Received: 28 September 2022 | Revised: 6 March 2023 | Accepted: 15 March 2023

DOI: 10.1111/all.15743

Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY EAACI WILEY

ORIGINAL ARTICLE

Asthma and Lower Airway Disease

Assessment of dupilumab in children with moderate-to-severe type 2 asthma with or without evidence of allergic asthma

Nikolaos G. Papadopoulos[1] | Stanley J. Szefler[2] | Leonard B. Bacharier[3] | Jorge F. Maspero[4] | Christian Domingo[5] | Alessandro Fiocchi[6] | Jason K. Lee[7] | Nadia Daizadeh[8] | David J. Lederer[9] | Megan Hardin[8] | Rebecca Gall[9] | Michel Djandji[8] | Shahid Siddiqui[9] | Juby A. Jacob-Nara[10] | Yamo Deniz[9] | Paul J. Rowe[10]

[1]Allergy Department, The 2nd Pediatric Clinic, University of Athens, Athens, Greece

[2]Department of Pediatrics, The Breathing Institute, The University of Colorado School of Medicine and Children's Hospital Colorado, Aurora, Colorado, USA

[3]Division of Allergy, Immunology and Pulmonary Medicine, The Monroe Carell Jr. Children's Hospital at Vanderbilt University Medical Center, Nashville, Tennessee, USA

[4]Allergy and Respiratory Medicine, The Fundación CIDEA, Buenos Aires, Argentina

[5]Pulmonary Service, The Corporació Sanitària Parc Taulí, Sabadell, Autonomous University of Barcelona, Barcelona, Spain

[6]Department of Allergy, The Bambino Gesù Children's Hospital, IRCCS, Rome, Italy

[7]Division of Adult Clinical Immunology and Allergy, Internal Medicine, Evidence Based Medical Educator and Toronto Allergy and Asthma Clinic, Toronto, Ontario, Canada

[8]Sanofi, Cambridge, Massachusetts, USA

[9]Regeneron Pharmaceuticals Inc., Tarrytown, New York, USA

[10]Sanofi, Bridgewater, New Jersey, USA

Correspondence
Nikolaos G. Papadopoulos, The 2nd Pediatric Clinic, University of Athens, 41 Fidippidou street, Athens, Attica 11527, Greece.
Email: ngp@allergy.gr

Funding information
Regeneron Pharmaceuticals Inc.; Sanofi

Abstract

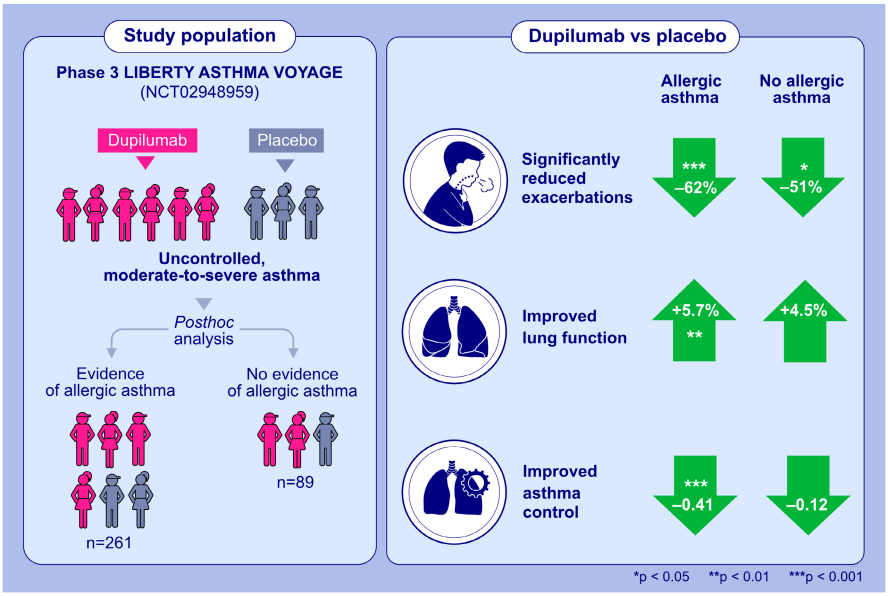
Background: Cytokines, such as interleukins (IL)-4/5/13, play a key role in multiple type 2 inflammatory diseases, including allergic asthma. Dupilumab, a human monoclonal antibody, blocks the shared receptor component for IL-4/IL-13, inhibiting signaling. In this post hoc analysis of VOYAGE (NCT02948959), dupilumab efficacy was evaluated in patients aged 6–11 years with type 2 asthma with or without evidence of allergic asthma (baseline serum total IgE ≥30 IU/mL and ≥1 perennial aeroallergen-specific IgE ≥0.35kU/L).

Methods: Annualized severe exacerbation rates (AER) and changes in pre-bronchodilator (Pre-BD) forced expiratory volume in one second (FEV_1), percent-predicted pre-BD FEV_1 ($ppFEV_1$), and Asthma Control Score (ACQ)-7 were assessed during the treatment period.

Abbreviations: ACQ-7-IA, Asthma Control Questionnaire 7-item version Interviewer-Administered; AER, adjusted annualized severe exacerbation rates; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroids; IgE, immunoglobulin E; IL, interleukin; ITT, intention-to-treat; MMRM, mixed-effect model with repeated measures; ppb, parts per billion; $ppFEV_1$, percent predicted forced expiratory volume in 1 second; q2w, every 2 weeks.

Results: 350 children (261 with and 89 without evidence of allergic asthma) were included. Dupilumab versus placebo significantly reduced AER in patients with (0.24 vs. 0.62, relative risk reduction [RRR]: 62% [95% CI, 39–76], $P < .0001$) and without (0.39 vs. 0.80, RRR: 51% [95% CI, 0–76], $P < .05$) evidence of allergic asthma. Significant improvements in ppFEV$_1$, pre-bronchodilator FEV$_1$, and ACQ-7 scores were observed in dupilumab versus placebo throughout the treatment period in patients with evidence of allergic asthma. In patients without evidence of allergic asthma, numerical improvements in pre-bronchodilator FEV$_1$ and asthma control were observed by Week 52.
Conclusion: Dupilumab versus placebo reduced asthma exacerbations in children with type 2 asthma irrespective of evidence of allergic asthma; similar trends were observed in changes in lung function. Significant improvement in asthma control was observed in patients with evidence of allergic asthma, but not in those without.

