Dupilumab leads to better-controlled asthma and quality of life in children: the VOYAGE study

Alessandro G. Fiocchi 1, Wanda Phipatanakul 2, Robert S. Zeiger 3, Sandy R. Durrani 4, Jeremy Cole 5, Jérôme Msihid 6, Rebecca Gall 7, Juby A. Jacob-Nara 7, Yamo Deniz 4, Paul J. Rowe 7, David J. Lederer 4, Megan Hardin 8, Yi Zhang 4 and Asif H. Khan 6

1Translational Research in Paediatric Specialities Area, Division of Allergy, Bambino Gesù Children’s Hospital IRCCS, Rome, Italy. 2Department of Allergy and Immunology, Boston Children’s Hospital and Department of Pediatrics, Harvard Medical School, Boston, MA, USA. 3Department of Clinical Science, Kaiser Permanente Bernard J. Tyson School of Medicine, Pasadena, CA, USA. 4Regeneron Pharmaceuticals Inc., Tarrytown, NY, USA. 5OK Clinical Research, Edmond, OK, USA. 6Sanofi, Gentilly, France. 7Sanofi, Bridgewater, NJ, USA. 8Sanofi, Cambridge, MA, USA.

Corresponding author: Alessandro G. Fiocchi (alessandro.fiocchi@allegriallergia.net)

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This novel analysis of VOYAGE demonstrates that dupilumab significantly improves asthma control and health-related quality of life in children 6–11 years old with moderate-to-severe type 2 asthma, as well as the quality of life of their caregivers.


Abstract

BackgroundDupilumab has shown long-term treatment benefits in children with uncontrolled asthma. We assessed in more detail the impact of dupilumab on asthma control and health-related quality of life (HRQoL) in children and their caregivers.

MethodsChildren aged 6–11 years with uncontrolled moderate-to-severe type 2 asthma (baseline blood eosinophils $\geq 150$ cells·µL$^{-1}$ or fractional exhaled nitric oxide $\geq 20$ ppb; $n=350$) were treated with dupilumab or placebo for 52 weeks in the VOYAGE study. Primary outcomes of these analyses were asthma control (change from baseline in Asthma Control Questionnaire 7 Interviewer-Administered (ACQ-7-IA) and achieving a clinically meaningful response of $\geq 0.5$ points); proportion of patients achieving well-controlled asthma or better (ACQ-7-IA $\leq 0.75$ points); effect on patients’ (Standardised Paediatric Asthma Quality of Life Questionnaire Interviewer-Administered (PAQLQ(S)-IA)) and caregivers’ (Paediatric Asthma Caregiver’s Quality of Life Questionnaire (PACQLQ)) HRQoL; and allergic rhinitis-related QoL.

ResultsDupilumab versus placebo significantly improved children’s ACQ-7-IA scores by week 4 with sustained improvements through week 52 (least squares mean difference at week 52: $-0.44$, 95% CI $-0.59$–$-0.30$; $p<0.0001$); a higher proportion achieved a clinically meaningful response (week 52: 86% versus 75%; $p=0.0051$). At weeks 24 and 52, more children who received dupilumab achieved well-controlled asthma (ACQ-7-IA $\leq 0.75$ points: 61% versus 43%; $p=0.0001$ and 70% versus 46%; $p<0.0001$, respectively). Significant improvements in PAQLQ(S)-IA and PACQLQ scores were observed by week 52.

ConclusionsIn children aged 6–11 years with moderate-to-severe type 2 asthma, dupilumab treatment was associated with rapid, sustained improvements in asthma control. HRQoL was significantly improved for children and their caregivers.

Introduction

Asthma leads chronic disease in children with the prevalence increasing in many countries [1]. Globally, 32–49% of patients with moderate symptoms and 39–70% with severe symptoms consider their asthma to be well or completely controlled [2]. Uncontrolled asthma remains highly prevalent among children [3], negatively impacting various aspects of health-related quality of life (HRQoL), for both the child and the parent/caregiver [4, 5]. Biological therapies positively impact the treatment of severe asthma and are used increasingly as add-on therapy for children with uncontrolled or moderate-to-severe disease. There is an
unmet need to better understand their role in improving various aspects of asthma control and effect on improving HRQoL in children and the consequent impact on caregivers.

