Dupilumab Efficacy and Safety in Adolescents with Moderate-to-Severe Atopic Dermatitis: Results from a Multicenter, Randomized, Placebo-Controlled, Double-Blind, Parallel-Group, Phase 3 Study

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Disclosures

AbbVie, Anacor Pharmaceuticals, Celgene, Dermira, Eli Lilly, Galderma, Genentech, GlaxoSmithKline, Leo Pharma, MedImmune, Menlo Therapeutics, Pfizer, Regeneron Pharmaceuticals, Inc., Sanofi, Valeant Pharmaceuticals International, Inc. – consultant; Amgen, Anacor Pharmaceuticals, Celgene, Chugai Pharma USA, Eli Lilly, Galderma, Genentech, GlaxoSmithKline, MedImmune, Novartis, Pfizer, Regeneron Pharmaceuticals, Inc., Roivant Sciences, Sanofi, Tioga Pharmaceuticals, Inc., Vanda Pharmaceuticals, Inc. – grants/research funding.

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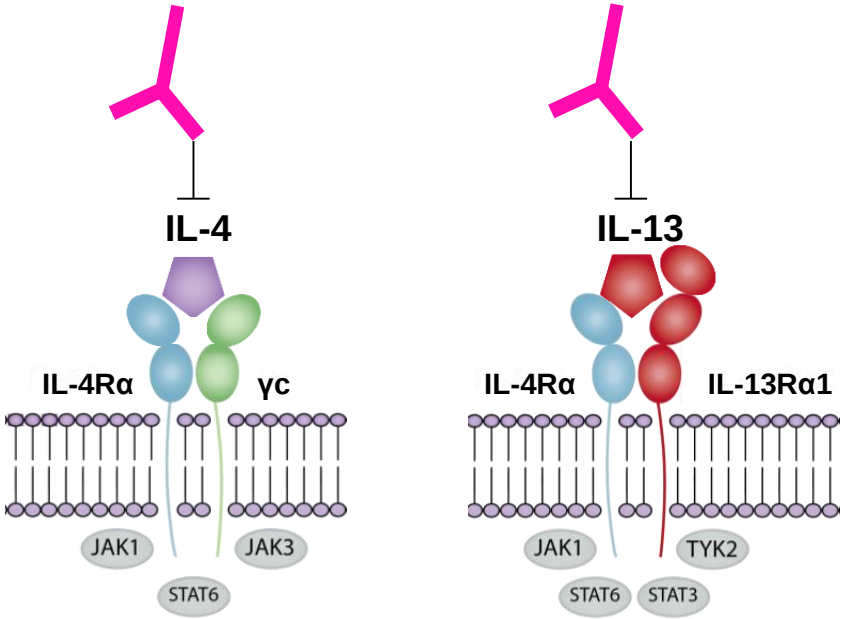
Background

- Atopic dermatitis (AD) is a chronic inflammatory skin disease often associated with atopic comorbidities[1]
- Among adolescents, the estimated prevalence of AD is 8.6% in the USA,[2] 10–15% in the UK,[3] and ≤ 5–10% in most European countries[3]
- AD profoundly affects quality of life of adolescents and family members[4]
  - Itching affects mood and sleep quality
  - Patients commonly have behavioral problems (anxiety, depression)
  - Chronic and relapsing nature of the disease negatively affects family quality of life
- Limited treatment options are available for adolescents[5–7]
  - No systemic agent currently provides a favorable long-term benefit–risk profile for pediatric patients with AD inadequately controlled by topical therapies

1. Shrestha S, et al. Adv Ther. 2017;34:1989-2006. 2. Shaw TE, et al. J Invest Dermatol. 2011;131:67-73.
3. Odhiambo JA, et al. J Allergy Clin Immunol. 2009;124:1251-8. 4. Ricci G, et al. Dermatol Reports. 2012;4:e1.
5. Wollenberg A, et al. J Eur Acad Dermatol Venereol. 2016:30:729-47. 6. Sidbury R, et al. J Am Acad Dermatol. 2014;71:327-49.
7. Ring J, et al. J Eur Acad Dermatol Venereol. 2012;26:1176-93.

Dupilumab: mechanism of action

- **Dupilumab is a fully human *VelocImmune*-derived® monoclonal antibody directed against the IL-4Rα subunit of the IL-4 and IL-13 receptors[1]**
- **IL-4** and **IL-13** are type 2 cytokines that mediate many features of AD[1]
- **Dupilumab** is approved in the EU for treatment of moderate-to-severe AD in adults who are candidates for systemic therapy and can be used with or without topical corticosteroids



Type I receptor

B cells, T cells, monocytes, eosinophils, fibroblasts

Type II receptor

Epithelial cells, smooth muscle cells, fibroblasts, monocytes, activated B cells

γc, common gamma chain; IL, interleukin; R, receptor; JAK, Janus kinase; STAT, signal transducer and activator of transcription; TYK2, tyrosine kinase type 2.

