Efficacy and safety of dupilumab in perennial allergic rhinitis and comorbid asthma

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Background: Dupilumab, an anti–IL-4 receptor α mAb, inhibits IL-4/IL-13 signaling, key drivers of type 2/T_H2 immune diseases (eg, atopic/allergic disease). In a pivotal, phase 2b study (NCT01854047), dupilumab reduced severe exacerbations, improved lung function and quality of life, and was generally well tolerated in patients with uncontrolled persistent asthma despite using medium-to-high-dose inhaled corticosteroids plus long-acting β2-agonists.

Objective: To examine dupilumab's effect on the 22-item Sino-Nasal Outcome Test (SNOT-22) total score and its allergic rhinitis (AR)-associated items in asthma patients with comorbid perennial allergic rhinitis (PAR).

Methods: A *post hoc* analysis reporting data from the phase 2b study for the 200 and 300 mg every 2 week (q2w) doses under investigation in phase 3 (NCT02414854) was carried out. PAR was defined at study entry as a specific response to typical perennial antigens (IgE ≥0.35 Ku/L).

Results: Overall, 241 (61%) patients had PAR. In asthma patients with PAR, dupilumab 300 mg q2w versus placebo significantly improved SNOT-22 total score (least squares mean difference, −5.98; 95% CI, −10.45 to −1.51; $P = .009$) and all 4 AR-associated symptoms evaluated (nasal blockage, −0.60; 95% CI, −0.96 to −0.25; runny nose, −0.67; 95% CI, −1.04 to −0.31; sneezing, −0.55; 95% CI, −0.89 to −0.21; postnasal discharge, −0.49; 95% CI, −0.83 to −0.16; all $P < .01$). Dupilumab 200 mg q2w demonstrated numerical, but not statistically significant, decreases in SNOT-22 total score (−1.82; 95% CI, −6.46 to 2.83; $P = .443$ vs placebo) and in each AR-associated symptom. In patients without PAR, no differences were observed for these measures versus placebo.

Conclusions: Dupilumab 300 mg q2w significantly improved AR-associated nasal symptoms in patients with uncontrolled persistent asthma and comorbid PAR. (J Allergy Clin Immunol 2018;142:171-7.)

Key words: *Asthma, allergic rhinitis, perennial allergic rhinitis, comorbidity, dupilumab, nasal symptoms*

Patients with uncontrolled, persistent asthma often have significantly impaired quality of life, together with a higher risk of disease exacerbation, asthma-induced hospitalization, and death.[1-3] These patients also have a high prevalence of comorbid type 2 immune diseases, of which allergic rhinitis (AR) is the most prevalent.[4] Other prevalent type 2 immune diseases that are comorbid with asthma include nasal polyposis (NP), sinusitis, atopic dermatitis (AD), and food allergy.[5] AR coexists in approximately 75% to 80% of all patients with asthma, and in up to 100% of those with atopic or allergic asthma.[6-8] Depending on both the geographical location and the allergen involved, AR can occur seasonally or perennially.[6,9] Seasonal AR is most commonly caused by pollens, whereas perennial AR (PAR) is typically the result of sensitization and exposure to indoor allergens such as dust mites, mold (if not seasonal), and animal dander.[6] Of the 2, PAR is generally considered more difficult to treat and, despite best care, patients often remain symptomatic.[10] Patients with PAR also have an increased risk of developing asthma, and epidemiological evidence suggests that comorbid AR is a marker for more difficult-to-control or severe asthma.[8,11-13] The cooccurrence of the 2 conditions is also associated with increased asthma-related hospitalizations, impaired quality of life, and higher total annual medical costs.[8,14-16] The type 2 inflammation that occurs in AR and asthma is very similar. The concept of a "united airways disease" or "1-airway, 1-disease" hypothesis has gained much credence, and is supported by epidemiological, pathophysiological, and clinical studies.[17-19] However, despite their similarities, AR and asthma are separate entities and management should be

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Abbreviations used
AD: Atopic dermatitis
AR: Allergic rhinitis
CRS: Chronic rhinosinusitis
CRSwNP: Chronic rhinosinusitis with nasal polyposis
ICS: Inhaled corticosteroid
LABA: Long-acting β2-agonist
NP: Nasal polyposis
PAR: Perennial allergic rhinitis
q2w: Every 2 weeks
SNOT-22: 22-item Sino-Nasal Outcome Test
TEAE: Treatment-emergent adverse event

symptom-focused, particularly because symptoms may worsen when the 2 conditions coexist. Nevertheless, the possibility that a single agent might be used to treat both diseases is an exciting prospect, and one that is consistent with a 1-airway hypothesis.