Type 2 inflammation is the most common driver of asthma in children [6]. Dupilumab, a fully human monoclonal antibody [7, 8], blocks the shared receptor for interleukin-4/13, key drivers of type 2 inflammation in several type 2 diseases including asthma [9], and is approved in the USA and European Union for the treatment of children ≥6 years with certain types of asthma. In the phase 3 Liberty Asthma VOYAGE study (ClinicalTrials.gov: NCT02948959), add-on dupilumab 100/200 mg versus matched placebo significantly reduced severe asthma exacerbations and rapidly improved lung function in children aged 6–11 years with uncontrolled moderate-to-severe asthma [10]. Overall safety was consistent with the known dupilumab safety profile [10]. While clinical improvements are important, as demonstrated in the primary analysis [10], how patients and caregivers feel is critical. In this analysis, including prespecified and post hoc measures, we expand on the primary analysis findings of improved asthma control with dupilumab treatment versus placebo at week 24 (measured by Asthma Control Questionnaire 7 Interviewer-Administered (ACQ-7-IA) scores) and we investigate the impact on HRQoL. Asthma control is typically reported as change from baseline or proportion of responders. Here we probed different levels of asthma control (controlled asthma, adequately controlled asthma and well-controlled asthma) for which different scores have been proposed [11]. We also assessed symptoms, activity limitation and emotional functioning of the children by domains in the Standardised Paediatric Asthma Quality of Life Questionnaire Interviewer-Administered (PAQLQ(S)-IA), the impact on allergic rhinitis-related QoL, and how a change in the child’s asthma could affect the caregiver and the impact on their activity limitation and emotional functioning. These aspects of asthma have not been assessed previously and provide more detailed perspectives of the treatment effect on asthma control and QoL.

Methods

Study subjects

VOYAGE enrolled children (6–11 years) with physician-diagnosed moderate-to-severe asthma, as per Global Initiative for Asthma 2015 guidelines [12]. Full study details have been described previously [10]. Two primary efficacy populations from VOYAGE were analysed: patients with type 2 inflammatory asthma (baseline blood eosinophils ≥150 cells·µL⁻¹ or fractional exhaled nitric oxide ≥20 ppb), and a subpopulation of patients with type 2 asthma and baseline blood eosinophil count ≥300 cells·µL⁻¹.

Study design

VOYAGE was a phase 3, randomised, double-blind, placebo-controlled, parallel-group, multinational study. Patients received dupilumab 2:1 (100/200 mg by body weight) or volume-matched placebo every 2 weeks for 52 weeks. All patients continued to receive standard background therapy. The primary end-point of VOYAGE was the annualised severe asthma exacerbation rate, which was reduced significantly with dupilumab [10]. Further details of the trial design are given in the supplementary material.

Outcomes

Interviewers administered all questionnaires to the children, with help from their parents or caregivers. Asthma control was assessed using the ACQ-7-IA, which includes five items on asthma symptoms as well as percentage predicted forced expiratory volume in 1 s and daily rescue bronchodilator use. Asthma-specific HRQoL was assessed using the PAQLQ(S)-IA. Allergic rhinitis-related HRQoL was assessed in children with a self-reported history of allergic rhinitis using the Paediatric Rhinoconjunctivitis Quality of Life Questionnaire Interviewer-Administered (PRQLQ-IA), Caregiver QoL was assessed using the Paediatric Asthma Caregiver’s Quality of Life Questionnaire (PACQLQ). All instruments have been validated in children with asthma or their caregivers [13, 14]. PAQLQ(S)-IA and PACQLQ were assessed in children ≥7 years old and their caregivers, respectively.

For the ACQ-7-IA, assessed end-points were the change from baseline in ACQ-7-IA and items scores over time. Clinically meaningful response was defined as an improvement from baseline of ≥0.5 points in ACQ-7-IA score [15]. At weeks 24 and 52, the proportion of patients achieving well-controlled (both ACQ-7-IA and ACQ-5-IA score ≤0.75 points), adequately controlled (both ACQ-7-IA and ACQ-5-IA score <1 point) and controlled asthma (both ACQ-7-IA and ACQ-5-IA score <1.5 points) was also assessed [11]. For the PAQLQ(S)-IA and PACQLQ, change from baseline over time was assessed for global score, plus the emotional function and activity limitation domain scores at weeks 24 and 52; additionally, change from baseline to weeks 24 and 52 in the symptoms domain score was assessed for the PAQLQ(S)-IA. Change from baseline in PRQLQ-IA score was assessed at weeks 24 and 52 in children with a medical history of allergic rhinitis. Clinically meaningful responses on the PAQLQ(S)-IA and PRQLQ-IA were defined as an improvement from baseline of ≥0.5 points in global score [14].
**Statistical analysis**

Data were analysed using an intention-to-treat approach for the two primary analysis populations presented here according to the assigned intervention, regardless of whether the intervention was received.

