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Dupilumab in adolescents with uncontrolled moderate-to-severe atopic dermatitis: results from a phase IIa open-label trial and subsequent phase III open-label extension

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Summary

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Conflicts of interest
Conflicts of interest statements can be found in Appendix S1 (see Supporting Information).

Trial Registration ClinicalTrials.gov-identifiers: NCT02407756 (R668-AD-1412), NCT02612454 (R668-AD-1434).

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Background Dupilumab (monoclonal antibody inhibiting IL-4/IL-13 signalling) is approved for use in adolescents aged ≥ 12 years with inadequately controlled moderate-to-severe atopic dermatitis (AD). Dupilumab significantly improved AD signs/symptoms in a 16-week, randomised, placebo-controlled phase III trial in adolescents (NCT03054428).

Objectives To characterize the pharmacokinetics of dupilumab, and long-term safety and efficacy in adolescents.

Methods This was a global, multicentre, phase IIa, open-label, ascending-dose, sequential cohort study with a phase III open-label extension (OLE) in adolescents with moderate-to-severe AD. In the phase IIa study, patients received one dupilumab dose (2 mg kg^{-1} or 4 mg kg^{-1}) and 8 weeks of pharmacokinetic sampling. Thereafter, patients received the same dose weekly for 4 weeks, with 8-week safety follow-up. Patients then enrolled in the OLE, continuing 2 mg kg^{-1} or 4 mg kg^{-1} dupilumab weekly. Primary end points were dupilumab concentration–time profile and incidence of treatment-emergent adverse events (TEAEs). Secondary outcomes included Eczema Area and Severity Index (EASI).

Results Forty adolescents received dupilumab in the phase IIa study; 36 enrolled in the OLE. Dupilumab showed nonlinear, target-mediated pharmacokinetics. Mean ± SD trough dupilumab concentrations in serum at week 48 (OLE) were 74 ± 19 mg L^{-1} and 161 ± 60 mg L^{-1} for 2 mg kg^{-1} and 4 mg kg^{-1}, respectively. Dupilumab was well tolerated over 52 weeks; the most common TEAEs were nasopharyngitis (week 52: 41% [2 mg kg^{-1}], 47% [4 mg kg^{-1}]) and AD exacerbation (29%, 42%). After one dupilumab dose in the phase IIa study, EASI improved from baseline to week 2 [mean ± SD reduction −34% ± 20% (2 mg kg^{-1}) and −51% ± 29% (4 mg kg^{-1})]. With continuing treatment, EASI scores improved further [week 52: −85% ± 12% (2 mg kg^{-1}) and −84% ± 20% (4 mg kg^{-1})].

Conclusions In adolescents with moderate-to-severe AD, dupilumab's pharmacokinetic profile was similar to that in adults. These 52-week safety and efficacy data support long-term use of dupilumab in this patient population.

What's already known about this topic?

- Adolescents with moderate-to-severe atopic dermatitis (AD) have high unmet medical need, with significant disease burden and limited treatment options.
- Dupilumab (monoclonal antibody against interleukin-4 receptor α) is approved for the treatment of adolescents with moderate-to-severe AD who are inadequately responsive to standard of care (U.S.A.) or candidates for systemic therapy (European Union).
- A 16-week, randomized, placebo-controlled phase III trial in adolescents demonstrated significant improvements in AD signs/symptoms with an acceptable safety profile.

What does this study add?

- These studies demonstrate the long-term safety and efficacy of dupilumab in adolescents with moderate-to-severe AD for up to 52 weeks of treatment, thus extending and reinforcing the findings from the 16-week dupilumab phase III trial.
- The data from these studies also support the use of dupilumab in combination with current standard of care (topical corticosteroids), which was not evaluated in the 16-week phase III monotherapy trial.

Atopic dermatitis (AD) is a chronic inflammatory skin condition characterized by pruritus, disruption of skin barrier function and type 2 inflammation.[1] The worldwide prevalence of AD in adolescents is estimated to be 0·2–24·6%.[2,3] AD has substantial detrimental effects on health-related quality of life (QoL). Adolescents with AD have a high prevalence of depression, anxiety and attention deficit–hyperactivity disorder,[4,5] and a greater risk of developing asthma, allergic rhinitis and food allergy,[6–9] which typically persist into adulthood.[7,10] Until recently, approved medications for adolescents with AD were limited to topical therapies, including topical corticosteroids (TCS) and topical calcineurin inhibitors (TCIs); however, their long-term application is limited by adherence and risk of side-effects.[1,11] Although systemic immunosuppressive agents are not approved for use in adolescents with AD (except for systemic corticosteroids and ciclosporin in patients aged ≥ 16 years in certain countries), they are sometimes used off label for severe AD refractory to topical therapy. Systemic immunosuppressive agents, such as azathioprine, methotrexate and mycophenolate, are only recommended for short-term use owing to risk of infections, malignancies, and hepatic, renal and haematological toxicities.[12–14] Consequently, there is still an overall unmet need for safe and effective treatments for adolescents with moderate-to-severe AD.

Dupilumab is a fully human VelocImmune®-derived[15,16] monoclonal antibody that blocks the shared receptor component for interleukin (IL)-4 and IL-13, thus inhibiting signalling of both IL-4 and IL-13. In randomized trials of adults with moderate-to-severe AD inadequately controlled with topical therapies, dupilumab had a favourable benefit-to-risk safety profile, improved disease severity and symptoms, and improved scores for anxiety, depression and QoL.[17–21] Positive outcomes have also been reported in asthma, chronic sinusitis with nasal polyps and eosinophilic oesophagitis, highlighting the importance of IL-4/IL-13 as drivers of multiple type 2 inflammatory diseases.[22–28] Dupilumab is approved for subcutaneous administration in the treatment of patients aged ≥ 12 years (400 mg loading dose followed by 200 mg every 2 weeks in adolescents aged ≥ 12 to < 18 years with a baseline body weight of < 60 kg, or 600 mg loading dose followed by 300 mg every 2 weeks for adolescents with a baseline body weight of ≥ 60 kg) in the U.S.A. with moderate-to-severe AD inadequately controlled with topical prescription therapies or when those therapies are not advisable;[29] in Japan for the treatment of adult patients with AD not adequately controlled with existing therapies; and in the European Union for use in patients aged ≥ 12 years with moderate-to-severe AD who are candidates for systemic therapy.[30] Dupilumab is also approved for certain patients with other type 2 inflammatory diseases, including asthma and chronic rhinosinusitis with nasal polyps, in a number of countries.[23,24,26–29]

We present the results of two studies evaluating dupilumab in adolescents with moderate-to-severe AD, with the objectives to investigate the pharmacokinetic (PK) profile, safety and efficacy of dupilumab (phase IIa study), and its long-term safety and efficacy [ongoing phase III open-label extension (OLE)].