1. Gandhi NA, et al. Nat Rev Drug Discov. 2016;15:35-50.

Objectives and study endpoints

Objective

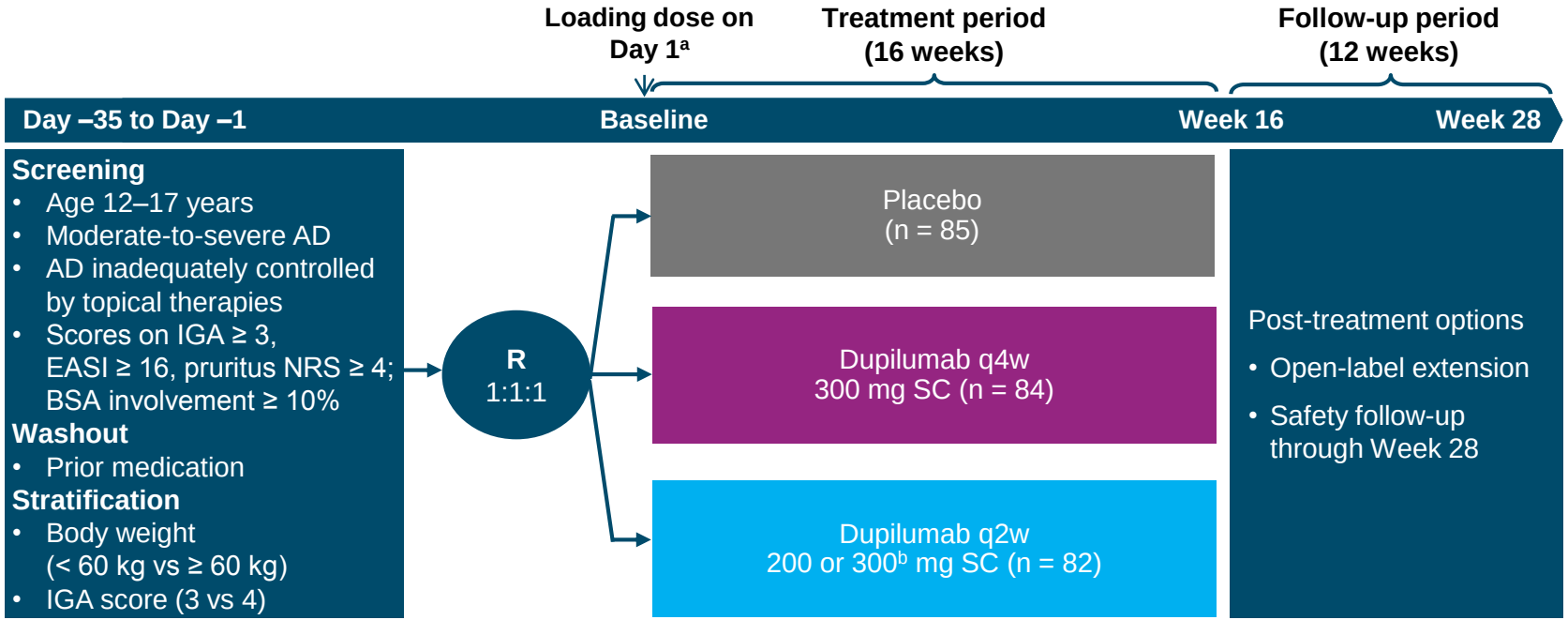
- To evaluate the efficacy and safety of dupilumab monotherapy versus placebo in adolescents with moderate-to-severe AD inadequately controlled by topical therapies

Study endpoints

- Co-primary
  - Proportion of patients with IGA score 0 or 1 at Week 16
  - Proportion of patients with EASI-75 at Week 16 (key secondary endpoint in USA)
- Key secondary
  - Percent change in EASI and peak pruritus NRS scores at Week 16
  - Proportion of patients with ≥ 3- or ≥ 4-point reduction in peak pruritus NRS score at Week 16
- Other secondary
  - EASI-50, EASI-90, percent change in SCORAD score, and changes in CDLQI, POEM, and HADS scores at Week 16

CDLQI, Children's Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; EASI-50(-75)(-90), ≥ 50%(75%)(90%) improvement from baseline in EASI score; HADS, Hospital Anxiety and Depression Scale; IGA, Investigator's Global Assessment; POEM, Patient-Oriented Eczema Measure; NRS, Numerical Rating Scale; SCORAD, SCOring Atopic Dermatitis.

AD-1526: randomized, double-blind, placebo-controlled, parallel-group phase 3 trial of dupilumab in adolescents with moderate-to-severe AD



Topical therapy and other systemic AD therapies were prohibited but allowed as rescue treatment for intolerable symptoms

[a]600 mg on Day 1. [b]Patients with body weight < 60 kg at baseline received 200 mg after a loading dose of 400 mg on Day 1.
BSA, body surface area; q2w, every 2 weeks; q4w, every 4 weeks; R, randomization; SC, subcutaneous.

Baseline demographics and characteristics

	Score range	Placebo (n = 85)	Dupilumab 300 mg q4w (n = 84)	Dupilumab 200 or 300 mg q2w (n = 82)
Age, years	–	14.5 (1.8)	14.4 (1.6)	14.5 (1.7)
Male, n (%)	–	53 (62.4)	52 (61.9)	43 (52.4)
Disease duration, years	–	12.3 (3.4)	11.9 (3.2)	12.5 (3.0)
Patients with IGA score 4, n (%)	0–4	46 (54.1)	46 (54.8)	43 (52.4)
EASI score	0–72	35.5 (14.0)	35.8 (14.8)	35.3 (13.8)
Peak pruritus NRS score	0–10	7.7 (1.6)	7.5 (1.8)	7.5 (1.5)
SCORAD score	0–103	70.4 (13.3)	69.8 (14.1)	70.6 (13.9)
CDLQI score	0–30	13.1 (6.7)	14.8 (7.4)	13.0 (6.2)
POEM score	0–28	21.1 (5.4)	21.1 (5.5)	21.0 (5.0)
HADS score	0–42	11.6 (7.8)	13.3 (8.2)	12.6 (8.0)
BSA affected by AD, %	0–100	56.4 (24.1)	56.9 (23.5)	56.0 (21.4)

Data are shown as mean (standard deviation) unless otherwise specified.

