The Posology of Dupilumab in Pediatric Patients With Atopic Dermatitis

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Dupilumab demonstrated efficacy with an acceptable safety profile in two randomized, double-blind, placebo-controlled, parallel-group, phase III trials in adolescents (12–17 years; LIBERTY AD ADOL) and children (6–11 years; LIBERTY AD PEDS) with atopic dermatitis (AD) treated for 16 weeks. Here, we present the pharmacokinetic profiles and exposure-response (E-R) relationships of dupilumab that guided the posology in these populations. A total of 251 adolescent patients with moderate-to-severe AD were randomized to subcutaneous dupilumab monotherapy every 2 weeks (q2w; 200 mg q2w, baseline weight < 60 kg; 300 mg q2w, ≥ 60 kg), dupilumab 300 mg every 4 weeks (q4w; non-weight tiered), or placebo; 367 children with severe AD were randomized to dupilumab q2w (100 mg q2w, baseline weight < 30 kg; 200 mg q2w, ≥ 30 kg), dupilumab 300 mg q4w, or placebo. Children received concomitant topical corticosteroids in addition to dupilumab, and loading doses were administered at the start of therapy. Mean dupilumab trough concentrations at week 16 for weight subcategories in each dosing regimen were compared with adult exposures for the approved dupilumab 300 mg q2w regimen. Positive E-R relationships were demonstrated between dupilumab trough concentrations and AD outcome measures across patient populations and regimens; no relationship was observed with treatment-emergent conjunctivitis. Based on these analyses, a weight-tiered posology was proposed for adolescents (200/300 mg q2w in patients 30–< 60 kg/≥ 60 kg) and children (300 mg q4w in patients 15–< 30 kg, 200 mg q2w in patients 30–< 60 kg) with moderate-to-severe AD.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Dupilumab was efficacious with an acceptable safety profile in phase III trials of adolescents and children 6–11 years with atopic dermatitis (AD), but the pharmacokinetic (PK) and exposure-response profiles used to guide dose selection in these populations have not yet been presented.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ This study reports the PK profile and dose selection of dupilumab in the first large confirmatory trials of a systemic treatment for adolescents with moderate-to-severe AD and children with severe AD.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ The recommended posology (200 mg q2w in adolescents < 60 kg and 300 mg q2w in adolescents ≥ 60 kg; 300 mg q4w in children < 30 kg and 200 mg q2w in children ≥ 30 kg) achieved trough concentrations similar or greater than adults receiving 300 mg q2w. Exposure-response relationships showed higher efficacy with increasing dupilumab concentrations. Logistic regression analysis showed no increase of probability of developing conjunctivitis with increasing exposure.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ These analyses supported two-tiered, weight-based dosing of dupilumab in adolescents and children with AD.

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Among children and adolescents, the worldwide prevalence of atopic dermatitis (AD) is estimated to be 10–24%.[1–3] Topical treatment with corticosteroids supplemented with calcineurin inhibitors is considered standard-of-care for moderate-to-severe AD in pediatric patients,[4–6] but this approach may not be sufficient for certain patients.[7] Until recently, corticosteroids have been the only systemic agents approved for the treatment of AD in children, despite guidelines that discourage this approach.[8] Other systemic agents have safety concerns that limit their long-term use in pediatric patients with AD.[9,10]

Dupilumab is a fully human VelocImmune®-derived monoclonal antibody[11,12] directed against interleukin-4 receptor alpha (IL-4Rα) that inhibits signaling of IL-4 and IL-13, cytokines that are key drivers of diseases with underlying type 2 inflammation. Dupilumab is approved across a spectrum of type 2 inflammatory diseases, specifically AD, asthma, and chronic rhinosinusitis with nasal polyposis.[13,14] In multiple phase III trials, dupilumab administered at doses of 300 mg subcutaneously every 2 weeks (q2w) or every week (qw) significantly improved signs, symptoms, and quality of life in adult patients with moderate-to-severe AD with an acceptable safety profile.[15–17]

In randomized, double-blind, placebo-controlled, phase III trials in adolescents (12–17 years) with moderate-to-severe AD and in children (6–11 years) with severe AD, dupilumab showed clinically meaningful and statistically significant improvements compared with placebo in AD signs, symptoms, and quality of life.[18,19] To our knowledge, these studies are the largest to date of a systemic treatment for pediatric AD, and the first confirmatory trials showing an acceptable safety profile of a monoclonal antibody in children and adolescents with AD. The primary results of these pivotal phase III trials led to the approval of dupilumab in both adolescents and children (ages 6–11) in the United States and the European Union.

Here, we present the pharmacokinetics (PKs), exposure-response (E-R; efficacy), and exposure-safety relationships of dupilumab in adolescents and children aged 6–11 years. These analyses support the posology of dupilumab for treatment of AD in these pediatric populations. The goal was to identify pediatric dose regimens that achieved exposures associated with the highest observed efficacy and that matched or exceeded the exposure in adults at the approved dose of 300 mg q2w, while remaining below the maximum observed exposure in adults (300 mg qw) in phase III studies.[15–17]

METHODS

Study design, patients, and treatments

R668-AD-1526 LIBERTY AD ADOL and R668-AD-1652 LIBERTY AD PEDS (ClinicalTrials.gov Identifiers: NCT03054428 and NCT03345914) were randomized, double-blind, placebo-controlled, parallel-group, phase III trials. Detailed information on the study methods was previously reported.[18,19]

LIBERTY AD ADOL consisted of the following 3 periods: screening of up to 5 weeks, a treatment period of 16 weeks, and a follow-up of 12 weeks (for patients not entering the open-label extension study). Patients were 12–17 years old and had moderate-to-severe AD inadequately controlled by topical therapies, as well as Investigator's Global Assessment (IGA) scores ≥ 3, Eczema Area and Severity Index (EASI) scores ≥ 16, Peak Pruritus Numerical Rating Scale (NRS) scores ≥ 4, body surface area (BSA) involvement of AD ≥ 10%, and weight ≥ 30 kg. Patients were randomized 1:1:1 (stratified by baseline weight and baseline disease severity) to subcutaneous dupilumab q2w (200 mg with 400 mg loading dose for baseline weight < 60 kg, 300 mg with 600 mg loading dose for patients ≥ 60 kg), 300 mg dupilumab every 4 weeks (q4w; regardless of baseline body weight) with 600 mg loading dose, or placebo q2w. To maintain blinding, all patients received a subcutaneous injection q2w with placebo in the weeks that dupilumab was not given. Systemic nonsteroidal immunosuppressants, systemic corticosteroids, topical corticosteroids (TCS), or topical calcineurin inhibitors could not be used during the study, except as rescue treatment.

LIBERTY AD PEDS consisted of an up to 9-week screening period, TCS standardization of 2 weeks followed by 16-week treatment, and 12-week follow-up (for patients not entering the open-label extension). Patients were 6–11 years old and had severe AD inadequately controlled by topical therapies, IGA scores of 4, EASI scores ≥ 21, BSA involvement of AD ≥ 15%, Peak Pruritus NRS ≥ 4, and weight ≥ 15 kg. Patients were randomized 1:1:1 (stratified by baseline weight and region) to dupilumab q2w (100 mg with 200 mg loading dose for baseline weight < 30 kg, or 200 mg with 400 mg loading dose for baseline weight ≥ 30 kg), 300 mg dupilumab q4w with 600 mg loading dose (regardless of baseline weight), or placebo. All patients received concomitant medium potency TCS.[9] High-potency TCSs were permitted as rescue medication.

The studies were conducted in accordance with the provisions of the Declaration of Helsinki, International Conference on Harmonization Good Clinical Practice guideline, and applicable regulatory requirements. The protocols were reviewed and approved by institutional review boards/ethics committees at all study sites. For all patients, written informed consent was obtained from a parent or legal guardian, and written assent was obtained from the patient.

