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Original Article

Dupilumab pharmacokinetics and effect on type 2 biomarkers in children with moderate-to-severe asthma

Daniel J. Jackson, MD[*]; Leonard B. Bacharier, MD[†]; Wanda Phipatanakul, MD[‡]; Lawrence Sher, MD[§]; Christian Domingo, MD[‖]; Nikolaos Papadopoulos, MD[¶]; Brian Modena, MD[#]; Ning Li, MS[**]; Changming Xia, PhD[††]; Mohamed A. Kamal, PharmD, PhD[††]; Myles Dillon, PhD[††]; Kelley Wolfe, MSc[‡‡]; Rebecca Gall, MD[††]; Nikhil Amin, MD[††]; Leda P. Mannent, MD[§§]; Elizabeth Laws, PhD[‡‡]; Paul J. Rowe, MD[‡‡]; Juby A. Jacob-Nara, MD[‡‡]; Yamo Deniz, MD[††]; David J. Lederer, MD[††]; Megan Hardin, MD[‖‖]; Christine Xu, PhD[‡‡]

[*] Department of Pediatrics, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin
[†] Division of Allergy, Immunology and Pulmonary Medicine, Monroe Carell Jr Children's Hospital at Vanderbilt University Medical Center, Nashville, Tennessee
[‡] Department of Allergy and Immunology, Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts
[§] Peninsula Research Associates, Rolling Hills Estates, California
[‖] Pulmonary Service, Corporació Sanitària Parc Taulí, Sabadell, Autonomous University of Barcelona (UAB), Barcelona, Spain
[¶] Allergy Department, Second Pediatric Clinic, University of Athens, Greece
[#] Department of Allergy and Immunology, Modena Allergy & Asthma, La Jolla, California
[**] Department of Immunology, Sanofi, Beijing, People's Republic of China
[††] Department of Immunology, Regeneron Pharmaceuticals Inc, Tarrytown, New York
[‡‡] Department of Immunology, Sanofi, Bridgewater, New Jersey
[§§] Department of Immunology, Sanofi, Chilly-Mazarin, France
[‖‖] Department of Immunology, Sanofi, Cambridge, Massachusetts

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ABSTRACT

Background: Type 2 inflammation is common in children with asthma. Dupilumab, a human antibody, blocks the signaling of interleukin -4 and -13, key and central drivers of type 2 inflammation. In the LIBERTY ASTHMA VOYAGE (NCT02948959) study, dupilumab reduced severe asthma exacerbations and improved lung function in children aged 6 to 11 years with uncontrolled, moderate-to-severe asthma.
Objective: To assess the pharmacokinetics of dupilumab and type 2 biomarker changes in children with type 2 asthma in VOYAGE.
Methods: Patients were randomized to dupilumab 100 mg (≤30 kg) or 200 mg (>30 kg) or placebo every 2 weeks for 52 weeks. Dupilumab concentrations and changes in type 2 biomarkers were assessed at each visit.
Results: Dupilumab concentrations in serum reached a steady state by week 12, with mean concentrations of 51.2 mg/L and 79.4 mg/L in children receiving dupilumab 100 mg every 2 weeks and 200 mg every 2 weeks, respectively (therapeutic range in adults and adolescents: 29-80 mg/L). Reductions in type 2 biomarkers were comparable between regimens, and greater in patients treated with dupilumab vs placebo. In children treated

Address correspondence to: Daniel J. Jackson, MD University of Wisconsin School of Medicine and Public Health, 600 Highland Avenue, CSC K4/936, Madison, WI 53575-9988. E-mail: djj@medicine.wisc.edu.

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with dupilumab 100 mg and 200 mg every 2 weeks, the median percent changes (Q1-Q3) from baseline at week 52 were, respectively, −78.6% (−86.3 to −69.80) and −78.6% (−84.9 to −70.1) for serum total immunoglobulin E, −53.6% (−66.4 to −34.6) and −43.7% (−58.6 to −28.5) for thymus and activation-regulated chemokine; −25.7% (−60.0 to 27.6) and −33.3% (−60.6 to 16.6) for blood eosinophils, and −47.7% (−73.8 to 18.9) and −55.6% (−73.6 to −20.0) for fractional exhaled nitric oxide.

Conclusion: Weight-tiered dose regimens achieved mean concentrations within the dupilumab therapeutic range. The median decreases in type 2 biomarker levels were similar between dose regimens.

Trial Registration: ClinicalTrials.gov Identifier: NCT02948959

Introduction

Asthma is one of the most common chronic diseases affecting children worldwide; its global prevalence is increasing in children and adolescents.[1–4] Diagnosing asthma in preschool children is difficult.[5] Wheezing typically occurs in 30% of children under the age of 3 years,[6] and it has been found that preschool children with stable multiple-trigger wheezing are at higher risk of developing asthma than those with episodic (viral) wheeze.[7] Asthma affects approximately 10% of children (aged 6 to 11 years); most of these present with a mild-to-moderate form of asthma.[8] However, 2% of children have severe asthma,[8] some with deficits in lung function that can potentially persist into adulthood.[9–11]

Asthma is a heterogeneous disease comprised of multiple phenotypes and endotypes; type 2 inflammation is the most common driver of asthma in children.[12,13] Type 2 inflammatory asthma is defined by eosinophilic airway inflammation, driven by CD4+ T helper 2 (T_H2) lymphocytes,[14] acting by means of the inflammatory cytokines interleukin (IL)-4, IL-5, and IL-13.[15,16] Furthermore, type 2 inflammation is also associated with elevated levels in biomarkers such as blood eosinophil counts, serum total immunoglobulin E (IgE), fractional exhaled nitric oxide (FeNO), and serum thymus and activation-regulated chemokine (TARC).[17,18] These biomarkers (specifically serum total IgE, blood eosinophils, and FeNO) are considered important clinical indicators of type 2 inflammation.[18] The Global Initiative for Asthma recommends using these biomarkers to identify patients with type 2 inflammation who are likely to benefit from targeted biologic therapy.[16,19]

Dupilumab, a fully human monoclonal antibody, binds the shared IL-4 alpha subunit (IL-4Rα) of the receptors for the type 2 cytokines IL-4 and IL-13, inhibiting their signaling.[20,21] The phase 3 LIBERTY ASTHMA VOYAGE study evaluated the efficacy and safety of dupilumab in children aged 6 to 11 years with uncontrolled, moderate-to-severe type 2 asthma during the 52 weeks of the treatment period.[22] Dupilumab reduced the annualized rate of severe asthma exacerbations, improved lung function, and enhanced asthma control compared with placebo in patients with evidence of type 2 inflammation (as identified by either blood eosinophils ≥150 cells/μL or FeNO ≥20 parts per billion [ppb]). The safety profile was consistent with the known safety profile of dupilumab.[22] Across 6 phase 1 studies, dupilumab exhibited target-mediated pharmacokinetics with parallel linear and nonlinear elimination and was well tolerated across a wide range of doses.[23] In addition, there was no difference in pharmacokinetics between adult and adolescent patients with asthma once adjusted for body weight, and pharmacokinetics were also similar between patients with oral corticosteroid–dependent or non–oral corticosteroid-dependent asthma.[24,25]

This analysis describes the pharmacokinetics of dupilumab and its effects on type 2 biomarker levels (serum total IgE, serum TARC, blood eosinophil counts, and FeNO) observed in children participating in VOYAGE, receiving either dupilumab 100 or 200 mg once every 2 weeks on the basis of a weight-tiered fixed-dose regimen for up to 52 weeks.

