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Dupilumab improves symptoms, quality of life, and productivity in uncontrolled persistent asthma

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ABSTRACT

Background: In a pivotal, phase 2b study (NCT01854047) in patients with uncontrolled persistent asthma, despite using medium-to-high-dose inhaled corticosteroids plus long-acting β2 agonists, dupilumab improved lung function, reduced severe exacerbations, and showed an acceptable safety profile.
Objective: To assess the impact of dupilumab on asthma control, symptoms, quality of life (QoL), and productivity.
Methods: Data are shown for the intention-to-treat population receiving dupilumab 200/300 mg every 2 weeks (doses being assessed in phase 3; NCT02414854), or placebo. Predefined analyses of total scores were conducted at week 24 for the 5-item Asthma Control Questionnaire (ACQ-5), patient-reported morning/evening (AM/PM) asthma symptoms, Asthma Quality of Life Questionnaire (AQLQ), and asthma-related productivity loss. Responder rate analyses for these measures, subgroup analyses by baseline characteristics, and asthma-related productivity loss analyses were conducted post hoc.
Results: Data from 465 patients were analyzed (158 placebo; 307 dupilumab). Both dupilumab doses significantly improved scores through week 24 (all outcomes, overall population). The proportion of patients meeting or exceeding the minimal clinically important difference for the overall population were significantly greater vs placebo ($P < .05$) for ACQ-5 (range, 72.6%-76.7% vs 61.4%), for AM/PM asthma symptoms score (48.7%-54.1% vs 34.2% and 52.7%-53.5% vs 34.2%, respectively) and for AQLQ (64.0%-65.0% vs 51.3%). The effect of dupilumab was consistent across most subgroups. Productivity loss was significantly higher in placebo- vs dupilumab-treated patients ($P < .0001$).
Conclusion: Dupilumab produced significant, clinically meaningful improvements in asthma control, symptoms, QoL, and productivity.
Registration: ClinicalTrials.gov Identifier: NCT01854047.

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Introduction

Asthma is a heterogeneous disease consisting of phenotypes defined, in part, by clinical parameters such as age of onset, presence of allergic features, degree of airway obstruction, obesity, sex, and smoking history.[1-3] These characteristics may be associated with outcome and treatment response.[3] Poor asthma control has been associated with increased risk of asthma exacerbations, asthma-related hospitalization,[4,5] poor quality of life (QoL),[6] adverse impact on productivity,[7,8] and possibly, increased risk of mortality.[9-11]

Dupilumab, a fully human monoclonal antibody directed against the interleukin (IL)-4 receptor-α, inhibits signaling of IL-4 and IL-13. These cytokines are key drivers of type 2/Th2 immune responses that occur in asthma, allergic rhinitis, food allergies, and atopic dermatitis (AD). Dupilumab is approved in the European Union, United States, and other countries for the treatment of adults with inadequately controlled moderate-to-severe AD. Dupilumab is under clinical development for the treatment of uncontrolled persistent asthma, chronic rhinosinusitis with nasal polyposis, and eosinophilic esophagitis.

A pivotal, phase 2b, dose-ranging study (ClinicalTrials.gov Identifier: NCT01854047) assessed the efficacy and safety of dupilumab in patients with uncontrolled persistent asthma despite the use of medium-to-high-dose inhaled corticosteroids (ICS) plus a long-acting β_2-agonist (LABA).[12] Dupilumab significantly reduced severe asthma exacerbation rates and improved pulmonary function in both the overall study population and in subgroups defined by baseline eosinophil count (<300 and ≥ 300 cells/μL), while also demonstrating an acceptable safety profile.[12] When assessed using standard patient-reported outcome (PRO) questionnaires at baseline, more than half of the patients in the study had at least a moderate degree of impaired physical or emotional functioning.[13] Secondary outcomes that measured asthma control, asthma symptoms, and disease-specific health-related QoL showed that patients receiving dupilumab had improvements in each of these outcomes, irrespective of baseline eosinophil count.[12]

Although the main goals of asthma treatment include reduction of symptoms, improvement in QoL, and prevention of exacerbations, clinical trials of new treatments have primarily focused on exacerbations and lung function as key endpoints. PROs such as symptom control and QoL are increasingly being recognized as being important in asthma, and regulatory agencies often request inclusion of these outcomes in clinical trials.[14-16] Furthermore, treatment effects on exacerbations, lung function, and PROs show only modest correlations, making each measure a useful independent assessment.

In this post hoc analysis of the phase 2b study, we aimed to further investigate the effect of dupilumab on PROs by examining individual patient response rates and consistency of effect in specific patient subgroups, defined by baseline characteristics. In addition, we examined whether dupilumab treatment could affect loss of productivity in the workplace attributable to asthma.

Methods

Study design, inclusion and exclusion criteria, and main efficacy and safety outcomes of this randomized, double-blind, placebo-controlled, parallel-group, multicenter, multinational, pivotal, phase 2b clinical trial have been described previously.[12] Main inclusion criteria were: adults; asthma diagnosis[17] for 12 months or longer; treatment with medium-to-high-dose ICS+LABA with a stable dose of ICS+LABA for 1 month or longer before screening; pre-bronchodilator forced expiratory volume in 1 second (FEV_1) 40% to 80% of predicted, with reversibility of at least 12% and at least 200 mL in FEV_1 after 200 to 400 μg salbutamol at screening; 5-item Asthma Control Questionnaire (ACQ-5) total score[18] 1.5 or higher at screening and study baseline; and 1 or more systemic corticosteroid burst therapy, hospital admission, or an emergency or urgent medical care visit that required treatment with systemic steroids for worsening asthma within 1 year before screening. Main exclusion criteria were diagnosis of chronic obstructive pulmonary disease or other lung disease impairing pulmonary function; β-adrenergic receptor blocker use; use of systemic corticosteroids within 28 days of, or during, the screening period; current smoker, more than 10 pack-years smoking history, or cessation of smoking within 6 months of screening.

Patients were randomized (1:1:1:1:1) by a centralized treatment allocation system to receive placebo or 1 of the doses of subcutaneous dupilumab (200 mg or 300 mg) every 2 weeks (q2w) or every 4 weeks (q4w) for 24 weeks, followed by a 16-week follow-up period. Because only the 200 mg and 300 mg every 2 weeks regimens were further evaluated in phase 3 clinical trials, this manuscript reports the findings with these doses. This study was done in accordance with the principles established in the Declaration of Helsinki and the International Conference on Harmonisation guidelines for Good Clinical Practice. All study documents and procedures were approved by the appropriate institutional review board or ethics committee at each study site (e-Appendix 1). All patients provided written informed consent before participation in the study.[12]

Asthma control was assessed as change from baseline to week 24 in ACQ-5 total score and individual items (frequency of waking during the night, asthma morning symptoms, activity limitation, shortness of breath, and wheezing caused by asthma).[18,19] The ACQ-5 scores range from 0 (excellent asthma control) to 6 (poor asthma control).

Asthma symptoms were assessed as change from baseline to week 24 in asthma symptom scores (range, 0-4), using daily patient self-reported morning (AM) and evening (PM) asthma symptoms recorded using an electronic diary. The AM asthma symptom score is a 1-item question recorded on rising and assesses asthma symptoms occurring at night (0 = no asthma symptoms, slept through night; 4 = bad night, awake most of night because of asthma). The PM asthma symptom score is a 1-item question recorded in the evening, and it assesses asthma symptoms that occurred during the day (0 = very well, no asthma symptoms; 4 = asthma very bad, unable to carry out daily activities as usual). Baseline AM or PM scores are the average of the respective scores recorded for 7 days.

