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CLINICAL TRIAL

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Dupilumab provides favourable long-term safety and efficacy in children aged ≥ 6 to < 12 years with uncontrolled severe atopic dermatitis: results from an open-label phase IIa study and subsequent phase III open-label extension study

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Summary

Background Children aged ≥ 6 to < 12 years with severe atopic dermatitis (AD) have limited treatment options. In a 16-week, randomized, placebo-controlled, phase III trial in children, dupilumab, a monoclonal antibody inhibiting interleukin (IL)-4/IL-13 signalling, significantly improved signs and symptoms with acceptable safety; longer-term safety and efficacy data are lacking.

Objectives To report the pharmacokinetic profile and long-term safety and efficacy of dupilumab in children (aged ≥ 6 to < 12 years) with severe AD.

Methods Children (aged ≥ 6 to < 12 years) with severe AD were enrolled in a global, multicentre, phase IIa, open-label, ascending-dose, sequential cohort study and subsequent open-label extension (OLE) study. Patients received single-dose dupilumab 2 or 4 mg kg^{-1} followed by 8-week pharmacokinetic sampling, then 2 or 4 mg kg^{-1} weekly for 4 weeks (phase IIa), followed by the same weekly regimen (OLE). Primary endpoints were dupilumab concentration–time profile and treatment-emergent adverse events (TEAEs); secondary assessments included Eczema Area and Severity Index (EASI) and Peak Pruritus Numeric Rating Scale (PP-NRS) score.

Results Of 38 children enrolled, 37 completed phase IIa and 33 continued to the OLE. Nonlinear, target-mediated pharmacokinetics characterized dupilumab concentrations (week 24–48 mean serum concentrations: 2 mg kg^{-1}, 61–77 mg L^{-1}; 4 mg kg^{-1}, 143–181 mg L^{-1}). TEAEs were mostly mild to moderate and transient; none led to treatment discontinuation. The most commonly reported TEAEs were nasopharyngitis (2 mg kg^{-1}, 47%; 4 mg kg^{-1}, 56%) and AD exacerbation (29% and 13%, respectively). Single-dose dupilumab rapidly improved AD with further improvements through week 52. Mean EASI and PP-NRS improved by −37%/−33% and −17%/−20% at week 2 (phase IIa) and −92%/−84% and −70%/−58% at week 52 (OLE), respectively.

Conclusions These safety and efficacy results support the use of dupilumab as a continuous long-term treatment for children aged ≥ 6 to < 12 years with severe AD.

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Conflicts of interest
See Appendix.

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What is already known about this topic?

- Severe atopic dermatitis (AD) has a marked negative impact on patient quality of life and can cause financial burden owing to a lack of effective treatments.
- Dupilumab significantly improved signs and symptoms of AD with an acceptable safety profile in a 16-week randomized, double-blind, placebo-controlled phase III study in children aged ≥ 6 to < 12 years with severe AD.

What does this study add?

- This study extends information on the safety, efficacy and pharmacokinetic profile of dupilumab treatment for up to 52 weeks in children aged ≥ 6 to < 12 years with severe AD.
- The results support the use of dupilumab as a continuous long-term treatment for children aged ≥ 6 to < 12 years with severe AD.

Atopic dermatitis (AD) is the most common inflammatory skin disease in children.[1] A recent analysis in children aged ≥ 6 to < 12 years showed a prevalence of up to 20%, of which severe AD accounted for up to 8%.[2] The disease has a marked negative impact on quality of life (QoL), including sleep deprivation, irritability, and stress and impact on family members,[3] and is associated with substantial financial burden.[4,5] Therapies that ameliorate severe disease with a favourable benefit–risk profile are limited in children with AD.[6–8] Systemic corticosteroids are strongly discouraged in children;[9] other systemic agents are used off-label and provide an unacceptable long-term benefit–risk profile for paediatric patients whose AD is inadequately controlled by topical therapies.[10] There are limited data from controlled studies to support the use of these agents in children.[6]

Dupilumab, a fully human VelocImmune®-derived monoclonal antibody,[11,12] blocks the shared receptor component for interleukin (IL)-4 and IL-13, thus inhibiting signalling of both IL-4 and IL-13. In a 16-week, randomized, double-blind, placebo-controlled phase III study of dupilumab in children aged ≥ 6 to < 12 years with severe AD, dupilumab significantly improved signs and symptoms with an acceptable safety profile.[13] However, AD is a chronic disease that requires continuous long-term treatment; therefore, long-term efficacy and safety data are important to support dupilumab use in this age group.