KEYWORDS
allergic, asthma, exacerbation, percentage predicted FEV$_1$, dupilumab



GRAPHICAL ABSTRACT

This post hoc analysis of VOYAGE (NCT02948959) evaluates efficacy of dupilumab in patients aged 6–11 years with type 2 asthma with or without evidence of allergic asthma. In type 2 patients, dupilumab versus placebo significantly reduced exacerbation rates irrespective of allergic status. Significant improvements versus placebo in lung function and asthma control were observed throughout the treatment period in patients with evidence of allergic asthma. In the small population of patients without evidence of allergic asthma, numerical improvements in lung function and asthma control were observed. Patients with type 2 inflammation at baseline (≥150 eosinophils/μl or FeNO ≥20 ppb).
Abbreviations: NCT, national clinical trial; VOYAGE, evaluation of dupilumab in children with uncontrolled asthma

1 | BACKGROUND

Type 2 inflammation is the most common type of inflammation seen in asthma in children[1,2] and is reflected by elevated levels of peripheral or sputum eosinophils, fractional exhaled nitric oxide (FeNO), and/or IgE, and includes asthma characterized as eosinophilic and/or allergic.[3–5] Allergic asthma, traditionally considered to be driven by an IgE-mediated process, is a subtype of type 2 inflammation.[6]

Dupilumab, a fully human monoclonal antibody,[7,8] blocks the shared receptor component for interleukin (IL)-4 and IL-13, type 2 inflammatory cytokines implicated in numerous allergic diseases ranging from asthma to atopic dermatitis,[9] thus inhibiting their signaling. It is approved in the USA for patients aged ≥6 years with moderate-to-severe asthma with an eosinophilic phenotype[10] and in the EU in patients aged ≥6 years with severe asthma with type 2 inflammation.[11]

The phase 3 LIBERTY ASTHMA VOYAGE study (NCT02948959) was a 52-week, randomized, double-blind, placebo-controlled clinical trial designed to evaluate the safety and efficacy of dupilumab in children aged 6–11 years with uncontrolled, moderate-to-severe asthma.[12] Dupilumab treatment versus placebo significantly reduced severe asthma exacerbations and rapidly improved lung function in children with type 2 asthma. These improvements were sustained throughout the 52-week treatment period and dupilumab was generally well-tolerated in this age group.[12]

In adult and adolescent patients with uncontrolled, moderate-to-severe asthma, dupilumab reduced severe asthma exacerbations and improved lung function and asthma control in patients with and without evidence of allergic asthma.[13] The potential impact of a patient's allergic status on dupilumab efficacy has not been evaluated in children. The aim of this post hoc analysis, therefore, was to explore the efficacy of dupilumab among patients with type 2 inflammatory asthma in VOYAGE, who did and did not have evidence of allergic asthma.

2 | METHODS

2.1 | Study design and oversight

Full details of the LIBERTY ASTHMA VOYAGE study have been previously published.[12] In brief, VOYAGE, a phase 3, randomized, double-blind, placebo-controlled, parallel-group, multinational study, assessed efficacy and safety of dupilumab in children aged 6–11 years with uncontrolled, moderate-to-severe asthma. Data were collected by the Investigators and analyzed by the sponsors according to a predefined statistical analysis plan. The study was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonization Good Clinical Practice guideline, and applicable regulatory requirements. An independent data and safety monitoring committee conducted blinded monitoring of patient safety data. The local institutional review board or ethics committee at each study center oversaw trial conduct and documentation. Parents or guardians of patients provided written informed consent before their participation in the trial. Pediatric patients provided assent according to the Ethics Committee approved standard practice for pediatric patients at each participating center.

2.2 | Patients and interventions

Children aged 6–11 years were eligible to participate in VOYAGE if they had physician-diagnosed moderate-to-severe asthma based on the GINA 2015 guidelines.[14] Full details of inclusion and exclusion criteria have been described previously.[12] Per protocol, enrolment of patients with baseline blood eosinophils <150 cells/μl was limited to 20% of the total population. Eligible patients were randomized to receive subcutaneous dupilumab or volume-matched placebo at the same dose every 2 weeks (q2w) for 52 weeks in a weight-tiered fashion: those with a bodyweight of ≤30 kg at randomization received dupilumab 100 mg or matched placebo while those with a bodyweight >30 kg received dupilumab 200 mg or matching placebo. The study period comprises from enrolment of the first participant on 21 April 2017, to study completion on 26 August 2020.

Patients included in this sub-analysis of VOYAGE were those with type 2 asthma, defined as baseline blood eosinophils ≥150 cells/μl or FeNO ≥20 ppb, patients with baseline eosinophils ≥150 cells/μl, and patients with FeNO ≥20 ppb at baseline. These patients were further stratified according to whether they met or did not meet the criteria for evidence of allergic asthma at baseline, using functional definitions that are narrower than definitions that would be used to identify patients with allergic asthma in clinical practice. Evidence of allergic asthma was defined as a total serum IgE ≥30 IU/mL and ≥1 perennial aeroallergen-specific IgE ≥0.35 kU/L at baseline as described previously.[13] Sensitization to the following perennial aeroallergens was assessed: *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, *Alternaria tenuis/alternata*, *Cladosporium herbarum*, cat and dog danders, German cockroach, and *Aspergillus fumigatus*.

2.3 | Endpoints

The primary endpoint was the annualized severe exacerbation rate during the 52-week treatment period. Severe exacerbations were defined as a deterioration of asthma requiring: (i) the use of systemic corticosteroids for ≥3 days, or (ii) hospitalization or emergency room visit because of asthma, requiring systemic corticosteroids. Secondary endpoints analyzed were the change from baseline over time in both pre-bronchodilator percent predicted forced expiratory volume in 1 second (ppFEV$_1$, key secondary endpoint) and absolute pre-bronchodilator FEV$_1$, and change from baseline in asthma control over time, as assessed using the Asthma Control Questionnaire 7-item version Interviewer-Administered (ACQ-7-IA). The effect of treatment on specific IgE to perennial aeroallergens over the 52-week treatment period was also examined in patients who had sensitization to one or more aeroallergens at baseline (≥0.35 kU/L).

2.4 | Statistical analysis

Data were analyzed on an intention-to-treat (ITT) basis according to the assigned intervention, irrespective of whether an intervention was received.[12] Data for both weight-tiered doses of dupilumab (100 or 200 mg q2w) or matched placebo were pooled for analysis.

Annualized severe exacerbation rates were analyzed using a negative binomial model, which included the total number of events observed from randomization up to Week 52 or last study contact date (whichever comes earlier) as the response variable, and included treatment group, age, baseline weight group (≤30 kg, >30 kg), region (pooled country), baseline eosinophil strata (<300 cells/μL, ≥300 cells/μL), baseline FeNO level (<20 ppb, ≥20 ppb), baseline inhaled corticosteroid dose (ICS) level (medium- or high-dose), and number of severe exacerbations within 1 year prior to the study as covariates, and log-transformed standardized observation duration as an offset variable.

Change from baseline in ppFEV$_1$ and absolute pre-bronchodilator FEV$_1$ were analyzed using a mixed-effect model with repeated measures (MMRM) approach, which used, as appropriate, change from baseline in ppFEV$_1$ or pre-bronchodilator FEV$_1$ up to Week 52 as the response variable, and included pooled treatment groups, baseline weight groups, region, ethnicity, baseline eosinophil strata, baseline FeNO level, baseline ICS dose level, visit, treatment by visit interaction, baseline value of the respective endpoint (percentage predicted or absolute FEV$_1$), and baseline-by-visit interaction as covariates. The change from baseline in pre-bronchodilator FEV$_1$ up to Week 52 was derived using MMRM model with all the covariates mentioned above along with age, sex, and baseline height.