Changes from baseline in ACQ-7-IA overall and item scores as well as PACQLQ and PAQLQ(S)-IA global and domain scores over time were analysed using a mixed effect model with repeated measures (MMRM) approach, following the same prespecified methodology presented in the primary publication [10]. Changes from baseline are reported as least squares (LS) means, which were derived from MMRM, along with their 95% confidence intervals.

For the comparison of the proportion of children achieving clinically meaningful improvement from baseline and those with well-controlled, adequately controlled or controlled asthma, the odds ratios versus placebo were derived from a logistic regression model.

All hypotheses were tested at a two-sided significance level of 0.05. No adjustments for multiplicity were made, except for change from baseline in the ACQ-7-IA at week 24.

All end-points were prespecified, except ACQ-5/7-IA asthma control end-points and PRQLQ-IA responder analyses which were post hoc. Further details of the methodology are given in the supplementary material.

Further details of the statistical analysis used are given in the supplementary material.

**Results**

**Study patients**

Of the 408 patients enrolled in VOYAGE, 350 (86%) had type 2 asthma at baseline and 259 (63%) had baseline blood eosinophils $\geq 300$ cells·$\mu$L$^{-1}$; of these, 318 patients with type 2 asthma and 239 patients with baseline blood eosinophils $\geq 300$ cells·$\mu$L$^{-1}$ were $\geq 7$ years old.

Baseline demographics and patient characteristics in each population were well balanced across treatment arms [10] with respect to mean age and gender. Most children (>87%) were White, approximately two-thirds were male (table 1 and supplementary table S1) and similar proportions were included from each season (supplementary table S2). In both populations, baseline global scores for the ACQ-5/7-IA and PAQLQ(S)-IA were comparable between dupilumab and placebo groups and, across groups, up to 78–88% of patients had a history of comorbid allergic rhinitis.

**Asthma control**

In the type 2 asthma population, dupilumab versus placebo improved total ACQ-7-IA scores by week 4 (LS mean difference (LSMD) versus placebo $-0.28$, 95% CI $-0.45$–$-0.11$; $p=0.0011$); these improvements were sustained through week 52 (LSMD $-0.44$, 95% CI $-0.59$–$-0.30$; $p<0.0001$) (supplementary figure S1). Significantly greater improvements in ACQ-7-IA item scores from baseline were seen for dupilumab versus placebo in all but item 1 (asthma-related night awakening) by week 24 and in all items by week 52 (supplementary figure S1). Similar results were observed in the eosinophils $\geq 300$ cells·$\mu$L$^{-1}$ population, except for item 1, which was also significant at week 24 in this population.

In children with type 2 asthma, a higher proportion of patients in the dupilumab versus placebo group were responders (79% versus 69% at week 24 and 86% versus 75% at week 52) (table 2); for dupilumab versus placebo, the OR increased from 1.82 (95% CI 1.02–3.24; $p=0.0411$) at week 24 to 2.57 (95% CI 1.33–4.98; $p=0.0051$) by week 52. Among these responders, a higher proportion of dupilumab-treated patients were exacerbation-free during the treatment period versus placebo (77.9% versus 67.1% at week 52) (supplementary figure S2). Among patients with at least one severe exacerbation during the treatment period, a higher proportion of patients in the dupilumab versus placebo group were responders (83.3% versus 60.9%) at week 52 (supplementary figure S3); in patients with no severe exacerbations the proportion of responders was higher but the difference versus placebo was less (87.4% versus 83.8%). Findings were similar in patients with baseline blood eosinophils $\geq 300$ cells·$\mu$L$^{-1}$.