Endpoints

A full list of prespecified study endpoints was previously reported.[18,19] Here, we assessed PK endpoints from baseline through week 16, including concentrations of functional dupilumab in serum (by treatment group over time/by body weight and treatment group); E-R relationships with categorical endpoints (the proportions of patients achieving IGA 0 or 1 [the primary endpoint] and ≥ 75% improvement from baseline in EASI [EASI-75]); and continuous efficacy endpoints (percentage change from baseline in EASI and Peak Pruritus NRS). IGA is a physician assessment for evaluating AD severity and is scored using a 5-point scale: 0 = clear, 1 = almost clear, 2 = mild, 3 = moderate, and 4 = severe.[20] IGA 0 or 1 is a binary response measure with a positive response defined as clear or almost clear and absence of response as mild, moderate, or severe. EASI is scored on a scale from 0 to 72 (with higher scores indicating greater severity), and comprises measures of regional BSA with key signs of inflammation, including erythema, induration/papulation/edema, excoriation, and lichenification.[21] For Peak Pruritus NRS, patients reported pruritus intensity daily (for adolescents) or twice daily (for children) using a scale from 0 to 10 (with higher values indicating worse itch), and weekly scores were calculated based on an average of the daily scores.[22]

Exposure-safety analyses were also performed on events of conjunctivitis (defined as all adverse events that were encoded as a Medical Dictionary for Regulatory Activities Preferred Term: atopic keratoconjunctivitis, conjunctivitis, conjunctivitis allergic, conjunctivitis bacterial, and conjunctivitis viral). Safety was reported in all patients who received at least one dose, and efficacy was reported in all enrolled patients.

PK assessment

Dupilumab concentrations were measured in serum samples collected at baseline and weeks 2 (adolescents only), 4, 8, 12, and 16, prior to study drug administration on dosing days. Additional samples were collected for PK during the follow-up period between weeks 16 and 28 for patients who did not participate in the open-label extension study. Here,

Table 1 Baseline demographics and disease characteristics

	Adolescents (12–17 years)					Children (6–11 years)				
Characteristic	Placebo (*n* = 85)	Dupilumab 300 mg q4w (< 60 kg) (*n* = 42)	Dupilumab 200 mg q2w (< 60 kg) (*n* = 43)	Dupilumab 300 mg q2w (≥ 60 kg) (*n* = 39)	Dupilumab 300 mg q4w (≥ 60 kg) (*n* = 42)	Placebo + TCS (*n* = 123)	Dupilumab 100 mg q2w (< 30 kg) + TCS (*n* = 63)	Dupilumab 300 mg q4w (< 30 kg) + TCS (*n* = 61)	Dupilumab 200 mg q2w (≥ 30 kg) + TCS (*n* = 59)	Dupilumab 300 mg q4w (≥ 30 kg) + TCS (*n* = 61)
Age, mean (SD), years	14.5 (1.8)	13.8 (1.5)	13.8 (1.6)	15.2 (1.6)	15.1 (1.4)	8.3 (1.8)	7.6 (1.4)	7.5 (1.4)	9.5 (1.4)	9.5 (1.5)
Male, *n* (%)	53 (62.4)	26 (61.9)	20 (46.5)	23 (59.0)	26 (61.9)	61 (49.6)	32 (50.8)	27 (44.3)	33 (55.9)	30 (49.2)
Weight, mean (SD), kg	64.4 (21.5)	50.7 (5.8)	48.5 (7.3)	84.4 (22.8)	80.9 (17.8)	31.5 (10.8)	24.5 (3.5)	23.8 (3.0)	40.2 (10.0)	38.1 (8.0)
Duration of AD, mean (SD), years	12.3 (3.4)	12.2 (2.1)	12.0 (2.8)	13.0 (3.1)	11.7 (4.0)	7.2 (2.2)	6.4 (2.1)	6.8 (1.7)	8.1 (2.3)	8.0 (2.9)
Baseline EASI score, mean (SD)	35.5 (14.0)	39.0 (17.0)	36.1 (14.6)	34.4 (13.1)	32.5 (11.7)	39.0 (12.0)	37.5 (10.0)	36.9 (12.4)	37.1 (11.8)	37.8 (12.6)
Patients with baseline IGA score, *n* (%)										
3	39 (45.9)	19 (45.2)	19 (44.2)	20 (51.3)	19 (45.2)	0	0	1 (1.6)	0	0
4	46 (54.1)	23 (54.8)	24 (55.8)	19 (48.7)	23 (54.8)	123 (100)	63 (100)	60 (98.4)	59 (100)	61 (100)
Peak Pruritus NRS, mean (SD)	7.7 (1.6)	7.4 (1.9)	7.5 (1.5)	7.6 (1.6)	7.6 (1.8)	7.7 (1.5)	7.9 (1.5)	7.9 (1.5)	7.6 (1.5)	7.7 (1.7)

AD, atopic dermatitis; EASI, Eczema Area Severity Index; IGA, Investigator's Global Assessment; NRS, Numerical Rating Scale; q2w, every 2 weeks; q4w, every 4 weeks; SD, standard deviation; TCS, topical corticosteroids.

Table 2 Key efficacy and safety outcomes

	Adolescents (12–17 years)					Children (6–11 years)				
Efficacy outcomes	**Placebo (*n* = 85)**	**Dupilumab 300 mg q4w (< 60 kg) (*n* = 42)**	**Dupilumab 200 mg q2w (< 60 kg) (*n* = 43)**	**Dupilumab 300 mg q2w (≥ 60 kg) (*n* = 39)**	**Dupilumab 300 mg q4w (≥ 60 kg) (*n* = 42)**	**Placebo + TCS (*n* = 123)**	**Dupilumab 100 mg q2w (< 30 kg) + TCS (*n* = 63)**	**Dupilumab 300 mg q4w (< 30 kg) + TCS (*n* = 61)**	**Dupilumab 200 mg q2w (≥ 30 kg) + TCS (*n* = 59)**	**Dupilumab 300 mg q4w (≥ 30 kg) + TCS (*n* = 61)**
Proportion of patients with IGA 0 or 1 at week 16, *n* (%)	2 (2.4)	7 (16.7)	13 (30.2)	7 (17.9)	8 (19.0)	14 (11.4)	13 (20.6)	18 (29.5)	23 (39.0)	22 (36.1)
Proportion of patients with EASI-75 at week 16, *n* (%)	7 (8.2)	18 (42.9)	20 (46.5)	14 (35.9)	14 (33.3)	33 (26.8)	38 (60.3)	46 (75.4)	44 (74.6)	39 (63.9)
LS mean percentage change from baseline to week 16 in EASI (SE)	−23.6 (5.5)	−68.5 (6.5)	−67.8 (6.0)	−63.7 (5.4)	−60.6 (6.0)	−48.6 (2.5)	−76.7 (3.04)	−84.3 (3.08)	−80.4 (3.6)	−79.9 (3.6)
LS mean percentage change from baseline to week 16 in Peak Pruritus NRS (SE)	−19.0 (4.1)	−47.7 (5.2)	−48.0 (4.9)	−48.0 (4.8)	−43.5 (5.1)	−25.9 (2.9)	−56.1 (3.9)	−55.1 (3.9)	−58.2 (4.0)	−54.3 (4.2)
Safety outcomes, *n* (%)	**Placebo (*n* = 85)**	**Dupilumab 300 mg q4w (< 60 kg) (*n* = 42)**	**Dupilumab 200 mg q2w (< 60 kg) (*n* = 43)**	**Dupilumab 300 mg q2w (≥ 60 kg) (*n* = 39)**	**Dupilumab 300 mg q4w (≥ 60 kg) (*n* = 41)**	**Placebo + TCS (*n* = 120)**	**Dupilumab 100 mg q2w (< 30 kg) + TCS (*n* = 63)**	**Dupilumab 300 mg q4w (< 30 kg) + TCS (*n* = 60)**	**Dupilumab 200 mg q2w (≥ 30 kg) + TCS (*n* = 59)**	**Dupilumab 300 mg q4w (≥ 30 kg) + TCS (*n* = 60)**
Dermatitis atopic (PT)	21 (24.7)	7 (16.7)	10 (23.3)	5 (12.8)	8 (19.5)	17 (14.2)	8 (12.7)	4 (6.7)	2 (3.4)	4 (6.7)
Skin infections (adjudicated)	17 (20.0)	5 (11.9)	7 (16.3)	2 (5.1)	6 (14.6)	16 (13.3)	5 (7.9)	4 (6.7)	5 (8.5)	3 (5.0)
Conjunctivitis[a]	4 (4.7)	7 (16.7)	5 (11.6)	3 (7.7)	3 (7.3)	5 (4.2)	13 (20.6)	4 (6.7)	5 (8.5)	4 (6.7)
Injection-site reactions (HLT)	3 (3.5)	3 (7.1)	3 (7.0)	4 (10.3)	2 (4.9)	7 (5.8)	5 (7.9)	6 (10.0)	8 (13.6)	6 (10.0)

Data previously reported.[16]

EASI, Eczema Area and Severity Index; EASI-75, ≥ 75% reduction from baseline in EASI; HLT, MedDRA high-level term; IGA, Investigator's Global Assessment; LS, least squares; MedDRA, Medical Dictionary for Regulatory Activities; NRS, Numerical Rating Scale; PT, MedDRA preferred term; q2w, every 2 weeks; q4w, every 4 weeks; SE, standard error; TCS, topical corticosteroids.

