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ORIGINAL RESEARCH ARTICLE

# Long-Term Efficacy and Safety of Dupilumab in Adolescents with Moderate-to-Severe Atopic Dermatitis: Results Through Week 52 from a Phase III Open-Label Extension Trial (LIBERTY AD PED-OLE)

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## Abstract

**Background** For adolescent patients (aged ≥ 12 to < 18 years) with uncontrolled moderate-to-severe atopic dermatitis (AD), 16 weeks of treatment with dupilumab resulted in substantial clinical benefit compared with placebo, with an acceptable safety profile. However, long-term data on the approved dose regimens of dupilumab in adolescents with AD are lacking.

**Objectives** This open-label extension study (LIBERTY AD PED-OLE, NCT02612454) reports the long-term safety, efficacy, and pharmacokinetics of dupilumab in adolescents with moderate-to-severe AD who had participated in dupilumab parent trials.

**Methods** Patients enrolled under the original study protocol received subcutaneous dupilumab according to a weight-based regimen (2 or 4 mg/kg every week). Following protocol amendment, patients were switched to subcutaneous dupilumab 300 mg every 4 weeks (q4w) irrespective of weight, and newly enrolled patients were started on dupilumab 300 mg q4w. Patients with an inadequate clinical response (Investigator's Global Assessment [IGA] score of 0/1 was not reached) to the q4w regimen could be uptitrated to the approved dupilumab dose regimens of 200 or 300 mg every 2 weeks (body weight < 60 or ≥ 60 kg, respectively). Patients whose IGA score of 0/1 was maintained continuously for a 12-week period after week 40 were discontinued from dupilumab, monitored for relapse, and re-initiated on dupilumab if required.

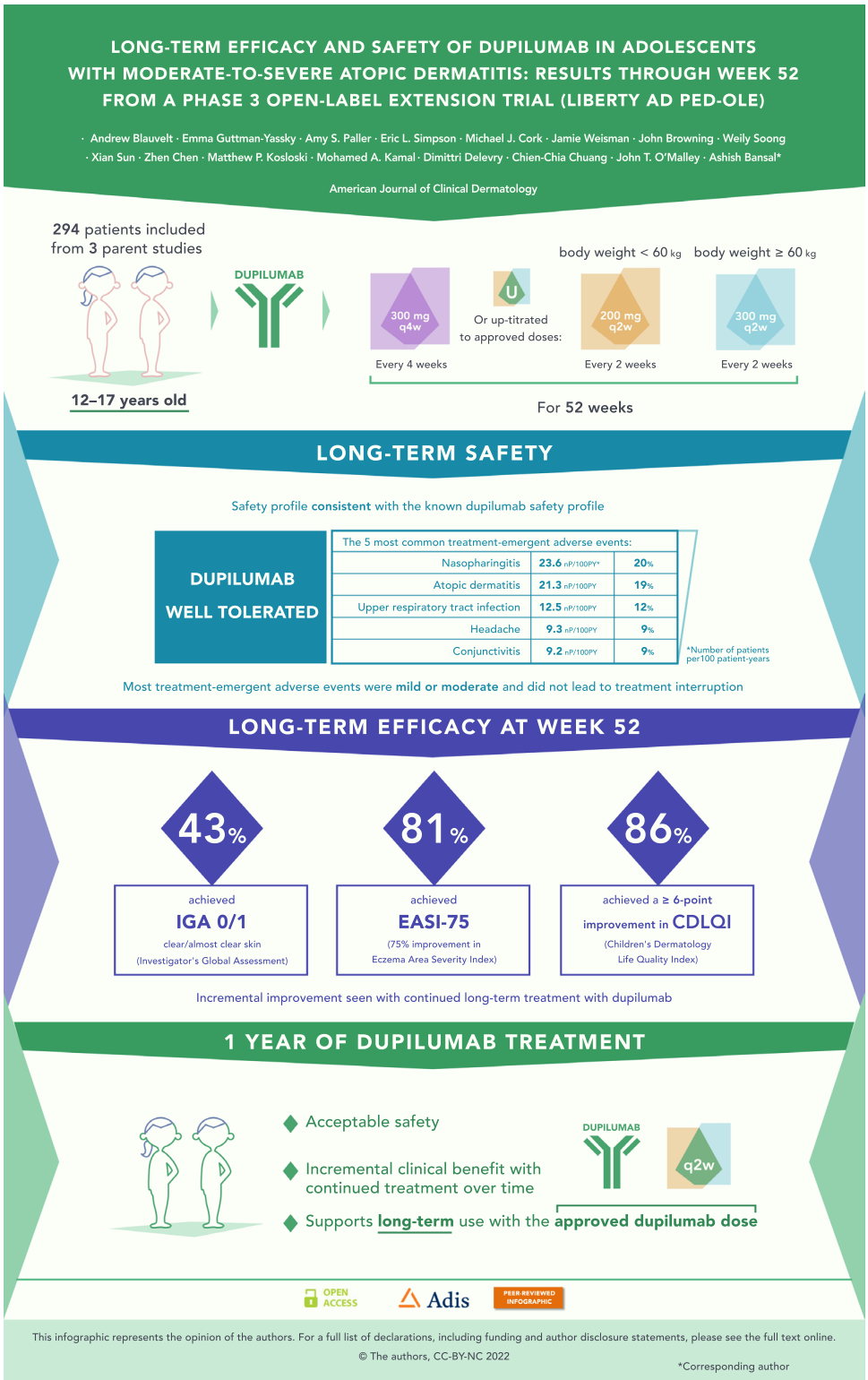
**Results** Data for 294 patients (mean age 14.7 years) were analyzed, 102 (34.7%) of whom had completed the 52-week visit at the database lock. The dupilumab long-term safety profile was comparable to that seen in adults and consistent with the known safety profile. Most treatment-emergent adverse events were mild/moderate. By week 52, 42.7% of patients had an IGA score of 0/1 (clear/almost clear), and 93.1%, 81.2%, and 56.4%, respectively, had at least a 50%, 75%, or 90% improvement in Eczema Area and Severity Index (EASI). Most (70.9%) patients required uptitration to the approved dupilumab dose regimen. The proportions of uptitrated patients with an IGA score of 0/1 or 75% improvement in EASI increased over time, reaching 35.7% and 51.9%, respectively, 48 weeks after the first uptitration visit. By week 52, 29.4% of patients had clear/almost clear skin sustained for 12 weeks and had stopped medication; 56.7% relapsed and were subsequently re-initiated on treatment, with a mean time to re-initiation of 17.5 (± standard deviation 17.3) weeks.

**Conclusions** Consistent with results seen with short-term treatment, long-term treatment with dupilumab showed an acceptable safety profile while providing incremental clinical benefit with continued treatment over time. The high proportion of patients who needed uptitration because of inadequate response to q4w dosing supports the q2w dose regimen as optimal for this age group. Finally, the majority of patients who stopped medication after having clear/almost clear skin sustained over 12 weeks experienced disease recurrence, suggesting the need for continued dupilumab dosing to maintain efficacy.

**Trial Registration** ClinicalTrials.gov Identifiers: NCT02612454, NCT02407756, NCT03054428, and NCT03050151.

Extended author information available on the last page of the article

## Infographic



**Plain Language Summary**

Atopic dermatitis, or eczema, is a common chronic skin disease that can cause intense and persistent itching and rashes. Atopic dermatitis remains a problem for many adolescent patients, even if they use a number of different treatments. Dupilumab is a newer treatment for atopic dermatitis. In short-term clinical studies, dupilumab improved the disease with acceptable safety. In this study, adolescents with moderate-to-severe atopic dermatitis who had completed one of the short-term studies continued dupilumab treatment for 1 year. The patients started treatment with dupilumab once every 4 weeks. But if their atopic dermatitis did not improve sufficiently, they were given dupilumab every 2 weeks. Through a year of treatment, there were no unexpected side effects. The side effects that did occur were mild or moderate in severity and in most cases did not lead to interruption of treatment. Almost half of the patients achieved skin that was clear or almost clear of atopic dermatitis during the study. But their atopic dermatitis often returned if they stopped being treated, and about half of them needed to start treatment again. Most patients needed to be treated every 2 weeks. The positive effects of dupilumab generally increased the longer patients were treated.

**Key Points**

For adolescent patients with uncontrolled atopic dermatitis (AD), short-term dupilumab treatment is efficacious with an acceptable safety profile. However, long-term safety and efficacy data for the approved dose regimen of dupilumab in adolescents with AD are limited.

In this long-term open-label extension study, dupilumab treatment every 4 weeks, or uptitrated to a weight-tiered dose regimen every 2 weeks, for up to 52 weeks showed an acceptable safety profile and provided sustained and substantial clinical benefits in AD signs and symptoms as well as improvements in quality of life.

Most patients required uptitration of dupilumab dosing during the study from every 4 weeks to the approved dose regimen in adolescent patients of every 2 weeks. The results also support continued use of dupilumab to maintain efficacy, since most responding patients who stopped medication experienced disease recurrence.