Methods

Study Design

Full details of the LIBERTY ASTHMA VOYAGE (NCT02948959) study design have been described previously.[22] In brief, VOYAGE was a multinational 52-week, phase 3, randomized, double-blind, placebo-controlled, parallel-group study assessing the efficacy and safety of dupilumab in children aged 6 to 11 years with uncontrolled, moderate-to-severe asthma. Children were randomized to either dupilumab 100 or 200 mg every 2 weeks without a loading dose (on the basis of a weight-tiered fixed-dose regimen: 100 mg for those weighing ≤30 kg and 200 mg for >30 kg) or placebo every 2 weeks as an add-on to the standard of care treatment. The randomization ratio was 2:1 for active-to-placebo groups.

The trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines with oversight from an independent data and safety monitoring committee and local review boards/ethics committees. Parents and guardians (for non-adult participants) of participants provided written informed consent, and the children provided assent according to local ethics committee-approved standard practice for pediatric participants. The 2 primary efficacy populations, both subsets of the intention-to-treat population, included patients with a type 2 inflammatory asthma phenotype (blood eosinophil levels ≥150 cells/μL or FeNO ≥20 ppb) and patients with a baseline blood eosinophil count of ≥300 cells/μL (a subgroup of the type 2 inflammatory asthma phenotype population). Both populations were selected on the basis of efficacy findings in studies of dupilumab involving adults and adolescents with asthma.[22,26,27]

Pharmacokinetic Analysis

All participants in the safety population (defined as patients exposed to study medication, regardless of the amount of treatment administered and whether they were randomized) with at least one nonmissing result for functional dupilumab concentration in serum were included in the pharmacokinetic (PK) population. Blood samples were collected at baseline and weeks 6, 12, 24, and 52 before dosing. Serum concentrations of functional dupilumab (the sum of dupilumab with at least 1 available binding site and dupilumab present in a 1:1 human IL-4Rα/dupilumab complex) were determined using a validated enzyme-linked immunoassay (ELISA) method.[28–31] The lower limit of quantification (LLOQ) was 0.078 mg/L.

Serum concentrations of dupilumab were summarized using arithmetic mean and SD, per sampling time by each dose regimen group, and overall treatment group. If the date and/or time of drug injection and/or sampling were missing, then the concentration was not included. For dupilumab-treated participants in whom concentration values were below the LLOQ, one-half of the LLOQ was used.[32]

Pharmacodynamic Biomarker Analysis

The effects of dupilumab on the median levels of the following type 2 biomarkers were assessed over the 52-week treatment period:

serum total IgE (IU/mL), serum TARC (ng/L), blood eosinophil count (cells/μL), and FeNO (ppb).

Serum samples were assayed at ViraCor-IBT Laboratories in Lees Summit, Missouri for the measurement of total IgE, using the ImmunoCAP platform (Phadia, Uppsala, Sweden). For the measurement of TARC, serum samples were assayed at PPD in Richmond, Virginia using a validated commercial ELISA assay (human CCL17/TARC Quantikine ELISA Kit #DDN00; R&D Systems Inc, Minneapolis, Minnesota) according to the manufacturer's instructions. Blood eosinophil levels were counted as part of the standard white blood cell differential cell count on a hematology autoanalyzer. The FeNO concentrations were measured before spirometry and after at least 1 hour of fasting using a NIOX instrument (Aerocrine AB, Solna, Sweden) or a similar analyzer using a flow rate of 50 mL/s.

All biomarkers were summarized in the exposed population (defined as participants who received at least 1 dose or part of a dose of study medication). The baseline value was the last value collected before the first dose. Descriptive statistics (including number, median, first quartile [Q1], and third quartile [Q3]) of biomarkers at baseline were summarized. For all parameter values at each visit, absolute change from baseline and percent changes from baseline were summarized descriptively by treatment group and time point.

Statistical Analysis of Biomarkers Levels Over Time

The median absolute values, median change from baseline, and median percentage change from baseline were analyzed descriptively in the dupilumab 100 mg every 2 weeks, dupilumab 200 mg every 2 weeks, and matched placebo arms for all available biomarkers at each visit. The differences between dupilumab 100 mg every 2 weeks/dupilumab 200 mg every 2 weeks and matching placebo in the median change from baseline and percent median change from baseline to week 52 (because this was the main result of interest, representing the final outcome of patients in the study with the longest follow-up, regardless of intermediate values) were analyzed using rank analysis of covariance model. Covariates included age, weight, region, baseline eosinophil level, baseline inhaled corticosteroid (ICS) dose level, and the corresponding baseline value. *P* values less than .05 were considered statistically significant nominally.

Results

Demographics

A total of 408 children aged 6 to 11 years with uncontrolled moderate-to-severe asthma were randomized to receive either dupilumab 100 mg every 2 weeks (bodyweight ≤30 kg; n = 91) or 200 mg every 2 weeks (bodyweight: >30 kg; n = 179), or matched placebo (n = 135). There were 3 patients in the dupilumab group who did not receive the assigned intervention. In total, 350 (86%) children participating in VOYAGE met the definition of type 2 inflammatory asthma phenotype (Table 1 and Fig 1). Of these, 236 children were in the dupilumab groups and 114 received a placebo. In the population of participants with blood eosinophil levels greater than or equal to 300 cells/μL, 175 children were in the dupilumab group, and 84 received

Table 1
Baseline Characteristics in Patients With Moderate-to-Severe Asthma With the Type 2 Inflammatory Asthma Phenotype in the VOYAGE Study

Characteristics	Type 2 inflammatory asthma phenotype	
	Placebo (n = 114)	Dupilumab (n = 236)
Age, mean (SD), y	9.0 (1.6)	8.9 (1.6)
Female, n (%)	36 (31.6)	84 (35.6)
Race, n (%)		
White	102 (89.5)	208 (88.1)
Black/of African descent	5 (4.4)	9 (3.8)
Asian	0	2 (0.8)
American Indian or Alaska Native	0	1 (0.4)
Other	7 (6.1)	16 (6.8)
Ethnicity, n (%)		
Hispanic or Latino	51 (44.7)	104 (44.1)
Body weight, mean (SD), kg	37.08 (11.6)	35.60 (10.0)
≤30 kg, n (%)	36 (31.6)	76 (32.2)
>30 kg, n (%)	78 (68.4)	160 (67.8)
BMI, mean (SD), kg/m^2	19.03 (3.94)	18.60 (3.51)
Use of high-dose ICS, n (%)	50 (43.9)	102 (43.2)
Severe asthma exacerbations in the past year, mean (SD), n	2.18 (1.6)	2.61 (2.6)
With atopic medical conditions,[a] n (%)	103 (90.4)	226 (95.8)
Pre-BD FEV_1, mean (SD), L	1.53 (0.46)	1.48 (0.39)
Post-BD FEV_1, mean (SD), L	1.74 (0.49)	1.75 (0.43)
Pre-BD $FEF_{25\%-75\%}$, mean (SD), L/sec	1.28 (0.53)	1.27 (0.54)
Pre-BD FVC, mean (SD), L	2.08 (0.57)	2.00 (0.48)
Pre-BD FEV_1/FVC ratio, mean (SD), %	73.53 (9.46)	73.96 (10.36)
ACQ-7-IA score, mean (SD)	2.12 (0.8)	2.15 (0.7)
Global PAQLQ-IA score, mean (SD)	4.92 (1.13)	4.95 (1.08)
Biomarkers		
Blood eosinophil count, median (Q1-Q3), cells/μL	440.0 (280.0-660.0)	510.0 (290.0-780.0)
Blood eosinophil count ≥ 150 cells/μL, n (%)	108 (94.7)	223 (94.5)
Serum total IgE, median (Q1-Q3), IU/mL	397.0 (144.0-862.0)	530.0 (213.0-1268.0)
FeNO, median (Q1-Q3), ppb	21.0 (13.0-34.0)	25.5 (12.0-45.0)
FeNO ≥ 20 ppb, n (%)	62 (54.4)	141 (59.7)
TARC, median (Q1-Q3), ng/L	416.50 (265.0-620.0)	403.0 (254.0-616.0)

Abbreviations: ACQ-7-IA, interviewer-administered 7-item Asthma Control Questionnaire; BD, bronchodilator; BMI, body mass index; $FEF_{25\%-75\%}$, forced expiratory flow at 25-75% of pulmonary volume; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroid; IgE, immunoglobulin E; PAQLQ-IA, interviewer-administered Pediatric Asthma Quality of Life Questionnaire; ppb, parts per billion; Q, quartile; TARC, thymus and activation-regulated chemokine.
NOTE. Adapted from Bacharier et al.[22]
[a]Atopic medical conditions defined in eTable 1.

