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ORIGINAL RESEARCH

Dupilumab Safety and Efficacy in a Phase III Open-Label Extension Trial in Children 6–11 Years of Age with Severe Atopic Dermatitis

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ABSTRACT

Background: For children aged 6–11 years with uncontrolled severe atopic dermatitis (AD), 16 weeks of treatment with dupilumab resulted in substantial clinical benefit compared with placebo with an acceptable safety profile. However, longer-term safety and efficacy data are important to inform longitudinal AD management.

Objectives: This analysis of data from an open-label extension study (LIBERTY AD PED-OLE, NCT02612454) reports the long-term safety, efficacy, and pharmacokinetics of dupilumab in children with severe AD who had participated in the pivotal dupilumab LIBERTY AD PEDS study (NCT03345914).

Methods: Enrolled patients initially received subcutaneous dupilumab 300 mg every 4 weeks (q4w). The q4w regimen could be uptitrated to dupilumab dose regimens of 200 or 300 mg every 2 weeks (q2w; for body weight < 60 or ≥ 60 kg, respectively) for patients who did not achieve an Investigator's Global Assessment (IGA) score of 0/1 (clear/almost clear skin) at

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week 16, or prior to week 16 as rescue treatment. Additional patients were uptitrated to a weight-tiered q2w regimen following a protocol amendment. Patients who maintained an IGA score of 0/1 continuously for a 12-week period after week 40 discontinued dupilumab. They were monitored for relapse and were reinitiated on dupilumab if required.

Results: Data for 321 patients (mean age 8.6 years) were analyzed, 254 (79%) of whom had completed the scheduled 52-week visit at the database lock. Most treatment-emergent adverse events were mild/moderate. By week 52, 41% of patients achieved an IGA score of 0/1, and 97%, 82%, and 50%, respectively, had at least a 50%, 75%, and 90% improvement from the parent study baseline in Eczema Area and Severity Index (EASI). By week 52, 29% of patients in the overall population had clear/almost clear skin sustained for 12 weeks and had stopped medication; of these, 40% relapsed and were subsequently reinitiated on treatment, with a mean time to reinitiation of 13.5 (standard deviation 5.2) weeks. Following reinitiation of dupilumab, 41% of the patients with evaluable data at the time of database lock had regained an IGA 0/1 clinical response.

Conclusions: Consistent with results seen in adults and adolescents, long-term treatment with dupilumab in children aged 6–11 years with severe AD showed an acceptable safety profile and incremental clinical benefit. A substantial proportion of children who stopped dupilumab treatment after achieving clear/almost clear skin subsequently experienced disease recurrence, and required reinitiation of dupilumab, suggesting that continuous treatment may be necessary for maintenance of clinical benefit.

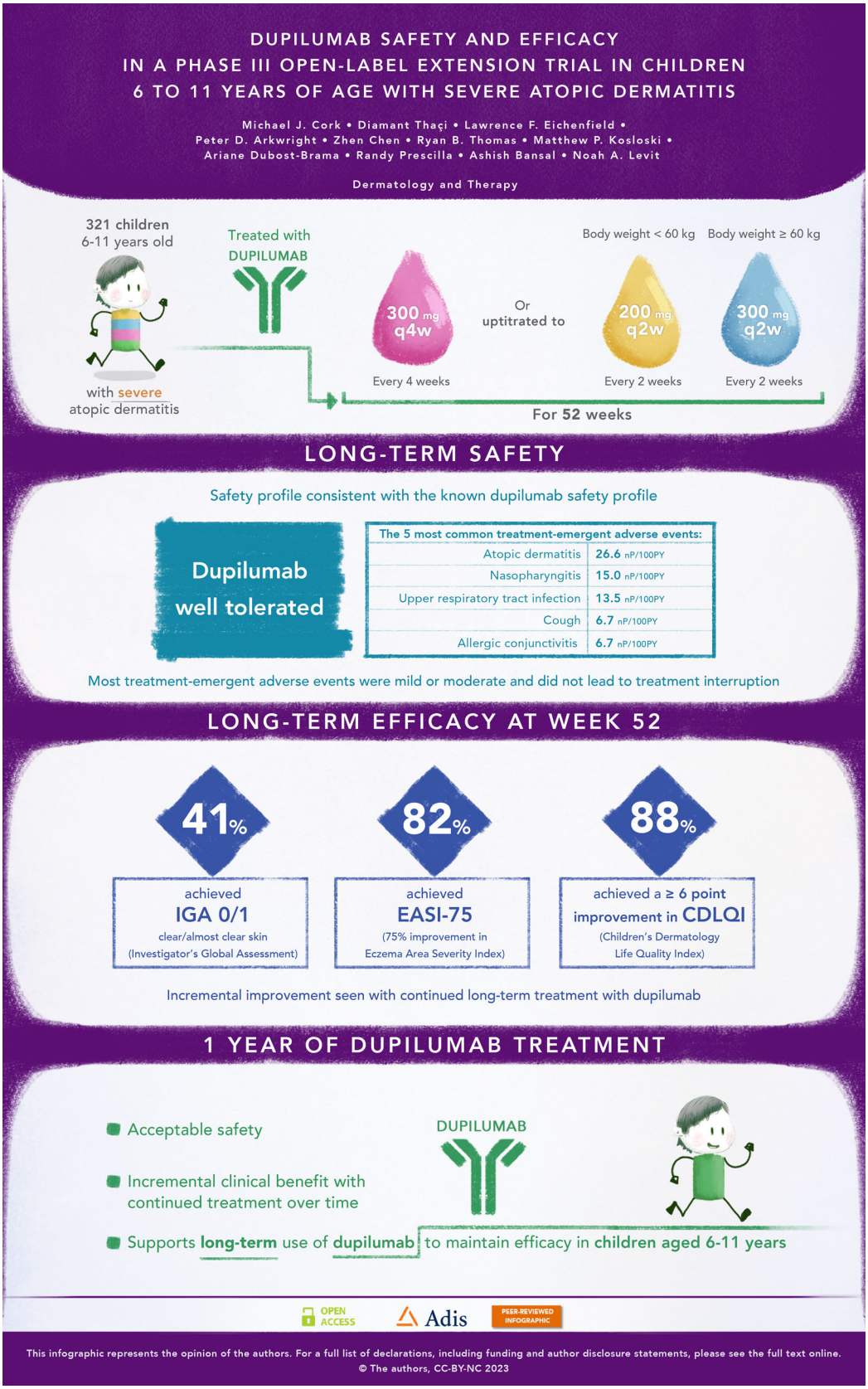
Trial Registration: ClinicalTrials.gov Identifier NCT02612454.

PLAIN LANGUAGE SUMMARY

Atopic dermatitis (AD) is a chronic disease that causes recurrent inflamed and rough skin rashes with itching and often soreness. In children with AD, treatment with a medication called dupilumab has shown improvements in their disease and quality of life. But most clinical trials of dupilumab in children have only lasted for 16 weeks. We investigated the effect of dupilumab in children treated for a longer time. The 321 children (aged 6–11 years) who were included in this study had taken part in a clinical trial of dupilumab because they had severe AD. They were treated with either dupilumab or a placebo (a dummy treatment) for 16 weeks. When that trial ended, they were then all treated with dupilumab for up to a year. Their average AD severity continued to get steadily better over a year of extended treatment, with almost all children reaching 50% skin improvement compared with their AD before treatment. Many children reached a point where their skin was clear or almost clear of AD for a period, and following the rules of the study they stopped taking dupilumab. In many of them, their AD slowly returned without treatment. But if they started to take dupilumab again, their AD improved, and some could even achieve skin clearance again. Over the longer term, the safety of dupilumab was similar to what was seen with short-term treatment. This study showed that children with AD aged 6–-11 years benefited from receiving dupilumab for a longer period of time.

