# Dupilumab Decreases Blood Biomarkers in Adolescents With Moderate-to-Severe Atopic Dermatitis: Data From a Phase 3 Trial (LIBERTY AD ADOL)

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## BACKGROUND

- Atopic dermatitis (AD) is a chronic inflammatory skin condition characterized by pruritus and disruption of skin-barrier function, predominantly driven by type 2 inflammation[1]
- In a majority of patients with moderate-to-severe AD, circulating C-C motif chemokine ligand 17 (CCL17, also known as thymus and activation-regulated chemokine [TARC]) and total IgE concentrations are elevated and correlate with disease severity[2–4]
- Serum TARC, IgE, and lactate dehydrogenase (LDH) have been suggested as biomarkers for monitoring AD disease activity and treatment response[4]
- Dupilumab is a fully human monoclonal antibody[5,6] that blocks the shared receptor component for interleukin (IL)-4 and IL-13, thus inhibiting signaling of both IL-4 and IL-13, which are key drivers of type 2 inflammation[7]

## OBJECTIVE

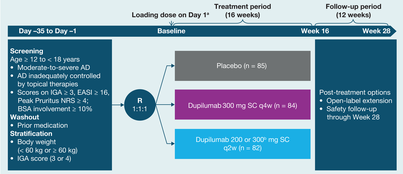
- **To evaluate blood levels of type 2 inflammatory markers in patients from a randomized, placebo-controlled, double-blind, phase 3 trial of dupilumab in adolescents with moderate-to-severe AD inadequately controlled by topical therapies (LIBERTY AD ADOL)**

## METHODS

### Study design

- LIBERTY AD ADOL (NCT03054428) study design has been published previously[8] and is summarized in **Figure 1**

**Figure 1. Study design.**




ªFor q2w, patients with body weight < 60 kg at baseline received a loading dose of 400 mg on Day 1, while patients with body weight ≥ 60 kg received a loading dose of 600 mg. All patients in every 4 weeks (q4w), regardless of weight, received a 600 mg loading dose. ᵇPatients with body weight < 60 kg received 200 mg of the study drug; patients with body weight ≥ 60 kg received 300 mg. BSA, body surface area; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; NRS, Numerical Rating Scale; R, randomization.

## RESULTS

### Baseline demographics and disease characteristics

- Demographics and baseline characteristics were similar across treatment groups and showed considerable disease burden at baseline; > 90% of patients had ≥ 1 comorbid type 2 inflammatory disease including allergic rhinitis, asthma, or food allergy (**Table 1**)
- Baseline blood levels of TARC, total IgE, LDH, and allergen-specific IgE are shown in **Table 2**

**Table 1. Baseline demographics and disease characteristics.ª**

| | Range | Placebo (n = 85) | Dupilumab 300 mg q4w (n = 84) | Dupilumab 200/300 mg q2w (n = 82) |
|---|---|---|---|---|
| Age, mean (SD), years | 12–17 | 14.5 (1.8) | 14.4 (1.6) | 14.5 (1.7) |
| Male, n (%) | – | 53 (62.4) | 52 (61.9) | 43 (52.4) |
| Weight, mean (SD), kg | – | 64.4 (21.5) | 65.8 (20.1) | 65.6 (24.5) |
| Duration of AD, mean (SD), years | – | 12.3 (3.4) | 11.9 (3.2) | 12.5 (3.0) |
| Patients with IGA score, n (%) | 0–4 | | | |
| 3 | – | 39 (45.9) | 38 (45.2) | 39 (47.6) |
| 4 | – | 46 (54.1) | 46 (54.8) | 43 (52.4) |
| EASI score, mean (SD) | 0–72 | 35.5 (14.0) | 35.8 (14.8) | 35.3 (13.8) |
| Peak pruritus NRS score, mean (SD) | 0–10 | 7.7 (1.6) | 7.5 (1.8) | 7.5 (1.5) |
| Percent BSA involvement, mean (SD) | 0–100 | 56.4 (24.1) | 56.9 (23.5) | 56.0 (21.4) |
| SCORAD score, mean (SD) | 0–103 | 70.4 (13.3) | 69.8 (14.1) | 70.6 (13.9) |
| CDLQI, mean (SD) | 0–30 | 13.1 (6.7) | 14.8 (7.4) | 13.0 (6.2) |
| POEM score, mean (SD) | 0–28 | 21.1 (5.4) | 21.1 (5.5) | 21.0 (5.0) |
| HADS score, mean (SD) | 0–42 | 11.6 (7.8) | 13.3 (8.2) | 12.6 (8.0) |
| Patients with ≥ 1 concurrent allergic condition, n (%) | – | 78 (91.8) | 73 (88.0) | 79 (96.3) |
| Allergic rhinitis | – | 57 (67.1) | 48 (57.8) | 59 (72.0) |
| Asthma | – | 46 (54.1) | 42 (50.6) | 46 (56.1) |
| Food allergy | – | 48 (56.5) | 52 (62.7) | 52 (63.4) |
| Allergic conjunctivitis | – | 16 (18.8) | 21 (25.3) | 20 (24.4) |
| Hives | – | 22 (25.9) | 28 (33.7) | 22 (26.8) |
| Chronic rhinosinusitis | – | 7 (8.2) | 6 (7.2) | 6 (7.3) |
| Nasal polyps | – | 2 (2.4) | 1 (1.2) | 2 (2.4) |
| Eosinophilic esophagitis | – | 0 | 0 | 1 (1.2) |
| Other allergies | – | 62 (72.9) | 53 (63.9) | 58 (70.7) |

