Original Article

Dupilumab Efficacy and Safety in Children With Moderate to Severe Asthma and High Blood Eosinophils: A *Post Hoc* Analysis of VOYAGE

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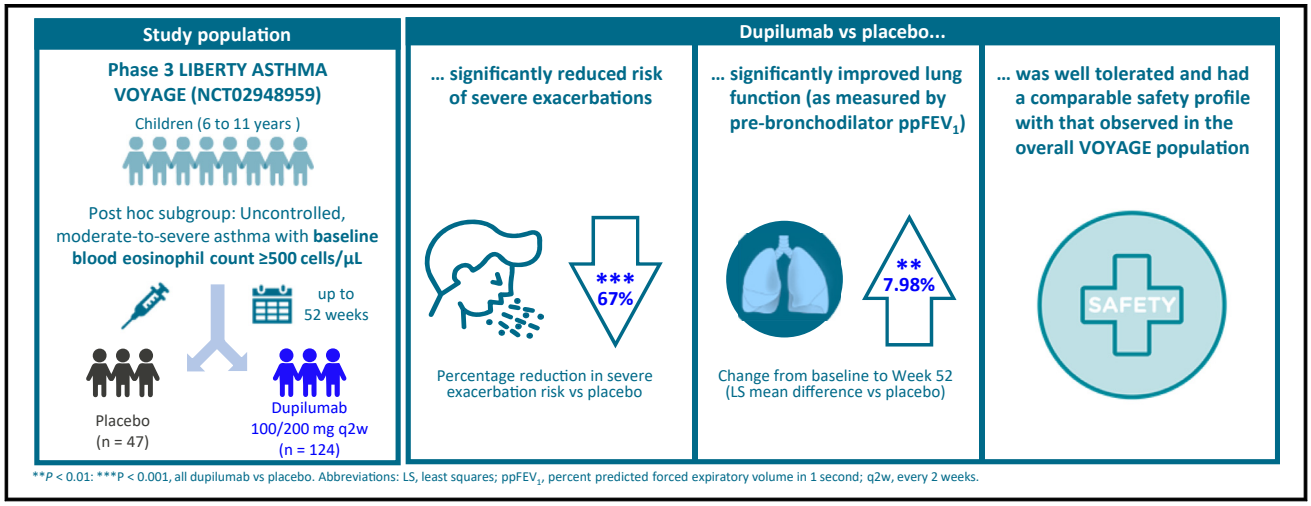
What is already known about this topic? Early, transient increases in blood eosinophil levels have been observed on initiation of dupilumab, which may put children with moderate to severe asthma and elevated blood eosinophil counts at risk of eosinophilia with dupilumab treatment.

What does this article add to our knowledge? In children with moderate to severe asthma and baseline blood eosinophils 500 to 1500 cells/μL, the safety profile and efficacy of dupilumab were consistent with the overall VOYAGE population.

How does this study impact current management guidelines? This study suggests that children with moderate to severe asthma and blood eosinophil counts greater than or equal to 500 cells/μL are not at increased risk for eosinophilia with dupilumab treatment.

VISUAL SUMMARY



BACKGROUND: Elevated blood or tissue eosinophils are considered to characterize type 2 inflammation in children with asthma and are associated with increased exacerbation rates and worse asthma control. Dupilumab, a human mAb that blocks type 2 inflammatory drivers IL-4 and IL-13, reduced severe exacerbation rates and improved lung function versus placebo in children aged 6

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Abbreviations used
FENO- fractional exhaled nitric oxide
ICS- inhaled corticosteroid
ppb- parts per billion
ppFEV$_1$- percent predicted FEV$_1$
q2w- every 2 weeks
SAE- serious adverse event
TEAE- treatment-emergent adverse event

to 11 years with uncontrolled moderate to severe asthma in the phase 3 LIBERTY ASTHMA VOYAGE study (NCT02948959).
OBJECTIVE: To assess dupilumab efficacy and safety in children from VOYAGE with moderate to severe asthma and greater than or equal to 500 and less than 1500 blood eosinophils/μL at baseline.
METHODS: Children received add-on dupilumab (100/200 mg by body weight) or matched placebo every 2 weeks for 52 weeks. We assessed annualized severe exacerbation rates, least squares mean change from baseline in prebronchodilator percent predicted FEV$_1$, and incidence of treatment-emergent adverse events.
RESULTS: In children with elevated baseline eosinophils (N = 174), dupilumab versus placebo significantly reduced annualized exacerbation rates by 67% (95% CI, 38%-82%; $P < .001$) and improved prebronchodilator percent predicted FEV$_1$ from baseline at weeks 24 and 52 (week 24 least squares mean difference, 7.58 percentage points; 95% CI, 2.85-12.31; $P = .002$; week 52 least squares mean difference, 7.98 percentage points; 95% CI, 2.17-13.78; $P = .007$). The incidence of treatment-emergent adverse events was similar with dupilumab and placebo.
CONCLUSIONS: Dupilumab significantly reduced severe exacerbations and improved lung function in children with moderate to severe asthma and baseline blood eosinophil counts greater than or equal to 500 and less than 1500 cells/μL, with a safety profile comparable with the overall study population. **(J Allergy Clin Immunol Pract 2024;■:■-■)**

