Efficacy and safety of dupilumab treatment with concomitant topical corticosteroids in children aged 6 months to 5 years with severe atopic dermatitis

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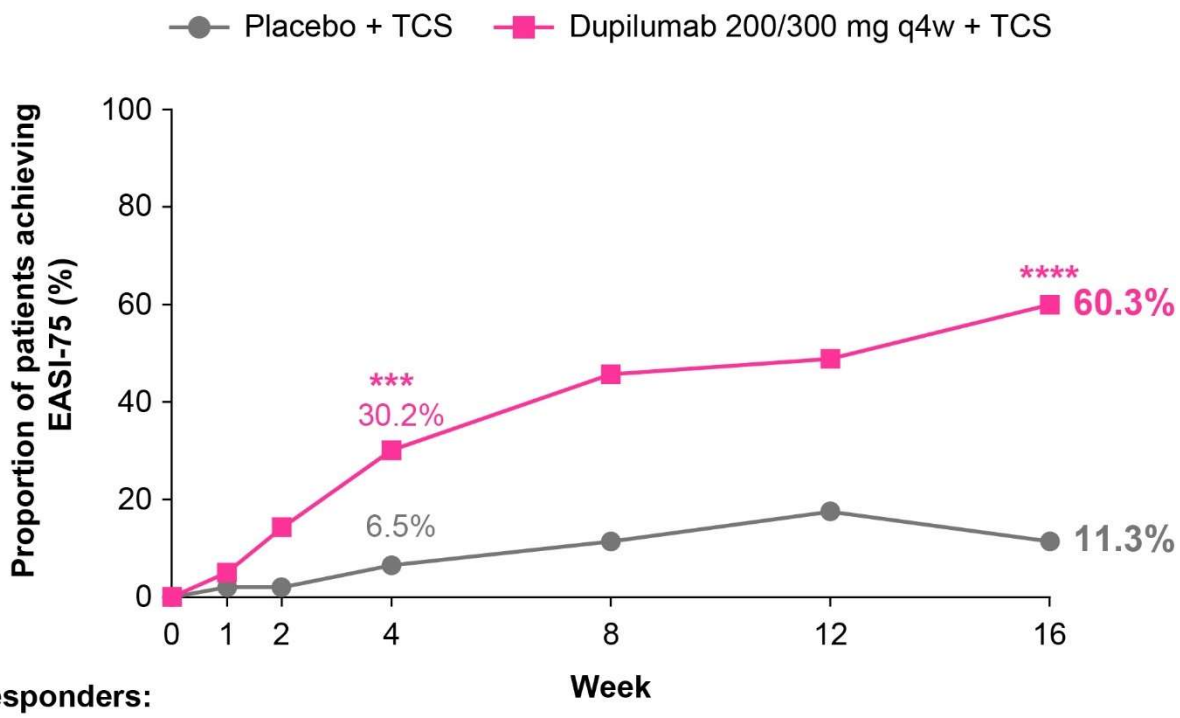
Supplementary Material