Quality of life was assessed as change from baseline to week 24 in the Asthma Quality of Life Questionnaire (AQLQ), a 32-item questionnaire composed of 4 health-related QoL domains (activity limitation, emotional function, exposure to environmental stimuli, and asthma symptoms) rated on a 7-point Likert-like scale (1 = totally limited, all the time, a very great deal, or severely limited; 7 = not at all limited, none, or no discomfort/distress).[20]

Productivity loss was measured using a patient-reported health care resource utilization questionnaire that included an assessment of the number of days lost from work, whether a patient experienced at least 1 day of sick leave from work because of a severe exacerbation event during the 24-week treatment period, and calculated the annualized rate of sick leave caused by severe exacerbation events. A severe exacerbation event was defined as the deterioration of asthma requiring use of systemic corticosteroids for at least 3 days or hospitalization or emergency room visit because of asthma requiring systemic corticosteroids.

To further explore the effects of dupilumab, analyses were also performed on subgroups of patients with baseline clinical characteristics associated with different asthma phenotypes. Subgroups included: sex, body mass index, age at asthma onset, FEV_1, FEV_1 percentage predicted, postbronchodilator reversibility, number of severe asthma exacerbations in the year before the study, ICS+LABA dose at randomization, eosinophil count, history of atopy (defined as 2 or more positive aeroallergen-specific IgE antibodies at baseline), and smoking history.

Results are reported for all patients randomized to receive placebo dupilumab 200 mg every 2 weeks or 300 mg every 2 weeks (ie, the dupilumab regimens under investigation in phase 3 [ClinicalTrials.gov Identifier: NCT02414854]). Changes from baseline at week 24 for ACQ-5, AM and PM asthma symptom scores, and AQLQ total scores for the intention-to-treat overall population, and by eosinophil count

less than 300 and at least 300 cells/μL were predefined endpoints in the original study.[12] Post hoc analyses included responder rates at week 24 for ACQ-5, AM/PM asthma symptom scores, AQLQ, and changes from baseline at week 24 for the individual items or domains of the ACQ-5 and AQLQ scores, subgroups, and productivity.

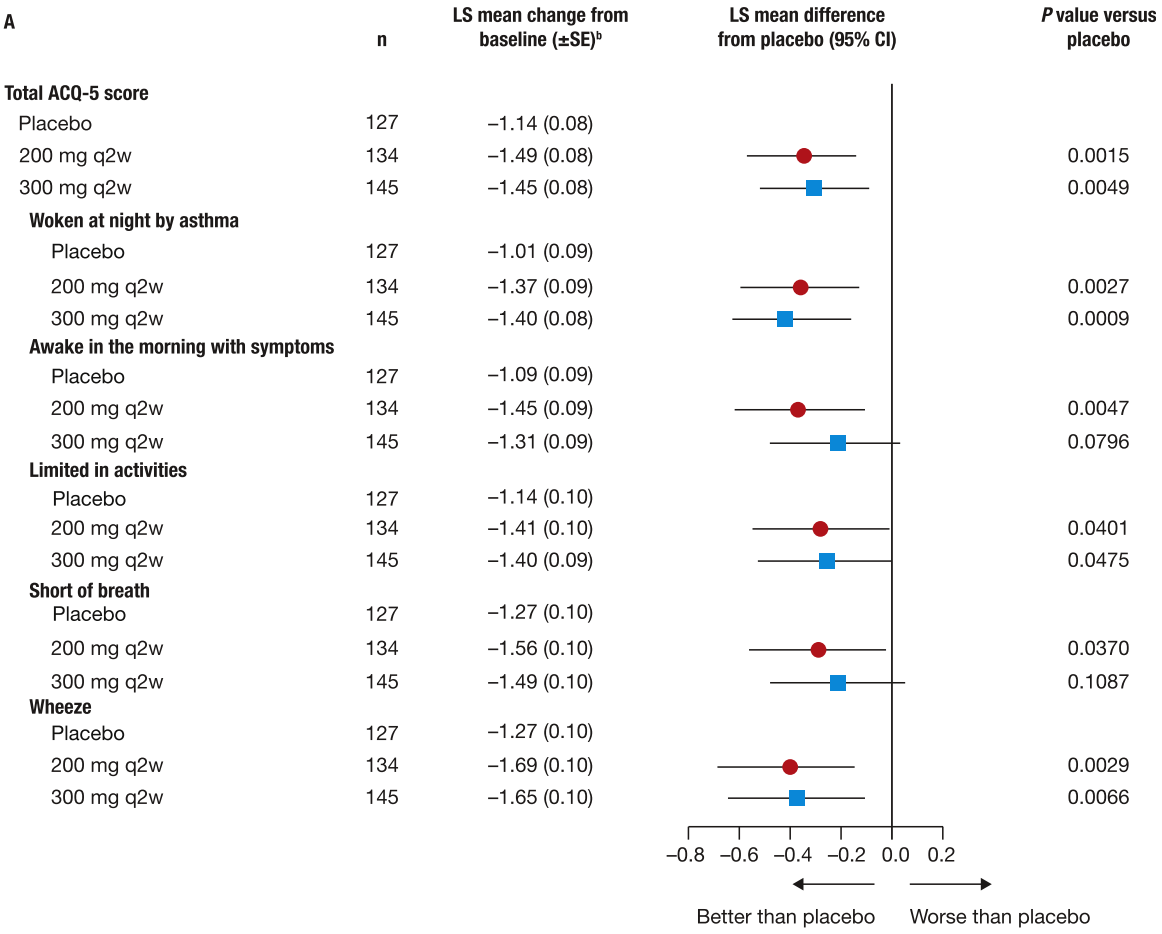
A mixed-effect model with repeated measures was used with changes from baseline scores to week 24 as dependent variables. Factors (fixed effects) for treatment, pooled countries/regions, visit, treatment-by-visit interaction, baseline eosinophil strata, baseline scores, and baseline-by-visit interaction were covariates, with an unstructured correlation matrix. The interactions were obtained using a mixed-effect model with repeated measures with additional terms for the subgroup under consideration, treatment-by-subgroup interaction, and subgroup-by-treatment-by-visit interaction.

Responder rates were defined as the proportions of patients with scores exceeding the threshold of the minimum clinically important difference (MCID). To aid clinical interpretability of the PRO findings, two MCIDs are presented for each questionnaire. The first analysis used an MCID of 0.5 for ACQ-5 and AQLQ[21,22] and 0.35 for AM/PM asthma symptom score. The ACQ-5 and AQLQ thresholds are based on published literature. The AM/PM MCID was derived using Cohen's rule (ie, scores beyond half the standard deviation [SD] are considered clinically meaningful). The second analysis used more conservative MCID estimates; selected MCIDs were 0.6 for ACQ and AQLQ and 0.4 for AM/PM symptoms. Responder rates were compared between treatment groups using multiple logistic regression models for each specific patient subgroup, with response status as the dependent variable and treatment, pooled countries/regions, and baseline score value as covariates.