The type 2 cytokines, IL-4, IL-5, and IL-13, play an important role in the pathogenesis of asthma and other type 2/IgE-mediated immune diseases.[20-23] In recent years, the development of mAb-based therapies against these targets has represented a significant advance in the treatment for these diseases.[23]

Dupilumab is a fully human mAb that targets the IL-4 receptor alpha (IL-4Rα) subunit, and thus inhibits the signaling of both IL-4 and IL-13 (because IL-13 shares the IL-4α chain), each of which is a key driver of type 2 immune diseases (eg, atopic/allergic disease). In a recent pivotal phase 2b dose-ranging study (ClinicalTrials.gov identifier NCT01854047), dupilumab reduced the rate of severe exacerbations, improved lung function and quality of life, and was generally well tolerated in patients with uncontrolled persistent asthma despite using medium-to-high-dose inhaled corticosteroids (ICSs) and long-acting β2-agonists (LABAs). These findings were observed both for the overall population and for subpopulations defined by high or low (≥300 or <300 cells/μL, respectively) baseline eosinophil count.[5]

Dupilumab is approved by the US Food and Drug Administration for the treatment of adult patients with moderate-to-severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable, and can be used with or without topical corticosteroids. Dupilumab is also approved by the European Union European Medicines Agency for use in adults with moderate-to-severe AD who are candidates for systemic therapy. Dupilumab is under investigation for the treatment of asthma, chronic rhinosinusitis (CRS) with nasal polyposis (CRSwNP), and eosinophilic esophagitis.[5,24,25] Therapy with a selective immunomodulator such as dupilumab would allow for systemic treatment that potentially could cover multiple atopic/allergic conditions that often occur concomitantly.

In this subanalysis of the pivotal phase 2b study, we examined the efficacy and safety of dupilumab in the subgroup of asthma patients with comorbid PAR.

METHODS

Study design and treatment

Study NCT01854047 was a randomized, double-blind, placebo-controlled, parallel group, pivotal phase 2b clinical trial conducted at 174 study sites worldwide that has been reported separately.[5] This *post hoc* analysis examines the subgroup of patients with comorbid PAR.

PAR was defined as a positive IgE antibody response of 0.35 Ku/L or more at study entry to any of the following antigens, each of which can cause PAR: *Aspergillus fumigatus*, cat dander, dust mite (*Dermatophagoides farinae*; *D pteronyssinus)*, dog dander, German cockroach, or Oriental cockroach. This threshold has been used by other researchers, because it provides an appropriate conservative estimate of allergic sensitization for subjects.[26]

As described in the primary article,[5] all patients were required to be on medium-to-high-dose ICS and a LABA. Patients were randomized in a 1:1:1:1:1 ratio to receive either 24 weeks of add-on therapy with subcutaneous dupilumab 200 or 300 mg every 2 weeks (q2w) or every 4 weeks, or placebo. In this subanalysis, data only for the intent-to-treat population who received placebo or the dupilumab doses of 200 or 300 mg q2w are reported; these doses are currently under investigation in a phase 3 study (NCT02414854).

Concomitant medications (including antihistamines and intranasal corticosteroids on a stable dose ≥30 days before visit 1) were permitted during the study with the exception of systemic (oral or injectable) corticosteroids, except if used to treat an asthma exacerbation; methylxanthines (eg, theophylline and aminophyllines); lipoxygenase inhibitors (eg, zileuton); chromones; anti-IgE therapy (eg, omalizumab); biological therapy; methotrexate; initiation of allergen immunotherapy within 3 months before visit 1; and intravenous immunoglobulin therapy.

Study outcomes and procedures

Primary and secondary end points in the overall population were described and reported previously.[5]

In this analysis, the effect of dupilumab on rhinitis-associated nasal symptoms was measured using the 22-item Sino-Nasal Outcome Test (SNOT-22). SNOT-22 is a validated patient-reported outcome tool used to delineate the presence and severity of sinonasal disorders and the impact of these on health-related quality of life; it considers both the severity and frequency of 22 individual symptoms.[26] Individual items are scored on a 6-point scale, with a higher score indicative of greater impairment (ie, 0 = "no problem" and 5 = "problem as bad as it can be"). The total score is the composite of each of the 22 items and is indicative of overall sinonasal health (range, 0-110). Among the individual items of SNOT-22, the following items are typically associated with AR: postnasal discharge, nasal blockage, runny nose, and sneezing.[12]

Outcome measures were examined in the subgroups of patients with or without PAR and included the change from baseline to week 24 in the SNOT-22 total score and each of the individual items typically associated with AR. Other end points reported here are the effect of dupilumab on the change from baseline to week 24 in FEV_1 (L), and the annualized rate of severe asthma exacerbation events during the 24-week treatment period. A severe exacerbation event was defined as deterioration in asthma that required the use of systemic corticosteroids for at least 3 days or asthma-related hospital admission or emergency department visit that required systemic corticosteroids.

Patients with a history of, or ongoing, NP were excluded from the analysis to avoid any possible confounding effects because the SNOT-22 tool is validated in patients with CRS[26] and the underlying pathology for NP is not related to PAR.

Statistical analysis

In this *post hoc* analysis, no control for type I error was applied. Treatment effect *P* values of .05 or less were considered to be statistically significant.

Continuous end-point variables (SNOT-22 and FEV_1 values at week 24 of treatment) were analyzed with a mixed-effect model with a repeated-measures approach. The model included change from baseline to week 24 as response variables, and factors (fixed effects) for treatment, baseline blood eosinophil strata, pooled countries/regions, visit, treatment-by-visit interaction, baseline value, and baseline-by-visit interaction. Missing data were not imputed.