Materials and methods

Study design and patient selection

The first study, a phase IIa, multicentre, open-label, ascending-dose, sequential cohort study (R668-AD-1412; NCT02407756), was conducted at multiple centres in Europe (Czech Republic, Hungary, Germany, Poland, the U.K.) and Canada. The study consisted of a screening period of up to 35

days, a baseline visit and two treatment phases: in part A, patients received a single dose of dupilumab followed by an 8-week sampling period for systemic drug concentration; in part B, patients received four weekly doses followed by an 8-week safety follow-up period (Figs S1 and S2; see Supporting Information). Patients were required to discontinue systemic treatments for AD (oral corticosteroids and non-steroidal immunosuppressants) for at least 2 weeks prior to the baseline visit. In addition, patients who did not complete part A per schedule, for example patients who received systemic corticosteroids or systemic nonsteroidal immunosuppressive agents as rescue treatment within 2 weeks of the scheduled start of the repeat dose, had a 2-week washout period of the rescue medication prior to starting part B of the study.

The second study, an ongoing phase III OLE (R668-AD-1434 LIBERTY AD PED-OLE; NCT02612454) enrolling paediatric patients who participated in previous dupilumab AD trials [the present phase IIa study, and phase III (NCT03054428) and phase I (NCT03050151) studies], includes centres from Canada, the Czech Republic, Germany, Hungary, Poland, the U.K. and the U.S.A. The study consists of a screening period (day −28 to day −1), a treatment period that lasts until regulatory approval of the product for the age group of the patients in their geographical region, and a 12-week follow-up period (Fig. S2). Patients were required to discontinue systemic treatments for AD (oral corticosteroids and nonsteroidal immunosuppressants) for at least 2 weeks prior to the baseline visit.

The patients selected for enrolment in the phase IIa and phase III OLE study included paediatric patients (aged ≥ 6 to < 18 years) with AD that was inadequately controlled with topical medications or for whom topical therapies were inadvisable. Eligible patients had AD for > 1 year before screening, based on American Academy of Dermatology criteria;[1] a baseline Investigator Global Assessment (IGA) of 3 or 4; and ≥ 10% of their body surface area (BSA) affected by AD. Patients who had a serious adverse event (SAE) deemed related to the study drug, or an adverse event (AE) related to the study drug and which led to discontinuation from the study, were excluded from the OLE. See Appendix S2 for full eligibility criteria (see Supporting Information).

The phase IIa and OLE data presented herein only include adolescents aged ≥ 12 to < 18 years with AD who had participated in the phase IIa study and continued into the OLE study.

Both studies were conducted in accordance with the principles established in the Declaration of Helsinki and the International Conference on Harmonisation guidelines for Good Clinical Practice. All study documents and procedures were approved by the appropriate institutional review boards/ethics committees at each study centre (Table S1; see Supporting Information). Assent and written informed consent were provided by the patients (as appropriate) and their parents or legal guardians. An independent data monitoring committee monitored patient safety.

Randomization and procedures

Patients received a single subcutaneous (SC) dose of 2 mg kg^{-1} or 4 mg kg^{-1} dupilumab on day 1, and blood samples were collected for 8 weeks to characterize the single-dose PK profile (part A). Patients then received four weekly doses of dupilumab and were followed for 8 weeks for safety evaluation (part B). To minimize the volume of blood sample collection and reduce the number of blood draws needed to acquire informative dupilumab concentration data, patients in part A were randomized to one of three semi-dense PK sampling schedules: days 2, 15, 36 and 57; days 4, 22, 43 and 57; or days 8, 29, 50 and 57. Dupilumab concentrations were assessed using a validated enzyme-linked immunosorbent assay, the lower limit of quantitation of which is 0·078 mg L^{-1}.

In the phase III OLE, patients aged ≥ 12 to < 18 years received 2 mg kg^{-1} or 4 mg kg^{-1} dupilumab SC weekly (up to a maximum of 300 mg).

Rescue medication was permitted in both studies at the investigator's discretion if medically necessary to control intolerable AD symptoms. See Appendix S2 for detailed descriptions of rescue treatments, prohibited medications and procedures.

Outcome measures

In the phase IIa study, the primary outcome was the characterization of the PK of dupilumab. The PK profile was assessed by integrating the full complement of sampling schedules to construct a single complete mean concentration–time profile for each group (naïve pooling). Secondary outcomes were assessed from baseline to week 20 (part B, week 12) and included incidence of AEs; percentage change from baseline in Eczema Area and Severity Index (EASI), Peak Pruritus Numerical Rating Scale (NRS) and SCORing Atopic Dermatitis (SCORAD); the proportion of patients achieving an IGA of 0 or 1 (clear or almost clear); and change from baseline in percentage of BSA (%BSA) affected by AD.

In the phase III OLE, the primary outcomes were incidence (%) and rate (events per patient year) of AEs. Secondary outcomes included incidence and rate of SAEs, AEs of special interest and efficacy up to week 52. See Appendix S2 in Supporting Information, for a full list of end points.

Pharmacokinetic analyses

PK analyses were conducted from the mean concentration–time profiles after integration of the three semi-dense sampling schedules. Mean peak dupilumab concentration in serum (C_{max}) and time to maximum mean concentration (t_{max}) were recorded. The area under the concentration–time curve from time zero to the time of last positive concentration (AUC_{last}, determined prior to the last mean concentration assessed at week 8) was calculated using the linear–trapezoidal rule using Phoenix WinNonlin (version 6·3; Certara, USA, Inc.,

Princeton, NJ, U.S.A.). C_{max} and t_{max} were determined by visual inspection of the mean concentration–time profile.

Statistical analyses

No formal sample size or power calculations were performed. PK, safety and efficacy variables were summarized descriptively. Furthermore, no inferential statistical tests were prespecified in the statistical analysis plan to allow comparison between the two treatment arms. Any differences observed in the descriptive summary of the PK, safety and efficacy variables were based on numerical comparisons. The analysis set for all statistical analyses for both studies included all patients who received any study drug. Patients in the PK population had to have ≥ 1 nonmissing functional dupilumab result following the first dose of the study drug.