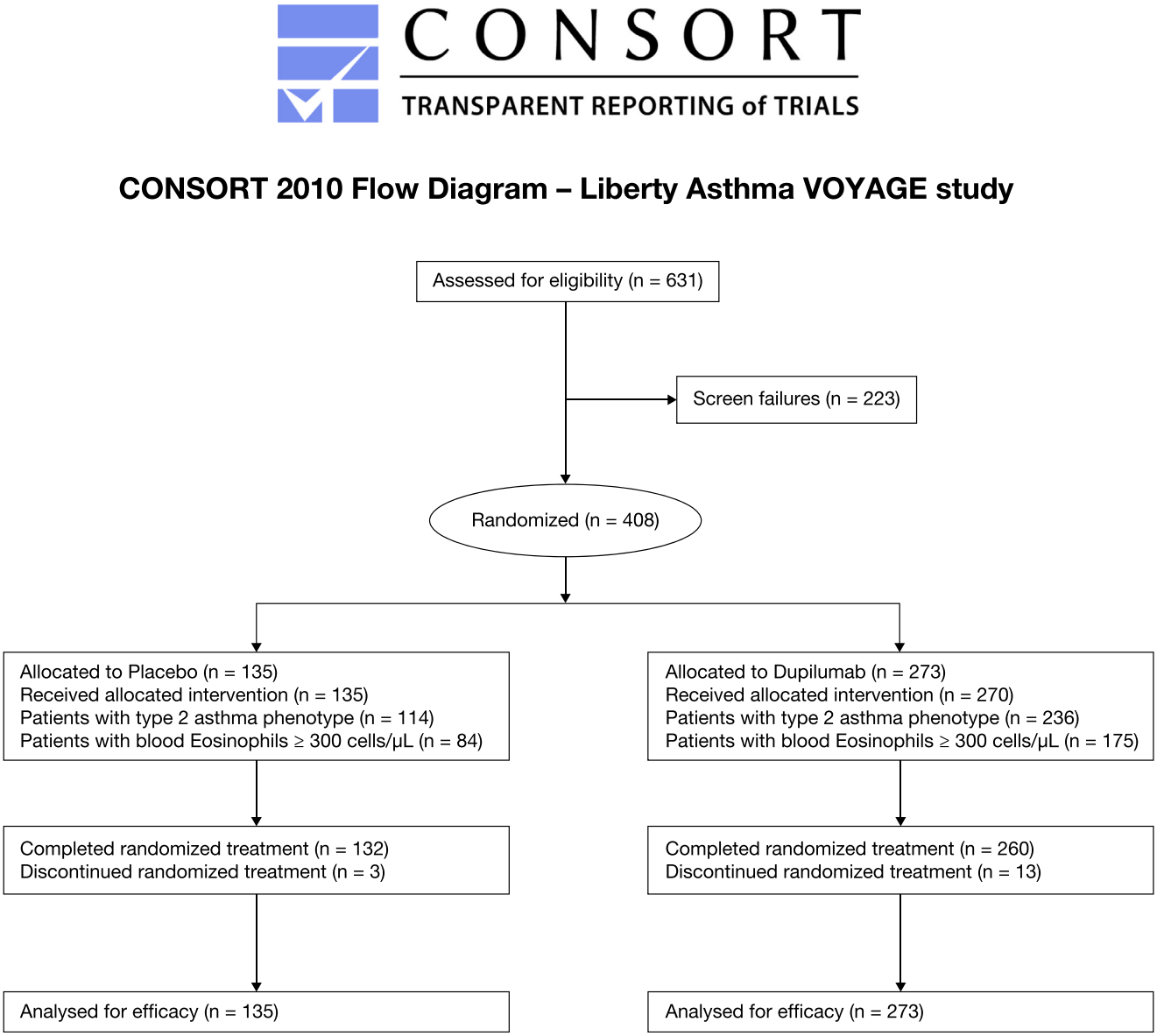

Figure 1. CONSORT diagram for the VOYAGE LIBERTY ASTHMA study – Adapted from Bacharier et al.[22] CONSORT, Consolidated Standards of Reporting Trials.

a placebo (Fig 1 and eTable 1). Demographic and clinical characteristics were balanced across the treatment arms.

Pharmacokinetics

Serum dupilumab concentrations in the pharmacokinetic (PK) population increased after treatment initiation and reached a steady state at week 12 (mean [± SD] dupilumab 100 mg every 2 weeks: 51.2 [± 24.0] mg/L; dupilumab 200 mg every 2 weeks: 79.4 [± 35.3] mg/L). Children receiving dupilumab 100 mg every 2 weeks exhibited lower mean serum concentrations than those receiving dupilumab 200 mg every 2 weeks throughout the treatment period (Fig 2). Dupilumab pharmacokinetics were similar in the population with a type 2 inflammatory phenotype, and the population with baseline blood eosinophils ≥300 cells/μL (Fig 2).

Pharmacodynamics

The median biomarker levels over time and median percentage change from baseline for all biomarkers in children with type 2 asthma are presented in Figures 3 and 4.

Serum Total Immunoglobulin E

The baseline median levels of serum total IgE in patients who received dupilumab 100 mg every 2 weeks were slightly higher compared with those in the group who received dupilumab 200 mg every 2 weeks (Fig 3A, eTable 2). Nevertheless, dupilumab reduced serum total IgE throughout the 52-week treatment period by a median of 78.6% at the end of treatment for both weight-tiered regimens (Fig 4A, eTable 2). The pattern of median changes from baseline was similar in both dupilumab dosing regimens and the magnitude of reductions was significantly greater compared with placebo ($P < .001$) (Fig 3A, eTable 2). A small increase in serum total IgE of 4.0% to 5.7% was observed in patients who received a matching placebo (Fig 4A, eTable 2).

Serum Thymus and Activation-Regulated Chemokine

The baseline median levels of serum TARC were similar between treatment groups within each of the baseline weight subgroups (>30 and ≤30 kg) (Fig 3B, eTable 2). At the first assessment at week 12, dupilumab reduced the median serum TARC levels by 45.8% and 43.3% (100 mg and 200 mg every 2 weeks dose regimens,