ªData are n (%) unless otherwise specified.
CDLQI, Children's Dermatology Life Quality Index; HADS, Hospital Anxiety and Depression Scale; POEM, Patient-Oriented Eczema Measure; SCORAD, SCORing Atopic Dermatitis; SD, standard deviation.

**Table 2. Median (IQR, Q1–Q3) baseline concentrations of blood biomarkers.**

| | Placebo (n = 85) | Dupilumab 300 mg q4w (n = 84) | Dupilumab 200/300 mg q2w (n = 82) |
|---|---|---|---|
| TARC (pg/mL) | 2,160.0 (1,120.0–6,000.0) | 2,095.0 (1,110.0–5,350.0) | 2,940.0 (974.0–7,320.0) |
| Total IgE (kU/L) | 3,983.0 (813.0–10,931.0) | 3,482.0 (728.0–10,000.0) | 3,739.5 (1,699.0–9,517.0) |
| LDH (U/L) | 259.0 (223.0–321.0) | 275.5 (227.0–362.0) | 277.0 (213.0–344.0) |
| Allergen-specific IgE | | | |
| Cat dander-specific IgE (kU/L) | 20.7 (1.4–62.3) | 27.9 (3.8–72.8) | 35.2 (4.7–69.2) |
| Cow's milk-specific IgE (kU/L) | 0.6 (0.2–4.9) | 0.5 (0.2–1.7) | 0.8 (0.2–3.2) |
| Egg white-specific IgE (kU/L) | 0.4 (0.1–5.6) | 0.7 (0.2–4.1) | 0.8 (0.2–3.5) |
| Peanut-specific IgE (kU/L) | 3.4 (0.2–47.9) | 3.5 (0.4–38.7) | 6.7 (0.5–46.3) |
| Dust mite-specific IgE (kU/L) | 39.9 (0.5–302.0) | 15.1 (1.7–93.3) | 27.7 (2.0–211.5) |

IQR, interquartile range; Q, quartile.

### Efficacy outcomes at Week 16

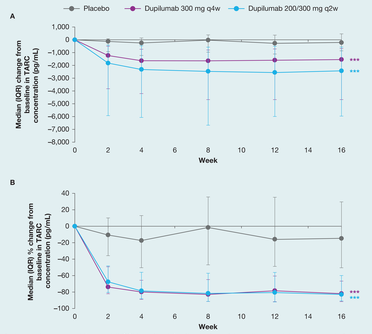
**Table 3. Efficacy outcomes at Week 16.[a,b]**

| | Placebo (n = 85) | Dupilumab 300 mg q4w (n = 84) | Dupilumab 200/300 mg q2w (n = 82) |
|---|---|---|---|
| Patients with IGA 0 or 1 | 2 (2.4) | 15 (17.9)[c] | 20 (24.4)[d] |
| Patients with EASI-75 | 7 (8.2) | 32 (38.1)[d] | 34 (41.5)[d] |
| Proportion of patients with ≥ 3-point improvement (reduction) in weekly average of daily Peak Pruritus NRS from baseline[e] | 8/85 (9.4) | 32/83 (38.6)[d] | 40/82 (48.8)[d] |
| Proportion of patients with ≥ 4-point improvement (reduction) in weekly average of daily Peak Pruritus NRS from baseline | 4/84 (4.8) | 22/83 (26.5)[f] | 30/82 (36.6)[d] |
| Least squares mean percent change from baseline in weekly average of daily Peak Pruritus NRS (SE) | –19.0 (4.1) | –45.5 (3.5)[d] | –47.9 (3.4)[d] |
| Percent BSA involvement, mean (SD)[g] | 42.1 (25.4) | 23.4 (19.9) | 26.4 (25.4) |
| Least squares mean percent change from baseline in SCORAD (SE) | –17.6 (3.8) | –47.5 (3.2)[d] | –51.6 (3.2)[d] |
| Least squares mean change from baseline in CDLQI (SE) | –5.1 (0.6) | –8.8 (0.5)[d] | –8.5 (0.5)[d] |
| Least squares mean change from baseline in POEM (SE) | –3.8 (1.0) | –9.5 (0.9)[d] | –10.1 (0.8)[d] |
| Least squares mean change from baseline in total HADS (SE) | –2.5 (0.8) | –5.2 (0.7)[h] | –3.8 (0.7)[i] |