[a]Includes PTs of conjunctivitis, conjunctivitis allergic, conjunctivitis bacterial, conjunctivitis viral, and atopic keratoconjunctivitis.

we present PK data through week 16. Functional dupilumab concentrations, which represent dupilumab molecules with either one or two binding sites available, were determined from serum samples using a validated enzyme-linked immunosorbent assay, as previously described.[23] In this functional PK assay, dupilumab is used as the assay standard, and human IL-4Rα served as the capture reagent. The lower limit of quantitation (LLOQ) of functional dupilumab is 0.0078 mg/L in undiluted human serum. The PK analysis set included all treated patients who received any amount of study drug and had at least one nonmissing functional dupilumab measurement following the first dose of study drug.

Population PK analysis

To determine how exposures of dupilumab at steady-state in adolescents and children receiving weight-tiered dose regimens compared with those achieved in adults with the approved 300 mg q2w regimen,[15–17] we conducted separate population PK analyses of dupilumab for these patient groups using the model structure previously reported for adult patients with moderate-to-severe AD who received dupilumab (**Supplementary Material**).[24–26]

Exposure-response analysis

Exposure-response relationships were investigated using scatter plots of dupilumab exposure vs. drug effect for continuous efficacy endpoints (percentage change from baseline in EASI and Peak Pruritus NRS) or logistic regression for binary efficacy endpoints (probability of achieving IGA 0 or 1 and EASI-75). Logistic regression analysis is used to explain a relationship between one dependent binary (yes/no) variable and one or more continuous or categorical independent variable (predictor). Logistic regression predicts the relative frequency of a binary endpoint (e.g., IGA 0 [clear] or 1 (almost clear)), enabling the visualization of a binary dependent variable as probability vs. an independent variable (e.g., drug concentration). Observed dupilumab trough concentration at week 16 was selected as the primary exposure metric. Nonlinear logistic regression analysis of efficacy endpoints used a nonlinear maximum effect (E_{max}; maximal response) function to characterize the E-R curve as well as to allow for a physiologically meaningful dose-response relationship (i.e., the sigmoid curve with a placebo response above zero probability and a plateau below a probability of 1 at high trough concentration). The NLMIXED procedure of Statistical Analysis Software (SAS) version 9.4 was used to fit nonlinear logistic regression models. The binomial distribution was specified and the logit link function was used. The logit function converts a probability ranging between 0 and 1 into a continuous logit space ranging from minus to plus infinity. The logistic (inverse-logit) transformation converts predictions in the logit space back to the probability space. A nonlinear function $E_0 + (E_{max} - E_0)\ ^*C_{trough}/(EC_{50} + C_{trough})$ was used to characterize the response in the logit space at concentrations below the LLOQ, in the nonlinear region of the E-R curve, as well as at the plateau. The probability of response at concentrations below the LLOQ is an inverse logit transformation of E0 and the plateau is an inverse logit function of E_{max}. The values and confidence intervals of E_0 and E_{max} were provided in the probability domain.

An exposure-safety analysis was also conducted using nonlinear logistic regression relating probability of conjunctivitis during the treatment period and week 16 dupilumab trough concentration. As the number of subjects with conjunctivitis was too low to utilize the E_{max} function, a linear logistic regression model was used. Placebo effect was accounted for as an additive effect in the active treatment group.

RESULTS

Patient disposition

In LIBERTY AD ADOL, 251 adolescents were randomized to 16 weeks' treatment with dupilumab q2w (weight-tiered: 200 mg for baseline weight < 60 kg, n = 43; 300 mg, baseline weight

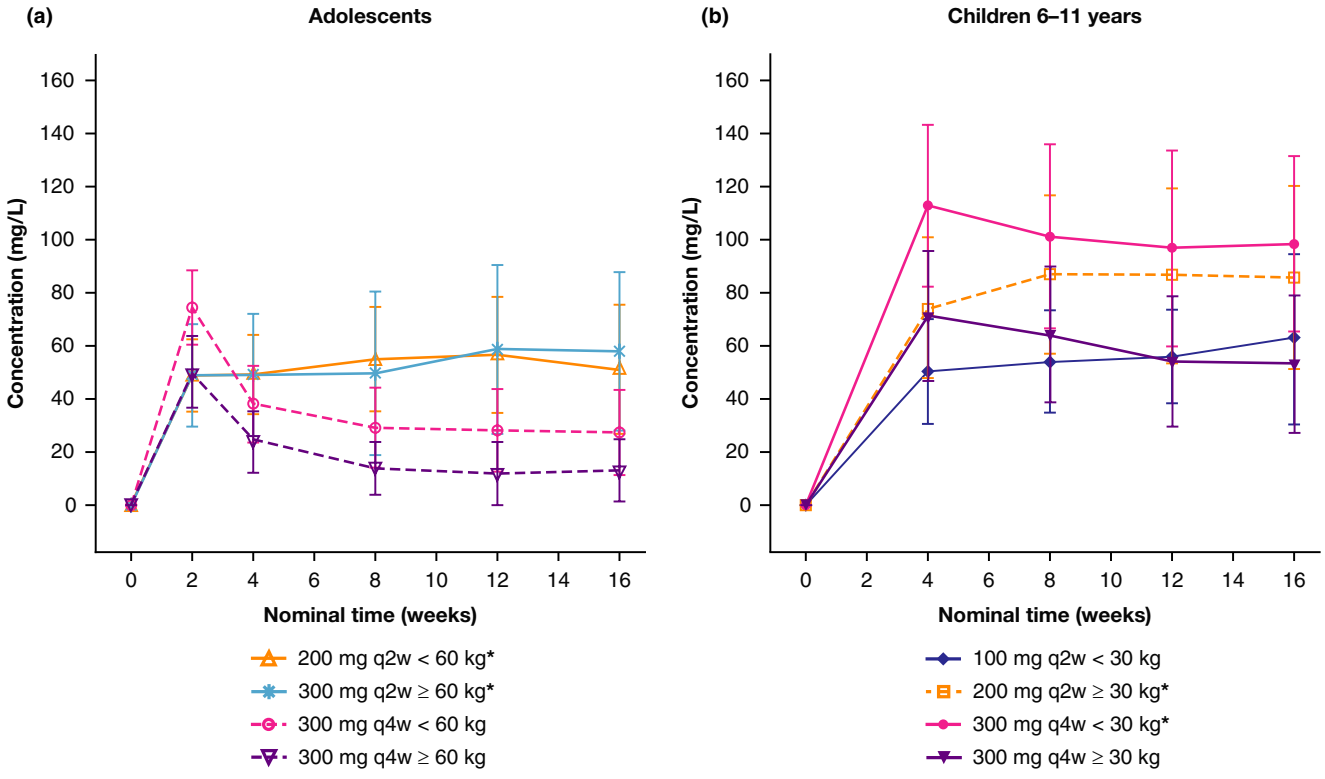

Figure 1 Mean (±SD) concentration-time course of dupilumab by treatment-weight group in (**a**) adolescents aged 12–17 and (**b**) children aged 6–11 years (PKAS). *US Food and Drug Administration approved doses. BLQs were set to 0. Nominal time points until week 16 were used for analysis. BLQ, below limit of quantification; PK, pharmacokinetics; PKAS, PK analysis set; q2w, every 2 weeks; q4w, every 4 weeks.