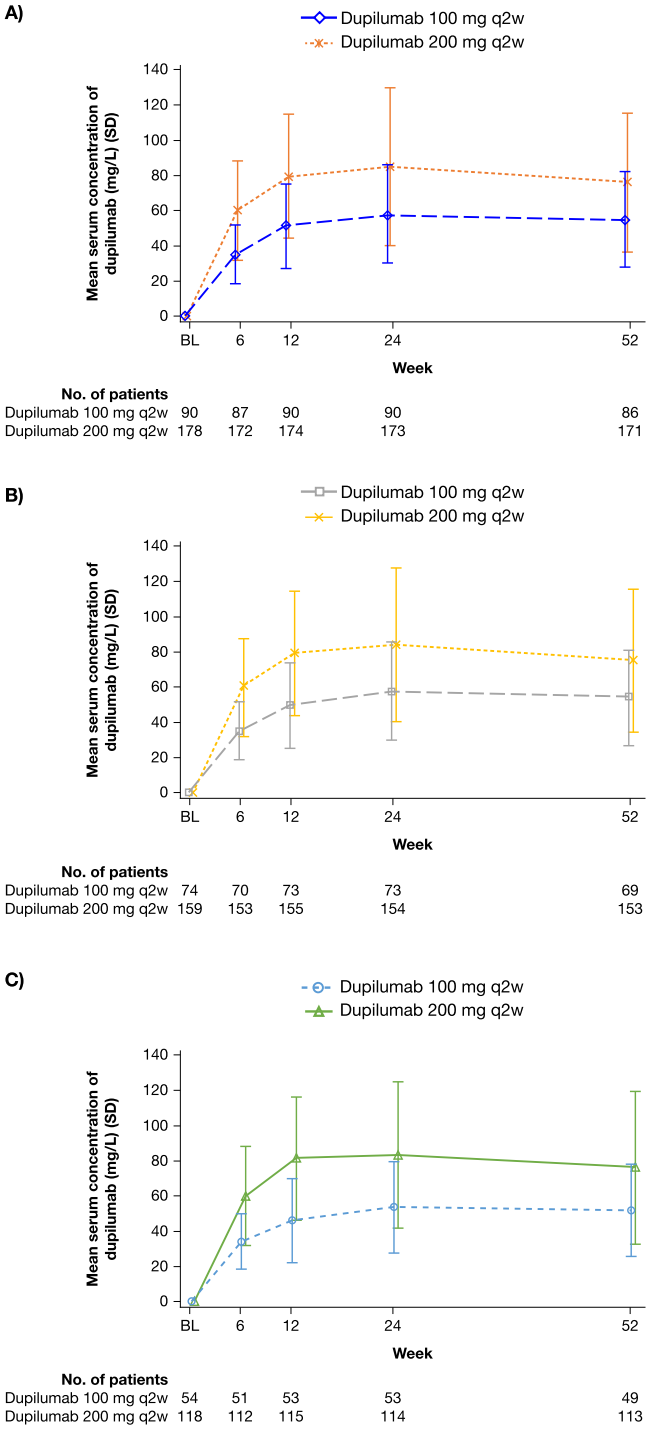

Figure 2. The serum concentration of dupilumab over time in (A) Pharmacokinetic (PK), (B) type 2 inflammatory asthma phenotype, and (C) children with blood eosinophils ≥300 cells/μL populations in the VOYAGE study. pharmacokinetic (PK), pharmacokinetic; every 2 weeks, every 2 weeks.

respectively) compared with baseline; these reductions were maintained up to week 52 (median percent decrease: −53.6% and −43.7%, respectively). Whereas small decreases were observed in the placebo population, these were significantly smaller than those in the dupilumab groups (−15.1% and −9.4% in the matched placebo arms, respectively) (Fig 4B, eTable 2). The change in the median serum TARC levels from baseline to week 52 was significantly lower in children receiving dupilumab vs placebo ($P < .001$), regardless of dose regimen (Fig 4B, eTable 2). The pattern of median changes from baseline was similar in both dupilumab dosing regimens, and the magnitude of reductions was greater compared with placebo (Fig 3B, eTable 2).

Blood Eosinophil Counts

The baseline median blood eosinophil counts were comparable across treatment arms (Fig 3C, eTable 2). Decreases in the median blood eosinophil levels were similar between placebo and the dupilumab 100 mg groups (−1.46% and 0%, respectively), and greater in patients treated with dupilumab 200 mg compared with its respective placebo group (−5.2% vs 0.74%), at week 12 (Fig 4C, eTable 2). By week 52, the median percentage decreases from baseline in blood eosinophil counts were greater in the dupilumab 100 mg and 200 mg groups than with placebo; at week 52, dupilumab vs placebo reduced median blood eosinophil count by 25.7% vs 17.5% ($P = .58$) in the dupilumab 100 mg every 2 weeks treatment arm and by 33.3% vs 6.2% ($P = .01$) in the dupilumab 200 mg every 2 weeks treatment arm (Fig 4C, eTable 2).

Fractional Exhaled Nitric Oxide

The baseline median levels of FeNO were slightly higher in the patient group receiving dupilumab 200 mg every 2 weeks and matching placebo vs those in the 100 mg every 2 weeks treatment arm and respective matching placebo (Fig 3D, eTable 2). Independent of dose, the dupilumab median FeNO levels at week 2 were reduced by 46.4% (dupilumab 100 mg every 2 weeks) and 55.7% (dupilumab 200 mg every 2 weeks) from baseline; these reductions were sustained to the end of treatment at week 52 (Fig 4D, eTable 2). In the placebo group, the FeNO concentrations remained unchanged over the 52-week period (Fig 3D). By week 52, the median FeNO values in the dupilumab group were 11.0 ppb and 12.0 ppb for the 100 mg and 200 mg treatment arms, respectively. The median percent change from baseline at week 52 was significantly lower for patients treated with dupilumab when compared with the placebo group ($P < .05$ for both treatment arms) (Fig 4, eTable 2).

Similar results for changes from baseline in serum total IgE, serum TARC, blood eosinophil count, and FeNO were observed for the population of children with blood eosinophils ≥300 cells/μL at baseline (eFigs 1-2, eTable 3).

Discussion

In our analysis of pharmacokinetics in children aged 6 to 11 years with moderate-to-severe asthma, dupilumab concentrations in serum reached a steady state at week 12 for both the 100 mg and 200 mg every 2 weeks weight-tiered dupilumab dosing regimens. The weight-tiered dupilumab regimens were selected to normalize dupilumab exposure to achieve exposure in the therapeutic range that was observed in adults and adolescents.[25] In children who participated in VOYAGE, steady-state dupilumab concentrations at week 12 were 51.2 mg/L and 79.4 mg/L for dupilumab 100 mg every 2 weeks and 200 mg every 2 weeks, respectively, compared with mean trough concentrations at steady state in adults (36.5 mg/L and 67.8 mg/L; dupilumab 200 mg and 300 mg every 2 weeks, respectively) and adolescents (46.7 mg/L and 106 mg/L; dupilumab 200 mg and 300 mg every 2 weeks, respectively).[25] Despite the regimen of 100 mg every 2 weeks having lower steady-state exposures compared with the regimen of 200 mg every 2 weeks, both regimens led to mean concentrations within the therapeutic range (29-80 mg/L) being observed in adults and adolescents,[25,28,33] and the differences in steady-state exposure between these dose regimens in the VOYAGE study did not translate to any pharmacodynamic differences across all biomarkers studied in children with asthma.