Keywords: Atopic dermatitis; Children; Dupilumab; Eczema; Efficacy; Long-term; Open-label; Pediatric; Quality of life; Safety

Infographic:


DUPILUMAB SAFETY AND EFFICACY
IN A PHASE III OPEN-LABEL EXTENSION TRIAL IN CHILDREN
6 TO 11 YEARS OF AGE WITH SEVERE ATOPIC DERMATITIS
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Dermatology and Therapy
321 children
6-11 years old
with severe
atopic dermatitis
Treated with
DUPILUMAB
300 mg
q4w
Every 4 weeks
Or
uptitrated to
Body weight < 60 kg
200 mg
q2w
Every 2 weeks
Body weight ≥ 60 kg
300 mg
q2w
Every 2 weeks
For 52 weeks
LONG-TERM SAFETY
Safety profile consistent with the known dupilumab safety profile
Dupilumab
well tolerated
The 5 most common treatment-emergent adverse events:
Atopic dermatitis 26.6 nP/100PY
Nasopharyngitis 15.0 nP/100PY
Upper respiratory tract infection 13.5 nP/100PY
Cough 6.7 nP/100PY
Allergic conjunctivitis 6.7 nP/100PY
Most treatment-emergent adverse events were mild or moderate and did not lead to treatment interruption
LONG-TERM EFFICACY AT WEEK 52
41%
achieved
IGA 0/1
clear/almost clear skin
(Investigator's Global Assessment)
82%
achieved
EASI-75
(75% improvement in
Eczema Area Severity Index)
88%
achieved a ≥ 6 point
improvement in CDLQI
(Children's Dermatology
Life Quality Index)
Incremental improvement seen with continued long-term treatment with dupilumab
1 YEAR OF DUPILUMAB TREATMENT
Acceptable safety
Incremental clinical benefit with
continued treatment over time
DUPILUMAB
Supports long-term use of dupilumab to maintain efficacy in children aged 6-11 years
OPEN ACCESS
Adis
PEER-REVIEWED INFOGRAPHIC
This infographic represents the opinion of the authors. For a full list of declarations, including funding and author disclosure statements, please see the full text online.
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Key Summary Points

For children with uncontrolled severe atopic dermatitis (AD), 16 weeks of treatment with dupilumab has proven efficacious, with an acceptable safety profile. However, long-term safety and efficacy data are important to inform the longitudinal management of chronic diseases such as AD.

This was an analysis of data from a long-term open-label extension study in children with severe AD aged 6–11 years. In children who had previously participated in a 16-week study, dupilumab treatment for up to 52 weeks, administered every 4 weeks or uptitrated to a weight-tiered dose regimen every 2 weeks, had an acceptable safety profile and provided sustained clinical benefits in reducing AD signs and symptoms, together with improvements in the health-related quality of life of patients.

The long-term phase III study design permitted uptitration from every 4 weeks to every 2 weeks, and also allowed for patients with sustained improvement to discontinue therapy. A substantial proportion of the patients who stopped dupilumab treatment experienced AD recrudescence, and uptitration was observed to benefit many patients. Together, this supports continuous dupilumab use to maintain efficacy.

DIGITAL FEATURES

This article is published with digital features, including an infographic and video abstract to facilitate understanding of the article. To view digital features for this article, go to https://doi.org/10.6084/m9.figshare.23857263.

INTRODUCTION

Atopic dermatitis (AD) is the most common inflammatory skin condition in children [1]. An international epidemiologic study performed across 18 countries estimated the prevalence of diagnosed AD in children aged 6–11 years to be about 13%, which was severe in up to 15% of cases [2]. AD has a substantial negative impact on the health-related quality of life (HRQoL) of both affected children and their families [3].

Dupilumab is a fully human, VelocImmune®-derived [4, 5] monoclonal antibody that blocks the shared receptor component for interleukin (IL)-4 and IL-13, inhibiting signaling of both IL-4 and IL-13 [6, 7], which are key drivers of type 2-mediated inflammation in multiple diseases [6, 8, 9]. Dupilumab is approved for pediatric patients aged ≥ 6 months with moderate-to-severe AD, and in pediatric populations with other type 2 conditions, such as asthma and eosinophilic esophagitis [10, 11]. Dupilumab has demonstrated significant efficacy and an acceptable safety profile in clinical trials [12–22].

For children aged 6–11 years with severe AD inadequately controlled by topical therapies, the available treatment options are limited, resulting in an unmet clinical need [23]. However, on the basis of the results from the LIBERTY AD PEDS trial (NCT03345914) [24], dupilumab was approved for use in this patient population [10, 11]. The weight-based dupilumab dose regimen approved by the US Food and Drug Administration (FDA) for children and adolescents with AD aged 6–17 years is 300 mg every 4 weeks (q4w) following an initial 600 mg dose (for body weight 15 to < 30 kg), 200 mg every 2 weeks (q2w) following an initial 400 mg dose (for body weight 30 to < 60 kg), or 300 mg q2w following an initial 600 mg dose (for body weight ≥ 60 kg) [10]. In Europe, dupilumab is approved for children aged 6–11 years with AD at a dose of 300 mg q4w following two initial 300 mg doses administered 2 weeks apart for patients with body weight 15 to < 60 kg and may be increased to 200 mg q2w based on physician's assessment [11].

In adolescents (aged ≥ 12 to < 18 years) with uncontrolled moderate-to-severe AD, 52 weeks of treatment with dupilumab provided an incremental clinical benefit with continued treatment over time, with a high proportion of patients benefiting from uptitration from q4w to q2w dosing [25]. Long-term data describing the safety and efficacy of the continuous use of dupilumab in children with AD aged 6–11 years are important to inform longitudinal disease management. An analysis that included a small subset of children aged 6–11 years who received dupilumab 2 mg/kg or 4 mg/kg in a phase IIa study, and subsequently continued dupilumab treatment in an open-label extension (OLE) study (2 mg/kg or 4 mg/kg weekly), showed early improvement in AD signs and symptoms, with results being maintained for up to 1 year of therapy [26]. However, long-term data on the approved dupilumab dose regimens in children aged 6–11 years are currently lacking. Additionally, data for children aged 6–11 years who are initiated on the q4w dupilumab dose regimen and then uptitrated to a more frequent q2w regimen have not been previously published. Moreover, it is unknown whether the continuous use of dupilumab over a long period can lead to sustained remission of skin lesions off-treatment in this age group.

The objective of this analysis is to report the long-term safety and efficacy, and pharmacokinetic (PK) profile, of dupilumab in children (aged 6–11 years) with severe AD, who had previously participated in the pivotal LIBERTY AD PEDS (NCT03345914) dupilumab trial and were subsequently enrolled in the LIBERTY AD PED-OLE study (NCT02612454). This analysis also examined whether an additional benefit was observed in patients who were uptitrated from the initial q4w dose regimen in LIBERTY AD PED-OLE to a weight-tiered q2w regimen. In addition, we examined whether there was disease relapse following discontinuation of treatment in patients who sustained clear or almost clear skin for 3 months at or beyond 40 weeks of open-label dupilumab treatment.

METHODS

Study Design

LIBERTY AD PED-OLE (NCT02612454) is an ongoing phase III OLE study in patients aged ≥ 6 months to < 18 years with moderate-to-severe AD who participated in dupilumab parent studies. LIBERTY AD PED-OLE consisted of a screening period (day −28 to day −1) between exit from the parent study and entry into the OLE study, a treatment period that lasted until regulatory approval of the product for the age group of the patient in their geographic region (or 5 years in patients aged 6–-11 years from March 2020 according to Protocol Amendment 4), and a 12-week follow-up period. Results are presented here, through week 52, for patients aged 6–11 years who had previously participated in the LIBERTY AD PEDS dupilumab trial and had severe AD at randomization for the parent study. The data cutoff date was 1 July 2020.

The full study design, and safety and efficacy results from the LIBERTY AD PEDS parent study have been previously reported [24]. Briefly, in LIBERTY AD PEDS, patients with severe AD were randomized 1:1:1 to placebo, dupilumab 300 mg q4w with a 600 mg loading dose, or a weight-tiered dupilumab regimen (100 mg q2w with loading dose 200 mg for body weight < 30 kg, or 200 mg q2w with loading dose 400 mg for body weight ≥ 30 kg) for 16 weeks.

Main Inclusion and Exclusion Criteria

Children (aged 6–11 years at the time of screening for the OLE study) who had previously participated in the LIBERTY AD PEDS dupilumab trial were eligible for inclusion in this analysis. The full inclusion and exclusion criteria for LIBERTY AD PEDS have been previously published [24]. Patients who had a serious adverse event (SAE) during the parent study that was deemed related to the study drug, or an adverse event (AE) related to the study drug that led to discontinuation from the parent study, were excluded from the OLE. See Appendix S1

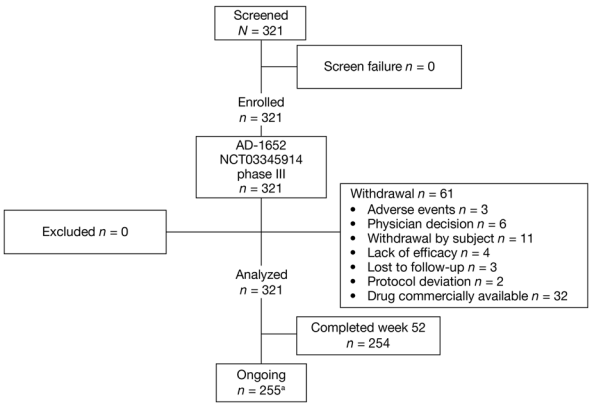

Fig. 1 Patient disposition. [a]Of the 260 patients who did not withdraw from the study, 255 were ongoing at the time of the database lock, and 5 had completed the study

in the Electronic Supplementary Material (ESM) for the full inclusion and exclusion criteria for LIBERTY AD PED-OLE.