≥ 60 kg, n = 39); dupilumab q4w (non-weight tiered: 300 mg, n = 84); or placebo (n = 85). In LIBERTY AD PEDS, 367 children aged 6–11 years were randomized to 16 weeks' treatment with dupilumab q2w (100 mg for baseline weight < 30 kg, n = 63; 200 mg for baseline weight ≥ 30 kg, n = 59); dupilumab q4w (300 mg, n = 122); or placebo (n = 123).

Efficacy and safety overview

In both studies, baseline demographics and characteristics were balanced between the treatment groups within each weight group (**Table 1**). A higher proportion of dupilumab-treated patients (all regimens across both studies) met the co-primary endpoints (IGA score of 0 or 1 at week 16 and EASI-75 at week 16) compared with the respective placebo regimens (**Table 2**). Dupilumab-treated patients also achieved greater improvement in Peak Pruritus NRS scores than placebo-treated patients. The most common adverse events reported in placebo-treated patients were exacerbations of AD and skin infections, and in dupilumab-treated patients, conjunctivitis and injection-site reactions were most common. For conjunctivitis, most cases were mild or moderate in severity and most recovered with treatment during study drug treatment. One patient in LIBERTY AD PEDS receiving 200 mg q2w + TCS discontinued treatment because of bacterial conjunctivitis of moderate severity.

Observed dupilumab concentrations

Reportable concentrations of functional dupilumab in serum were available for 164 dupilumab-treated adolescent patients and 241 dupilumab-treated children aged 6–11 years. In adolescents, the mean concentration-time profile of dupilumab in patients < 60 kg receiving 200 mg q2w was comparable to that of patients ≥ 60 kg receiving 300 mg q2w (**Figure 1a**). Concentrations of both q2w regimens were higher than concentrations of 300 mg q4w at all time points except week 2 in patients < 60 kg or ≥ 60 kg. In children, mean concentration time profiles of dupilumab were generally similar for patients ≥ 30 kg receiving 200 mg q2w and patients < 30 kg receiving 300 mg q4w, and both regimens exhibited higher exposure than patients < 30 kg receiving 100 mg q2w or patients ≥ 30 kg receiving 300 mg q4w (**Figure 1b**). Steady-state trough concentrations were reached by week 12 for both the q4w and q2w regimens in adolescents and children.

Week 16 trough concentrations were compared across all age groups by regimen and by weight category, and benchmarked to exposures in the phase III studies for adults at the approved 300 mg q2w regimen[25] (**Figure 2**). In adolescents, mean trough concentrations for 200 mg q2w in patients < 60 kg (51.3 mg/L) and 300 mg q2w in patients ≥ 60 kg (57.9 mg/L) were lower than in adults (74.6 mg/L). Mean trough concentrations in adolescent patients receiving 300 mg q4w with a body weight < 60 kg (27.2 mg/L) or

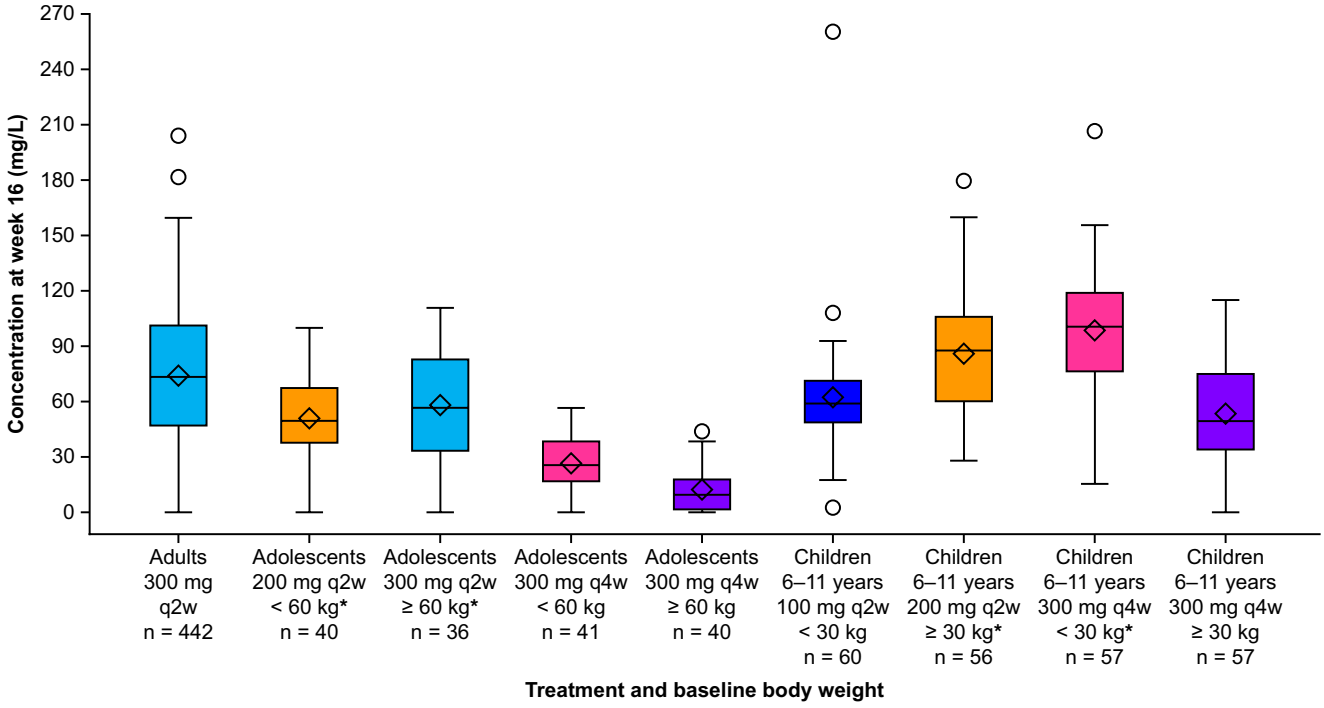

Figure 2 Concentrations of functional dupilumab in serum at week 16 by body weight group and dose group in adults, adolescents aged 12–17 years, and children aged 6–11 years. Mean values: adults 300 mg q2w, 74.6 mg/L; adolescents 200 mg q2w < 60 kg, 51.3 mg/L; 300 mg q2w ≥ 60 kg, 57.9 mg/L; 300 mg q4w < 60 kg, 27.2 mg/L; 300 mg q4w ≥ 60 kg, 12.7 mg/L; children 100 mg q2w < 30 kg, 62.6 mg/L; 200 mg q2w ≥ 30 kg, 86.0 mg/L; 300 mg q4w < 30 kg, 98.7 mg/L; 300 mg q4w ≥ 30 kg, 53.9 mg/L. All dose regimens were compared to adults. *US Food and Drug Administration approved doses. Diamonds signify mean values; vertical lines extending from top to bottom are the maximum value below upper fence and minimum value above lower fence, respectively; circles are outliers defined by the "1.5 rule", namely, when less than (Q1 – 1.5*IQR) or greater than (Q3 + 1.5*IQR), with IQR = Q3–Q1. Outliers above a concentration of 165 mg/L were removed from analysis to enable data visualization and comparison of dose regimens. BLQs were set to 0. Adults are patients in studies R668-AD-1334 and R668-AD-1416; adolescents are patients in study R668-AD-1526; and children (6–11 years) are patients in study R668-AD-1652. BLQ, below limit of quantification; IQR, interquartile range; 2qw, every 2 weeks; q4w, every 4 weeks.