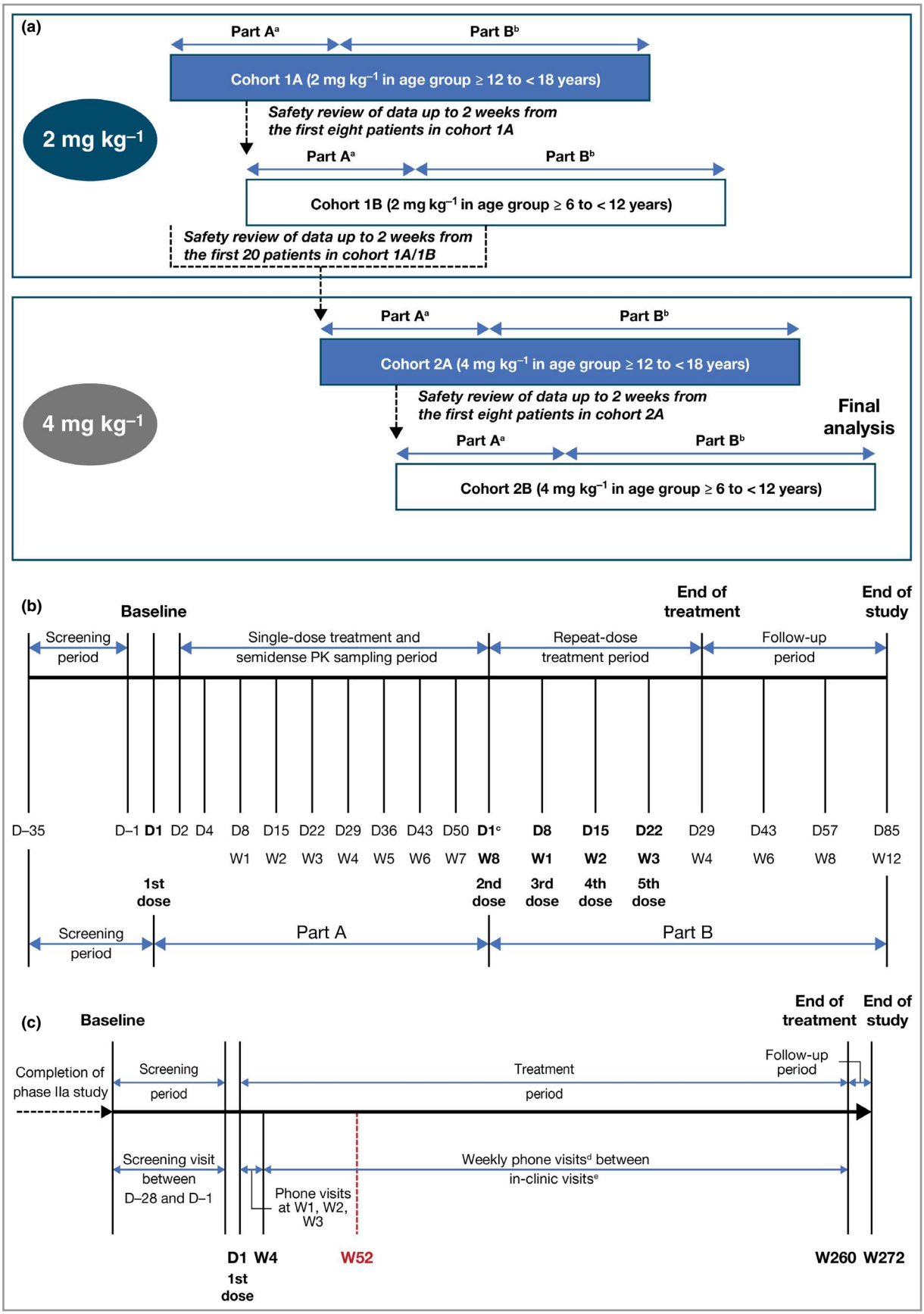
We previously reported the short- and long-term (up to 52 weeks) clinical safety, efficacy and pharmacokinetic (PK) profile of dupilumab in adolescents (aged ≥ 12 to < 18 years) with moderate-to-severe AD in an open-label phase IIa study (NCT02407756) and an ongoing phase III open-label extension (OLE) study (NCT02612454; LIBERTY AD PED-OLE).[14] Here we present an analysis of the safety, efficacy and PK profile of dupilumab in children aged ≥ 6 to < 12 years included in these studies.

Materials and methods

Study design and oversight

The study designs for both studies have been previously reported.[14] R668-AD-1412 (NCT02407756), a phase IIa, multicentre, open-label, ascending-dose, two-part, sequential cohort study, investigated the PK profile, safety, and efficacy of dupilumab (Figure 1a, b). In part A, patients received single-dose subcutaneous dupilumab (2 or 4 mg kg^{-1}) with 8 weeks of follow-up; in part B, patients received four weekly (qw) doses of subcutaneous dupilumab (2 or 4 mg kg^{-1})

Figure 1 Phase IIa study. (a) Design per original protocol. (b) Study flow diagram of phase IIa study. (c) Study flow diagram of phase III open-label extension (OLE) study. D, day; PK, pharmacokinetic; W, week. Only data from the subset of patients aged ≥ 6 to < 12 years are reported in this article. [a]Part A, single dose followed by an 8-week follow-up period with semidense sampling for systemic drug concentration. [b]Part B, four weekly doses followed by an 8-week safety follow-up period. The analysis presented here focuses on patients aged ≥ 6 to < 12 years who participated in the previous phase IIa study before the data cutoff date of 22 July 2019. Data are presented up to week 52. [c]For patients who completed part A per schedule, day-1 visit of part B was the same visit as week-8 visit of part A. For patients who did not complete part A per schedule (e.g. patients who received systemic corticosteroid or systemic nonsteroidal immunosuppressive drugs as rescue within 2 weeks of scheduled start of repeat dose and required 2 weeks of washout of the rescue medication), week-8 visit of part A and day-1 visit of part B were two independent visits; these patients were to complete the week-8 visit of part A and start visits for part B independent of part A. [d]On visits in which study drug administration was planned, patients had the option to come to the clinic to have the study drug administered by site staff. [e]In-clinic visits occurred every 3 months.



with an 8-week follow-up. A single 4-mg kg^{-1} dose in paediatric patients was expected to provide similar exposure as a single 300-mg dose in adults. The 2-mg kg^{-1} dose was chosen as the initial starting dose to evaluate the safety of dupilumab before progressing to the 4-mg kg^{-1} dose. The main inclusion criteria for children were age ≥ 6 to < 12 years, documented recent history (≤ 6 months before the screening visit) of inadequate response to topical AD medication(s), body surface area involvement ≥ 10% with AD lesions, and an Investigator's Global Assessment (IGA) score of 4 at baseline. Other inclusion criteria were identical to those previously reported in adolescents.[14] The study was conducted at multiple centres in Europe (Czech Republic, Hungary, Germany, Poland, UK) and Canada (Table S1; see Supporting Information).

R668-AD-1434 (LIBERTY AD PED-OLE; NCT02612454) is an ongoing, long-term, OLE phase III study enrolling paediatric patients who participated in previous dupilumab AD trials, including the phase IIa study reported here and a phase III study in children aged ≥ 6 to < 12 years (LIBERTY AD PEDS; R668-AD-1652) (Figure 1c) (long-term safety and efficacy data were not available from the phase III study at the time of publication; the phase III study data will be reported in a future manuscript).[13] The aim of the OLE is to assess the long-term safety and efficacy of dupilumab.

Children aged ≥ 6 to < 12 years were included if they had participated in a previous dupilumab study and adequately completed the visits and assessments required per protocol in the previous study. Patients were excluded if they developed a serious adverse event (SAE) or an adverse event (AE) deemed related to dupilumab that presented an unreasonable risk for the patient during the previous study. Full inclusion and exclusion criteria have been previously reported.[14] In the OLE study, patients continued to receive their assigned treatment regimen as in the phase IIa study (2 or 4 mg kg^{-1} administered qw).

Low- and mid-potency topical corticosteroids (TCS), topical calcineurin inhibitors, or both were allowed at the discretion of the investigator in either study. The use of systemic treatments for AD (systemic immunosuppressants and corticosteroids) was prohibited. If required, rescue treatment could be considered, initially with higher-potency TCS and then escalated to systemic treatment (corticosteroids or noncorticosteroid immunosuppressants; study treatment discontinuation was required during rescue treatment use).[14]

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

The phase IIa and OLE data presented here only include children aged ≥ 6 to < 12 years who participated in both studies. The OLE data is provided for 52 weeks of treatment.