Treatment

As per the LIBERTY AD PED-OLE protocol, patients aged 6–11 years who met the eligibility criteria and had received either dupilumab or placebo in the parent study were started on dupilumab 300 mg q4w on day 1 of the OLE study. Patients who did not achieve an Investigator's Global Assessment (IGA) score of 0/1 (clear/almost clear skin) within at least 16 weeks from the date of initiation of treatment with the 300 mg q4w regimen were uptitrated to a weight-tiered q2w regimen of 200 mg q2w (for body weight < 60 kg) or 300 mg q2w (for body weight ≥ 60 kg) from week 16, or prior to week 16 as rescue treatment at the discretion of the treating physician. Additionally, following finalization of Protocol Amendment 4 in March 2020, all remaining patients with body weight ≥ 30 to < 60 kg or ≥ 60 kg who were still receiving the 300 mg q4w regimen were moved to the relevant weight-tiered regimen of 200 mg or 300 mg q2w, respectively. Patients with body weight ≥ 15 to < 30 kg remained on the 300 mg q4w regimen (unless previously uptitrated). Once patients had been uptitrated to a q2w regimen, they continued on this dose frequency throughout the remainder of the study.

Table 1 Patient demographics and clinical characteristics at baseline of open-label extension

Characteristic	All patients ($N = 321$)
Age, years	8.6 ± 1.7
Sex, male	159 (49.5)
Country	
Canada	14 (4.4)
Czech Republic	10 (3.1)
Germany	7 (2.2)
Poland	85 (26.5)
UK	12 (3.7)
USA	193 (60.1)
Race	
White	230 (71.7)
Black or African American	51 (15.9)
Asian	25 (7.8)
American Indian or Alaska Native	1 (0.3)
Other	12 (3.7)
Not reported	2 (0.6)
Ethnicity	
Not Hispanic or Latino	288 (89.7)
Hispanic or Latino	33 (10.3)
Weight, kg	31.4 ± 8.6
Weight group	
< 30 kg	154 (48.0)
≥ 30 kg	167 (52.0)
BMI, kg/m^2	17.7 ± 3.0
BMI $\geq$ 85th percentile of population	87 (27.1)
Duration of AD, years	7.4 ± 2.2
IGA (0–4)	
0	7 (2.2)
1	55 (17.1)
2	113 (35.2)
3	89 (27.7)

Table 1 continued

Characteristic	All patients (N = 321)
4	57 (17.8)
EASI (range 0–72)	14.5 ± 15.1
% BSA affected by AD (range 0–100%)	26.9 ± 24.8
SCORAD (0–103)	40.0 ± 21.8
CDLQI (0–30)	6.8 ± 6.6
Patients with current history of allergic/atopic conditions excluding AD	321 (100.0)
Food allergy	206 (64.2)
Allergic rhinitis	190 (59.2)
Asthma	148 (46.1)
Allergic conjunctivitis	37 (11.5)
Hives	32 (10.0)
Chronic rhinosinusitis	8 (2.5)
Eosinophilic esophagitis	2 (0.6)
Aspirin sensitivity	1 (0.3)
Nasal polyps	1 (0.3)
Other allergies	199 (62.0)
Patients receiving prior systemic medications for AD	183 (57.0)
Patients receiving prior systemic corticosteroids	128 (39.9)
Patients receiving prior systemic nonsteroidal immunosuppressants	159 (49.5)
Cyclosporine	78 (24.3)
Methotrexate	29 (9.0)
Azathioprine	7 (2.2)
Mycophenolate mofetil	6 (1.9)

Data presented as n (%) or mean ± standard deviation unless otherwise indicated

AD atopic dermatitis, *BSA* body surface area, *CDLQI* Children's Dermatology Life Quality Index, *EASI* Eczema Area and Severity Index, *IGA* Investigator's Global Assessment, *NRS*, numerical rating scale, *SCORAD* SCORing Atopic Dermatitis

Patients were permitted to use concomitant topical corticosteroids and topical calcineurin inhibitors without restriction, and topical crisaborole was also permitted if approved locally for treatment of AD. Systemic medications for AD, including corticosteroids and nonsteroidal immunosuppressants, were not permitted except as rescue treatment. Concomitant use of topical corticosteroids or other AD therapies was not standardized.

Patients who had an IGA score of 0/1 maintained continuously for a 12-week period, beginning at week 40 or later, were discontinued from dupilumab (for example, a patient with an IGA score of 0 or 1 through week 40 to week 52, inclusive, would be discontinued from the study drug at week 52). In these patients, AD disease activity was closely monitored during the remaining study visits. For patients who experienced a relapse of disease (defined as IGA score $\geq$ 2), treatment with dupilumab could be reinitiated. However, for such patients, investigators were encouraged to first consider treatment with topical therapy (e.g., medium-potency topical corticosteroids (TCS)) and to reinitiate dupilumab only if a patient did not experience an adequate response after at least 7 days of topical treatment. Such patients were reinitiated on the same dose regimen of dupilumab that they had been receiving at the time of discontinuation.

Outcomes

The primary outcomes of the LIBERTY AD PED-OLE study were the incidence and rate (patients per 100 patient-years [100PY] and/or events per 100PY) of treatment-emergent adverse events (TEAEs) through the last study visit.

Key secondary outcomes were incidence and rate (patients and/or events per 100PY) of treatment-emergent SAEs and incidence and rate (patients and/or events per 100PY) of TEAEs of special interest, (e.g., conjunctivitis, injection-site reactions, skin infections [excluding herpes viral infections], and herpes viral infections).

Other secondary outcomes included: proportion of patients with an IGA score of 0/1

Table 2 Safety assessment

TEAEs	**All patients** ***N*** **= 321**	
	***n*E**	***n*E/100PY**
Total number of TEAEs	1434	344.1
Total number of serious TEAEs	18	4.3
Total number of severe TEAEs	16	3.8
Total number of TEAEs related to treatment	170	40.8
Total number of TEAEs related to permanent treatment discontinuation	3	0.7
	*n*P (%)	*n*P/100PY
Patients with any TEAE	255 (79.4)	172.0
Patients with any serious TEAE	15 (4.7)	3.7
Patients with any severe TEAE	13 (4.0)	3.2
Patients with any TEAEs related to treatment	59 (18.4)	16.6
Patients with any TEAEs leading to permanent discontinuation	3 (0.9)	0.7
Conjunctivitis cluster[a]	47 (14.6)	12.8
Injection-site reactions (HLT)	18 (5.6)	4.5
Skin infections (SOC), excluding herpes viral infections	42 (13.1)	10.9
Herpes viral infections (HLT)	24 (7.5)	6.0
Most common TEAEs reported in $\geq$ 3% of patients (PT)		
Dermatitis atopic	92 (28.7)[b]	26.6
Nasopharyngitis	55 (17.1)	15.0
Upper respiratory tract infection	50 (15.6)	13.5
Cough	26 (8.1)	6.7
Conjunctivitis allergic	26 (8.1)	6.7
Pyrexia	25 (7.8)	6.3
Headache	25 (7.8)	6.3
Asthma	18 (5.6)	4.5
Pharyngitis streptococcal	16 (5.0)	4.0
Conjunctivitis	14 (4.4)	3.5
Urticaria	14 (4.4)	3.5
Oropharyngeal pain	14 (4.4)	3.5
Influenza	13 (4.0)	3.2
Vomiting	13 (4.0)	3.2
Oral herpes	12 (3.7)	2.9

Table 2 continued

TEAEs	All patients*N* = 321	
	***n*E**	***n*E/100PY**
Viral upper respiratory tract infection	11 (3.4)	2.7
Rhinitis allergic	11 (3.4)	2.7
Gastroenteritis	10 (3.1)	2.5
Sinusitis	10 (3.1)	2.5
Rhinorrhea	10 (3.1)	2.5

AD atopic dermatitis, *ESM* Electronic Supplementary Material; *HLT* high level term, *nE* number of events, *nP* number of patients, *nE/100 PY* number of events per 100 patient-years, *nP/100 PY* number of patients per 100 patient-years, *PT* preferred term, *q2w* every 2 weeks, *q4w* every 4 weeks, *SOC* system organ class, *TEAE* treatment-emergent adverse event

[a]Conjunctivitis cluster includes conjunctivitis, bacterial conjunctivitis, viral conjunctivitis, allergic conjunctivitis, and atopic keratoconjunctivitis; further details of conjunctivitis are presented in Table S4 in the ESM

[b]28 patients in the 300 mg q4w dose group, and 64 patients in the 200/300 mg q2w dose group; 73 patients experienced AD exacerbation while on the 300 mg q4w dose or within the first 2 weeks following uptitration (n = 28 for 300 mg q4w; n = 45 for 200/300 mg q2w dose group)

(clear/almost clear) by visit through week 52; proportion of patients with Eczema Area and Severity Index (EASI)-50/75/90 (≥ 50%/75%/90% reduction in EASI from baseline of parent study) by visit through week 52; change and percentage change from parent study baseline in EASI by visit through week 52; change from baseline of parent study in body surface area (BSA) affected by AD by visit through week 52; percentage change from baseline of parent study in SCORing Atopic Dermatitis (SCORAD) by visit through week 52; change from baseline of parent study in Children's Dermatology Life Quality Index (CDLQI) by visit through week 52; proportion of patients with uptitration and time in weeks from start of dupilumab 300 mg q4w in the OLE to the first uptitration; proportion of patients with sustained IGA 0/1 response at week 52; time to reinitiation of dupilumab treatment following relapse after first sustained achievement of IGA 0/1; number of patients regaining IGA 0/1 following reinitiation; time in weeks from drug withdrawal to last assessment off drug; time in weeks from drug reinitiation to the last assessment; and trough concentrations of functional dupilumab in serum. Since precise evaluation of itch requires daily assessment, itch was not included as an outcome, to minimize patient burden and ensure the highest possible patient retention in this long-term study.