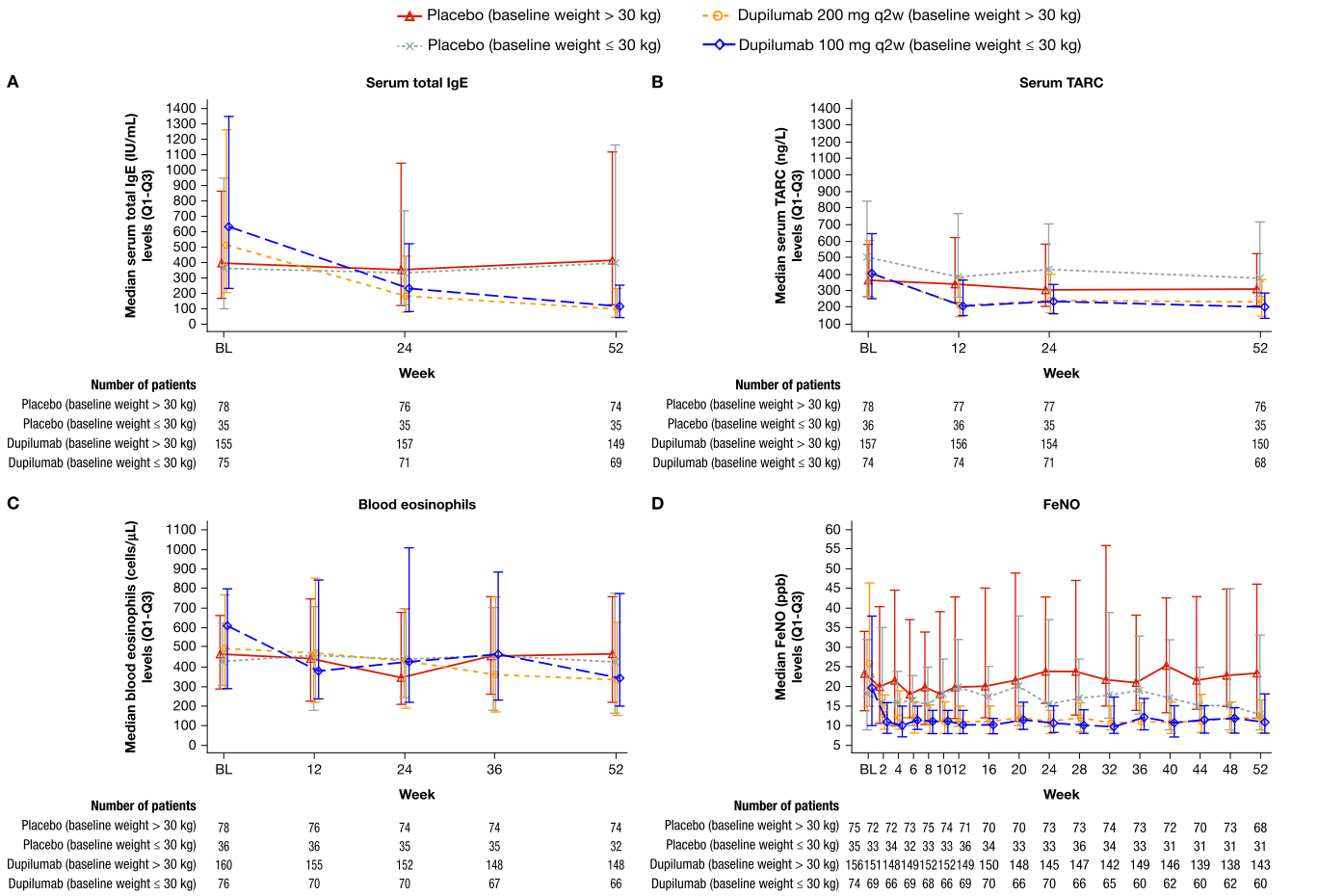

Figure 3. Median (Q1-Q3) biomarker levels over time in children with a type 2 inflammatory asthma phenotype participating in VOYAGE: (A) serum total IgE, (B) serum TARC, (C) blood eosinophil count, and (D) FeNO. FeNO, fractional exhaled nitric oxide; IgE, immunoglobulin E; TARC, thymus and activation-regulated chemokine.

As a fully human monoclonal antibody that targets the shared IL-4Rα component of the IL-4 and IL-13 receptors, dupilumab inhibits 2 canonical cytokines that drive type 2 inflammation.[17,21,34] Treatment with dupilumab resulted in comparable and substantial decreases in type 2 biomarker levels in both weight-tiered dose groups. In line with previously published data from dupilumab studies in adults and adolescents with moderate-to-severe asthma, and across analyses observed in patients with other types 2 inflammatory diseases including atopic dermatitis (AD), chronic rhinosinusitis with nasal polyps, and eosinophilic esophagitis,[17,26] reductions in type 2 biomarkers were observed in the full data set of children in the VOYAGE study.

Immunoglobulin E is the principal immunoglobulin involved in type 2 inflammation. Dupilumab resulted in a progressive decrease in serum total IgE levels throughout the treatment period in children with moderate-to-severe asthma in both weight-tiered dose groups. This reduction is in line with the mechanistic roles of IL-4 and IL-13 in driving B cell activation and IgE class switching.[16] Blockade of these processes, which has been exhibited in preclinical studies of dupilumab, may result in a reduction in the overall number of IgE-secreting plasmablasts and preexisting IgE-secreting cells, and thus, IgE levels.[17,21] These data are also in line with what has previously been observed in adults and adolescents (aged ≥ 12 years) with uncontrolled, moderate-to-severe asthma in the 52-week phase 3 LIBERTY ASTHMA QUEST study,[26] and in an earlier 12-week study in adults with moderate-to-severe asthma and elevated blood eosinophil levels.[35] Similar effects have also been found in dupilumab-treated patients with other type 2 inflammatory conditions.[17]

Thymus and activation-regulated chemokine is involved in the recruitment of T_H2 lymphocytes and eosinophils to their target tissues, supporting its key role in type 2 inflammation.[17,36,37] The extent of TARC reductions observed in this analysis was similar in both weight-tiered dose groups. In a study of dupilumab in adults with moderate-to-severe asthma and elevated blood eosinophil counts, reductions in TARC levels were observed as early as week 1 after initiation of dupilumab,[27] and similar reductions were seen over a 52-week treatment period in adults and adolescents with uncontrolled, moderate-to-severe asthma in the QUEST trial.[26] Rapid reductions in TARC in response to dupilumab treatment have also been exhibited across other type 2 inflammatory conditions.[17]

Eosinophils are key cellular modulators of type 2 inflammation, with a pathologic role principally in the tissue rather than in the bloodstream.[38–40] Interleukin-4 and IL-13 both have roles in promoting the migration of eosinophils into tissue and, thus, a blockade of these IL limits eosinophils traffic from blood to bronchial mucosa which causes an immediate increase of eosinophils in the bloodstream. A reduction in blood eosinophil counts may reflect reduced T_H2 differentiation from naive T cells (T_H0) through IL-4 blockade, which in turn, reduces eosinophil levels because of a lack of T_H2 cell support.[17,40–42]

Fractional exhaled nitric oxide, which is recommended for airway inflammation monitoring,[43] has been recognized as a potentially clinically useful biomarker of response.[15,44] The results presented in this study reveal that FeNO reductions were rapid and sustained regardless of the dupilumab dose regimen in children with moderate-to-