## 1 Introduction

Atopic dermatitis (AD) is a common chronic inflammatory skin condition that has a substantial negative impact on the health-related quality of life of patients. AD is characterized by intense pruritus, disruption of skin barrier function, and type 2 inflammation [1]. The prevalence of AD in adolescents is estimated to be up to 24.6% [2, 3]. A substantial proportion of adolescents have persistent disease [4], and patients with higher severity of disease have been shown to have lower rates of remission [5].

Until recently, adolescents with AD inadequately controlled by topical therapies had limited treatment options. Although systemic immunosuppressive agents are sometimes used off label for severe AD refractory to topical therapy, the use of some of these agents, such as cyclosporine, methotrexate, azathioprine, and mycophenolate mofetil, especially in the long term, is associated with a risk of infections, malignancies, and/or hepatic, renal, and hematologic toxicities [6–8]. There are currently no peer-reviewed published studies reporting long-term data on any systemic therapy other than dupilumab for children or adolescents with AD.

Dupilumab is a fully human VelocImmune®-derived [9, 10] monoclonal antibody that blocks interleukin (IL)-4Rα, the shared receptor component for IL-4 and IL-13, inhibiting signaling of both IL-4 and IL-13 [11, 12], which are central and key drivers of AD and other type 2-mediated diseases [11, 13]. Dupilumab is approved for patients with AD, asthma, and chronic rhinosinusitis with nasal polyps [14, 15]. The approved dupilumab dose regimen for adolescents with AD is an initial dose of 400 mg (for body weight $<60$ kg) or 600 mg (for body weight $\geq 60$ kg) followed by 200 mg (for body weight $<60$ kg) or 300 mg (for body weight $\geq 60$ kg) every 2 weeks (q2w) [16].

Dupilumab has demonstrated significant efficacy and an acceptable safety profile in patients with type 2 inflammatory diseases [17–26]. In the randomized, double-blinded, placebo-controlled, phase III LIBERTY AD ADOL study in adolescent patients (aged $\geq 12$ to $<18$ years) with moderate-to-severe AD, 16 weeks of treatment with dupilumab resulted in significant improvements in AD signs, symptoms, and quality of life compared with placebo, with an acceptable safety profile [27]. Another analysis of a small subset of adolescents who received dupilumab 2 or 4 mg/kg every week (qw) in a phase IIa study, and continued in an open-label extension (OLE) study, showed early improvement in signs and symptoms, with results maintained for up to a year of therapy [28]. However, long-term data on the approved dose regimen of dupilumab for adolescents with AD are currently lacking. Data are also lacking on whether the continuous use of dupilumab over a long period can lead to sustained clear or almost clear skin (Investigator's

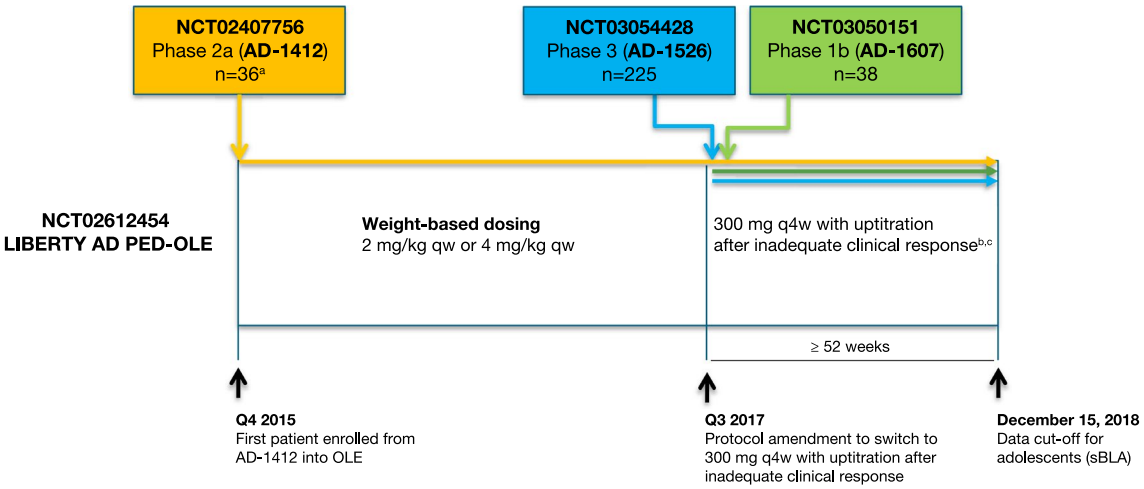



**Fig. 1** LIBERTY AD PED-OLE study schematic. [a]36 patients enrolled from R668-AD-1412 phase IIa study; five patients received only the weight-based dose regimen and were excluded, 31 patients from R668-AD-1412 were analyzed. [b]Patients enrolled from R668-AD-1412 switched from weight-based dosing to 300 mg q4w at the time of protocol amendment, with uptitration after inadequate response, whereas all patients enrolled from R668-AD-1526 and R668-AD-1607 started directly on the q4w or q2w regimen. [c]Uptitration to 200 mg (body weight < 60 kg) or 300 mg (body weight ≥ 60 kg) q2w at week 16 upon inadequate clinical response, or prior to week 16 if deemed necessary by the investigator. *AD* atopic dermatitis, *OLE* open-label extension, *qw* weekly, *q2w* every 2 weeks, *q4w* every 4 weeks, *sBLA* supplemental Biologics License Application

Global Assessment [IGA] score of 0 or 1) in adolescents with AD.

The objective of this OLE study (LIBERTY AD PED-OLE, NCT02612454) was to report the long-term safety and efficacy, and pharmacokinetic profile, of dupilumab in adolescents (aged ≥ 12 to < 18 years) with moderate-to-severe AD who had previously participated in dupilumab trials and were subsequently enrolled in the LIBERTY AD PED-OLE study. This analysis includes data for patients who were initiated on dupilumab every 4 weeks (q4w) and then uptitrated to the weight-tiered q2w dose regimen, currently approved to treat adolescents with moderate-to-severe AD, which examined whether uptitration to the q2w regimen provided additional benefit to patients who did not respond to the q4w regimen. Data on achievement of IGA 0/1, relapse, and re-initiation of therapy in adolescent patients treated with dupilumab for over 1 year are also presented.

## 2 Methods

### 2.1 Study Design

LIBERTY AD PED-OLE is an ongoing OLE study in patients aged ≥ 6 months to < 18 years with moderate-to-severe AD who participated in dupilumab parent studies. Results are presented for the cohort aged ≥ 12 to < 18 years from the study, with a data cutoff date of December 15, 2018. Previous studies (referred to as "parent studies" in this manuscript) for this age cohort were the phase IIa study R668-AD-1412 (NCT02407756) [28], the phase III study LIBERTY AD ADOL (R668-AD-1526; NCT03054428) [27], and the phase Ib R668-AD-1607 study (NCT03050151) [29] (Fig. 1).

In LIBERTY AD PED-OLE, adolescent patients with moderate-to-severe AD who had previously participated in dupilumab trials received dupilumab 300 mg q4w, but could be uptitrated to 200 mg (for body weight < 60 kg) or 300 mg (for body weight ≥ 60 kg) q2w at week 16 upon inadequate clinical response, or prior to week 16 if deemed necessary by the investigator. The dupilumab 200/300 mg q2w weight-tiered dose regimen was intended to match the exposure in adults receiving the approved 300 mg q2w regimen. Adolescent patients from study R668-AD-1412 were initially assigned to receive dupilumab 2 or 4 mg/kg qw but were switched to the q4w regimen with optional uptitration to q2w following a protocol amendment. At the time the q4w regimen and uptitration to weight-tiered q2w regimens were introduced in this study, both were under evaluation for adolescents participating in LIBERTY AD ADOL. Inadequate clinical response was defined as not having an IGA score of 0/1 (clear/almost clear skin) during at least 16 weeks from the date of initiation of treatment with the 300 mg q4w regimen.

The full study designs of the parent studies R668-AD-1412 and LIBERTY AD ADOL have been previously reported [27, 28]. Briefly, R668-AD-1412 [28] was a phase IIa, multicenter, open-label, ascending-dose, sequential cohort study in 40 adolescents (aged ≥ 12 to < 18 years) with moderate-to-severe AD. It was conducted at multiple

centers in Europe (Czech Republic, Hungary, Germany, Poland, the UK) and Canada. The study design consisted of a screening period, a baseline visit, and two treatment phases. In the first treatment phase, patients received a single dose of dupilumab (2 or 4 mg/kg) followed by an 8-week sampling period for pharmacokinetic measurements. The second phase consisted of the same dupilumab dose qw for 4 weeks followed by an 8-week safety follow-up period. Patients were then eligible to enroll in an OLE study.

LIBERTY AD ADOL (R668-AD-1526) [27] was a randomized, double-blinded, placebo-controlled, parallel-group phase III trial conducted at 45 centers in the USA and Canada. A total of 251 adolescents (aged ≥ 12 to < 18 years) with moderate-to-severe AD that was inadequately controlled with topical therapies, or for whom topical therapy was inadvisable, were randomized (1:1:1) to receive 16 weeks of monotherapy treatment with subcutaneous dupilumab 300 mg q4w, dupilumab 200/300 mg q2w (200 mg for patient baseline body weight < 60 kg; 300 mg for baseline bodyweight ≥ 60 kg), or placebo. Following the 16-week treatment period, patients were eligible to enter an OLE study.

