)	2.26 (1.77)	2.24 (2.11)	2.57 (2.33)	2.22 (1.67)
ACQ-5 score[c], mean (SD)	2.82 (0.82)	2.88 (0.74)	2.98 (0.86)	2.82 (0.76)	2.90 (0.87)	2.89 (0.82)	2.91 (0.79)
AQLQ(S) global score, mean (SD)	3.84 (1.06)	3.91 (1.16)	3.70 (1.15)	4.15 (1.05)	4.18 (1.10)	4.13 (1.04)	4.04 (1.02)
Biomarker levels							
Blood eosinophil count, median (IQR), cells/μL	280.0 (190.0-450.0)	280.0 (150.0-550.0)	260.0 (160.0-420.0)	280.0 (130.0-485.0)	250.0 (130.0-470.0)	280.0 (150.0-510.0)	250.0 (130.0-470.0)
Total IgE, median (IQR), IU/mL	216.0 (94.0-463.0)	151.0 (47.0-428.0)	163.0 (78.0-405.0)	176.0 (52.0-406.0)	151.0 (51.0-459.0)	160.5 (62.0-363.0)	175.5 (59.5-450.0)
FeNO, median (IQR), ppb	30.0 (18.0-41.0)	27.0 (15.0-41.0)	29.0 (13.0-62.0)	23.0 (14.0-38.0)	23.0 (14.0-39.0)	27.0 (15.5-43.5)	24.0 (15.0-42.0)
Medium-dose ICS at baseline, n	78	69	74	144	310	151	303
Age, mean (SD), years	47.4 (14.1)	47.9 (14.6)	46.7 (12.6)	47.5 (17.3)	46.2 (16.6)	46.7 (15.5)	46.4 (16.1)
Age <18 y, n (%)	0	0	0	15 (10.4)	28 (9.0)	15 (9.9)	23 (7.6)
Female sex, n (%)	48 (61.5)	47 (68.1)	48 (64.9)	87 (60.4)	186 (60.0)	96 (63.6)	191 (61.6)

(Continues)

TABLE 1 (Continued)

	Dupilumab phase 2b			Dupilumab phase 3 QUEST			
	Placebo[a]	Dupilumab 200 mg q2w	Dupilumab 300 mg q2w	Matching placebo to dupilumab 200 mg q2w	Dupilumab 200 mg q2w	Matching placebo to dupilumab 300 mg q2w	Dupilumab 300 mg q2w
Ongoing atopic medical condition, n (%)	55 (73.3)	55 (80.9)	49 (69.0)	118 (81.9)	249 (80.3)	127 (84.1)	255 (84.2)
Prebronchodilator FEV_1, mean (SD), L	1.95 (0.58)	1.87 (0.52)	1.91 (0.54)	1.80 (0.67)	1.88 (0.66)	1.86 (0.62)	1.87 (0.59)
Percent predicted, mean (SD)	62.9 (10.5)	62.9 (10.3)	61.3 (10.2)	58.9 (13.7)	60.4 (13.2)	60.4 (14.3)	60.6 (12.2)
Postbronchodilator FEV_1, mean (SD), L	NA	NA	NA	2.23 (0.79)	2.27 (0.79)	2.25 (0.77)	2.24 (0.73)
FEV_1 reversibility[b], mean (SD), %	29.84 (16.08)	27.89 (16.40)	26.89 (15.92)	27.17 (21.48)	26.39 (21.95)	25.99 (19.05)	23.31 (20.14)
Severe asthma exacerbations in past year, mean (SD), n	1.95 (1.67)	1.45 (0.83)	1.96 (1.59)	1.85 (1.30)	1.91 (3.14)	2.03 (1.71)	1.82 (2.03)
ACQ-5 score[c], mean (SD)	2.57 (0.76)	2.55 (0.86)	2.64 (0.68)	2.59 (0.68)	2.62 (0.70)	2.61 (0.69)	2.62 (0.70)
AQLQ(S) global score[d], mean (SD)	4.35 (1.10)	4.19 (1.15)	4.14 (1.07)	4.39 (0.97)	4.43 (1.05)	4.52 (0.98)	4.53 (1.03)
Biomarker levels							
Blood eosinophil count, median (IQR), cells/μL	245.0 (150.0-420.0)	240.0 (180.0-400.0)	270.0 (160.0-380.0)	260.0 (140.0-490.0)	250.0 (120.0-450.0)	245.0 (130.0-420.0)	250.0 (130.0-450.0)
Total IgE, median (IQR), IU/mL	182.0 (84.0-430.0)	237.0 (51.0-647.0)	168.5 (73.0-409.0)	173.5 (75.0-493.0)	158.0 (65.0-441.0)	188.0 (52.5-482.0)	172.5 (66.0-454.0)
FeNO, median (IQR), ppb	28.0 (16.0-53.0)	32.0 (18.0-52.0)	28.0 (16.0-48.0)	27.0 (16.0-51.5)	24.0 (16.0-47.0)	27.0 (16.0-51.0)	24.0 (13.0-43.0)

Abbreviations: ACQ-5, 5-Item Asthma Control Questionnaire; AQLQ[S], Asthma Quality of Life Questionnaire [Standardized]; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 s; HRQoL, health-related quality of life; ICS, inhaled corticosteroids; IgE, immunoglobulin E; IQR, interquartile range; NA, not applicable; ppb, parts per billion; q2w, every 2 wk; SD, standard deviation.

[a]In the phase 2b study, the same amount of placebo was given regardless of dupilumab dose (not volume-matched).

[b]Forced expiratory volume in 1 s (L) reversibility indicates the change in FEV_1 between prebronchodilator and postbronchodilator measurements.

[c]5-item asthma control questionnaire is a patient-reported measure of the adequacy of asthma control and change in asthma control that occurs either spontaneously or as a result of treatment. Scores range between 0 (totally controlled) and 6 (severely uncontrolled).