Change from baseline in ACQ-7-IA score over time was derived from an MMRM model with change from baseline in ACQ-7-IA score up to Week 52 as the response variable and pooled treatment groups, age, baseline weight group, region, baseline eosinophil strata, baseline FeNO level, baseline ICS dose level, visit, treatment-by-visit interaction, baseline ACQ-7-IA score, and baseline-by-visit interaction as covariates.

Change from baseline in total IgE and specific IgE over time were analyzed using the Wilcoxon rank-sum test for patients in the safety population.

3 | RESULTS

3.1 | Study patients

350 patients randomized in VOYAGE (86% of the overall VOYAGE ITT population) had type 2 asthma at baseline, defined as baseline eosinophil count of ≥150 cells/μl or FeNO ≥20 ppb, and were included in this analysis. Of these, 261 (75%) met the criteria used to define evidence of allergic asthma: placebo $n=81$, dupilumab $n=180$. The remaining 89 (25%) patients (placebo $n=33$, dupilumab $n=56$) did not meet these criteria (IgE <30 IU/mL or no positive specific IgE among the aeroallergens tested). In the subgroup of patients with blood eosinophils ≥150 cells/μL, 251 met the criteria for allergic asthma (placebo $n=79$, dupilumab $n=172$), whereas the remaining 80 (placebo $n=29$, dupilumab $n=51$) did not. In the subgroup of patients with FeNO ≥20 ppb, 176 met the criteria for allergic asthma (placebo $n=53$, dupilumab $n=123$), whereas the remaining 27 (placebo $n=9$, dupilumab $n=18$) did not.

The baseline characteristics of patients with type 2 inflammation with and without evidence of allergic asthma are provided in Table 1. Baseline characteristics were similar across treatment arms and subgroups. Patients with evidence of allergic asthma at baseline had higher median levels of total serum IgE than those without evidence of allergic asthma (with evidence of allergic asthma: 569 [placebo] and 680 [dupilumab] IU/mL; without evidence of allergic asthma: 69.5 [placebo] and 113.5 [dupilumab] IU/mL).

3.2 | Annualized rate of severe asthma exacerbations

Overall, dupilumab reduced annualized severe exacerbation rates relative to placebo in patients with and without evidence of allergic asthma. In the subgroup of patients with type 2 asthma and evidence of allergic asthma, the adjusted annualized severe asthma exacerbation event rate was 0.24 (95% confidence interval [CI], 0.16–0.36) in the dupilumab group versus 0.62 (95% CI, 0.40–0.94) in the placebo group (relative risk reduction [RRR] vs. placebo of 62% [95% CI, 39–76]; $P<.0001$) (Figure 1). In the subgroup of patients with type 2 asthma with no evidence of allergic asthma, the adjusted annualized severe asthma exacerbation event rates were 0.39 (95% CI, 0.23–0.68) versus 0.80 (95% CI, 0.47–1.37) for dupilumab and placebo groups, respectively (RRR vs. placebo of 51% [95% CI, 0–76]; $P=.0494$). There was no statistical evidence that the treatment effect of dupilumab on exacerbations varied by allergic asthma status ($P_{interaction}=0.6011$).

Similar results were seen in the subgroup of patients with ≥150 eosinophils/μL, irrespective of allergic phenotype, and in patients with ≥20 ppb FeNO and allergic asthma at baseline (Figure S1). Patient numbers were very low in the subgroup of patients with ≥20 ppb FeNO without evidence of allergic asthma ($n=9$ [placebo] and $n=18$ [dupilumab]), therefore statistical comparisons were not possible in this subgroup, but trends were similar.

3.3 | Lung function

3.3.1 | Percentage of predicted pre-bronchodilator FEV$_1$

In the sub-group of patients with type 2 asthma and evidence of allergic asthma, dupilumab significantly improved pre-bronchodilator ppFEV$_1$ from baseline compared with matched placebo (Figure 2). Significant improvements versus placebo were observed as early as the first assessment at Week 2, and these persisted throughout the 52-week treatment period, with an LS mean difference versus placebo of 5.71 (95% CI, 2.02–9.39, $P=.003$), and 9.27 (95% CI, 5.16–13.37, $P<.0001$), at Weeks 12 and 52, respectively. In the sub-group of type 2 patients without evidence of allergic asthma, numerical improvements in ppFEV$_1$ compared to placebo were observed, with an LS mean difference versus placebo of 4.53 (95% CI, −1.30–10.35, $P=.126$), and 3.93 (95% CI, −2.41–10.26, $P=.221$), at Weeks 12 and 52, respectively (Figure 2). Significant improvements compared to placebo were observed at Week 4, 6, and 48 ($P<.05$) but at all other timepoints the improvements were numerical and not significant.

Similar results were seen in the subgroups of patients with ≥150 eosinophils/μL and patients with ≥20 ppb FeNO at baseline, except in those with elevated FeNO without evidence of allergic asthma, where no differences were found between dupilumab and placebo (Figure S2).

TABLE 1 Baseline characteristics of VOYAGE patients with type 2 asthma[a] with or without evidence of allergic asthma[b].

	Type 2 with evidence of allergic asthma		Type 2 without evidence of allergic asthma	
	Placebo	Dupilumab	Placebo	Dupilumab
Characteristic	***n* = 81**	***n* = 180**	***n* = 33**	***n* = 56**
Median age (min–max), years	9 (6–11)	9 (6–11)	8 (6–11)	9 (6–11)
Male sex, *n* (%)	59 (72.8)	118 (65.6)	19 (57.6)	34 (60.7)
Race				
White	69 (85.2)	155 (86.1)	33 (100)	53 (94.6)
Black/of African descent	5 (6.2)	9 (5.0)	0 (0)	0 (0)
Asian	0 (0)	2 (1.1)	0 (0)	0 (0)
American Indian or Alaska Native	0 (0)	1 (0.6)	0 (0)	0 (0)
Native Hawaiian or Other Pacific Islander	0 (0)	0 (0)	0 (0)	0 (0)
Other	7 (8.6)	13 (7.2)	0 (0)	3 (5.4)
Ethnicity				
Hispanic or Latino	37 (45.7)	76 (42.2)	14 (42.4)	28 (50.0)
Not Hispanic or Latino	44 (54.3)	104 (57.8)	19 (57.6)	28 (50.0)
BMI, mean (SD), kg/m^2	18.70 (3.36)	18.66 (3.62)	19.81 (5.05)	18.41 (3.17)
Age at asthma onset, mean (SD), years	3.8 (2.7)	3.2 (2.5)	3.8 (2.4)	3.3 (2.5)
Number of exacerbations in the past year, mean (SD)	2.10 (1.26)	2.64 (2.79)	2.36 (2.12)	2.52 (1.73)
Pre-bronchodilator FEV_1, mean (SD), L	1.54 (0.46)	1.48 (0.39)	1.49 (0.45)	1.47 (0.38)
Pre-bronchodilator $ppFEV_1$, mean (SD), %	78.62 (14.97)	76.67 (14.56)	77.73 (13.51)	80.84 (13.42)
ACQ-7-IA score, mean (SD)	2.10 (0.73)	2.17 (0.74)	2.15 (0.85)	2.06 (0.57)
Blood eosinophil count, median (Q1–Q3), cells/μL	490.0 (320.0–710.0)	575.0 (360.0–800.0)	360.0 (210.0–470.0)	290.0 (185.0–605.0)
FeNO, ppb, median (Q1–Q3)	25.0 (16.0–39.0)	29.5 (17.0–47.0)	14.5 (9.0–20.0)	13.00 (8.0–23.0)
Total IgE, IU/mL, median (Q1–Q3)	569.0 (270.0–1013.0)	680.0 (348.0–1462.5)	69.5 (26.5–312.5)	113.5 (32.0–286.0)

Abbreviations: ACQ-7-IA, Asthma Control Questionnaire 7-item version Interviewer-Administered; BMI, body mass index; FeNO, fractional exhaled nitric oxide; ppb, parts per billion; $ppFEV_1$, percent predicted forced expiratory volume in 1 second; SD, standard deviation.

