Clinically Meaningful Responses in Moderate-to-Severe Atopic Dermatitis Patients Treated With Dupilumab

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BACKGROUND

- The primary end points of proportion of patients achieving Investigator's Global Assessment (IGA) scores of 0 or 1 and proportion of patients achieving improvement of ≥ 75% in Eczema Area and Severity (EASI) scores are the regulatory standards used in clinical trials, but these end points do not capture the full range of clinical benefits of treatment; clinically meaningful response thresholds in tools commonly used to assess signs, symptoms, and QoL in AD include:
  - ≥ 50% improvement in EASI score (EASI-50, signs)[1]
  - ≥ 3-point improvement (reduction) in Peak Pruritus NRS (symptoms)[2]
  - ≥ 4-point improvement (reduction) on the DLQI QoL[3,4]
- Dupilumab, a fully human monoclonal antibody[5,6], blocks the shared receptor component for interleukin (IL)-4 and IL-13, thus inhibiting signalling of both IL-4 and IL-13, which are key drivers of type 2 inflammation[7]
- In the USA, dupilumab is approved for subcutaneous administration every 2 weeks (q2w) for the treatment of patients aged 12 and older with moderate-to-severe AD inadequately controlled with topical prescription therapies or when those therapies are not advisable[8], for the treatment of adult AD patients not adequately controlled with existing therapies in Japan, and for use in adults with moderate-to-severe AD who are candidates for systemic therapy in the EU[9]

OBJECTIVE

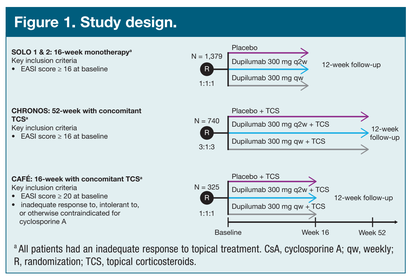
- **To determine the proportion of patients with moderate-to-severe AD treated with dupilumab achieving a clinically meaningful response in one or more of the three major AD domains (signs, symptoms, and QoL), in the phase 3 trials LIBERTY AD SOLO 1 & 2,[10] LIBERTY AD CHRONOS[1] and LIBERTY AD CAFÉ[11]**

METHODS

End points

- Clinically meaningful response was measured via analysis of proportion of patients who achieved:
  - EASI-50[1] OR
  - Improvement (reduction) of ≥ 3 points from baseline in weekly average of daily Peak Pruritus NRS[2] OR
  - Improvement (reduction) in DLQI score ≥ 4 points from baseline[3,4]
- Considering the high disease burden at baseline, the 50% improvement from baseline in EASI score as assessed by EASI-50 can be considered as a clinically meaningful response[1]

Figure 1. Study design.

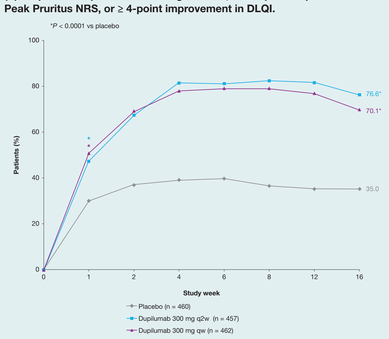


[a] All patients had an inadequate response to topical treatment. CsA, cyclosporine A; qw, weekly; R, randomization; TCS, topical corticosteroids.

RESULTS

Figure 2. Composite endpoint in SOLO 1 & 2 trials.

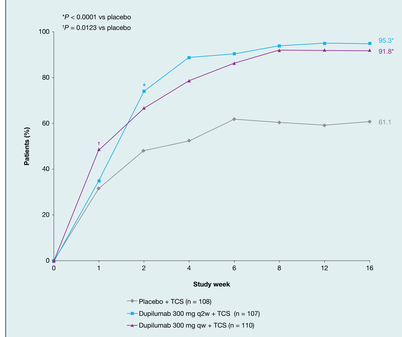
(A) Proportion of patients achieving EASI-50, or ≥ 3-point improvement in Peak Pruritus NRS, or ≥ 4-point improvement in DLQI.



(B) Among patients who achieved the composite endpoint the Venn diagrams show distribution of patients achieving any combination of endpoints at Week 16.

Figure 3. Composite endpoint in CAFÉ trial.

(A) Proportion of patients achieving EASI-50, or Peak Pruritus NRS ≥ 3-point improvement, or DLQI ≥ 4-point improvement.



(B) Among patients who achieved the composite endpoint the Venn diagrams show distribution of patients achieving any combination of endpoints at Week 16.

