Dupilumab Provides Clinically Meaningful Responses Versus Placebo: A Post Hoc Analysis of a Phase 3 Trial in Adolescents With Moderate-to-Severe Atopic Dermatitis Among Patients Not Achieving Investigator's Global Assessment Score of 0/1

Eric L. Simpson[1], Ashish Bansal[2], Mark Boguniewicz[3,4], Andrew Blauvelt[5], Emma Guttman-Yassky[6,7], Zhen Chen[2], Ana B. Rossi[8], Abhijit Gadkari[2]

[1]Oregon Health and Science University, Portland, OR, USA; [2]Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA; [3]National Jewish Health, Denver, CO, USA; [4]University of Colorado School of Medicine, Denver, CO, USA; [5]Oregon Medical Research Center, Portland, OR, USA; [6]Icahn School of Medicine at Mount Sinai Medical Center, New York, NY, USA; [7]Rockefeller University, New York, NY, USA; [8]Sanofi Genzyme, Cambridge, MA, USA; [9]Sanofi, Chilly-Mazarin, France

BACKGROUND

- Dupilumab, a fully human monoclonal antibody, blocks the shared receptor component for interleukin (IL)-4 and IL-13, thus inhibiting signaling of both IL-4 and IL-13, key drivers of type 2 inflammation in multiple diseases.[1]
- In the USA, achieving an Investigator's Global Assessment (IGA) score of 0 or 1, corresponding to clear or almost clear signs, is used by regulatory authorities to judge the effectiveness of atopic dermatitis (AD) treatments
  - In adult patients with moderate-to-severe AD who did not achieve an IGA score of 0 or 1 after 16 weeks of treatment, dupilumab vs placebo induced statistically and clinically significant benefits in multiple validated outcome measures, including signs, symptoms, and quality of life[2]

OBJECTIVE

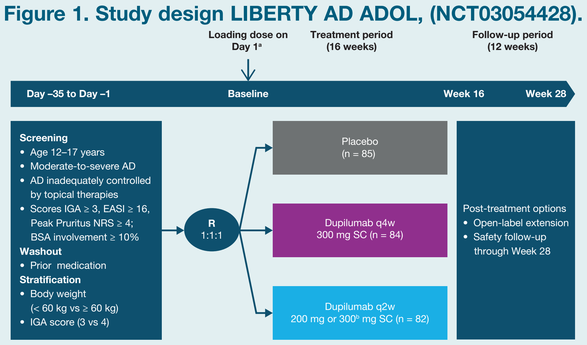
- **To determine clinically meaningful responses (in signs, symptoms, and quality of life) to dupilumab treatment among adolescent patients with moderate-to-severe AD who did not achieve IGA scores of 0 or 1 at Week 16 in a phase 3 study**

METHODS

Outcomes

- This post hoc analysis was performed in the subgroup of patients with IGA > 1 at Week 16
- Clinically meaningful responses were defined as
  - ≥ 50% improvement from baseline in EASI (EASI-50)
  - ≥ 3-point improvement in weekly average of Peak Pruritus Numerical Rating Scale (NRS) score
  - ≥ 6-point improvement in Children's Dermatology Life Quality Index (CDLQI)
- Additionally, a composite endpoint was defined based on achieving at least 1 of the above 3 outcome measures

Figure 1. Study design LIBERTY AD ADOL, (NCT03054428).



Topical therapy and other systemic AD therapies were prohibited but allowed as rescue treatment for intolerable symptoms. [a]For 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 q4w, regardless of weight, received a 600 mg loading dose. bIn the q2w group, patients 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; q2w, every two weeks; q4w, every four weeks; R, randomization; SC, subcutaneous.

RESULTS

Safety

- Overall rates of treatment-emergent adverse events (TEAEs) were similar between treatment groups in both the safety analysis population (**Table 2**) and the IGA > 1 subgroup (75.8%/67.6%/68.7% in dupilumab 200 mg/ 300 mg q2w, dupilumab 300 mg q4w, and placebo groups, respectively)
- In the IGA > 1 subgroup, there was 1 discontinuation due to adverse events in the placebo group, and 1 serious adverse event reported with placebo; no discontinuations due to TEAEs or serious TEAEs were reported with dupilumab

RESULTS (CONT.)

Table 1. Baseline demographics for patients with IGA > 1 at Week 16.