[a]Type 2 asthma is defined as patients with asthma with baseline blood eosinophils ≥150 cells/μL or FeNO ≥20 ppb at baseline.

[b]The allergic asthma phenotype is defined as patients with asthma and serum total IgE ≥30 IU/mL and ≥1 perennial aeroallergen-specific IgE ≥0.35kU/L at baseline.

The *P*-values for interaction between treatment arm assignment and allergic asthma status were 0.605 at Week 12 and 0.132 at Week 52 for the change from baseline in $ppFEV_1$ endpoint.

3.3.2 | Absolute pre-bronchodilator FEV_1

In the sub-group of patients with type 2 asthma and evidence of allergic asthma, dupilumab significantly improved the absolute pre-bronchodilator FEV_1 from baseline compared with matched placebo, with improvements observed as early as Week 2 and sustained over the treatment period (Figure 3). At Week 2, the LS mean difference in pre-bronchodilator FEV_1 improvement over baseline versus placebo was 0.10 L (95% CI, 0.03–0.17, $P = .003$), which further increased to 0.12 L (95% CI, 0.04–0.19, $P = .002$) at Week 12 and 0.20 L (95% CI, 0.12–0.29, $P < .0001$) at Week 52. Similar to the findings for the $ppFEV_1$ endpoint, in patients without allergic asthma, the magnitude of improvements in absolute pre-bronchodilator FEV_1 relative to placebo was lower than in patients with allergic asthma, with an LS mean difference of −0.002 L (95% CI, −0.10–0.10, $P = .98$) at Week 2 and numerical improvements over baseline of 0.07 L (95% CI, −0.04–0.18, $P = .184$) at Week 12, and 0.07 L (95% CI, −0.06–0.21, $P = .266$) at Week 52.

The p-values for interaction between treatment arm assignment and allergic asthma status were 0.35 at Week 12 and 0.06 at Week 52 for the change from baseline in absolute FEV_1 endpoint.

3.4 | Asthma control (ACQ-7-IA scores)

Dupilumab significantly improved ACQ-7-IA scores compared with placebo in patients with evidence of allergic asthma. Improvements were rapid, with significant improvements versus placebo evident as early as the first assessment at Week 2, and these improvements

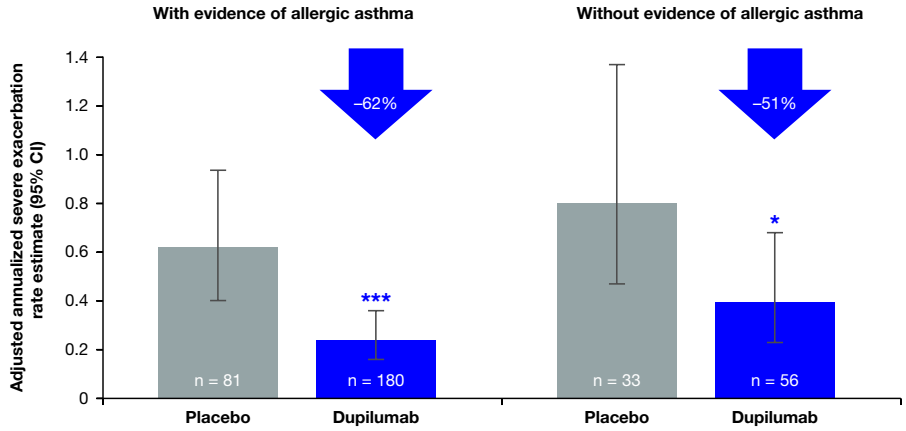


FIGURE 1 Effect of dupilumab on annualized severe exacerbation rates in pediatric patients with type 2 asthma[a] with or without evidence of allergic asthma[b]. *$P < .05$; ***$P < .001$ versus placebo. [a]Type 2 asthma is defined as patients with asthma with baseline blood eosinophils ≥150 cells/μL or FeNO ≥20 ppb at baseline. [b]The allergic asthma phenotype is defined as patients with asthma and serum total IgE ≥30 IU/mL and ≥1 perennial aeroallergen-specific IgE ≥0.35 kU/L at baseline.

were sustained throughout the study remaining significant versus placebo at all timepoints (Figure 4). At Week 24, the LS mean difference versus placebo was −0.41 (95% CI, −0.61 to −0.22, $P < .0001$). In the subgroup of type 2 patients without evidence of allergic asthma, little difference between treatments was observed throughout the treatment period (Figure 4), with an LS mean difference versus placebo of −0.12 (95% CI, −0.47 to −0.24, $P = .522$) at Week 24.

The *P*-values for interaction between treatment arm assignment and allergic asthma status were 0.11 at Week 24 and 0.14 at Week 52 for the change from baseline in ACQ-7-IA endpoint.

3.5 | Total IgE

Dupilumab reduced levels of total IgE over time in patients with type 2 inflammatory asthma, irrespective of their allergic status (Figure S3 of this article's Online Repository). In patients with evidence of an allergic asthma phenotype, median concentrations of total serum IgE were reduced by 78.8% by Week 52, versus a 0.9% increase in patients on placebo ($P < .0001$). In patients without evidence of an allergic asthma phenotype, even though baseline concentrations were much lower, dupilumab still reduced median IgE levels by 77.8% over the 52-week treatment duration, versus a 7.8% increase in patients on placebo ($P < .0001$) (Figure S3).

The p-values for interaction between treatment arm assignment and allergic asthma status were 0.70 at Week 24 and 0.13 at Week 52 for the percent change from baseline in total IgE levels over time endpoint.