Key words: *Asthma; Exacerbation; Percentage predicted FEV$_1$; Dupilumab; Eosinophilia*

INTRODUCTION

Type 2 inflammation, the most common type of inflammation observed in children with asthma, is primarily driven by the cytokines IL-4, IL-5, and IL-13, and characterized by elevated type 2 biomarkers such as blood or sputum eosinophil counts, fractional exhaled nitric oxide (FENO) and, in allergen-driven asthma, elevated total/specific IgE.[1-3] Whether allergic or nonallergic asthma, type 2 inflammation is associated with elevated blood and airway eosinophils. These cells are involved in immune-modulatory responses in asthma, leading to airway hyperresponsiveness, damage to the epithelial lining, increased mucus secretion, and airway remodeling.[1,4] Elevated levels of eosinophils are commonly observed in the airways of children with severe asthma compared with other inflammatory cells.[1] Elevated peripheral eosinophil counts have been found to be predictors of asthma exacerbations in children, with increasing peripheral eosinophil counts associated with increasing exacerbation risk.[5-8]

Dupilumab is a fully human mAb that blocks the shared receptor component for IL-4 and IL-13, key and central drivers of type 2 inflammation in multiple diseases.[3,9,10] It is approved in the United States for children aged 6 years and older with moderate to severe asthma with an eosinophilic phenotype[11] and in the European Union in children aged 6 years and older with severe asthma with type 2 inflammation.[12]

In the phase 3 LIBERTY ASTHMA VOYAGE study (NCT02948959), add-on dupilumab 100/200 mg by body weight given every 2 weeks (q2w) versus placebo reduced severe asthma exacerbations and improved percent predicted FEV$_1$ (ppFEV$_1$) as early as week 12 of treatment in children aged 6 to 11 years with moderate to severe type 2 asthma (defined as baseline blood eosinophil counts ≥150 cells/μL or FENO ≥20 parts per billion [ppb]).[13] Similar results were seen in the subgroup of children with blood eosinophil counts greater than or equal to 300 cells/μL at baseline—a subgroup of children with type 2 inflammatory asthma of interest to clinicians. Dupilumab was generally well tolerated in this study with an acceptable safety profile.[13]

This *post hoc* analysis evaluated dupilumab safety and efficacy in children with moderate to severe asthma and baseline blood eosinophils greater than or equal to 500 cells/μL enrolled in the

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Conflicts of interest: D. J. Jackson reports consulting for AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline (GSK), Novartis, Regeneron Pharmaceuticals, Inc, Sanofi, and Vifor Pharma and participation on a data and safety monitoring board for Pfizer. E. Hamelmann reports participating as speaker and an advisory board member for Aimmune Therapeutics, ALK, AstraZeneca, Boehringer Ingelheim, GSK, HAL Allergy, Novartis, Nutricia, Sanofi, and Stallergenes Greer. G. Roberts reports participation on a data and safety monitoring board for Merck and as a speaker and advisory board member for ALK-Abelló. L. B. Bacharier reports speaker fees from AstraZeneca, GSK, Regeneron Pharmaceuticals, Inc, and Sanofi, participation on a data and safety monitoring board for Cystic Fibrosis Foundation and DBV Technologies, and research support from the National Institutes of Health, Sanofi, and Vectura. C. Xia, R. Gall, A. Coleman, A. Radwan, and Y. Deniz are employees and shareholders of Regeneron Pharmaceuticals, Inc. O. Ledanois, K. Tawo, J. A. Jacob-Nara, and P. J. Rowe are employees of Sanofi and may hold stock and/or stock options in the company.