History of comorbid type 2 immune conditions

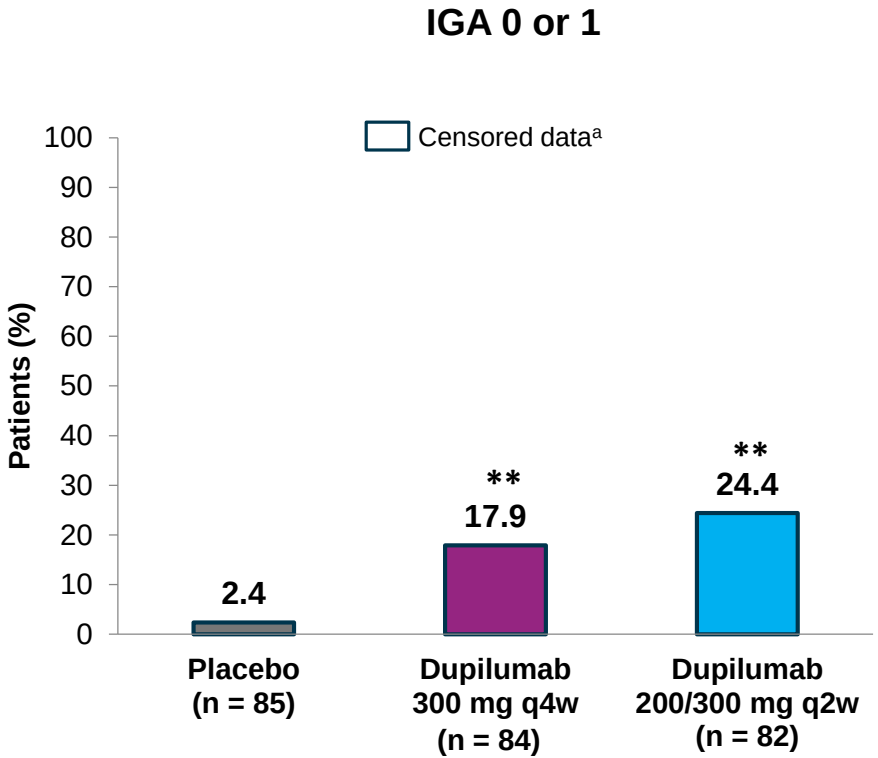
	Placebo (n = 85)	Dupilumab 300 mg q4w (n = 84)	Dupilumab 200 or 300 mg q2w (n = 82)	All patients (n = 251)
Patients with at least 1 allergic condition, n (%)	78 (91.8)	73 (88.0)	79 (96.3)	230 (92.0)
Allergic rhinitis	57 (67.1)	48 (57.8)	59 (72.0)	164 (65.6)
Asthma	46 (54.1)	42 (50.6)	46 (56.1)	134 (53.6)
Food allergy	48 (56.5)	52 (62.7)	52 (63.4)	152 (60.8)
Allergic conjunctivitis	16 (18.8)	21 (25.3)	20 (24.4)	57 (22.8)
Hives	22 (25.9)	28 (33.7)	22 (26.8)	72 (28.8)
Chronic rhinosinusitis	7 (8.2)	6 (7.2)	6 (7.3)	19 (7.6)
Nasal polyps	2 (2.4)	1 (1.2)	2 (2.4)	5 (2.0)
Eosinophilic esophagitis	0	0	1 (1.2)	1 (0.4)
Other allergies[a]	62 (72.9)	53 (63.9)	58 (70.7)	173 (69.2)

[a]Including allergies to medications, animals, plants, mold, dust mites, etc.