Analyses

For this study, no formal sample size was estimated and no power calculations were performed. All efficacy and clinical safety variables were analyzed using the safety analysis set. The safety analysis set consisted of all patients who received one or more doses of dupilumab 300 mg q4w. Patients who were uptitrated were analyzed according to the uptitrated regimen. All safety data were included from the baseline of the OLE up to the database lock.

All efficacy analyses were descriptive. All observed values, regardless of whether rescue treatment was used, or if data were collected after withdrawal from study treatment, were used for analysis. No missing values were imputed.

PK analyses were descriptive and are summarized for all patients assigned to dupilumab 300 mg q4w at the start of the study and who

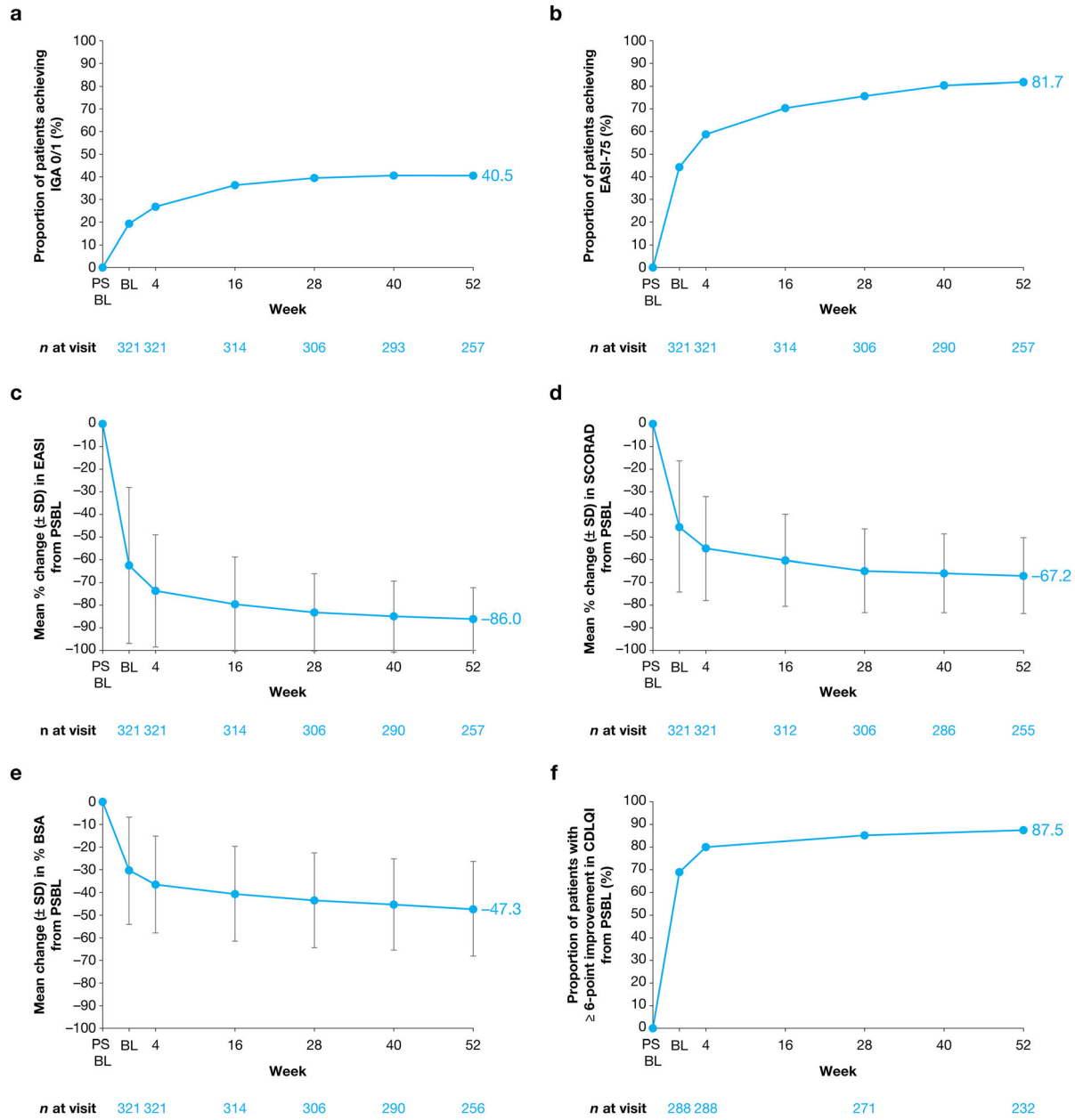

Fig. 2 Efficacy outcomes from PSBL through week 52. Proportion of patients achieving **a** IGA 0/1 or **b** EASI-75; mean % change from BL through week 52 in **c** EASI, **d** total SCORAD, and **e** BSA affected; and **f** proportion of patients with ≥ 6-point improvement in CDLQI from BL. *BL* baseline of OLE, *BSA* body surface area, *CDLQI* Children's Dermatology Life Quality Index (range 0–30), *EASI* Eczema Area and Severity Index, *EASI-75* patients achieving a 75% reduction in EASI compared with PSBL, *IGA* Investigator's Global Assessment, *PSBL* parent study baseline, *SCORAD* SCORing Atopic Dermatitis, *SD* standard deviation

had one or more nonmissing drug concentration results following the first dose of study drug. Blood samples for determination of trough concentrations of functional dupilumab in serum (C_{trough}) were collected prior to dosing at baseline, and at weeks 16 and 52. Treatment groups in concentration–time profiles correspond to the initially assigned treatment

Table 3 Efficacy assessment at weeks 4, 16, and 52 as observed

Efficacy assessment	Week 4 *N* = 321	Week 16 *N* = 314	Week 52 *N* = 257
Proportion of patients achieving IGA 0 or 1	86 (26.8)	114 (36.3)	104 (40.5)
Proportion of patients achieving EASI-50	273 (85.0)	288 (91.7)	250 (97.3)
Proportion of patients achieving EASI-75	188 (58.6)	220 (70.1)	210 (81.7)
Proportion of patients achieving EASI-90	110 (34.3)	121 (38.5)	129 (50.2)
Percentage change from baseline of parent study in EASI	−73.7 ± 24.8	−79.6 ± 20.8	−86.0 ± 13.9
Change from baseline of parent study in EASI	−27.6 ± 12.2	−30.0 ± 11.5	−32.5 ± 11.3
Change from baseline of parent study in % BSA affected by AD	−36.5 ± 21.3	−40.6 ± 20.8	−47.3 ± 20.8 (*n* = 256)
Percentage change from baseline of parent study SCORAD	−55.2 ± 22.8	−60.4 ± 20.2 (*n* = 312)	−67.2 ± 16.7 (*n* = 255)
Change from baseline of parent study in CDLQI[a]	−10.1 ± 6.8	–	−12.3 ± 7.1 (*n* = 255)
Proportion of patients with ≥ 6-point improvement in CDLQI[b]	230/288 (79.9)	–	203/232 (87.5)

Data presented as *n* (%), *n/N1* (%), or mean ± standard deviation

AD atopic dermatitis, *BSA* body surface area, *CDLQI* Children's Dermatology Life Quality Index, *EASI* Eczema Area and Severity Index, *EASI-50/75/90* patients achieving a 50%/75%/90% reduction in EASI compared with parent study baseline, *IGA* Investigator's Global Assessment, *NRS* numerical rating scale, *POEM* Patient-Oriented Eczema Measurement, *SCORAD* SCORing Atopic Dermatitis, *N1* patients with nonmissing EASI or IGA scores at each week

[a]CDLQI was not assessed at week 16

[b]Among patients with CDLQI ≥ 6 at parent study baseline

regimen (at baseline), or the last administered dose (at weeks 16 and 52).