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TABLE I. Baseline demographic and clinical characteristics of children with moderate to severe asthma with blood eosinophils ≥500 cells/μL at VOYAGE baseline—ITT population

Characteristic	Placebo (n = 48)	Dupilumab (n = 126)
Sex: female, n (%)	16 (33)	38 (30)
Age (y), mean ± SD	9.2 ± 1.5	8.8 ± 1.6
High ICS dose, n (%)	24 (50)	54 (43)
Severe asthma exacerbations in previous year (n), mean ± SD	2.02 ± 1.25	3.06 ± 3.22
Severe asthma exacerbations in previous year, n (%)		
1	23 (48)	44 (35)
2	10 (21)	32 (25)
3	10 (21)	13 (10)
≥4	5 (10)	37 (29)
Prebronchodilator FEV_1 (L), mean ± SD	1.51 ± 0.44	1.42 ± 0.40
Prebronchodilator ppFEV_1 (%), mean ± SD	77.57 ± 16.40	78.00 ± 16.65
Prebronchodilator ppFEV_1<80%, n (%)	27 (56.3)	63 (50.0)
FEV_1 reversibility (L), mean ± SD	0.25 ± 0.20	0.27 ± 0.21
With ongoing atopic medical condition,* n (%)	47 (97.9)	125 (99.2)
Eosinophils (cells/μL), median (Q1-Q3)	675.0 (570.0-955.0)	760.0 (620.0-1070.0)
F_{ENO} (ppb), median (Q1-Q3)	28.0 (17.0-45.0)	28.0 (16.0-48.0)
Total IgE (IU/mL), median (Q1-Q3)	554.0 (215.0-1144.0)	754.50 (425.0-1666.0)

ITT, Intention-to-treat.

*A patient is considered to have ongoing atopic medical condition if he or she has any of the following ongoing conditions: atopic dermatitis, allergic conjunctivitis, allergic rhinitis, eosinophilic esophagitis, food allergy, hives; or has baseline total IgE ≥100 IU/mL and at least 1 aeroallergen specific IgE is positive (≥0.35 IU/mL) at baseline.

VOYAGE study and evaluated both general safety and eosinophilia-related safety of dupilumab in this population.

METHODS

Study design and oversight

Full details of the LIBERTY ASTHMA VOYAGE (NCT02948959) study have been described previously.[13] In brief, VOYAGE was a 52-week phase 3, randomized, double-blind, placebo-controlled, parallel-group, multinational study that assessed the efficacy and safety of dupilumab in children aged 6 to 11 years with uncontrolled moderate to severe asthma.[13] The study was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonisation 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. All parents/guardians provided written informed consent before participating in the trial. All children provided assent according to the Ethics Committee (Institutional Review Board/Independent Ethics Committee)-approved standard practice for pediatric patients at each study center.

Patients and interventions

Children aged 6 to 11 years were eligible to participate in VOYAGE if they had physician-diagnosed moderate to severe asthma based on the Global Initiative for Asthma (GINA) 2020 guidelines.[13,14] Full details of inclusion and exclusion criteria have been described previously.[13] Patients with blood eosinophils more than 1500 cells/μL at baseline were excluded from VOYAGE. Eligible patients were randomized 2:1 to receive subcutaneous dupilumab (100/200 mg by body weight at randomization) every 2 weeks, or volume-matched placebo, for 52 weeks.[13] This *post hoc* analysis included children in VOYAGE with high eosinophil counts defined as blood eosinophil counts greater than or equal to 500 cells/μL at baseline.

End points

The efficacy end points assessed in this analysis included (1) annualized severe exacerbation rate during the 52-week treatment period (defined as a deterioration of asthma requiring the use of systemic corticosteroids for at least 3 days, or asthma-related hospitalization or emergency department visit leading to administration of systemic corticosteroids); (2) least squares mean change from baseline in prebronchodilator ppFEV_1 (relative difference values: difference between postbaseline values and baseline values); and (3) mean (± SE) change from baseline in blood eosinophil count.

A severe asthma exacerbation before the study was defined as any treatment with 1 or more systemic (oral or parenteral) steroid bursts for worsening asthma or hospitalization or an emergency/urgent medical care visit for worsening asthma. Measurement of prebronchodilator FEV_1 was performed after a bronchodilator wash-out period determined by the duration of action of the bronchodilator (eg, ≥6 hours after the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol, ≥12 hours after the last dose of long-acting β_2-agonist, and ≥24 hours after the last dose of long-acting muscarinic antagonist).

Safety data were collected for the 52-week treatment period. Safety end points included frequency of patients reporting treatment-emergent adverse events (TEAEs), including System Organ Classes with adverse events occurring with a frequency of 5% or more by preferred term in any treatment group, and treatment-emergent serious adverse events (SAEs).