Prior use of systemic AD therapies

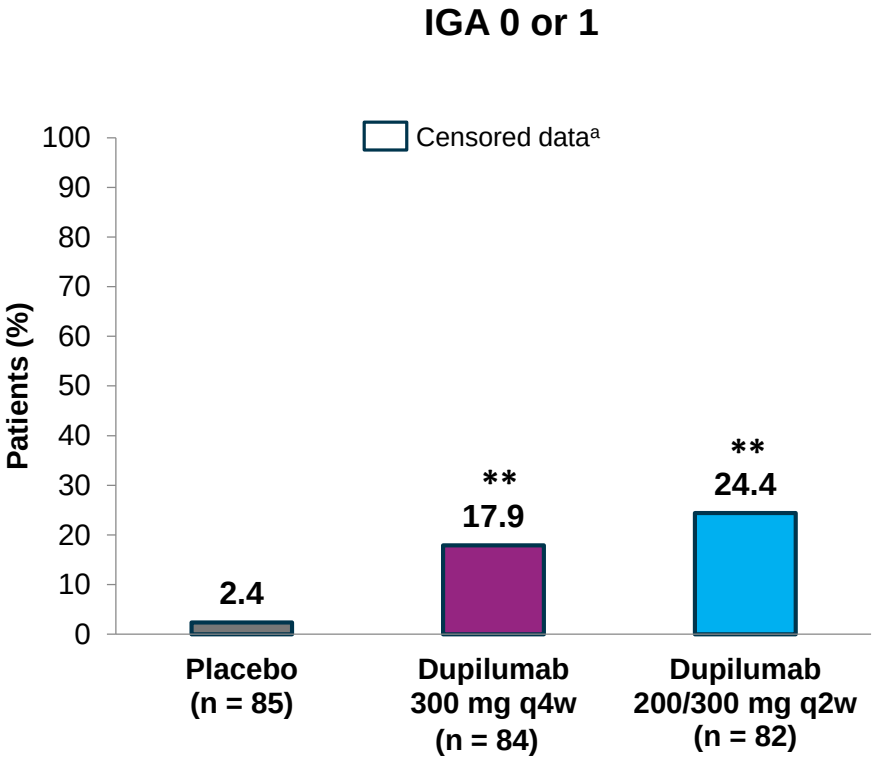
	Placebo (n = 85)	Dupilumab 300 mg q4w (n = 84)	Dupilumab 200 or 300 mg q2w (n = 82)	All patients (n = 251)
Patients with prior systemic medication, n (%)	33 (38.8)	38 (45.8)	35 (42.7)	106 (42.4)
Corticosteroids	21 (24.7)	27 (32.5)	21 (25.6)	69 (27.6)
Nonsteroidal immunosuppressants	17 (20.0)	15 (18.1)	20 (24.4)	52 (20.8)
Azathioprine	1 (1.2)	1 (1.2)	0	2 (0.8)
Cyclosporine	12 (14.1)	6 (7.2)	14 (17.1)	32 (12.8)
Methotrexate	6 (7.1)	10 (12.0)	10 (12.2)	26 (10.4)
Mycophenolate	0	1 (1.2)	2 (2.4)	3 (1.2)

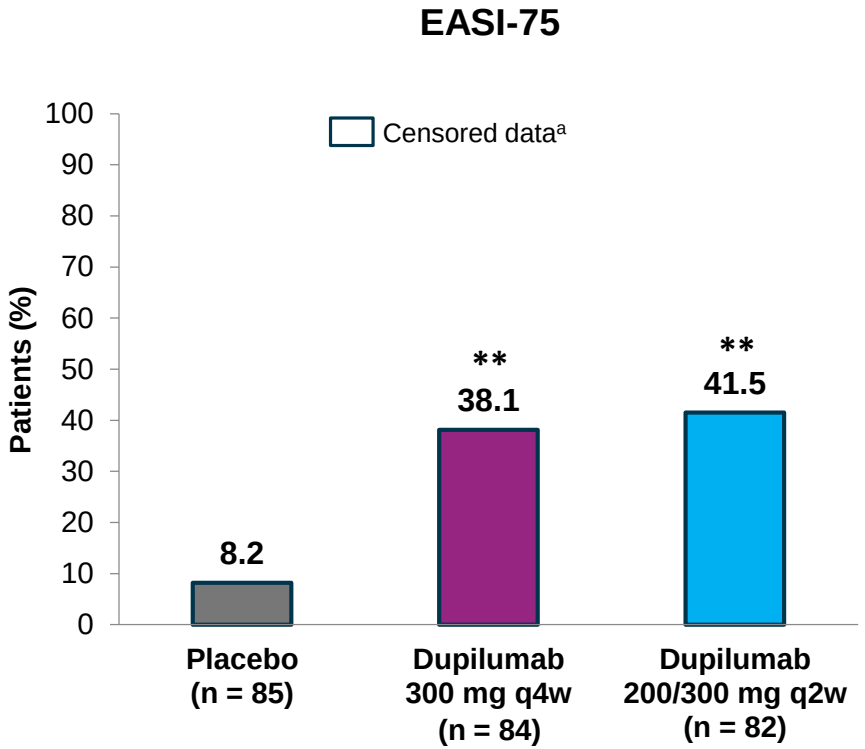
Co-primary endpoints: Patients with IGA 0 or 1 or EASI-75 at Week 16



*P < 0.05, **P < 0.001 vs placebo. [a]Patient considered nonresponder after rescue treatment use.