Table 1
Baseline Characteristics (ITT Population)

		Dupilumab	
	Placebo (n = 158)	200 mg every 2 weeks (n = 150)	300 mg every 2 weeks (n = 157)
Demographic characteristics			
Mean age, years (SD)	49.0 (12.7)	51.0 (13.4)	47.5 (12.4)
Male sex, n (%)	54 (34.2)	54 (36.0)	54 (34.4)
Race, n (%)			
White	119 (75.3)	114 (76.0)	129 (82.2)
Black or African American	9 (5.7)	9 (6.0)	5 (3.2)
Asian	25 (15.8)	25 (16.7)	22 (14.0)
Other	5 (3.2)	2 (1.3)	1 (0.6)
Employment status at baseline			
Full-time, n (%)	79 (52.3)	65 (45.8)	69 (46.9)
Part-time, n (%)	14 (9.3)	16 (11.3)	18 (12.2)
Unemployed, n (%)	46 (30.5)	43 (30.3)	47 (32.0)
Retired, n (%)	12 (7.9)	18 (12.7)	13 (8.8)
Missing, n	7	8	10
Clinical characteristics			
BMI $\geq$ 30 kg/m^2, n (%)	60 (38.0)	65 (43.3)	63 (40.1)
Mean baseline eosinophils/μL (SD)	342.3 (300.0)	361.1 (352.7)	322.9 (245.1)
Time since first asthma diagnosis			
Number	158	149	156
Mean, years (SD)	21.96 (16.46)	23.95 (15.73)	20.21 (13.43)
Mean FEV_1, L (SD)	1.82 (0.55)	1.79 (0.52)	1.85 (0.53)
Mean FEV_1, % predicted (SD)	60.96 (10.72)	61.23 (11.00)	60.76 (10.39)
Number of asthma exacerbations in past year			
Number of patients	158	150	157
Mean (SD)	2.27 (2.25)	1.85 (1.43)	2.37 (2.29)
High-dose ICS+LABA use[a]			
Patients, n	155	144	153
n (%)	77 (49.7)	75 (52.1)	79 (51.6)
Any type 2 related comorbidity,[b] n (%)	108 (70.1)	106 (71.1)	104 (67.5)
Atopic dermatitis	16 (10.4)	10 (6.7)	16 (10.4)
Allergic rhinitis	102 (66.2)	99 (66.4)	94 (61.0)
Chronic rhinosinusitis[c]	18 (11.7)	23 (15.4)	32 (20.8)
Nasal polyposis	18 (11.7)	25 (16.8)	30 (19.5)
Food allergy	17 (11.0)	18 (12.1)	13 (8.4)
PROs			
ACQ-5 total score (0 to 6, where 6 is worst)			
Patients, n	158	150	157
Mean (SD)	2.69 (0.80)	2.73 (0.82)	2.80 (0.83)
AQLQ total score (1 to 7, where 1 is worst)			
Patients, n	156	148	153
Mean (SD)	4.12 (1.10)	4.03 (1.15)	3.91 (1.13)
Mean AM/PM symptom score (0 to 4, where 4 is worst)			
AM score (SD)	1.17 (0.79)	1.24 (0.81)	1.25 (0.78)
PM score (SD)	1.32 (0.81)	1.42 (0.79)	1.47 (0.85)
Smoking history			
Patients, n	158	150	157
Former smoker, n (%)	34 (21.5)	32 (21.3)	36 (22.9)
Pack-year			
Patients, n	34	32	35
Mean (SD)	4.31 (3.13)	4.33 (3.15)	3.88 (3.42)

Abbreviations: ACQ-5, 5-item Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; BMI, body mass index; FEV_1, forced expiratory volume (L) in 1 second; ICS, inhaled corticosteroids; ITT, intention to treat; LABA, long-acting β_2-agonist; PRO, patient-reported outcome; SD, standard deviation.
[a]Use of ICS+LABA was recorded in an electronic diary.
[b]Assessed by clinical history.
[c]Chronic rhinosinusitis included patients with and without nasal polyposis.



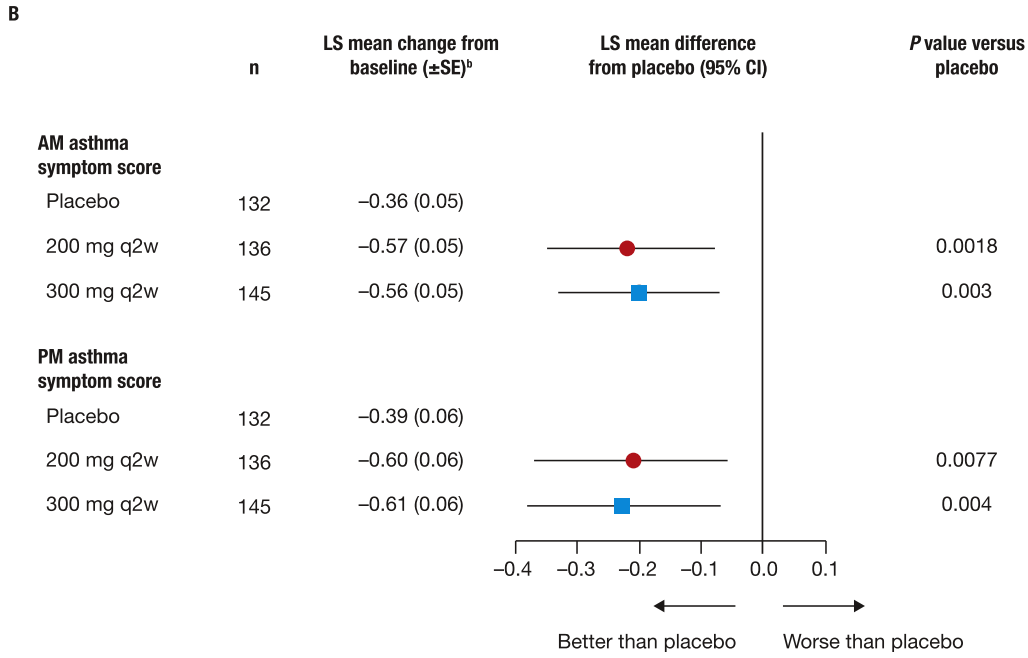


Figure 1. Effect of dupilumab at week 24 on: A: ACQ-5 total score and individual items; B: AM/PM asthma symptom score; and C: AQLQ total score and related domains. ACQ-5, 5-item Asthma Control Questionnaire; AM/PM, patient-reported morning/evening asthma symptoms; AQLQ, Asthma Quality of Life Questionnaire; CI, confidence interval; LS, least squares; q2w, every 2 weeks; SE, standard error.