Systemic corticosteroids (oral or injectable) were permitted only for the treatment of asthma exacerbations. In such cases, any FEV_1 or SNOT-22 measurements collected during their use were excluded from data analysis to reduce the confounding effect of systemic corticosteroids.

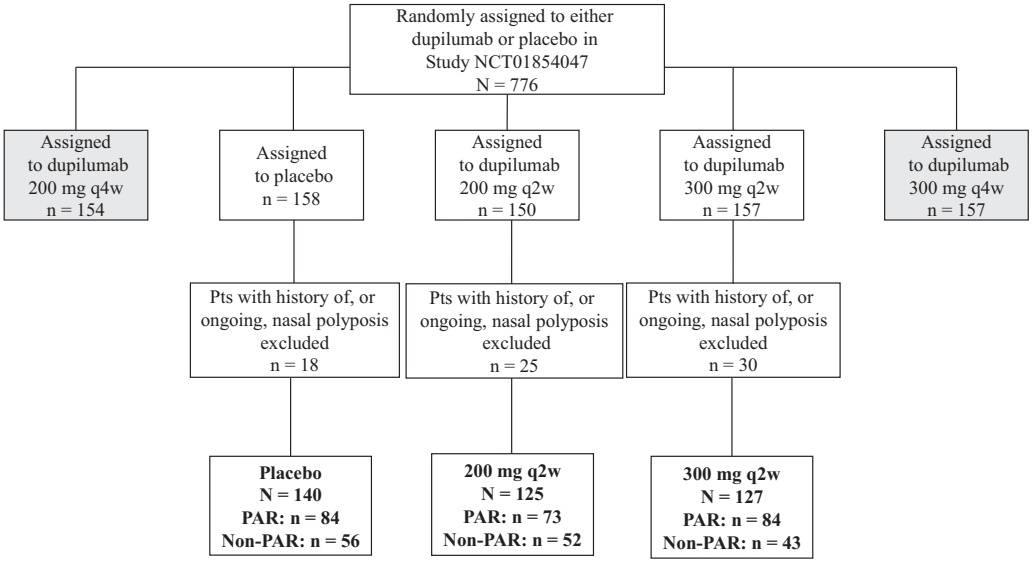

FIG 1. CONSORT diagram. Intention-to-treat patients from study NCT01854047 who received dupilumab 200 or 300 mg q2w or placebo by PAR/non-PAR status (patients receiving dupilumab 200 or 300 mg q4w [shaded] are not reported). *CONSORT*, Consolidated Standards of Reporting Trials; *q4w*, every 4 weeks; *Pts*, patients.

The annualized rate of severe asthma exacerbation events occurring during the 24-week treatment period was derived using a negative binomial regression model with the total number of events onset between the first dose and last dose date plus 14 days as the response variable. Treatment group, baseline eosinophil strata, pooled countries or regions, and number of asthma events in the year before the study were included as covariates, and log-transformed treatment duration as the offset variable.

Treatment-emergent adverse events (TEAEs) were studied in the safety population, defined as randomized patients who received 1 or more dose or part of a dose of the investigational medicinal product analyzed according to the actual treatment received.

SAS version 9.2 (SAS Institute Inc, Cary, NC) was used for all analyses.

RESULTS

Baseline demographic and clinical characteristics

Between June 2013 and June 2014, 776 patients were randomly assigned to 1 of the 5 arms of study NCT01854047. Of these, 465 patients were assigned to either of the q2w dupilumab regimens (200 mg, n = 150; 300 mg, n = 157) or to placebo (n = 158) (Fig 1). A total of 73 patients with either a history of, or ongoing, NP were excluded from the analysis to preclude any confounding effects due to overlapping symptoms.

On the basis of positive IgE antibody responses to the common PAR allergens described above, 241 (61.5%) patients were identified as having PAR. The resulting analysis population comprised 392 patients (241 patients with PAR and 151 patients without PAR; Fig 1).

Baseline characteristics of patients with and without PAR are presented in Table I. Overall, most patients with asthma in the intent-to-treat population were women (68%); however, a higher percentage of male patients had comorbid PAR. A numerically higher proportion of Asian patients and black or African American patients was observed in the PAR subgroup (vs non-PAR), although numbers per subgroup were small. Comorbid history of AR was higher in the PAR subgroup (vs non-PAR). Patients with PAR had received their asthma diagnosis relatively later than patients without PAR. SNOT-22 total score was numerically lower in patients with PAR than in those without PAR, likely due to SNOT-22 total score including items unrelated to AR. No other meaningful differences between the 2 groups of patients were noted. Baseline characteristics for the overall population (including the every 4-week regimens) have been reported previously.[5]

Efficacy

In patients with PAR, dupilumab 300 mg q2w significantly improved SNOT-22 total score relative to placebo at week 24 (least squares mean difference, −5.98; 95% CI, −10.45 to −1.51; $P = .0088$ vs placebo; Fig 2; see Table E1 in this article's Online Repository at www.jacionline.org). A numerically smaller decrease in SNOT-22 total score was observed with the lower dupilumab dose of 200 mg q2w than with placebo, but it did not reach statistical significance ($P = .4426$). In patients without PAR, no differences in SNOT-22 total score were observed relative to placebo for either dupilumab q2w regimen.