Statistical analyses

Efficacy and safety analyses were performed for the group of patients from VOYAGE with blood eosinophil counts greater than or equal to 500 cells/μL at baseline. The intention-to-treat population (N = 174) was used for efficacy analyses and summary of

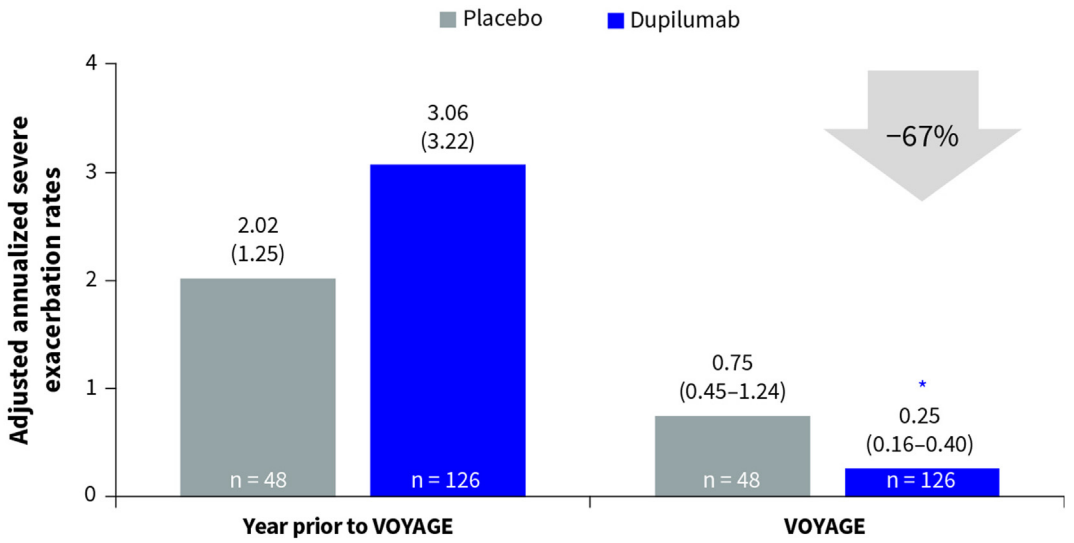


FIGURE 1. Annualized severe exacerbation rates in children with moderate to severe asthma and blood eosinophil counts greater than or equal to 500 cells/μL at VOYAGE baseline—ITT population. *$P < .001$ vs matching placebo. *ITT,* Intention-to-treat.

baseline demographic and disease characteristics. Safety data were tabulated from the safety population (N = 171).

Annualized severe exacerbation rates were derived using a negative binomial model, with the total number of events occurring from randomization up to week 52 or last contact date (whichever came earlier) as the response variable, pooled treatment groups, age, baseline weight group (≤30 kg, >30 kg), baseline FENO level (<20 ppb, ≥20 ppb), baseline inhaled corticosteroid (ICS) dose level, region, and number of severe exacerbation events within 1 year before the study as covariates, and log-transformed standardized observation duration as an offset variable.

Risk of severe exacerbation at week 52 was derived using a negative binomial model, with the total number of events onset from week 12 up to week 52 visit or last contact date (whichever came earlier) as the response variable, the treatment group, baseline weight group, age, region, baseline eosinophil level, baseline FENO level, baseline ICS dose level, and number of severe exacerbation events within 1 year before the study as covariates, and log-transformed standardized observation duration as an offset variable.

Change from baseline in prebronchodilator $ppFEV_1$ was derived using a mixed-effect model with repeated-measures approach, with change from baseline in prebronchodilator $ppFEV_1$ values up to week 52 as the response variable, and treatment, baseline weight group, region, ethnicity, baseline eosinophil level, baseline FENO level, baseline ICS dose level, visit, Treatment × Visit interaction, baseline $ppFEV_1$ value, and Baseline × visit interaction as covariates. Analyses of FEV_1 were performed using race-neutral reference equations.[15]

RESULTS

Study patients

Of the 408 children who underwent randomization in VOYAGE, 174 had blood eosinophil counts greater than or equal to 500 cells/μL at baseline and were included in this analysis: 126 were randomized to dupilumab 100/200 mg q2w by body weight and 48 to matched placebo q2w. Baseline characteristics were similar across treatment arms, although the occurrence of 4 or more severe asthma exacerbations in the previous year and baseline eosinophils tended to be higher in children treated with dupilumab versus placebo. The baseline characteristics of children included in this analysis are provided in Table I.

Annualized rate of severe asthma exacerbations

In children with moderate to severe asthma and baseline eosinophils greater than or equal to 500 cells/μL, the adjusted annualized severe asthma exacerbation rate over VOYAGE was 0.249 (95% CI, 0.156-0.397) in the dupilumab group and 0.749 (95% CI, 0.453-1.239) in the placebo group, with a relative risk reduction versus placebo of 67% (95% CI, 38%-82%; $P < .001$) (Figure 1).