If a PK drug concentration was missing, data were set to missing and only observed data were used. Data after rescue treatment use during part B of the phase IIa study were set to missing. Missing values during the first 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 imputation was made. For the phase III open-label extension, an all-observed method was employed, regardless of whether rescue treatment was used or if data were collected after withdrawal from study treatment. No missing values were imputed. SAS version 9·2 (SAS Institute Inc., Cary, NC, U.S.A.) was used for all analyses.

Results

Patients

Of the 88 paediatric patients screened for the phase IIa study, 78 (89%) were enrolled, including 40 adolescents (Fig. S3; see Supporting Information). Two adolescents did not complete the study treatment, one in the cohort receiving 2 mg kg^{-1} dupilumab (due to receiving a rabies vaccination) and one in the cohort receiving 4 mg kg^{-1} dupilumab (due to needle phobia). A total of 36 adolescents (including three younger patients from the phase IIa study who reached the age of 12 years at the time rolling over to OLE) continued to the phase III OLE, and 34 completed ≥ 52 weeks of treatment with 2 mg kg^{-1} or 4 mg kg^{-1} dupilumab weekly. Two patients did not complete the OLE study: one was lost to follow-up and one withdrew consent (Fig. S3).

Mean ± SD age was 15 ± 2 years and 14 ± 2 years in the 2 mg kg^{-1} and 4 mg kg^{-1} groups, respectively, and mean duration of AD was 12 and 13 years, respectively (Table 1). At baseline in the phase IIa study, mean ± SD EASI was 35 ± 17 and 29 ± 15 in the 2 mg kg^{-1} and 4 mg kg^{-1} groups, respectively, and 26 ± 17 and 21 ± 18 at baseline of the OLE. Most patients had moderate-to-severe pruritus and extensive involvement of their skin surface at the phase IIa baseline. A total of 35% (2 mg kg^{-1}) and 30% (4 mg kg^{-1}) of patients had received noncorticosteroid immunosuppressants prior to baseline of the phase IIa study, including ciclosporin or azathioprine, and 25% and 20%, respectively, did not respond to noncorticosteroid immunosuppressants. Most patients had other concomitant atopic/allergic diseases, including asthma, allergic rhinitis and food allergies.

Pharmacokinetics

After a single dose, mean ± SD C_{max} was 10 ± 2 mg L^{-1} and 23 ± 9 mg L^{-1} for the 2 mg kg^{-1} and 4 mg kg^{-1} dupilumab dose groups, respectively; t_{max} was 4–8 days (Fig. 1 and Fig. S4; see Supporting Information). After pooling of the single-dose concentration data, the estimated AUC_{last} (based on the mean profile) was 104 day × mg L^{-1} and 362 day × mg L^{-1} in the 2 mg kg^{-1} and 4 mg kg^{-1} groups, respectively. In the OLE, mean dupilumab concentrations increased in a slightly greater-than-dose-proportional manner from baseline to week 48 between the 2 mg kg^{-1} and 4 mg kg^{-1} regimens, achieving mean ± SD trough dupilumab concentrations in serum (C_{trough}) of 74 ± 19 mg L^{-1} and 161 ± 60 mg L^{-1}, respectively (Figs 1 and S4).

Safety

In the phase IIa study, 50% and 65% of patients in the 2 mg kg^{-1} and 4 mg kg^{-1} dupilumab groups experienced one or more treatment-emergent adverse events (TEAEs) during part A, respectively, and 40% and 55% during part B (Table 2). Two SAEs were reported in each dose group: a 17-year-old patient in the 2 mg kg^{-1} group presented with palpitations and infected AD, and a 13-year-old patient in the 4 mg kg^{-1} group reported staphylococcal skin infection and infected AD (Table 3). None of the SAEs was considered related to study treatment, and no TEAEs led to permanent study drug discontinuation. The most frequent TEAEs were nasopharyngitis and AD exacerbation (during the period when dupilumab was not being administered). Incidences of skin infections were low; injection-site reactions were mild and occurred in one patient per group (Table 3). No conjunctivitis events were reported (Table 3).

In the OLE, nearly all adolescents reported one or more TEAE (Table 2). Three patients experienced an SAE (patent ductus arteriosus, food allergy and ankle fracture), which were not considered related to study treatment. No TEAEs led to permanent treatment discontinuation. The most common TEAEs in this study were nasopharyngitis and AD exacerbation (Table 3). The incidence of skin infections was 29% and 42% for the 2 mg kg^{-1} and 4 mg $kg^{-}1$ arms, respectively. Injection-site reactions occurred in 18% and 11% of patients, respectively, but most of these events were mild in intensity. Conjunctivitis was reported in 18% and 16% of patients in the 2 mg kg^{-1} and 4 mg kg^{-1} dose groups, respectively. No conjunctivitis events were serious, and all cases recovered/resolved during the treatment period. TEAEs of special interest included suicidal behaviour, and systemic or severe hypersensitivity, and were reported for one patient each in the 2 mg kg^{-1} group. No deaths were reported in either study.

Table 1 Baseline demographics and disease characteristics

	Phase IIa study		Phase III OLE	
	Dupilumab 2 mg kg^{-1} (n = 20)	Dupilumab 4 mg kg^{-1} (n = 20)	Dupilumab 2 mg kg^{-1} (n = 17)	Dupilumab 4 mg kg^{-1} (n = 19)
Mean ± SD age (years)	15 ± 2	14 ± 2	15 ± 2	14 ± 2
Male sex	9 (45)	9 (45)	6 (35)	11 (58)
Mean ± SD weight (kg)	53 ± 12	56 ± 13	53 ± 10	57 ± 14
Mean ± SD BMI (kg m^{-2})	20 ± 3	22 ± 4	20 ± 3	22 ± 4
Mean ± SD duration of AD (years)	12 ± 4	13 ± 2	12 ± 4	13 ± 2
Mean ± SD EASI[a]	35 ± 17	29 ± 15	26 ± 17	21 ± 18
IGA[b]				
4	12 (60)	9 (45)	5 (29)	4 (21)
3	8 (40)	11 (55)	11 (65)	11 (58)
2	0	0	1 (6)	4 (21)
Mean ± SD SCORAD[c]	68 ± 13	63 ± 14	56 ± 17	54 ± 24
Mean ± SD Peak Pruritus NRS[d]	6 ± 2	7 ± 2	5 ± 2	5 ± 3
Mean ± SD %BSA affected	52 ± 25	46 ± 25	40 ± 26	37 ± 27
Mean ± SD POEM[e]	NA	NA	15 ± 7	16 ± 8
Mean ± SD CDLQI[f]	NA	NA	9 ± 5	9 ± 8
Any previous noncorticosteroid immunosuppressants	7 (35)[a]	6 (30)[g]	4 (24)[g]	3 (16)[g]
No response to previous noncorticosteroid immunosuppressants	5 (25)[g]	4 (20)[g]	NA	NA
Any other atopic condition[h]	15 (75)	15 (75)	15 (88)	15 (79)
Allergic rhinitis	9 (45)	8 (40)	10 (59)	9 (47)
Food allergy	7 (35)	10 (50)	8 (47)	11 (58)
Asthma	6 (30)	9 (45)	7 (41)	8 (42)
Allergic conjunctivitis	5 (25)	7 (35)	6 (35)	7 (37)
Chronic rhinosinusitis	0	3 (15)	0	3 (16)
Urticaria	1 (5)	1 (5)	1 (6)	1 (5)
Other allergies	11 (55)	13 (65)	11 (65)	14 (74)