3.6 | Perennial aeroallergen-specific IgE

The effect of treatment on allergen-specific IgE levels in patients who were positive (≥0.35 kU/L) at baseline for one or more of the perennial aeroallergens examined is presented in Figure S4 of this article's Online Repository. In dupilumab-treated patients, substantial reductions from baseline over the 52-week treatment period were observed in allergen-specific IgE levels to *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, and German cockroach both in patients with mono-allergen sensitization to the respective aeroallergen and in those with multi-allergen sensitization (i.e., patients with allergen-specific IgE ≥0.35 kU/L for more than one aeroallergen). Similar reductions over time were observed in multi-allergen-sensitized patients treated with dupilumab who were allergic to dog and cat dander and *Alternaria tenuis/alternata*. However, no differences between dupilumab and placebo were observed in patients who were mono-sensitized to *Cladosporium herbarum* and *Alternaria tenuis/alternata*. Dupilumab treatment did not affect serum IgE levels to *Cladosporium herbarum/hormodendrum* or *Aspergillus fumigatus* whether in mono- or multi-allergen sensitized patients. No change was observed with placebo treatment on specific IgE levels to any of the eight perennial aeroallergens assessed.

3.7 | Safety

In the primary analysis,[12] dupilumab was well tolerated with an acceptable safety profile. In this analysis, the incidence of treatment emergent adverse events was balanced across treatment groups (Table S1).

4 | DISCUSSION

In this post hoc analysis of LIBERTY ASTHMA VOYAGE, conducted in children aged 6–11 years with moderate-to-severe asthma, dupilumab significantly reduced the rate of severe exacerbations and improved lung function (ppFEV$_1$ and absolute FEV$_1$) and asthma control (ACQ-7-IA scores) in patients with type 2 asthma (baseline blood eosinophils ≥150 cells/μL or ≥20 ppb FeNO) and

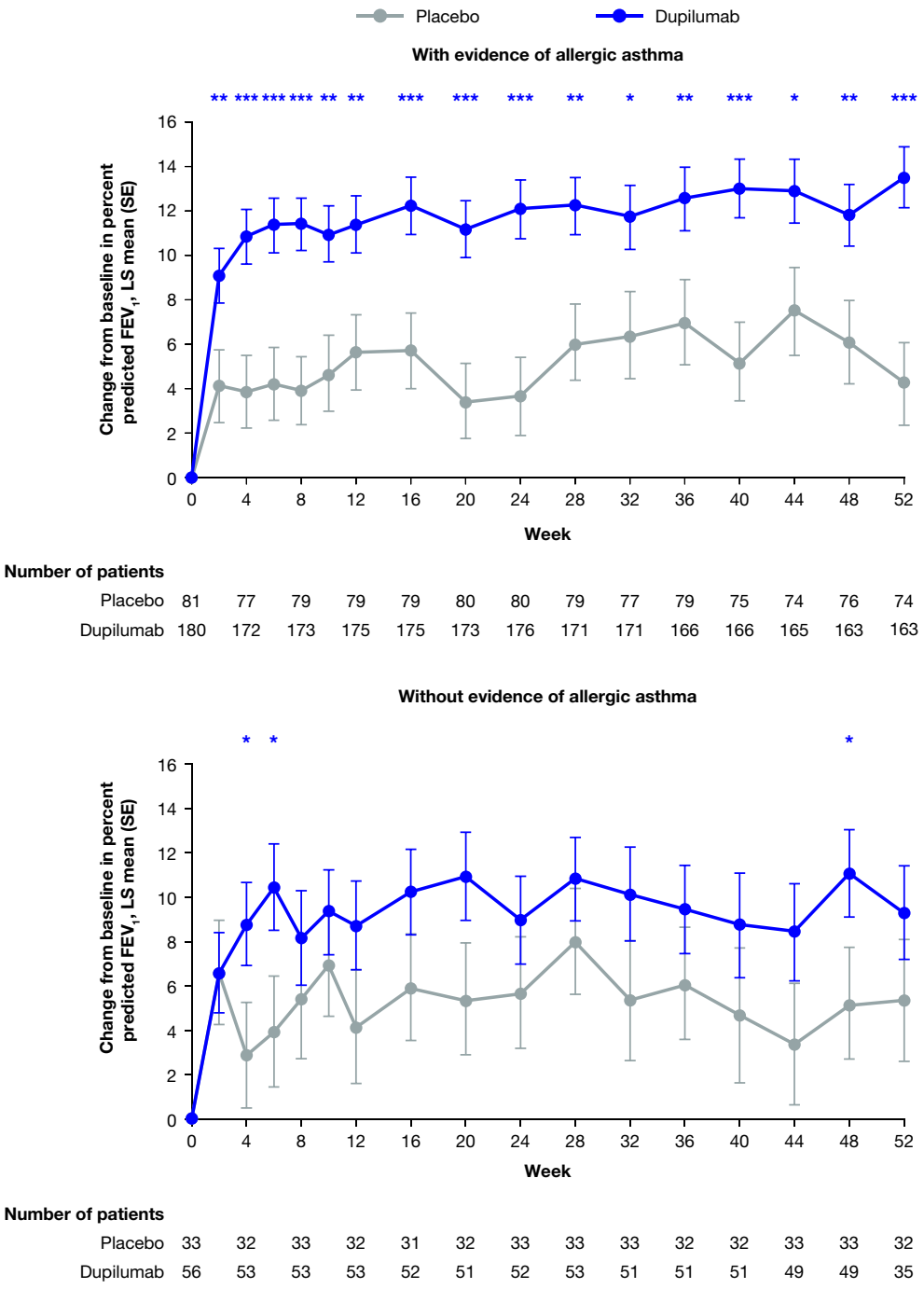


FIGURE 2 Change from baseline over time in pre-bronchodilator ppFEV$_1$ in patients with type 2 asthma[a] with or without evidence of allergic asthma[b]. *$P < .05$, **$P < .01$, ***$P < .001$ versus placebo. [a]Type 2 asthma is defined as patients with asthma with baseline blood eosinophils ≥150 cells/μL or FeNO ≥20 ppb at baseline. [b]The allergic asthma phenotype is defined as patients with asthma and serum total IgE ≥30 IU/mL and ≥1 perennial aeroallergen-specific IgE ≥0.35 kU/L at baseline.

evidence of allergic asthma, with similar trends observed in patients without evidence of allergic asthma. As reported previously, similar treatment effects were observed in QUEST in adult and adolescent patient populations with type 2 asthma irrespective of their allergic status at baseline.[13] The improvements in lung function and asthma control in the subgroup with evidence of allergic asthma were rapid, observed by Week 2, and were sustained throughout the treatment period. Dupilumab versus placebo also improved lung function in patients with type 2 without evidence of allergic asthma, although these differences were not significant at most timepoints. These findings are consistent with the efficacy profile seen in QUEST patients with uncontrolled, moderate-to-severe asthma where clinical efficacy with regard to exacerbation rates, lung function, and asthma control was observed *irrespective* of evidence of allergic status: dupilumab versus placebo significantly reduced exacerbation rates and improved lung function and

