Dupilumab Improves Symptoms of Anxiety and Depression in Adults and Adolescents With Moderate-to-Severe Atopic Dermatitis: A Post Hoc Analysis of Three Phase 3 Trials (LIBERTY AD SOLO 1 and 2 and ADOL)

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BACKGROUND

- Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by intense pruritus[1]
- Patients with AD have an increased risk of anxiety and depression,[2,3] which often correlates with AD severity
- The Hospital Anxiety and Depression Scale (HADS) is a tool that is validated for patients with AD and used to identify patients with symptoms of anxiety and depression in non-psychiatric settings[4]
  - HADS contains 2 components, the anxiety (HADS-A) and depression (HADS-D) subscales, which make up the total score
- Dupilumab is a fully human[5,6] monoclonal antibody that blocks the shared receptor component for interleukin (IL)-4 and IL-13, inhibiting signaling of both IL-4 and IL-13, which are key drivers of type 2-mediated inflammation in multiple diseases[7,8]
- In the randomized phase 3 SOLO 1 and 2 trials in adults with moderate-to-severe AD, 16-week treatment with dupilumab vs placebo significantly improved AD signs, symptoms, and quality of life[9]
- Furthermore, in the randomized phase 3 ADOL trial in adolescents with uncontrolled, moderate-to-severe AD, 16-week treatment with dupilumab vs placebo significantly improved AD signs, symptoms, and quality of life[10]

OBJECTIVE

- **To evaluate the effect of dupilumab on anxiety and depression in adults and adolescents with moderate-to-severe AD**

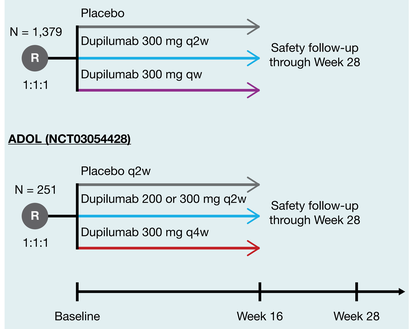
METHODS

Study design

- Detailed descriptions of the study populations and methodologies have been previously published,[9,10] and are summarized below and in **Figure 1**
  - ADOL adolescent patients received 200/300 mg dupilumab q2w (patients with body weight < 60 kg received 200 mg of the study drug; patients with body weight ≥ 60 kg received 300 mg), or 300 mg q4w, or placebo

METHODS (CONT.)

Figure 1. Study designs.



q4w, every 4 weeks; R, randomization.

Analysis

- Efficacy was analyzed in all randomized patients (full analysis set), and safety outcomes were analyzed in patients who received ≥ 1 dose of study drug
- Continuous endpoints are reported as least squares (LS) means with standard errors (SEs)
  - Data were treated as missing after rescue medication use or early discontinuation
  - Missing data were imputed using multiple imputation with analysis of covariance, with treatment group, disease severity, study identifier (SOLO), and region (SOLO) or baseline weight (ADOL) as fixed factors
- Categorical endpoints were analyzed using a Cochran–Mantel–Haenszel test adjusted by the same fixed factors as continuous endpoints
  - Patients were considered non-responders from the time of rescue medication use or withdrawal
- Safety was assessed among patients who received ≥ 1 dose of any study drug

RESULTS

Patients

- 1,379 adults were randomized in the SOLO trials, and 251 adolescents were randomized in the ADOL trial
- Baseline demographics and characteristics were balanced between the treatment groups in the individual trials (**Table 1**)
- Adolescents had numerically higher baseline disease severity than adults

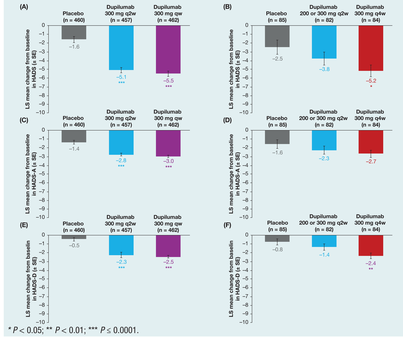
Table 1. Baseline demographics and clinical characteristics.