Prebronchodilator $ppFEV_1$

At week 52, dupilumab significantly improved prebronchodilator $ppFEV_1$ in children with eosinophil counts greater than or equal to 500 cells/μL at baseline compared with placebo (Figure 2). Significant improvements versus placebo were observed as early as week 2, and were maintained throughout the 52-week treatment period, with a least squares mean difference versus placebo of 7.41 percentage points (95% CI, 2.48-12.34; $P = .003$) at week 24 and 7.76 percentage points (95% CI, 1.70-13.82; $P = .012$) at week 52.

Blood eosinophil count over time

In children with moderate to severe asthma and baseline blood eosinophil count greater than or equal to 500 cells/μL, dupilumab treatment resulted in a transient increase in mean ± SE blood eosinophils at week 12 of VOYAGE, which was reduced by week 24; by week 52, mean ± SE blood eosinophils were below baseline values. Children who received placebo showed a similar transient and small increase in mean ± SE blood eosinophils at week 12, which also resolved by week 24, with levels falling to below baseline and to similar levels to the dupilumab group by week 52 (Figure 3, *A*). A sustained decrease in median (Q1-Q3) blood eosinophils was observed in both dupilumab and

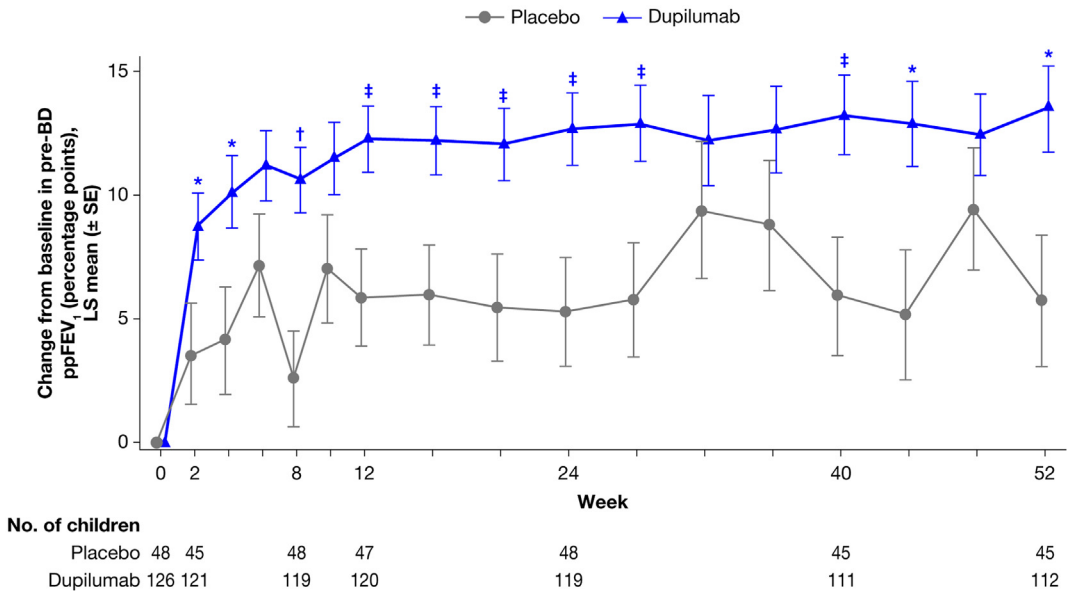


FIGURE 2. Relative difference change from baseline in prebronchodilator $ppFEV_1$ over time in children with moderate to severe asthma and blood eosinophils greater than or equal to 500 cells/μL at VOYAGE baseline—ITT population. *$P < .05$, †$P < .001$, ‡$P < .01$ vs matching placebo. *BL,* Baseline; *ITT,* intention-to-treat; *LS,* least squares; *pre-BD,* prebronchodilator.

placebo groups from baseline to week 52. At week 52, median (Q1-Q3) blood eosinophil levels were reduced to below baseline for both dupilumab and placebo groups (Figure 3, *B*).