Co-primary endpoints: Patients with IGA 0 or 1 or EASI-75 at Week 16





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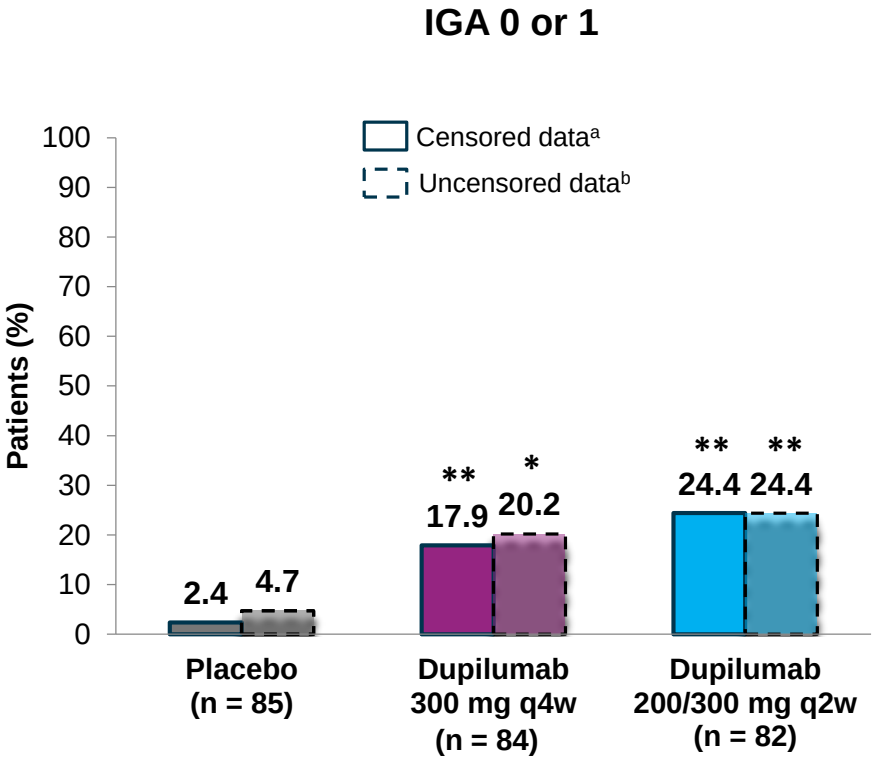
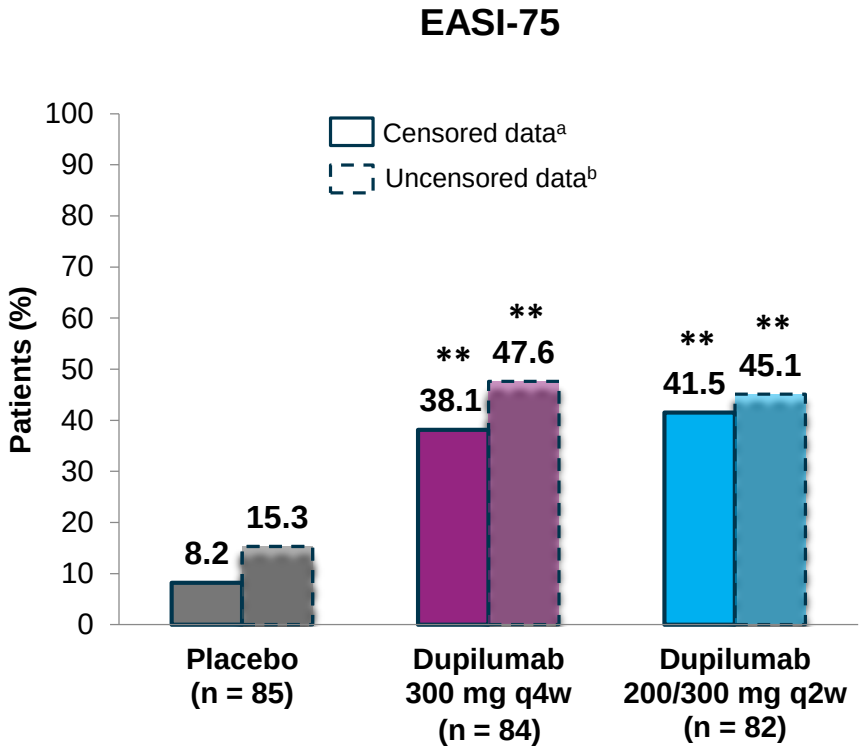
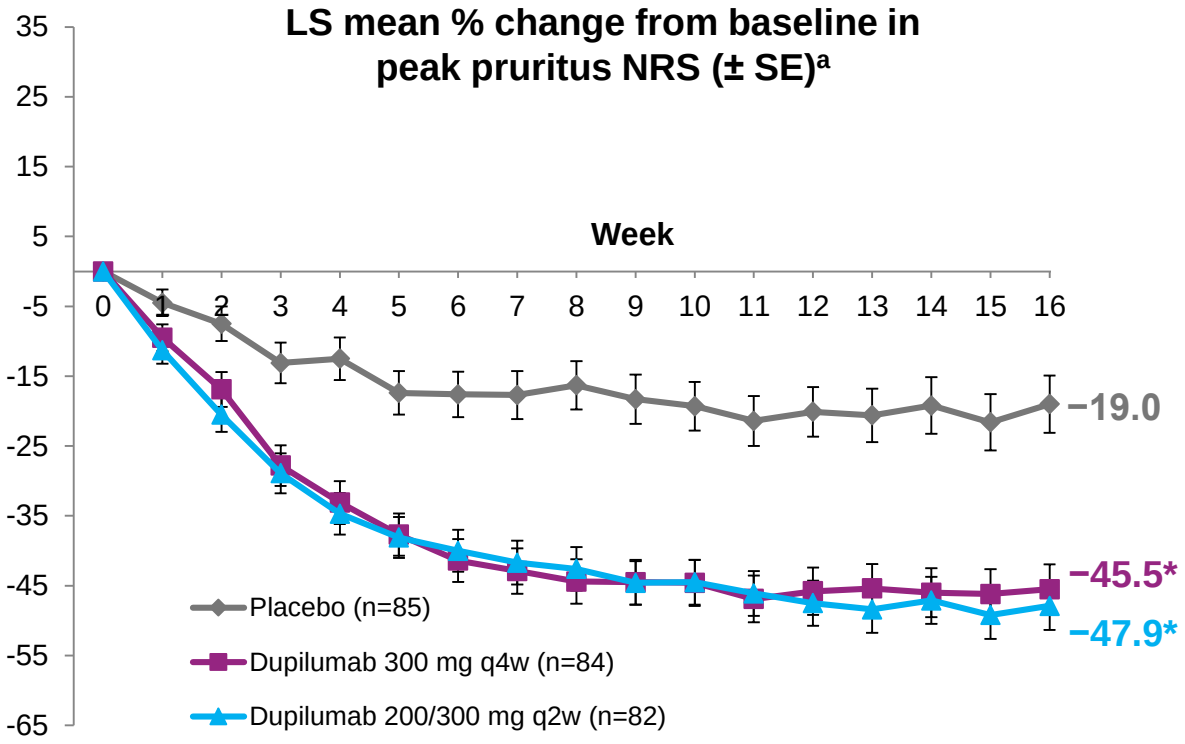