R668-AD-1607 [29] was a multicenter phase Ib study aiming to collect actual-use data concerning the technical performance and user interactions of the dupilumab autoinjector device when used by patients or caregivers. Other outcomes included safety, efficacy, and systemic exposure of dupilumab administered using the autoinjector device versus prefilled syringe. Included patients were aged ≥ 12 years with moderate-to-severe AD inadequately controlled with topical medications or for whom topical treatment was medically inadvisable. The study was conducted in two parts. In part A, patients were randomized to receive subcutaneous dupilumab 200 mg q2w using an autoinjector device or prefilled syringe for 12 weeks. When part A was fully enrolled, in part B patients were randomized to receive subcutaneous dupilumab 300 mg q2w using an autoinjector device or prefilled syringe for 12 weeks. In part A and part B, patients were followed-up for a 12-week post-treatment period. Patients were then eligible to enroll in an OLE study.

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, and a 12-week follow-up period.

## 2.2 Main Inclusion and Exclusion Criteria

Adolescents (aged ≥ 12 to < 18 years at time of screening for the OLE study) with moderate-to-severe AD were eligible for inclusion in LIBERTY AD PED-OLE if they had participated in a previous dupilumab trial and completed all visits/assessments (for R668-AD-1412) or at least 50% of visits and assessments (for LIBERTY AD ADOL and R668-AD-1607). Patients from the placebo arm of the LIBERTY AD ADOL trial were also allowed to participate in LIBERTY AD PED-OLE.

Patients who had a serious adverse event (SAE) during the parent study 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 in the electronic supplementary material (ESM) for full eligibility criteria.

## 2.3 Treatment

According to the original LIBERTY AD PED-OLE study protocol, patients received subcutaneous dupilumab according to a weight-based regimen of 2 or 4 mg/kg qw. Once pharmacokinetic data from the phase II study R668-AD-1412 became available for adolescents, the protocol was amended in the third quarter of 2017 (protocol version R668-AD-1434.01), and patients were switched to a regimen of dupilumab 300 mg q4w. Patients enrolled in LIBERTY AD PED-OLE after implementation of the amended protocol were started directly on subcutaneous dupilumab 300 mg q4w.

Patients with an inadequate clinical response to the 300 mg q4w regimen at week 16 (or 16 weeks after switching, for patients on the original weight-based regimen), defined as not having an IGA score of 0/1, could be uptitrated at the investigator's discretion to a regimen of dupilumab 200 mg q2w (for patient body weight < 60 kg) or 300 mg q2w (for patient body weight ≥ 60 kg). Patients could also be uptitrated prior to week 16 if the patient had an IGA score of 3/4 and the investigator felt the patient needed rescue treatment. Patients who had been uptitrated continued on this regimen for the remainder of the study.

During the study, the use of concomitant topical corticosteroids and topical calcineurin inhibitors was allowed without restriction, and topical crisaborole was also permitted if approved locally for treatment of AD. However, 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 sustained remission from AD, defined as continuous maintenance of an IGA score of 0/1 for a 12-week period after week 40, were discontinued from dupilumab (e.g., a patient who had an IGA score of 0/1 from week 40 through week 52, inclusive, was discontinued from study drug at week 52; similarly, a patient who had an IGA score 0/1 from week 52 through week 64, inclusive, was discontinued from study drug at week 64, etc.). Disease activity was closely monitored in these patients

during the remaining study visits, and treatment with study drug was re-initiated in patients who experienced a relapse of disease (IGA score ≥ 2). In these cases, investigators were encouraged to consider treatment with topical therapy (e.g., medium potency topical corticosteroids) and to re-initiate dupilumab only for patients who did not experience adequate response after at least 7 days of topical treatment. Such patients were re-initiated (without a loading dose) on the same dose regimen of dupilumab that they were on at the time of discontinuation.

Patients who turned 18 years of age during the study and were located in a geographic region where the drug is commercially available for the treatment of AD in adults were treated with study drug only until the date of their 18th birthday. These patients had an end-of-treatment visit after their 18th birthday, followed by an end-of-study visit after 12 weeks.

## 2.4 Outcomes

The primary outcomes of LIBERTY AD PED-OLE were the incidence and rate (patients per 100 patient-years [100PY] and/or events per 100PY) of treatment-emergent AEs (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, such as anaphylactic reactions, systemic or severe hypersensitivity reactions, malignancies, helminthic infections, suicide-related events, any type of (severe or serious) conjunctivitis or blepharitis, and keratitis.

Other secondary outcomes included proportion of patients with an IGA score of 0/1 (clear/almost clear) by visit through week 52; proportion of patients with Eczema Area and Severity Index (EASI)-75 (≥ 75% reduction in EASI from baseline of parent study) by visit through week 52; percentage change from parent study baseline in EASI and according to SCORing Atopic Dermatitis (SCORAD) by visit through week 52; mean change in absolute EASI by visit through week 52; change from parent study baseline in body surface area (BSA) affected and EASI by visit through week 52; change from parent study baseline in Children's Dermatology Life Quality Index (CDLQI) by visit through week 52; proportion of patients achieving EASI-50/-75/-90 (≥ 50%/≥ 75%/≥ 90% reduction, respectively, in EASI from parent study baseline) by visit through week 52; and assessment of trough concentrations of functional dupilumab in serum after treatment with dupilumab. Post hoc analyses were performed to evaluate the proportion of patients with IGA 0/1 sustained over 12 weeks at week 52; time to re-initiation of dupilumab therapy following relapse after first sustained achievement of IGA 0/1; and number of patients regaining IGA 0/1 following treatment re-initiation. Data on Peak Pruritus Numerical Rating Scale have been reported in the phase II and III parent studies and for patients on 2 or 4 mg/kg qw dose regimens in the current study [27, 28]; Peak Pruritus Numerical Rating Scale was not assessed in the OLE with the dupilumab q4w or q2w dose regimens. The proportion of patients achieving a ≥ 6-point improvement in CDLQI was also evaluated. The improvement threshold for CDLQI was based on the published minimal clinically important difference in the adolescent AD population [30]. The proportion of patients who required uptitration from the q4w to the q2w regimen was also evaluated. Furthermore, in patients uptitrated to the q2w regimen, the efficacy of dupilumab was evaluated according to key outcome measures such as achievement of IGA 0/1 or EASI-75 and mean percentage change in EASI from time of uptitration.

## 2.5 Analyses

Based on the numbers of patients enrolled in or screened for the parent dupilumab studies, it was anticipated that approximately 300 adolescent patients would be enrolled in this OLE study. No formal sample size was estimated or power calculations performed for this study.

The safety analysis set included all patients who received one or more dose of dupilumab 300 mg q4w. Efficacy and all clinical safety variables were analyzed using the safety analysis set. Patients who were uptitrated were analyzed according to this regimen. All safety data were included from the baseline of the OLE up to the database lock. For patients enrolled from the R668-AD-1412 study, the 1-year safety and efficacy data for the weight-based regimen of 2 or 4 mg/kg qw have been previously reported [28]. This manuscript includes longitudinal data for a dose of dupilumab 300 mg q4w or from patients uptitrated to the approved weight-tiered dose of dupilumab 200/300 mg q2w for the same patients from R668-AD-1412 and the data for patients enrolled from the R668-AD-1526 and R668-AD-1607 parent studies. For the evaluation of conjunctivitis, grouped Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms (PT) consistent with conjunctivitis and selected eye disorder terms were selected for further analysis. A compiled term was used, including all PTs containing the word “conjunctivitis” (conjunctivitis, conjunctivitis allergic, conjunctivitis bacterial, conjunctivitis viral, and atopic keratoconjunctivitis).

Efficacy outcomes were analyzed descriptively among patients with available values at each visit (e.g., outcomes at week 16 were evaluated among patients with data available at the week 16 visit, etc.). All observed values were used for analysis, regardless of whether rescue treatment was used or data were collected after withdrawal from study treatment. No missing values were imputed.

The pharmacokinetic analysis included all patients assigned to dupilumab 300 mg q4w at the start of the study and who had one or more non-missing drug concentration result following the first dose of study drug; the pharmacokinetics of dupilumab in patients from R668-AD-1412 initially assigned to 2 or 4 mg/kg qw were previously reported, and these patients were excluded. Blood samples for determination of trough concentrations of functional dupilumab in serum ($C_{trough}$) were collected prior to dosing at baseline, week 16, and week 52. Treatment groups for each time point correspond to the initially assigned treatment regimen (baseline) or the previously administered dose (weeks 16 and 52).

For continuous variables, descriptive statistics included the following: the number of patients reflected in the calculation (*n*), mean, median, Q1 (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.

### 2.6 Compliance with Ethical Standards

LIBERTY AD PED-OLE and the parent studies [27–29] 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. All patients provided written consent/assent, and at least one parent or guardian for each adolescent patient 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.