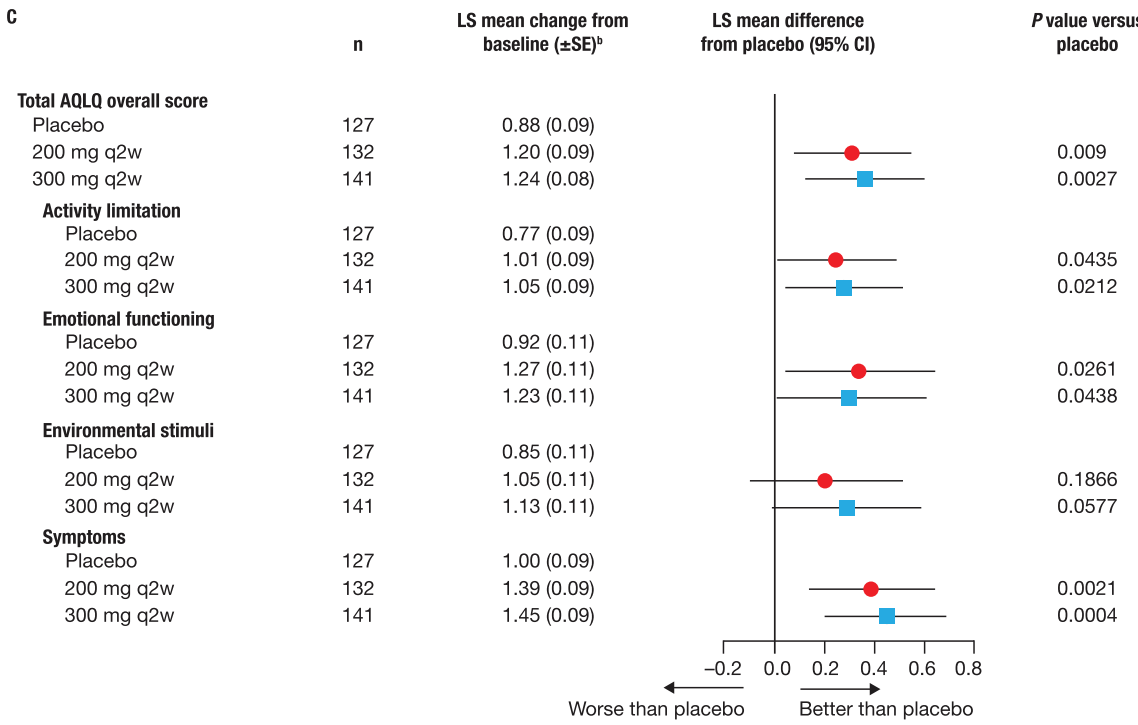


Figure 1. Continued.

Unadjusted rates for productivity loss were derived using total number of days of sick leave during the treatment period (between first dose date and last dose date +14 days) divided by total number of patient-years followed in the treatment period. *P* values were estimated using adjusted analyses; Poisson model with the total number of events onset between first dose date and last dose date +14 days as the response variable; treatment, pooled countries/regions, and number of asthma events prior to the study as covariates; and log-transformed standardized treatment duration as an offset variable.

No type I error adjustments for multiplicity were applied in reporting the results. $P \leq .05$ were considered statistically significant.

Results

Baseline Disease Burden

Seven hundred seventy-six patients were enrolled in the phase 2b trial; this analysis, which examines both predefined and post hoc endpoints, included 465 patients randomized to either the placebo group (n = 158), or to the dupilumab group (200 mg every 2 weeks or 300 mg every 2 weeks; n = 307). Overall, demographics, clinical characteristics, and PRO scores were generally similar across the treatment groups at baseline (Table 1).

PROs

At week 24, both dupilumab regimens (200 and 300 mg every 2 weeks) resulted in significant improvements in ACQ-5 total score (least squares mean difference vs placebo −0.35 and −0.31, respectively; Fig 1A, eFig 1), AM asthma symptom score (−0.22 and −0.20; Fig 1B, eFig 2), PM asthma symptom score (−0.21 and −0.23; Fig 1B, eFig 3), and AQLQ total score (0.32 and 0.36; Fig 1C, eFig 4) (all $P < .01$).

Dupilumab 200 mg every 2 weeks significantly improved each individual item of the ACQ-5 vs placebo, whereas dupilumab 300 mg every 2 weeks significantly improved 3 of the 5 items (Fig 1A). With the exception of "environmental stimuli," both doses

Table 2
Proportions of Responders at Week 24[a]

			Dupilumab	
		Placebo (n = 158)	200 mg q2w (n = 150)	300 mg q2w (n = 157)
Proportion of patients meeting or exceeding the MCID[b]	ACQ-5 total score	61.4	76.7[e]	72.6[d]
	AM asthma symptom score	34.2	48.7[d]	54.1[e]
	PM asthma symptom score	34.2	52.7[e]	53.5[e]
	AQLQ total score	51.3	64.0[d]	65.0[d]
Proportion of patients meeting or exceeding the MCID[c]	ACQ-5 total score	60.1	76.7[e]	72.6[d]
	AM asthma symptom score	31.0	46.7[e]	51.0[e]
	PM asthma symptom score	31.0	50.0[e]	51.6[e]
	AQLQ total score	47.5	60.7[d]	63.1[e]

Abbreviations: ACQ-5, 5-item Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; MCID, minimal clinically important difference; q2w, every 2 weeks.
[a]Patients who met the corresponding criterion are considered as responders. Patients who did not meet the criterion or had missing value are considered as non-responders. P-values are derived from a logistic regression model with treatment, region (Asia, Latin America, East Europe, or Western Countries), baseline eosinophil stratum, and baseline score as covariates.
[b]For this analysis, MCIDs are 0.5 for ACQ-5 and AQLQ, and 0.35 for AM/PM asthma symptom scores.
[c]For this analysis, MCIDs are 0.6 for ACQ-5 and AQLQ, and 0.40 for AM/PM asthma symptom scores.
[d]$P < 0.05$ vs placebo.
[e]$P \leq 0.01$ vs placebo.

Table 3
Effect of Dupilumab on Productivity Loss

	Placebo (n = 158)	Dupilumab	
		200 mg every 2 weeks (n = 150)	300 mg every 2 weeks (n = 157)
Total number of severe exacerbation events	75	20	23
Total number of patients employed ITT	93 (58.9%)	81 (54.0%)	87 (55.4%)
Number of employed patients with ≥1 day of sick leave (work) due to severe exacerbation event			
Yes	11 (11.8%)	4 (4.9%)	5 (5.7%)
No	82 (88.2%)	77 (95.1%)	82 (94.3%)
Total days of sick leave (work) due to severe exacerbation event	92	22	24
Total days of sick leave (work) due to severe exacerbation event/per severe exacerbations	1.23	1.10	1.04
Total patient-years followed	41.1	35.9	38.9
Unadjusted annualized days of sick leave due to severe exacerbation event (days/year)[a]	2.238	0.613[b]	0.617[b]

Abbreviation: ITT, intention to treat.
[a]The total number of events during the treatment period (between first dose date and last dose date + 14 days) divided by the total number of patient-years followed in the treatment period.
[b]$P < .0001$ with adjusted analyses; Poisson model with the total number of events onset between first dose date and last dose date + 14 days as the response variable, treatment, pooled countries/regions, and number of asthma events because of the study as covariates, and log-transformed standardized (in years) treatment duration as an offset variable.

of dupilumab significantly improved all AQLQ domains compared with placebo (Fig 1C).

PRO MCID Analysis

LS mean change from baseline was higher than the MCID for all treatment cohorts on the ACQ-5 total score, AM and PM asthma symptom score, and total AQLQ overall score (Fig 1). The proportion of patients meeting or exceeding the respective MCIDs for each of the PROs assessed are shown in Table 2. Responder rates were greater for dupilumab-treated patients compared to placebo on the ACQ-5, the AM and PM asthma symptom scores and the AQLQ ($P < .05$ for the 200 mg q2w and 300 mg q2w dose vs placebo for all tests).