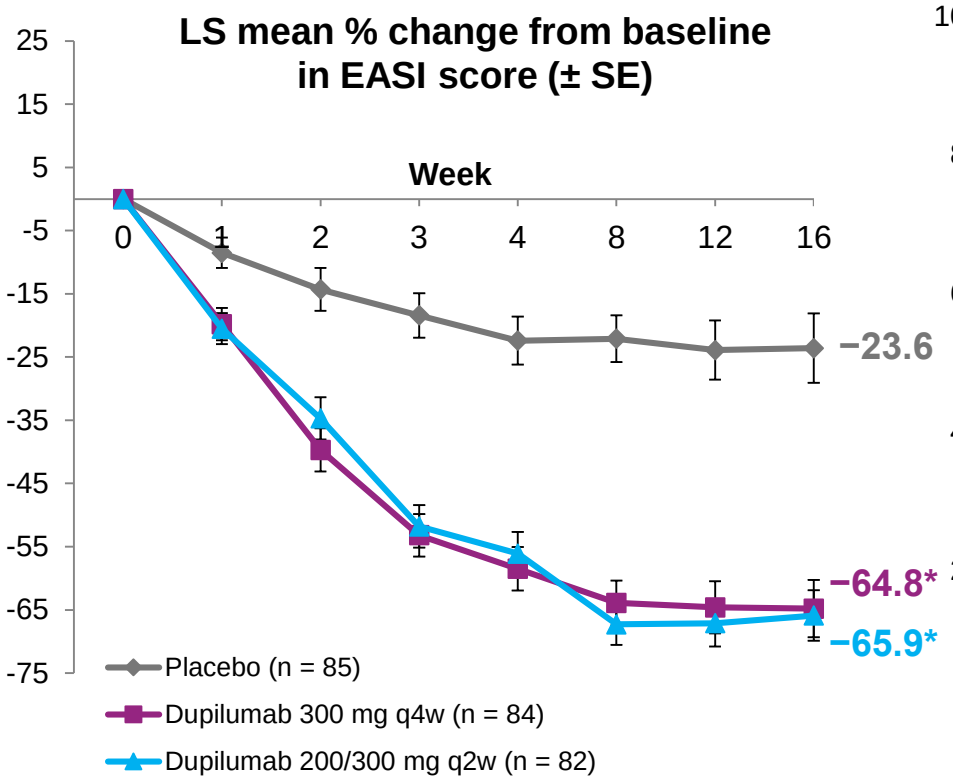
*P < 0.05, **P < 0.001 vs placebo. [a]Patient considered nonresponder after rescue treatment use. [b]All observed values regardless of rescue treatment use.

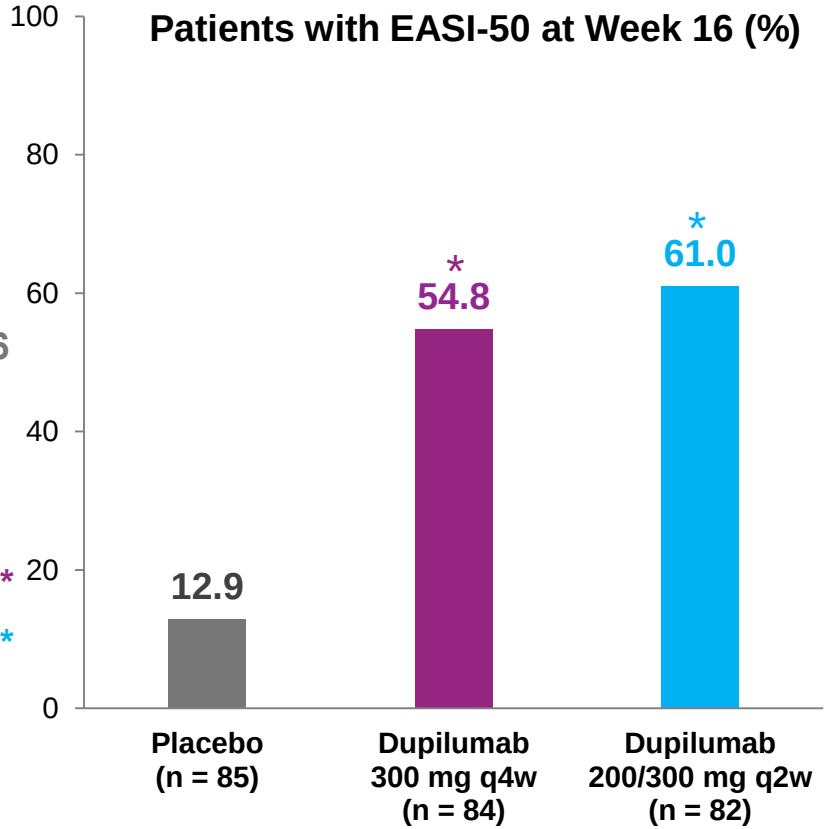
Peak pruritus NRS score from baseline to Week 16