For continuous variables, descriptive statistics included the following: the number of patients reflected in the calculation (*n*), mean, median, Q1 (quartile 1; 25th percentile), Q3 (75th percentile), standard deviation (SD), minimum, and maximum. For categorical or ordinal data, frequencies and percentages are displayed for each category. No formal statistical hypotheses were tested.

Compliance with Ethical Standards

LIBERTY AD PED-OLE and the parent study, LIBERTY AD PEDS [24], were conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and with the International Council for Harmonisation guidelines for good clinical practice and applicable regulatory requirements. Patients (as appropriate based on age of the child and country-specific requirements) provided written consent/assent, and at least one parent or guardian for each child provided written informed consent. At each study site, the protocol, informed-consent form, and patient information were approved by an institutional review board and independent ethics committee.

Table 4 Proportions of patients with uptitration

Patients with uptitration	All patients $N = 321$
Number of patients who received at least one q4w dose	321
Number of patients who received q4w dose for at least 16 weeks or uptitrated	317
Number of patients with uptitration	185[a,b,c]/317 (58.4)
Number of patients with uptitration prior to week 16	38/317 (12.0)
Number of patients with uptitration at or after week 16	147/317 (46.4)
Time in weeks from start of q4w dose to first uptitration visit (patients uptitrated owing to lack of achievement of IGA 0/1)	$n = 163$ 22.8 ± 16.0
Median (Q1–Q3)	16.0 (16.0–28.0)
Minimum; maximum	4.0; 76.0

Data presented as *n/N1* (%) or mean ± standard deviation unless otherwise indicated
Dupilumab q2w dosing regimen is off label in patients < 30 kg in the USA
IGA Investigator's Global Assessment, *N1* number of patients who received q4w dose for at least 16 weeks (patient is analyzed based on the final dose), *Q1–Q3* first to third quartile, *q2w* every 2 weeks, *q4w* every 4 weeks
[a]This includes 163 patients owing to lack of achievement of IGA 0/1, and 22 according to Protocol Amendment 4
[b]86 patients (47%) belonged to weight group < 30 kg and 99 (54%) to weight group ≥ 30 kg
[c]This analysis includes patients who were uptitrated after more than 1 year; data for those patients will not be reflected in Fig. 4 owing to the 52-week data cut-off

RESULTS

Of the 321 patients screened from the LIBERTY AD-PEDS parent study, all patients met the inclusion criteria (Fig. 1). At the time of the database lock (1 July 2020), 321 patients had been enrolled in LIBERTY AD PED-OLE and were included in the safety analysis set. Of the 321 patients, 61 patients had withdrawn from the study prematurely at the time of the database lock, 254 (79%) had completed the scheduled week 52 visit, 255 (79%) were ongoing, and 5 (2%) had completed the study. The most common reasons for premature study discontinuation were the drug having become commercially available ($n = 32$; 10%), withdrawal by the patient ($n = 11$; 3%), and physician's decision ($n = 6$; 2%).

Patient Baseline Demographics and Clinical Characteristics

The mean age of the patients was 8.6 years, approximately half (50%) were male, and the majority (72%) were White, although other races were also represented in the study population (Table 1). Almost 30% of enrolled patients were overweight (body mass index [BMI] ≥ 85th percentile for age and sex), and most had been diagnosed with AD at an early age, with a mean (SD) duration of AD of 7.4 (2.2) years. A substantial proportion of patients (46%) had moderate-to-severe AD at the OLE baseline. All patients had one or more comorbid allergic conditions at baseline. Additionally, 57% of children had received one or more systemic immunosuppressant medications for AD

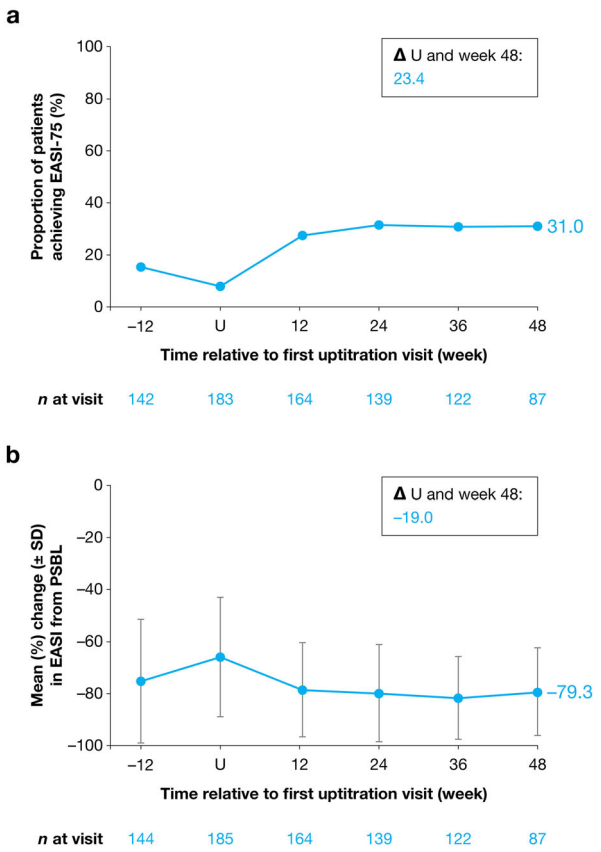

Fig. 3 Proportion of uptitrated patients achieving **a** EASI-75; and **b** mean % change in EASI from PSBL in uptitrated patients. *EASI* Eczema Area and Severity Index, *EASI-75* patients achieving a 75% reduction in EASI from PSBL *PSBL* parent study baseline, *SD* standard deviation, *U* time of uptitration

(besides dupilumab) in the past, which is suggestive of severe disease.

Safety Assessment

Safety data for the 321 included patients are presented from the baseline of OLE up to the database lock. The majority (79%) of patients reported ≥ 1 TEAE, most of which were mild or moderate in intensity (Table 2), and transient in duration. Of the 1434 TEAEs reported (344.1 events per 100PY), 170 (40.8 events per 100PY) were judged as being related to treatment, 16 (3.8 events per 100PY; 13 patients [4%]) were severe, and 18 (4.3 events per 100PY; 15 patients [5%]) were serious (Table 2; Table S1 in the ESM). Of the serious TEAEs, most were transient in duration, and the majority were either resolved or were resolving at the time of the database lock. No severe TEAEs resulted in treatment discontinuation. Three patients (1%) had a TEAE that led to permanent treatment discontinuation (Table S2 in the ESM): one event each of optic nerve drusen, worsening of conjunctivitis bacterial, and atopic dermatitis flare (face) (see Appendix S2 in the ESM for patient narratives). Twenty-five TEAEs of special interest (6.0 events per 100PY; 20 patients) were reported (Table S3 in the ESM).

The most frequently reported TEAEs (≥ 3% patients) were dermatitis atopic (29%; 26.6 patients per 100PY), nasopharyngitis (17%; 15.0 patients per 100PY), and upper respiratory tract infection (16%; 13.5 patients per 100PY) (Table 2). For the majority of patients who experienced an exacerbation of AD as a TEAE (dermatitis atopic), the event occurred while they were receiving the 300 mg q4w dose, or within the first 2 weeks following uptitration (73/92 patients). Injection-site reactions (Medical Dictionary for Regulatory Activities [MedDRA] high level term [HLT]) were reported in 18 patients (6%; 4.5 patients per 100PY).

Treatment-emergent conjunctivitis was reported in 47 patients (15%; 12.8 patients per 100PY) (Table 2; Table S4 in the ESM). The majority of conjunctivitis events were mild or moderate and had resolved by the time of the database lock. Herpes viral infections (MedDRA HLT) were reported in 24 patients (8%; 6.0 patients per 100PY) (Table 2; Table S5 in the ESM), among which oral herpes infections were the most common, being reported in 12 patients (4%; 2.9 patients per 100PY). Other skin and soft tissue infections were reported in 14 patients (4%; 3.4 patients per 100PY) (Table S5 in the ESM), among which impetigo was the most common, being reported in 9 patients (3%; 2.2 patients per 100PY). Further details of conjunctivitis and skin infections are presented in Tables S4 and S5 in the ESM, respectively.