In patients with PAR, dupilumab 300 mg q2w also significantly improved scores for each of the 4 SNOT-22 items commonly associated with AR compared with placebo (all $P < .01$; Fig 2; Table E1). By week 24, the improvement in score relative to placebo was −0.60 (95% CI, −0.96 to −0.25) (48.5% reduction from baseline) for nasal blockage, −0.67 (95% CI, −1.04 to −0.31) (57.1% reduction from baseline) for runny nose, −0.55 (95% CI, −0.89 to −0.21) (46.5% reduction from baseline) for sneezing, and −0.49 (95% CI, −0.83 to −0.16) (52.2% reduction from baseline) for postnasal discharge (Fig 2; Table E1). No significant improvements in the scores for each of the individual items were observed in patients who received the dupilumab 200 mg q2w regimen. In patients without PAR, no differences relative to placebo were observed for each of the individual symptoms commonly associated with AR.

With regard to lung function, dupilumab 300 mg q2w increased FEV_1 from baseline to week 24 of treatment by 12.9% in the subgroup of patients with PAR, resulting in a significant mean

TABLE I. Baseline characteristics by PAR subgroup

Characteristic	Patients with PAR (n = 241)			Patients without PAR (n = 151)		
		Dupilumab			Dupilumab	
	Placebo (n = 84)	200 mg q2w (n = 73)	300 mg q2w (n = 84)	Placebo (n = 56)	200 mg q2w (n = 52)	300 mg q2w (n = 43)
Age (y), mean ± SD	47.9 ± 12.9	46.6 ± 14.6	45.0 ± 13.2	51.9 ± 13.2	55.6 ± 10.5	48.8 ± 11.5
Sex, n (%)						
Male	34 (40.5)	24 (32.9)	34 (40.5)	12 (21.4)	14 (26.9)	8 (18.6)
Female	50 (59.5)	49 (67.1)	50 (59.5)	44 (78.6)	38 (73.1)	35 (81.4)
Race, n (%)						
White	55 (65.5)	48 (65.8)	68 (81.0)	47 (83.9)	45 (86.5)	37 (86.0)
Black or African American	8 (9.5)	6 (8.2)	5 (6.0)	1 (1.8)	2 (3.8)	0
Asian	18 (21.4)	17 (23.3)	10 (11.9)	7 (12.5)	5 (9.6)	6 (14.0)
Other	3 (3.6)	2 (2.7)	1 (1.2)	1 (1.8)	0	0
Body mass index (kg/m^2), mean ± SD	29.25 ± 6.87	29.54 ± 5.74	30.01 ± 6.55	29.43 ± 5.92	30.91 ± 6.39	29.43 ± 6.78
Body mass index ≥30 kg/m^2, n (%)	32 (38.1)	30 (41.1)	38 (45.2)	22 (39.3)	27 (51.9)	18 (41.9)
Baseline eosinophil count (cells/μL), mean ± SD	0.29 ± 0.19	0.33 ± 0.32	0.27 ± 0.20	0.35 ± 0.34	0.34 ± 0.40	0.30 ± 0.21
Time since first asthma diagnosis (y), mean ± SD	25.81 ± 17.98	27.82 ± 17.31	21.68 ± 14.15	15.50 ± 13.04	20.85 ± 14.30	17.90 ± 12.98
FEV_1 (L), mean ± SD	1.86 ± 0.55	1.83 ± 0.52	1.94 ± 0.57	1.69 ± 0.49	1.68 ± 0.46	1.75 ± 0.43
FEV_1 predicted (%), mean ± SD	60.54 ± 10.36	61.82 ± 11.24	61.23 ± 10.63	61.11 ± 11.31	61.02 ± 9.91	61.72 ± 9.67
Asthma exacerbations in past year (n), mean ± SD	1.85 ± 1.28	1.90 ± 1.72	1.96 ± 1.25	2.54 ± 2.26	1.63 ± 1.03	2.33 ± 2.60
High ICS + LABA use at baseline, n (%)*	40 (48.2)	27 (39.1)	40 (47.6)	30 (55.6)	29 (58.0)	19 (48.7)
Baseline SNOT-22 total score, mean ± SD	31.22 ± 19.30	31.45 ± 18.67	29.33 ± 15.27	37.75 ± 20.77	35.35 ± 17.25	42.51 ± 19.61
Salbutamol puffs/d (n), mean ± SD†	2.88 ± 3.11	3.08 ± 2.69	3.14 ± 2.75	2.42 ± 1.99	2.80 ± 2.83	3.40 ± 3.16
Comorbid medical history, n (%)						
AD	11 (13.3)	5 (6.9)	10 (12.0)	2 (3.8)	4 (7.7)	4 (9.8)
AR	59 (71.1)	54 (75.0)	53 (63.9)	30 (56.6)	29 (55.8)	21 (51.2)
Former smoker, n (%)	18 (21.4)	17 (23.3)	20 (23.8)	13 (23.2)	9 (17.3)	9 (20.9)
Number of pack-years (n), mean ± SD	4.05 ± 3.06	3.59 ± 2.93	4.29 ± 3.46	4.75 ± 3.14	5.93 ± 3.78	3.07 ± 3.38

*Use of ICS plus LABA was recorded in an electronic diary.

