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SHORT REPORT

Impact of Lung Function on Asthma Exacerbation Rates in Children Treated with Dupilumab: The VOYAGE Study

Theresa W Guilbert[1], Kevin R Murphy[2], Eckard Hamelmann[3], Kristie R Ross[4], Atul Gupta[5], Alessandro Fiocchi[6], Changming Xia[7], Rebecca Gall[7], Olivier Ledanois[8], Amr Radwan[7], Juby A Jacob-Nara[9], Paul J Rowe[9], Yamo Deniz[7]

[1]Cincinnati Children's Hospital and University of Cincinnati, Cincinnati, OH, USA; [2]Boys Town National Research Hospital, Omaha, NE, USA; [3]Department of Pediatrics, Children's Center Bethel, University of Bielefeld, Bielefeld, Germany; [4]UH Rainbow Babies and Children's Hospital, Cleveland, OH, USA; [5]King's College Hospital, London, UK; [6]Bambino Gesù Children's Hospital IRCCS, Rome, Italy; [7]Regeneron Pharmaceuticals Inc., Tarrytown, NY, USA; [8]Sanofi, Paris, France; [9]Sanofi, Bridgewater, NJ, USA

Correspondence: Theresa W Guilbert, Cincinnati Children's Hospital and University of Cincinnati, Cincinnati, OH, USA, Tel +1 513-636-6771, Email theresa.guilbert@cchmc.org

Background: Severe, uncontrolled asthma and asthma exacerbations in children are associated with abnormal lung function and airway development, and increased risk of chronic obstructive lung disease in adulthood. The rationale for this post hoc analysis was to explore the relationship between changes in asthma exacerbation rates and lung function in children treated with dupilumab.

Methods: This post hoc analysis included children aged 6 to 11 years with uncontrolled, moderate-to-severe type 2 asthma (blood eosinophils ≥150 cells/μL or fractional exhaled nitric oxide ≥20 ppb) who received dupilumab or placebo in the phase 3 LIBERTY ASTHMA VOYAGE study (NCT02948959). Endpoints were the proportion of patients achieving clinically meaningful improvements (≥5% or ≥10%) in pre-bronchodilator percent-predicted forced expiratory volume in 1 second ($ppFEV_1$) by Week 12, annualized severe asthma exacerbation rates from Week 12–52, and mean change from baseline in $ppFEV_1$ to Week 12.

Results: At Week 12 of VOYAGE, 141/236 (60%) of children treated with dupilumab and 57/114 (50%) of children receiving placebo showed improvements of ≥5% in $ppFEV_1$; 106/236 (45%) children receiving dupilumab and 36/114 (32%) receiving placebo achieved improvements in $ppFEV_1$ ≥10%. During the Week 12–52 treatment period, dupilumab vs placebo significantly reduced severe exacerbation rates in all subgroups by 52–60% (all $P<0.05$). Dupilumab treatment resulted in rapid and sustained improvements in $ppFEV_1$ (Week 12 least squares mean difference [95% CI] vs placebo: 3.54 [0.30, 6.78] percentage points; $P=0.03$) in children who achieved improvements of ≥5%.

Conclusion: Dupilumab vs placebo significantly improved pre-bronchodilator $ppFEV_1$, with a higher proportion of patients achieving a clinically meaningful response at Week 12. Dupilumab also significantly reduced severe exacerbation rates, independent of pre-bronchodilator $ppFEV_1$ response at Week 12.

Trial Registration: NCT02948959.

Keywords: asthma, children, dupilumab, exacerbations, lung function, moderate-to-severe asthma, percent-predicted FEV_1, uncontrolled asthma

Introduction

Asthma, the most prevalent chronic airway disease in children, is often associated with abnormal lung function and airway development, with an increased risk of severe and uncontrolled asthma and the development of chronic obstructive lung disease in adulthood.[1–3] Decline in pre-bronchodilator percent predicted forced expiratory volume in 1 second ($ppFEV_1$) in patients with severe asthma is associated with increased exacerbation rates, emphasizing the importance of sustaining normal lung function as a treatment goal to prevent asthma exacerbations.[4,5]

In children, type 2 inflammation is the most common driver of asthma, and a key mechanism driving susceptibility to asthma exacerbations.[6] Dupilumab, a fully human monoclonal antibody,[7,8] blocks interleukin (IL)-4 and IL-13 signaling, key and central drivers in numerous type 2 inflammatory diseases.[9] In the phase 3 LIBERTY ASTHMA VOYAGE study