[d]Asthma quality of life questionnaire (standardized) is a patient-reported measure of asthma-specific HRQoL. Higher scores indicate better HRQoL; a global score is rated on a 7-point Likert-like scale (7 = "not impaired at all" to 1 = "severely impaired").

subgroups of patients receiving high-dose ICS had relatively worse lung function, asthma control, and prior exacerbations, indicative of their greater disease severity and needed a higher dose of controller medication (Table 1). Furthermore, baseline demographics for each subgroup are shown in Tables S2-5.

3.2 | Annualized rate of severe asthma exacerbations

In the overall ITT population of the phase 2b study, dupilumab 200 and 300 mg q2w compared with placebo significantly reduced adjusted annualized severe exacerbation rates in the subgroup receiving high-dose ICS at baseline by 56% ($P = .004$) and 57% ($P = .002$), respectively (Figure 1). Numerical reductions vs placebo were observed in the subgroup on high-dose ICS with blood eosinophil counts ≥300 cells/μL at baseline ($P = .524$ and $P = .149$, respectively), and significant reductions vs placebo were observed in subgroups on high-dose ICS with blood eosinophil count ≥150 cells/μL ($P < .05$ and $P < .01$), FeNO ≥25 ppb ($P < .01$ and $P < .05$), and blood eosinophil count ≥150 cells/μL or FeNO ≥25 ppb ($P < .01$ for both) (Figure 1). In the phase 2b study, adjusted severe exacerbation rates could not be calculated for the subgroups of patients receiving medium-dose ICS as the number of events was deemed too small to provide valid estimates from an adjusted model; therefore, unadjusted data are presented. In the subgroup receiving medium-dose ICS at baseline, the reductions in the unadjusted annualized severe exacerbation rate for patients receiving dupilumab 200 and 300 mg q2w vs placebo were 67.5%/62.4% vs 46.3% (Figure S2). Consistent numerical improvements vs placebo were also observed for each subgroup when further stratified by blood eosinophil and FeNO levels at baseline (Figure S2).

In the overall ITT population of QUEST, dupilumab 200 and 300 mg q2w compared with placebo significantly reduced adjusted annualized severe exacerbation rates in patients receiving high-dose ICS at baseline by 46% ($P < .001$) and 39% ($P = .002$), respectively (Figure 1); when further stratified by baseline type 2 biomarker status (blood eosinophil count and/or FeNO levels), a greater magnitude of treatment effect was observed in patients with type 2-high phenotype with reductions vs placebo ranging from 48% to 69% (all $P < .001$) (Figure 1). In patients on medium-dose ICS at baseline, significant reductions in adjusted annualized severe exacerbation rates by 51% ($P = .0004$) and 53% ($P < .0001$), respectively, were observed; this was also seen for each subgroup when further stratified by blood eosinophil and FeNO levels at baseline (Figure S2).