Data are n (%) unless otherwise indicated. OLE, open-label extension; BMI, body mass index; AD, atopic dermatitis; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; SCORAD, SCORing Atopic Dermatitis; NRS, Numerical Rating Scale; BSA, body surface area; POEM, Patient Oriented Eczema Measure; NA, not applicable; CDLQI, Children's Dermatology Life Quality Index. [a]Scores on the EASI range from 0 to 72, with higher scores indicating greater severity; a change of 6·6 has been estimated to be the clinically meaningful within-person change or response definition. [b]Scores on the IGA scale range from 0 to 4, with higher scores indicating greater severity; the clinically meaningful within-person change or response definition for this scale has not been determined. [c]SCORAD is a combined score of investigator-reported disease severity and affected BSA and patient-reported symptoms of itch and sleep loss; scores range from 0 to 103, with higher scores indicating greater severity. A change of 8·7 has been estimated as the clinically meaningful within-person change or response definition. [d]The peak score on the NRS for pruritus is a patient-reported measure that assesses the maximum itch intensity in the previous 24 h on a scale ranging from 0 to 10, with higher values indicating worse itching. The clinically meaningful within-person change or response definition is 4 points. [e]The POEM, a composite measure of patient-reported symptoms, including the effect of symptoms on sleep, evaluates the frequency of symptoms (including itching) and the effect of AD on sleep on a scale of 0 to 28, with higher scores indicating greater severity; the clinically meaningful within-person change or response definition is 6 points. [f]The CDLQI evaluates health-related quality of life (QoL) on a scale of 0 to 30, with higher scores indicating greater impact on QoL. The clinically meaningful within-person change or response definition is 6 points. [g]Includes azathioprine and ciclosporin. [h]Excludes AD.

Efficacy

By week 2 of the phase IIa study, EASI decreased by a mean ± SD of −34% ± 20% and −51% ± 29% after a single dose of 2 mg kg^{-1} and 4 mg kg^{-1} dupilumab, respectively (Table 4, Fig. 2a). Improvements in EASI were maintained up to week 52, with a mean ± SD reduction of −85% ± 12% and −84% ± 20% for the 2 mg kg^{-1} and 4 mg kg^{-1} groups, respectively (Table 4, Fig. 2a, Figs S5a and S6a; see Supporting Information).

The proportion of adolescents achieving EASI-50 (≥ 50% improvement from baseline in EASI) at week 12 was 70% in the 2 mg kg^{-1} group and 75% in the 4 mg kg^{-1} group, increasing in the OLE to 100% and 89%, respectively, at week 52 (Table 4, Fig. 2b). EASI-75 (≥ 75% improvement from baseline in EASI) was achieved by 55% and 40% of patients in the 2 mg kg^{-1} and 4 mg kg^{-1} groups, respectively, at week 12, increasing in the OLE to 88% and 78%, respectively, at week 52 (Table 4, Fig. 2c). The proportion of patients with IGA 0 or 1 at week 12 was 10% in the 2 mg kg^{-1} group and 35% in the 4 mg kg^{-1} group, increasing to 38% and 44%, respectively, at week 52 of the OLE (Table 4, Fig. 2d).