At week 24, 61% of children with type 2 asthma achieved well-controlled asthma (ACQ-7-IA score $\leq 0.75$ points) with dupilumab versus 43% with placebo; 65% achieved adequately controlled asthma (ACQ-7-IA score $<1$ point) with dupilumab versus 53% with placebo; 79% achieved controlled asthma (ACQ-7-IA score $<1.5$ points) with dupilumab versus 70% with placebo. At week 52, percentages were 70% versus 46%, 76% versus 54% and 85% versus 73%, respectively (figure 1a). Dupilumab-treated children were significantly more likely to achieve controlled, adequately controlled or well-controlled asthma.
### TABLE 1
Baseline demographics and clinical characteristics in the population with type 2 inflammatory asthma phenotype and in the population with baseline blood eosinophils $\geq 300$ cells$\cdot$µL$^{-1}$

<table>
<thead>
<tr>
<th></th>
<th>Type 2 inflammatory phenotype</th>
<th>Baseline blood eosinophils $\geq 300$ cells$\cdot$µL$^{-1}$</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (n=114)</td>
<td>Dupilumab (n=236)</td>
</tr>
<tr>
<td>Age, years</td>
<td>9.0±1.6</td>
<td>8.9±1.6</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>78 (68.4)</td>
<td>152 (64.4)</td>
</tr>
<tr>
<td>Race (White)</td>
<td>102 (89.5)</td>
<td>208 (88.1)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>37.08±11.6</td>
<td>35.60±10.0</td>
</tr>
<tr>
<td>Patients using high-dose ICS</td>
<td>50 (43.9)</td>
<td>102 (43.2)</td>
</tr>
<tr>
<td>ACQ-7-IA score$^#$</td>
<td>2.12±0.8</td>
<td>2.15±0.7</td>
</tr>
<tr>
<td>ACQ-7-IA &lt;1.5$^\dagger$ (controlled asthma)</td>
<td>17 (14.9)</td>
<td>32 (13.6)</td>
</tr>
<tr>
<td>ACQ-7-IA &lt;1$^\dagger$ (adequately controlled asthma)</td>
<td>6 (5.3)</td>
<td>7 (3.0)</td>
</tr>
<tr>
<td>ACQ-7-IA $\leq$ 0.75$^\dagger$ (well-controlled asthma)</td>
<td>5 (4.4)</td>
<td>3 (1.3)</td>
</tr>
<tr>
<td>PAQLQ(S)-IA global score$^+$</td>
<td>4.92±1.3</td>
<td>4.95±1.08</td>
</tr>
<tr>
<td>PAQLQ(S)-IA symptoms score</td>
<td>4.71±1.17</td>
<td>4.71±1.12</td>
</tr>
<tr>
<td>PAQLQ(S)-IA activity limitation score</td>
<td>4.91±1.11</td>
<td>4.90±1.14</td>
</tr>
<tr>
<td>Patients with ongoing allergic rhinitis$^§$</td>
<td>89 (78.1)</td>
<td>200 (84.7)</td>
</tr>
<tr>
<td>PRQLQ-IA global score$^\ddagger$</td>
<td>2.17±1.12</td>
<td>2.00±1.11</td>
</tr>
<tr>
<td>PACQLQ activity limitation score</td>
<td>4.43±1.61</td>
<td>4.56±1.56</td>
</tr>
<tr>
<td>PACQLQ emotional function score</td>
<td>4.30±1.40</td>
<td>4.39±1.33</td>
</tr>
</tbody>
</table>

Data are presented as n (%) or mean±SD. ICS: inhaled corticosteroid; ACQ-7-IA: Asthma Control Questionnaire 7 Interviewer-Administered; PAQLQ(S)-IA: Standardised Paediatric Asthma Quality of Life Questionnaire Interviewer-Administered (for children $\geq 7$ years old at randomisation); PRQLQ-IA: Paediatric Rhinoconjunctivitis Quality of Life Questionnaire Interviewer-Administered (in children with a history of allergic rhinitis); PACQLQ: Paediatric Asthma Caregiver’s Quality of Life Questionnaire (for caregivers of children $\geq 7$ years old at randomisation). $^#$: scores on the ACQ-7-IA range from 0 (totally controlled) to 6 (severely uncontrolled); $^\dagger$: at screening the ACQ was one of the criteria for assessing control in addition to three others, therefore some patients who met the other criteria might have been included despite already scoring <1.5 points for the ACQ; $^+$: scores on the PAQLQ(S)-IA range from 1 to 7, with higher scores indicating better quality of life; $^§$: self-reported; $^\ddagger$: scores on the PRQLQ-IA range from 0 to 6, with lower scores indicating better quality of life; $^\ddagger\ddagger$: scores on the PACQLQ range from 1 to 7, with higher scores indicating better quality of life. Full baseline characteristics reported by Bacharier et al. [10].