†Includes the use of levosalbutamol for symptom relief; the number of salbutamol or levosalbutamol inhalations was recorded daily by the patients; alternatively, salbutamol and levosalbutamol nebulizers were used and converted to number of puffs.

increase of 0.13 L in FEV_1 versus placebo (95% CI, 0.01 to 0.25; $P = .0337$; Table II). A numerical but not statistically significant improvement was also observed with dupilumab 200 mg q2w (0.10 L; 95% CI, −0.03 to 0.22; $P = .1256$; Table II). In patients without PAR, the 200 mg q2w dupilumab dose regimen significantly increased FEV_1 from baseline to week 24 (19.0%), with an increase of 0.15 L (95% CI, 0.01 to 0.30) relative to placebo ($P = .0403$; Table II). No significant difference was observed for patients without PAR treated with dupilumab 300 mg q2w (0.08 L; 95% CI, −0.08 to 0.23; $P = .3310$; Table II).

Over the 24-week treatment period, dupilumab 300 mg q2w significantly reduced the annualized rate of severe asthma exacerbations in patients with PAR (51.7% risk reduction; $P = .0373$) compared with placebo. A numerical but not statistically significant difference was observed with the 200 mg q2w dose (51.5% risk reduction; $P = .0506$; Table III). In patients without PAR, both the 200 and 300 mg q2w dupilumab dose regimens significantly reduced the annualized rate of severe asthma exacerbations compared with placebo (200 mg q2w: 83.0% risk reduction, $P = .0002$; 300 mg q2w: 76.8% risk reduction, $P = .0012$; Table III).

Safety

Safety data for the overall population have been reported previously[5]; in brief, dupilumab was generally well tolerated, with similar rates of TEAEs observed across all treatment groups (75%-83% with dupilumab vs 75% with placebo).

In this analysis, similar rates of TEAEs were observed between patients with and without PAR across all treatment groups (Table IV). In patients with PAR, the TEAEs (preferred term) that occurred in 10% or more of patients and that occurred more frequently in the safety population of the q2w dose regimens combined than in placebo-treated patients were headache (dupilumab, 9.5%-16.4%; placebo, 7.1%) and injection-site erythema (dupilumab, 17.8%-20.2%; placebo, 8.3%). In patients without PAR, the TEAE (preferred term) that occurred in 10% or more of patients and that occurred more frequently in the safety population of the q2w dose regimens combined than in placebo-treated patients was injection-site erythema (dupilumab, 10.0%-26.2%; placebo, 8.9%). Rates of injection-site reactions (high-level term) according to the presence or absence of PAR are presented in Table IV.

DISCUSSION

Our data are hypothesis-generating, and suggest that dupilumab 300 mg q2w added to medium-to-high-dose ICS + LABA therapy significantly improves symptoms of PAR (SNOT-22 rhinitis-associated symptoms and total SNOT-22 score) in patients with uncontrolled, persistent asthma and comorbid PAR. These are important findings because comorbid AR is known to worsen overall asthma control.[8,27]

These data reporting the outcomes of dupilumab treatment in patients with concomitant PAR and asthma are novel. Previously, treatment with the anti-IgE mAb omalizumab was shown to be