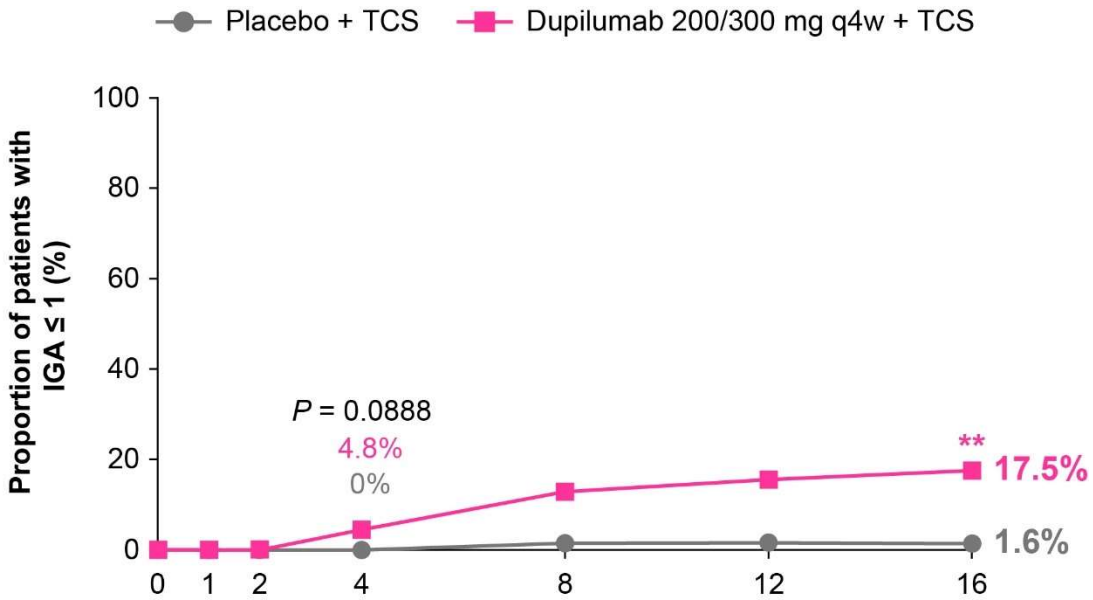
Figures

(a)



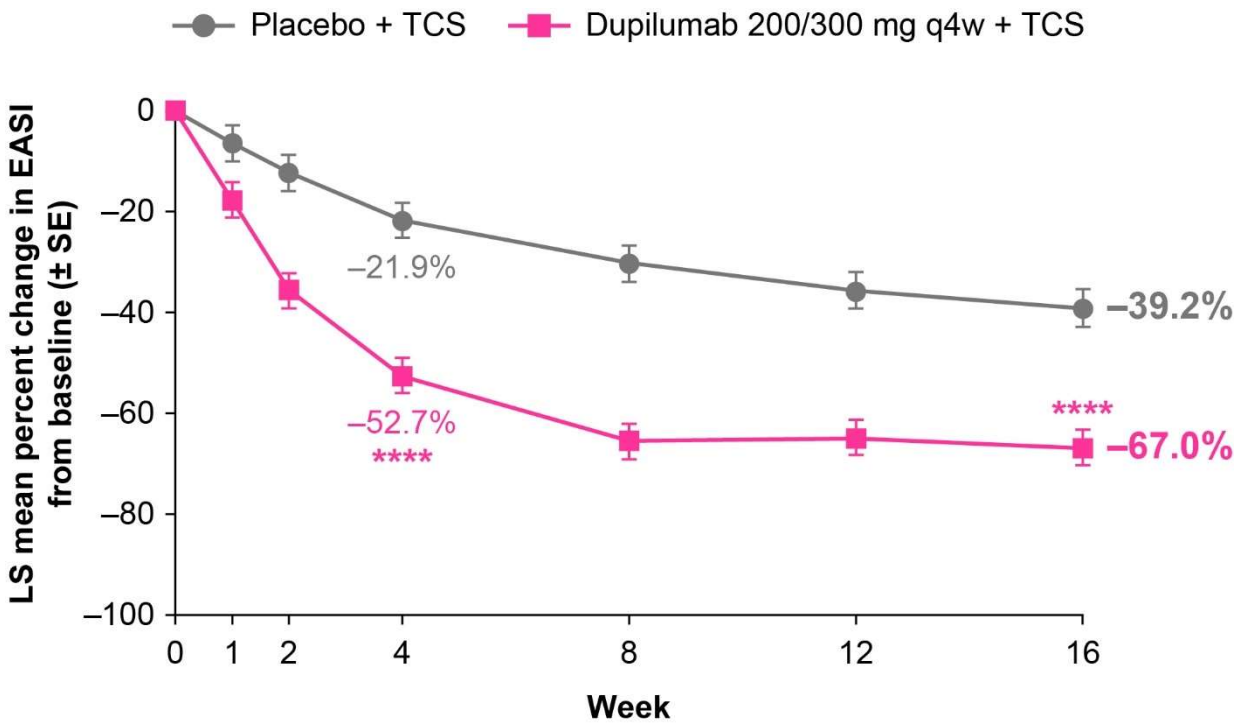
No. of responders:						
Placebo + TCS	1	1	4	7	11	7
Dupilumab + TCS	3	9	19	29	31	38