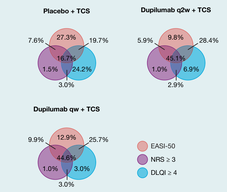
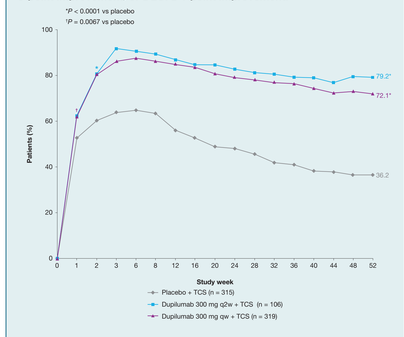


Figure 4. Composite endpoint in CHRONOS trial.

(A) Proportion of patients achieving EASI-50, or Peak Pruritus NRS ≥ 3-point improvement, or DLQI ≥ 4-point improvement.



(B) Among patients who achieved the composite endpoint the Venn diagrams show distribution of patients achieving any combination of endpoints at Week 16 and Week 52.

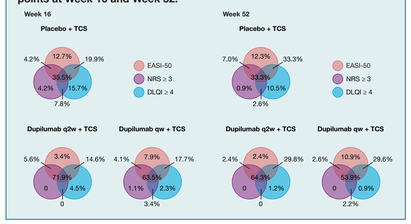
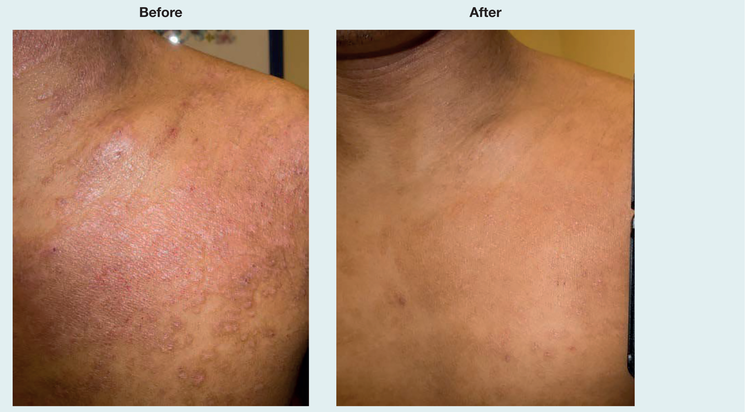


Figure 5. Patient case.



IGA 0 or 1	✗
EASI-75	✓
EASI-50	✓
Pruritus ≥3 points	✓
DLQI ≥6 points	✓
POEM ≥6 points	✓

BSA, body surface area affected by AD; SCORAD, SCORing Atopic Dermatitis.
This is an individual case and not representative of results from all patients. Example of patients achieving clinically meaningful improvement in one, two or three domains. The table indicates whether the patient's response met the de ned threshold of clinical signi cance for each outcome. The spider graphic shows percentage of improvement in each outcome. The color scale graphic displays change in absolute values from baseline (purple dot) to Week 16 (blue dot) for each outcome.

Table 1. Baseline demographics and disease characteristics.

	SOLO pooled			CAFÉ			CHRONOS		
	Placebo qw (n = 460)	Dupilumab 300 mg q2w (n = 457)	Dupilumab 300 mg qw (n = 462)	Placebo qw + TCS (n = 108)	Dupilumab 300 mg q2w + TCS (n = 107)	Dupilumab 300 mg qw + TCS (n = 110)	Placebo qw + TCS (n = 315)	Dupilumab 300 mg q2w + TCS (n = 106)	Dupilumab 300 mg qw + TCS (n = 319)
Age, mean (SD), years	38.4 (14.03)	38.3 (14.37)	38.2 (14.48)	38.9 (13.35)	37.5 (12.89)	38.7 (13.21)	36.6 (13.01)	39.6 (13.98)	36.9 (13.67)
Male sex, n (%)	250 (54.3)	267 (58.4)	281 (60.8)	68 (63.0)	65 (60.7)	66 (60.0)	193 (61.3)	62 (58.5)	191 (59.9)
EASI score, mean (SD)	34.0 (14.38)	32.4 (13.32)	32.5 (13.34)	32.9 (10.80)	33.3 (9.93)	33.1 (11.02)	32.6 (12.93)	33.6 (13.30)	32.1 (12.76)
Peak Pruritus NRS, mean (SD)	7.4 (1.81)	7.4 (1.76)	7.3 (1.94)	6.4 (2.23)	6.6 (2.10)	6.2 (2.01)	7.3 (1.84)	7.4 (1.66)	7.1 (1.90)
DLQI, mean (SD)	15.1 (7.47)	14.7 (7.25)	15.1 (7.47)	13.2 (7.60)	14.5 (7.63)	13.8 (8.03)	14.7 (7.37)	14.5 (7.31)	14.4 (7.17)

SD, standard deviation; NRS, Numerical Rating Scale; DLQI, Dermatology Life Quality Index

Table 2. Overall safety.