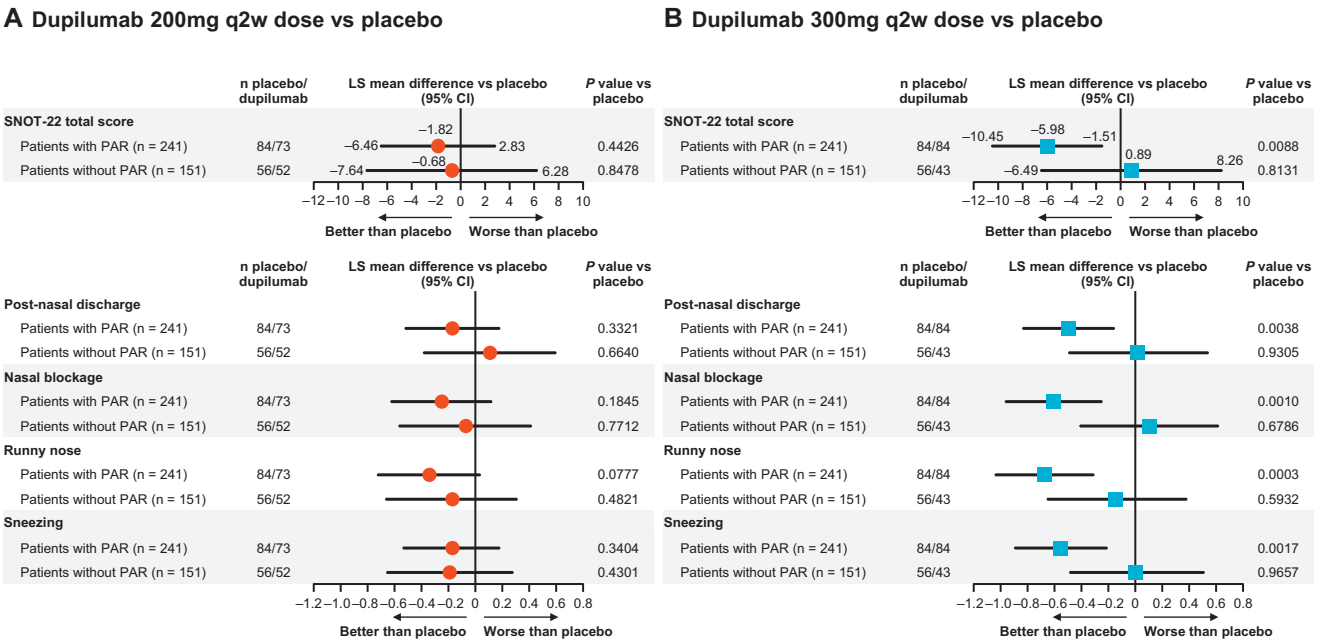

FIG 2. LS mean difference and 95% CI for SNOT-22 total score and PAR-associated individual items at week 24 in asthma patients with or without PAR for dupilumab 200 mg q2w vs placebo (**A**) and dupilumab 300 mg q2w vs placebo (**B**). Negative values are indicative of better improvement for nasal symptoms. *LS*, Least squares.

TABLE II. Change in FEV_1 at week 24 relative to baseline in asthma patients with or without PAR

	Patients with PAR (n = 241)			Patients without PAR (n = 151)		
		Dupilumab			Dupilumab	
Mean change in FEV_1 from baseline	**Placebo (n = 84)**	**200 mg q2w (n = 73)**	**300 mg q2w (n = 84)**	**Placebo (n = 56)**	**200 mg q2w (n = 52)**	**300 mg q2w (n = 43)**
Patients with data at week 24, n	69	63	76	43	47	39
LS mean change (SE)*	0.12 (0.04)	0.22 (0.05)	0.25 (0.04)	0.17 (0.05)	0.32 (0.05)	0.24 (0.06)
LS mean difference vs placebo (95% CI)*		0.10 (−0.03 to 0.22)	0.13 (0.01 to 0.25)		0.15 (0.01 to 0.30)	0.08 (−0.08 to 0.23)
P value vs placebo*		.1256	.0337		.0403	.3310

LS, Least squares.
*Derived from a mixed-effect model with repeated measures with change in FEV_1 (L) score from baseline up to week 24 as dependent variables; factors (fixed effects) for treatment, baseline eosinophil strata, pooled countries/regions, visit, treatment-by-visit interaction, FEV_1 (L) baseline value, and baseline-by-visit interaction as the covariates, unstructured correlation matrix.

effective in preventing asthma exacerbations and improving quality of life in patients with concomitant allergic asthma and persistent AR.[28] Dupilumab has demonstrated efficacy in 2 other type 2 immune-mediated diseases: AD[24] (for which it has received approval) and CRSwNP (in a proof-of-concept study).[25] The results observed with dupilumab in this *post hoc* analysis (ie, evidence of efficacy in patients with PAR), along with the efficacy demonstrated in patients with AD and CRSwNP, support the concept of recognizing and treating patients with type 2 immune diseases in a holistic way.

In addition, dupilumab improved lung function and exacerbation rates in patients with PAR as well as patients without PAR. These findings are consistent with the results of the overall population studied.[5]

Unsurprisingly, no differences relative to placebo were observed in patients without PAR with regard to AR-associated symptoms. This was expected, because treatment-related differences in symptoms typically associated with PAR would be unlikely to be evident in patients lacking this comorbidity. Indeed, the findings serve to internally validate the overall results because patients with PAR had preferential efficacy (at the 300 mg q2w dose) on outcomes related to AR symptoms compared with patients without PAR. These data suggest that dupilumab by its dual blocking action targets key primary drivers of type 2 inflammation, and may have a beneficial effect in treating patients with asthma and concomitant PAR, one of the most frequently associated type 2 comorbidities.[4] Indeed, more attention needs to be given to treatments that concomitantly address asthma comorbidities.

Although nasal symptom control was consistently and significantly improved with the highest dose of dupilumab studied (300 mg 2qw) compared with placebo, no differences were observed for the 200 mg q2w dose. This suggests that, at least in the subgroup of patients with PAR, 300 mg q2w represents the most beneficial dose.

Dupilumab 300 mg q2w also significantly improved lung function (FEV_1) and reduced severe exacerbations compared with

TABLE III. Annualized severe exacerbation rates by PAR subgroup

	Patients with PAR (n = 241)			Patients without PAR (n = 151)		
		Dupilumab			Dupilumab	
Adjusted annualized severe exacerbation event rate*	Placebo (n = 84)	200 mg q2w (n = 73)	300 mg q2w (n = 84)	Placebo (n = 56)	200 mg q2w (n = 52)	300 mg q2w (n = 43)
Estimate (95% CI)	0.413 (0.260- 0.656)	0.200 (0.110- 0.366)	0.199 (0.114- 0.348)	0.904 (0.592- 1.380)	0.153 (0.065- 0.364)	0.210 (0.094- 0.468)
Risk reduction vs placebo (%)		51.5	51.7		83.0	76.8
P value vs placebo		.0506	.0373		.0002	.0012

*Derived using a negative binomial model with the total number of events onset between first dose date and last dose date + 14 d as the response variable; treatment, baseline eosinophil strata, pooled countries/regions, and number of asthma events in the year before the study as the covariates; and log-transformed standardized treatment duration as the offset variable.