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(NCT02948959), add-on dupilumab given every 2 weeks (q2w), vs placebo, demonstrated significant improvements in pre-bronchodilator ppFEV$_1$ in children (6 to 11 years) with uncontrolled, moderate-to-severe type 2 asthma (blood eosinophil count ≥150 cells/μL or fractional exhaled nitric oxide [FeNO] ≥20 ppb).[10]

This post hoc analysis of VOYAGE assessed lung function responder rates and dupilumab efficacy in reducing exacerbation rates in children with uncontrolled, moderate-to-severe type 2 asthma who both did and did not achieve clinically meaningful improvements in pre-bronchodilator ppFEV$_1$ at Week 12 of treatment. The rationale for this post hoc analysis was to explore the relationship between changes in asthma exacerbation rates and lung function in children treated with dupilumab.

Methods

The phase 3 LIBERTY ASTHMA VOYAGE study assessed the efficacy and safety of add-on dupilumab in children (6 to 11 years) with uncontrolled, moderate-to-severe asthma. Full details of the study have been reported previously.[10] In brief, children were randomized to either dupilumab 100 or 200 mg q2w (by body weight) or placebo, subcutaneously, every 2 weeks for 52 weeks in addition to maintenance background medication. For this post hoc analysis of VOYAGE, children with moderate-to-severe type 2 asthma were stratified into 4 subgroups: those who achieved clinically meaningful improvements in pre-bronchodilator ppFEV$_1$ of ≥5% or ≥10% at Week 12 of VOYAGE[11,12] and those who did not (<5% or <10% change from baseline in ppFEV$_1$). This analysis assessed the proportion of children who had an improvement from baseline in ppFEV$_1$ of ≥5%, ≥10%, <5%, or <10% at VOYAGE Week 12, annualized severe asthma exacerbation rates during the Week 12–52 treatment period in the overall population and all subgroups, and a least squares mean change from baseline in pre-bronchodilator ppFEV$_1$ over time.

Annualized severe exacerbation rates were derived using a negative binomial model with the total number of events from Week 12 to Week 52 as the response variable, with treatment group, age, region, baseline eosinophil level, baseline FeNO level, baseline ICS dose level, and number of severe exacerbation events within 1 year prior to the study as covariates, and log-transformed standardized observation duration as an offset variable. The least squares mean difference in change from baseline in pre-bronchodilator ppFEV$_1$ was derived using a mixed model for repeated measures (MMRM) approach with change from baseline in pre-bronchodilator ppFEV$_1$ values as the response variable, and treatment, baseline weight group, region, ethnicity, baseline eosinophil level, baseline FeNO level, baseline ICS dose level, visit, treatment by-visit interaction, baseline ppFEV$_1$, and baseline-by-visit interaction as covariates.

Results

A total of 350 children with moderate-to-severe type 2 asthma were included in this analysis (dupilumab: n = 236; placebo: n = 114). Demographic and clinical characteristics of the patients across subgroups were generally similar at baseline (Table 1). However, children with <5% or <10% improvement in pre-bronchodilator ppFEV$_1$ by Week 12 presented, on average, with a higher pre-bronchodilator FEV$_1$ and ppFEV$_1$, and had lower FEV$_1$ reversibility, defined as 10% change in FEV$_1$ at baseline,[13] than those who achieved ppFEV$_1$ improvement of ≥5% or ≥10%.

At Week 12 of VOYAGE, 141/236 (60%) children receiving dupilumab and 57/114 (50%) receiving placebo achieved an improvement in ppFEV$_1$ of ≥5% (P=0.0847), 106/236 (45%) children receiving dupilumab and 36/114 (32%) receiving placebo achieved improvements in ppFEV$_1$ of ≥10% (P=0.0173).

During the Week 12–52 treatment period, dupilumab vs placebo significantly reduced annualized severe exacerbation rates by 59–60% (all P<0.05) in children who achieved ppFEV$_1$ improvements of ≥5% and ≥10%, and by 52% (all P<0.05) in those who did not (Figure 1).