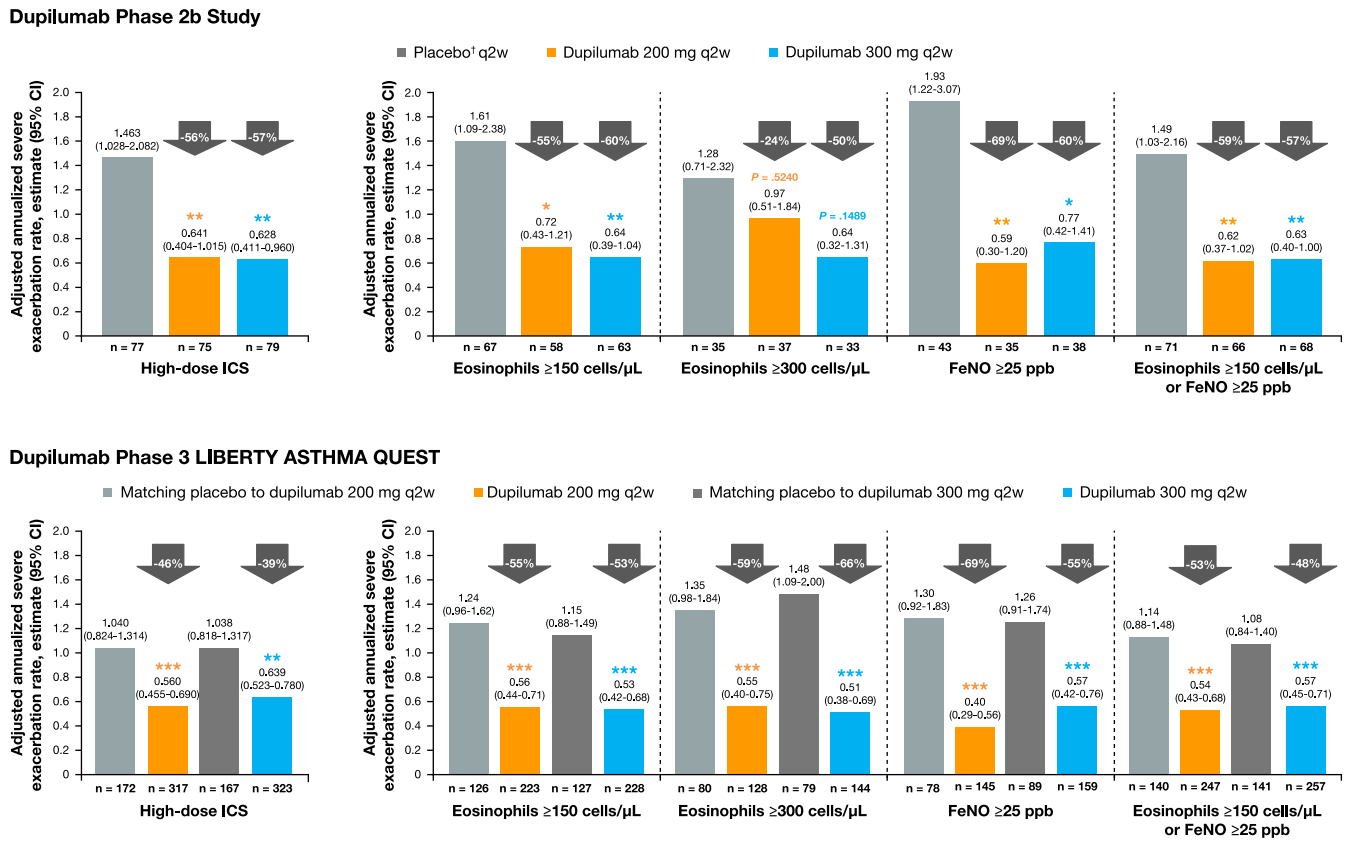


FIGURE 1 Annualized rate of severe exacerbations in dupilumab-treated patients (q2w) vs placebo during the 24-wk treatment period in the phase 2b study and 52-wk treatment period in the phase 3 QUEST study on high-dose ICS at baseline and further stratified by baseline eosinophil and FeNO levels. †In the phase 2b study, the same amount of placebo was given regardless of dupilumab dose (not volume-matched as in the phase 3 QUEST study). ***$P < .001$, **$P < .01$, *$P < .05$ vs placebo. CI, confidence interval; FeNO, fractional exhaled nitic oxide; q2w, every 2 wk

3.3 | Prebronchodilator FEV_1

In the overall ITT population of the phase 2b study, treatment with dupilumab 200 and 300 mg q2w vs placebo improved pre-BD FEV_1 in patients receiving high-dose ICS at baseline by least squares (LS) mean difference (95% confidence interval [CI]) of 0.14 L (0.03-0.24; $P = .011$) and 0.19 L (0.09-0.30; $P = .0002$), respectively, by Week 2. This improvement was sustained up to 24 weeks (0.21 L [0.09-0.32; $P = .0005$] and 0.22 L [0.11-0.34; $P = .0001$]; Figure S3). When further stratified by baseline eosinophils or FeNO levels, statistically significant improvements vs placebo were consistently observed as early as Week 2 (LS mean difference range: 0.14-0.21 L and 0.18-0.23 L, all $P < .05$, respectively), with one exception (dupilumab 200 mg q2w patients with a baseline blood eosinophil count of ≥300 cells/μL [0.09 L; $P = .263$]), where a statistically significant improvement was reached first by Week 4. In all subgroups, these improvements were maintained throughout the 24-week treatment duration (LS mean difference range: 0.18-0.22 L and 0.19-0.24 L, respectively; all $P < .05$) (Figure 2, Table S6). Improvements in pre-BD FEV_1 were also observed for the medium-dose ICS group; at Week 2, the LS mean difference (95% CI) vs placebo was 0.14 L (0.03-0.26; $P = .01$) and 0.11 L (−0.01-0.22; $P = .06$). This numerical improvement was sustained up to 24 weeks (0.13 L [−0.01-0.26; $P = .06$] and 0.09 L [−0.04-0.22; $P = .18$]; Figure S3). Similar results were observed for each subgroup when further stratified by blood eosinophil and FeNO levels at baseline (Figure S4, Table S7).

In the overall ITT population of the QUEST study, dupilumab 200 and 300 mg q2w vs placebo rapidly improved pre-BD FEV_1 in the high-dose ICS subgroup by LS mean difference (95% CI) of 0.12 L (0.05-0.18; $P = .0004$) and 0.16 L (0.09-0.22; $P < .0001$), respectively, at Week 2. This improvement was sustained over the 52-week treatment period (0.20 L [0.12-0.28; $P < .0001$] and 0.13 L [0.05-0.21; $P = .002$]; Figure S3). When further stratified by baseline eosinophils or FeNO levels, statistically significant improvements vs placebo were consistently observed as early as Week 2 (LS mean difference range: 0.13-0.23 L and 0.19-0.30 L, respectively; all $P < .001$) and were maintained throughout the 52-week treatment period (LS mean difference range: 0.23-0.36 L and 0.15-0.25 L, respectively; all $P < .05$) (Figure 2, Table S6). At Week 2, treatment with dupilumab 200 and 300 mg q2w vs placebo also significantly improved pre-BD FEV_1 in the medium-dose ICS subgroup by LS mean difference (95% CI) 0.18 L [0.11-0.25] and 0.14 L [0.07-0.21], respectively; both $P < .0001$; with sustained improvements by Week 52 of 0.20 L (0.11-0.29; $P < .0001$), and 0.14 L (0.06-0.23; $P = .0009$), respectively (Figure S3). Similar results were observed in subgroups further stratified by baseline eosinophils or FeNO levels (Figure S4, Table S7).

3.4 | Asthma control (ACQ-5 scores)

In the overall ITT population of the phase 2b study, treatment with dupilumab 200 and 300 mg q2w vs placebo improved asthma control in patients requiring high-dose ICS at baseline (LS mean difference from baseline [95% CI] at Week 24: −0.49 [−0.82 to −0.16; $P = .004$] and −0.42 [−0.74 to −0.10; $P = .01$, respectively]; Figure S5). These improvements were also observed in the subgroups stratified by baseline eosinophils or FeNO (Figure 3). Improvements in ACQ-5 scores were also seen in patients requiring medium-dose ICS at baseline (LS mean difference from baseline [95% CI] at Week 24: −0.35 [−0.65 to −0.05; $P = .02$] and −0.28 [−0.57 to 0.01; $P = .06$], respectively; Figure S5) and in the subgroups stratified by baseline eosinophils or FeNO (Figure S6).