TABLE IV. Overview of TEAEs in the safety population

	Patients with PAR (n = 241)			Non-PAR patients (n = 148)		
		Dupilumab			Dupilumab	
TEAEs	Placebo (n = 84)	200 mg q2w (n = 73)	300 mg q2w (n = 84)	Placebo (n = 56)	200 mg q2w (n = 50)	300 mg q2w (n = 42)
Any TEAEs*	60 (71.4)	58 (79.5)	66 (78.6)	42 (75.0)	41 (82.0)	30 (71.4)
Any serious TEAEs	5 (6.0)	5 (6.8)	3 (3.6)	3 (5.4)	3 (6.0)	4 (9.5)
Treatment discontinuation due to TEAEs	1 (1.2)	3 (4.1)	3 (3.6)	2 (3.6)	2 (4.0)	0
Any TEAE leading to death	0	0	0	0	0	0
Injection-site reactions (HLT)†	12 (14.3)	16 (21.9)	22 (26.2)	7 (12.5)	10 (20.0)	12 (28.6)

HLT, High-level term (Medical Dictionary for Regulatory Activities).
*All values are n (%). Safety population was defined as randomized patients receiving ≥1 dose or part of a dose of the investigational medicinal product, analyzed according to the treatment actually received.
†Injection-site reactions due to noninvestigational medicinal products were excluded.

placebo in patients with comorbid PAR. These findings are in line with the significant improvements in both lung function and rate of exacerbations observed for the q2w regimens, both in the overall study population and in subgroups with 300 or more eosinophils per microliter and less than 300 eosinophils per microliter at baseline.[5] As also reported previously, these improvements were maintained throughout the 24-week treatment period in both groups of patients, thus providing further validation that the simultaneous inhibition of IL-4 and IL-13 signaling with dupilumab plays an important role in treating uncontrolled persistent asthma, irrespective of PAR status.

Of the 392 patients receiving dupilumab (200 or 300 mg q2w) or placebo in this study, 241 (61%) patients had PAR. Previous estimates of between 75% and 100% have been reported for AR[6-8]; indeed, focus groups suggest that AR comorbid with asthma is underdiagnosed, proposing that patients with either condition should always be evaluated for comorbid presence of the other.[6]

It has been previously shown that asthma patients with comorbid AR have worse outcomes and greater utilization of health care resources than those without comorbid AR.[29] These patients with AR represent a subgroup of asthma sufferers with a clear unmet need for treatment options over and above ICS + LABA therapies.

In line with what was already observed in the overall population, similar rates of TEAEs were observed across treatment groups for patients with PAR versus patients without PAR, indicating that dupilumab was well tolerated with an acceptable safety profile in these patient subgroups.

There are some limitations to this analysis. It was *post hoc*. PAR was defined at study entry as a specific response to typical perennial antigens (IgE ≥0.35 Ku/L), which, strictly speaking, denotes allergen sensitization rather than presence of PAR *per se*. Furthermore, on the basis of PAR and non-PAR definitions used, patients with concomitant seasonal AR may have been included in the PAR group as well as in the non-PAR group (~50% of the patients without PAR, as per the definition used in this *post hoc* analysis, reported AR in their comorbid medical history). Use of intranasal corticosteroids or antihistamines was not systemically monitored in this study and therefore the impact of their use is unclear. SNOT-22 is validated in patients with CRS[30] and not in patients with PAR comorbid with asthma and, as such, the minimal clinically important difference in patients with PAR is not known. In addition, a few patients with CRS were included in this subanalysis (PAR: placebo, n = 11; dupilumab 200 mg q2w, n = 9; dupilumab 300 mg q2w, n = 10. Non-PAR: placebo, n = 3; dupilumab 200 mg q2w, n = 5; dupilumab 300 mg q2w, n = 6). However, given that the numbers involved were small, it is unlikely that the results would differ appreciably if these patients had been excluded. SNOT-22 score is not a validated instrument for the assessment of AR control; however, individual item scores reported here are of symptoms typically associated with AR. As such, this analysis could serve as the basis for future prospective studies comprising greater numbers of patients. Currently, both q2w doses of dupilumab are undergoing phase 3 evaluation for the treatment of patients with uncontrolled persistent asthma (NCT02414854).

Conclusions

AR is a common and often inadequately treated condition that is frequently comorbid with asthma and has the potential to worsen asthma control. In this analysis, dupilumab 300 mg q2w, when added to ICS + LABA therapy, exhibited evidence of potential benefit by significantly improving nasal symptoms in patients with uncontrolled persistent asthma and comorbid PAR. Dupilumab 300 mg q2w also significantly reduced all 4 of the individual items typically associated with AR: postnasal discharge, nasal blockage, runny nose, and sneezing. No differences relative to placebo were observed for patients treated with dupilumab 200 mg q2w.

Consistent with previously reported data, dupilumab as add-on therapy to medium-to-high-dose ICS + LABA simultaneously improved lung function (FEV_1), reduced the rate of severe exacerbations, and improved upper (nasal) airway symptoms in patients with uncontrolled persistent asthma and comorbid PAR.