Dupilumab also improved pre-bronchodilator ppFEV$_1$ as early as Week 2 across all subgroups, and these improvements were generally sustained throughout the treatment period (Figure 2, Tables S1 and S2). At Week 12, dupilumab vs placebo improved pre-bronchodilator ppFEV$_1$ by a least squares mean difference (95% CI) of 3.54 (0.30, 6.78) percentage points (P=0.03) in children who achieved an improvement in ppFEV$_1$ of ≥5%. At Week 52, dupilumab vs placebo improved pre-bronchodilator ppFEV$_1$ by least squares mean difference (95% CI) of 5.40 (0.28, 10.51) percentage points (P=0.04) in children with moderate-to-severe type 2 asthma who had an improvement in ppFEV$_1$ of ≥5%, by 6.67 (0.10, 13.25) percentage points (P=0.047) in those with ≥10% improvement in ppFEV$_1$, and by 7.10 (3.42, 10.78) percentage points (P<0.001) in children who had <5%, and 5.58 (2.31, 8.84) percentage points (P<0.001) in those with <10% improvement in ppFEV$_1$ (Figure 2, Tables S1 and S2).

Table 1 Baseline Demographic and Disease Characteristics of Children with Moderate-to-Severe Asthma Who Did or Did Not Achieve 5% and 10% Improvements in Pre-Bronchodilator ppFEV$_1$ from Baseline to Week 12

Characteristic	Patients with Improvements in Pre-Bronchodilator ppFEV$_1$ of...							
	... ≥5%		... ≥10%		... <5%		... <10%	
	PBO	DPL 100/200mg	PBO	DPL 100/200mg	PBO	DPL 100/200mg	PBO	DPL 100/200mg
	n = 57	n = 141	n = 36	n = 106	n = 54	n = 87	n = 75	n = 122
Age, mean (SD), year	8.9 (1.6)	8.8 (1.6)	9.0 (1.7)	8.8 (1.7)	9.0 (1.5)	9.1 (1.7)	9.0 (1.5)	9.0 (1.6)
Female, n (%)	18 (31.6)	46 (32.6)	11 (30.6)	33 (31.1)	17 (31.5)	33 (37.9)	24 (32.0)	46 (37.7)
Weight, mean (SD), kg	37.0 (11.4)	34.9 (10.3)	36.6 (12.6)	36.0 (11.0)	37.7 (11.9)	36.8 (9.5)	37.7 (11.1)	35.3 (9.2)
Use of high-dose ICS, n (%)	27 (47.4)	57 (40.4)	19 (52.8)	40 (37.7)	21 (38.9)	42 (48.3)	29 (38.7)	59 (48.4)
Number of severe asthma exacerbations[†] in the past year, mean (SD), n	2.2 (1.69)	2.5 (2.55)	2.0 (1.01)	2.3 (1.86)	2.1 (1.34)	2.7 (2.68)	2.2 (1.72)	2.8 (3.09)
Pre-BD FEV$_1$, mean (SD), L	1.44 (0.45)	1.38 (0.37)	1.33 (0.38)	1.33 (0.39)	1.78 (0.48)	1.82 (0.39)	1.64 (0.45)	1.60 (0.34)
Pre-BD ppFEV$_1$, mean (SD), %	75.2 (14.4)	73.3 (14.8)	69.7 (12.2)	70.2 (14.9)	82.2 (13.9)	84.6 (10.3)	82.9 (13.7)	84.0 (10.1)
FEV$_1$ reversibility, mean (SD), %	20.2 (15.7)	27.6 (24.0)	25.6 (16.6)	31.3 (25.9)	9.7 (11.6)	12.2 (12.3)	9.9 (10.6)	13.2 (11.9)
ACQ-7-IA score, mean (SD)	2.18 (0.76)	2.22 (0.73)	2.34 (0.77)	2.25 (0.67)	2.05 (0.77)	2.05 (0.65)	2.01 (0.74)	2.07 (0.72)
Biomarkers								
Blood eosinophil count, Giga/L	n = 57	n = 141	n = 36	n = 106	n = 54	n = 87	n = 75	n = 122
Mean (SD)	0.474 (0.307)	0.640 (0.389)	0.528 (0.337)	0.613 (0.392)	0.575 (0.415)	0.515 (0.382)	0.521 (0.380)	0.574 (0.389)
Median (Q1–Q3)	0.410 (0.280–0.620)	0.580 (0.310–0.830)	0.475 (0.290–0.695)	0.535 (0.290–0.770)	0.480 (0.310–0.670)	0.420 (0.250–0.650)	0.440 (0.280–0.660)	0.480 (0.280–0.780)
Blood eosinophil count, n (%)								
≥150 cells/μL	53 (93.0)	135 (95.7)	34 (94.4)	101 (95.3)	52 (96.3)	81 (93.1)	71 (94.7)	115 (94.3)
Total IgE, IU/mL	n = 57	n = 138	n = 36	n = 105	n = 52	n = 87	n = 74	n = 120
Mean (SD)	725.2 (1094.6)	957.2 (1171.7)	708.6 (1145.9)	969.4 (1227.6)	923.7 (1234.9)	882.0 (1053.1)	875.4 (1175.4)	891.9 (1031.9)
Median (Q1–Q3)	329.0 (75.0–762.0)	517.5 (210.0–1263.0)	342.0 (69.0–659.5)	509.0 (184.0–1163.0)	413.0 (215.0–952.0)	514.0 (202.0–1268.0)	401.0 (168.0–952.0)	522.0 (226.0–1275.0)
FeNO, ppb	n = 55	n = 139	n = 35	n = 105	n = 52	n = 83	n = 72	n = 117
Mean (SD)	29.0 (25.5)	34.1 (26.2)	31.3 (28.8)	33.2 (22.9)	27.7 (21.8)	29.0 (21.9)	26.9 (20.8)	31.3 (26.4)
Median (Q1–Q3)	20.0 (13.0–34.0)	27.0 (13.0–47.0)	22.0 (11.0–34.0)	27.0 (13.0–47.0)	23.0 (13.5–33.5)	24.0 (11.0–41.0)	21.0 (13.5–33.5)	24.0 (12.0–41.0)
FeNO, n (%)								
≥20 ppb	29 (52.7)	91 (65.5)	18 (51.4)	69 (65.7)	30 (57.7)	48 (57.8)	41 (56.9)	70 (59.8)