*P < 0.001 vs placebo. [a]Weekly average of daily peak pruritus NRS score. LS, least squares; SE, standard error.

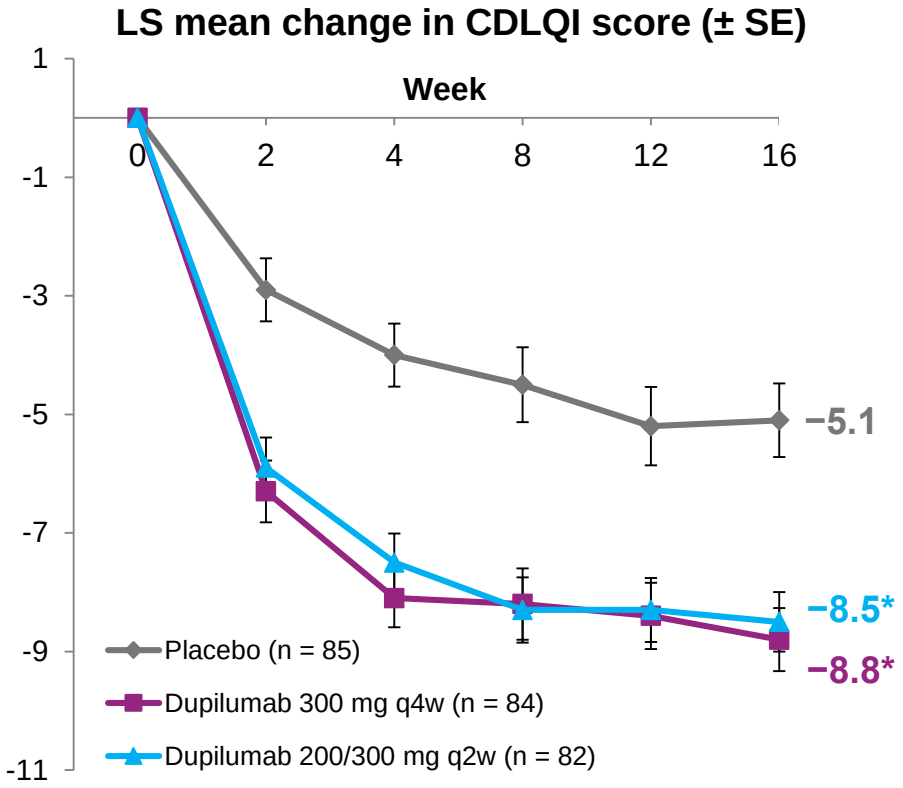
Percentage change in EASI score and patients with EASI-50 at Week 16

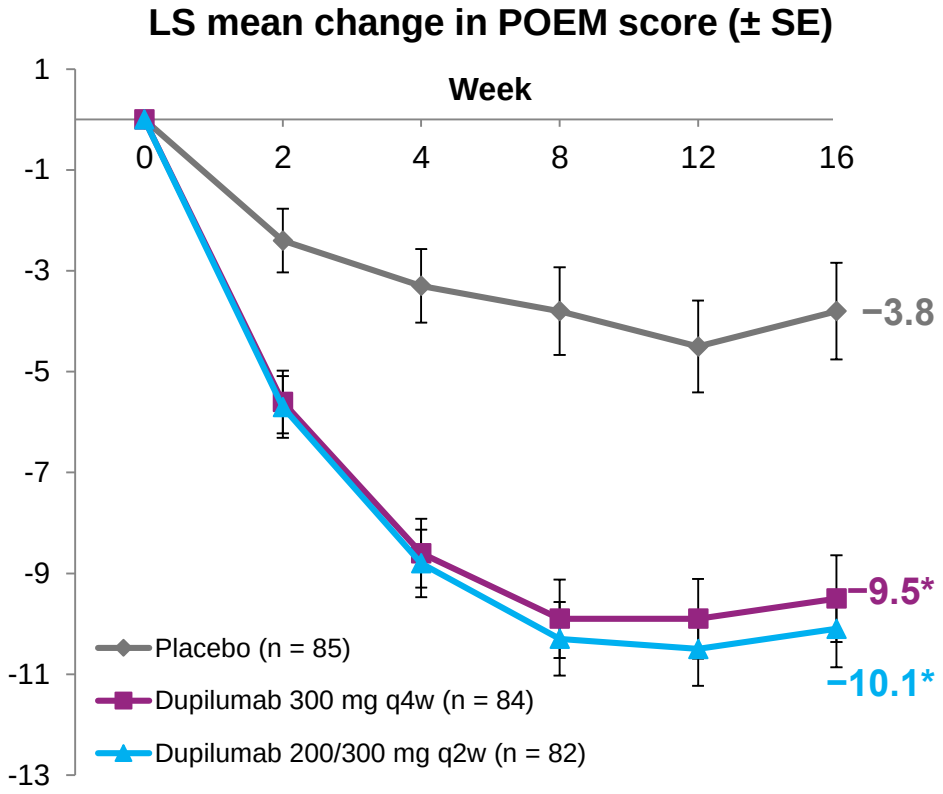




*P < 0.001 vs placebo.