Outcomes

The full list of prespecified endpoints has been previously reported.[14] The primary endpoint of the phase IIa study was concentration of functional dupilumab in serum over time and other PK parameters. The main secondary outcomes included incidence of treatment-emergent AEs (TEAEs) and percentage changes from baseline in Eczema Area and Severity Index (EASI), SCORing Atopic Dermatitis (SCORAD) and Peak Pruritus Numerical Rating Scale (NRS). The phase III OLE primary endpoints were incidence and rate [events per patient-year (PY)] of TEAEs. The main secondary endpoints included incidence and rate (events per PY) of serious TEAEs and TEAEs of special interest, the proportion of patients with an IGA score of 0 or 1, the proportion of patients with ≥ 75% reduction in EASI (EASI 75) from baseline of the parent study, the percentage change from baseline of the parent study in EASI score and SCORAD score, and the change from OLE baseline in Patient-Oriented Eczema Measure (POEM) and Children's Dermatology Life Quality Index (CDLQI).

Pharmacokinetics

PK samples were collected in a semidense manner in part A of the phase IIa study and at sparse timepoints in part B of the phase IIa and the OLE studies. To limit blood draws in this paediatric population, patients were randomized to a sampling schedule that included a subset of potential timepoints (Appendix S1; see Supporting Information). The mean concentration–time profiles were generated from pooling of all collected samples and used to determine the time to maximum mean concentration (t_{max}) and area under the concentration–time curve from time zero to the time of last measurable concentration in part A (AUC_{last}). Maximum dupilumab concentration in serum (c_{max}) were calculated for patients with PK samples collected at the t_{max} timepoint. In the OLE, steady-state C_{trough} samples were evaluated over weeks 24–48. Serum samples for dupilumab were analysed using a validated enzyme-linked immunosorbent assay, with a lower limit of quantitation set at 0·078 mg L^{-1}. The PK analysis set included patients with at least one nonmissing functional dupilumab result following the first dose of the study drug.

Statistical analysis

No formal sample size or power calculations were performed. PK, safety and efficacy variables were summarized descriptively; no inferential statistical tests were prespecified in the statistical analysis plan to allow comparison between treatment arms. Any differences observed in the descriptive summary of the PK, safety and efficacy variables were based on numerical

Table 1 Baseline demographics and disease characteristics

	Phase IIa study (N = 37)		Phase III OLE study (N = 33)	
	2 mg kg^{-1} (n = 18)	4 mg kg^{-1} (n = 19)	2 mg kg^{-1} (n = 17)	4 mg kg^{-1} (n = 16)
Mean age ± SD (range) (years)	8 ± 2 (6–11)	8 ± 2 (6–11)	9 ± 2 (6–11)	8 ± 2 (6–11)
Race, n (%)				
White	17 (94)	18 (95)	16 (94)	15 (94)
Black or African American	0	1 (5)	0	1 (6)
Other	1 (6)	0	1 (6)	0
Male sex, n (%)	9 (50)	11 (58)	8 (47)	9 (56)
Mean ± SD weight (kg)	30·8 ± 8·7	29·6 ± 9·8	30·9 ± 9·0	29·3 ± 8·6
Mean ± SD BMI (kg m^{-2})	17·5 ± 2·8	16·8 ± 2·0	16·9 ± 3·0	17·0 ± 2·2
Mean ± SD duration of AD (years)	7 ± 2	7 ± 2	7 ± 3	8 ± 2
Mean ± SD EASI score (scale 0–72)	33 ± 16	39 ± 19	21 ± 18	32 ± 20
IGA score, n (%) (scale 0–4)				
0 or 1	N/A	N/A	1 (6)	0
2	N/A	N/A	3 (18)	1 (6)
3	1 (6)[a]	0	9 (53)	7 (44)
4	17 (94)	19 (100)	4 (24)	8 (50)
Mean ± SD Peak Pruritus NRS (scale 0–10)	6 ± 2	7 ± 2	6 ± 3	6 ± 2
Mean ± SD BSA affected by AD (%)	59 ± 22	62 ± 30	37 ± 27	50 ± 31
Mean ± SD SCORAD (scale 0–103)	66 ± 13	73 ± 13	52 ± 17	67 ± 18
Mean ± SD POEM (scale 0–28)	N/A	N/A	17 ± 8	20 ± 5
Mean ± SD CDLQI (scale 0–30)	N/A	N/A	12 ± 8	12 ± 4
Any previous nonsteroidal systemic immunosuppressants, n (%)	3 (17)	7 (37)	N/A	N/A
Azathioprine	0	2 (11)	N/A	N/A
Ciclosporin A	3 (17)	5 (26)	N/A	N/A
No response to previous nonsteroidal systemic immunosuppressants	1 (6)	5 (26)	N/A	N/A
Patients with current history of atopic allergic conditions excluding AD, n (%)	14 (78)	17 (89)	N/A	N/A
Allergic rhinitis	9 (50)	10 (53)	N/A	N/A
Food allergy	10 (56)	14 (74)	N/A	N/A
Asthma	7 (39)	9 (47)	N/A	N/A
Allergic conjunctivitis	3 (17)	5 (26)	N/A	N/A
Chronic rhinosinusitis	0	1 (5)	N/A	N/A
Urticaria	1 (6)	0	N/A	N/A
Other allergies	12 (67)	12 (63)	N/A	N/A

AD, atopic dermatitis; BMI, body mass index; BSA, body surface area; CDLQI, Children's Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; N/A, not applicable; NRS, Numerical Rating Scale; OLE, open-label extension; POEM, Patient-Oriented Eczema Measure; SCORAD, SCORing Atopic Dermatitis. [a]One patient from this age group enrolled in the study had a baseline disease severity of IGA = 3 but was still included in the analyses sets.

comparisons. Exposure-adjusted analyses were calculated as described in Appendix S2 (see Supporting Information). The safety and efficacy analysis sets for all statistical analyses for both studies included all patients who received any study drug. Data after rescue treatment use during part B of the phase IIa study were set to missing. For continuous endpoints, missing values during the 4-week repeat-dose treatment period of part B up to the end-of-treatment visit were imputed by the last observation carried forward method. After the end of treatment in part B, no missing data were imputed. For categorical variables, patients with missing values were considered as nonresponders. Patients withdrawn from the study were counted as nonresponders after withdrawal. Patients who received rescue treatment during part B were considered nonresponders from the time of rescue use. For the phase III OLE study, an all-observed method was employed, regardless of rescue treatment use or whether data were collected after withdrawal from treatment (no missing values imputed). Statistical Analysis Software version 9·2 (SAS Institute, Inc., Cary, NC, USA) was used for all analyses.