### TABLE 2
Responder analysis at weeks 24 and 52 for change from baseline in the Asthma Control Questionnaire 7 Interviewer-Administered (ACQ-7-IA) in children aged 6–11 years with moderate-to-severe asthma with type 2 phenotype at baseline and baseline blood eosinophils $\geq 300$ cells$\cdot$µL$^{-1}$

<table>
<thead>
<tr>
<th></th>
<th>Type 2 inflammatory phenotype</th>
<th>Baseline blood eosinophils $\geq 300$ cells$\cdot$µL$^{-1}$</th>
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<tbody>
<tr>
<td></td>
<td>Placebo (n=114)</td>
<td>Duplicumab (n=236)</td>
</tr>
<tr>
<td>Week 24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Responder, n (%)$^*$</td>
<td>79 (69.3)</td>
<td>187 (79.2)</td>
</tr>
<tr>
<td>OR (95% CI) versus placebo$^*$</td>
<td>1.02 (1.02–3.24)</td>
<td></td>
</tr>
<tr>
<td>p-value versus placebo$^*$</td>
<td>0.0411</td>
<td></td>
</tr>
<tr>
<td>Week 52</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Responder, n (%)$^*$</td>
<td>85 (74.6)</td>
<td>204 (86.4)</td>
</tr>
<tr>
<td>OR versus placebo$^*$</td>
<td>2.57 (1.33–4.98)</td>
<td></td>
</tr>
<tr>
<td>p-value versus placebo$^*$</td>
<td>0.0051</td>
<td></td>
</tr>
</tbody>
</table>

$^*$: patients who met the corresponding criterion are considered as responders, whereas patients who did not meet the criterion or had missing values are considered as non-responders; $^\ddagger$: derived from a logistic regression model with treatment, age, weight group, region, baseline eosinophil level, baseline fractional exhaled nitric oxide level, baseline inhaled corticosteroid dose level and baseline ACQ-7-IA score as covariates.
asthma at weeks 24 and 52 (figure 1a). The same magnitude of increase was seen in the proportion of children achieving well-controlled asthma at week 52 when asthma control was measured using ACQ-5-IA scores, and similar but less pronounced patterns were seen in the proportion of children achieving adequately controlled and controlled asthma, compared with ACQ-7-IA scores (supplementary figure S4). Similar results were observed in the eosinophils $\geq 300$ cells·μL$^{-1}$ population (figure 1b and supplementary figure S4b).

**Asthma HRQoL (PAQLQ(S)-IA)**

Dupilumab versus placebo significantly improved HRQoL as demonstrated by change from baseline in PAQLQ(S)-IA scores in both populations (figure 2a and b). In the type 2 population, the LSMD for

### Figure 1

**Proportions of patients with controlled, adequately controlled and well-controlled asthma at weeks 24 and 52.** Results are in children aged 6–11 years with moderate-to-severe asthma and a) type 2 inflammatory phenotype at baseline (n=350) or b) baseline eosinophils $\geq 300$ cells·μL$^{-1}$ (n=259). Controlled asthma is defined as Asthma Control Questionnaire 7 Interviewer-Administered (ACQ-7-IA) score $<1.5$ points; adequately controlled asthma is defined as ACQ-7-IA score $<1$ point and well-controlled asthma is defined as ACQ-7-IA score $\leq 0.75$ points. The odds ratio was derived from a logistic regression model with treatment, age, weight group, region, baseline eosinophil level, baseline fractional exhaled nitric oxide level, baseline inhaled corticosteroid dose level and baseline ACQ-7-IA score as covariates. Note: n numbers are equal at each time-point for the respective subgroup.
Dupilumab versus placebo was significant from week 36 onwards and was 0.34 (95% CI 0.16–0.52; p=0.0002) at week 52. Significant improvements for dupilumab versus placebo were observed from week 24 onwards in the eosinophils $\geq 300$ cells·µL$^{-1}$ population. Additionally, improvements were observed in individual domain scores of emotional function, activity limitation and symptoms at week 24; these were significant for all domains at week 52 for both populations (figure 2c and d).