## 3 Results

Of the 304 patients screened, five patients did not meet the inclusion criteria (Fig. 2). At the time of the database lock, 299 patients had been enrolled in LIBERTY AD PED-OLE and were included in the safety analysis set (36 from R668-AD-1412, 38 from R668-AD-1607, and 225 from LIBERTY AD ADOL). Of the 36 patients enrolled from R668-AD-1412, five patients received only the weight-based dose regimen and were therefore not included in this analysis. A total of 294 patients were analyzed. Of the 294 patients, 102 (34.7%) had completed the 52-week visit at the time of the database lock, 43 (14.6%) patients had discontinued the study prematurely, and 253 patients were continuing therapy. The most common reasons for study discontinuation were withdrawal by the patient ($n = 17$; 5.8%), lack of efficacy ($n = 11$; 3.7%), and the patient turning 18 years of age ($n = 10$; 3.4%).

### 3.1 Patient Baseline Demographics and Clinical Characteristics

The mean age of the patients was 14.7 years, and the majority were White (69.0%) and male (56.8%), but the study population included representation from other ethnicities (Table 1). Consistent with what has been previously reported in the literature, a high proportion of enrolled patients (41.2%) were overweight (body mass index $\geq$ 85th percentile for age and sex). The majority of patients had moderate-to-severe disease at baseline, with 47.3% having IGA 3 and 24.8% having IGA 4 (Table 1). This was likely a reflection of the treatment interruption (28-day screening period) between the parent study and the OLE study and the inclusion of patients from the placebo arm of LIBERTY AD ADOL. Additionally, all patients (100%) had one or more comorbid allergic conditions at baseline, reflecting the high type 2 burden of disease in this adolescent patient population. Most patients (61.9%) had received one or more prior systemic immunosuppressive medications for AD besides dupilumab, reflecting the high unmet medical need in this population.

### 3.2 Safety Assessment

The safety data for the 294 included patients are presented from the baseline of the OLE up to the database lock. The majority (73.8%) of patients reported one or more TEAE, most of which were mild or moderate (Table 2) and transient in duration. Of the 1131 TEAEs reported (370.2 events per 100PY), 120 (39.3 events per 100PY) were considered related to treatment, 12 (3.9 events per 100PY) were severe, and five (1.6 events per 100PY) were serious: one event each of patent ductus arteriosus, injection-site edema, food allergy, herpes simplex infection, and ankle fracture (Table S1 in the ESM). All serious TEAEs resolved over time, and none led to treatment discontinuation. Two adverse events (0.7 events per 100PY) led to treatment discontinuations (one event of moderate bilateral conjunctivitis [see Appendix S2 in the ESM for a patient narrative] and one event of moderate worsening of AD) (Table S2 in the ESM). Six TEAEs of special interest were reported: one event (0.3 events per 100PY) each of severe viral conjunctivitis, severe allergic conjunctivitis, mild atopic keratoconjunctivitis, mild suicidal ideation, moderate depression, and moderate allergic reaction to egg (Table S3 in the ESM).

The most frequently reported TEAEs were nasopharyngitis (20.4%; 23.6 patients per 100PY), AD (19.0%; 21.3 patients per 100PY), upper respiratory tract infection (11.9%; 12.5 patients per 100PY), and headache (8.8%; 9.3 patients per 100PY). Injection-site reactions were reported in 19 patients (6.5%; 6.6 patients per 100PY), and conjunctivitis (according to descriptions given by the investigators)

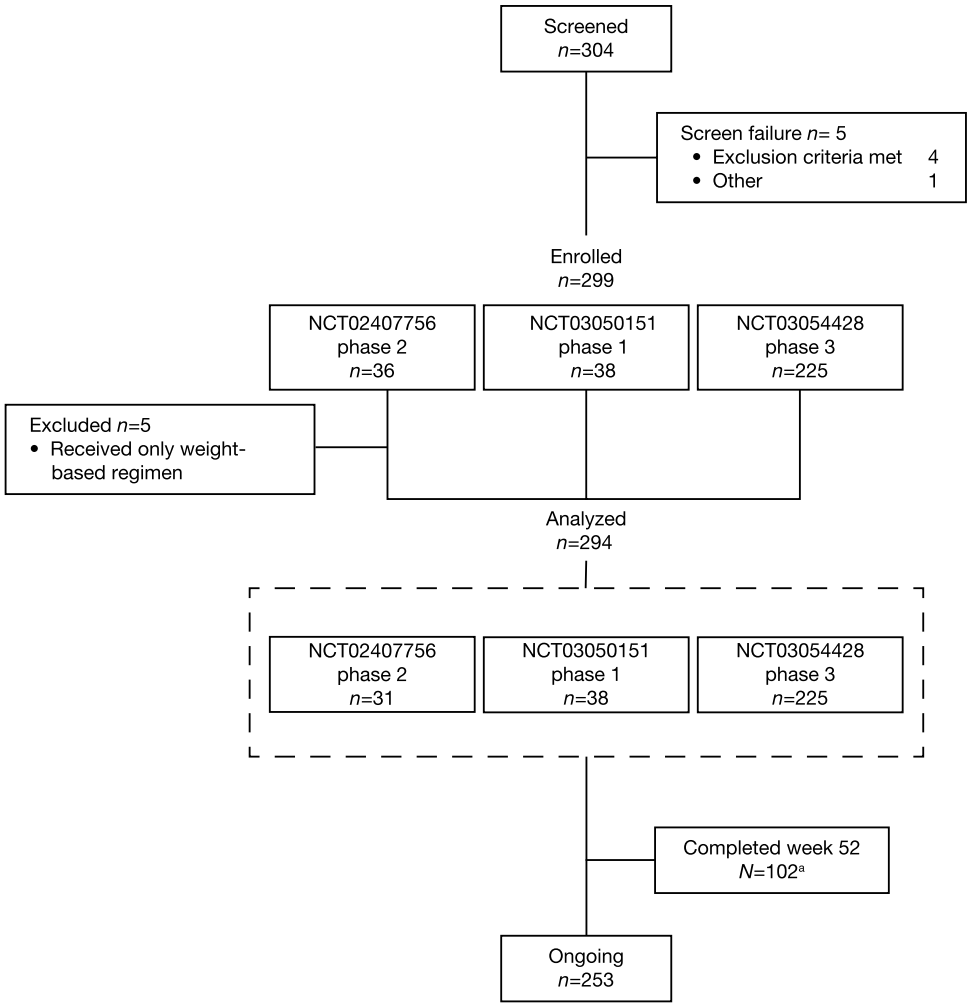



**Fig. 2** Patient disposition. [a]Although 102 patients completed the week 52 visit, partial data (e.g., IGA data) were available for a further single patient who was not formally considered to have completed 52 weeks; IGA data for 103 patients have been included in the efficacy analyses. *IGA* Investigator's Global Assessment

was reported in 26 patients (8.8%; 9.2 patients per 100PY), including conjunctivitis (12 patients; 4.1%), bacterial conjunctivitis (six patients; 2.0%), viral conjunctivitis (two patients; 0.7%), allergic conjunctivitis (11 patients; 3.7%), and atopic keratoconjunctivitis (one patient; 0.3%). Herpesvirus infections (MedDRA high-level term) were reported in 18 patients (6.1%; 6.3 events per 100PY) (Table S4 in the ESM). Further details of skin infections and conjunctivitis are presented in Tables S4 and S5 in the ESM, respectively.

### 3.3 Efficacy Outcomes

Efficacy data for the 294 patients included in the analysis are presented from the baseline of the parent study up to week 52 of treatment on the regimen of dupilumab 300 mg q4w or uptitrated to weight-tiered dupilumab q2w in the OLE. Clinical signs showed substantial improvement over time. The proportions of patients with an IGA score of 0/1 (Fig. 3a) or EASI-75 (Fig. 3b) increased from parent study baseline through week 52. By week 52, 42.7% of patients (44/103) had an IGA score of 0/1, and 93.1%, 81.2%, and 56.4% of patients had EASI-50, EASI-75, and EASI-90, respectively (Table 3). Additionally, 86.4% of patients had at least mild disease (IGA $\leq 2$) (Fig. S1a in the ESM).

The mean percent changes in EASI (Fig. 3c) and SCORAD (Fig. 3d) showed substantial improvement from the parent study baseline through week 52, with mean percent $\pm$ SD change of $-83.5\% \pm 23.5$ in EASI and $-65.0\% \pm 21.3$ in SCORAD at week 52 (Table 3). At week 52, the mean EASI was 5.3, with a mean change from parent study baseline of $-28.5$ (Fig. S1b and S1c in the ESM). The percentage of BSA affected decreased from the parent study baseline through week 52 (Fig. 3e), with a mean $\pm$ SD change in percentage of BSA affected of $-42.7 \pm 26.2$ at week 52 (Table 3).