Table 3 Summary of simulated steady-state exposure to dupilumab by treatment group and weight in children aged 6–11 years, adolescents, and adults with AD

Exposure variable	Children (6–11 years)				Adolescents (12–17 years)			Adults	
	Dupilumab 100 mg q2w (< 30 kg) + TCS	Dupilumab 300 mg q4w (< 30 kg) + TCS	Dupilumab 200 mg q2w (≥ 30 kg) + TCS	Dupilumab 300 mg q4w (≥ 30 kg) + TCS	Dupilumab 200 mg q2w (≤ 60 kg)	Dupilumab 300 mg q2w (≥ 60 kg)	Dupilumab 300 mg q4w (< 60 kg)	Dupilumab 300 mg q4w (≥ 60 kg)	Dupilumab 300 mg q2w	Dupilumab 300 mg qw
$C_{troughSS}$ (mg/L)	62.8 (35.5, 110)	87.7 (43.1, 155)	98.5 (47.9, 164)	65.3 (20.9, 140)	57.0 (27.9, 113)	58.6 (22.8, 115)	22.3 (6.0, 59.2)	6.3 (0, 26.8)	72.9 (32.7, 153)	189 (96.1, 351)
C_{maxSS} (mg/L)	103 (64.0, 161)	219 (149, 325)	153 (84.2, 230)	149 (70.0, 252)	81.1 (49.1, 142)	83.9 (40.9, 144)	68.1 (43.0, 114)	37.5 (18, 66.1)	97.2 (49.9, 187)	205 (108, 372)
AUC_{SS} mg*day/L)	2,346 (1,438, 3,828)	4,073 (2,689, 6,241)	3,548 (1,904, 5,502)	3,054 (1,358, 5,550)	1,994 (1,126, 3,637)	2,060 (946, 3,730)	1,295 (709, 2,457)	634 (226, 1,333)	2,477 (1,203, 4,819)	5,564 (2,893, 10,194)

Parameters are shown as median (5th percentile and 95th percentile). Steady-state AUC was calculated per 28 days to simplify comparison across treatments (based on base models developed using phase III data).

AD, atopic dermatitis; AUC, area under the curve; C_{maxSS}, steady-state maximum serum concentration; $C_{troughSS}$, steady-state trough concentration; qw, once weekly; q2w, every 2 weeks; q4w, every 4 weeks; SS, steady state.

≥ 60 kg (12.7 mg/L) were ~ 37% and ~ 17% of mean trough concentrations in adults, respectively. With the 300 mg q4w regimen, a greater proportion of adolescents had a week 16 trough concentration at or near the LLOQ (0.0780 mg/L in undiluted human serum) compared with the 200/300 mg q2w regimen (**Figure S1**). In children, week 16 trough concentrations for 300 mg q4w in patients < 30 kg (98.7 mg/L) and 200 mg q2w in patients ≥ 30 kg (86.0 mg/L) both exceeded that of the adult 300 mg q2w regimen, whereas mean trough concentrations in children < 30 kg on 100 mg q2w (62.6 mg/L) and ≥ 30 kg on 300 mg q4w (53.9 mg/L) were lower but within a similar range as q2w regimens in adult and adolescent patients (**Figure 2**).

Population PK

The population PK model structure adequately described the observed dupilumab concentrations in adolescents and children aged 6–11 years. Simulated exposure metrics at steady-state by age group and dosing regimen are shown in **Table 3**. The model-based analysis shows that in adolescents, exposures are slightly lower overall than in adults and children aged 6–11 years, and in children aged 6–11 years receiving 200 mg q2w at body weight ≥ 30 kg and 300 mg q4w at body weight < 30 kg, the 5th percentile of trough concentration at steady-state is similar to or greater than that of adults receiving 300 mg q2w. Although exposures of the selected regimens in children are generally higher than those in adults receiving 300 mg q2w, the 95th percentile of maximum concentration at steady-state is lower in children aged 6–11 years receiving 200 mg q2w at body weight ≥ 30 kg and 300 mg q4w at body weight < 30 kg compared with adults receiving 300 mg qw (the maximum exposure tested in adults).

Exposure-efficacy analyses

A total of 245 adolescents and 360 children (6–11 years) had PK and time-matched efficacy data as measured by EASI, IGA, and Peak Pruritus NRS at week 16.

The goal of these E-R analyses was to identify the dosing regimens for which the distribution of trough concentrations resulted in exposures associated with maximal efficacy response (the plateau region of the E-R curves). In **Figure 3a**, nonlinear logistic regression analysis, which incorporates a hill function, describes the E-R relationships of the probability of achieving IGA scores of 0 or 1 (clear and almost clear, respectively) vs. trough concentration (mg/L) at week 16 by age group. Parameter estimates of the nonlinear hill function including E_{max} and half-maximal effective concentration (EC_{50}) are provided in **Supplementary Table S1**. The median trough concentration exposure achieved by the 300 mg q4w regimen in children < 30 kg (87.7 mg/L) lies closer to the peak of the E-R relationship compared with the 100 mg q2w regimen, which achieves a lower median trough concentration at steady state (62.8 mg/L; **Table 3**). Similarly, in children ≥ 30 kg, the median trough concentration exposure achieved by the 200 mg q2w regimen (98.5 mg/L) was higher than for the 300 mg q4w regimen (65.3 mg/L) and was closer to the plateau of the E-R relationship (**Table 3**). This analysis also confirms that the weight-tiered dosing regimen of 200/300 mg q2w in adolescents achieves a predicted steady-state trough concentration approaching the