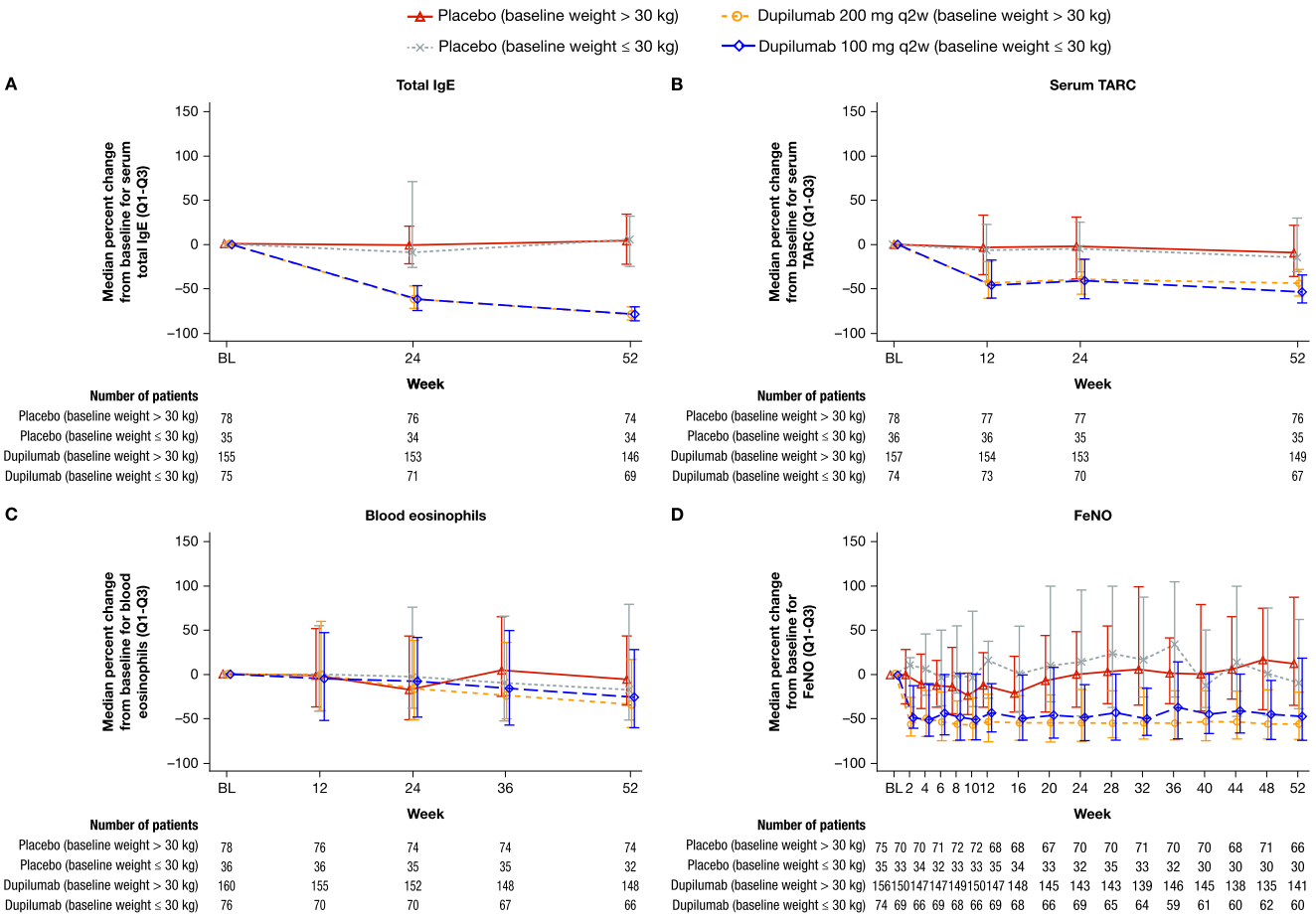

Figure 4. Median percentage change (Q1-Q3) from baseline in biomarker levels over time in children with a type 2 inflammatory asthma phenotype participating in VOYAGE: (A) serum total IgE, (B) serum TARC, (C) blood eosinophil count, and (D) FeNO. FeNO, fractional exhaled nitric oxide; IgE, immunoglobulin E; TARC, thymus and activation-regulated chemokine.

severe type 2 asthma. The observed results further support the indication of dupilumab's dual mode of action blocking IL-4 and IL-13 signaling, as IL-13 has been found to be involved in a multitude of pathobiological aspects of asthma, including raising FeNO levels by activating epithelial nitric oxide synthase through its effect on STAT6.[45,46] In the phase 2b and phase 3 QUEST studies, treatment with dupilumab exhibited reductions in FeNO levels and revealed that these changes were correlated with improvements in lung function as measured by FEV_1.[26,47]

Limitations of our study include a lack of any direct assays of biomarkers in airway tissues. This may have been partially ameliorated by the use of FeNO as a biomarker.[15,48,49]

Conclusion

The weight-tiered dose regimens that were selected to normalize dupilumab exposure achieved serum dupilumab concentrations within the therapeutic range. Both dose regimens led to significant reductions in a broad range of biomarkers of type 2 inflammation, indicating that dupilumab effectively targets the underlying inflammatory pathways that contribute to asthma pathogenesis in children with moderate-to-severe type 2 asthma. These reductions were sustained over the 52-week treatment period of the VOYAGE trial. Despite differences in exposure between the weight tiers, the median decreases in type 2 biomarker levels were similar among patients. Future longitudinal studies will determine whether these effects also translate to better long-term outcomes.

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Supplementary Data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.anai.2023.03.014.

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Supplementary Data

eTable 1
Baseline Characteristics in Children With Moderate-to-Severe Asthma and Blood Eosinophils ≥ 300 cells/μL at Baseline

Characteristics	Blood eosinophils ≥ 300 cells/μL	
	Placebo (n = 84)	Dupilumab (n = 175)
Age, mean (SD), y	9.0 (1.5)	8.9 (1.6)
Female, n (%)	26 (31.0)	59 (33.7)
Race, n (%)		
White	75 (89.3)	151 (86.3)
Black/of African descent	5 (6.0)	8 (4.6)
Asian/Oriental	0	2 (1.1)
American Indian or Alaska Native	0	1 (0.6)
Other	4 (4.8)	13 (7.4)
Ethnicity, n (%)		
Hispanic or Latino	35 (41.7)	76 (43.4)
Not Hispanic or Latino	49 (58.3)	99 (56.6)
Body weight, mean (SD), kg	36.97 (11.7)	35.45 (10.0)
≤30 kg, n (%)	28 (33.3)	56 (32.0)
>30 kg, n (%)	56 (66.7)	119 (68.0)
BMI, mean (SD), kg/m^2	18.99 (3.96)	18.53 (3.66)
Use of high-dose ICS, n (%)	41 (48.8)	74 (42.3)
Severe asthma exacerbations in past year, mean (SD), n	2.37 (1.7)	2.78 (2.9)
With atopic medical conditions,[a] n (%)	79 (94.0)	171 (97.7)
Pre-BD FEV_1, mean (SD), L	1.52 (0.48)	1.45 (0.39)
Post-BD FEV_1, mean (SD), L	1.75 (0.53)	1.74 (0.44)
Pre-BD $FEF_{25\%-75\%}$, mean (SD), L/sec	1.24 (0.54)	1.23 (0.52)
Pre-BD FVC, mean (SD), L	2.09 (0.61)	1.98 (0.48)
Pre-BD FEV_1/FVC ratio, mean (SD), %	72.46 (9.55)	73.39 (10.62)
ACQ-7-AI score, mean (SD)	2.15 (0.8)	2.16 (0.7)
Global PAQLQ-IA score, mean (SD)	4.89 (1.09)	4.96 (1.13)
Biomarkers		
Blood eosinophil count, median (Q1-Q3), cells/μL	530.0 (420.0-730.0)	660.0 (480.0-910.0)
Blood eosinophil count ≥ 150 cells/μL, n (%)	84 (100)	175 (100)
Total IgE, median (Q1-Q3), IU/mL	554.0 (215.0-1101.0)	599.5 (331.0-1470.0)
FeNO, median (Q1-Q3), ppb	24.5 (15.5-39.5)	28.0 (13.0-47.0)
FeNO ≥ 20 ppb, n (%)	52 (61.9)	114 (65.1)
TARC, median (Q1-Q3), ng/L	420.0 (255.5-607.5)	422.5 (274.0-688.0)

Abbreviations: ACQ-7-IA, interviewer-administered 7-item asthma control questionnaire; BD, bronchodilator; BMI, body mass index; $FEF_{25\%-75\%}$, forced expiratory flow at 25–75% of pulmonary volume; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroid; IgE, immunoglobulin E; IU, international unit; PAQLQ-IA, interviewer-administered Pediatric Asthma Quality of Life Questionnaire; ppb, parts per billion; Q, quartile; TARC, thymus and activation-regulated chemokine.
NOTE. Adapted from Bacharier et al.[22]
[a]An atopic medical condition was defined as the presence of one or more of the following ongoing conditions: atopic dermatitis, allergic conjunctivitis, allergic rhinitis, eosinophilic esophagitis, food allergy, or hives or a baseline total IgE level of at least 100 IU/mL and positivity (≥ 0.35 IU/mL) for at least 1 aeroallergen-specific IgE at baseline.