Patients also showed improvement in health-related quality of life, with 86.4% having a $\geq 6$-point improvement in CDLQI by week 52; many experienced this improvement as early as week 4 (Fig. 3f). The mean $\pm$ SD change from

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

| Characteristic | All patients ($N=294$) |
|---|---|
| Age, years | 14.7 ± 1.7 |
| Sex, male | 167 (56.8) |
| Race | |
| White | 203 (69.0) |
| Black or African American | 30 (10.2) |
| Asian | 42 (14.3) |
| American Indian or Alaska Native | 2 (0.7) |
| Native Hawaiian or other Pacific Islander | 5 (1.7) |
| Other | 8 (2.7) |
| Not reported | 4 (1.4) |
| Ethnicity | |
| Not Hispanic or Latino | 242 (82.3) |
| Hispanic or Latino | 52 (17.7) |
| Weight, kg | 64.8 ± 20.2 |
| Weight group, kg | |
| < 60 | 146 (49.7) |
| ≥ 60 | 148 (50.3) |
| BMI, kg/m$^2$ | 24.1 ± 6.0 |
| BMI ≥ 85th percentile of population | 121 (41.2) |
| Duration of AD, years | 12.5 ± 3.2 |
| IGA | |
| 0 | 4 (1.4) |
| 1 | 23 (7.8) |
| 2 | 55 (18.7) |
| 3 | 139 (47.3) |
| 4 | 73 (24.8) |
| EASI | 19.9 ± 15.6 |
| BSA affected by AD | 34.1 ± 25.3 |
| SCORAD | 46.7 ± 21.3 |
| CDLQI | 7.0 ± 6.1 |
| Patients with ongoing or history of allergic/atopic conditions | 294 (100) |
| Allergic rhinitis | 185 (62.9) |
| Food allergy | 171 (58.2) |
| Asthma | 147 (50.0) |
| Hives | 72 (24.5) |
| Allergic conjunctivitis | 65 (22.1) |
| Chronic rhinosinusitis | 16 (5.4) |
| Nasal polyps | 5 (1.7) |
| Aspirin sensitivity | 4 (1.4) |
| Eosinophilic esophagitis | 1 (0.3) |
| Other allergies | 200 (68.0) |
| Patients receiving prior systemic medications for AD | 182 (61.9) |
| Patients receiving prior systemic corticosteroids | 124 (42.2) |
| Patients receiving prior systemic nonsteroidal immunosuppressants | 138 (46.9) |
| Cyclosporine | 71 (24.1) |
| Methotrexate | 43 (14.6) |
| Mycophenolate mofetil | 10 (3.4) |
| Azathioprine | 7 (2.4) |

Data are 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, *IGA* Investigator's Global Assessment, *SCORAD* SCORing Atopic Dermatitis

**Table 2** Safety assessment

| TEAEs | All patients ($N=294$) | |
|---|---|---|
| | nE | nE/100PY |
| Total number of TEAEs | 1131 | 370.2 |
| Total number of serious TEAEs | 5 | 1.6 |
| Total number of severe TEAEs | 12 | 3.9 |
| Total number of TEAEs related to treatment | 120 | 39.3 |
| Total number of TEAEs related to permanent treatment discontinuation | 2 | 0.7 |
| | *n* (%) | nP/100PY |
| Patients with any TEAE | 217 (73.8) | 194.6 |
| Patients with any serious TEAE | 5 (1.7) | 1.7 |
| Patients with any severe TEAE | 11 (3.7) | 3.8 |
| Patients with any TEAEs related to treatment | 53 (18.0) | 20.2 |
| Patients with any TEAEs leading to permanent discontinuation | 2 (0.7) | 0.7 |
| Conjunctivitis cluster[a] | 26 (8.8) | 9.2 |
| Injection-site reactions (HLT) | 19 (6.5) | 6.6 |
| Skin infections and infestations (SOC)[b] | 37 (12.6) | 13.9 |
| Most common TEAEs reported in ≥3% of patients (PT) | | |
| Nasopharyngitis | 60 (20.4) | 23.6 |
| Dermatitis atopic | 56 (19.0) | 21.3 |
| Upper respiratory tract infection | 35 (11.9) | 12.5 |
| Headache | 26 (8.8) | 9.3 |
| Oropharyngeal pain | 16 (5.4) | 5.6 |
| Vomiting | 13 (4.4) | 4.5 |
| Influenza | 13 (4.4) | 4.4 |
| Oral herpes | 12 (4.1) | 4.2 |
| Conjunctivitis | 12 (4.1) | 4.1 |
| Pyrexia | 12 (4.1) | 4.1 |
| Acne | 11 (3.7) | 3.8 |
| Conjunctivitis allergic | 11 (3.7) | 3.7 |
| Diarrhea | 10 (3.4) | 3.5 |
| Abdominal pain upper | 10 (3.4) | 3.4 |
| Cough | 9 (3.1) | 3.1 |
| Sinusitis | 9 (3.1) | 3.0 |
| Viral upper respiratory tract infection | 9 (3.1) | 3.0 |

*ESM* electronic supplementary material, *HLT* MedDRA high-level term, *MedDRA* Medical Dictionary for Regulatory Activities, *nE* number of events, *nP* number of patients, *PT* MedDRA preferred term; *100PY* 100 patient-years, *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]Further details of skin infections are presented in Table S5 in the ESM

parent study baseline in CDLQI was $-11.8 \pm 6.7$ at week 52 (Table 3).

Patients showed clinical improvement regardless of baseline body weight. In particular, the increase from parent study baseline through week 52 in the proportion of patients achieving IGA 0/1 (36.5 and 49.0% for baseline body weight $<60$ or $\geq 60$ kg, respectively) and EASI-75 (86.0 and 76.5%, respectively), and the improvements in EASI (mean percent change from baseline $-87.0$ and $-80.1$%, respectively), were similar irrespective of patient baseline body weight (Fig. 4).

At the time of database lock, of the 294 patients included in the analysis, 289 had received dupilumab q4w or q2w regimens for at least 16 weeks in the OLE. During the course of treatment, 70.9% (205/289) of patients required uptitration (36.3% prior to week 16, and 34.6% after week 16), with

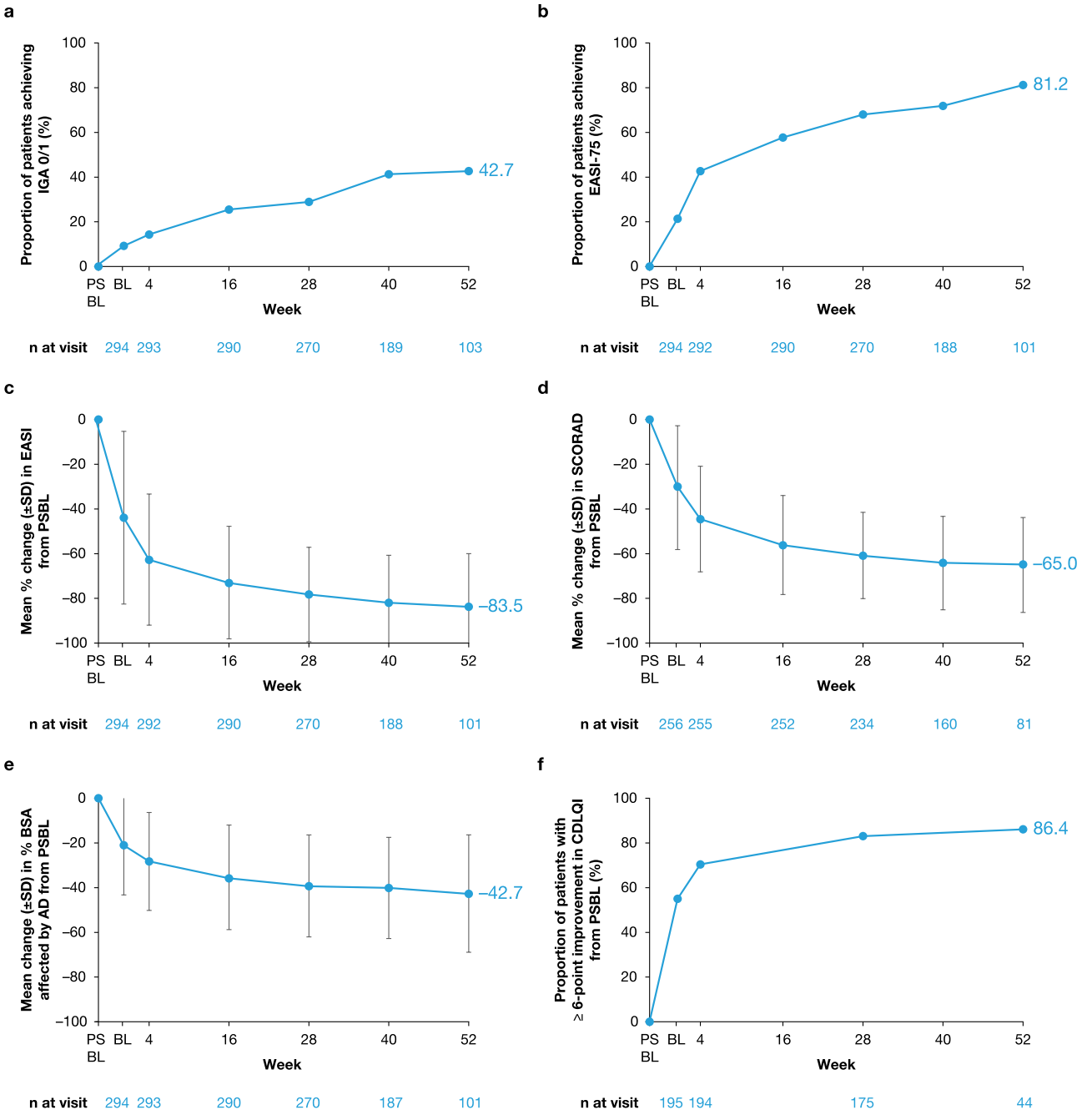



**Fig. 3** Efficacy outcomes from PSBL through week 52. [a]Proportion of patients achieving (**a**) IGA 0/1 or (**b**) EASI-75, mean % change from BL through week 52 in (**c**) EASI, (**d**) total SCORAD, and (**e**) BSA affected, and (**f**) proportion of patients with ≥6-point improvement in CDLQI[b] from BL. [a]102 patients completed the week 52 visit at the time of database lock. Partial data (e.g., IGA data) were available for a further single patient who was not formally considered to have completed 52 weeks; IGA data for 103 patients were included in the efficacy analyses. 101, 101, 81, and 44 patients had EASI, BSA, SCORAD, and CDLQI assessment, respectively, at week 52. SCORAD data were not collected in R668-AD-1607. CDLQI data were not collected in R668-AD-1412 and R668-AD-1607. [b]In adolescents with moderate-to-severe AD, a within-patient change of 6–8 points in CDLQI is considered to be a minimum clinically meaningful difference. *AD* atopic dermatitis, *BL* baseline, *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