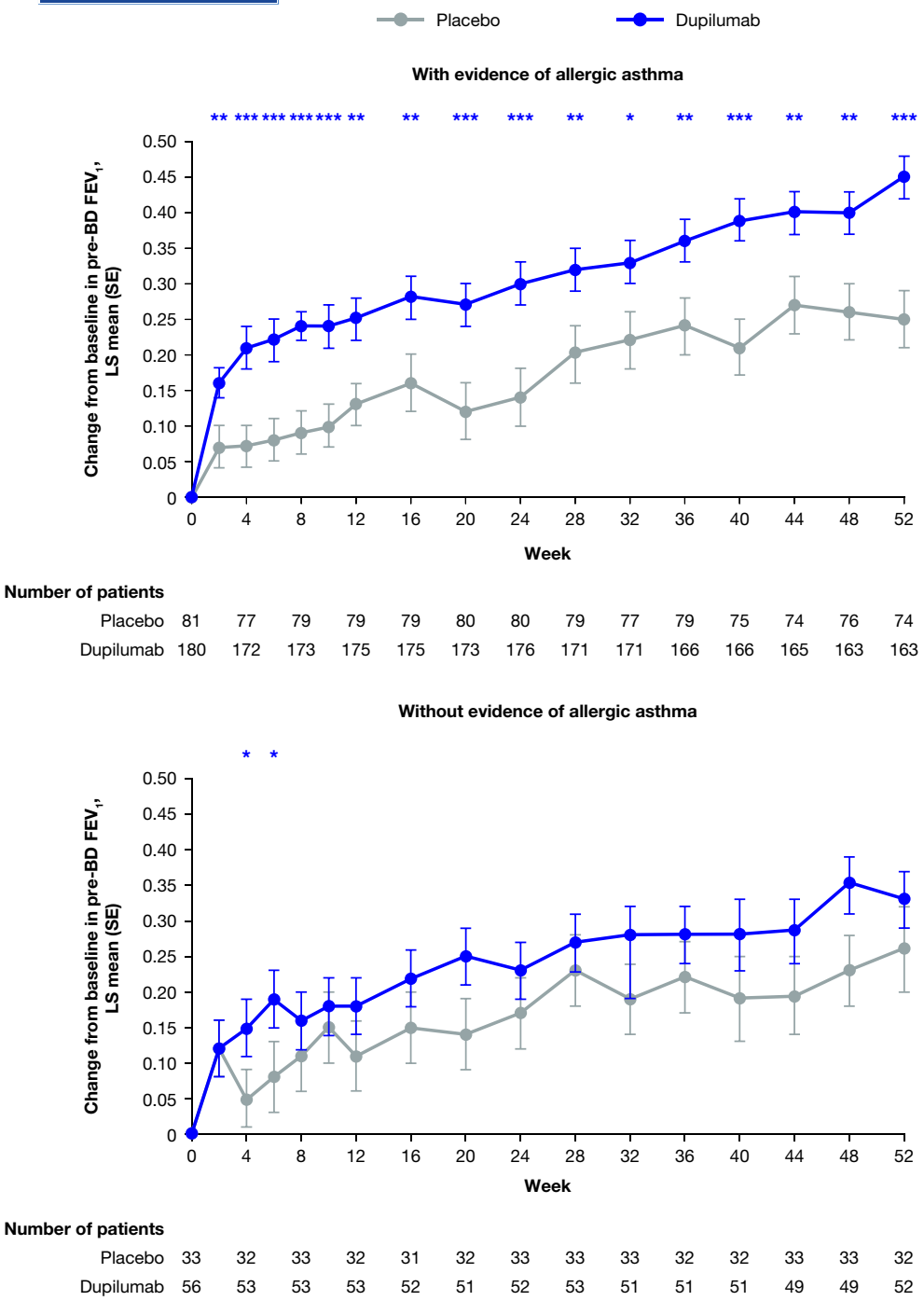


FIGURE 3 Change from baseline over time in absolute pre-bronchodilator FEV_1 in patients with type 2 asthma[a] with or without evidence of allergic asthma[b]. *$P < .05$, **$P < .01$, ***$P < .001$ versus placebo. [a]Type 2 asthma is defined as patients with asthma with baseline blood eosinophils ≥150 cells/μL or FeNO ≥20 ppb at baseline. [b]The allergic asthma phenotype is defined as patients with asthma and serum total IgE ≥30 IU/mL and ≥1 perennial aeroallergen-specific IgE ≥0.35 kU/L at baseline.

asthma control for both patients with and without evidence of allergic asthma, at most timepoints.[13]

The results for annualized exacerbation rates support the efficacy of dupilumab in children with type 2 asthma irrespective of evidence of allergic asthma, highlighting that suppression of IL-4 and IL-13 leads to clinically meaningful improvements in type 2 inflammatory asthma irrespective of the patient's allergic status. Given that 75% of children with type 2 asthma included in this analysis also had evidence of allergic asthma, determining the efficacy of dupilumab in this patient population is important, particularly since allergens are known to trigger asthma attacks in 60%–90% of children.[15]