Similarly, in the overall ITT population of QUEST, consistent improvements in asthma control were observed for patients with high-dose ICS at baseline (LS mean difference from baseline [95% CI] vs placebo at Week 24: −0.31 [−0.51 to −0.11; $P = .002$] and −0.13 [−0.33 to 0.07; $P = .21$], respectively; Week 52: −0.34 [−0.54 to −0.14; $P = .0009$] and −0.15 [−0.35 to 0.05; $P = .14$], respectively; Figure S5) and in subgroups stratified by baseline eosinophils or FeNO (Figure 3). This was also the case in patients requiring medium-dose ICS at baseline (LS mean difference from baseline [95% CI] vs placebo at Week 24: −0.40 [−0.59 to −0.22; $P = .0001$] and −0.27 [−0.45 to −0.09; $P = .003$], respectively; Week 52: −0.44 [−0.63 to −0.24; $P < .0001$] and −0.29 [−0.48 to −0.10; $P = .002$], respectively; Figure S5) and in the subgroups stratified by baseline eosinophils or FeNO (Figure S6).

3.5 | ACQ-5 responder analysis

Many of the improvements in asthma control were clinically significant as evidenced by the differences vs placebo in ACQ-5 scores reaching or exceeding the MCID of 0.5.[24] In the high-dose ICS subgroup of the phase 2b study, after 24 weeks, the proportion of responders in dupilumab-treated patients was 75% (56/75 patients; odds ratio [OR] 2.59 [1.29, 5.20]; $P = .007$) and 76% (60/79 patients; OR 2.85 [1.43, 5.68]; $P = .003$) vs 53% (41/77) of placebo-treated patients.

In the overall ITT population of QUEST, at 24 weeks, a numerical increase in responders was observed in the high-dose ICS at baseline subgroup treated with dupilumab 200 and 300 mg q2w vs matched placebos, respectively: 75% (238/317 patients) vs 69% (118/172 patients) (OR vs placebo [95%CI] 1.36 [0.90, 2.08]; $P = .15$) and 72% (231/323) vs 62% (104/167) (OR 1.51 [1.00, 2.26]; $P = .05$]) (Table S8). Numerical improvements in responder rates were also observed in the medium-dose ICS subgroups for both studies (Table S9).

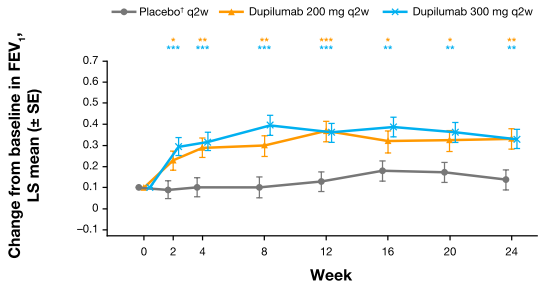
4 | DISCUSSION

In this analysis of data from the pivotal phase 2b and phase 3 LIBERTY ASTHMA QUEST studies, dupilumab 200 and 300 mg q2w vs placebo reduced severe exacerbation rates and improved FEV_1 (L), asthma control (ACQ-5), and rate of responders (ACQ improvement of MCID ≥ 0.5) in patients with uncontrolled, type 2-high persistent

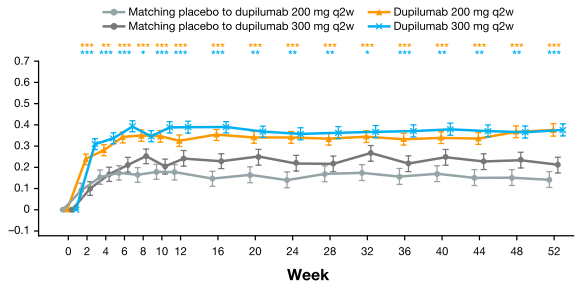
Dupilumab phase 2b study

Dupilumab phase 3 LIBERTY ASTHMA QUEST

Baseline blood eosinophils ≥150 cells/μL

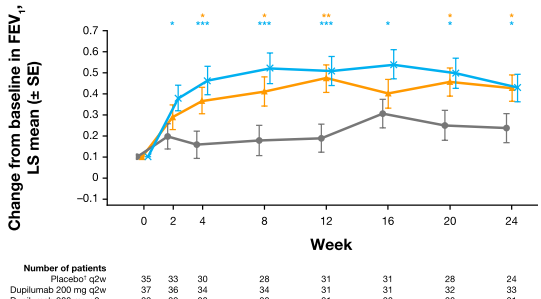


Number of patients								
Placebo† q2w	67	64	60	49	50	56	52	46
Dupilumab 200 mg q2w	58	57	55	53	51	51	51	52
Dupilumab 300 mg q2w	63	62	57	56	60	59	57	59

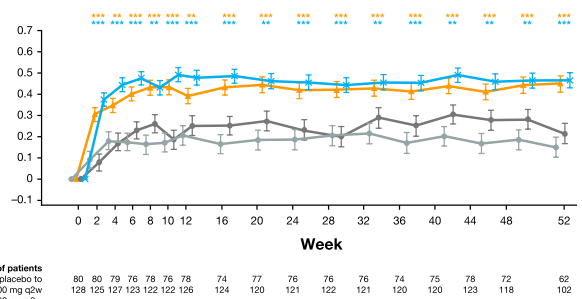


Number of patients																	
Matching placebo to dupilumab 200 mg q2w	126	126	123	120	121	118	121	118	121	118	118	116	116	116	118	113	98
Dupilumab 200 mg q2w	223	217	217	215	214	214	219	216	210	213	211	210	211	207	211	206	176
Matching placebo to dupilumab 300 mg q2w	127	125	124	123	121	121	122	120	118	112	118	115	118	116	114	113	103
Dupilumab 300 mg q2w	228	226	223	224	219	215	219	220	217	218	208	205	210	208	202	201	174