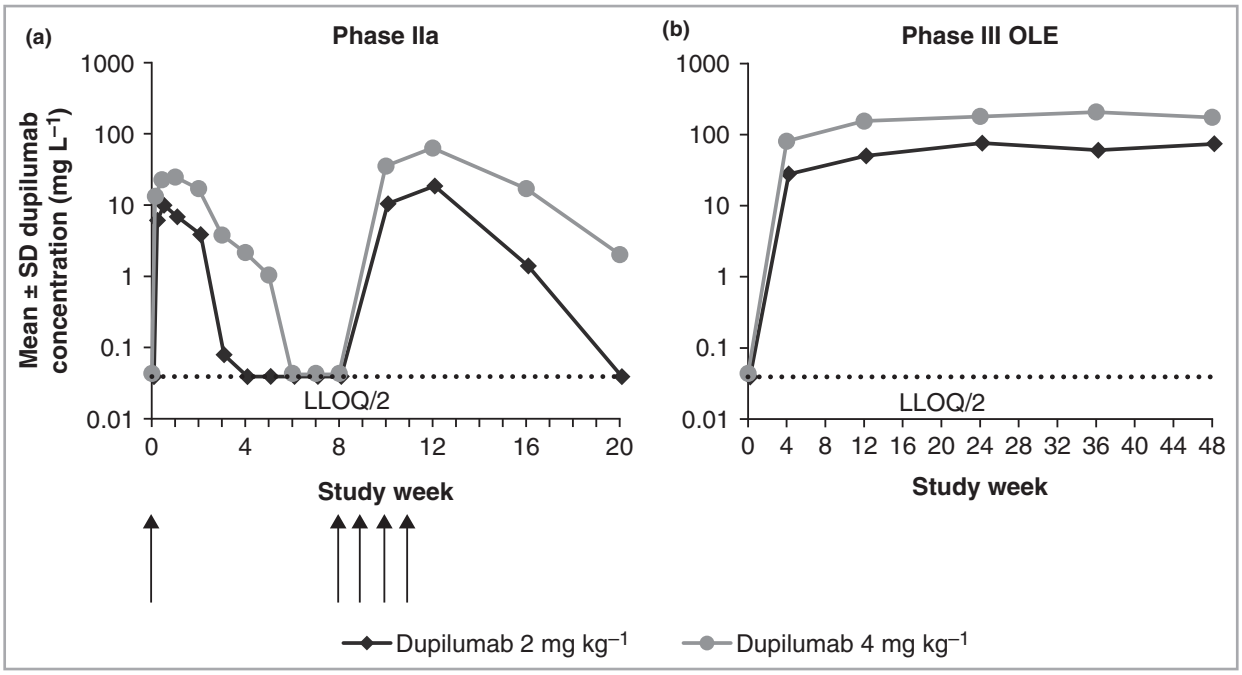

Fig 1. Mean log-scaled concentrations of dupilumab in serum vs. nominal time. (a) Concentration–time profile of the phase IIa study. Vertical arrows represent time points at which dupilumab 2 mg kg^{-1} or 4 mg kg^{-1} was administered. (b) Concentration–time profile of the phase III open-label extension (OLE). Patients in the OLE received dupilumab 2 mg kg^{-1} weekly or 4 mg kg^{-1} weekly. Linear-scale concentration–time profiles and patient numbers are shown in Figure S4 (see Supporting Information). LLOQ, lower limit of concentration.

Table 2 Overview of treatment-emergent adverse events (TEAEs)

	Phase IIa study				Phase III OLE[a]			
	Dupilumab 2 mg kg^{-1} (n = 20)		Dupilumab 4 mg kg^{-1} (n = 20)		Dupilumab 2 mg kg^{-1} (n = 17)	Dupilumab 4 mg kg^{-1} (n = 19)	Dupilumab 2 mg kg^{-1} (n = 17)	Dupilumab 4 mg kg^{-1} (n = 19)
	Part A	Part B	Part A	Part B				
TEAEs	n				n		nE/100 PY[b]	
Total TEAEs	19	16	40	31	161	253	485	718
Total serious TEAEs	1	1	1	1	3	0	9	0
Total TEAEs related to treatment	0	2	6	5	6	19	18	54
Total TEAEs related to permanent treatment discontinuation	0	0	0	0	0	0	0	0
Patients with TEAEs	n (%)				n (%)		nP/100 PY[c]	
Any TEAE	10 (50)	8 (40)	13 (65)	11 (55)	17 (100)	18 (95)	331	267
Any serious TEAE	1 (5)	1 (5)	1 (5)	1 (5)	3 (18)	0	10	0
TEAEs related to treatment	0	1 (5)	2 (10)	3 (15)	5 (29)	5 (26)	19	17
TEAEs leading to discontinuation	0	0	0	0	0	0	0	0

OLE, open-label extension; nE/100 PY, number of events per 100 patient years; nP/100PY, number of patients with ≥ 1 event per 100 patient years. [a]Includes all TEAEs reported up to the first visit when patients switched from weight-based dosing (2 mg kg^{-1} or 4 mg kg^{-1}) to a fixed dose regimen of 300 mg every 4 weeks. [b]The TEAE rate per PY was defined as the number of TEAEs divided by total PY in the TEAE period; the total PY was calculated as the sum of duration of the TEAE period in the OLE for all patients. [c]The number of patients with ≥ 1 TEAE per PY was defined as the number of patients with ≥ 1 TEAE divided by total PY among patients in the study and at risk of an initial occurrence of the event; for patients with an event, the number of PY was calculated up to the date of the first event; for patients without an event, it corresponded to the duration of the TEAE period.

Table 3 Treatment-emergent adverse event (TEAE) profile

	Phase IIa study				Phase III OLE[a]			
	Dupilumab 2 mg kg^{-1} (n = 20)		Dupilumab 4 mg kg^{-1} (n = 20)		Dupilumab 2 mg kg^{-1} (n = 17)	Dupilumab 4 mg kg^{-1} (n = 19)	Dupilumab 2 mg kg^{-1} (n = 17)	Dupilumab 4 mg kg^{-1} (n = 19)
	Part A	Part B	Part A	Part B				
Patients with TEAEs	n (%)				n (%)		nP/100 PY[b]	
Any infection (SOC)	3 (15)	4 (20)	8 (40)	6 (30)	14 (82)	17 (89)	100	136
Skin infection	0	1 (5)	3 (15)	3 (15)	5 (29)	8 (42)	18	34
Nonherpetic skin infections[c]	0	1 (5)	3 (15)	3 (15)	3 (18)	4 (21)	10	13
Herpes viral infections (HLT)[d]	0	0	1 (5)	1 (5)	3 (18)	4 (21)	10	14
Injection-site reactions (HLT)[e]	0	1 (5)	1 (5)	0	3 (18)	2 (11)	10	6
Conjunctivitis[f]	0	0	0	0	3 (18)	3 (16)	10	9
Most common TEAEs (PT)[g]								
Nasopharyngitis	1 (5)	2 (10)	6 (30)	4 (20)	7 (41)	9 (47)	28	37
Dermatitis atopic	2 (10)	0	3 (15)	1 (5)	5 (29)	8 (42)	18	27
Headache	1 (5)	1 (5)	0	1 (5)	6 (35)	5 (26)	24	16
Oropharyngeal pain	0	1 (5)	0	0	4 (24)	5 (26)	14	16
Tonsillitis	0	0	0	0	1 (6)	5 (26)	3	16
URTI	1 (5)	1 (5)	1 (5)	0	4 (24)	4 (21)	13	13
Diarrhoea	0	0	1 (5)	0	4 (24)	4 (21)	14	13
Oral herpes	0	0	0	0	3 (18)	4 (21)	10	14
Cough	0	0	1 (5)	1 (5)	4 (24)	2 (11)	13	6
Vomiting	1 (5)	0	0	2 (10)	3 (18)	2 (11)	11	6
Pyrexia	2 (10)	1 (5)	0	0	2 (12)	2 (11)	7	6
Rhinitis allergic	2 (10)	0	0	0	3 (18)	1 (5)	11	3
Dermatitis infected	0	1 (5)	2 (10)	2 (10)	0	1 (5)	0	3