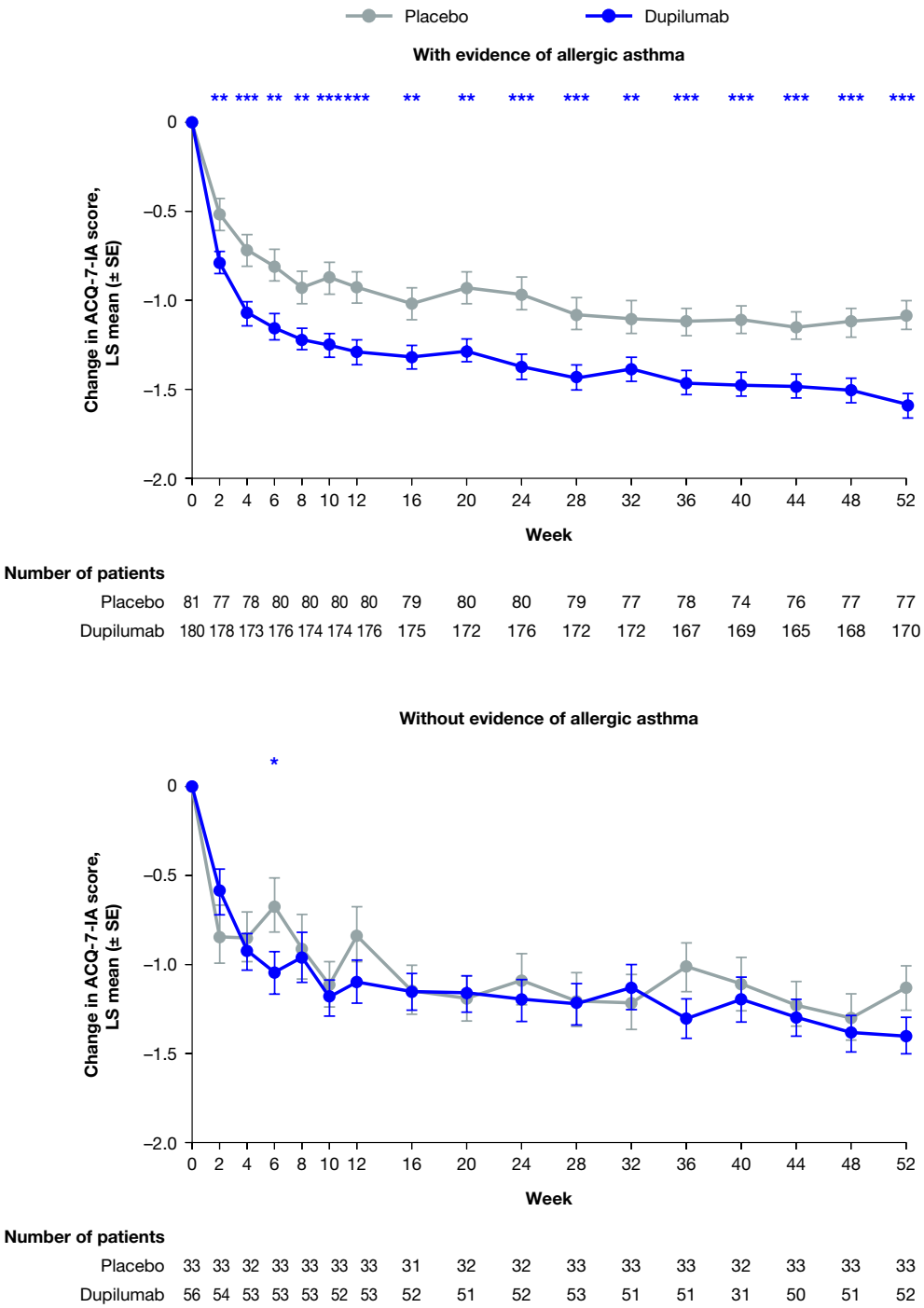


FIGURE 4 Change from baseline over time in ACQ-7-IA score in patients with type 2 asthma[a] with or without evidence of allergic asthma[b]. *$P < .05$, **$P < .01$, ***$P < .001$ versus placebo. [a]Type 2 asthma is defined as patients with asthma with baseline blood eosinophils ≥150 cells/μL or FeNO ≥20 ppb at baseline. [b]The allergic asthma phenotype is defined as patients with asthma and serum total IgE ≥30 IU/mL and ≥1 perennial aeroallergen-specific IgE ≥0.35 kU/L at baseline.

In the small population that did not have evidence of allergic asthma despite having evidence of type 2 inflammation, numerical improvements in lung function, were observed. Differences versus placebo in FEV_1 and ACQ-7-IA scores were not significant at most timepoints; however, small patient numbers in this post hoc analysis may provide inadequate statistical power. Additionally, in the subgroup without evidence of allergic asthma, dupilumab improved absolute pre-BD FEV_1 over baseline by 330 mL at Week 52; Santanello et al. have previously reported that patients perceive improvements in pre-BD $FEV_1 > 230$ mL as an indication of treatment success.[16]

The steady and sustained decrease in total IgE over the 52-week treatment period observed in dupilumab-treated patients with evidence of allergic asthma, is consistent with the mechanism of

action of dupilumab with reductions even greater than in QUEST,[17] and was also reported in the overall VOYAGE population.[12] In contrast, IgE levels in placebo patients without evidence of allergic asthma, who already had lower levels at baseline compared with the population with evidence of allergic asthma, remained stable or even rose slightly relative to baseline. Dupilumab treatment also reduced allergen-specific serum IgE levels against six of the eight perennial aeroallergens tested. Why dupilumab did not affect specific IgE levels in two of the three fungal allergens tested (*Cladosporium herbarum/hormodendrum* and *Aspergillus fumigatus*) but was effective at reducing IgE directed against *Alternaria tenuis/alternata* is presently unclear. In addition, reductions for IgE against three allergens were only observed in patients with multi-allergen sensitizations, who had higher baseline concentrations of total serum IgE compared with those who had only one (mono) sensitization or non-sensitized patients. Since polysensitization to ≥2 food and/or aeroallergens is a known risk factor for the development of asthma,[18] it may be the case that patients who exhibited multi-allergen sensitization may have been more responsive to suppression of type 2 inflammation.

A limitation of this study was the post hoc nature of the analyses, as the study was not primarily designed or powered to investigate differences between type 2 patients with or without evidence of allergic asthma. As only 25% of type 2 patients had no evidence of allergic asthma, and the study design included a 2:1 dupilumab: placebo treatment allocation, the proportion of patients without evidence of allergic asthma receiving placebo was less than 10% of the total population evaluated. Therefore, although findings in the population with evidence of allergic asthma are robust, the inconsistent statistical significance observed across efficacy variables in the non-allergic population should be interpreted with caution.

Second, the racial distribution of patients included in the study also potentially limits extrapolation across populations. The vast majority of patients were White (>85% in each analysis group), and therefore results may differ in more racial diverse populations.

Another limitation was how allergic status was identified. The allergic status was identified post hoc to a defined set of common aeroallergens, percutaneous allergy skin testing was not performed and allergic reactions to the panel of aeroallergens were based solely on specific IgE levels at a baseline of ≥0.35 kU/L. Furthermore, as no pollen or spore counts or home allergen levels were performed during the study to assess the amount of allergen present in individual participants' homes and/or geographic areas, it is not possible to ascertain the degree to which each patient was exposed to these allergens.

A further limitation is the definition of allergic asthma used in this study, as it allows that the subgroup of patients without evidence of allergic asthma may have had either IgE ≥30 IU/mL or ≥1 positive specific allergen. Also, some patients without evidence of allergic asthma may have been sensitized to allergens not included in the panel. Further studies to investigate the efficacy of dupilumab treatment more specifically in children with moderate-to-severe type 2 asthma with or without evidence of allergic asthma might be needed to help physicians optimally tailor treatment in this patient population.

The majority of children aged 6–11 years with moderate-to-severe asthma from VOYAGE presented characteristics of type 2 inflammation at baseline (elevated blood eosinophils or FeNO). Among the VOYAGE patients with type 2 asthma, the majority also exhibited evidence of allergic asthma. Dupilumab versus matched placebo significantly reduced severe exacerbation rates irrespective of evidence of allergic asthma at baseline. Improvements in lung function parameters were also observed but to a lower degree in patients without evidence of allergic asthma.

Taken together, these data support the role of dupilumab in treating pediatric patients aged 6–11 years with moderate-to-severe asthma, regardless of evidence of allergic asthma. However, the patient cohort without evidence of allergic asthma was small as mentioned earlier, thus the data should be interpreted with caution. Patients with evidence of allergic asthma demonstrated clinically meaningful responses to dupilumab treatment, supporting the role of IL-4 and IL-13, and thus type 2 inflammation, as key drivers of certain patients with allergic asthma. The position of dupilumab among other biologics in severe allergic pediatric asthma remains to be determined by comparative studies, aimed at identifying the most appropriate biomarkers of responsiveness.[19,20]

AUTHOR CONTRIBUTIONS

Leonard B. Bacharier, Jorge F. Maspero, Alessandro Fiocchi acquired data. David J. Lederer, Megan Hardin, Rebecca Gall, Michel Djandji, Shahid Siddiqui, Juby A. Jacob-Nara, Yamo Deniz, Paul J Rowe contributed to the conception and design of the study. Nadia Daizadeh did statistical analyses. All authors participated in the interpretation of the data, provided critical feedback and final approval for submission, and took responsibility for the accuracy, completeness, and protocol adherence of data and analyses. All investigators had confidentiality agreements with the sponsors.