In children with type 2 asthma, a higher proportion of patients receiving dupilumab were responders (73% versus 65%, respectively, at week 24 and 76% versus 68%, respectively, at week 52; OR at week 52 was 1.89, 95% CI 1.02–3.52; p=0.0428) (supplementary figure S5). A similar pattern of response was seen in patients with eosinophils $\geq 300$ cells·µL$^{-1}$.

**HRQoL in children with asthma and a history of comorbid allergic rhinitis (PRQLQ-IA)**

In children with asthma and a history of allergic rhinitis (82.6%), significantly greater improvements in PRQLQ-IA global score were observed for dupilumab versus placebo at weeks 24 and 52 in both populations (a, c) and for eosinophils $\geq 300$ cells·µL$^{-1}$ (b, d).

**FIGURE 2** a, b) Least squares (LS) mean change from baseline over time in Standardised Paediatric Asthma Quality of Life Questionnaire Interviewer-Administered (PAQLQ(S)-IA) global score. c, d) LS mean improvement from baseline versus placebo in PAQLQ(S)-IA domain scores. Results are in children aged 7–11 years with moderate-to-severe asthma and a, c) type 2 inflammatory phenotype at baseline or b, d) baseline blood eosinophils $\geq 300$ cells·µL$^{-1}$. The change from baseline over time was analysed using the change from baseline at each scheduled post-baseline visit up to week 52 as the response variable, and treatment groups, age, baseline body weight dose group ($>30$ or $\leq 30$ kg), baseline eosinophil strata ($<300$ or $\geq 300$ cells·µL$^{-1}$), baseline fractional exhaled nitric oxide level ($<20$ or $>20$ ppb), baseline inhaled corticosteroid dose level (medium or high), geographic region, visit, baseline score-by-visit interaction, baseline score and treatment-by-visit interaction as covariates. When performing these analyses in the population with baseline blood eosinophils $\geq 300$ cells·µL$^{-1}$, the baseline eosinophil level was removed as a covariate.

https://doi.org/10.1183/13993003.00558-2023
populations. LSMD versus placebo was $-0.42$ (95% CI $-0.70$--$-0.14$; $p=0.0039$) at week 24 and $-0.47$ (95% CI $-0.73$--$-0.20$; $p=0.0006$) at week 52 (supplementary figure S6). In children with type 2 asthma, a higher proportion of those receiving dupilumab were responders (51% versus 34% at week 24 and 53% versus 45% at week 52, respectively). A similar pattern was observed in children with baseline blood eosinophils $\geq 300$ cells·µL$^{-1}$.

**Caregiver QoL (PACQLQ)**

The LSMD change from baseline in PACQLQ global score among caregivers of children with type 2 asthma receiving dupilumab was 0.25 (95% CI 0.00--0.50; $p=0.0531$) at week 24 and 0.47 (95% CI 0.22--0.72; $p=0.0003$) at week 52 versus placebo (figure 3a). Significant improvements for dupilumab versus placebo were observed earlier from week 12 onwards in caregivers of patients with baseline blood eosinophils $\geq 300$ cells·µL$^{-1}$ (figure 3b). Domains of activity limitation and emotional function showed significantly greater improvements by week 52 for caregivers of both populations (supplementary figure S7).

**Discussion**

Children are no less likely than adults with asthma to experience the impacts of illness on aspects of their lives beyond just physiological illness or treatment effect [16]. Uncontrolled moderate-to-severe asthma in young children adversely affects patients’ HRQoL and daily activities, including school activity and extracurricular activities such as sports, with associated excess absenteeism from school [17]. Negative impacts of uncontrolled disease also extend to the QoL of parents and caregivers of young children [18]. This analysis demonstrates that add-on dupilumab improves asthma control in young children and HRQoL for both children and caregivers.

In the primary VOYAGE publication, dupilumab treatment demonstrated significant improvements in change from baseline in the ACQ-7-IA at week 24 [10]. The data presented here provide novel and detailed analyses of dupilumab treatment effects on various levels of asthma control, providing more comprehensive overviews beyond asthma control scores.