Productivity Loss

Employment status at baseline (either full- or part-time) was comparable across treatment groups (Table 1). Assessment of productivity loss related to severe exacerbation events revealed a total of 22 and 24 days of sick leave in the dupilumab 200 and 300 mg every 2 weeks groups, respectively, compared with 92 days with placebo ($P < .001$). These translate to unadjusted annualized rates of sick leave because of severe exacerbations of 0.6 days per patient receiving either dose of dupilumab regimen vs 2.2 days for placebo-treated patients ($P < .0001$ for either dupilumab dose; Table 3), which amounts to a 73% and 72% reduction in loss of productivity for the dupilumab 200 and 300 mg every 2 weeks regimens vs placebo, respectively.

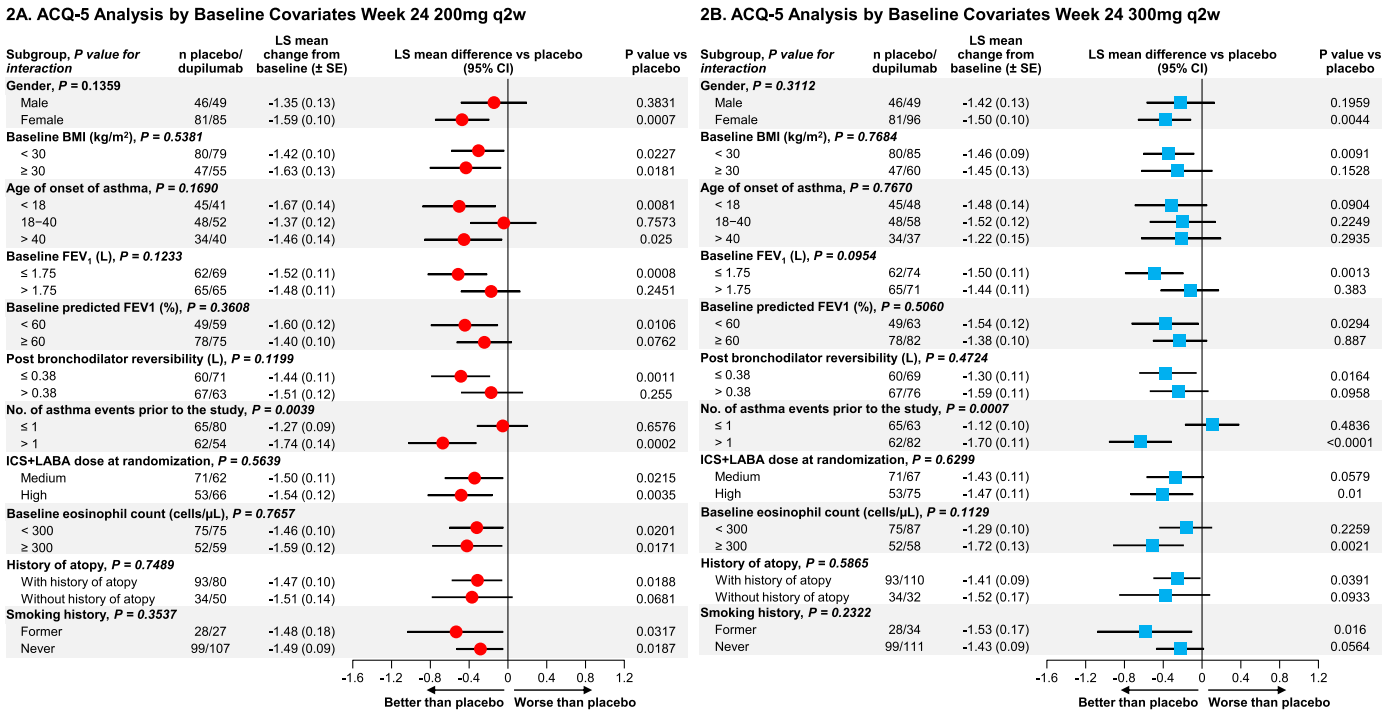


Figure 2. ACQ-5, analysis by baseline covariates. A: ACQ-5 analysis by baseline covariates, Week 24 200 mg every 2 weeks; B: ACQ-5 analysis by baseline covariates, Week 24 300 mg every 2 weeks. ACQ-5, 5-item Asthma Control Questionnaire; BMI, body mass index; FEV_1, forced expiratory volume (L) in 1 second; ICS; inhaled corticosteroids; LABA, long-acting β_2-agonist; q2w, every 2 weeks; SE, standard error.

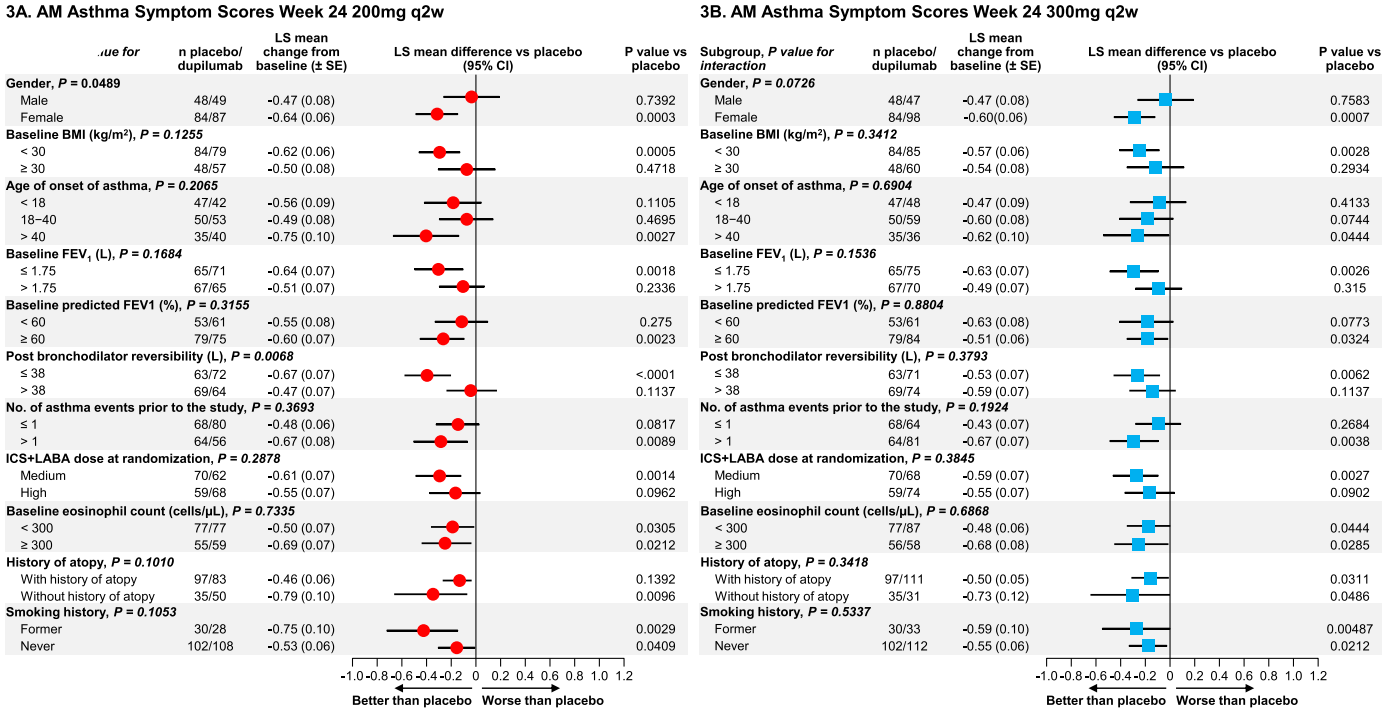


Figure 3. Morning asthma symptom scores, analysis by baseline covariates. A: Morning asthma symptom scores, Week 24 200 mg every 2 weeks; B: Morning asthma symptom scores, week 24 300 mg every 2 weeks.