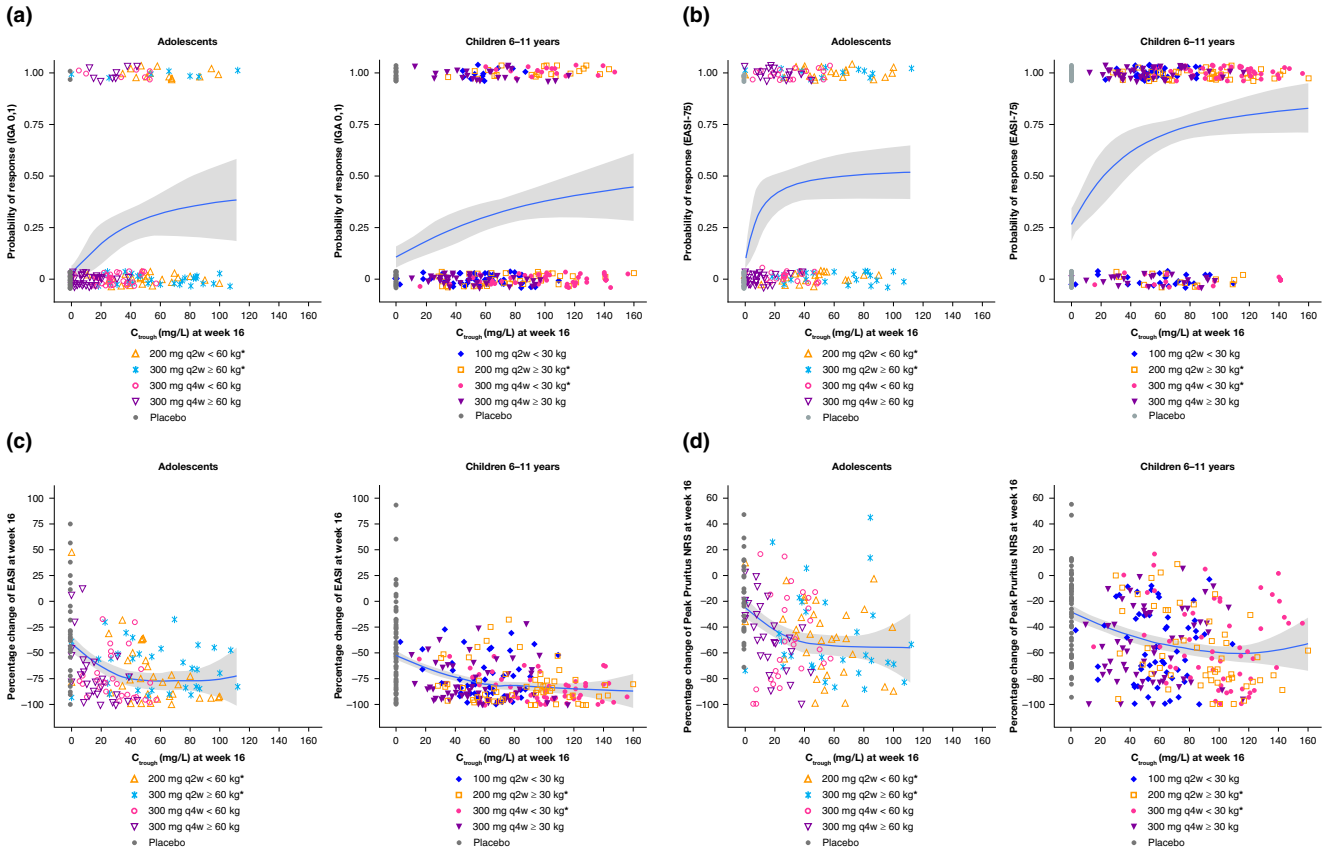

Figure 3 Exposure-efficacy relationships. (**a**) Probability of response (proportions of patients with) for IGA 0 or 1 by week 16 dupilumab concentrations. (**b**) Probability of response (proportions of patients with) for EASI-75 by week 16 concentrations. (**c**) Percentage change in EASI from baseline to week 16 vs. trough concentration (CRAS). (**d**) Percentage change in Peak Pruritus Numerical Rating Scale (NRS) from baseline to week 16 vs. C_{trough} (CRAS). *US Food and Drug Administration approved doses. Outliers above concentrations of 165 mg/L were removed from analysis. BLQs were set to 0. BLQ, below limit of quantification; CRAS, concentration-response analysis set; $C_{trough,}$ trough concentration; EASI, Eczema Area and Severity Index; EASI-75, ≥ 75% reduction from baseline in EASI; PK, pharmacokinetics; PKAS, PK analysis set; q2w, every 2 weeks; q4w, every 4 weeks. (**a, b)** Blue line = mean regression line, gray area = confidence area around regression line. (**c, d)** Blue line = locally estimated scatterplot smoothing (LOESS), gray area = 95% confidence interval.

plateau of their respective E-R curve of achieving IGA scores of 0 or 1. Similar results were observed across age groups at week 16 for the E-R relationships of EASI-75 (**Figure 3b**), percentage change from baseline in EASI (**Figure 3c**), and percentage change from baseline in Peak Pruritus NRS (**Figure 3d**).

Exposure-safety analysis

As dupilumab-treated patients had higher incidences of conjunctivitis than placebo-treated patients in the phase III adult[27] and adolescent[18] AD trials, potential relationships between trough concentrations and the probability of developing conjunctivitis were evaluated in adolescents and children. Linear logistic regression analysis showed no association between incidence of conjunctivitis and concentration of dupilumab for either adolescents or children (**Figure 4**).

DISCUSSION

In the pediatric dupilumab development program, randomized, placebo-controlled, phase III trials assessing efficacy and safety were conducted in adolescents and children aged 6–11 years with AD. These trials included multiple treatment regimens within each age group. All studied regimens met primary and secondary endpoints in the primary statistical comparison with placebo, but these studies were not powered for performing efficacy comparisons between the dupilumab treatment groups.[18,19]

Although PK comparison to adults was performed in the current analysis, it was an important, but not sufficient, criterion for dupilumab dose selection in these pediatric populations, unlike the case in a full extrapolation.[28] Adult PK served as an important reference for dupilumab, but as it is the first systemic therapy with a novel mechanism of action in adolescents and children with AD, it was necessary to evaluate the totality of the data. Efficacy, safety, PK, and E-R were therefore evaluated when selecting the optimal posology of dupilumab in these pediatric populations, and the following criteria were considered: (1) large numerical differences in efficacy outcomes (**Table 2**); (2) absence of dose-limiting adverse events and assessment of exposure-safety relationships; (3) E-R relationships, specifically where exposures for the majority of patients receiving a given dose regimen were associated with maximal efficacy; and (4) comparable distribution of exposure metrics in pediatric patients relative to adults, especially the lower extreme of steady-state trough concentrations.

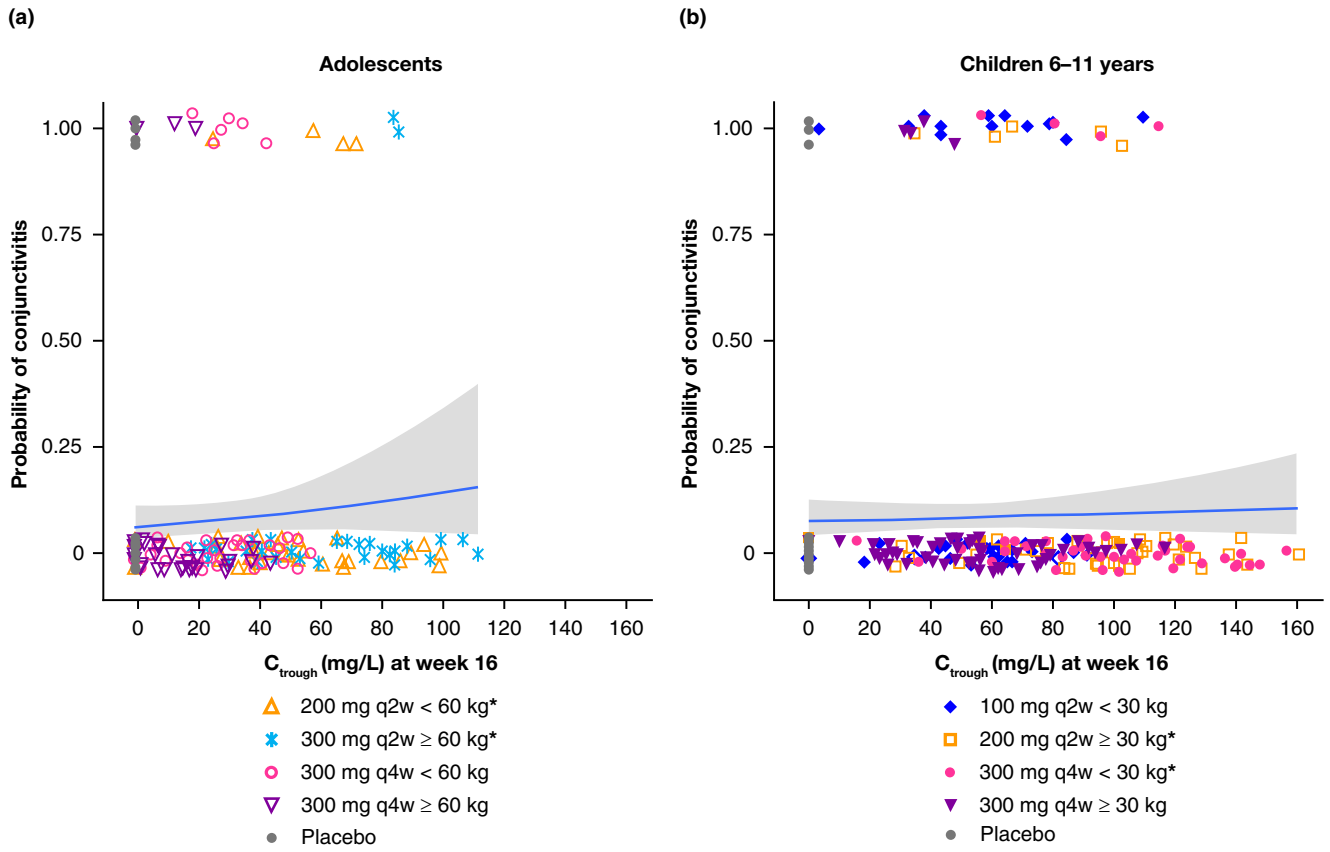

Figure 4 Logistic regression analysis between events of conjunctivitis and concentration of dupilumab. *US Food and Drug Administration approved doses. Outliers above concentrations of 165 mg/L were removed from analysis. BLQs were set to 0. Blue line = mean regression line, gray area = confidence area around regression line. BLQ, below limit of quantification; $C_{trough,}$ trough concentration; q2w, every 2 weeks; q4w, every 4 weeks.