Patients with asthma who have higher baseline ACQ-7-IA scores and achieve a change in score $\geq 0.5$ points may still have substantial lack of disease control [19]. In contrast, a score of 0.75 points is optimal to identify patients with well-controlled asthma [11]. At baseline in children with type 2 asthma, only 1.3% in the dupilumab and 4.4% in the placebo group had well-controlled asthma; with add-on dupilumab versus placebo, 61% versus 43% at week 24 and 70% versus 46% at week 52 reported well-controlled asthma, respectively. Although the proportions of patients who achieved well-controlled asthma versus placebo were

![FIGURE 3 Least squares (LS) mean change from baseline in Paediatric Asthma Caregiver’s Quality of Life Questionnaire (PACQLQ) global score over time in children with moderate-to-severe asthma. Results are in caregivers of children aged 7–11 years with a) type 2 phenotype or b) baseline blood eosinophils $\geq 300$ cells·µL$^{-1}$. The change from baseline over time was analysed using the change from baseline at each scheduled post-baseline visit up to week 52 as the response variable, and treatment groups, age, baseline body weight dose group (>30 or $\leq$30 kg), baseline eosinophil strata (<300 or $\geq 300$ cells·µL$^{-1}$), baseline fractional exhaled nitric oxide level ($\leq$20 or $>$20 ppb), baseline inhaled corticosteroid dose level (medium or high), geographic region, visit, baseline score-by-visit interaction, baseline score and treatment-by-visit interaction as covariates. When performing these analyses in the population with baseline blood eosinophils $\geq 300$ cells·µL$^{-1}$, the baseline eosinophil level was removed as a covariate.](https://doi.org/10.1183/13993003.00558-2023)
lower than the proportion who achieved controlled and adequately controlled asthma, the odds of achieving well-controlled asthma was highest. Higher proportions of dupilumab-receiving children were responders at both weeks 24 and 52, and were more likely to achieve a change in score ≥0.5 points versus placebo. To examine if asthma control improved independently of lung function improvement or short-acting bronchodilator use, we assessed ACQ-5-IA scores (omitting these items) and saw similar patterns in the increased proportions of responders across the asthma control categories, albeit to a lesser degree in some. Responders were more likely to be exacerbation-free, suggesting that improved asthma control may have important implications for reducing exacerbation-associated systemic glucocorticosteroid use, hospitalisations or emergency department visits. The relationship between exacerbations, lung function and asthma control is a complex one that merits further investigation.

This study also assessed the impact of disease and treatment on HRQoL in children. Patient-reported outcomes are defined as a measure of the patient’s experience or perception of their QoL, impact of disease and treatment effect. Importantly, interviewers asked children directly about their HRQoL using the PAQLQ(S)-IA, avoiding the proxy effect often seen when parents/caregivers answer questions for children [20]. Although proxies cannot give an accurate account of the individual patient’s experience [20], they are the only tools to assess the broader impact of asthma in young children. Using the PAQLQ(S)-IA to assess HRQoL revealed a generally diminished HRQoL among children with uncontrolled asthma, worsening when comorbid allergic rhinitis was present.

Asthma control correlates with patient QoL [21]. Here we show improvements in both these outcomes, signifying a holistic treatment effect of dupilumab in children with asthma.

Over 80% of children in this study had a medical history of comorbid allergic rhinitis, in line with previous publications [22]. Allergic rhinitis is one of the most prevalent allergic diseases in children, often associated with asthma, carries a significant disease burden [23] and is linked to an increase in the risk of severe exacerbations across all age groups [24]. Similar to what was observed for HRQoL in the overall type 2 population, dupilumab also improved HRQoL in children with a history of comorbid allergic rhinitis, which is in line with previously published literature on the treatment effects of dupilumab in adults and adolescents [25].

Childhood asthma can burden caregivers, affecting emotional function and work responsibilities, and limiting daily activities [18]. In addition to interviewing children on their QoL, we included an assessment of the burden on parents/caregivers of children with uncontrolled asthma. Including both child and family assessments allows clinicians a broader and more accurate understanding of the true effect of the disease and/or treatment on both parties [26]. Further, involving the family by assessing caregiver burden improves outcomes in children with asthma [27]. Shared decision making involving caregivers is necessary to ensure that treatment responds both to children’s symptoms (which may evolve) and family needs and concerns [27].