Results

Patients

A total of 38 children (aged ≥ 6 to < 12 years) were enrolled (Figure S1; see Supporting Information). One patient (3%) in the 4 mg kg^{-1} dose group was withdrawn from the study during part A (withdrawal of consent owing to fear of study injections). Overall, 37 children (97%) completed parts A and

B. All 37 patients continued in the paediatric OLE; four patients turned 12 years of age at the time of enrolment and are not included in this analysis. The mean durations between the last dose in the phase IIa study and the first dose in the OLE were 118 days and 97 days for the 2-mg kg^{-1} and 4-mg kg^{-1} dose groups, respectively.

Baseline demographics and disease characteristics are shown in Table 1. The mean (± SD) age was 8 years (± 2) and the mean duration of AD was 7 years (± 2) in both dose groups. Disease characteristics at phase IIa study baseline were consistent with severe AD (Table 1). Mean (± SD) EASI scores were 33 (± 16) and 39 (± 19), Peak Pruritus NRS scores were 6 (± 2) and 7 (± 2) and percentages of body surface area affected were 59% (± 22) and 62% (± 30) in the 2-mg kg^{-1} and 4-mg kg^{-1} groups, respectively. Baseline disease severity was numerically higher in the 4-mg kg^{-1} group compared with the 2-mg kg^{-1} group in both the phase IIa and OLE studies (Table 1). Three patients (17%) in the 2-mg kg^{-1} group and seven patients (37%) in the 4-mg kg^{-1} group received nonsteroidal immunosuppressants prior to baseline of the phase IIa study; one patient (6%) and five patients (26%) did not respond to this treatment, respectively. Most patients (78%, 2 mg kg^{-1}; 89%, 4 mg kg^{-1}) had other concomitant atopic/allergic diseases, including asthma, allergic rhinitis and food allergy (Table 1).

Dupilumab pharmacokinetic profile

Following a single subcutaneous dose of dupilumab on day 1 of the phase IIa study, AUC_{last} calculated from the mean concentration–time profile in serum was 160 day × mg L^{-1} and 330 day × mg L^{-1} for the 2 mg kg^{-1} and 4 mg kg^{-1} groups, respectively. In the 2-mg kg^{-1} group, t_{max} was observed at 2 days after dosing with a c_{max} (± SD) of 14·3 mg L^{-1} (± 5·9). In the 4-mg kg^{-1} group, t_{max} was observed 4 days after dosing with a c_{max} (± SD) of 32·4 mg L^{-1} (± 7·0) (Figure 2a, Figure S2a; see Supporting Information). In the OLE, steady-state dupilumab trough mean (± SD) concentrations at weeks 24–48 ranged from 61·3 (± 35·0) to 76·8 mg L^{-1} (± 35·8) in the 2-mg kg^{-1} qw group and 143 (± 40·3) to 181 mg L^{-1} (± 65·9) in the 4-mg kg^{-1} qw group (Figure 2a, Figure S2a; see Supporting Information).

Safety assessment

The majority of reported TEAEs in the phase IIa were of mild or moderate severity (14% of patients reported a severe TEAE). The overall incidence of serious TEAEs was low, with two patients (11%) experiencing a serious TEAE, both of whom were in the 4-mg kg^{-1} dose group in part A of the study (Table 2). Serious TEAEs included bacterial arthritis, infected dermatitis and AD exacerbation, which were deemed not related to treatment (Appendix S3; see Supporting Information). None of the events led to permanent treatment discontinuation (Table 2).

The most frequent TEAEs were nasopharyngitis and AD exacerbation (Table 2). The proportion of patients with TEAEs was numerically higher in the 4-mg kg^{-1} dose cohort than in the 2-mg kg^{-1} dose cohort (Table 2), which was driven by higher incidence of skin infections (high-level term), cough

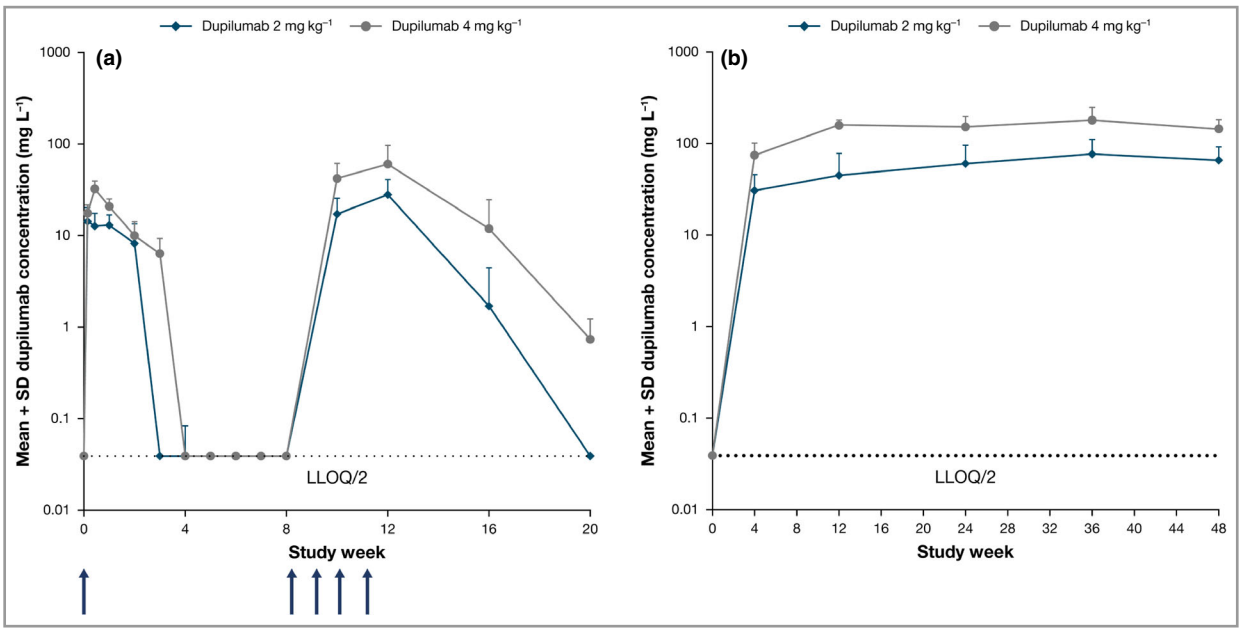


Figure 2 (a) Mean log-scaled concentrations of dupilumab in serum vs. nominal time: concentration–time profile of the phase IIa study. (b) Mean log-scaled concentrations of dupilumab in serum vs. nominal time: concentration–time profile of the phase III open-label extension (OLE) study.Horizontal arrows show timepoints of dupilumab administration. For both panels, concentrations below the limit of quantitation were set as LLOQ/2. LLOQ, lower limit of quantitation.