(b)

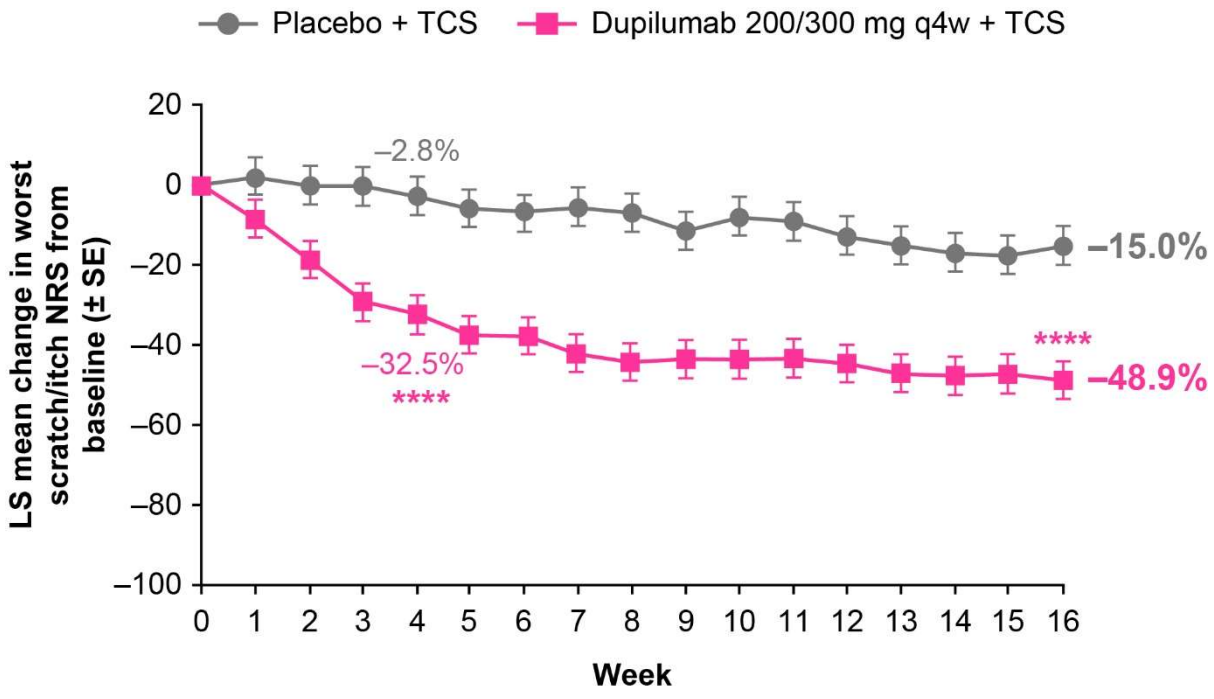


No. of responders:						
Placebo + TCS	0	0	0	1	1	1
Dupilumab + TCS	0	0	3	8	10	11

(c)


Placebo + TCS
Dupilumab 200/300 mg q4w + TCS
LS mean percent change in EASI from baseline (± SE)
0
–20
–40
–60
–80
–100
–21.9%
–39.2%
–52.7%
****
****
–67.0%
0 1 2 4 8 12 16
Week

(d)


Placebo + TCS
Dupilumab 200/300 mg q4w + TCS
LS mean change in worst scratch/itch NRS from baseline (± SE)
20
0
–20
–40
–60
–80
–100
–2.8%
–15.0%
–32.5%
****
****
–48.9%
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
Week

(e)