Notes: [†]Severe asthma exacerbation prior to the study is defined as any treatment with 1 systemic (oral or parenteral) steroid bursts or more for worsening asthma or hospitalization or an emergency/urgent medical care visit for worsening asthma.

Abbreviations: ACQ-7-IA, Investigator Administered 7-item Asthma Control Questionnaire; BD, bronchodilator; DPL, dupilumab; ICS, inhaled corticosteroid; FeNO, fractional exhaled nitric oxide; FEV$_1$, forced expiratory volume in 1 second; PBO, placebo; ppFEV$_1$, percent predicted FEV$_1$; Q, quartile; SD, standard deviation.

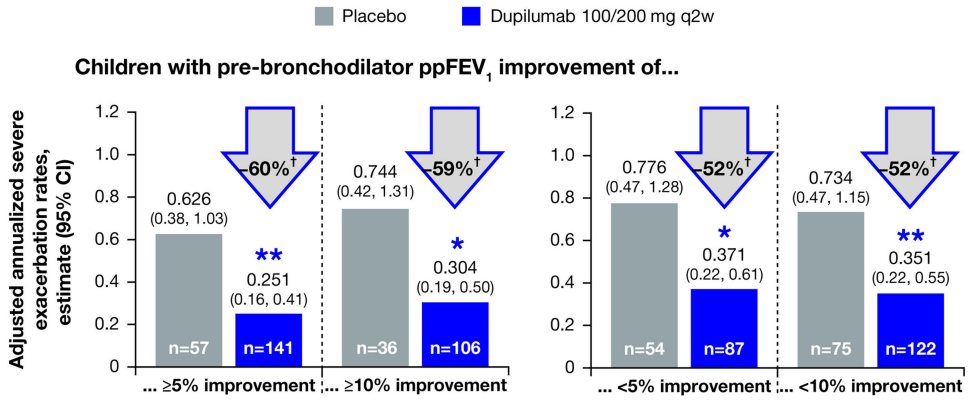

Figure 1 Reduction in severe asthma exacerbation rates during the VOYAGE Week 12 to 52 treatment period in children with moderate-to-severe asthma who did or did not achieve 5% and 10% improvements in pre-bronchodilator ppFEV$_1$ from baseline by Week 12.

Notes: * $P < 0.05$, ** $P < 0.01$ vs matching placebo. †Reduction in relative risk vs matching placebo. Note: 11 patients with missing pre-bronchodilator ppFEV$_1$ data at Week 12 are excluded from the analysis. All severe exacerbation events that occurred during Week 12 to 52 treatment period were included, regardless of whether the patient was on treatment.