Baseline blood eosinophils ≥300 cells/μL

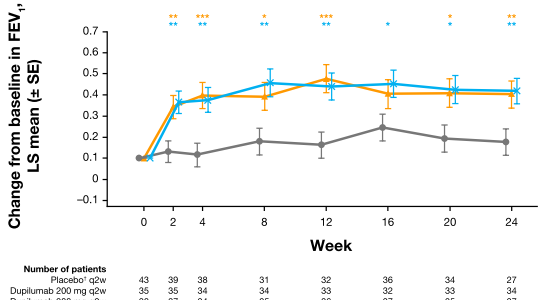


Number of patients								
Placebo† q2w	35	33	30	28	31	31	28	24
Dupilumab 200 mg q2w	37	36	34	34	31	31	32	33
Dupilumab 300 mg q2w	33	32	30	30	31	30	30	31

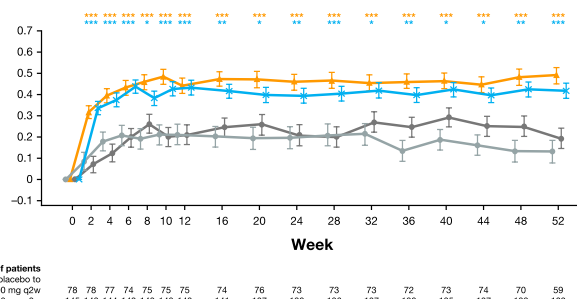


Number of patients																	
Matching placebo to dupilumab 200 mg q2w	80	80	79	76	78	76	78	74	77	76	76	76	74	75	78	72	62
Dupilumab 200 mg q2w	128	125	127	123	122	122	126	124	120	121	122	121	120	120	123	118	102
Matching placebo to dupilumab 300 mg q2w	79	79	79	78	76	77	77	77	75	69	74	73	74	73	72	72	65
Dupilumab 300 mg q2w	144	143	141	143	139	137	140	141	139	138	135	129	132	132	129	129	111

Baseline FeNO ≥25 ppb

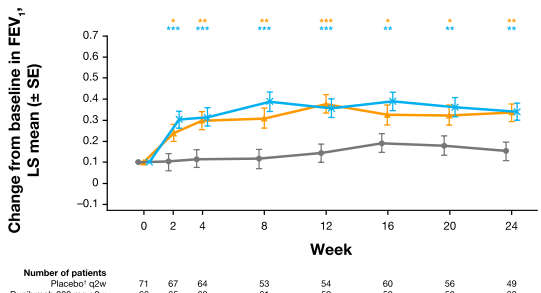


Number of patients								
Placebo† q2w	43	39	38	31	32	36	34	27
Dupilumab 200 mg q2w	35	35	34	34	33	32	33	34
Dupilumab 300 mg q2w	38	37	34	35	36	37	35	37

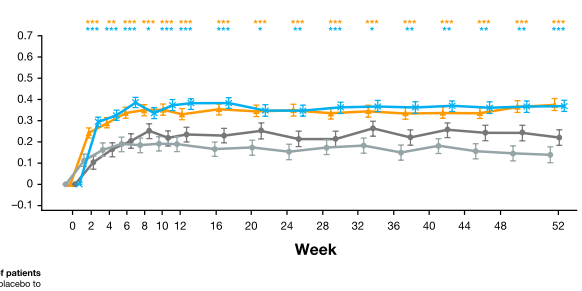


Number of patients																	
Matching placebo to dupilumab 200 mg q2w	78	78	77	74	75	75	75	74	76	73	73	73	72	73	74	70	59
Dupilumab 200 mg q2w	145	142	144	142	142	140	143	141	137	138	136	137	138	135	137	132	109
Matching placebo to dupilumab 300 mg q2w	89	87	85	86	84	85	85	82	82	80	81	80	80	80	79	81	71
Dupilumab 300 mg q2w	159	158	154	157	153	150	152	155	155	154	148	143	147	148	142	143	124

Baseline blood eosinophils ≥150 cells/μL or FeNO ≥25 ppb



Number of patients								
Placebo† q2w	71	67	64	53	54	60	56	49
Dupilumab 200 mg q2w	66	65	63	61	59	59	59	60
Dupilumab 300 mg q2w	68	67	62	61	65	64	62	64



Number of patients																	
Matching placebo to dupilumab 200 mg q2w	140	140	137	134	135	132	135	132	135	132	131	129	130	130	132	127	109
Dupilumab 200 mg q2w	247	241	241	239	238	238	243	240	233	236	233	233	234	230	234	229	192
Matching placebo to dupilumab 300 mg q2w	141	139	137	137	135	135	136	133	131	125	131	128	130	129	127	126	113
Dupilumab 300 mg q2w	257	255	250	252	247	241	246	247	245	246	236	230	237	236	229	228	193

FIGURE 2 Least squares mean change from baseline in FEV_1 (L) during the 24-wk treatment period in the phase 2b study in patients with uncontrolled, persistent asthma and 52-wk treatment period in the phase 3 QUEST study in patients with uncontrolled, moderate-to-severe asthma on high-dose ICS at baseline and further stratified by baseline eosinophil and FeNO levels. †In the phase 2b study, the same amount of placebo was given regardless of dupilumab dose (not volume-matched as in the phase 3 QUEST study). ***$P < .001$, **$P < .01$, *$P < .05$ vs placebo. FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 s; ICS, inhaled corticosteroids; LS, least squares; q2w, every 2 wk; SE, standard error

or moderate-to-severe asthma taking high-dose ICS at baseline. Improvements were observed across each of the subgroups as early as the first time point assessed and were sustained until treatment end in both studies.