Table 2 Safety assessment

	Phase IIa study (N = 37)				Phase III OLE study (N = 33)			
	2 mg kg^{-1} (n = 18)		4 mg kg^{-1} (n = 19)		2 mg kg^{-1} (n = 17)	4 mg kg^{-1} (n = 16)	2 mg kg^{-1} (n = 17)	4 mg kg^{-1} (n = 16)
	Part A	Part B	Part A	Part B				
Number of TEAEs	n				n		nE per 100 PYs	
Total TEAEs	18	23	47	47	136	139	353	458
Total serious TEAEs[a]	0	0	3	0	2	5	5	16
Total TEAEs related to treatment	0	1	4	4	14	2	36	7
Total serious TEAEs related to treatment	0	0	0	0	0	0	0	0
Total TEAEs resulting in permanent study drug discontinuation	0	0	0	0	0	0	0	0
Patients with TEAEs	n (%)				n (%)		nP per 100 PYs	
Any TEAE	9 (50)	10 (56)	16 (84)	17 (89)	16 (94)	16 (100)	266	471
Any serious TEAE	0	0	2 (11)	0	2 (12)	3 (19)	6	11
Any TEAE related to treatment	0	1 (6)	3 (16)	3 (16)	4 (24)	2 (13)	13	7
Any TEAE leading to treatment discontinuation	0	0	0	0	0	0	0	0
Patients with TEAE resulting in death	0	0	0	0	0	0	0	0
Any infection (SOC)	6 (33)	8 (44)	10 (53)	12 (63)	12 (71)	15 (94)	98	209
Skin infection (HLT)	1 (6)	1 (6)	7 (37)	5 (26)	5 (29)	6 (38)	17	25
Nonherpetic skin infections (adjudicated)	1 (6)	1 (6)	6 (32)	5 (26)	4 (24)	3 (19)	12	11
Herpes viral infections (HLT)	1 (6)	0	1 (5)	0	2 (12)	4 (25)	6	15
Injection-site reactions (HLT)	0	0	1 (5)	1 (5)	2 (12)	1 (6)	5	3
Conjunctivitis[b]	0	0	1 (5)	2 (11)	2 (12)	5 (31)	5	21
Most common TEAEs[c]								
Nasopharyngitis	3 (17)	4 (22)	6 (32)	4 (21)	8 (47)	9 (56)	35	37
Dermatitis atopic	4 (22)	4 (22)	5 (26)	3 (16)	5 (29)	2 (13)	16	7
Cough	0	1 (6)	5 (26)	3 (16)	2 (12)	5 (31)	6	20
Dermatitis infected	1 (6)	0	3 (16)	2 (11)	2 (12)	0	5	0
Headache	0	1 (6)	2 (11)	1 (5)	4 (24)	2 (13)	13	7
Upper respiratory tract infection	0	1 (6)	0	1 (5)	2 (12)	4 (25)	6	16
Herpes simplex	0	0	0	0	0	4 (25)	0	15

HLT, high-level term; MedDRA, Medical Dictionary for Regulatory Activities; nE, number of events; nP, number of patients; OLE, open-label extension; PT, preferred term; PYs, patient-years; SOC, system organ class; TEAE, treatment-emergent adverse event. [a]Serious TEAEs reported in the OLE included lymphadenopathy, anaphylactic reaction, pneumonia, allergy test, arthralgia, complex regional pain syndrome and postural dizziness. [b]Includes PTs, conjunctivitis allergic, conjunctivitis bacterial, conjunctivitis, conjunctivitis viral and atopic keratoconjunctivitis. [c]Includes all MedDRA PTs reported in ≥ 15% or ≥ 20% of patients in any treatment group of the phase IIa study or phase III OLE, respectively.

(preferred term) and infected dermatitis (preferred term). Skin infections and AD exacerbation occurred mostly in patients not on dupilumab treatment at the time of TEAE onset (follow-up periods of parts A or B). Injection-site reactions were mild, occurring in the 4-mg kg^{-1} dose group alone (Table 2). Three patients reported conjunctivitis events, all in the 4-mg kg^{-1} group (in both parts A and B), none of which were severe, serious or led to treatment discontinuation; conjunctivitis resolved in two patients. One patient per dose group reported nonherpetic viral infections in part A.

In the OLE, nearly all children reported at least one TEAE (Table 2). However, serious TEAEs were rare, with two patients (12%) and three patients (19%) experiencing at least one serious TEAE in the 2-mg kg^{-1} and 4-mg kg^{-1} dose groups, respectively; none were related to treatment or led to discontinuation of study drug. In the OLE, the most frequent TEAEs were nasopharyngitis and AD exacerbation (Table 2). The proportions of patients with TEAEs, including skin infections, were comparable in the 4-mg kg^{-1} and 2-mg kg^{-1} groups. However, there was a trend towards numerically

Table 3 Efficacy assessment

	Dupilumab 2 mg kg^{-1}					Dupilumab 4 mg kg^{-1}				
	Phase IIa study (n = 18)		Phase III OLE (n = 17)			Phase IIa study (n = 19)		Phase III OLE (n = 16)		
	Week 2	Week 12	Week 0[a]	Week 16	Week 52	Week 2	Week 12	Week 0[a]	Week 16	Week 52
Mean ± SD EASI (n)	23 ± 18 (18)	9 ± 13 (16)	21 ± 18 (17)	9 ± 14 (17)	2 ± 3 (17)	26 ± 16 (18)	16 ± 15 (19)	32 ± 20 (16)	7 ± 8 (15)	5 ± 5 (16)
Mean ± SD percentage change in EASI from baseline of phase IIa study (N1)	−37 ± 34 (18)	−76 ± 25 (16)	−37 ± 37 (17)	−73 ± 42 (170)	−92 ± 14 (17)	−33 ± 28 (18)	−63 ± 25 (19)	−20 ± 32 (16)	−84 ± 14 (15)	−84 ± 17 (16)
Patients achieving EASI 50 from baseline of phase IIa study, n/N (%)	7/18 (39)	14/18 (78)	7/17 (41)	16/17 (94)	16/17 (94)	5/19 (26)	11/19 (58)	3/16 (19)	14/15 (93)	15/16 (94)
Patients achieving EASI 75 from baseline of phase IIa study, n/N (%)	3/18 (17)	10/18 (56)	4/17 (24)	10/17 (59)	16/17 (94)	2/19 (11)	9/19 (47)	1/16 (6)	11/15 (73)	12/16 (75)
Patients with EASI 90 from baseline of phase IIa study, n/N (%)	1/18 (6)	6/18 (33)	0/17 (0)	7/17 (41)	12/17 (71)	0/19 (0)	5/19 (26)	0/16 (0)	5/15 (33)	7/16 (44)
Patients achieving IGA score 0 or 1, n/N (%)	1/18 (6)	3/18 (17)	1/17 (6)	6/17 (35)	13/17 (76)	0/19 (0)	4/19 (21)	0/16 (0)	6/15 (40)	4/16 (25)
Mean ± SD Peak Pruritus NRS (N1)	5 ± 3 (17)	3 ± 2 (16)	6 ± 3 (17)	3 ± 2 (17)	2 ± 2 (17)	5 ± 3 (18)	4 ± 2 (19)	6 ± 2 (16)	3 ± 2 (16)	3 ± 2 (16)