ªCoprimary outcomes were the proportion of patients with EASI75 and IGA score 0/1 at Week 16.
ᵇData are n (%) unless otherwise specified.
ᶜ*P* = 0.0007 vs placebo.
ᵈ*P* < 0.0001 vs placebo.
ᵉAn improvement of ≥ 3 points from baseline in Peak Pruritus NRS score represents a clinically meaningful response.[9,10]
ᶠ*P* = 0.0001.
ᵍAll observed data values regardless of rescue treatment use.
ʰNominal *P* = 0.0133 vs placebo.
ⁱNominal *P* = 0.2203 vs placebo.
SE, standard error.

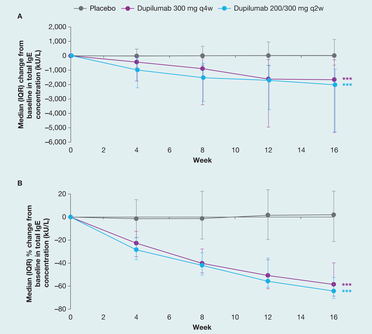
### Blood biomarker levels at Week 16

**Figure 2. (A) Median change and (B) median percent change from baseline in TARC concentration over time.ª**



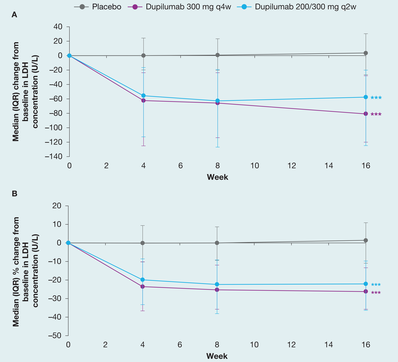

ªLast observation carried forward (LOCF) method for the last post-baseline available observed status prior to rescue treatment to visit Week 16 was carried forward to impute missing data.
***Nominal *P* < 0.0001 vs placebo at Weeks 2, 4, 8, 12, and 16.

**Figure 3. (A) Median change and (B) median percent change from baseline in total IgE concentration over time.ª**




ªLOCF method for the last post-baseline available observed status prior to rescue treatment to visit Week 16 was carried forward to impute missing data.
***Nominal *P* < 0.0001 vs placebo at Weeks 4, 8, 12, and 16.

**Figure 4. (A) Median change and (B) median percent change from baseline in LDH concentration over time.ª**




ªLOCF method for the last post-baseline available observed status prior to rescue treatment to visit Week 16 was carried forward to impute missing data.
***Nominal *P* < 0.0001 vs placebo at Weeks 4, 8, and 16.

**Table 4. Proportion of patients achieving normalized status in blood levels of total IgE and LDH at Week 16.[a,b]**

| | Placebo (n = 80) | Dupilumab 300 mg q4w (n = 77) | Dupilumab 200/300 mg q2w (n = 77) |
|---|---|---|---|
| Total IgE[c] | 2 (2.5) | 7 (9.1)[d] | 3 (3.9)[e] |
| LDH[f] | 4 (28.6) | 16 (88.9)[g] | 16 (88.9)[h] |

ªData are n (%).
ᵇLOCF method for the last post-baseline available observed status prior to rescue treatment to visit Week 16 was carried forward to impute missing data.
ᶜNumber of patients evaluated were 80 in placebo group, 77 in dupilumab 300 mg q4w group, and 77 in dupilumab 200/300 q2w group.
ᵈ*P* = 0.0681.
ᵉ*P* = 0.6377.
ᶠNumber of patients evaluated were 14 in placebo group, 18 in dupilumab 300 mg q4w group, and 18 in dupilumab 200/300 q2w group.
ᵍ*P* = 0.0008.
ʰ*P* = 0.0021.
All *P* values are nominal.