There are currently 5 biologic add-on treatments for patients with uncontrolled severe asthma that target underlying type 2 inflammatory processes: dupilumab, benralizumab, reslizumab, mepolizumab, and omalizumab. As previously outlined, dupilumab blocks the shared receptor component for IL-4/IL-13, key and central drivers of type 2 inflammation.[14-17] It is approved in the EU[26] as add-on maintenance treatment in patients aged ≥12 years with severe asthma with type 2 inflammation characterized by raised blood eosinophils and/or raised FeNO levels who are inadequately controlled with a high-dose ICS plus another medicinal product for maintenance treatment. It is also approved in the USA[27] and other countries[28] as an add-on maintenance treatment in patients with moderate-to-severe asthma aged ≥12 years with an eosinophilic phenotype or with oral corticosteroid-dependent asthma.[19,20,29] Benralizumab, reslizumab, and mepolizumab are monoclonal antibodies targeting IL-5, a key component in eosinophil activation, proliferation, and degranulation. Benralizumab binds the alpha chain of the IL-5 (IL-5α) eosinophil cell surface receptor, blocking IL-5 binding and has been evaluated in phase 3 studies in patients ≥12 years.[30] Mepolizumab and reslizumab bind directly to IL-5, which in turn blocks binding with IL-5α.[31,32] Mepolizumab has been evaluated in patients aged ≥6 years and reslizumab in patients ≥18 years. Omalizumab, an anti-IgE monoclonal antibody that has been evaluated in patients ≥6 years, binds IgE and inhibits basophil and mast cell release of proinflammatory mediators.[33]

Consistent with findings from the parent studies and other dupilumab studies,[19,20,29] a generally greater magnitude of dupilumab efficacy was observed in patients with a type 2-high endotype. In the QUEST study, the highest magnitude of reduction in annualized severe exacerbation rate was observed in patients with type 2-high endotypes, with differences vs placebo of 48%-69%, compared with 39%-46% in all patients in the high-dose ICS subgroup and of 58%-74%, compared with 51%-53% in all patients in medium-dose ICS subgroup. Of note, in the QUEST study, in patients taking high-dose ICS a significant reduction in the adjusted annualized severe exacerbation rate with dupilumab vs matched placebo was observed in the subgroup of patients with baseline eosinophils ≥300 μ/L; a similar trend was observed in the phase 2b study although the effect did not reach statistical significance, likely due to low patient numbers in the subgroups of the phase 2b study. These observations were also seen in patients taking medium-dose ICS in the QUEST study; in the phase 2b study, adjusted severe exacerbation rates could not be calculated for the subgroups of patients receiving medium-dose ICS as the number of events was deemed too small to provide valid estimates from an adjusted model, but non-significant reductions in the unadjusted annualized severe exacerbation rate were observed with dupilumab vs matched placebo. In both the phase 2b and QUEST studies, higher magnitudes of responses were seen in change from baseline in FEV_1 compared with matched placebo in patients with type 2-high asthma taking high-dose ICS. This result was echoed in patients taking medium-dose ICS in the phase 3 QUEST study.

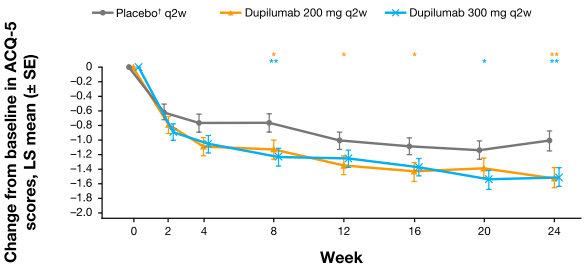
Similar findings have also been observed with the other biologic add-on therapies in patients with type 2-high asthma on medium-to-high-dose ICS. In the benralizumab phase 3 SIROCCO and CALIMA studies, significant reductions in annual asthma exacerbation rates and improvements in FEV_1 and asthma symptom scores compared with placebo were observed in patients with high-dose ICS and baseline blood eosinophils ≥300 cells/μL.[34,35] The phase 3 BREATH reslizumab studies also demonstrated reductions of clinical asthma exacerbations of 50%-59% and improvements in FEV_1, asthma control, forced vital capacity, and rescue short-acting beta agonist use compared with placebo in patients with eosinophils ≥400 cells/μL (ITT population), and with lower efficacy in patients with <400 cells/μL (ITT population).[36,37] Higher efficacy in reduction of severe exacerbations, and improvement of FEV_1 and ACQ-5 in patients with higher baseline blood eosinophils compared with patients with lower levels were also demonstrated in the DREAM, MENSA, and MUSCA phase 3 mepolizumab studies.[38-40] Finally, significantly greater reductions in asthma exacerbations were seen in patients with raised FeNO (≥19.5 ppb), eosinophils (≥260 cells/μL), and periostin (≥50 ng/mL) who were treated with omalizumab in the EXTRA phase 3 study, compared with placebo recipients.[41] Although elevated eosinophils in peripheral blood have been associated with type 2 asthma, their levels can be significantly influenced by the use of ICS.[42] Thus, peripheral blood eosinophilia as a type 2 inflammation marker should always be interpreted in view of the current dose of ICS. This could also account for the efficacy of dupilumab being demonstrated irrespective of the baseline ICS dose used by the patients.