PROs in Patient Subgroups

The effect of dupilumab on ACQ-5 total score, AM/PM asthma symptom scores, and AQLQ total score for each of the subgroups examined is shown in Figures 2 through 5. Significant improvements from baseline to week 24 were observed in many of the subgroups for both dupilumab regimens compared with placebo.

Significant treatment-by-subgroup interactions were seen for the following baseline characteristics: sex, number of exacerbations in the previous year, FEV_1, eosinophil count, and postbronchodilator reversibility (Fig. 2-5). The magnitude of the treatment effect varied by subgroup but was consistently favored by dupilumab treatment. ICS/LABA dose level at randomization, history of atopy, and smoking history had nonsignificant treatment-by-subgroup interactions for

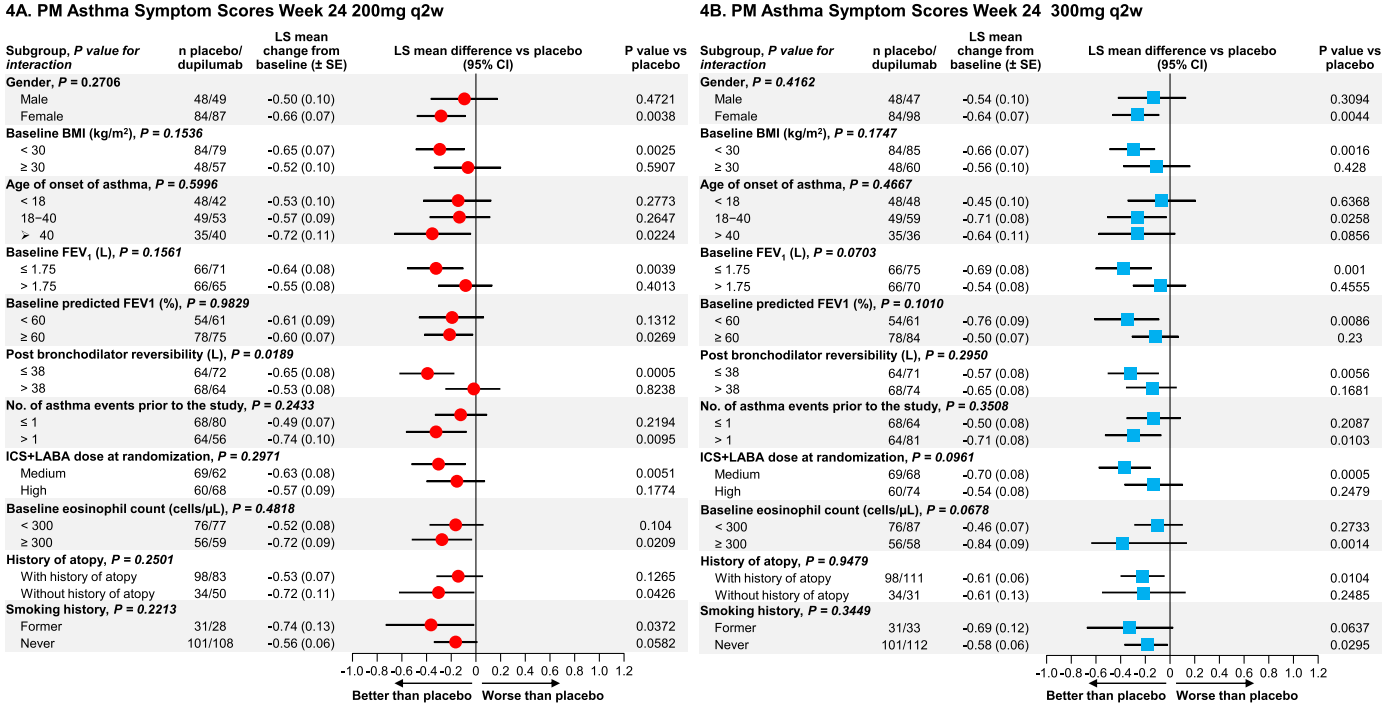


Figure 4. Evening asthma symptom scores, analysis by baseline covariates. A: Evening asthma symptom scores, week 24 200 mg every 2 weeks; B: Evening asthma symptom scores, week 24 300 mg every 2 weeks.