Abbreviations: BD, bronchodilator; CI, confidence interval; ppFEV$_1$, percent predicted forced expiratory volume in 1 second.

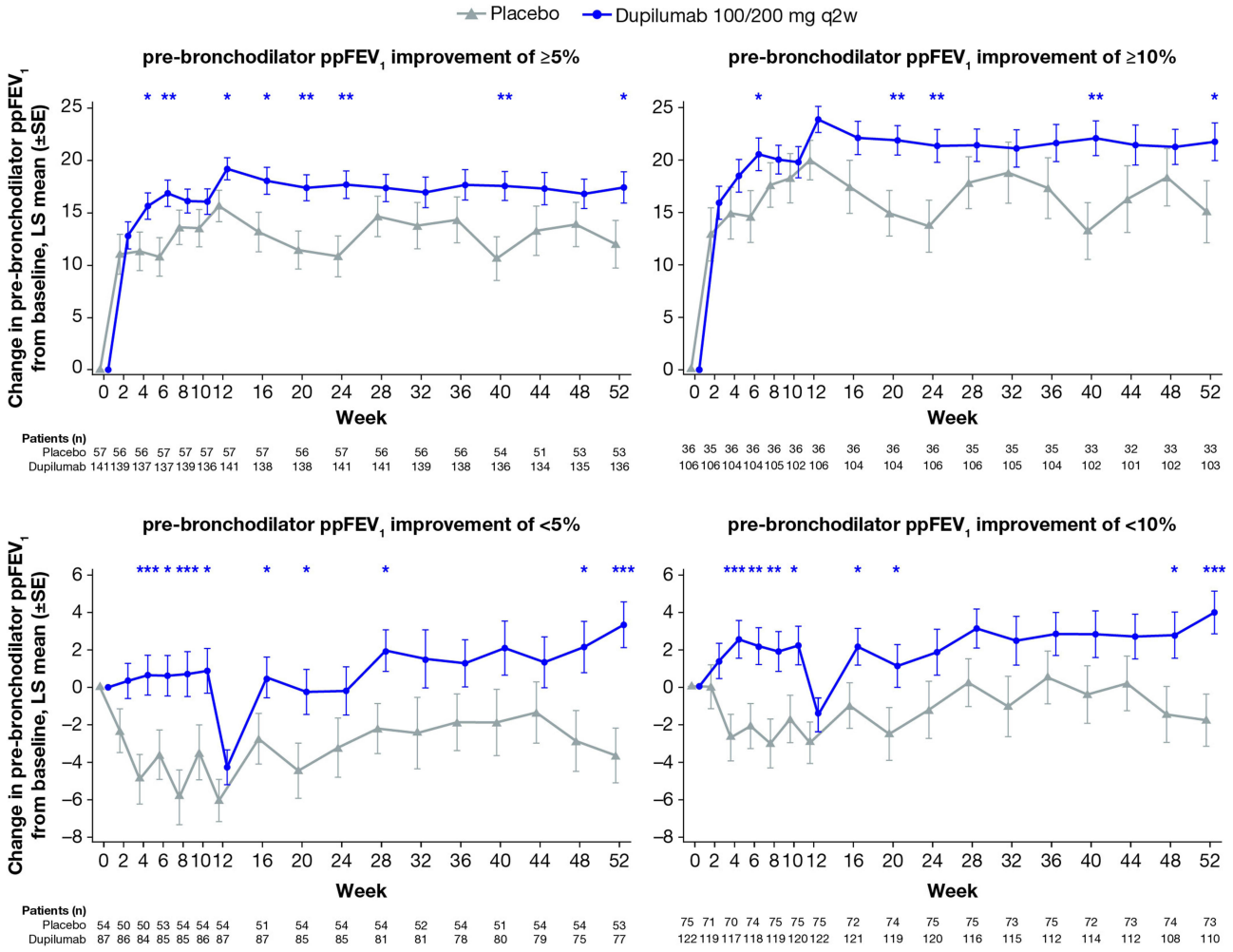

Figure 2 Change of pre-bronchodilator ppFEV$_1$ over time in children with moderate-to-severe asthma who did or did not achieve 5% and 10% improvements in pre-bronchodilator ppFEV$_1$ from baseline by Week 12.

Notes: *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ vs matching placebo. Eleven patients with missing pre-bronchodilator ppFEV$_1$ data at Week 12 are excluded from the analysis.