(continued)

Table 3 (continued)

	Dupilumab 2 mg kg^{-1}					Dupilumab 4 mg kg^{-1}				
	Phase IIa study (n = 18)		Phase III OLE (n = 17)			Phase IIa study (n = 19)		Phase III OLE (n = 16)		
	Week 2	Week 12	Week 0[a]	Week 16	Week 52	Week 2	Week 12	Week 0[a]	Week 16	Week 52
Mean ± SD percentage change in Peak Pruritus NRS from baseline of phase IIa study (N1)	−17 ± 46 (17)	−42 ± 35 (16)	−9 ± 39 (17)	−50 ± 42 (17)	−70 ± 32 (17)	−20 ± 47 (18)	−40 ± 41 (19)	5 ± 68 (16)	−51 ± 44 (16)	−58 ± 33 (16)
Patients with ≥ 3-point improvement in Peak Pruritus NRS from baseline of phase IIa study, n/N (%)	4/18 (22)	7/18 (39)	4/17 (24)	11/17 (65)	14/17 (82)	7/19 (37)	10/19 (53)	6/16 (38)	11/16 (69)	11/16 (69)
Patients with ≥ 4-point improvement in Peak Pruritus NRS from baseline of phase IIa study, n/N (%)	2/18 (11)	5/18 (28)	1/17 (6)	9/17 (53)	11/17 (65)	5/19 (26)	9/19 (47)	3/16 (19)	11/16 (69)	11/16 (69)
Mean ± SD SCORAD (N1)	51 ± 20 (17)	28 ± 15 (16)	52 ± 17 (17)	26 ± 20 (17)	14 ± 11 (17)	52 ± 15 (18)	38 ± 17 (19)	67 ± 18 (16)	29 ± 15 (15)	24 ± 14 (16)
Mean ± SD percentage change in SCORAD from baseline of phase IIa study (N1)	−25 ± 21 (17)	−58 ± 23 (16)	−22 ± 20 (17)	−61 ± 31 (17)	−79 ± 16 (17)	−28 ± 19 (18)	−47 ± 24 (19)	−10 ± 23 (16)	−62 ± 18 (15)	−67 ± 19 (16)

EASI, Eczema Area and Severity Index; EASI 50/75/90, ≥ 50%/75%/90% improvement from baseline in EASI; IGA, Investigator's Global Assessment; N1, patients with available measurements at the particular timepoint; NRS, Numerical Rating Scale; OLE, open-label extension; SCORAD, SCORing Atopic Dermatitis. [a]The mean durations between the last dose in the phase IIa study and the first dose in the phase III OLE were 118 and 97 days for the 2-mg kg^{-1}and 4-mg kg^{-1} dose groups, respectively.

higher TEAEs in the 4-mg kg^{-1} compared with the 2-mg kg^{-1} group when exposure-adjusted incidence (number of patients per 100 PY) was examined (Table 2). Two patients (12%) and four patients (25%) reported herpes viral infection (Table 2). Injection-site reactions were mild and occurred in three patients across both dose groups (Table 2). Seven patients reported conjunctivitis events; two patients (12%) and five patients (31%) in the 2-mg kg^{-1} and 4-mg kg^{-1} group, respectively (Table 2). Conjunctivitis was reported as treatment-related in one patient (6%) in the 4-mg kg^{-1} group. Most patients with conjunctivitis events were treated with topical eyedrops, including antibacterial and antiallergic eyedrops (Table S2; see Supporting Information). No events were severe, serious or led to treatment discontinuation, and conjunctivitis resolved in all patients. Details of conjunctivitis cases are provided in Table S2 (see Supporting Information). The most common treatments administered for skin infections in the phase IIa and OLE studies were topical antimicrobials. Details of skin infection cases for which systemic antibiotics were administered are provided in Table S3 (see Supporting Information).

Efficacy outcomes

By week 2 of the phase IIa study, EASI decreased with a mean (± SD) percentage change from baseline of −37 (± 34) and −33 (± 28) after a single dose of dupilumab 2 mg kg^{-1} and 4 mg kg^{-1}, respectively; improvements in EASI were maintained up to week 52 in the OLE [−92 (± 14) and −84 (± 17) in 2-mg kg^{-1} and 4-mg kg^{-1} groups, respectively (Table 3, Figure 3a, Figure S3a; see Supporting Information)]. The proportions of patients achieving EASI 75 or IGA 0/1 at week 12 in the phase IIa study further increased until week 52 in the OLE. By week 12 of the phase IIa study, 56% and 47% of patients receiving dupilumab 2 mg kg^{-1} and 4 mg kg^{-1} achieved EASI 75, with proportions increasing to 94% and 75% at week 52 of the OLE, respectively (Table 3, Figure 3b). Similarly, by week 12 of the phase IIa study, 17% and 21% of patients receiving dupilumab 2 mg kg^{-1} and 4 mg kg^{-1} achieved IGA 0/1 with proportions further increasing to 76% and 25% at week 52 of the OLE, respectively (Table 3, Figure 3c).

Peak Pruritus NRS scores decreased from baseline by a mean (± SD) percentage of −17% (± 46) and −20% (± 47) at week 2 of the phase IIa study, after a single dose of dupilumab 2 mg kg^{-1} and 4 mg kg^{-1}, respectively; improvements were maintained up to week 52 in the OLE [−70% (± 32) and −58% (± 33), 2 mg kg^{-1} and 4 mg kg^{-1}, respectively] (Table 3, Figure 3d). Further improvements in other pruritus outcomes (patients with ≥ 3-point or ≥ 4-point reduction from baseline in Peak Pruritus NRS) were seen until week 52 in the OLE (Table 3, Figure 3e, Figure S3d; see Supporting Information).

Sustained improvements were also seen in EASI 50, EASI 90, SCORAD and percentage body surface area affected by AD in the phase IIa and OLE study up to week 52 (Table 3, Figure 3f,g, Figure S3b, c, e, f; see Supporting Information). AD symptoms and QoL as assessed by POEM and CDLQI showed improvement from baseline to week 48 of the OLE (Figure 3h, Figure S3g; see Supporting Information).