OLE, open-label extension; nP/100PY, number of patients with ≥1 event per 100 patient-years; SOC, Medical Dictionary for Regulatory Activities (MedDRA) system organ class; HLT, MedDRA high level term; PT, MedDRA preferred term; URTI, upper respiratory tract infection. [a]Includes all TEAEs reported up to the first visit when patients switched from weight-based dosing (2 mg kg^{-1} or 4 mg kg^{-1}) to a fixed dose regimen of 300 mg every 4 weeks. [b]The number of patients with ≥ 1 TEAE per PY was defined as the number of patients with ≥ 1 TEAE divided by total PY among patients in the study and at risk of an initial occurrence of the event; for patients with an event, the number of PY was calculated up to the date of the first event; for patients without an event, it corresponded to the duration of the TEAE period. [c]Includes MedDRA PTs angular cheilitis, bacterial disease carrier, dermatitis infected, folliculitis, hordeolum, molluscum contagiosum, skin bacterial infection, staphylococcal skin infections and tinea infections. [d]Includes MedDRA PTs herpes simplex, nasal herpes and oral herpes. [e]Includes MedDRA PTs injection-site oedema, injection-site haemorrhage, injection-site induration, injection-site irritation, injection-site mass and injection-site swelling. [f]Includes MedDRA PTs conjunctivitis, conjunctivitis allergic and conjunctivitis bacterial. [g]Includes all MedDRA PTs reported in ≥ 10% or ≥ 20% of patients in any treatment group of the phase IIa study or phase III OLE, respectively.

The mean ± SD reduction in Peak Pruritus NRS from baseline to week 12 was −31% ± 68% and −38% ± 34% for the 2 mg kg^{-1} and the 4 mg kg^{-1} groups, respectively, and −68% ± 22% and −66% ± 25% by week 52 (Table 5, Fig. 2e). The proportions of patients who achieved ≥ 3 point improvement in Peak Pruritus NRS at week 12 of the phase IIa and week 52 of the phase III OLE, respectively, were 50% and 75%, respectively, for the 2 mg kg^{-1} group and 45% and 78%, respectively, for the 4 mg kg^{-1} group (Table 5, Fig. 2f). A ≥ 4 point improvement in Peak Pruritus NRS was achieved by 40% of adolescents in both treatment groups at week 12 and increased to 69% for the 2 mg kg^{-1} group and 72% for the 4 mg kg^{-1} group at week 52 (Table 5).

Sustained improvements were also seen in EASI-90 (≥ 90% improvement from baseline in EASI), SCORAD and %BSA in both studies (Tables 4 and 5, Figs. S5b and S6b,c). Moreover, the frequency of symptoms and QoL, as assessed by the Patient Oriented Eczema Measure and Children's Dermatology Life Quality Index, respectively, in the OLE, showed improvements by week 12, which were maintained up to week 52 (Fig. S6d,e).

Concomitant medication

Overall, 85% and 65% of patients in the 2 mg kg^{-1} and 4 mg kg^{-1} dupilumab groups of the phase IIa study, respectively, used TCS as concomitant medication (Table S2; see Supporting Information). The most commonly used TCS in both treatment arms was potent (group III). TCIs were used by 55% and 30% of adolescents in the 2 mg kg^{-1} and 4 mg kg^{-1} groups, respectively.

In the OLE, 65% and 74% of adolescents in the 2 mg kg^{-1} and 4 mg kg^{-1} groups, respectively, used TCS, with most using potent (group III) TCS (Table S2). TCI use was 41% and 16% in the in the 2 mg kg^{-1} and 4 mg kg^{-1} groups, respectively.

Table 4 Efficacy results [Investigator's Global Assessment (IGA)/Eczema Area and Severity Index (EASI) end points]

	Dupilumab 2 mg kg^{-1}					Dupilumab 4 mg kg^{-1}				
	Phase IIa study (n = 20)		Phase III OLE (n = 17)			Phase IIa study (n = 20)		Phase III OLE (n = 19)		
	Week 2	Week 12	Baseline	Week 16	Week 52	Week 2	Week 12	Baseline	Week 16	Week 52
Mean ± SD EASI	23 ± 14	12 ± 13	26 ± 17	7 ± 7	4 ± 4	16 ± 16	11 ± 15	21 ± 18	6 ± 8	5 ± 8
Mean ± SD EASI, % change from baseline of phase IIa study, n	−34 ± 20, 19	−66 ± 29, 19	−19 ± 37, 17	−81 ± 15, 17	−85 ± 12, 16	−51 ± 29, 20	−70 ± 24, 19	−37 ± 30, 19	−82 ± 20, 19	−84 ± 20, 18
Patients achieving EASI-50 from baseline of phase IIa study	4/20 (20)	14/20 (70)	4/17 (24)	17/17 (100)	16/16 (100)	13/20 (65)	15/20 (75)	7/19 (37)	18/19 (95)	16/18 (89)
Patients achieving EASI-75 from baseline of phase IIa study	1/20 (5)	11/20 (55)	1/17 (6)	12/17 (71)	14/16 (88)	6/20 (30)	8/20 (40)	1/19 (5)	13/19 (68)	14/18 (78)
Patients achieving EASI-90 from baseline of phase IIa study	0/20	4/20 (20)	1/17 (6)	6/17 (35)	7/16 (44)	1/20 (5)	5/20 (25)	1/19 (5)	10/19 (53)	11/18 (61)
Patients achieving IGA 0 or 1 from baseline of phase IIa study	0/20	2/20 (10)	0/17	6/17 (35)	6/16 (38)	2/20 (10)	7/20 (35)	0/19	9/19 (47)	8/18 (44)

Data are n (%) unless otherwise indicated. OLE, open-label extension; EASI-50/-75/-90, ≥ 50%/≥ 75%/≥ 90% improvement from baseline in EASI.

Rescue medication

Five adolescents in the phase IIa study received rescue medication (four in the 2 mg kg^{-1} dupilumab group and one in the 4 mg kg^{-1} dupilumab group). Only one adolescent in the 2 mg kg^{-1} group of the OLE received rescue treatment (systemic corticosteroids).