The longer q4w interval was considered for pediatric patients in order to provide a more convenient dosing frequency, particularly for younger children. However, in adolescents, the steady-state trough concentration exposure achieved with 300 mg q4w dosing was lower than in adults receiving the approved 300 mg q2w regimen. Dupilumab exhibits nonlinear PK with a rapid, target-mediated elimination phase that is protracted at longer dosing intervals. The nonlinear PK resulted in a greater proportion of week 16 trough concentrations at or near the LLOQ among adolescents receiving the 300 mg q4w regimen, in particular, those of higher body weight, compared with those receiving the q2w regimen (**Figure S1**).[24,25] In adolescents, the number of below the limit of quantifications was 2 (1.28%) in the 200/300 mg q2w treatment group vs. 7 (4.49%) in the 300 mg q4w treatment group. Trough concentration exposures associated with the 300 mg q4w regimen, unlike the weight-tiered regimen (200/300 mg q2w), were more likely to fall below the plateau of the E-R relationships to the probability of achieving efficacy as measured by IGA scores of 0 or 1, EASI-75, and a percent change from baseline in EASI and Peak Pruritus NRS scores.

Although the 200/300 mg q2w regimen achieved slightly lower trough concentration exposures in adolescents compared with adults, these exposures were at or near the plateau of the E-R relationships (**Figure 3**). In the phase III trial, adolescents with a body weight < 60 kg receiving 200 mg q2w and those ≥ 60 kg receiving 300 mg q2w achieved steady-state trough concentrations with a similar central tendency and variance, indicating that dosing based on the 60 kg weight cutoff normalizes dupilumab exposure within the adolescent population. Finally, although the primary efficacy outcome with this weight-tiered regimen was slightly lower than in adults receiving 300 mg q2w, the placebo-adjusted responses between adolescents and adults were similar.[15–18] For these reasons, a weight-tiered posology was proposed for adolescents (200/300 mg q2w in patients 30–< 60 kg/≥ 60 kg).

Dose selection in children aged 6–11 years was less straightforward than in adolescents. Although *a priori* modeling suggested that the studied dose regimens would provide equivalent exposure, the observed mean trough concentration at steady-state was lower for the 100 mg q2w regimen in children < 30 kg than for the 200 mg q2w regimen in children ≥ 30 kg or the 300 mg q2w regimen in adults. This is consistent with fewer patients on the 100 mg q2w regimen achieving IGA scores of 0 or 1 (**Table 2**). Patients on the 100 mg q2w regimen also had an inexplicably higher incidence of conjunctivitis compared with the other dosing regimens studied, including placebo (**Table 2**). For these reasons, the 300 mg q4w regimen was proposed for children < 30 kg. Although

the 300 mg q4w regimen was administered irrespective of weight, study enrollment was stratified around a 30 kg body weight, and equivalent numbers of children were enrolled in the < 30 kg and ≥ 30 kg subgroups (n = 57) (**Figure 2**). Among children receiving the 300 mg q4w regimen, the distribution of trough concentration in the heavier-weight tier (≥ 30 kg) was consistently lower than in the 300 mg q2w regimen in adults, whereas children in the lighter-weight tier (< 30 kg) achieved steady-state exposures similar to or greater than the approved adult regimen. These exposures were not associated with an increase in adverse events. Whereas further increases in exposure to small-molecule drugs may lead to higher rates of off-target adverse events, once antagonistic monoclonal antibodies, such as dupilumab, reach concentrations sufficient to saturate the target receptor, excess antibody is pharmacologically inert. In addition to PK, assessment of E-R relationships revealed that the selected regimens that achieved the highest trough concentrations in children (i.e., 300 mg q4w in children < 30 kg and 200 mg q2w in children ≥ 30 kg) resulted in exposures for most patients associated with maximal response for multiple efficacy endpoints.

Dupilumab regimens are intended to achieve concentrations sufficient to saturate IL-4 receptors throughout the dosing interval, and dupilumab efficacy is driven by trough concentrations at steady-state. Hence, the E-R analysis conducted used C_{trough} at week 16 as the exposure metric, however, similar results are expected if the area under the curve (AUC) is used as the exposure metric because both parameters of exposure are highly correlated (**Figure S2**).

A loading dose reduces the time to reach saturating concentrations and allows for a rapid onset of effect. Trough concentrations of dupilumab demonstrated modest accumulation after subsequent doses for q2w regimens in pediatric patients, but the highest exposures of q4w regimens were observed following the loading dose; for the 600 mg load/300 mg q4w regimen selected for children < 30 kg, mean trough concentrations at week 4 were ~ 16% higher than at week 16. The safety profile of dupilumab in children was comparable across the q2w and q4w regimens. Although initial exposures in these children were higher than for the approved 300 mg q2w regimen in adults, they remained within the range seen in adults with moderate-to-severe AD receiving 300 mg qw in phase III trials.[15–17]

Last, exposure-safety analyses revealed that incidence of conjunctivitis, which was identified as an adverse event of special interest in phase III adult AD trials,[27] was not associated with increasing dupilumab exposure in adolescents nor children.

Important differences between the adolescent and children 6–11 years of age study protocols likely impacted comparative E-R results. Adolescents had moderate or severe baseline IGA and received dupilumab monotherapy, whereas all children aged 6–11 years had severe baseline IGA and received concomitant TCS. Comparative E-R results suggest that more severe baseline disease and the addition of TCS resulted in a greater number of children achieving E_{max} compared with adolescents, as supported by a median probability of achieving EASI-75 that approached an E_{max} of 0.8 for children aged 6–11 years on the higher end of the exposure range, compared with 0.5 for adolescents (**Figure 3b**). The E_{max} for achieving IGA scores of 0 or 1 was also higher in children, albeit more subtly (**Figure 3a**). The randomized, controlled trials in these pediatric populations were not designed as dose ranging studies; they studied regimens intended to provide optimal efficacy in these age groups, and lack of efficacy data at lower concentrations resulted in estimation of certain parameters (e.g., EC_{50}) with wide confidence intervals (**Table S1**).

The analyses presented herein were performed sequentially, based on timing of data availability. An integrated E-R analysis using nonlinear, mixed-effects modeling in a pooled data set of adults, adolescents, and children, and utilizing the full time course of drug concentration and response, would enable a more robust investigation of the effect of these factors on E-R across age groups. This type of integrated analysis would also enable simulation of clinical scenarios not studied, such as the anticipated response to dupilumab in children with moderate AD or adolescents receiving concomitant TCS therapy.

CONCLUSIONS

These combined clinical pharmacology, primary efficacy, and safety data analyses support the following weight-tiered pediatric dosing regimens: in adolescents with moderate-severe AD weighing < 60 kg, a 400 mg loading dose followed by 200 mg q2w; for those ≥ 60 kg, a 600 mg loading dose followed by 300 mg q2w; in children aged 6–11 years with severe AD weighing < 30 kg, a 600 mg loading dose followed by 300 mg q4w, and for those ≥ 30 kg, a 400 mg loading dose followed by 200 mg q2w. Despite slight differences in exposure, these results confirm both within- and between-population normalization of dupilumab exposure as measured by steady-state trough concentration with weight-tiered regimens. Furthermore, E-R analyses demonstrated greater efficacy with increasing dupilumab trough concentrations, and conjunctivitis incidence was not associated with higher dupilumab exposure.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

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CONFLICT OF INTEREST

M.A.K., P.K., M.P.K., K.S., Y.Z., M.R., C-H.L., X.S., B.S., A.B., N.A-H., and J.D.D. are employees and shareholders of Regeneron Pharmaceuticals, Inc. E.L.S. has been an advisor for Celgene and Merck; a consultant for Anacor Pharmaceuticals, Asubio, Celgene, Galderma, Genentech, Medicis Pharmaceutical, and Merck; and has received research support from Amgen, Celgene, Chugai, Galderma, and Regeneron Pharmaceuticals, Inc. A.S.P. has been a consultant for AbbVie, Abeona Therapeutics, Almirall, Asana BioSciences, Boehringer Ingelheim, BridgeBio, Dermavant, Dermira, Eli Lilly, Exicure, Forté, Incyte, InMed Pharmaceuticals, Janssen, LEO Pharma, LifeMax, Novartis, Pfizer, RAPT Therapeutics, Regeneron Pharmaceuticals, Inc., Sanofi Genzyme,

Sol-Gel, and UCB; has been on the data safety monitoring board of Bausch, Galderma, and Novan; and a Principal Investigator (funding to institution) for AbbVie, AnaptysBio, Eli Lilly, Incyte, Janssen, Lenus Pharma, LEO Pharma, Novartis, Regeneron Pharmaceuticals, Inc, and UCB. E.C.S. has been a consultant for Dermavant, Eli Lilly, Pfizer, Regeneron Pharmaceuticals, Inc., and Verrica Pharmaceuticals; has been on the data safety monitoring board of GlaxoSmithKline, LEO Pharma, and Novan; and has been the Principal Investigator in clinical trials for Eli Lilly, Janssen, Regeneron Pharmaceuticals, Inc., Stiefel, and Verrica Pharmaceuticals. V.K. and C.X. are employees of and may hold stock options in Sanofi Genzyme.