**Table 3** Efficacy assessment at week 52

| Efficacy assessment | All patients ($N=294$) |
|---|---|
| Proportion of patients achieving IGA 0/1 | 44/103 (42.7) |
| Proportion of patients achieving EASI-50 | 94/101 (93.1) |
| Proportion of patients achieving EASI-75 | 82/101 (81.2) |
| Proportion of patients achieving EASI-90 | 57/101 (56.4) |
| Percentage change from baseline of parent study in EASI | −83.5 ± 23.5 |
| Change from baseline of parent study in EASI | −28.5 ± 14.9 |
| Change from baseline of parent study in % BSA affected by AD | −42.7 ± 26.2 |
| Percentage change from baseline of parent study SCORAD | −65.0 ± 21.3 |
| Change from baseline of parent study in CDLQI | −11.8 ± 6.7 |

Data are presented as *n*/*N*1 (%) 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, *N1* patients with non-missing EASI or IGA scores at each week, *SCORAD* SCORing Atopic Dermatitis

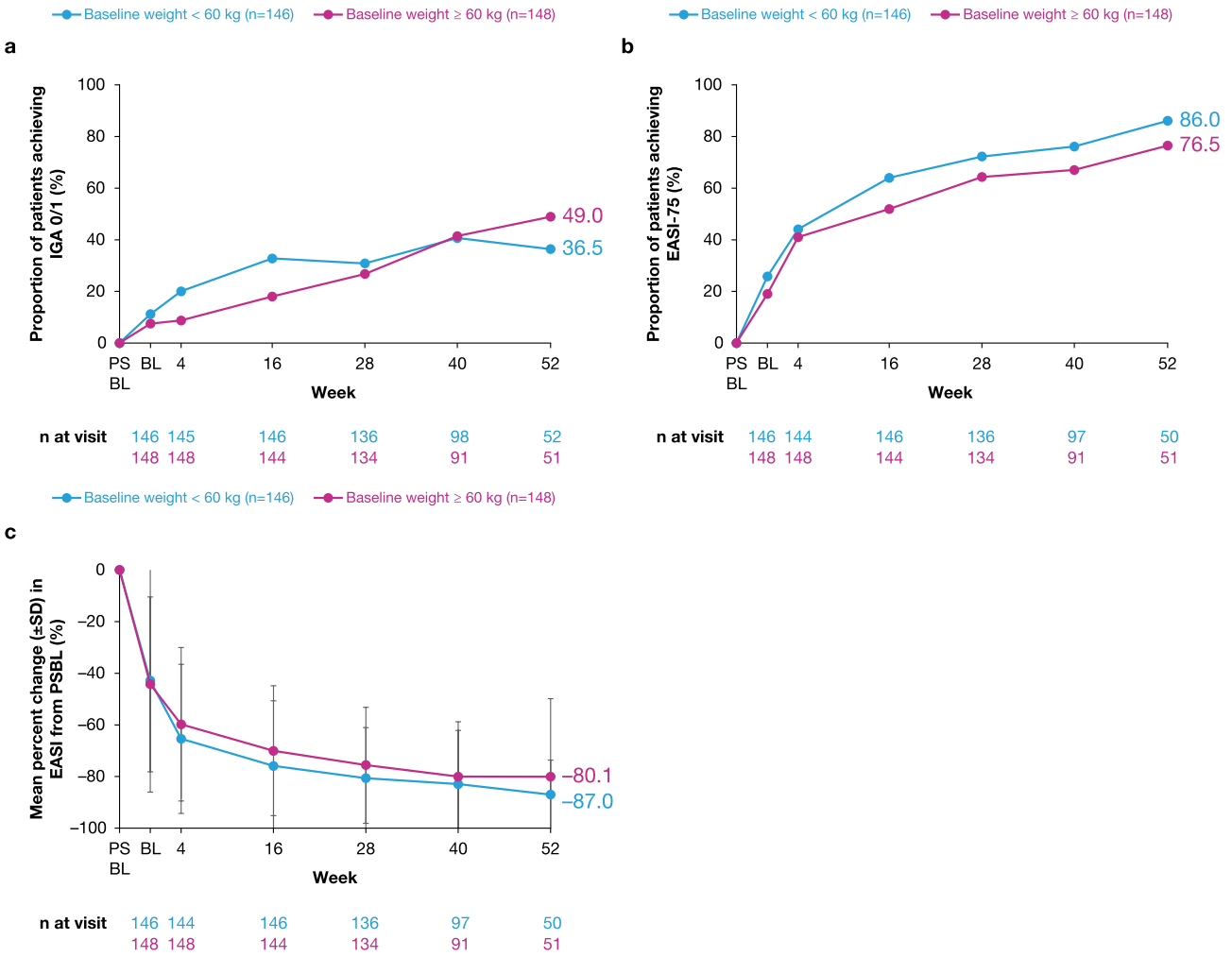



**Fig. 4** Efficacy outcomes from PSBL through week 52 by patient baseline weight. Proportion of patients achieving (**a**) IGA 0/1 or (**b**) EASI-75, and (**c**) mean % change in EASI. *BL* baseline, *EASI* Eczema Area and Severity Index, *EASI-75* patients achieving a ≥ 75% reduction in EASI compared with PSBL, *IGA* Investigator's Global Assessment, *PSBL* parent study baseline, *SD* standard deviation

a mean ± SD time to uptitration of 12.5 ± 9.8 weeks (median 12.0 [Q1 4.0–Q3 16.0] weeks) (Table 4). The proportion of uptitrated patients with IGA 0/1 and the proportion with EASI-75 increased over time from the point of uptitration (Fig. 5a, b), reaching 35.7 and 51.9%, respectively, 48 weeks after first uptitration visit. The mean ± SD percentage change in EASI from the parent study baseline showed substantial improvement from the point of uptitration in uptitrated patients, reaching − 84.3% ± 13.7 at 48 weeks after the first uptitration visit (Fig. 5c).

By week 52, 29.4% (30/102) of patients had clear/almost clear skin (IGA 0/1) sustained over 12 weeks (Table 5). Of these, 17 patients (56.7%) had experienced relapse at the time of the data cutoff and were re-initiated on treatment. The mean ± SD time to dupilumab re-initiation following relapse after first record of IGA 0/1 sustained over 12 weeks was 17.5 ± 17.3 weeks. Of the 11 patients who re-initiated the drug, and for whom another IGA assessment was performed following re-initiation, ten (90.9%) regained IGA 0/1 (Table 5 and Fig. 6).

### 3.4 Dupilumab Pharmacokinetic Profile

Mean trough concentrations of functional dupilumab in the serum of patients assigned to the regimen of dupilumab 300 mg q4w at the start of the study reached a steady state of approximately 20 mg/L by week 16, and this was maintained through week 52 in patients who continued to receive dupilumab 300 mg q4w. Mean concentrations were higher in patients uptitrated to a 200/300 mg q2w regimen at week 16 (55.3 mg/L) and week 52 (75.9 mg/L) (Fig. 7).

## 4 Discussion

In adolescents aged ≥ 12 to < 18 years with inadequately controlled moderate-to-severe AD, dupilumab treatment for up to 52 weeks in the LIBERTY AD PED-OLE study provided incremental and substantial clinical benefit in AD signs and symptoms, as well as improvements in quality of life. This clinical benefit was achieved irrespective of patient baseline body weight. A trend towards further improvement in efficacy measures over time with continued dupilumab treatment was seen, and patients who were uptitrated because of inadequate responses with the dupilumab q4w regimen were shown to subsequently achieve clinically meaningful responses with the q2w regimen. A previous analysis demonstrated the efficacy and safety of dupilumab in a small number of adolescents who received either 2 or 4 mg/kg qw [28]. The results from LIBERTY AD PED-OLE reinforce the long-term results shown previously. Importantly, the analysis presented here included data for the treatment regimen approved for treating adolescents with moderate-to-severe AD.