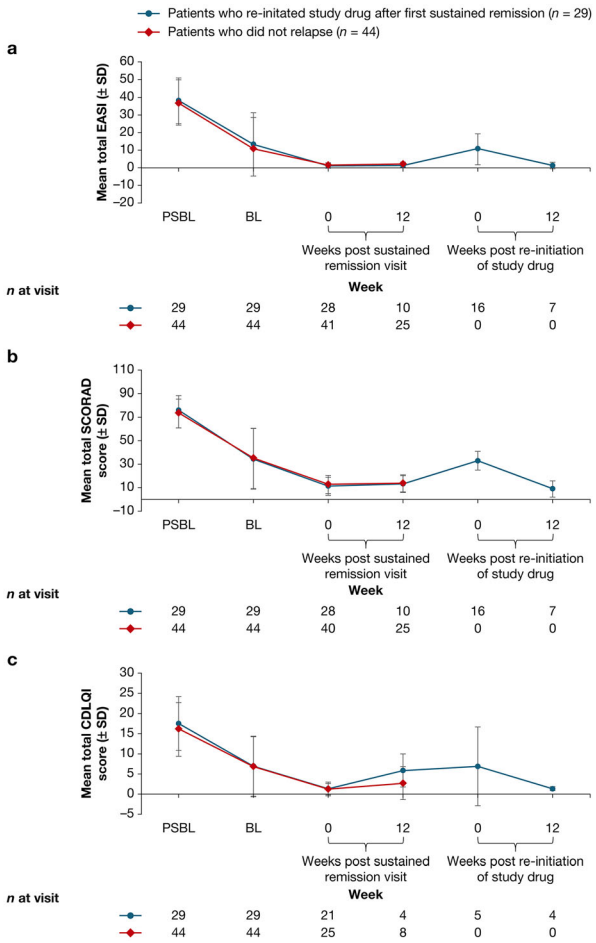

Fig. 4 Mean total EASI (**a**), SCORAD (**b**), and CDLQI (**c**) score from PSBL to week 24 post remission of skin lesions and week 12 post reinitiation of study drug. Once sustained remission of skin lesions was reached, the patients were discontinued from study drug, disease activity was closely monitored, and dupilumab was reinitiated if these patients had a relapse of disease (IGA score ≥ 2). *BL* baseline, *CDLQI* Children's Dermatology Life Quality Index, *EASI* Eczema Area and Severity Index, *IGA* Investigator's Global Assessment, *PSBL* parent study baseline, *SCORAD* SCORing Atopic Dermatitis, *SD* standard deviation

Efficacy Outcomes

Efficacy data for the 321 patients included in the analysis are presented from the baseline of the parent study up to week 52 of treatment in the OLE for patients on the dupilumab 300 mg q4w regimen, up to week 48 post uptitration for patients uptitrated to the weight-tiered q2w regimen, and up to week 12 after first sustained remission of skin lesions for patients who did not relapse, or up to week 12 after reinitiation of dupilumab for patients who did relapse.

There was an incremental improvement in AD clinical signs over time, with improvement being evident by week 4, and sustained with continued dupilumab treatment through week 52 (Fig. 2; Table 3). The proportion of patients achieving an IGA score 0/1 (Fig. 2a) or achieving EASI-75 (Fig. 2b) increased from the baseline of the parent study through week 52 of the OLE. By week 52, of 257 patients, 41% (104) had achieved an IGA score of 0/1, and 97% (250), 82% (210), and 50% (129) of patients had achieved EASI-50, EASI-75, and EASI-90, respectively (Table 3).

Similar incremental improvements through week 52 were seen for achievement of IGA 0/1 or EASI-75 in patients with body weight < 30 kg or ≥ 30 kg (Fig. S1a and b in the ESM). Additionally, at week 52, 88% of patients had clear/almost clear skin or mild disease (IGA ≤ 2) (Fig. S2a in the ESM).

The mean percent changes from the parent study baseline in EASI (Fig. 2c) and SCORAD (Fig. 2d) showed substantial improvement through week 52, with mean percent (SD) change of −86% (13.9) in EASI, and −67% (16.7) in SCORAD at week 52. At week 52, the mean (SD) EASI was 5.2 (5.6), with a mean (SD) change in EASI from the parent study baseline of −32.5 (11.3) (Fig. S2b and c in the ESM). A similar incremental improvement in EASI through week 52 was seen in patients with body weight < 30 kg or ≥ 30 kg (Fig. S1c in the ESM).

The percentage of BSA affected by AD decreased from the parent study baseline through week 52 (Fig. 2e), with a mean (SD) percent change in BSA affected of −47.3 (20.8) at week 52 (Table 3).

Additionally, patients showed an incremental improvement in HRQoL from parent study baseline through week 52, with 88% of patients having a clinically meaningful (≥ 6-point) improvement in CDLQI by week 52 (Fig. 2f). The mean (SD) change in CDLQI from parent study baseline at week 52 was −12.3 (7.1) (Table 3).

Table 5 Baseline characteristics of patients with uptitration according to EASI-75 response status

Characteristic	Patients who achieved EASI-75 following uptitration *N* = 90	Patients who did not achieve EASI-75 following uptitration *N* = 95	Uptitrated patients *N* = 185	Patients who did not receive uptitration *N* = 136
Age, years	8.5 ± 1.6	8.4 ± 1.6	8.5 ± 1.6	8.7 ± 1.8
Sex, male	44 (48.9)	45 (47.4)	89 (48.1)	70 (51.5)
Race				
White	66 (73.3)	69 (72.6)	135 (73.0)	95 (69.9)
Black or African American	12 (13.3)	17 (17.9)	29 (15.7)	22 (16.2)
Asian	8 (8.9)	3 (3.2)	11 (5.9)	14 (10.3)
American Indian or Alaska Native	0	1 (1.1)	1 (0.5)	0
Other	3 (3.3)	5 (5.3)	8 (4.3)	4 (2.9)
Not reported	1 (1.1)	0	1 (0.5)	1 (0.7)
AD duration, years	7.5 ± 1.8	7.4 ± 2.0	7.5 ± 1.9	7.4 ± 2.4
Weight, kg	31.0 ± 8.4	32.5 ± 9.5	31.7 ± 9.0	30.9 ± 8.0
< 30 kg	42 (46.7)	44 (46.3)	86 (46.5)	68 (50.0)
≥ 30 kg	48 (53.3)	51 (53.7)	99 (53.5)	68 (50.0)
BMI, kg/m^2	17.8 ± 3.0	18.3 ± 3.2	18.1 ± 3.1	17.3 ± 2.7
IGA				
0	0	2 (2.1)	2 (1.1)	5 (3.7)
1	5 (5.6)	14 (14.7)	19 (10.3)	36 (26.5)
2	23 (25.6)	41 (43.2)	64 (34.6)	49 (36.0)
3	28 (31.1)	30 (31.6)	58 (31.4)	31 (22.8)
4	34 (37.8)	8 (8.4)	42 (22.7)	15 (11.0)
EASI	22.9 ± 17.2	11.8 ± 11.8	17.2 ± 15.7	10.9 ± 13.5
Percent BSA affected by AD	37.8 ± 26.6	22.5 ± 20.6	29.9 ± 24.8	22.6 ± 24.3
CDLQI	9.2 ± 6.8	5.9 ± 6.0	7.5 ± 6.6	5.9 ± 6.4

Data presented as *n* (%) or mean ± standard deviation unless otherwise indicated
AD atopic dermatitis, *BMI* body mass index, *BSA* body surface area, *CDLQI* Children's Dermatology Life Quality Index, *EASI* Eczema Area and Severity Index, *EASI-75* 75% improvement in EASI, *IGA* Investigator's Global Assessment, *q4w* every 4 weeks

Table 6 Proportion of patients with sustained remission of skin lesions, time to reinitiation, and efficacy upon reinitiation

Patients			**All patients** ***N*** **= 321**
Proportion of patients with sustained remission at week 52 and who stopped dupilumab, *n/N1* (%)			73/254 (28.7)
Patients who reinitiated treatment after relapse, *n/N2*			29/73 (39.7)
Time in weeks to study drug reinitiation after first sustained remission			
Mean ± SD			13.5 ± 5.2
Median (minimum; maximum)			12.0 (4.0; 24.0)
Patients regaining IGA 0/1 following reinitiation, *n/N3* (%)[a,b]			8/20 (40.0)
Time in weeks to remission following reinitiation			
n			8
Mean ± SD			11.6 ± 3.1
Median (minimum; maximum)			11.7 (8.1; 18.0)
Patients	**Patients with sustained remission** ***N*** **= 73**	**Patients who relapsed and reinitiated study drug after first sustained remission** ***N*** **= 29**	**Patients who did not relapse** ***N*** **= 44**
Time in weeks from drug withdrawal to last assessment off drug			
n	72	29	43
Mean ± SD	13.3 ± 11.7	11.2 ± 11.7	14.7 ± 11.7
Median (minimum; maximum)	13.3 (0.1; 55.7)	4.9 (0.1; 55.7)	15.7 (0.1; 42.0)
Time in weeks from drug reinitiation to the last assessment			
n		19[c]	
Mean ± SD	–	7.2 ± 7.2	–
Median (minimum; maximum)	–	8.1 (0.1; 23.6)	–