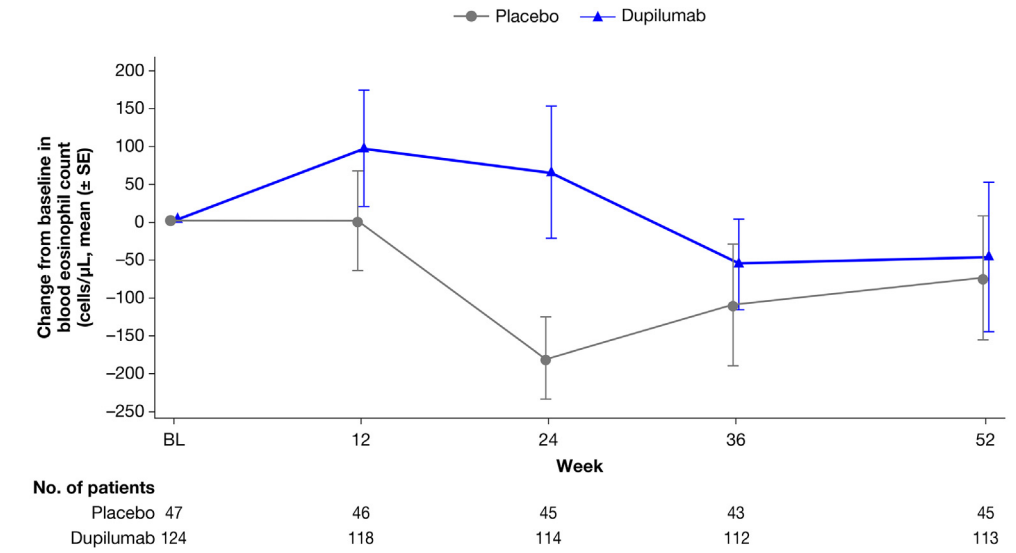
Safety

In VOYAGE, dupilumab was shown to be well tolerated with an acceptable safety profile in the overall safety population. In this *post hoc* analysis of children with baseline blood eosinophil counts greater than or equal to 500 cells/μL, the incidence of TEAEs was broadly similar between children who received dupilumab and those who received placebo (Table II), with at least 1 event reported in 106 (85.5%) and 35 (74.5%) children in the dupilumab group and the placebo group, respectively. Most were mild or moderate in intensity. Treatment-emergent SAEs were reported in 10 (8.1%) children in the dupilumab group and 2 (4.3%) children in the placebo group. Most were considered not to be related to treatment by the investigator. Treatment was discontinued in 1 child in the dupilumab group, who had a baseline eosinophil count of 600 cells/μL, due to a TEAE of moderate intensity (erythema multiforme) that was nonserious and resolved following corrective treatment. The most common TEAEs reported in children with baseline blood eosinophil counts greater than or equal to 500 cells/μL were similar to those in the overall VOYAGE safety population (Table II).

In children with blood eosinophil counts greater than or equal to 500 cells/μL, on-treatment eosinophilia (defined as >3000 cells/μL) was detected in 15 (12.1%) and 1 (2.1%) children receiving dupilumab and placebo, respectively, all of which were mild to moderate in intensity, with 3 (2.4%) cases in the dupilumab group being considered related to treatment by the investigator (Table III). All children with on-treatment eosinophilia were recovered or recovering by the end of the study. Corrective treatment was required in 1 child in the dupilumab group, who had a baseline eosinophil count of 800 cells/μL. The child reported generalized myalgia and arthralgia alongside eosinophilia and was subsequently diagnosed with enterobiasis. The child was successfully treated with mebendazole, with resolution of myalgia and arthralgia, and of eosinophilia. Dupilumab treatment was temporarily interrupted until eosinophilia had resolved. Eosinophilia in this child was considered not likely to be related to dupilumab. Only 1 treatment-emergent SAE of eosinophilia occurred during the study in a child with a prior history of hypereosinophilia who was treated with dupilumab. The child was hospitalized to rule out suspected parasitic infection; treatment with dupilumab was continued. The event was not considered related to treatment and was resolved by the end of the study.

DISCUSSION

Although asthma is traditionally defined as a chronic respiratory disease characterized by reversible airflow obstruction and airway hyperresponsiveness and inflammation, current definitions acknowledge its heterogeneous nature, with varying demographic, clinical, and pathophysiologic characteristics clustered into distinct phenotypes.[16] Given the complexity of the disease and the distinct mechanisms driving airway inflammation for each phenotype, a generalized approach to asthma treatment may not be effective in some cases, and phenotype-guided therapies are needed. For instance, although ICSs are the mainstay of therapy for asthma, children with moderate to severe disease may remain symptomatic and at risk for severe exacerbations despite ICS use. In such cases, phenotype-guided treatment with biologics may be used as add-on therapy, especially in children with a type 2 inflammatory asthma phenotype.[16] Several biologics have already been approved for use in children aged 6 to 11 years with asthma: omalizumab (anti-IgE),[17] mepolizumab (anti—IL-5),[18] benralizumab (anti—IL-5),[19] and dupilumab (anti—IL-4/13).[11] The phase 3 LIBERTY ASTHMA VOYAGE