Abbreviations: BD, bronchodilator; LS, least squares; ppFEV$_1$, percent-predicted forced expiratory volume in 1 second; SE, standard error.

Additionally, when looking at symptom improvement, dupilumab improved ACQ-7-IA at Week 4 among those with <10% improvement in $ppFEV_1$ (least squares mean difference [95% CI] vs placebo: −0.31 [−0.54, −0.08] percentage points; $P<0.05$) and among those with <5% improvement in $ppFEV_1$ (least squares mean difference [95% CI] vs placebo: −0.33 [−0.60, −0.06] percentage points; $P<0.05$). Changes in ACQ-7-IA in those with ≥10% and ≥5% improvements in $ppFEV_1$ were not statistically significant at Week 4. In the VOYAGE study, adverse events were reported in 83.0% of the dupilumab group and in 79.9% of the placebo group.[10] The most common adverse event occurring in ≥5% of the patients was viral infection of the upper respiratory tract, which was reported in 12.2% of the dupilumab group and 9.7% of the placebo group. Serious adverse events were reported in 4.8% of the dupilumab group and in 4.5% of the placebo group.

Discussion

In this post hoc analysis of children aged 6 to 11 years with uncontrolled moderate-to-severe type 2 asthma, treatment with dupilumab resulted in a greater proportion of children meeting the criteria for clinically meaningful response in pre-bronchodilator $ppFEV_1$ compared with those receiving placebo.

Children treated with dupilumab vs placebo, who had a positive response in pre-bronchodilator $ppFEV_1$ at Week 12, showed a 60% risk reduction in severe exacerbation rates; dupilumab also reduced exacerbation rates by 52% in children who did not meet the 5% or 10% threshold of $ppFEV_1$ improvement. These findings are similar to those reported in adolescent and adult patients treated with dupilumab in LIBERTY ASTHMA QUEST[14] and support the idea that the effects of dupilumab in reducing exacerbations are independent of an early pre-bronchodilator FEV_1 response[15]. This suggests that, even in children with a modest pre-bronchodilator $ppFEV_1$ response, beneficial treatment effects with dupilumab are likely. This sustained improvement and reduced exacerbation rate over time can be explained by the mechanism of action of dupilumab. Dupilumab, which is a monoclonal antibody used to treat inflammatory conditions, works by way of inhibiting the signaling of IL-13 and IL-4, which are involved in various allergic and inflammatory responses in the body. This targeted mechanism of action allows for persistent inhibition of the immune response related to these cytokines and thus the inhibition of further mediators in the downstream cascade. In addition, with long-term inhibition of the inflammatory actions of IL-13 and IL-4 comes the opportunity for previously damaged tissue to be repaired and return to higher levels of function, leading to better overall lung function and reduced exacerbations. Thus, dupilumab may reduce exacerbations even if there is an absence of direct significant improvement in respiratory function due to the unique anti-inflammatory mechanism detailed above. Reduced FEV_1 in children is associated with increased risk of severe asthma exacerbations, therefore maintaining normal lung function will be critical for exacerbation prevention.[4,5] Additionally, lung function impairment during childhood is a significant predictor of abnormal longitudinal patterns of lung-function growth and decline in adulthood.[3] Therefore, improving lung function during childhood could be an important factor for preventing the development of chronic obstructive lung disease in adulthood.

Conclusion

In summary, treatment with dupilumab significantly improved pre-bronchodilator $ppFEV_1$. A greater proportion of patients treated with dupilumab achieved a clinically meaningful response in $ppFEV_1$ at Week 12 vs placebo. Dupilumab also significantly reduced severe exacerbation rates regardless of improvements in lung function, although stronger responses in lung function were associated with numerically lower exacerbation rates. This is highly relevant for individuals with type 2 asthma, specifically children, who may not show a direct significant response in $ppFEV_1$, since treatment with dupilumab is likely to result in overall decreased exacerbations and thus increased quality of life.

Abbreviations

ACQ-7-IA, 7 question asthma control questionnaire; BD, Bronchodilator; FeNO, Fractional exhaled nitric oxide; FEV_1, Forced expiratory volume in 1 second; IL, Interleukin; MMRM, mixed model for repeated measures; $ppFEV_1$, Percentage predicted forced expiratory volume in 1 second.

Data Sharing Statement

Qualified researchers may request access to patient-level data and related study documents including the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan, and dataset specifications. Patient-level data will be anonymized, and study documents will be redacted to protect the privacy of our trial participants. Further details on Sanofi's data sharing criteria, eligible studies, and process for requesting access can be found at: https://www.vivli.org/.