AUTHOR CONTRIBUTIONS

M.A.K. and M.P.K. wrote the manuscript. A.B., B.S., M.A.K., and J.D.D. designed the research. A.S.P., E.C.S., E.L.S., M.A.K., and P.K. performed the research. A.B., A.S.P., B.S., C-H.L., C.X., E.C.S., E.L.S., J.D.D., M.A.K., M.P.K., N.A-H., P.K., K.S., Y.Z., M.R., V.K., and X.S. analyzed the data.

1. Abuabara, K., Yu, A.M., Okhovat, J.-P., Allen, I.E. & Langan, S.M. The prevalence of atopic dermatitis beyond childhood: a systematic review and meta-analysis of longitudinal studies. *Allergy* **73**, 696–704 (2018).
2. Shaw, T.E., Currie, G.P., Koudelka, C.W. & Simpson, E.L. Eczema prevalence in the United States: data from the 2003 National Survey of Children's Health. *J. Invest. Dermatol.* **131**, 67–73 (2011).
3. Odhiambo, J.A., Williams, H.C., Clayton, T.O., Robertson, C.F. & Asher, M.I. & ISAAC Phase Three Study Group. Global variations in prevalence of eczema symptoms in children from ISAAC Phase Three. *J. Allergy Clin. Immunol.* **124**, 1251–1258 (2009).
4. Wollenberg, A. *et al*. ETFAD/EADV eczema task force 2015 position paper on diagnosis and treatment of atopic dermatitis in adult and paediatric patients. *J. Eur. Acad. Dermatol. Venereol.* **30**, 729–747 (2016).
5. Sidbury, R. *et al*. Guidelines of care for the management of atopic dermatitis: section 3. Management and treatment with phototherapy and systemic agents. *J. Am. Acad. Dermatol.* **71**, 327–349 (2014).
6. Ring, J. *et al*. Guidelines for treatment of atopic eczema (atopic dermatitis) part II. *J. Eur. Acad. Dermatol. Venereol.* **26**, 1176–1193 (2012).
7. Nguyen, H.L., Anderson, K.R. & Tollefson, M.M. New and emerging therapies for pediatric atopic dermatitis. *Paediatr. Drugs* **21**, 239–260 (2019).
8. Drucker, A.M. *et al*. Use of systemic corticosteroids for atopic dermatitis: International Eczema Council consensus statement. *Br. J. Dermatol.* **178**, 768–775 (2018).
9. Eichenfield, L.F. *et al*. Guidelines of care for the management of atopic dermatitis: section 1. Diagnosis and assessment of atopic dermatitis. *J. Am. Acad. Dermatol.* **70**, 338–351 (2014).
10. Wollenberg, A. *et al*. Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part II. *J. Eur. Acad. Dermatol. Venereol.* **32**, 850–878 (2018).
11. Macdonald, L.E. *et al*. Precise and in situ genetic humanization of 6 Mb of mouse immunoglobulin genes. *Proc. Natl. Acad. Sci. U S A* **111**, 5147–5152 (2014).
12. Murphy, A.J. *et al*. Mice with megabase humanization of their immunoglobulin genes generate antibodies as efficiently as normal mice. *Proc. Natl. Acad. Sci. U S A* **111**, 5153–5158 (2014).
13. U.S. Food and Drug Administration. Dupixent (dupilumab). Highlights of prescribing information <https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761055s020lbl.pdf> (2021). Accessed April 7, 2021.
14. European Medicines Agency. Dupixent (dupilumab). Summary of product characteristics <https://www.ema.europa.eu/en/documents/product-information/dupixent-epar-product-information_en.pdf> (2021). Accessed January 29, 2021.
15. Simpson, E.L. *et al*. Two phase 3 trials of dupilumab versus placebo in atopic dermatitis. *N. Engl. J. Med.* **375**, 2335–2348 (2016).
16. Blauvelt, A. *et al*. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial. *Lancet* **389**, 2287–2303 (2017).
17. de Bruin-Weller, M. *et al*. Dupilumab with concomitant topical corticosteroid treatment in adults with atopic dermatitis with an inadequate response or intolerance to ciclosporin A or when this treatment is medically inadvisable: a placebo-controlled, randomized phase III clinical trial (LIBERTY AD CAFÉ). *Br. J. Dermatol.* **178**, 1083–1101 (2018).
18. Simpson, E.L. *et al*. Efficacy and safety of dupilumab in adolescents with uncontrolled moderate to severe atopic dermatitis: a phase 3 randomized clinical trial. *JAMA Dermatol.* **156**, 44–56 (2020).
19. Paller, A.S. *et al*. Efficacy and safety of dupilumab with concomitant topical corticosteroids in children 6 to 11 years old with severe atopic dermatitis: a randomized, double-blinded, placebo-controlled phase 3 trial. *J. Am. Acad. Dermatol.* **83**, 1282–1293 (2020).
20. Futamura, M., Leshem, Y.A., Thomas, K.S., Nankervis, H., Williams, H.C. & Simpson, E.L. A systematic review of Investigator Global Assessment (IGA) in atopic dermatitis (AD) trials: many options, no standards. *J. Am. Acad. Dermatol.* **74**, 288–294 (2016).
21. Hanifin, J.M., Thurston, M., Otomo, M., Cherill, R., Tofte, S.J. & Graeber, M. The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis. *EASI Evaluator Group. Exp. Dermatol.* **10**, 11–18 (2001).
22. Yosipovitch, G. *et al*. Peak Pruritus Numerical Rating Scale: psychometric validation and responder definition for assessing itch in moderate-to-severe atopic dermatitis. *Br. J. Dermatol.* **181**, 761–769 (2019).
23. Davis, J.D. *et al*. Evaluation of potential disease-mediated drug-drug interaction in patients with moderate-to-severe atopic dermatitis receiving dupilumab. *Clin. Pharmacol. Ther.* **104**, 1146–1154 (2018).
24. Kovalenko, P. *et al*. Exploratory population PK analysis of dupilumab, a fully human monoclonal antibody against IL-4Rα, in atopic dermatitis patients and normal volunteers. *CPT Pharmacometrics Syst. Pharmacol.* **5**, 617–624 (2016).
25. Kovalenko, P. *et al*. Base and covariate population pharmacokinetic analyses of dupilumab using phase 3 data. *Clin. Pharmacol. Drug Dev.* **9**, 756–767 (2020).
26. Kovalenko, P. *et al*. Base and covariate population pharmacokinetic analyses of dupilumab in adolescents and children ≥6 to <12 years of age utilizing phase 3 data. *Clin. Pharmacol. Drug Dev.* https://doi.org/10.1002/cpdd.986. Epub ahead of print.
27. Akinlade, B. *et al*. Conjunctivitis in dupilumab clinical trials. *Br. J. Dermatol.* **181**, 459–473 (2019).
28. U.S. Food and Drug Administration. Draft guidance for industry: general clinical pharmacology considerations for pediatric studies for drugs and biological products <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425885.pdf> (2014). Accessed January 29, 2021.