ACKNOWLEDGMENTS

This research was sponsored by Sanofi and Regeneron Pharmaceuticals Inc.; ClinicalTrials.gov Identifier: NCT02948959. Medical writing/editorial assistance was provided by Natalia Crespo, of Excerpta Medica, and was funded by Sanofi and Regeneron Pharmaceuticals Inc., according to the Good Publication Practice guideline.

FUNDING INFORMATION

Funded by Sanofi and Regeneron Pharmaceuticals Inc.; ClinicalTrials.gov identifier: NCT02948959.

CONFLICT OF INTEREST STATEMENT

Papadopoulos NG: AstraZeneca, Boehringer Ingelheim, GSK, HAL Allergy, Menarini, Mylan, Novartis, Nutricia, OM Pharma, Regeneron Pharmaceuticals Inc., Sanofi—speaker, advisory board member.

Szefler SJ: AstraZeneca, GSK, Moderna, OM Pharma, Propeller Health, Regeneron Pharmaceuticals Inc., Sanofi—consultant fees paid to the university. Bacharier LB: AstraZeneca, GSK, Regeneron Pharmaceuticals Inc., Sanofi—speaker fees; Cystic Fibrosis Foundation, Vertex, AstraZeneca, DBV Technologies—data and safety monitoring board; NIH, Sanofi—research support. Maspero JF: AstraZeneca, Sanofi—consultant; GSK, Menarini, Novartis, Uriach—speaker fees; Novartis—research grants. Domingo C: ALK, Allergy Therapeutics, Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, Esteve, Ferrer Pharma, GSK, HAL Allergy, Inmunotek, Menarini, Novartis, Pfizer, sanofi-aventis, Stallergenes Greer, Takeda, Teva—travel and speaker fees. Fiocchi AG: Danone SA, Hipp GmbH, Abbott SA, Novartis, Ferrero—speaker, advisory board member. Sanofi, Novartis, Ferrero—research grants. Lee JK: AstraZeneca, GSK, Novartis, Regeneron Pharmaceuticals Inc., Genentech, Sanofi, ALK, Medexus, Miravo, Bausch Health, Takeda, CSL—speaking fees. Research funding and clinical trials from AstraZeneca, GSK, Takeda, Regeneron Pharmaceuticals Inc., Novartis, Genentech, Sanofi. Daizadeh N: Sanofi—former employee, may hold stock and/or stock options in the company. Hardin M, Jacob-Nara JA, Djandji M, Rowe PJ: Sanofi—employees, may hold stock and/or stock options in the company. Lederer DJ, Deniz Y, Gall R, Siddiqui S: Regeneron Pharmaceuticals Inc.—employees and share holders.

ORCID

Nikolaos G. Papadopoulos https://orcid.org/0000-0002-4448-3468
Jorge F. Maspero https://orcid.org/0000-0001-9750-2346
Alessandro Fiocchi https://orcid.org/0000-0002-2549-0523

REFERENCES

1. Licari A, Manti S, Castagnoli R, Leonardi S, Marseglia GL. Measuring inflammation in paediatric severe asthma: biomarkers in clinical practice. *Breathe (Sheff)*. 2020;16(1):190301.
2. Zoratti EM, Krouse RZ, Babineau DC, et al. Asthma phenotypes in inner-city children. *J Allergy Clin Immunol*. 2016;138(4):1016-1029.
3. Canonica GW, Blasi F, Crimi N, et al. Defining type 2 asthma and patients eligible for dupilumab in Italy: a biomarker-based analysis. *Clin Mol Allergy*. 2021;19(1):5.
4. Fahy JV. Type 2 inflammation in asthma—present in most, absent in many. *Nat Rev Immunol*. 2015;15(1):57-65.
5. Wenzel SE. Emergence of biomolecular pathways to define novel asthma phenotypes. Type-2 immunity and beyond. *Am J Respir Cell Mol Biol*. 2016 Jul;55(1):1-4.
6. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. 2022 Accessed October 24, 2022. www.ginasthma.org
7. Macdonald LE, Karow M, Stevens S, et al. Precise and in situ genetic humanization of 6 Mb of mouse immunoglobulin genes. *Proc Natl Acad Sci USA*. 2014;111:5147-5152.
8. Murphy AJ, Macdonald LE, Stevens S, et al. Mice with megabase humanization of their immunoglobulin genes generate antibodies as efficiently as normal mice. *Proc Natl Acad Sci USA*. 2014;111:5153-5158.
9. Gandhi NA, Bennett BL, Graham NM, Pirozzi G, Stahl N, Yancopoulos GD. Targeting key proximal drivers of type 2 inflammation in disease. *Nat Rev Drug Discov*. 2016 Jan;15(1):35-50.
10. DUPIXENT® (dupilumab). *Highlights of Prescribing Information*. US Food and Drug Administration. 2022. Accessed October 24, 2022. https://www.regeneron.com/sites/default/files/Dupixent_FPI.pdf
11. DUPIXENT® (dupilumab). *Summary of Product Characteristics*. European Medicines Agency. 2022. Accessed October 24, 2022. https://www.ema.europa.eu/en/documents/product-information/dupixent-epar-product-information_en.pdf
12. Bacharier LB, Maspero JF, Katelaris CH, et al. Dupilumab in children with uncontrolled moderate-to-severe asthma. *N Engl J Med*. 2021;385:2230-2240.
13. Corren J, Castro M, O'Riordan T, et al. Dupilumab efficacy in patients with uncontrolled, moderate-to-severe allergic asthma. *J Allergy Clin Immunol Pract*. 2020;8(2):516-526.
14. Global strategy for asthma management and prevention. Updated 2015. Accessed October 24, 2022 https://ginasthma.org/wp-content/uploads/2016/01/GINA_Pocket_2015.pdf
15. Do DC, Zhao Y, Gao P. Cockroach allergen exposure and risk of asthma. *Allergy*. 2016;71(4):463-474.
16. Santanello NC, Zhang J, Seidenberg B, Reiss TF, Barber BL. What are minimal important changes for asthma measures in a clinical trial? *Eur Respir J*. 1999;14(1):23-27.
17. Castro M, Corren J, Pavord ID, et al. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. *N Engl J Med*. 2018;378:2486-2496.
18. Biagini Myers JM, Schauberger E, He H, et al. A pediatric asthma risk score to better predict asthma development in young children. *J Allergy Clin Immunol*. 2019;143(5):1803-1810.e2.
19. Charriot J, Maravic M, Huguet M, Vachier I, Suehs C, Bourdin A. "Real-life" management of patients with severe asthma in the biologics era: can we do better? *World Allergy Organ J*. 2021;14(4):100528.
20. Yu L, Zhang H, Pan J, Ye L. Pediatric usage of omalizumab: a promising one. *World Allergy Organ J*. 2021;14(12):100614.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Papadopoulos NG, Szefler SJ, Bacharier LB, et al. Assessment of dupilumab in children with moderate-to-severe type 2 asthma with or without evidence of allergic asthma. *Allergy*. 2023;78:2157-2167. doi:10.1111/all.15743