eTable 2
Pharmacodynamic Changes in Biomarker Levels Over Time in Children With a Type 2 Inflammatory Asthma Phenotype Participating in VOYAGE

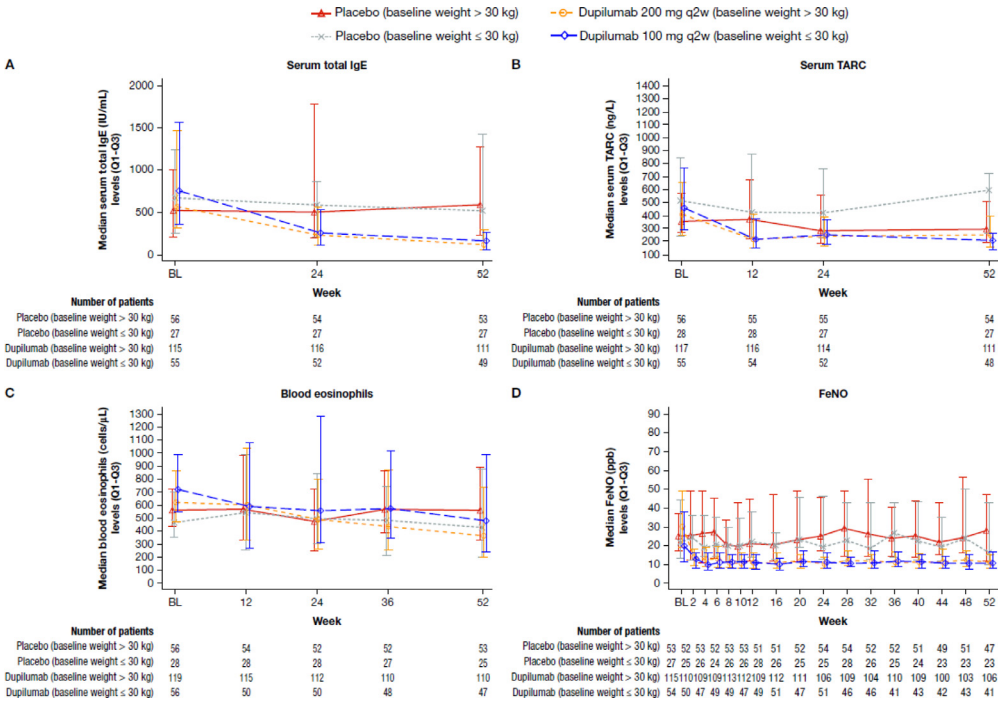
Biomarkers	Dupilumab 100 mg every 2 wk		Dupilumab 200 mg every 2 wk	
	Placebo	Dupilumab	Placebo	Dupilumab
Serum total IgE, IU/mL				
Baseline,	n = 35	n = 75	n = 78	n = 155
Median (Q1-Q3)	355.0 (104.0-952.0)	641.0 (231.0-1350.0)	401.0 (165.0-862.0)	512.0 (202.0-1263.0)
Week 52	n = 35	n = 69	n = 74	n = 149
Median (Q1-Q3)	395.0 (93.0-1167.0)	111.0 (41.0-245.0)	417.5 (128.0-1123.0)	93.0 (41.0-229.0)
Change from BL, median (Q1-Q3)	2.5 (−136.0 to 103.0)	−423.0 (−1063.0 to −151.0)	1.5 (−63.0 to 118.0)	−368.0 (−921.0 to −147.0)
P value (vs placebo)		<.001		<.001
Percentage change from BL, median (Q1-Q3)	5.7 (−25.0 to 32.1)	−78.6 (−86.3 to −69.8)	4.0 (−22.4 to 33.8)	−78.6 (−84.9 to −70.1)
P value (vs placebo)		<.001		<.001
Serum TARC, ng/mL				
Baseline,	n = 36	n = 74	n = 78	n = 157
Median (Q1-Q3)	502.5 (268.5-844.5)	401.0 (254.0-646.0)	364.0 (265.0-579.0)	404.0 (255.0-601.0)
Week 52	n = 35	n = 68	n = 76	n = 150
Median (Q1-Q3)	375.0 (264.0-714.0)	204.5 (133.5-290.0)	307.0 (212.5-522.5)	235.0 (145.0-359.0)
Change from BL, median (Q1-Q3)	−69.0 (−176.0 to 71.0)	−200.0 (−359.5 to −107.0)	−30.5 (−141.5 to 52.5)	−178.0 (−332.0 to −82.0)
P value (vs placebo)		<.001		<.001
Percentage change from BL, median (Q1-Q3)	−15.1 (−30.8 to 29.6)	−53.6 (−66.4 to −34.7)	−9.4 (−36.3 to 21.4)	−43.7 (−58.6 to −28.5)
P value (vs placebo)		<.001		<.001
Blood eosinophil counts, cells/μL				
Baseline,	n = 36	n = 76	n = 78	n = 160
Median (Q1-Q3)	420.0 (305.0-625.0)	610.0 (290.0-795.0)	460.0 (280.0-660.0)	495.0 (290.0-765.0)
Week 52	n = 32	n = 66	n = 74	n = 148
Median (Q1-Q3)	425.0 (165.0-775.0)	340.0 (200.0-770.0)	465.0 (220.0-760.0)	335.0 (150.0-625.0)
Change from BL, median (Q1-Q3)	−60.0 (−215.0 to 260.0)	−105.0 (−290.0 to 100.0)	−25.0 (−220.0 to 150.0)	−130.0 (−330.0 to 85.0)
P value (vs placebo)		0.26		0.04
Percentage change from BL, median (Q1-Q3)	−17.5 (−51. 5 to 79.8)	−25.7 (−60.0 to 27.6)	−6.2 (−34.2 to 43.8)	−33.3 (−60.6 to 16.6)
P value (vs placebo)		.58		.01
FeNO, ppb				
Baseline,	n = 35	n = 74	n = 75	n = 156
Median (Q1-Q3)	18.0 (9.0-32.0)	20.0 (10.0-38.0)	23.0 (14.0-34.0)	26.0 (15.0-46.5)
Week 52	n = 31	n = 60	n = 68	n = 143
Median (Q1-Q3)	13.0 (9.0-33.0)	11.0 (8.0-18.0)	23.5 (12.0-46.0)	12.0 (8.0-17.0)
Change from BL, median (Q1-Q3)	−1.0 (−9.0 to 6.0)	−7.0 (−26.0 to 2.5)	1.0 (−6.0 to 13.0)	−14.0 (−29.0 to −3.0)
P value (vs placebo)		.07		<.001
Percentage change from BL, median (Q1-Q3)	−9.8 (−38.5 to 62.5)	−47.7 (−73.8 to 18.9)	10.6 (−33.3 to 87.5)	−55.6 (−73.6 to −20.0)
P value (vs placebo)		.03		<.001

Abbreviations: BL, baseline; FeNO, fractional exhaled nitric oxide; IgE, immunoglobulin E; ppb, parts per billion; Q, quartile; every 2 weeks, every 2 weeks; TARC, thymus and activation-regulated chemokine.