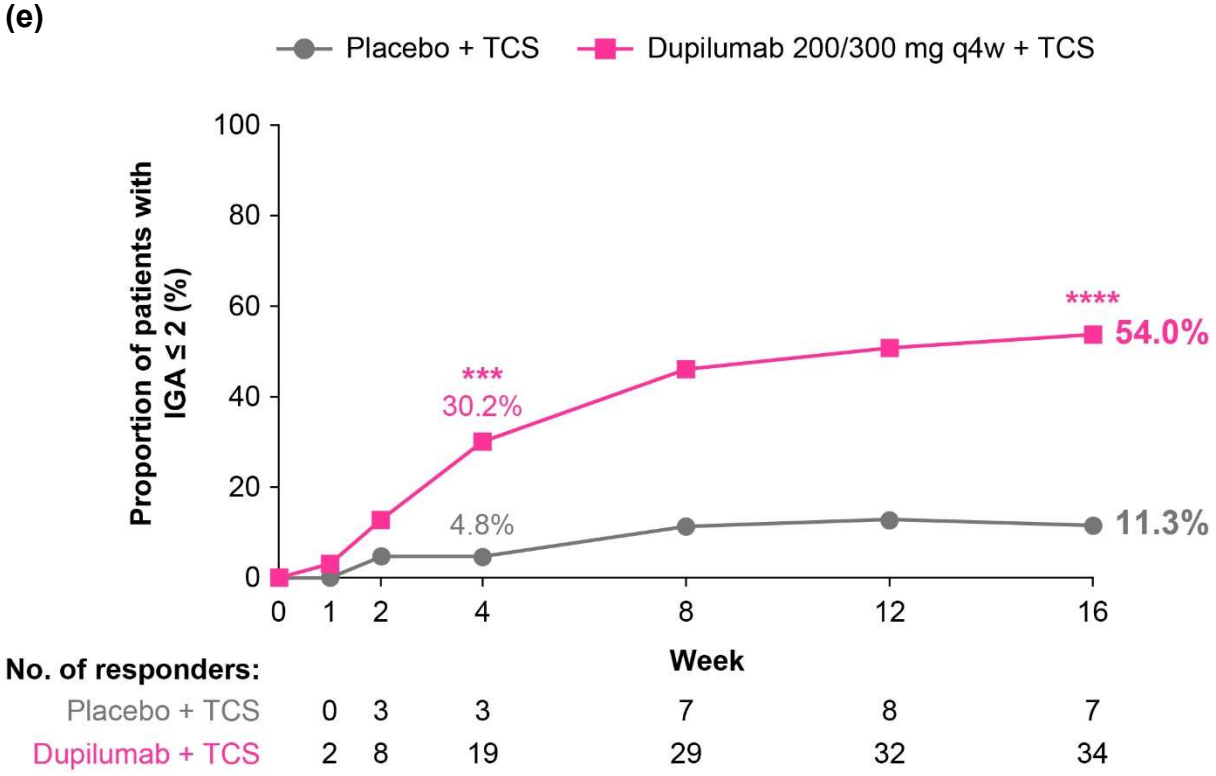


Figure S1 Sensitivity analyses (observed regardless of rescue). (a) Proportion of patients with EASI-75 through week 16. (b) Proportion of patients with IGA ≤ 1 through week 16. (c) LS mean percent change in EASI score from baseline through week 16. (d) LS mean percent change in Worst Scratch/Itch NRS score from baseline through week 16. (e) Proportion of patients with IGA ≤ 2 through week 16. ***P* < 0.01; ****P* < 0.001; *****P* < 0.0001, all vs. corresponding placebo + TCS. EASI, Eczema Area and Severity Index; EASI-75, 75% decrease in EASI; IGA, Investigator's Global Assessment; LS, least squares; NRS, Numerical Rating Scale; q4w, every 4 weeks; TCS, topical corticosteroids.