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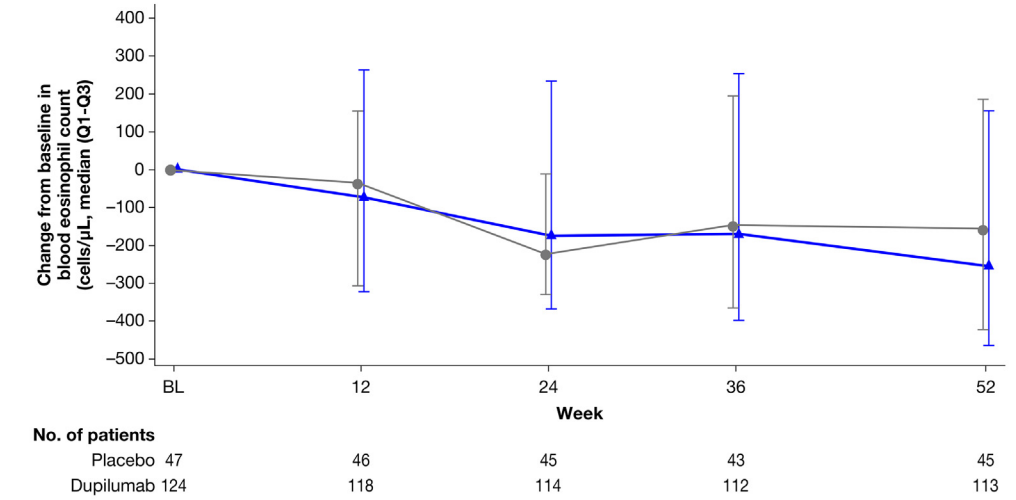

Median (Q1: Q3) change, cells/µl

Placebo	0	−45 (−320 : +150)	−230 (−340 : −20)	−160 (−380 : +190)	−170 (−440 : +180)
Dupilumab	0	−80 (−330 : +260)	−180 (−380 : +230)	−180 (−410 : +250)	−270 (−480 : +150)

B

FIGURE 3. Changes in blood eosinophils over time in children with moderate to severe asthma and blood eosinophil counts greater than or equal to 500 cells/µL at VOYAGE baseline reported as (**A**) mean change ± SE and (**B**) median changes (Q1-Q3)—safety population. *BL,* Baseline; *Q,* quartile.

study demonstrated the efficacy of dupilumab in reducing severe asthma exacerbations and improving lung function in children aged 6 to 11 years with uncontrolled moderate to severe asthma.[13]

The current *post hoc* analysis evaluated the efficacy and safety of dupilumab in the subgroup of children from VOYAGE with eosinophils greater than or equal to 500 cells/µL at baseline. This patient group is of interest to clinicians due to the role that eosinophils play in the pathophysiology of asthma and their association with increased disease burden. These cells comprise a predominant inflammatory cell type in the airways of children with severe disease,[1] and have been shown to correlate with airway hyperresponsiveness, asthma severity, asthma exacerbations, and hospitalizations in children with asthma, and may be predictive of future exacerbation risk.[1,5-8]

Results of this *post hoc* analysis of VOYAGE in children aged 6 to 11 years with moderate to severe asthma showed that dupilumab treatment led to significant reductions in severe exacerbation rate and improvements in lung function ($ppFEV_1$) in patients with blood eosinophil count greater than or equal to 500

TABLE II. Summary of safety findings and TEAEs by System Organ Class with any preferred term frequency ≥5% in children with moderate to severe asthma and blood eosinophil count ≥500 cells/μL at VOYAGE baseline—Safety population

Adverse events, n (%)	Placebo (n = 47)	Dupilumab (n = 124)
Children with any TEAE	35 (74.5)	106 (85.5)
Children with any treatment-emergent SAE	2 (4.3)	10 (8.1)
Children with any TEAE leading to permanent treatment discontinuation	0	1 (1.08)
Children with any TEAE leading to death	0	0
Infections	29 (61.7)	85 (68.5)
Nasopharyngitis	9 (19.1)	27 (21.8)
Viral upper respiratory tract infection	3 (6.4)	18 (14.5)
Upper respiratory tract infection	7 (14.9)	15 (12.1)
Pharyngitis	8 (17.0)	11 (8.9)
Influenza	3 (6.4)	10 (8.1)
Bronchitis	6 (12.8)	7 (5.6)
Sinusitis	4 (8.5)	3 (2.4)
Acute otitis media	3 (6.4)	2 (1.6)
Blood and lymphatic system disorder	2 (4.3)	14 (11.3)
Eosinophilia	1 (2.1)	13 (10.5)
Nervous system disorders	6 (12.8)	12 (9.7)
Headache	6 (12.8)	11 (8.9)
Respiratory, thoracic, and mediastinal disorders	10 (21.3)	29 (23.4)
Allergic rhinitis	5 (10.6)	12 (9.7)
Gastrointestinal disorders	5 (10.6)	17 (13.7)
Vomiting	4 (8.5)	2 (1.6)
Skin and subcutaneous tissue disorders	5 (10.6)	18 (14.5)
Atopic dermatitis	2 (4.3)	9 (7.3)
General disorders and administration- site disorders	9 (19.1)	29 (23.4)
Injection-site erythema	5 (10.6)	16 (12.9)
Injection-site edema	3 (6.4)	13 (10.5)
Pyrexia	1 (2.1)	8 (6.5)
Injection-site nodule	1 (2.1)	7 (5.6)
Injection-site rash	4 (8.5)	0