The strength of this analysis is its randomized, double-blind design, its large population sizes, and the inclusion of patients regardless of ICS dose at baseline. One of the limitations was that the findings are constrained by the low sample sizes in some of the subgroups, as these were not defined a priori. The studies were not powered specifically to investigate differences between patients with asthma with high/medium-dose ICS and eosinophils ≥150 cells/μL or ≥300 cells/μL, FeNO ≥25 ppb, or eosinophils ≥150 cells/μL or FeNO ≥25 ppb. In addition, a large placebo effect on asthma control was observed in the QUEST study, possibly due to increased

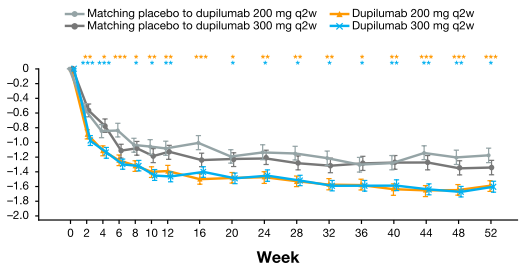
Dupilumab phase 2b study

Dupilumab phase 3 LIBERTY ASTHMA QUEST

Baseline blood eosinophils ≥150 cells/μL

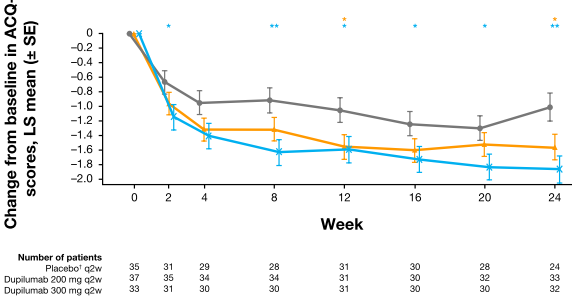


Number of patients								
Placebo† q2w	67	61	58	49	50	55	51	46
Dupilumab 200 mg q2w	58	55	55	53	51	50	51	51
Dupilumab 300 mg q2w	63	59	54	55	59	59	57	60

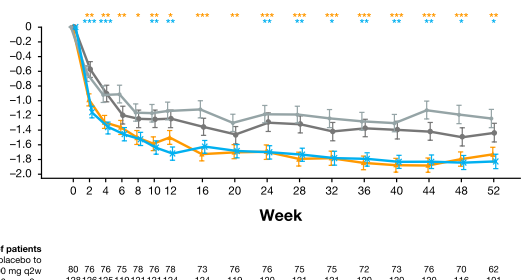


Number of patients																	
Matching placebo to dupilumab 200 mg q2w	126	120	119	119	121	117	120	115	119	117	116	113	113	112	116	109	97
Dupilumab 200 mg q2w	223	217	215	211	212	210	216	216	210	211	209	209	210	205	206	201	172
Matching placebo to dupilumab 300 mg q2w	127	122	120	121	121	118	123	119	115	112	119	114	117	113	114	110	101
Dupilumab 300 mg q2w	228	222	218	217	211	212	215	215	213	212	208	201	204	202	195	196	171

Baseline blood eosinophils ≥300 cells/μL

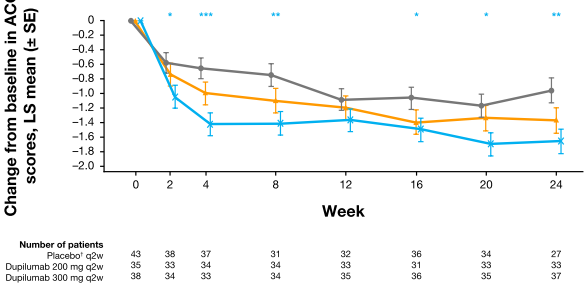


Number of patients								
Placebo† q2w	35	31	29	28	31	30	28	24
Dupilumab 200 mg q2w	37	35	34	34	31	30	32	33
Dupilumab 300 mg q2w	33	31	30	30	31	30	30	32

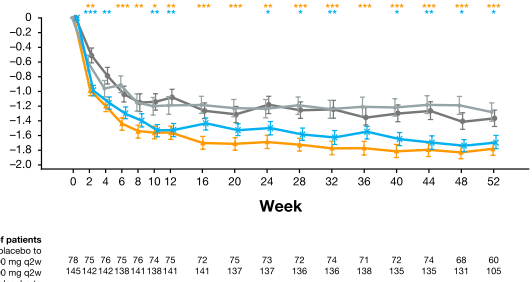


Number of patients																	
Matching placebo to dupilumab 200 mg q2w	80	76	76	75	78	76	78	73	76	76	75	75	72	73	76	70	62
Dupilumab 200 mg q2w	128	126	125	119	121	121	124	124	119	120	121	121	120	120	120	116	101
Matching placebo to dupilumab 300 mg q2w	79	77	77	76	77	75	78	77	72	69	75	71	73	71	70	69	63
Dupilumab 300 mg q2w	144	140	137	139	134	136	139	138	136	134	134	128	129	128	125	128	110

Baseline FeNO ≥25 ppb

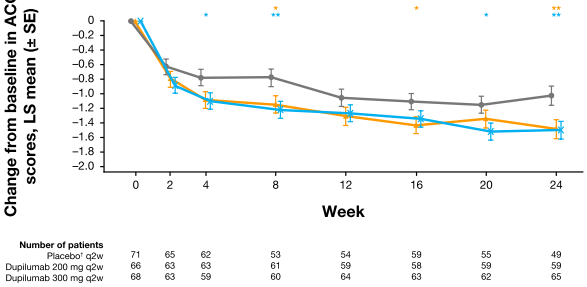


Number of patients								
Placebo† q2w	43	38	37	31	32	36	34	27
Dupilumab 200 mg q2w	35	33	34	34	33	31	33	33
Dupilumab 300 mg q2w	38	34	33	34	35	36	35	37

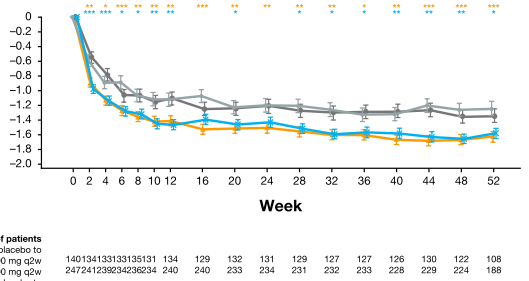


Number of patients																	
Matching placebo to dupilumab 200 mg q2w	78	75	76	75	76	74	75	72	75	73	72	74	71	72	74	68	60
Dupilumab 200 mg q2w	145	142	142	138	141	138	141	141	137	137	136	136	138	135	135	131	105
Matching placebo to dupilumab 300 mg q2w	89	85	83	85	84	83	86	82	78	80	82	80	80	79	78	80	70
Dupilumab 300 mg q2w	159	157	153	152	147	147	151	152	151	150	145	141	141	143	137	139	122