The long-term safety profile was consistent with the results previously obtained in longitudinal studies in adult patients with AD [31] and with the short-term profile seen in previous phase III trials of dupilumab in adolescents with moderate-to-severe AD [27]. Only two patients discontinued because of a TEAE, including one patient with moderate bilateral conjunctivitis and one patient with worsening AD. Five serious TEAEs were reported during the course of the study. The reported events of conjunctivitis were mainly mild or moderate, and none were categorized as SAEs. One case of severe allergic conjunctivitis and one case of severe viral conjunctivitis were reported, neither of which led to treatment discontinuation.

**Table 4** Proportions of patients with uptitration

| Patients with uptitration | All patients ($N = 294$) |
|---|---|
| Number of patients who received at least one q4w dose | 293[a] |
| Number of patients who received q4w dose for at least 16 weeks | 289 |
| Number of patients with uptitration | 205/289 (70.9) |
| Number of patients with uptitration prior to week 16 | 105/289 (36.3) |
| Number of patients with uptitration at or after week 16 | 100/289 (34.6) |
| Time in weeks from start of q4w dose to first uptitration visit | 12.5 ± 9.8 |
| Median (Q1–Q3) | 12.0 (4.0–16.0) |
| Minimum; maximum | 2.0; 52.0 |

Data are presented as *n*/*N*1 (%) or mean ± standard deviation unless otherwise indicated

*N1* number of patients who received q4w dose for at least 16 weeks, *q4w* every 4 weeks

[a]One patient uptitrated to 300 mg every 2 weeks directly from 2 mg/kg every week without receiving a q4w dose. This patient was analyzed based on the final dose

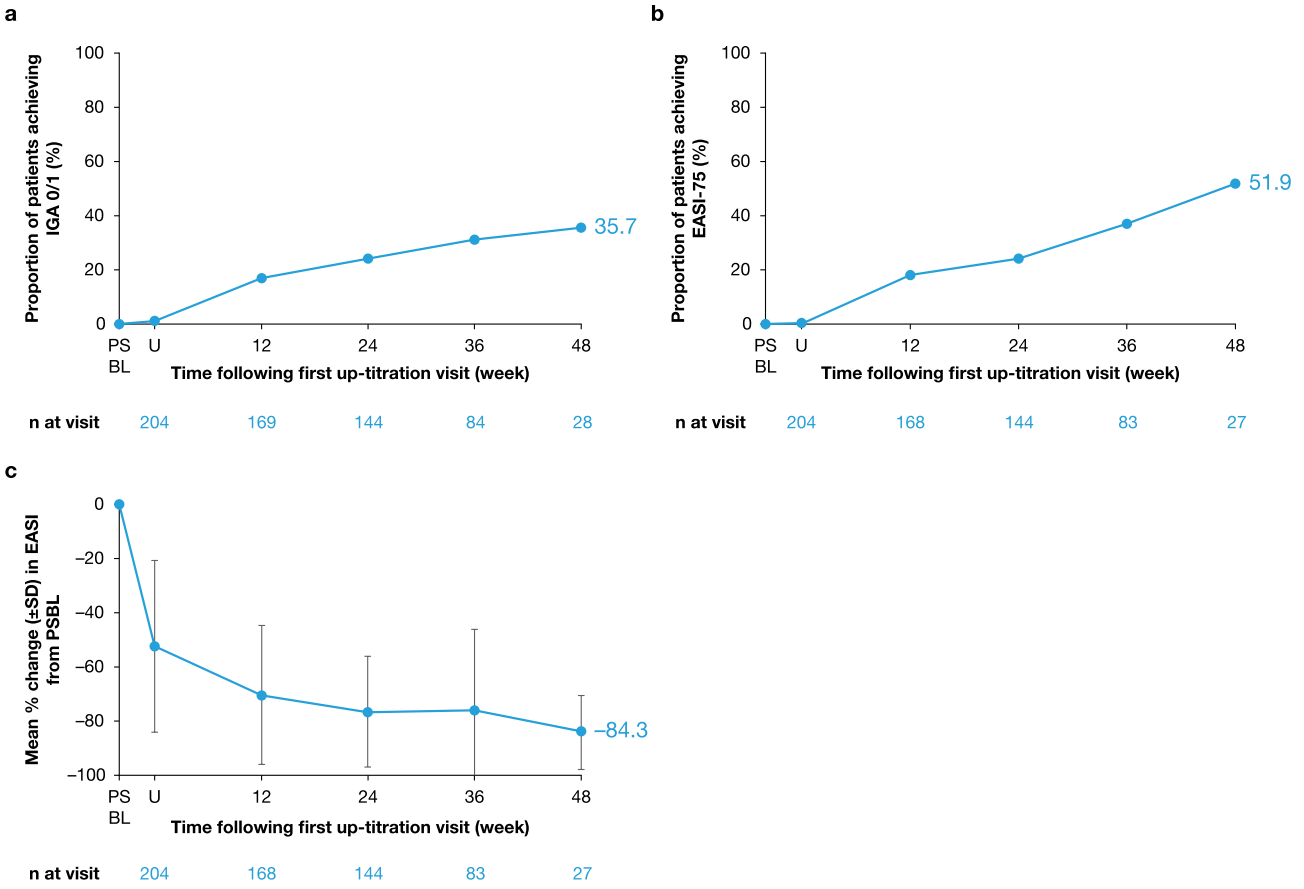



**Fig. 5** Proportion of uptitrated patients achieving (**a**) IGA 0/1 or (**b**) EASI-75, and (**c**) mean % change in EASI from PSBL in uptitrated patients. *BL* baseline, *EASI* Eczema Area and Severity Index, *EASI-75* patients achieving a ≥ 75% reduction in EASI from PSBL, *IGA* Investigator's Global Assessment, *PSBL* parent study baseline, *SD* standard deviation, *U* time of uptitration

**Table 5** Proportion of patients with Investigator's Global Assessment 0/1 sustained over 12 weeks, time to re-initiation following relapse, and efficacy upon re-initiation

| Patients | All patients ($N = 294$) |
|---|---|
| Proportion of patients with IGA 0/1 sustained over 12 weeks at week 52, *n*/*N*1 (%) | 30/102 (29.4) |
| Patients who re-initiated treatment after relapse, *n*/*N*2 (%) | 17/30 (56.7) |
| Time in weeks to study drug re-initiation following relapse | 17.5 ± 17.3 |
| Minimum; maximum | 2.0; 64.0 |
| Patients regaining IGA 0/1 following re-initiation, *n*/*N*3 (%) | 10/11 (90.9) |
| Time in weeks to achievement of IGA 0/1 following re-initiation, mean ± SD | 20.7 ± 18.9 |
| Minimum; maximum | 3.7; 64.0 |

Patients who maintained an IGA score of 0 or 1 continuously for a 12-week period after week 40 were discontinued from study drug (e.g., a patient who had an IGA score of 0 or 1 from week 40 through week 52, inclusive, was discontinued from the study drug at week 52; similarly, a patient who had an IGA score of 0 or 1 from week 52 through week 64, inclusive, was discontinued from study drug at week 64, and so on)

*IGA* Investigator's Global Assessment, *N1* patients who completed treatment up to week 52, *N2* patients who achieved IGA 0/1 sustained over 12 weeks at week 52, *N3* patients who re-initiated study drug treatment after relapse: only includes patients for whom another IGA assessment was performed subsequent to re-initiation, *SD* standard deviation

During the study, most adolescent patients (70.9%) were uptitrated from the dupilumab q4w to the q2w dose regimen, according to the study protocol, when not recording an IGA score of 0/1 after 16 weeks of treatment with the q4w dose regimen, or prior to week 16 at the discretion of the investigator. Mean trough concentrations of dupilumab from