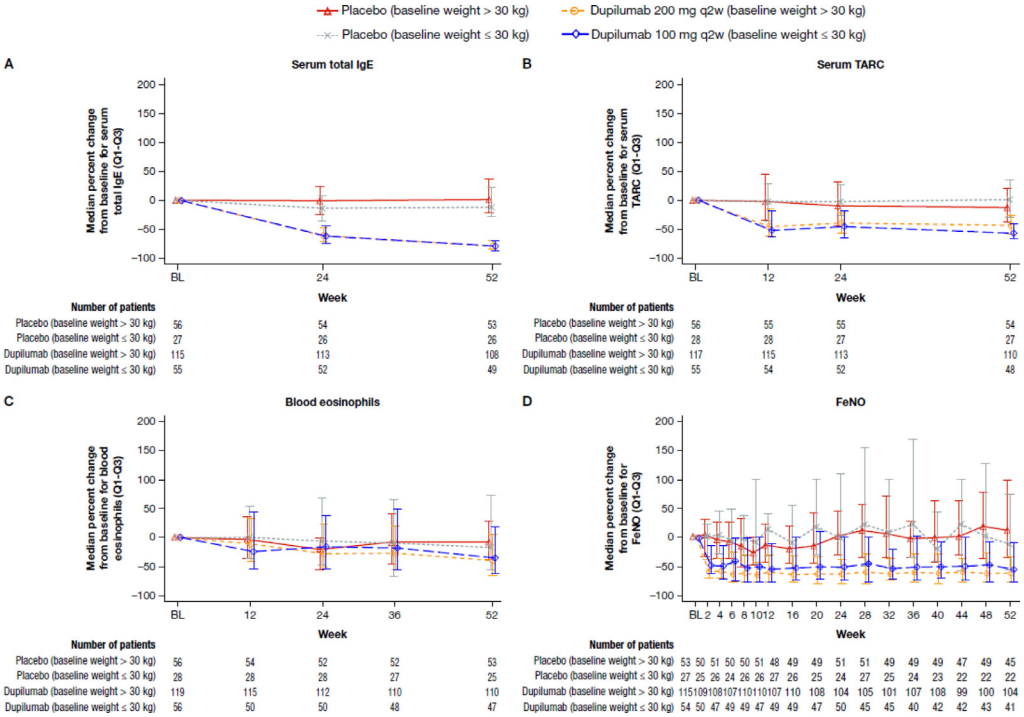
eTable 3
Pharmacodynamic Changes in Biomarker Levels Over Time in Children With Moderate-to-Severe Asthma and Blood Eosinophils ≥ 300 cells/μL at Baseline

Biomarkers	Dupilumab 100 mg every 2 wk		Dupilumab 200 mg every 2 wk	
	Placebo	Dupilumab	Placebo	Dupilumab
Serum total IgE, IU/mL				
Baseline,	n = 27	n = 55	n = 56	n = 115
Median (Q1-Q3)	668.0 (240.0-1235.0)	746.0 (357.0-1561.0)	515.0 (205.5-997.5)	561.0 (310.0-1470.0)
Week 52	n = 27	n = 49	n = 53	n = 111
Median (Q1-Q3)	516.0 (165.0-1417.0)	158.0 (55.0-257.0)	591.0 (229.0-1265.0)	118.0 (62.0-295.0)
Change from BL, median (Q1-Q3)	−52.0 (−190.0 to 74.0)	−570.0 (−1391.0 to −213.0)	1.0 (−71.0 to 194.0)	−422.5 (−1135.5 to −200.0)
P value (vs placebo)		<.001		<.001
Percentage change from BL, median (Q1-Q3)	−11.9 (−28.5 to 22.6)	−78.6 (−86.4 to −69.6)	0.9 (−21.2 to 36.5)	−78.6 (−84.6 to −70.2)
P value (vs placebo)		<.001		<.001
Serum TARC, ng/L				
Baseline,	n = 28	n = 55	n = 56	n = 117
Median (Q1-Q3)	516.0 (243.00-844.5)	459.0 (286.00-761.0)	348.5 (272.00-574.0)	404.0 (244.00-653.0)
Week 52	n = 27	n = 48	n = 54	n = 111
Median (Q1-Q3)	598.0 (264.0-722.0)	210.0 (132.5-290.0)	294.0 (203.0-511.0)	251.0 (158.0-394.0)
Change from BL, median (Q1-Q3)	7.0 (−139.0 to 138.0)	−231.0 (−502.5 to −142.5)	−49.0 (−152.0 to 45.0)	−180.5 (−348.0 to −74.0)
P value (vs placebo)		<.001		<.001
Percentage change from BL, median (Q1-Q3)	1.2 (−29.1 to 34.1)	−56.6 (−66.9 to −41.2)	−12.3 (−37.5 to 19.7)	−43.5 (−58.6 to −26.7)
P value (vs placebo)		<.001		<.001
Blood eosinophil counts, cells/μL				
Baseline,	n = 28	n = 56	n = 56	n = 119
Median (Q1-Q3)	465.0 (355.0-705.0)	720.0 (550.0-990.0)	560.0 (440.0-725.0)	620.0 (470.0-860.0)
Week 52	n = 25	n = 47	n = 53	n = 110
Median (Q1-Q3)	430.0 (200.0-880.0)	480.0 (240.0-990.0)	560.0 (330.0-890.0)	365.0 (200.0-740.0)
Change from BL, median (Q1-Q3)	−80.0 (−250.0 to 340.0)	−200.0 (−460.0 to 170.0)	−40.0 (−280.0 to 140.0)	−240.0 (−410.0 to 40.0)
P value (vs placebo)		0.12		0.04
Percentage change from BL, median (Q1-Q3)	−17.1 (−56.3 to 72.6)	−35.3 (−62.1 to 17.9)	−8.2 (−37.5 to 28.0)	−39.9 (−65.0 to 6.5)
P value (vs placebo)		0.16		.01
FeNO, ppb				
Baseline,	n = 27	n = 54	n = 53	n = 115
Median (Q1-Q3)	21.0 (13.0-44.0)	20.0 (11.0-38.0)	25.0 (17.0-37.0)	30.0 (19.0-49.0)
Week 52	n = 23	n = 41	n = 47	n = 106
Median (Q1-Q3)	16.0 (10.0-43.0)	11.0 (8.0-14.0)	28.0 (12.0-47.0)	11.0 (8.0-15.0)
Change from BL, median (Q1-Q3)	−1.0 (−17.0 to 25.0)	−9.0 (−28.0 to −2.0)	2.0 (−8.0 to 19.0)	−15.0 (−40.0 to −6.0)
P value (vs placebo)		.001		<.001
Percentage change from BL, median (Q1-Q3)	−12.9 (−56.4 to 75.0)	−54.5 (−77.8 to −11.1)	11.1 (−34.8 to 100.0)	−62.1 (−76.8 to −33.7)
P value (vs placebo)		.001		<.001

Abbreviations: BL, baseline; FeNO, fractional exhaled nitric oxide; IgE, immunoglobulin E; ppb, parts per billion; Q, quartile; every 2 weeks, every 2 weeks; TARC, thymus and activation-regulated chemokine.



eFigure 1. Median (Q1-Q3) change in biomarker levels in children with asthma and with eosinophils ≥ 300 cells/μL at baseline: (A) total serum IgE, (B) serum TARC, (C) blood eosinophils, and (D) FeNO. BL, baseline; FeNO, fractional exhaled nitric oxide; IgE, immunoglobulin E; ppb, parts per billion; Q, quartile; every 2 weeks, every 2 weeks; TARC, thymus and activation-regulated chemokine.



eFigure 2. Median percentage change from baseline (Q1-Q3) in biomarker levels in children with asthma with eosinophil levels of at least 300 cells/μL at baseline: (A) total serum IgE, (B) serum TARC, (C) blood eosinophils, and (D) FeNO. BL, baseline; FeNO, fractional exhaled nitric oxide; IgE, immunoglobulin E; Q, quartile; every 2 weeks, every 2 weeks; TARC, thymus and activation-regulated chemokine.