These data suggest that dupilumab (300 mg q2w) as add-on therapy to medium-to-high-dose ICS + LABA may have a role in nasal symptom relief for this important subgroup of patients with uncontrolled persistent asthma and comorbid PAR. Future studies are required to investigate the benefit of dupilumab in this patient subgroup.

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Clinical implications: A systemic therapy with a selective immunomodulator that treats both AR and uncontrolled persistent asthma may improve outcomes in patients with comorbid AR and asthma.

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TABLE E1. Change in SNOT-22 total score and PAR-associated individual items at week 24 relative to baseline in asthma patients with or without PAR

Mean change from baseline in SNOT-22 total score and PAR-associated individual items	Patients with PAR (n = 241)			Patients without PAR (n = 151)		
		Dupilumab			Dupilumab	
	Placebo (n = 84)	200 mg q2w (n = 73)	300 mg q2w (n = 84)	Placebo (n = 56)	200 mg q2w (n = 52)	300 mg q2w (n = 43)
SNOT-22 total score						
Baseline score, mean ± SD	31.22 ± 19.30	31.45 ± 18.67	29.33 ± 15.27	37.75 ± 20.77	35.35 ± 17.25	42.51 ± 19.61
Patients with available data at week 24, n	70	60	71	42	47	39
LS mean change (SE)*	−6.79 (1.62)	−8.61 (1.74)	−12.77 (1.63)	−7.65 (2.61)	−8.33 (2.55)	−6.76 (2.79)
LS mean difference vs placebo (95% CI)*		−1.82 (−6.46 to 2.83)	−5.98 (−10.45 to −1.51)		−0.68 (−7.64 to 6.28)	0.89 (−6.49 to 8.26)
P value vs placebo*		.4426	.0088		.8478	.8131
Postnasal discharge						
Baseline score, mean ± SD	1.47 ± 1.32	1.24 ± 1.28	1.36 ± 1.28	1.84 ± 1.42	1.90 ± 1.14	2.12 ± 1.50
Patients with available data at week 24, n	70	60	71	42	47	39
LS mean change (SE)*	−0.21 (0.12)	−0.39 (0.13)	−0.71 (0.12)	−0.53 (0.18)	−0.42 (0.18)	−0.50 (0.19)
LS mean difference vs placebo (95% CI)*		−0.17 (−0.52 to 0.18)	−0.49 (−0.83 to −0.16)		0.11 (−0.38 to 0.60)	0.02 (−0.49 to 0.54)
P value vs placebo*		.3321	.0038		.6640	.9305
Nasal blockage						
Baseline score, mean ± SD	1.95 ± 1.33	1.83 ± 1.46	1.98 ± 1.46	1.96 ± 1.22	1.87 ± 1.12	2.07 ± 1.27
Patients with available data at week 24, n	70	60	71	42	47	39
LS mean change (SE)*	−0.36 (0.13)	−0.61 (0.14)	−0.96 (0.13)	−0.42 (0.18)	−0.49 (0.18)	−0.31 (0.19)
LS mean difference vs placebo (95% CI)*		−0.25 (−0.62 to 0.12)	−0.60 (−0.96 to −0.25)		−0.07 (−0.56 to 0.42)	0.11 (−0.41 to 0.62)
P value vs placebo*		.1845	.0010		.7712	.6786
Runny nose						
Baseline score, mean ± SD	1.83 ± 1.30	1.87 ± 1.44	1.61 ± 1.22	1.69 ± 1.27	1.69 ± 1.20	2.12 ± 1.47
Patients with available data at week 24, n	70	60	71	42	47	39
LS mean change (SE)*	−0.25 (0.13)	−0.59 (0.14)	−0.92 (0.13)	−0.33 (0.18)	−0.50 (0.18)	−0.47 (0.19)
LS mean difference vs placebo (95% CI)*		−0.34 (−0.72 to 0.04)	−0.67 (−1.04 to −0.31)		−0.17 (−0.66 to 0.31)	−0.14 (−0.65 to 0.38)
P value vs placebo*		.0777	.0003		.4821	.5932
Sneezing						
Baseline score, mean ± SD	1.82 ± 1.22	2.13 ± 1.31	1.85 ± 1.25	1.89 ± 1.27	1.79 ± 1.13	2.24 ± 1.18
Patients with available data at week 24, n	70	60	71	42	47	39
LS mean change (SE)*	−0.31 (0.12)	−0.48 (0.13)	−0.86 (0.12)	−0.46 (0.18)	−0.64 (0.17)	−0.45 (0.19)
LS mean difference vs placebo (95% CI)*		−0.17 (−0.53 to 0.18)	−0.55 (−0.89 to −0.21)		−0.19 (−0.65 to 0.28)	0.01 (−0.48 to 0.51)
P value vs placebo*		.3404	.0017		.4301	.9657

LS, Least squares.

*Derived from a mixed-effect model with repeated measures with change in FEV_1 (L) score from baseline up to week 24 as the dependent variable; factors (fixed effects) for treatment, baseline eosinophil strata, pooled countries/regions, visit, treatment-by-visit interaction, FEV_1 (L) baseline value, and baseline-by-visit interaction as the covariates, unstructured correlation matrix.