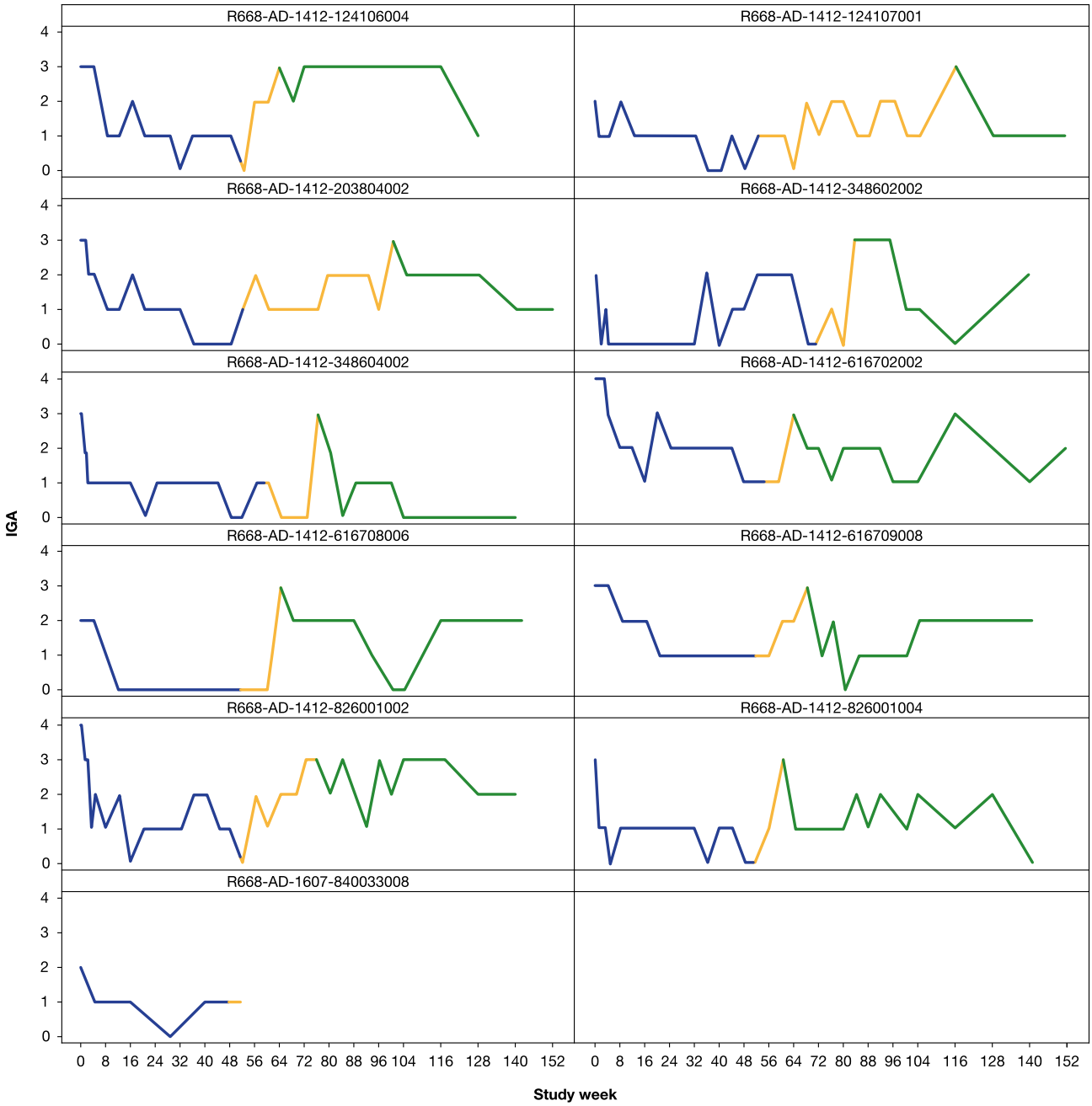



**Fig. 6** IGA assessment for the 11[a] patients who relapsed and were re-initiated on dupilumab[b]. [a]17 patients relapsed and were re-initiated on dupilumab; the data in the figure are presented for the 11 for whom another IGA assessment was performed subsequent to re-initiation. [b]The *blue segment* depicts the period from baseline to the last dupilumab treatment before recording IGA 0/1 sustained over 12 weeks; the *orange segment* depicts the period from the last dupilumab treatment before achieving IGA 0/1 sustained over 12 weeks to dupilumab re-initiation; the *green segment* depicts the period from dupilumab re-initiation to the last IGA assessment. *IGA* Investigator's Global Assessment

weeks 16 to 52 were higher for adolescent patients receiving dupilumab 200/300 mg q2w than for those receiving 300 mg q4w and were consistent with mean steady-state concentrations at week 16 in the pivotal phase III study of dupilumab in adolescents with moderate-to-severe AD receiving dupilumab 300 mg q4w (19.8 mg/L) or 200/300 mg q2w (54.5 mg/L) [27]. Importantly, a substantial proportion of patients who were nonresponders to the q4w regimen in this study may have had suboptimal exposure to dupilumab and achieved a response following uptitration to the q2w regimen, suggesting that the approved q2w dose regimen is optimal for adolescents in the corresponding weight groups.

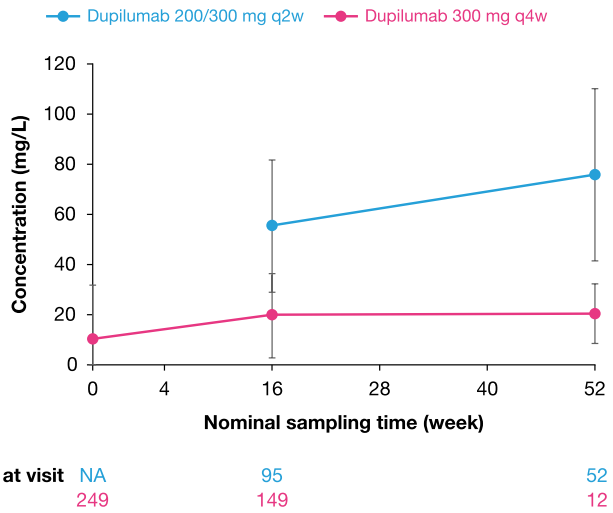



**Fig. 7** Mean (±standard deviation) concentrations of functional dupilumab in serum at weeks 0, 16, and 52. Concentrations below the lower limit of quantification were set to 0. Patients from parent studies R668-AD-1526 or R668-AD-1607 are shown. Patients may have been eligible for uptitration during the study. Treatment group was defined by the initially administered dose in study R668-AD-1434 at week 0 and by the last dose received prior to sample collection for subsequent visits. *NA* not applicable, *q2w* every 2 weeks, *q4w* every 4 weeks

During the follow-up period, the majority of patients with IGA 0/1 sustained for a continuous 12-week period who then discontinued dupilumab experienced disease recurrence, suggesting the need for continuous administration of dupilumab. Importantly, our data suggest that dupilumab can be re-initiated in the event of a treatment interruption, and patients can again report IGA 0/1. Of note, 13 of 30 patients (43%) did not relapse after stopping dupilumab, with a median follow-up period of 18.0 weeks (Q1 12.0–Q3 18.0). This intriguing finding may suggest a potential disease-modifying role of dupilumab in some pediatric patients with AD. However, the data are limited in terms of both the number of patients studied and the duration of follow-up. The limited number of patients precludes further subgroup analyses to determine demographic and baseline disease characteristics that might be predictive of long-term remission without need for further treatment in these patients. Furthermore, pediatric patients with AD can outgrow their disease or go into long-term disease remission with subsequent flare-ups. Hence, it is not possible to comment, given the current study design, on whether the lack of relapse in these patients was because of spontaneous remission or disease modification by dupilumab. More investigation with a larger number of patients, including in younger pediatric age groups, and longer follow-up are needed to further answer this question.

A key strength of this study is that the analyses are based on long-term (up to 1 year) treatment, including the approved dose regimen of dupilumab in a large group of patients, thus providing data relevant to clinicians managing AD in adolescents over time. Limitations include the open-label, nonrandomized nature of the study. Patients were included in the study from three different parent studies, introducing some heterogeneity into the OLE patient population. Additionally, the concomitant use of topical corticosteroids or other AD therapies was not standardized; the efficacy data were presented as observed analysis and did not account for potential confounding factors resulting from additional AD therapies.

## 5 Conclusions

Dupilumab treatment demonstrated acceptable safety and sustained efficacy in adolescents aged ≥ 12 to < 18 years with inadequately controlled moderate-to-severe AD. These results support the long-term continuous use of dupilumab in this patient population. Additionally, the need for uptitration in most patients during the course of the study to the approved q2w regimen suggests that this regimen is optimal for adolescent patients with AD. Finally, the dupilumab long-term safety profile was comparable to that seen in adults, with safety consistent with the known dupilumab safety profile.

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s40257-022-00683-2.

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## Declarations

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**Conflict of interest** Andrew Blauvelt is a scientific advisor and clinical study investigator for AbbVie, Abcentra, Aligos, Almirall, Amgen, Arcutis, Arena, Aslan, Athenex, Boehringer Ingelheim, Bristol Myers Squibb, Dermavant, Eli Lilly and Company, Evommune, Forte, Galderma, Incyte, Janssen, Landos, LEO Pharma, Novartis, Pfizer, Rapt, Regeneron Pharmaceuticals, Inc., Sanofi Genzyme, Sun Pharma, UCB Pharma, and Vibliome. Emma Guttman-Yassky has received personal fees from AbbVie, Allergan, Amgen, Asana BioSciences, Celgene, Concert, Dermavant, Dermira, DS Biopharma, Eli Lilly and Company, Escalier BioSciences, Galderma, Glenmark, Kyowa Kirin, LEO Pharma, Mitsubishi Tanabe, Novartis, Pfizer, Regeneron Pharmaceuticals, Inc., and Sanofi; and has received grants paid to the institution from

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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.

**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.

**Consent to participate** All patients provided written consent/assent, and at least one parent or guardian for each adolescent patient provided written informed consent. All people named in the Acknowledgements section gave written permission to be named in the manuscript.

**Consent for publication** Not applicable.

**Author contributions** Andrew Blauvelt and Ashish Bansal contributed to the study concept and design. Andrew Blauvelt, Emma Guttman-Yassky, Amy S. Paller, Eric L. Simpson, Michael J. Cork, Jamie Weisman, John Browning, and Weily Soong acquired data. Xian Sun and Zhen Chen conducted the statistical analyses of the data. All authors interpreted the data, provided critical feedback on the manuscript, approved the final manuscript for submission, and are accountable for the accuracy and integrity of the manuscript.



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