	Adult patients (SOLO 1 & 2 pooled)			Adolescent patients (ADOL)		
	Placebo (n = 460)	Dupilumab 300 mg q2w (n = 457)	Dupilumab 300 mg qw (n = 462)	Placebo (n = 85)	Dupilumab 200/300 mg q2w (n = 82)	Dupilumab 300 mg q4w (n = 84)
Age, mean (SD), years	38.4 (14.03)	38.3 (14.37)	38.2 (14.48)	14.5 (1.78)	14.5 (1.74)	14.4 (1.59)
Male, n (%)	250 (54.3)	267 (58.4)	281 (60.8)	53 (62.4)	43 (52.4)	52 (61.9)
Duration of AD, mean (SD), years	28.8 (14.43)	27.9 (15.20)	27.6 (15.38)	12.3 (3.44)	12.5 (2.97)	11.9 (3.18)
Patients with IGA score = 4, n (%)	225 (48.9)	223 (48.8)	218 (47.2)	46 (54.1)	43 (52.4)	46 (54.8)
EASI score, mean (SD)	34.0 (14.38)	32.4 (13.32)	32.5 (13.34)	35.5 (13.97)	35.3 (13.84)	35.8 (14.82)
Peak Pruritus NRS score, mean (SD)	7.4 (1.81)	7.4 (1.76)	7.3 (1.94)	7.7 (1.62)	7.5 (1.52)	7.5 (1.84)
BSA affected by AD, mean (SD), %	55.8 (23.25)	53.7 (22.21)	54.1 (22.29)	56.4 (24.13)	56.0 (21.40)	56.9 (23.51)
SCORAD score, mean (SD)	68.8 (14.45)	67.1 (13.71)	67.5 (13.34)	70.4 (13.25)	70.6 (13.89)	69.8 (14.12)
POEM score, mean (SD)	20.6 (5.9)	20.3 (6.0)	20.7 (5.9)	21.1 (5.4)	21.0 (5.0)	21.1 (5.5)
(C)DLQI total score, mean (SD)	15.1 (7.47)	14.7 (7.25)	15.1 (7.47)	13.1 (6.72)	13.0 (6.21)	14.8 (7.38)
HADS total score, mean (SD)	13.2 (8.33)	13.0 (7.43)	13.7 (8.15)	11.6 (7.76)	12.6 (8.04)	13.3 (8.17)
HADS-A score, mean (SD)	7.4 (4.52)	7.3 (4.14)	7.4 (4.18)	7.4 (4.41)	8.1 (4.62)	8.0 (4.87)
HADS-A ≥ 8, n (%)	183 (39.8)	196 (42.9)	209 (45.2)	41 (48.2)	47 (57.3)	42 (50.0)
HADS-A ≥ 11, n (%)	108 (23.5)	97 (21.2)	97 (21.0)	17 (20.0)	24 (29.3)	25 (29.8)
HADS-D score, mean (SD)	5.7 (4.56)	5.7 (4.07)	6.2 (4.67)	4.3 (3.86)	4.4 (4.15)	5.2 (4.17)
HADS-D ≥ 8, n (%)	139 (30.2)	148 (32.4)	160 (34.6)	14 (16.5)	19 (23.2)	23 (27.4)
HADS-D ≥ 11, n (%)	71 (15.4)	61 (13.3)	75 (16.2)	6 (7.1)	8 (9.8)	10 (11.9)

EASI scores reported on scale from 0 to 72, Peak Pruritus NRS scores reported on scale from 0 to 10, SCORAD scores reported on scale from 0 to 103, POEM scores reported on scale from 0 to 28, (C)DLQI scores reported on scale from 0 to 30, HADS scores reported on scale from 0 to 21. BSA, body surface area; (C)DLQI, (Children's) Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; n, number of patients; NRS, Numerical Rating Scale; POEM, Patient-Oriented Eczema Measure; SCORAD, SCORing Atopic Dermatitis; SD, standard deviation.

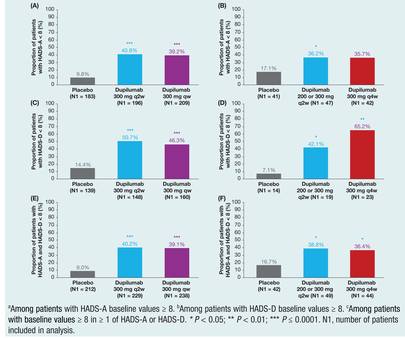
Efficacy assessment

Figure 2. Change from baseline to Week 16 in: total HADS, (A) SOLO and (B) ADOL; HADS-A, (C) SOLO and (D) ADOL; and HADS-D, (E) SOLO and (F) ADOL.



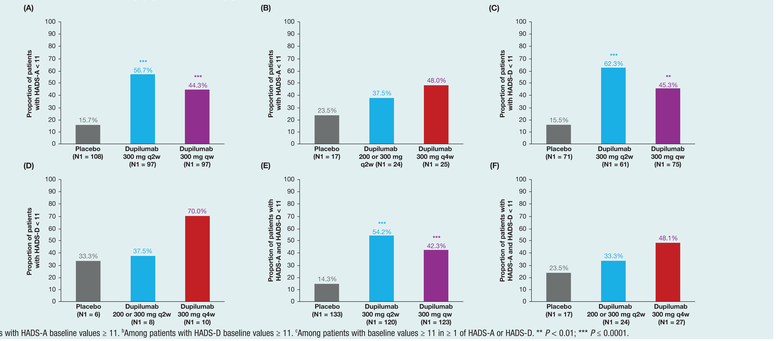
* $P < 0.05$; ** $P < 0.01$; *** $P \leq 0.0001$.