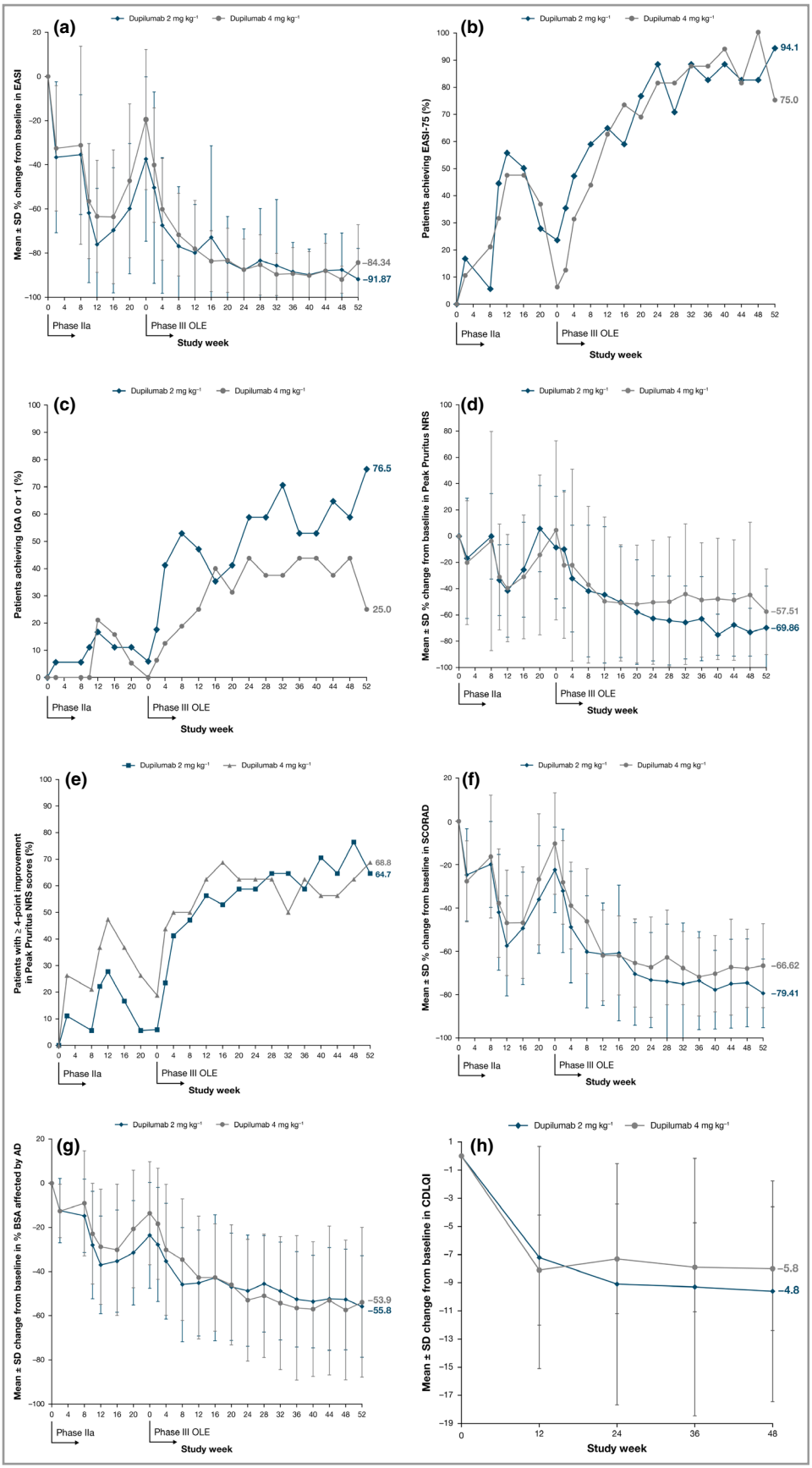
Concomitant medications

Overall, 89% of patients in the 2-mg kg^{-1} dupilumab group and 95% of patients in the 4-mg kg^{-1} dupilumab group of the phase IIa study used topical treatment as concomitant medication (Table S4; see Supporting Information); the most commonly used topical treatment in both treatment arms was potent TCS (group III). In the OLE, 82% (2 mg kg^{-1}) and 94% (4 mg kg^{-1}) of children used concomitant topical medication, with the majority (65% and 69%) using potent (group III) TCS (Table S4; see Supporting Information).

Discussion

Children have a developing and potentially immature immune system, and the immune mechanisms underlying AD in children may differ from those in adults.[15,16] Hence, it was important to assess the safety and efficacy of long-term dupilumab-mediated IL-4 receptor α blockade in dedicated clinical trials in children with AD aged ≥ 6 to < 12 years and to compare the results with those observed in previous adult and adolescent studies. In children aged ≥ 6 to < 12 years with severe AD, dupilumab treatment for up to 52 weeks was well tolerated with a favourable safety profile consistent with the known dupilumab safety profile from studies in adolescents and adults with moderate-to-severe AD.[14,17–20] No AEs led to

Figure 3 Efficacy endpoints. (a) Percentage change in EASI from baseline of the phase IIa study to week 52 of the phase III OLE. (b) Proportion of patients achieving EASI 75 from the baseline of the phase IIa study to week 52 of the phase III OLE. (c) Proportion of patients achieving IGA scores of 0 or 1 from the baseline of the phase IIa study to week 52 of the phase III OLE. (d) Percentage change in Peak Pruritus NRS from the baseline of the phase IIa study to week 52 of the phase III OLE. (e) Proportion of patients with ≥ 4-point improvement from baseline in Peak Pruritus NRS at all in-clinic visits postbaseline of parent study through week 52 of OLE study. (f) Percentage change in SCORAD from baseline of the phase IIa study to week 52 of the phase III OLE. (g) Change in BSA affected by AD from baseline of the phase IIa study to week 52 of the phase III OLE study. (h) Change in CDLQI from baseline of the OLE study to week 48.AD, atopic dermatitis; BSA, body surface area; CDLQI, Children's Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; EASI 75, ≥ 75% improvement from baseline in EASI; IGA, Investigator's Global Assessment; NRS, Numerical Rating Scale; OLE, open-label extension; SCORAD, SCORing Atopic Dermatitis. The mean durations between the last dose in the phase IIa study and the first dose in the phase III OLE were 118 and 97 days for the 2-mg kg^{-1} and 4-mg kg^{-1} dose groups, respectively.



treatment discontinuation, and none of the reported serious TEAEs were considered related to dupilumab.