The caregiver burden was reflected in our study’s baseline scores on the PACQLQ. Importantly, overall caregiver HRQoL showed an improvement coincident with improved control of their child’s asthma with dupilumab. PACQLQ domains of activity limitation and emotional function, the latter often impaired due to caregiver anxiety over the child’s condition [4], also improved with dupilumab treatment.

The high placebo responses observed (e.g. ∼40% achieved well-controlled asthma) have been reported in adult dupilumab studies [25, 28] and in studies with omalizumab and mepolizumab [29, 30]. Biological treatments are used as additional (“add-on”) treatments to a background of standard care. It is likely that the high placebo response seen here relates to increased adherence to controller medications, together with other reported placebo effect factors, like increased patient expectations of treatment, improved clinical monitoring during clinical studies and self-prompted lifestyle changes [31].

Limitations of the VOYAGE trial have been reported, including a relatively homogenous population, with a majority of White children [10]. Limitations inherent to measures of patient-reported symptoms, such as comorbid allergic rhinitis, in children include the age at which children can reliably report, the role of parents in assessments and failure to consider the context within which children experience their disease [16]. Further, children may less reliably be able to assess subjective criteria, like HRQoL impacts [16]. Our use of the PAQLQ(S)-IA, which places its assessment questions within a child’s “world” by asking about the impacts of disease on their school or play environment, could improve children’s understanding of these criteria. However, our use of an interview-administered format rather than a direct child response may have affected the children’s answers or candour in unknown ways.

https://doi.org/10.1183/13993003.00558-2023
In conclusion, our study demonstrated that dupilumab improved both asthma control and HRQoL in children with asthma, thus improving overall asthma care for patients who have limited treatment options. Research that further explores the impacts of asthma treatment and disease control on the HRQoL of patients and their caregivers is needed to improve our understanding of the multidimensional effects of treatment in children.

This study is registered at ClinicalTrials.gov with identifier number NCT02948959. 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 anonymised 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: www.vivli.org

Ethics approval: VOYAGE was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guideline, and was approved by local institutional review boards or ethics committees.

Author contributions: J. Mshihid, R. Gall, J.A. Jacob-Nara, Y. Deniz, P.J. Rowe, D.J. Lederer, M. Hardin, Y. Zhang and A.H. Khan contributed to project concept, study design and study implementation. A.G. Fiocchi, W. Phipatanakul, R.S. Zeiger, S.R. Durrani and J. Cole contributed to data collection. J. Mshihid contributed to data and statistical analysis. 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 authors had full access to all of the data and took final responsibility to submit for publication. All investigators had confidentiality agreements with the sponsors.

Conflict of interest: A.G. Fiocchi has served as an advisory board member for Abbott, Danone, DBV Technologies, HiPP Organic, Novartis and Stallegenes Greer, and reports research sponsorship from Danone, Ferrero, HiPP Organic and Sanofi. W. Phipatanakul has served as a consultant and has received clinical trial support/medication support from Genentech, GSK for Asthma Therapeutics, Merck, Regeneron Pharmaceuticals Inc. and Sanofi. R.S. Zeiger has served as a deputy editor for the AAAAI and a consultant for the ACAAI, received research support from ALK and the NIH, received research support from and served as an advisory board member for AstraZeneca, Genentech-Novartis, GSK and Teva, served as an advisory board member for Sanofi-Regeneron Pharmaceuticals Inc., and reports royalties from UpToDate. J. Cole has no conflicts of interest to disclose. J. Mshihid, J.A. Jacob-Nara, P.J. Rowe, M. Hardin and A.H. Khan are Sanofi employees and may hold stock and/or stock options in the company. S.R. Durrani, R. Gall, Y. Deniz and D.J. Lederer are employees and shareholders of Regeneron Pharmaceuticals Inc. Y. Zhang is a former employee of Regeneron Pharmaceuticals Inc. and may hold shares and/or share options in the company.

Support statement: This research was sponsored by Sanofi and Regeneron Pharmaceuticals Inc. Support for data analysis and statistics was provided by Carole Mercier (Aixial; www.aixialgroup.com) funded by Sanofi and Regeneron Pharmaceuticals Inc. Medical writing/editorial assistance was provided by Elis Sutton (Excerpta Medica; https://excerptamedica.com), and was funded by Sanofi and Regeneron Pharmaceuticals Inc., according to the Good Publication Practice guidelines. Funding information for this article has been deposited with the Crossref Funder Registry.

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