Figure 3. Proportions of patients at Week 16 with: HADS-A < 8[a], (A) SOLO and (B) ADOL; HADS-D < 8[b], (C) SOLO and (D) ADOL; and HADS-A < 8[c] and HADS-D < 8[c], (E) SOLO and (F) ADOL.



[a]Among patients with HADS-A baseline values ≥ 8. [b]Among patients with HADS-D baseline values ≥ 8. [c]Among patients with baseline values ≥ 8 in ≥ 1 of HADS-A or HADS-D. * $P < 0.05$; ** $P < 0.01$; *** $P \leq 0.0001$. N1, number of patients included in analysis.

Figure 4. Proportions of patients at Week 16 with: HADS-A < 11[a], (A) SOLO and (B) ADOL; HADS-D < 11[b], (C) SOLO and (D) ADOL; and HADS-A < 11[c] and HADS-D < 11[c], (E) SOLO and (F) ADOL.



[a]Among patients with HADS-A baseline values ≥ 11. [b]Among patients with HADS-D baseline values ≥ 11. [c]Among patients with baseline values ≥ 11 in ≥ 1 of HADS-A or HADS-D. ** $P < 0.01$; *** $P \leq 0.0001$.

Safety

Table 2. Safety assessment during the treatment period.

Patients with event, n (%)	Adult patients (SOLO 1 & 2 pooled)			Adolescent patients (ADOL)		
	Placebo (n = 456)	Dupilumab 300 mg q2w (n = 465)	Dupilumab 300 mg qw (n = 455)	Placebo (n = 85)	Dupilumab 200/300 mg q2w (n = 82)	Dupilumab 300 mg q4w (n = 83)
≥ 1 TEAE	313 (68.6)	321 (69.0)	307 (67.5)	59 (69.4)	59 (72.0)	53 (63.9)
TEAE leading to permanent study discontinuation	7 (1.5)	6 (1.3)	7 (1.5)	1 (1.2)	0	0
Death	0	0	1 (0.2)[a]	0	0	0
Treatment-emergent SAE	24 (5.3)	11 (2.4)	10 (2.2)	1 (1.2)	0	0
TEAEs occurring in ≥ 5% of patients in any group in any trial (PT)						
Dermatitis atopic	148 (32.5)	62 (13.3)	59 (13.0)	21 (24.7)	15 (18.3)	15 (18.1)
Nasopharyngitis	39 (8.6)	42 (9.0)	45 (9.9)	4 (4.7)	3 (3.7)	9 (10.8)
Upper respiratory tract infection	10 (2.2)	13 (2.8)	20 (4.4)	15 (17.6)	10 (12.2)	6 (7.2)
Headache	24 (5.3)	40 (8.6)	33 (7.3)	9 (10.6)	9 (11.0)	4 (4.8)
Injection-site reaction	28 (6.1)	51 (11.0)	72 (15.8)	1 (1.2)	0	1 (1.2)
Conjunctivitis[b]	10 (2.2)	45 (9.7)	33 (7.3)	4 (4.7)	8 (9.8)	9 (10.8)

[a]Death was unrelated to treatment (for a full description of the events, see Simpson, et al. 2016[9]); [b]Includes the following PTs: conjunctivitis, conjunctivitis bacterial, conjunctivitis viral, conjunctivitis allergic, and atopic keratoconjunctivitis. MedDRA, Medical Dictionary for Regulatory Activities; PT, MedDRA Preferred Term; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

CONCLUSIONS

- **A large proportion of adult and adolescent patients with AD had symptoms of anxiety or depression at baseline, indicative of a high burden of AD**
- **Dupilumab monotherapy improved symptoms of anxiety and depression in adult and adolescent patients with AD, and was well tolerated with an acceptable safety profile**

References: 1. Weidinger S, Novak N. Lancet. 2016;387:1109-22. 2. Yu SH, Silverberg JI. J Invest Dermatol. 2015;135:3183-6. 3. Eckert L, et al. J Am Acad Dermatol. 2017;77:274-9. 4. Silverberg JI, et al. J Invest Dermatol. 2019;139:1388-91. 5. Macdonald LE, et al. Proc Natl Acad Sci U S A. 2014;111:5147-52. 6. Murphy AJ, et al. Proc Natl Acad Sci U S A. 2014;111:5153-8. 7. Gandhi NA, et al. Nat Rev Drug Discov. 2016;15:35-50. 8. Gandhi NA, et al. Expert Rev Clin Immunol. 2017;13:425-37. 9. Simpson EL, et al. N Engl J Med. 2016;375:2335-48. 10. Simpson EL, et al. JAMA Derm. 2019; Nov 6 [Epub ahead of print]. doi: https://doi.org/10.1001/jamadermatol.2019.3336.

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