Ethics Approval and Consent to Participate

The VOYAGE trial was conducted in accordance with the principles of the Declaration of Helsinki, the Good Clinical Practice guidelines of the International Council for Harmonization, and applicable regulatory requirements. The local institutional review board or ethics committee at each trial center oversaw the conduct and documentation of the trial (Washington University School of Medicine, 660 S. Euclid Ave., Campus Box 8089, St. Louis, MO, 63110, UNITED STATES; Lead investigator: Dr Bacharier) (additional information available in Appendix 1 and 2). Parents or guardians of patients provided written informed consent. The children provided assent according to the standard practice for pediatric patients that had been approved by the ethics committee at each participating center.

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Author Contributions

All authors made a significant contribution to the work reported, whether in the conception, study design, execution, acquisition of data, analysis, and interpretation. All of the authors took part in drafting, revising and critically reviewing the article; gave final approval of the version to be published; agreed on the journal to which the article has been submitted, and agree to be accountable for all aspects of the work, according to ICMJE authorship criteria. All authors ensured that questions related to the accuracy or integrity of any part of the work were appropriately investigated.

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Disclosure

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References

1. Bui DS, Walters HE, Burgess JA, et al. Childhood respiratory risk factor profiles and middle-age lung function: a prospective cohort study from the first to sixth decade. *Ann Am Thoracic Soc*. 2018;15(9):1057–1066. doi:10.1513/annalsats.201806-374oc
2. Dharmage SC, Perret JL, Custovic A. Epidemiology of asthma in children and adults. *Front Pediatr*. 2019;7. doi:10.3389/fped.2019.00246
3. McGeachie MJ, Yates KP, Zhou X, et al. Patterns of growth and decline in lung function in persistent childhood asthma. *N Engl J Med*. 2016;374 (19):1842–1852. doi:10.1056/nejmoa1513737
4. Fuhlbrigge AL, Kitch BT, Paltiel AD, et al. FEV_1 is associated with risk of asthma attacks in a pediatric population. *J Allergy Clin Immunol*. 2001;107(1):61–67. doi:10.1067/mai.2001.111590
5. Fielding S, Pijnenburg M, de Jongste JC, et al. Change in FEV_1 and FeNO measurements as predictors of future asthma outcomes in children. *Chest*. 2019;155(2):331–341. doi:10.1016/j.chest.2018.10.009
6. Dunican EM, Fahy JV. The role of type 2 inflammation in the pathogenesis of asthma exacerbations. *Ann Am Thoracic Soc*. 2015;12(Supplement 2):S144–S149. doi:10.1513/annalsats.201506-377aw
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*. 2014;111(14):5147–5152. doi:10.1073/pnas.1323896111
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*. 2014;111(14):5153–5158. doi:10.1073/pnas.1324022111
9. Gandhi NA, Pirozzi G, Graham NM. Commonality of the IL-4/IL-13 pathway in atopic diseases. *Expert Rev Clin Immunol*. 2017;13(5):425–437. doi:10.1080/1744666x.2017.1298443
10. Bacharier LB, Maspero JF, Katelaris CH, et al. Dupilumab in children with uncontrolled moderate-to-severe asthma. *N Engl J Med*. 2021;385 (24):2230–2240. doi:10.1056/nejmoa2106567
11. 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. doi:10.1034/j.1399-3003.1999.14a06.x
12. Szefler SJ, Phillips BR, Martinez FD, et al. Characterization of within-subject responses to fluticasone and montelukast in childhood asthma. *J Allergy Clin Immunol*. 2005;115(2):233–242. doi:10.1016/j.jaci.2004.11.014
13. Stanojevic S, Kaminsky DA, Miller MR, et al. ERS/ATS technical standard on interpretive strategies for routine lung function tests. *Eur Respir J*. 2021;60(1):2101499. doi:10.1183/13993003.01499-2021
14. Castro M, Corren J, Pavord ID, et al. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. *N Engl J Med*. 2018;378 (26):2486–2496. doi:10.1056/nejmoa1804092
15. Hanania NA, Maspero JF, Halpin DM, et al. Improvement in lung function with dupilumab does not predict its effects on reducing asthma exacerbation. *J Asthma Allergy*. 2022;15:851–854. doi:10.2147/jaa.s354013