	Placebo (n = 83)	Dupilumab 300 mg q4w (n = 69)	Dupilumab 200 mg or 300 mg q2w (n = 62)
Age, mean (SD), years	14.4 (1.8)	14.3 (1.5)	14.6 (1.7)
Male, n (%)	51 (61)	44 (64)	30 (48)
Weight, mean (SD), kg	64.0 (21.1)	66.3 (20.5)	65.9 (20.6)
Body mass index, mean (SD), kg/m^2	23.9 (6.1)	24.1 (5.9)	24.9 (6.2)
Duration of AD, mean (SD), years	12.2 (3.5)	12.1 (3.1)	12.5 (3.0)
IGA score = 4, n (%)	45 (54)	44 (64)	35 (57)
EASI, mean (SD)	35.4 (13.9)	37.8 (14.7)	37.5 (14.4)
SCORAD total score, mean (SD)	70.3 (13.3)	71.7 (14.0)	72.5 (14.0)
AD BSA involvement, mean (SD), %	56.4 (24.4)	58.6 (23.5)	59.4 (22.4)
Peak Pruritus NRS score, mean (SD)	7.7 (1.6)	7.8 (1.7)	7.6 (1.4)
CDLQI, mean (SD)	13.0 (6.7)	15.4 (7.5)	14.3 (6.1)
Patients with ≥ 1 concurrent atopic condition besides AD, n (%)	76 (92)	61 (88)	61 (98)
Allergic conjunctivitis (keratoconjunctivitis)	15 (18)	20 (29)	15 (24)
Allergic rhinitis	55 (66)	38 (55)	44 (71)
Asthma	44 (53)	37 (54)	34 (55)
Chronic rhinosinusitis	7 (8)	5 (7)	4 (7)
Food allergy	46 (55)	43 (62)	42 (68)
Hives	22 (27)	23 (33)	20 (32)
Nasal polyps	2 (2)	0	2 (3)
Other allergies[a]	61 (74)	49 (71)	46 (74)

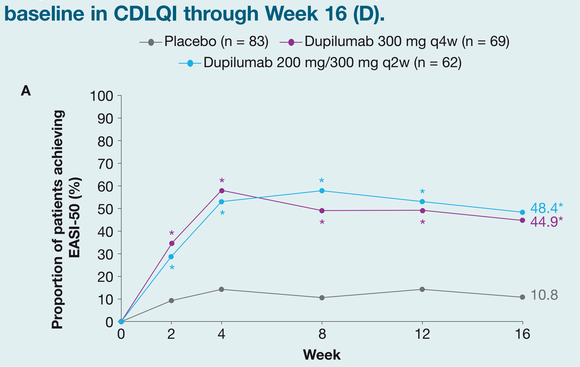
[a]Includes allergies to medications, animals, plants, mold, dust mites, etc. SCORAD, SCORing Atopic Dermatitis; SD, standard deviation.

Table 2. Safety in overall study population.

Patients with event, n (%)	Safety analysis population N = 250		
	Placebo (n = 85)	Dupilumab 300 mg q4w (n = 83)	Dupilumab 200 mg or 300 mg q2w (n = 82)
Any 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
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)

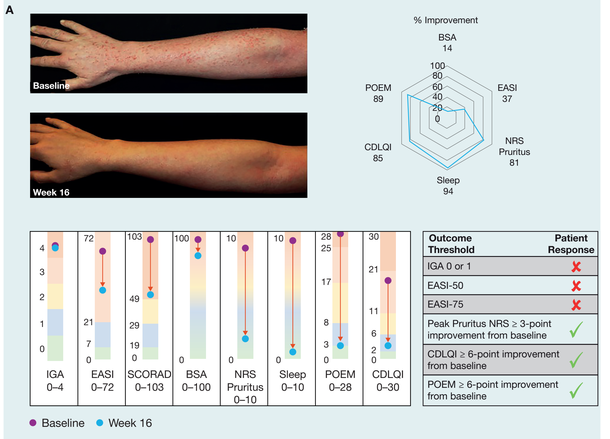
[a]By PT, in ≥ 5% of patients in any treatment group. [b]Includes the PTs atopic keratoconjunctivitis, conjunctivitis, conjunctivitis allergic, conjunctivitis bacterial, and conjunctivitis viral. HLT, MedDRA high-level term; MedDRA, Medical Dictionary for Regulatory Activities; PT, MedDRA preferred term;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

Figure 2. Proportions of patients achieving EASI-50 through Week 16 (A), ≥ 3-point reduction from baseline in daily Peak Pruritus NRS scores through Day 15 (B), ≥ 6-point reduction from baseline in CDLQI through Week 16 (C), EASI-50 or ≥ 3-point reduction from baseline in weekly average of daily Peak Pruritus NRS scores or ≥ 6-point reduction from baseline in CDLQI through Week 16 (D).



*P < 0.01 vs placebo; †P < 0.05 vs placebo.

Figure 3. Example of patients who did not achieve IGA 0 or 1 at Week 16 but derived benefit in symptoms and quality of life.



These are individual cases and not representative of results from all patients.
The spider graphics show LS mean percent reduction in each outcome; lines closer to the outer edge of the spider plot represent greater improvement from baseline. The rainbow graphics display change in absolute values from baseline (purple) to Week 16 (blue) for each outcome.

CONCLUSIONS

- **The majority of adolescent patients treated with dupilumab who did not achieve an IGA score of 0/1 at Week 16 achieved clinically meaningful improvement in AD signs, symptoms, and quality of life vs placebo**
- **These results suggest that the IGA response should be interpreted within the context of additional outcome measures that more comprehensively characterize changes with treatment in AD signs, symptoms, and quality of life**

References: 1. Gandhi NA, et al. Nat Rev Drug Discov. 2016;15:35-50. 2. Silverberg JI, et al. Br J Dermatol. 2019. [Epub ahead of print]. doi: 10.1111/bjd.17791.

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