Changes in CDLQI and POEM scores to Week 16





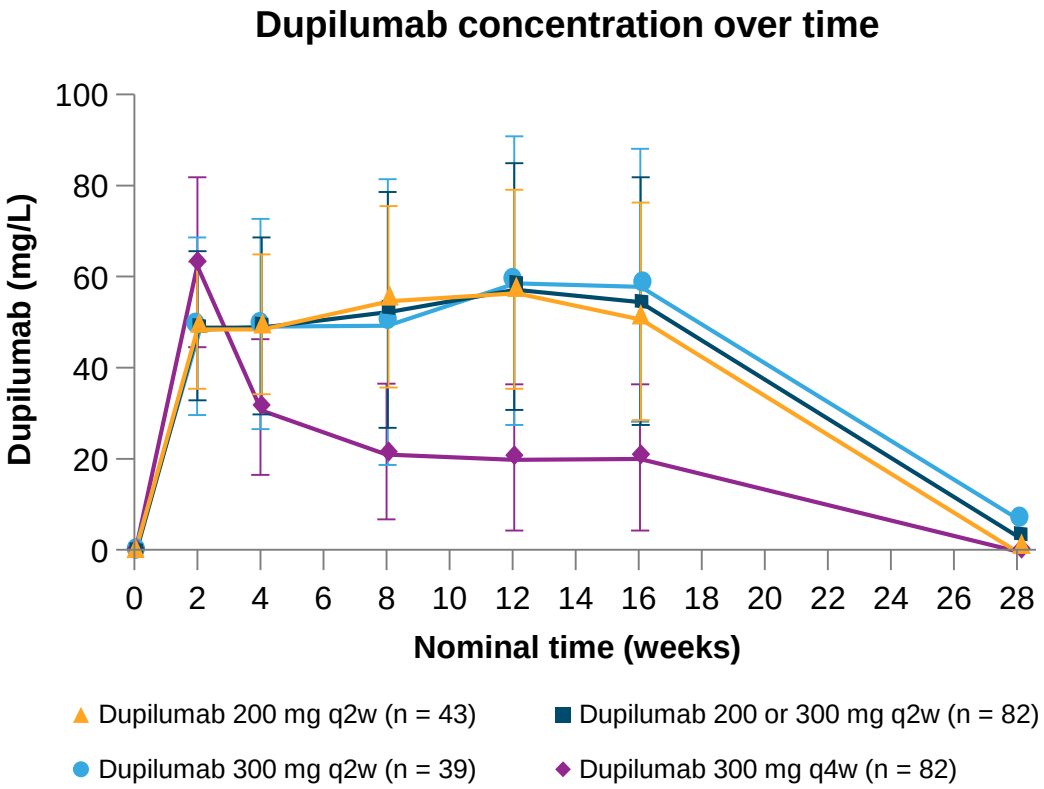
*P < 0.001 vs placebo.

Adverse events during the 16-week treatment period

Patients with event, n (%)	Placebo (n = 85)	Dupilumab 300 mg q4w (n = 84)	Dupilumab 200 or 300 mg q2w (n = 82)
TEAE	59 (69.4)	53 (63.9)	59 (72.0)
TEAE leading to discontinuation of study drug	1 (1.2)	0	0
Serious TEAE	1 (1.2)	0	0
Death	0	0	0
The most common TEAEs[a]			
Dermatitis atopic (PT)	21 (24.7)	15 (18.1)	15 (18.3)
Skin infection (adjudicated)	17 (20.0)	11 (13.3)	9 (11.0)
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)
Conjunctivitis[b]	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 reactions (HLT)	3 (3.5)	5 (6.0)	7 (8.5)
Herpes viral infections (HLT)	3 (3.5)	4 (4.8)	1 (1.2)

[a]By PT, in ≥ 5% of patients in any treatment group. [b]Includes the PTs atopic keratoconjunctivitis, conjunctivitis, conjunctivitis allergic, conjunctivitis bacterial, conjunctivitis viral.
HLT, MedDRA high-level term; MedDRA, Medical Dictionary for Regulatory Activities; PT, MedDRA preferred term; SOC, system organ class; TEAE, treatment-emergent adverse event.

Mean serum concentration of functional dupilumab



Conclusions

- In adolescents with moderate-to-severe AD, dupilumab treatment resulted in clinically meaningful and statistically significant improvements in AD signs and symptoms (including pruritus) and quality of life
- For most categorical endpoints, the q2w regimen was numerically superior to the q4w regimen
- The safety profile of dupilumab was acceptable; rates of conjunctivitis and injection-site reactions were higher with dupilumab, whereas rates of AD exacerbation and non-herpetic skin infections were higher with placebo
- Both placebo-corrected efficacy and safety of dupilumab in adolescents were similar to those observed in adults