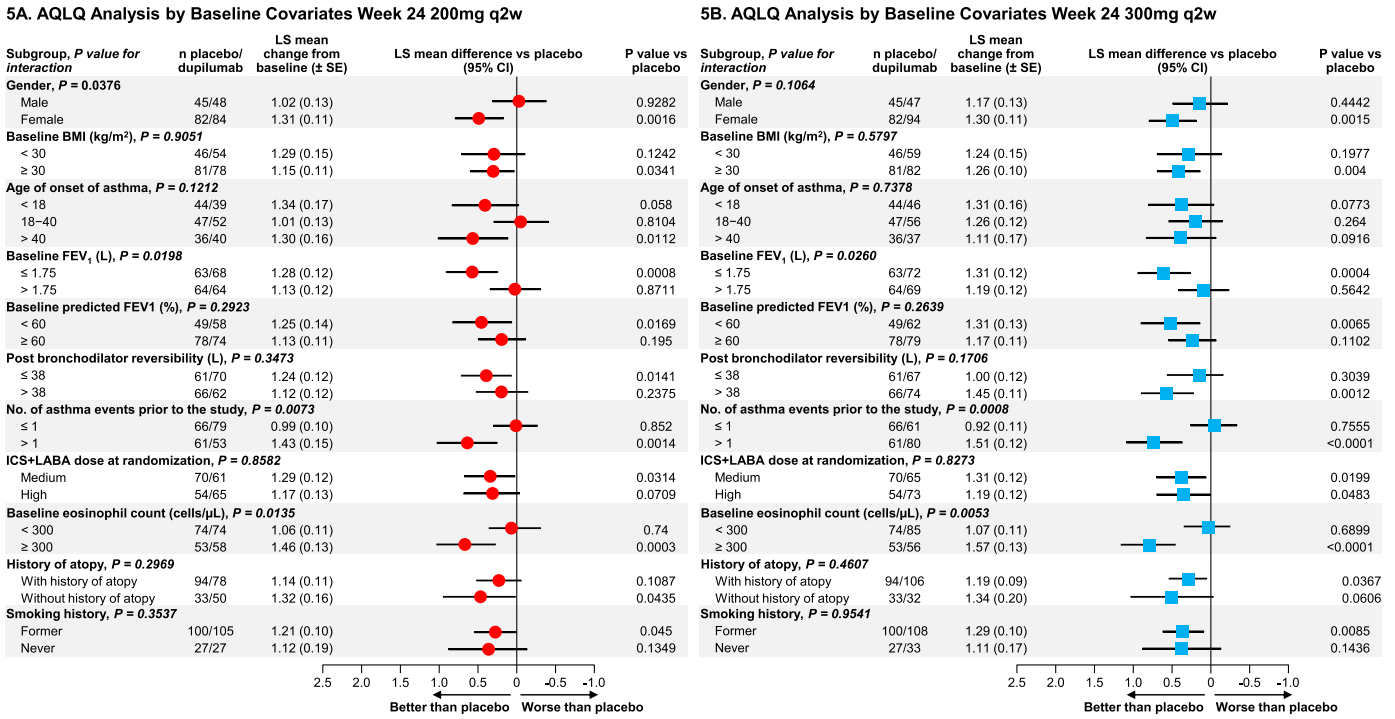


Figure 5. AQLQ, analysis by baseline covariates. A: AQLQ analysis by baseline covariates, week 24 200 mg every 2 weeks; B: AQLQ analysis by baseline covariates, week 24 300 mg every 2 weeks. ACQ-5, 5-item Asthma Control Questionnaire; BMI, body mass index; FEV_1, forced expiratory volume (L) in 1 second; ICS; inhaled corticosteroids; LABA, long-acting β_2-agonist; q2w, every 2 weeks; SE, standard error.

ACQ-5, AQLQ, and AM/PM asthma symptom scores. Patients with baseline characteristics usually associated with more severe asthma, including history of more than 1 exacerbation in the prior year or baseline FEV_1 of at least 1.75L, showed a better response to both dupilumab regimens vs placebo in ACQ-5, AM/PM asthma symptom scores, and AQLQ score ($P < .05$ for all) (Fig. 2-5).

Safety

As reported in detail in the primary manuscript, rates of treatment-emergent adverse events were similar across treatment groups, as were rates of serious treatment-emergent adverse events.[12] Injection-site reactions occurred more often in active treatment groups, and they were dose-related (20% and 26% for dupilumab 200 and 300 mg every 2 weeks, respectively, vs 13% for placebo).[12]

Discussion

Despite receiving medium-to-high-dose ICS+LABA therapy, patients with uncontrolled persistent asthma are characterized by a multidimensional burden of disease, including recurrent exacerbations, reduced lung function, and reduced QoL. In addition, patients with uncontrolled persistent asthma often suffer from other allergic comorbidities such as chronic sinusitis and AD, further complicating the treatment of these patients.

In this pivotal phase 2b trial, dupilumab every 2 weeks dose regimens significantly improved lung function, severe exacerbation rates, and patient-centered outcomes (asthma symptoms, asthma control, and QoL) relative to placebo when added to medium-to-high-dose ICS+LABA therapy in adults with uncontrolled persistent asthma.[12] Significant improvements in all of these endpoints were observed in both the overall population and patients with eosinophil counts of at least 300 cells/μL. Lung function and exacerbation rates were also significantly improved in patients with eosinophil counts less than 300 cells/μL.[12]

In this post hoc analysis, we demonstrated that dupilumab significantly improved asthma control, asthma symptoms, QoL, and workplace productivity in the overall population, as well as in a majority of subgroups evaluated; results from the MCID analysis showed that the improvements were clinically meaningful, and consistent with analysis of previously reported mean changes in PROs, where a greater proportion of dupilumab-treated patients benefited from treatment compared to placebo.

Of particular note, significant improvements were observed in patients with a history of more than 1 exacerbation at baseline, or FEV_1 of at least 1.75 L (both dupilumab every 2 weeks dose regimens) at baseline, but not patients with 1 exacerbation or baseline FEV_1 greater than 1.75 L. Although a consistent significant improvement was observed with baseline eosinophil count of at least 300 cells/μL for dupilumab vs placebo, patients with less than 300 cells/μL only observed an improvement in ACQ-5 with 200 mg every 2 weeks dupilumab vs placebo. These observations suggest that dupilumab may have a greater effect on PROs in patients with more severe asthma and a higher type 2 inflammatory signal at baseline.

Additionally, despite the small sample size (which is an important limitation of this analysis), a significant improvement was observed with dupilumab (200 and 300 mg every 2 weeks) on patient-reported AM asthma symptoms in patient subgroups with eosinophils of at least 300 cells/μL and less than 300 cells/μL; this is a unique finding compared with those of other studies investigating the use of anti-IL-5 in this patient population. These data are consistent with the overall benefit of dupilumab observed in patients with eosinophils at least 300 cells/μL and less than 300 cells/μL.[12] Because of the small number of patients with less than 150 eosinophils/μL (n = 30 on the 200 mg every 2 weeks and n = 28 on the 300 mg every 2 weeks dupilumab arms), these data were not presented, because no meaningful comparisons could be drawn between the dupilumab and placebo groups. Larger, ongoing phase 3 studies will be needed to confirm these preliminary findings.

Another important finding from this post-hoc analysis is the effect of dupilumab on work productivity improvement. To our knowledge,

this is the only double-blind, randomized controlled trial that demonstrates the effects of a biologic (dupilumab) on workplace productivity in patients with uncontrolled persistent asthma. Furthermore, no evidence has been seen of significant improvement in productivity in patients with uncontrolled persistent asthma treated with biologics targeting IL-5.[23]

In conclusion, patients with uncontrolled persistent asthma who do not respond to currently available therapies are in need of additional treatment options. This analysis demonstrates that dupilumab every 2 weeks regimens provide significant and clinically meaningful improvements in asthma control, asthma symptoms, and QoL and significantly improve workplace productivity. Furthermore, improvements in these PROs were observed across a range of asthma phenotypes determined by baseline clinical characteristics.

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Supplementary Data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.anai.2018.08.005.