TABLE III. Summary of safety outcomes in children with moderate to severe asthma and blood eosinophil count ≥500 cells/μL at VOYAGE baseline who experienced treatment-emergent eosinophilia*—Safety population

Children with ≥500 cells/μL at baseline, n (%)	Placebo (n = 47)	Dupilumab (n = 124)
Children with any TEAE	1 (2.1)	15 (12.1)
Children with any treatment-emergent SAE	0	1 (0.8)
Children with any TEAE leading to permanent treatment discontinuation	0	0
Children with any TEAE related to treatment reported by investigator	0	3 (2.4)
Children with any TEAE leading to death	0	0
Maximal intensity		
Mild	1 (2.1)	8 (6.5)
Moderate	0	7 (5.6)
Severe	0	0
Corrective treatment		
No	1 (2.1)	14 (11.3)
Yes	0	1 (0.8)
Outcome		
Fatal	0	0
Not recovered/resolved	0	0
Recovered	1 (2.1)	14 (11.3)
Recovered with sequelae	0	0
Recovering	0	1 (0.8)
Unknown	0	0

*Defined as >3000 cells/μL and includes children with the high-level term "Eosinophilic disorders" or the preferred term "Eosinophil count increased."

cells/μL at baseline. This was similar to the efficacy observed in the overall population of children with moderate to severe asthma in VOYAGE,[13] highlighting that the mechanism of action of dupilumab in asthma—suppression of IL-4 and IL-13—leads to similar clinically meaningful improvements in patients with a range of eosinophil levels more than 150 cells/μL at baseline.[3,9,10] These results emphasize the potential of blood-based biomarkers, such as blood eosinophil counts, in identifying patients for whom personalized medicine targeting the type 2 inflammatory pathway may prove to be beneficial.[3]

Evaluation of blood eosinophil levels over time in this subgroup with blood eosinophil count greater than or equal to 500 cells/μL at baseline also yielded similar results to the overall population in the VOYAGE study. In both populations, median blood eosinophil counts slowly dropped to below baseline levels during 52 weeks, after an early and transient increase in mean levels that was resolved by week 24 of the study. These results are consistent with the hypothesis that dupilumab blockage of IL-4 and IL-13 suppresses tissue migration of eosinophils but not eosinophil production or egress from bone marrow.[10,13,20] However, the magnitude of change in blood eosinophil counts is small and does not predict improvement in clinical outcomes.

Dupilumab showed a generally acceptable safety profile in the population of children with moderate to severe asthma and elevated blood eosinophils that was consistent with the overall population from VOYAGE.[13] Here, safety was also assessed in children with greater than or equal to 500 cells/μL at baseline who developed eosinophilia during the study; treatment-emergent eosinophilia was reported in 15 (12.1%) and 1 (2.1%) children treated with dupilumab and placebo, respectively. All events of on-treatment eosinophilia were categorized as mild or moderate and most were nonserious. Most reported eosinophilia events in this subgroup did not require corrective treatment and were resolved by the end of the study. In the overall population in VOYAGE, 2 children experienced symptomatic eosinophilia, 1 of whom was part of the subgroup evaluated in this analysis. Eosinophilia for this patient was assessed as not related to treatment. These results highlight the suitability of dupilumab for the treatment of children with asthma who may be at risk for developing eosinophilia. These findings suggest that there is no need to assess eosinophil counts after initiating dupilumab unless there is concern for symptomatic eosinophilia.

This analysis has some limitations, the first of which is its *post hoc* nature. The current study was not designed or powered to investigate differences between patients with and without elevated eosinophil counts at baseline. In addition, children with eosinophils more than 1500 cells/μL at screening were excluded

from VOYAGE. Finally, the patient population enrolled in VOYAGE was predominantly White, with only a small percentage of Black children included,[13] limiting the generalizability of the findings of this study to a wider, more diverse population of children with asthma.

Conclusions

Treatment with dupilumab led to meaningful improvements in lung function and a significant reduction in asthma exacerbations compared with placebo in children with moderate to severe asthma with baseline blood eosinophil counts between 500 and 1500 cells/μL. Dupilumab was generally well tolerated in this cohort, with a safety profile comparable with that of the overall study population.

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