	SOLO pooled (16 weeks)			CAFÉ (16 weeks)			CHRONOS (52 weeks)		
Patients with, n (%)	Placebo qw (n = 456)	Dupilumab 300 mg q2w (n = 465)	Dupilumab 300 mg qw (n = 455)	Placebo qw + TCS (n = 108)	Dupilumab 300 mg q2w + TCS (n = 107)	Dupilumab 300 mg qw + TCS (n = 110)	Placebo qw + TCS (n = 315)	Dupilumab 300 mg q2w + TCS (n = 110)	Dupilumab 300 mg qw + TCS (n = 315)
Any TEAE	313 (68.6)	321 (69.0)	307 (67.5)	75 (69.4)	77 (72.0)	76 (69.1)	268 (85.1)	97 (88.2)	263 (83.5)
TEAEs leading to discontinuation	7 (1.5)	6 (1.3)	7 (1.5)	1 (0.9)	0	2 (1.8)	25 (7.9)	2 (1.8)	9 (2.9)
Death	0	0	1 (0.2)	0	0	0	0	0	1 (0.3)
Any TE SAE	24 (5.3)	11 (2.4)	10 (2.2)	2 (1.9)	2 (1.9)	2 (1.8)	16 (5.1)	4 (3.6)	10 (3.2)
Nasopharyngitis[a]	39 (8.6)	42 (9.0)	45 (9.9)	18 (16.7)	22 (20.6)	17 (15.5)	64 (20.3)	26 (23.6)	66 (21.0)
Dermatitis atopic[a]	148 (32.5)	62 (13.3)	59 (13.0)	16 (14.8)	8 (7.5)	9 (8.2)	179 (56.8)	51 (46.4)	111 (35.2)
Injection-site reaction[a]	28 (6.1)	51 (11.0)	72 (15.8)	0	1 (0.9)	4 (3.6)	25 (7.9)	16 (14.5)	61 (19.4)
Conjunctivitis[b]	10 (2.2)	45 (9.7)	33 (7.3)	12 (11.1)	30 (28.0)	18 (16.4)	25 (7.9)	15 (13.6)	61 (19.4)

[a]MedDRA preferred term. [b]Conjunctivitis including MedDRA preferred terms for conjunctivitis, conjunctivitis allergic, conjunctivitis bacterial, conjunctivitis viral, and atopic keratoconjunctivitis. MedDRA, Medical Dictionary for Regulatory Activities; TE SAE, treatment-emergent serious adverse event.

CONCLUSIONS

- **A large majority of moderate-to-severe AD patients treated with dupilumab with or without TCS reported clinically meaningful improvement in at least one of the 3 key domains of AD compared with placebo measured by the proportion of patients achieving EASI-50 or ≥ 3-point improvement in Peak Pruritus NRS or ≥ 4-point improvement in DLQI**
- **In the SOLO pooled population, significant improvements were seen at Week 1 with both dupilumab treatment regimens vs placebo, and lasted through Week 16**
- **In the CAFÉ trial, improvements were seen at Week 1 with qw + TCS, while q2w + TCS showed improvements by Week 2; all improvements lasted through Week 16**
- **In the CHRONOS trial, improvements were seen at Week 2 with both dupilumab + TCS treatment regimens vs placebo + TCS which lasted through Week 52**
- **In all presented trials, dupilumab had an acceptable safety profile**

References

1. Blauvelt A, et al. Lancet. 2017;389:2287-2303. 2. Yosipovitch G, et al. Br J Dermatol. 2019. doi: 10.1111/bjd.17744. [Epub ahead of print] 3. Basra MK, et al. Dermatology. 2015;230:27-33. 4. Badia X, et al. Br J Dermatol. 1999;141:698-702. 5. MacDonald LE, et al. Proc Natl Acad Sci USA. 2014;111:5147–52. 6. Murphy AJ, et al. Proc Natl Acad Sci USA. 2014;111:5153–8. 7. Gandhi N, et al. Expert Rev Clin Immunol. 2017;13:425-37. 8. DUPIXENT® (dupilumab). Highlights of prescribing information. FDA 2019. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761055s012lbl.pdf. Accessed April 7, 2019. 9. DUPIXENT® (dupilumab). Summary of product characteristics. EMA 2017. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/dupixent. Accessed April 7, 2019. 10. Simpson EL, N Engl J Med. 2016;375(24):2335-48. 11. de Bruin-Weller, et al. Br J Dermatol. 2018;178:1083-101.

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