Relapse defined as having an IGA score ≥ 2. Patients who have sustained remission of the disease as defined by maintenance of an IGA score of 0 or 1 continuously for a 12-week period after week 40 will be discontinued from study drug (e.g., a patient who has an IGA score of 0 or 1 through week 40 to week 52, inclusive, will be discontinued from the study drug at week 52; similarly, a patient who has an IGA score of 0 or 1 through week 52 to week 64, inclusive, will be discontinued from study drug at week 64, and so on)

CDLQI Children's Dermatology Life Quality Index, EASI Eczema Area and Severity Index, IGA Investigator's Global Assessment, *N1* patients who completed treatment up to week 52, *N2* patients with sustained remission at week 52, *N3* patients who reinitiated study drug treatment after relapse with date of reinitiation available, *SCORAD* SCORing Atopic Dermatitis, *SD* standard deviation

[a]Data on reinitiation available from 20/29 patients

[b]The 12 patients who did not regain IGA 0/1 are still ongoing in study

[c]20 patients reinitiated treatment; however, one patient underwent all disease assessments (EASI/SCORAD/CDLQI) prior to drug reinitiation after relapse and is therefore not included in this analysis

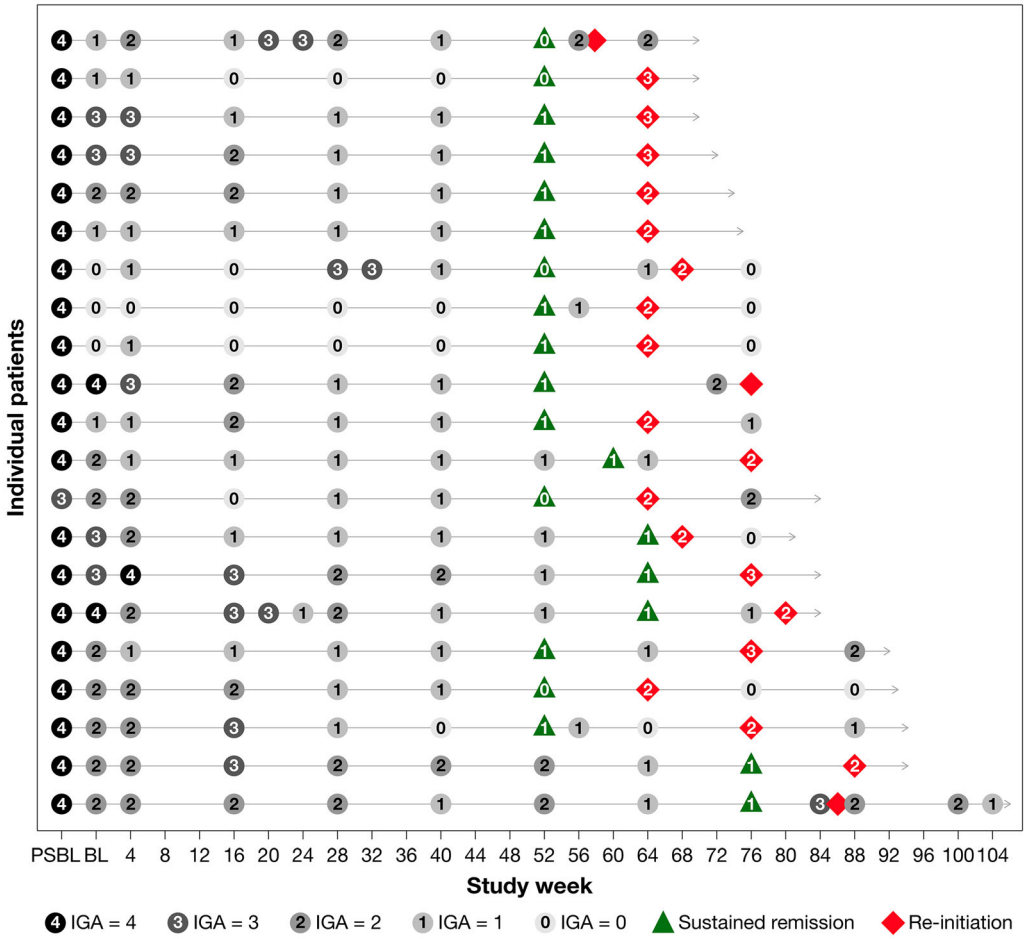

Fig. 5 IGA assessment for the 21 patients[a] who relapsed and were reinitiated on dupilumab. [a]This plot includes data from 21 patients; the reinitiation date was not available for one patient, who was therefore not included in Table 6. *BL* baseline, *IGA* Investigator's Global Assessment, *PSBL* parent study BL

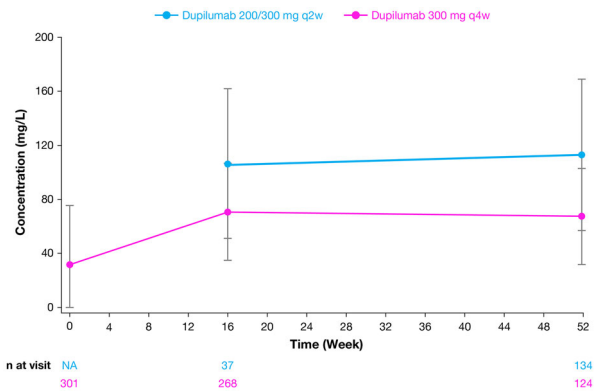

Fig. 6 Pharmacokinetics: mean (SD) concentrations of functional dupilumab in serum at weeks 0, 16, and 52. *NA* not applicable, *q2w* every 2 weeks, *q4w* every 4 weeks

Most patients (79%) used topical medications for AD during the study, which were most often TCS (79%) (Table S6 in the ESM). However, the proportion of patients using topical medications for AD decreased over time from 75% between baseline and week 26, to 14% between weeks 79 and 104 (Table S6 in the ESM).

At the time of the database lock, 185 of the 317 patients (58%) who had received the q4w regimen had been uptitrated to the weight-tiered q2w regimen ($n = 163$ owing to lack of achievement of IGA 0/1, of whom 19% were uptitrated before week 16; $n = 22$ according to Protocol Amendment 4, of whom 32% were uptitrated before week 16), with a median (Q1–Q3) time to first uptitration visit among

those uptitrated owing to lack of achievement of IGA 0/1 of 16.0 (16.0–28.0) weeks (Table 4). Of the 163 patients who were uptitrated owing to lack of achievement of IGA 0/1, 85 (52.0%) were ≥ 30 kg at baseline. Among patients who underwent uptitration, there was a worsening of disease prior to uptitration, with a decrease in the proportion of patients achieving EASI-75 to 8% at the uptitration visit (Fig. 3a), which improved to 31% at 48 weeks after uptitration to the q2w regimen, an increase of 23.4 percentage points. Prior to uptitration, the mean percent change in EASI from parent study baseline was −66%, which improved following uptitration, reaching −79% after 48 weeks (Fig. 3b). The greatest clinical benefit of uptitration was seen in patients with higher disease severity or a greater proportion of BSA affected at the OLE baseline (Table 5). Notably, neither patient weight nor BMI were associated with clinical benefit from the more frequent q2w dosing regimen (Table 5).

More than a quarter of patients who completed the scheduled week 52 visit (73/254; 29%) achieved sustained 12-weeks' IGA 0/1 response on therapy and consequently stopped treatment with dupilumab. Of these patients, 29 (40%) relapsed and were reinitiated on dupilumab, with a mean (SD) time to reinitiation of 13.5 (5.2) weeks (Table 6). Mean EASI, SCORAD, and CDLQI scores gradually worsened up to week 24 following discontinuation of dupilumab, but each measure improved within 12 weeks from the point of reinitiation of dupilumab in patients who were subsequently reinitiated (Fig. 4a–c). Incremental, though slower worsening across signs, symptoms, and quality of life was also suggested after dupilumab discontinuation in patients who had achieved a sustained IGA 0/1 response and did not subsequently reinitiate dupilumab (Fig. 4a–c).

Among patients who relapsed and were reinitiated on dupilumab after the first sustained remission, 40% (8/20) regained IGA 0/1, with a mean (SD) time to recapturing IGA 0/1 response of 11.6 (3.1) weeks, and a mean (SD) time from dupilumab reinitiation to last assessment of 7.2 (7.2) weeks (Fig. 5; Table 6).

Dupilumab PK Profile

Mean trough concentrations of functional dupilumab in serum of patients assigned to the regimen of dupilumab 300 mg q4w at the start of the study reached a steady state of approximately 70 mg/L by week 16, which was maintained through week 52 in patients who continued to receive dupilumab 300 mg q4w (Fig. 6). Mean concentrations were higher in patients after uptitration to a 200/300 mg q2w regimen at approximately 110 mg/L (weeks 16 and 52).

DISCUSSION

In children aged 6–11 years with inadequately controlled severe AD at the parent study baseline, dupilumab treatment for up to 52 weeks in the LIBERTY AD PED-OLE study provided sustained and substantial clinical benefit in AD signs and symptoms, and in quality of life.