**Table 5. (A) Median (IQR, Q1–Q3) change and (B) median (IQR, Q1–Q3) percent change in allergen-specific IgE concentrations at Week 16.[a,b]**

| Allergen | Placebo (n = 85) | Dupilumab 300 mg q4w (n = 84) | Dupilumab 200/300 mg q2w (n = 82) |
|---|---|---|---|
| **A** | | | |
| Cat dander | 0.1 (–0.5, 8.9) | –4.8 (–26.9, –0.6)*** | –12.6 (–29.4, –1.2)*** |
| Cow's milk | 0 (–0.1, 0.2) | –0.2 (–0.6, 0)*** | –0.3 (–0.9, –0.1)*** |
| Egg white | 0 (–0.1, 0.2) | –0.3 (–1.0, 0)*** | –0.2 (–1.3, 0)*** |
| Peanut | 0 (–0.2, 2.9) | –0.8 (–4.0, 0)*** | –2.1 (–20.8, –0.2)*** |
| Dust mite | 0 (–6.1, 1.8) | –5 (–49.8, –0.5)*** | –10.1 (–94.0, –1.0)*** |
| **B** | | | |
| Cat dander | 8.9 (–10.66, 35.30) | –43.16 (–58.09, –18.75)*** | –45.35 (–64.57, –18.40)*** |
| Cow's milk | 0 (–17.39, 34.55) | –42.18 (–60.88, –9.52)*** | –47.54 (–60.61, –21.92)*** |
| Egg white | 0 (–12.18, 20.00) | –40.97 (–58.43, 0)*** | –41.83 (–59.26, 0)*** |
| Peanut | 0.19 (–11.19, 32.07) | –38.75 (–57.25, 0)*** | –51.81 (–64.30, –23.68)*** |
| Dust mite | 0 (–14.77, 26.57) | –49.83 (–58.46, –32.25)*** | –51.97 (–62.87, –29.40)*** |

ªLOCF method for the last post-baseline available observed status prior to rescue treatment to visit Week 16 was carried forward to impute missing data.
ᵇConcentrations of allergen-specific IgE reported as kU/L.
***In (A), nominal *P* < 0.0001 vs placebo; in (B), *P* < 0.0001 vs placebo.

### Safety

**Table 6. Adverse events during the study treatment period.ª**

| | Placebo (n = 85) | Dupilumab 300 mg q4w (n = 83) | Dupilumab 200/300 mg q2w (n = 82) |
|---|---|---|---|
| Number of patients with | | | |
| TEAE | 59 (69.4) | 53 (63.9) | 59 (72.0) |
| TEAE leading to permanent discontinuation of study drug | 1 (1.2) | 0 | 0 |
| Serious TEAE | 1 (1.2) | 0 | 0 |
| Death | 0 | 0 | 0 |
| Most common TEAEsᵇ | | | |
| Dermatitis atopic (PT) | 21 (24.7) | 15 (18.1) | 15 (18.3) |
| Skin infections (adjudicated) | 17 (20.0) | 11 (13.3) | 9 (11.0) |
| Skin infections excluding herpetic skin infections (adjudicated) | 16 (18.8) | 8 (9.6) | 8 (9.8) |
| Upper respiratory tract infection (PT) | 15 (17.6) | 6 (7.2) | 10 (12.2) |
| Headache (PT) | 9 (10.6) | 4 (4.8) | 9 (11.0) |
| Conjunctivitisᶜ | 4 (4.7) | 9 (10.8) | 8 (9.8) |
| Nasopharyngitis (PT) | 4 (4.7) | 9 (10.8) | 3 (3.7) |
| Infections and infestations (SOC) | 37 (43.5) | 38 (45.8) | 34 (41.5) |
| Injection-site reaction (HLT) | 3 (3.5) | 5 (6.0) | 7 (8.5) |
| Herpes viral infections (HLT) | 3 (3.5) | 4 (4.8) | 1 (1.2) |

ªData are n (%).
ᵇPTs occurring in ≥ 5% of patients in any treatment group.
ᶜIncludes MedDRA PT: atopic keratoconjunctivitis, conjunctivitis, conjunctivitis allergic, conjunctivitis bacterial, and conjunctivitis viral.
HLT, MedDRA High Level Term; MedDRA, Medical Dictionary for Regulatory Activities; PT, MedDRA Preferred Term; SOC, MedDRA System Organ Class. TEAE, treatment-emergent adverse event

## CONCLUSIONS

- **Dupilumab treatment for 16 weeks resulted in a marked reduction in blood levels of multiple type 2 inflammatory biomarkers (i.e., TARC, total IgE, LDH, and allergen-specific IgE); these effects were accompanied by previously reported improvements in AD signs and symptoms[10]**

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