Discussion

The phase IIa study and phase III OLE were the earliest studies of dupilumab in adolescents to characterize its PK and long-term safety and efficacy profile. The results from these studies support use of dupilumab for the long-term management of moderate-to-severe AD in adolescents. The PK profile was characterized by nonlinear, target-mediated kinetics, consistent with the profile in adults with moderate-to-severe AD.[31] A better assessment of attainment of steady state was obtained in the OLE, where the 2 mg kg^{-1} and 4 mg kg^{-1} weekly regimens led to a mean steady-state C_{trough} similar to that reported for the 300 mg every 2 weeks (≈75 mg L^{-1}) and weekly (≈180 mg L^{-1}) regimens in adults, respectively.[32] The trend toward linear, dose-proportional kinetics of C_{trough} between the 2 mg kg^{-1} and 4 mg kg^{-1} weekly regimens in the OLE provides support for selection of these phase III dose levels and exposures and is indicative of saturating the target-mediated pathway (i.e. the minimum condition needed for optimal efficacy). The slightly greater-than-dose-proportionality in C_{trough} between the 2 mg kg^{-1} and 4 mg kg^{-1} weekly regimens suggests that there is likely a greater proportion of patients achieving saturation of the target-mediated pathway at 4 mg kg^{-1} vs. 2 mg kg^{-1}.

No new safety signals were observed in adolescents with moderate-to-severe AD, compared with the known safety profile of dupilumab in adults with moderate-to-severe AD.[17–21] Although 4 mg kg^{-1} dupilumab was associated with more TEAEs than 2 mg kg^{-1} during the phase IIa study, the incidence of TEAEs was comparable between the two treatment groups in the OLE. None of the SAEs observed in either of the studies was deemed to be related to dupilumab. Skin infections were reported for both treatment groups, with a higher incidence for the 4 mg kg^{-1} dose in both studies. However, studies in adults showed that dupilumab is associated with reduced risk of skin infections vs. placebo and does not increase overall infection rates vs. placebo in patients with AD.[17–21] Injection-site reactions and conjunctivitis AEs were mild to moderate and did not lead to treatment discontinuation. The most common AEs were AD exacerbation and infected AD. AD exacerbation may have resulted from insufficient treatment, as it occurred several weeks after receiving a single dose of dupilumab in the phase IIa study. The OLE showed that the safety profile associated with long-term treatment (up to 52 weeks) with dupilumab in adolescents is consistent with that seen with short-term treatment (up to 16 weeks).

The phase IIa study provided preliminary evidence of dupilumab efficacy in adolescents, with early improvements in

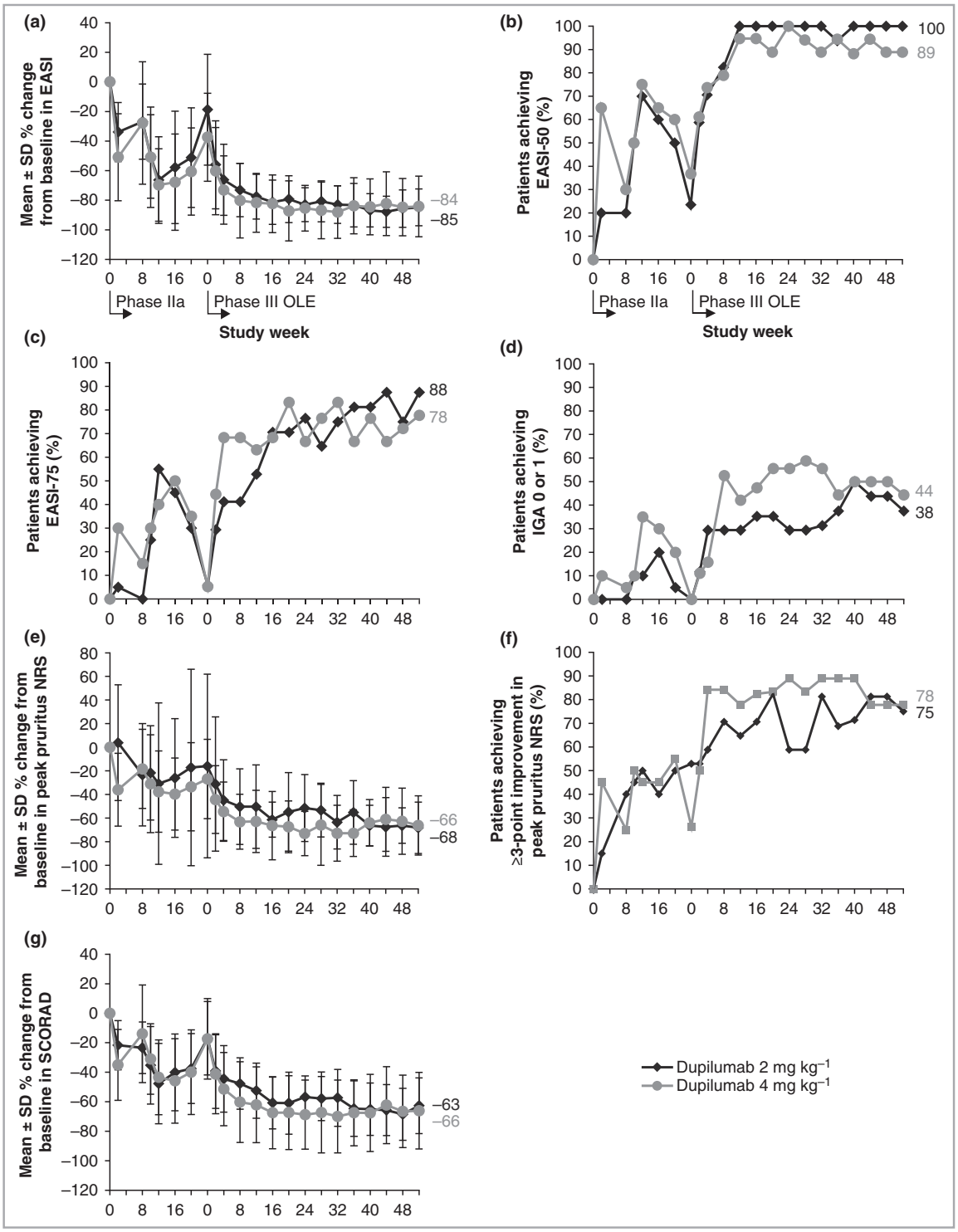

Fig 2. Efficacy end points. (a) Percentage change in Eczema Area and Severity Index (EASI) from baseline of the phase IIa study to week 52 of the phase III open-label extension (OLE). (b) Proportion of patients achieving EASI-50 (≥50% improvement from baseline) from the baseline of the phase IIa study to week 52 of the phase III OLE. (c) Proportion of patients achieving EASI-75 (≥ 75% improvement from baseline in EASI) from the baseline of the phase IIa study to week 52 of the phase III OLE. (d) Proportion of patients achieving Investigator's Global Assessment (IGA) scores of 0 or 1 from the baseline of the phase IIa study to week 52 of the phase III OLE. (e) Percentage change in Peak Pruritus Numerical Rating Scale (NRS) from the baseline of the phase IIa study to week 52 of the phase III OLE. (f) Proportion of patients achieving a reduction of ≥ 3 points in Peak Pruritus NRS from the baseline of the phase IIa study to week 52 of the phase III OLE. (g) Percentage change in SCORing Atopic Dermatitis (SCORAD) from the baseline of the phase IIa study to week 52 of the phase III OLE.