The overall safety profile in children was consistent with the results previously obtained in OLE trials in adult [27] and adolescent [25] patients with AD, and with the safety profile seen in the pivotal 16-week phase III trial in children [18], and in infants and preschool children aged 6 months to 5 years [22]. Furthermore, the long-term efficacy results were similar to those previously reported in long-term OLE studies of dupilumab in adult [27] and adolescent [25] patients with AD.

Three TEAEs (0.7 events per 100PY) led to permanent study drug discontinuation: bacterial conjunctivitis, optic disc drusen, and AD exacerbation. No SAEs were considered related to dupilumab use, and all resolved over time with continued treatment. Exacerbation of AD occurred in 92 patients, with the majority of cases being reported in patients receiving the 300 mg q4w regimen or within the first 2 weeks following uptitration to the weight-tiered q2w regimen, suggesting that some patients may receive additional clinical benefit from a higher-frequency dose regimen. In the USA, the FDA-approved posology for pediatric patients of body weight > 30 to < 60 kg with moderate-to-severe AD is 200 mg q2w [10]. In Europe,

patients aged 6–11 years of body weight > 30 to < 60 kg with severe AD are initiated at 300 mg q4w and may be uptitrated to 200 mg q2w; uptitration in Europe may also be considered for patients with body weight 15 to < 30 kg [11].

The long-term results from this OLE study reinforce the efficacy and safety results of a previous phase IIa and OLE study that included a small number of children aged 6–11 years with severe AD, who received either 2 mg/kg or 4 mg/kg dupilumab weekly [26]. Importantly, the current analysis of patients from the LIBERTY AD PED-OLE study included data for the treatment regimen approved in the USA for children aged 6–11 years with moderate-to-severe AD [10].

A trend was seen over time toward further improvement in efficacy measures with continued dupilumab treatment. While the majority of patients used topical medications for AD during the study, the proportion of patients who used topical medications decreased over the course of treatment with dupilumab.

During the study, more than half of the patients (58%) who had been on the q4w regimen were uptitrated to the weight-tiered q2w regimen, 163 patients owing to lack of achievement of IGA 0/1 on the less-frequent dosing regimen, and 22 patients owing to the protocol amendment. A substantial proportion of patients in the uptitrated group subsequently achieved clinical benefit, as confirmed by the improved response following uptitration. Patients with higher disease severity at the OLE baseline, or greater proportion of BSA affected, achieved the greatest clinical benefit from uptitration.

Mean trough concentrations for pediatric patients receiving dupilumab 300 mg q4w in this study (~ 70 mg/L) were consistent with observations for the same dose regimen in the pivotal LIBERTY AD PEDS phase III study of dupilumab in children, aged 6–11 years, with severe AD [22] and similar to those of adults receiving 300 mg q2w (72.9 mg/L) [28]. Uptitration to q2w dosing for pediatric patients in the OLE was associated with higher mean trough concentrations (~ 110 mg/L). Exposure–response analyses in the LIBERTY AD PEDS study indicated modest benefits on IGA and EASI endpoints associated with the higher q2w exposures, but additional improvement in efficacy endpoints for patients in this OLE study following uptitration were greater than what may have been predicted from drug exposure alone [28]. The response-based uptitration criteria in this study may have selected for a subset of patients more likely to benefit from higher dupilumab exposure, potentially those patients with more severe disease. Notably, while body size is inversely correlated with dupilumab exposure at a fixed dose, in the present analysis neither patient weight nor BMI were associated with higher rates of uptitration or greater clinical benefit following uptitration.

During the study, more than a quarter of patients achieved IGA 0/1 sustained for 12 weeks and were discontinued from dupilumab therapy. In most of these patients, a gradual disease worsening across signs, symptoms, and HRQoL was observed following withdrawal of dupilumab, and a substantial proportion of patients subsequently relapsed and needed to be reinitiated on therapy. In patients who achieved a sustained IGA 0/1 response, EASI scores were close to zero, while SCORAD scores were higher. This is likely due to the weight of subjective symptoms in the total SCORAD score versus total EASI score.

Following reinitiation of dupilumab, approximately 40% of patients regained clinical response (IGA 0/1). As a mean of 12 weeks is required to recapture IGA 0/1 and since the reinitiated patients were only followed up for a mean of 7 weeks, the response upon reinitiation may be underestimated and a longer follow-up period is needed to draw further conclusions.

Our study shows that patients who undergo treatment interruption (which is relevant to real-life clinical practice, in which patients may need to discontinue treatment for a variety of reasons), who relapse, and reinitiate dupilumab treatment, can re-achieve a meaningful clinical response. These observations are in line with a similar analysis of adolescent AD patients (aged ≥ 12 to < 18 years) treated with dupilumab in the LIBERTY AD PED-OLE study [25].

A key strength of this study is that the safety and efficacy analyses are based on long-term (up to 1 year) treatment, using the approved dosing regimen of dupilumab in a large group of children aged ≥ 6 to < 12 years. The presented data are directly relevant to clinicians who manage children with AD in clinical practice. Limitations include the open-label, nonrandomized nature of the study. Additionally, throughout the study, the concomitant use of TCS or other AD therapies was not standardized. Efficacy data are presented as observed, and do not account for potential confounding factors resulting from these additional AD therapies. It is also possible that some patients on the q4w regimen may have continued to improve without uptitration to q2w.

CONCLUSIONS

Dupilumab treatment demonstrated acceptable long-term safety and sustained efficacy in children aged 6–11 years with inadequately controlled severe AD. The dupilumab long-term safety profile was comparable to that seen in adults and adolescents and was consistent with the known dupilumab safety profile.

A significant proportion of patients who discontinued treatment after having achieved sustained remission of skin lesions required reinitiation of dupilumab treatment. These patients could recapture clinically meaningful improvements in signs, symptoms, and HRQoL upon reinitiation of dupilumab. These data suggest that uninterrupted treatment, even in patients who achieve sustained clearance of skin lesions, may be recommended. In patients who were uptitrated to the q2w regimen, the greatest clinical benefit was seen in patients with higher AD disease severity or greater proportion of BSA affected at the OLE baseline.

The results support the long-term uninterrupted use of dupilumab in this patient population. Further study of children aged 6–11 years treated with dupilumab in LIBERTY AD PED-OLE remains ongoing to evaluate the longer-term safety and efficacy in this age group.

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Data Availability. Qualified researchers may request access to study documents (including the clinical study report, study protocol with any amendments, blank case report form, and statistical analysis plan) that support the methods and findings reported in this manuscript. Individual anonymized participant data will be considered for sharing once the indication has been approved by a regulatory body, if there is legal authority to share the data and there is not a reasonable likelihood of

participant re-identification. Submit requests to https://vivli.org.

Declarations

Conflict of interest. Michael J. Cork has been a consultant and/or investigator for Astellas Pharma, 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. Diamant Thaçi has been a consultant/advisory board member and/or investigator for AbbVie, Almirall, Amgen, Beiersdorf, BMS, Boehringer Ingelheim, Celltrion, Eli Lilly, Galderma, Janssen-Cilag, Kyowa-Kirin, LEO Pharma, Novartis, Pfizer, Regeneron Pharmaceuticals Inc., Roche-Posay, Samsung, Sanofi, Sun Pharma, and UCB. Lawrence F. Eichenfield has received honoraria for consulting services from AbbVie, Aslan, BMS, Dermavant, Eli Lilly, Forté, Galderma, Incyte, Janssen, Otsuka, Novartis, Pfizer, Regeneron Pharmaceuticals Inc., and Sanofi and has received study support (to institution) from AbbVie, Arcutis, Bausch, Castle Biosciences, Dermavant, Galderma, Incyte, Pfizer, Regeneron Pharmaceuticals Inc., and Sanofi. Peter D. Arkwright has been an investigator for Regeneron Pharmaceuticals Inc. and has received a research grant from and been an advisor for Sanofi. Zhen Chen, Ryan B. Thomas, Matthew P. Kosloski, and Ashish Bansal are employees and shareholders of Regeneron Pharmaceuticals Inc. Ariane Dubost-Brama and Randy Prescilla are employees of Sanofi, and may hold stock and/or stock options in the company. Noah A. Levit is a former employee and shareholder of Regeneron Pharmaceuticals Inc., currently an employee of the Dermatology Physicians of Connecticut, Fairfield, CT, USA.

Ethics Approval. The study was conducted following the ethical principles derived from the Declaration of Helsinki, the International Conference on Harmonisation guidelines, Good Clinical Practice, and local applicable regulatory requirements. Written informed consent was obtained from all patients and the patients' parents/guardians prior to commencement of any study treatment. At each study site, the protocol, informed-consent form, and patient information were approved by an institutional review board and independent ethics committee.

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