Although TEAE incidence was higher in the 4-mg kg^{-1} dose group compared with the 2-mg kg^{-1} dose group in the phase IIa study, TEAE incidences were comparable in the OLE. No substantial differences in SAEs or TEAEs leading to treatment discontinuation were observed between the two dose regimens. Moreover, patients in this sequential cohort study were not randomized to dose regimens, leading to differences in OLE baseline disease severity, and the number of patients in each dose regimen was small; therefore, a rigorous comparison between the dose regimens was not possible.

The serious event of septic arthritis reported in the phase IIa study was deemed not related to dupilumab. The investigator noted that the patient's skin was colonized with staphylococci and skin breakdown from scratching can enable bacteria to enter the bloodstream, resulting in invasive infection at metaphyses and, subsequently, arthritis.[21,22]

Although a higher incidence of skin infection was noted with the 4-mg kg^{-1} dose compared with the 2-mg kg^{-1} dose in the phase IIa study, rates were similar in the OLE. Skin infections occurred mostly in patients not treated with dupilumab at the time of TEAE onset (patients were in the follow-up periods of parts A or B). A very high proportion of patients with AD have skin colonization with *Staphylococcus aureus*,[23] and patients with AD are prone to developing skin infections. Phase III trials in adults and adolescents with AD showed that the incidence of skin infections was numerically lower in patients treated with dupilumab compared with placebo.[20,24] For comparison with exposure-adjusted incidence of skin infections in the OLE study reported here (17–25 patients per 100 PYs), a 1-year open-label study in adolescents observed skin infections in 18–34 patients per 100 PYs[14] and a 3-year open-label study in adults found the incidence to be five patients per 100 PYs.[25]

The rates of conjunctivitis in the phase IIa study were small, an observation also made in a similar analysis of adolescents,[14] which could be explained in part by the short study duration and low number of dupilumab doses. Furthermore, the studies reported here were conducted before investigators developed a heightened awareness of conjunctivitis as an AE associated with dupilumab, which may lead to higher reporting in more recent studies. The incidences of conjunctivitis in the OLE in children aged ≥ 6 to < 12 years reported here (five to 21 patients per 100 PYs) were similar to those reported in adolescents (nine to 10 patients per 100 PYs)[14] and adults (12 patients per 100 PYs).[25]

AD signs and symptoms, including pruritus, showed rapid improvements with single-dose dupilumab in the phase IIa study. Improvements in clinical scores (EASI, SCORAD) and Peak Pruritus NRS were observed as early as week 2, with further improvement on continued treatment up to week 52 in the OLE. QoL was also improved with long-term treatment. Comparison of the two doses showed a numerical trend towards higher responses with 2 mg kg^{-1} vs. 4 mg kg^{-1} in the treatment of AD signs and symptoms in both the phase IIa and OLE studies. However, the number of patients in each treatment arm was small, precluding any meaningful conclusions. Moreover, the baseline disease severity in the 4-mg kg^{-1} group was higher than the baseline severity in the 2-mg kg^{-1} group, which could have led to this difference.

The overall efficacy results were similar to those observed in the first report of these two studies in adolescents with moderate-to-severe AD.[14] The efficacy and safety from another randomized placebo-controlled phase III study in children aged ≥ 6 to < 12 years with severe AD receiving dupilumab with concomitant TCS in a larger sample size of this patient population were generally similar to our results.[13] To compare efficacy outcomes reported here with other systemic medications in children, treatment of patients aged 2–16 years with ciclosporin at a dose of 5 mg kg^{-1} in a randomized double-blinded placebo-controlled study led to reduction in disease severity by 50% at week 12.[26] Efficacy was sustained with continuous treatment through week 52. In an open-label uncontrolled study in paediatric patients aged 2–16 years, treatment with ciclosporin 5 mg kg^{-1} led to a 57% reduction in disease severity at week 6.[27]

The PK profile in children with severe AD was similar to that in adults and adolescents with moderate-to-severe AD and characterized by nonlinear target-mediated kinetics.[14,28] Mean C_{trough} values at steady state for the 2-mg kg^{-1} qw dosing regimen in children were equivalent to the every 2 weeks (q2w) dosing regimen approved by the US Food and Drug Administration in adults (300 mg) and adolescents (200/300 mg, tiered by bodyweight), whereas the steady-state C_{trough} for the 4-mg kg^{-1} qw regimen in children was equivalent to the 300-mg qw regimen in adults. The observation of numerically higher efficacy with 2 mg kg^{-1} compared with 4 mg kg^{-1}, which most likely occurred by chance, is not inconsistent with the observation that maximal efficacy, and hence saturation of IL-4 receptor α, occurs at mean steady-state C_{trough} of dupilumab equivalent to that achieved by the 300-mg q2w regimen in adults (approximately 70 mg L^{-1}). Importantly, the lack of incremental efficacy seen with 4 mg kg^{-1} coupled with the PK data support the evaluation of the q2w regimen rather than the qw regimen in the pivotal phase III study in children aged ≥ 6 to < 12 years.[13]

Strengths of this analysis include results based on continuous treatment with dupilumab for up to 1 year. Limitations include the open-label nature of the studies, lack of a comparator arm and the small sample size. The 5-year OLE study is ongoing at the time of this report, and future publications will report larger cohorts and longer treatment durations.

These safety and efficacy results support the use of dupilumab as continuous long-term treatment for children aged ≥ 6 to < 12 years with severe AD.

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Appendix

Conflicts of interest. M.J.C. has acted as an investigator and consultant for AbbVie, Astellas, Boots, Dermavant, Galapagos, Galderma, Hyphens Pharma, Johnson & Johnson, LEO Pharma, L'Oréal, Menlo Therapeutics, Novartis, Oxagen, Pfizer, Procter & Gamble, Reckitt Benckiser, Regeneron Pharmaceuticals, Inc. and Sanofi Genzyme. D.T. has received research support from AbbVie, Almirall, DS-Biopharma, Eli Lilly, Galapagos, Galderma, LEO Pharma, MorphoSys, Novartis, Pfizer, Regeneron Pharmaceuticals, Inc., Sanofi and independent advisor honoraria from AbbVie and Novartis. D.T. has been a consultant for AbbVie, Beiersdorf, DS-Biopharma, Galapagos, MorphoSys,

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Appendix S1 Semidense pharmacokinetic sampling.

Appendix S2 Statistical analysis.

Appendix S3 Patient narratives for serious adverse events.

Table S1 Study sites institutional review boards and independent ethics committees.

Table S2 Conjunctivitis cases.

Table S3 Systemic antibiotic use for skin infections.

Table S4 Concomitant medication use.

Figure S1 CONSORT diagram of patient disposition.

Figure S2 Mean concentrations of dupilumab in serum vs. nominal time.

Figure S3 Additional efficacy endpoints.