Table 5 Efficacy results (other end points)

	Dupilumab 2 mg kg^{-1}					Dupilumab 4 mg kg^{-1}				
	Phase IIa study (n = 20)		Phase III OLE (n = 17)			Phase IIa study (n = 20)		Phase III OLE (n = 19)		
	Week 2	Week 12	Baseline	Week 16	Week 52	Week 2	Week 12	Baseline	Week 16	Week 52
Mean ± SD Peak Pruritus NRS	6 ± 2	3 ± 2	5 ± 2	2 ± 1	2 ± 1	4 ± 2	4 ± 3	5 ± 3	2 ± 2	2 ± 2
Mean ± SD Peak Pruritus NRS % change from baseline of phase IIa study, n	4 ± 49, 19	−31 ± 68, 19	−16 ± 78, 17	−61 ± 15, 17	−68 ± 22, 16	−36 ± 31, 20	−38 ± 34, 19	−27 ± 34, 19	−66 ± 29, 17	−66 ± 25, 18
Patients achieving Peak Pruritus NRS improvement of ≥3 points from baseline of phase IIa study	3/20 (15)	10/20 (50)	9/17 (53)	12/17 (71)	12/16 (75)	9/20 (45)	9/20 (45)	5/19 (26)	14/17 (82)	14/18 (78)
Patients achieving Peak Pruritus NRS improvement of ≥ 4 points from baseline of phase IIa study	2/20 (10)	8/20 (40)	5/17 (29)	10/17 (59)	11/16 (69)	7/20 (35)	8/20 (40)	4/19 (21)	13/17 (76)	13/18 (72)
Mean ± SD SCORAD	54 ± 15	35 ± 19	56 ± 17	27 ± 15	25 ± 14	41 ± 21	35 ± 20	54 ± 24	21 ± 17	23 ± 17
Mean ± SD SCORAD, % change from baseline of phase IIa study, n	−22 (17), 19	−48 (27), 19	−17 (25), 17	−61 (18), 17	−63 (19), 16	−35 (24), 20	−43 (25), 19	−17 (27), 19	−67 (24), 19	−66 (26), 18
Mean ± SD %BSA	41 ± 24	22 ± 24	40 ± 26	14 ± 15	8 ± 10	33 ± 26	20 ± 24	37 ± 27	15 ± 20	9 ± 11
Mean ± SD %BSA, change from baseline of phase IIa study, n	−13 ± 16, 19	−29 ± 21, 19	−12 ± 24, 17	−39 ± 21, 17	−44 ± 24, 16	−13 ± 15, 20	−25 ± 21, 19	−13 ± 14, 19	−34 ± 23, 19	−42 ± 25, 18

Data are n (%) unless otherwise indicated. OLE, open-label extension; NRS, Numerical Rating Scale; SCORAD, SCORing Atopic Dermatitis; BSA, body surface area.

EASI and Peak Pruritus NRS after a single dose of dupilumab. There was no clear dose response, as the two dose regimens provided comparable response on most end points, except for IGA 0 or 1; a higher proportion of adolescents achieved IGA of 0 or 1 in the 4 mg kg^{-1} cohort than in the 2 mg kg^{-1} cohort. Most of these patients continued to receive dupilumab in the OLE, and improvements were maintained for up to 52 weeks of treatment. With continuous treatment in the OLE, there was a further reduction in disease severity on multiple domains, including intensity and extent of signs, symptoms (e.g. pruritus) and QoL.

Although the effect of dupilumab in atopic/allergic comorbidities was not analysed in these studies, dupilumab-mediated improvements were observed in comorbid type 2 conditions like asthma, allergic rhinitis and food/aero-allergies in the phase III adolescent study.[33] This, together with the high rates of atopic/allergic comorbidities in both adolescent patient populations, support the underlying role of IL-4/IL-13-driven type 2 inflammation in these diseases. Although the safety and efficacy results are generally consistent with previous studies of dupilumab in adults with AD, they should be interpreted with caution as the populations presented here were small. Moreover, there was no placebo arm, and the studies were open-label. Patients were not randomized to the two dupilumab dose regimens at the start of the phase IIa study. As noted, concomitant use of TCS was allowed, but not standardized, in the phase IIa study and the OLE, which may have confounded efficacy measurements. In addition, patients receiving repeated dosing had already been exposed to dupilumab (i.e. were not treatment naïve), which may have influenced outcomes in both studies. As the number of patients included in the study was small and efficacy was not the primary objective, P-values vs. baseline were not reported. Finally, it should be noted that although the exposure with the 2 mg kg^{-1} weekly regimen was comparable to that in adolescents treated with the every-two-weeks regimen in the phase III study (Simpson *et al.* submitted for publication), the regimens used in the phase IIa and OLE studies were not the actual currently approved every-two-weeks regimen in the adolescent patient population.

In summary, in adolescents with moderate-to-severe AD, dupilumab exhibited a PK profile similar to adults. Findings from the OLE support the long-term safety and efficacy of dupilumab in adolescents with moderate-to-severe AD, extending and reinforcing the findings from a randomized, double-blind, placebo-controlled phase III trial (NCT03054428) and recently published case series (Simpson *et al.* submitted for publication).[33,34]

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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 Conflicts of interest.

Appendix S2 Study investigators, inclusion criteria for the phase IIa study, exclusion criteria for the phase IIa study, inclusion criteria for the phase III open-label extension, exclusion criteria for the phase III open-label extension, rescue treatment, prohibited medications and procedures, and primary and secondary end points.

Fig S1. Phase IIa study design per original protocol.

Fig S2. Study flow diagram of the phase IIa study and phase III open-label extension.

Fig S3. CONSORT diagram of patient disposition.

Fig S4. Mean concentration of dupilumab in serum vs. nominal time.

Fig S5. Additional efficacy end points of the phase IIa study and phase III open-label extension.

Fig S6. Additional efficacy end points of the phase III open-label extension study.

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

Table S2. Concomitant medication use.