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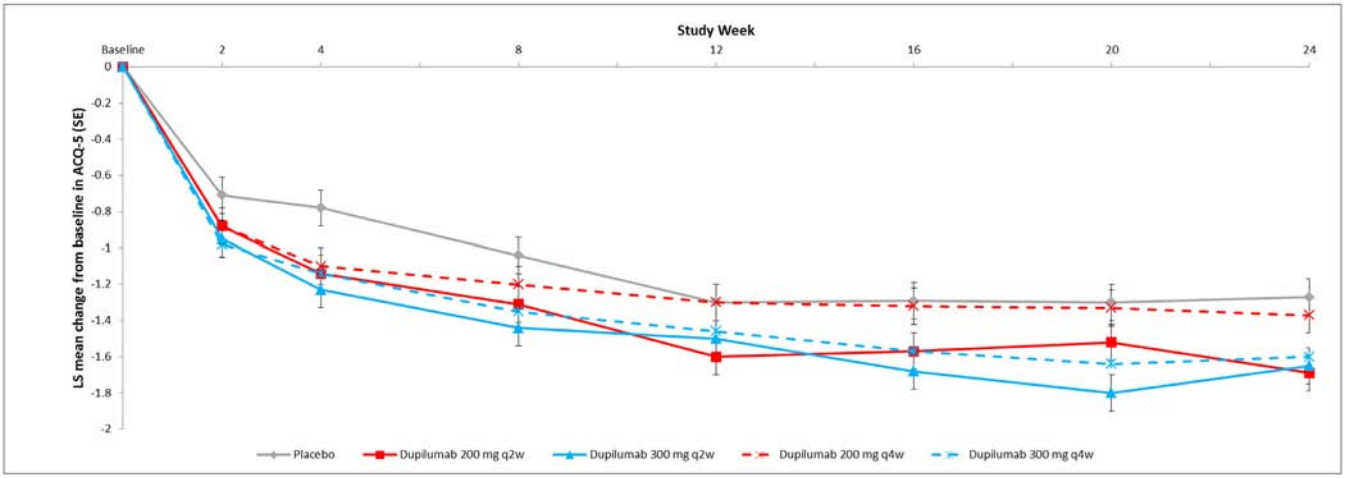
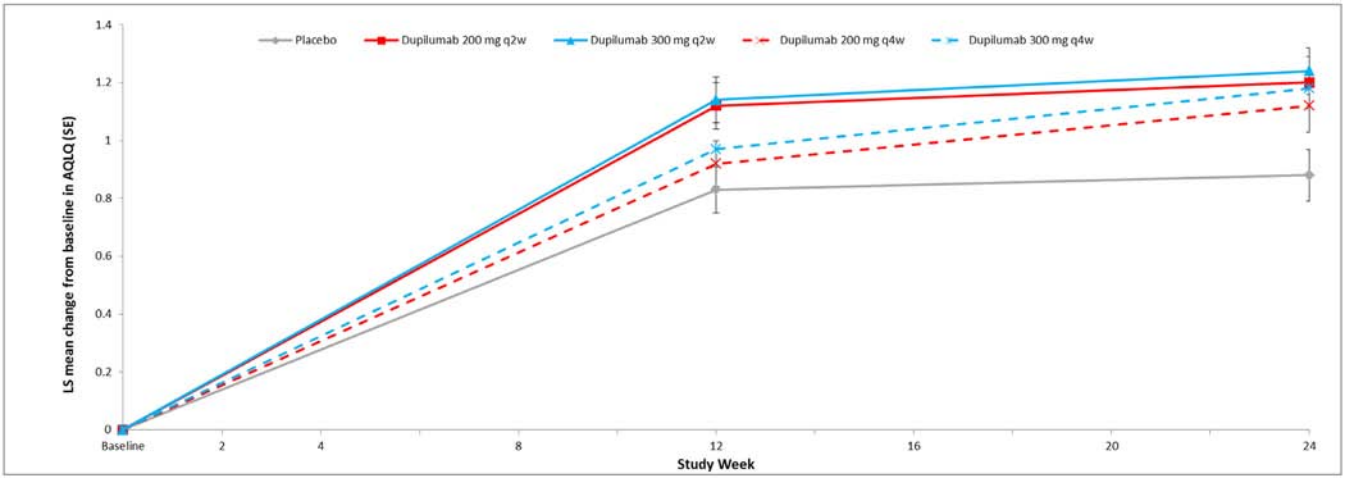
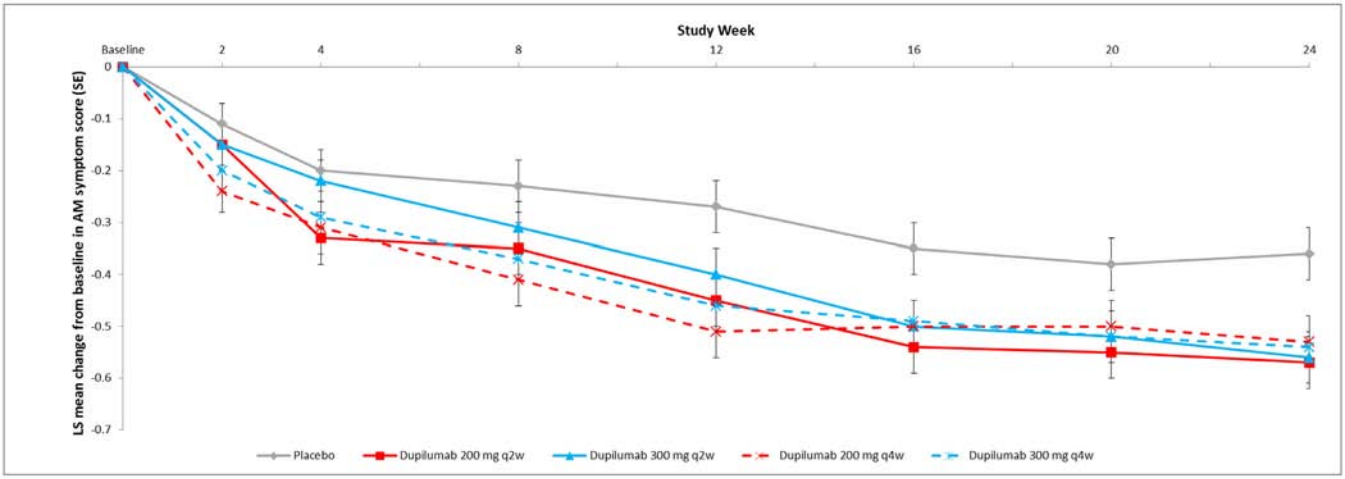


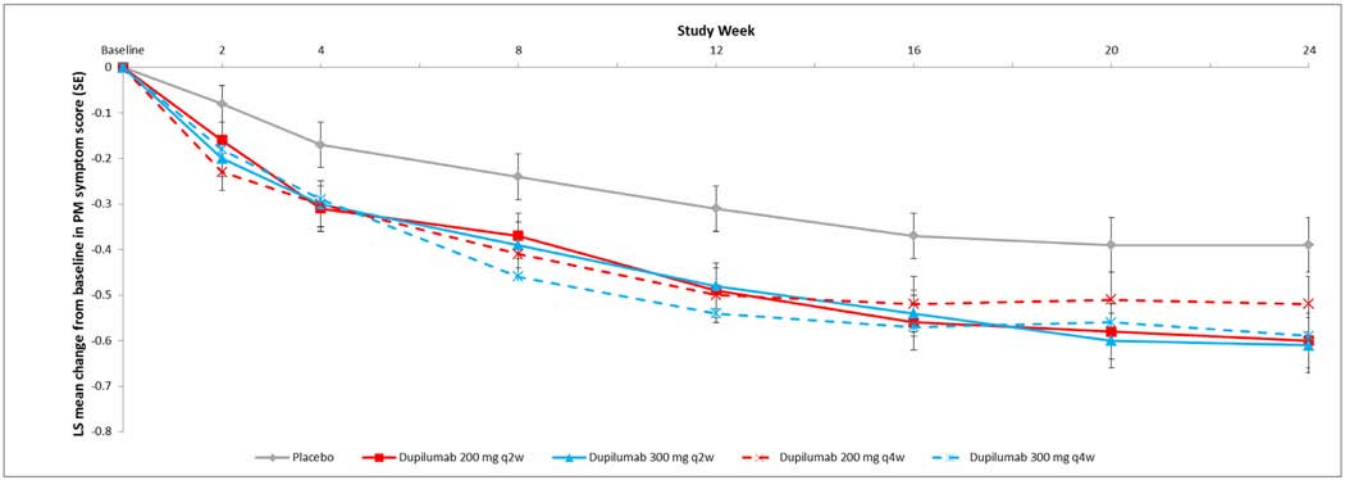
eFigure 1. Change from baseline in ACQ-5 over time in the overall population.



eFigure 2. Change from baseline in AQLQ over time in the overall population.



eFigure 3. Change from baseline in morning asthma symptom scores over time in the overall population.



eFigure 4. Change from baseline in evening asthma symptom scores over time in the overall population.