Baseline blood eosinophils ≥150 cells/μL or FeNO ≥25 ppb



Number of patients								
Placebo† q2w	71	65	62	53	54	59	55	49
Dupilumab 200 mg q2w	66	63	63	61	59	58	59	59
Dupilumab 300 mg q2w	68	63	59	60	64	63	62	65



Number of patients																	
Matching placebo to dupilumab 200 mg q2w	140	134	133	133	135	131	134	129	132	131	129	127	127	126	130	122	108
Dupilumab 200 mg q2w	247	241	239	234	236	234	240	240	233	234	231	232	233	228	229	224	188
Matching placebo to dupilumab 300 mg q2w	141	136	133	135	135	132	137	132	128	125	132	127	129	126	127	123	111
Dupilumab 300 mg q2w	257	251	246	245	239	238	243	243	240	240	233	227	230	229	221	221	189

FIGURE 3 Least squares mean change from baseline in ACQ-5 scores during the 24-wk treatment period in the phase 2b study in patients with uncontrolled, persistent asthma and 52-wk treatment period in the phase 3 QUEST study in patients with uncontrolled, moderate-to-severe asthma on high-dose ICS at baseline and further stratified by baseline eosinophil and FeNO levels. †In the phase 2b study, the same amount of placebo was given regardless of dupilumab dose (not volume-matched as in the phase 3 QUEST study). ***$P < .001$, **$P < .01$, *$P < .05$ vs placebo. ACQ-5, 5-item asthma control questionnaire; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 s; ICS, inhaled corticosteroids; LS, least squares; q2w, every 2 wk; SE, standard error

adherence in patients in the placebo group, which may have contributed to the differences in ACQ-5 improvement from baseline for dupilumab vs placebo not being statistically significant. Finally, due to the timings of the trial, old versions of the GINA guidelines were used when designing the studies and this analysis.

5 | CONCLUSIONS

In conclusion, the outcomes of these 2 pivotal dupilumab studies confirm that dupilumab is effective across a spectrum of patients on high-dose ICS at baseline with raised type 2 biomarkers and 1 or 2 additional controllers. Efficacy was also demonstrated in patients with type 2-high asthma on medium-dose ICS at baseline with 1-2 additional controllers. Improvements in lung function were seen within 2 weeks, sustained throughout treatment, and generally of greater magnitude in subgroups of patients with elevated baseline levels of type 2 biomarkers (blood eosinophils ≥150 cells/μL or ≥300 cells/μL or FeNO ≥25 ppb).

CONFLICT OF INTEREST

Arnaud Bourdin reports non-financial support from GlaxoSmithKline (GSK), during the conduct of the study; personal fees from AstraZeneca, grants and personal fees from Boehringer Ingelheim, Chiesi, GSK, Novartis, and Sanofi-Regeneron; other from Acceleron, Actelion, Galapagos, MSD, Nuvaira, Pulmonx, United Therapeutic, and Vertex, outside the submitted work. Alberto A. Papi reports grants, personal fees, non-financial support and other from GlaxoSmithKline, Boehringer Ingelheim, Chiesi Farmaceutici, and TEVA; grants, personal fees and non-financial support from AstraZeneca and Menarini; personal fees, non-financial support and other from Mundipharma, Zambon, Novartis, and Sanofi/Regeneron; personal fees from Roche and Edmondpharma; and grants from Fondazione Maugeri and Fondazione Chiesi; outside the submitted work. Jonathan Corren reports research support from Sanofi outside the submitted work. J. Christian Virchow reports personal fees from AstraZeneca, Avontec, Bayer, Bencard, Bionorica, Boehringer Ingelheim, Chiesi, Essex/Schering-Plough, GSK, Janssen-Cilag, Leti, MEDA, Merck, MSD, Mundipharma, Novartis, Nycomed/Altana, Pfizer, Revotar, Sandoz-Hexal, Stallergens, Teva, UCB/Schwarz-Pharma, Zydus/Cadila, and possibly others; other for Avontec, Boehringer Ingelheim, Chiesi, Essex/Schering-Plough, GSK, Janssen-Cilag, MEDA, MSD, Mundipharma, Novartis, Regeneron, Revotar, Roche, Sanofi-Aventis, Sandoz-Hexal, Teva, UCB/Schwarz-Pharma, and possibly others; and research grants from Deutsche Forschungsgesellschaft, Land Mecklenburg-Vorpommern, GSK, and MSD. Megan S. Rice reports personal fees and other from Sanofi, outside the submitted work. Yamo Deniz reports personal fees and other from Regeneron Pharmaceuticals, Inc, outside the submitted work. Michel Djandji reports personal fees and other from Sanofi, outside the submitted work. Paul Rowe reports personal fees and other from Sanofi, outside the submitted work. Ian D. Pavord reports personal fees from AstraZeneca, Boehringer Ingelheim, Aerocrine, Almirall, Novartis, GlaxoSmithKline, Genentech, and Regeneron; other from Teva, Chiesi, Sanofi, Circassia, and Knopp; grants from NIHR, outside the submitted work.

AUTHOR'S CONTRIBUTIONS

MSR, YD, and MD contributed to project concept, study design, and study implementation; AB, AAP, and JC contributed to data collection; MSR contributed to data and statistical analysis; all authors contributed to data analysis and interpretation, and critical revision of the mansucript; all authors critically reviewed and approved the final version of the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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