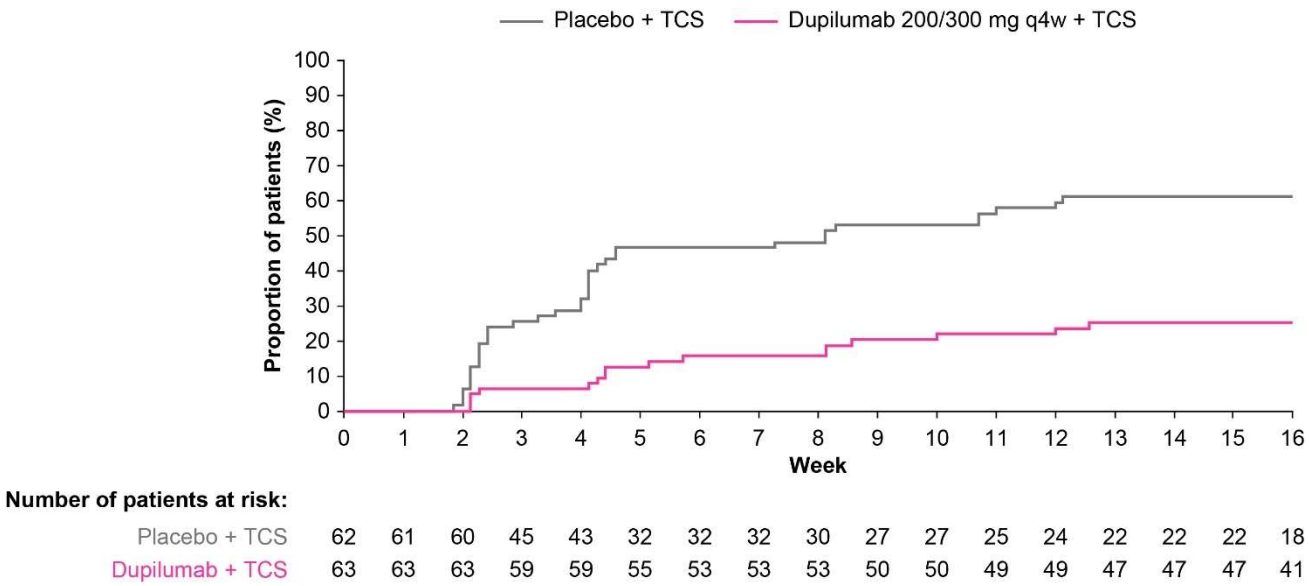
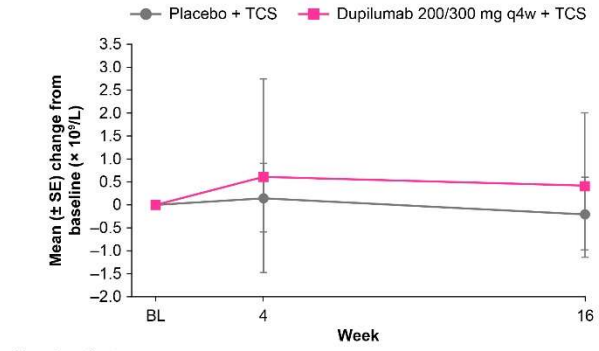


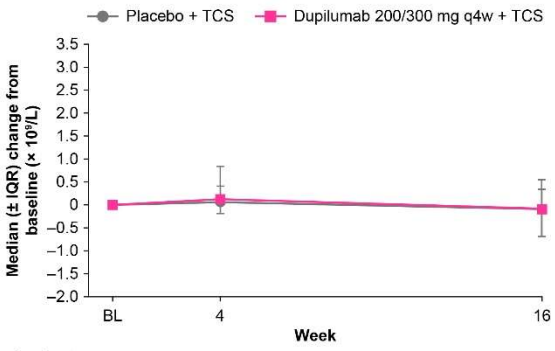
Figure S2 Kaplan-Meier curve of time to first use of rescue treatment (topical and systemic) from baseline through week 16. Q4w, every 4 weeks; TCS, topical corticosteroids.

(a)

Eosinophil count



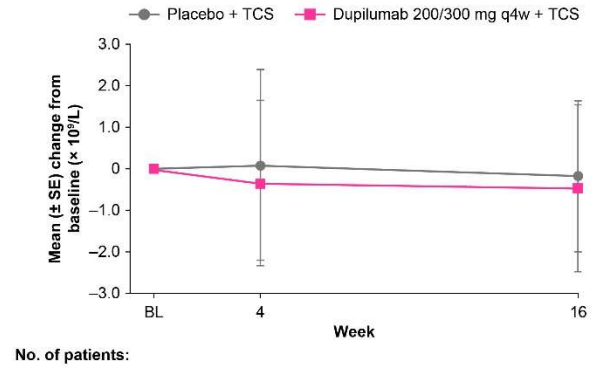
No. of patients:			
Placebo + TCS	62	58	56
Dupilumab + TCS	62	57	54



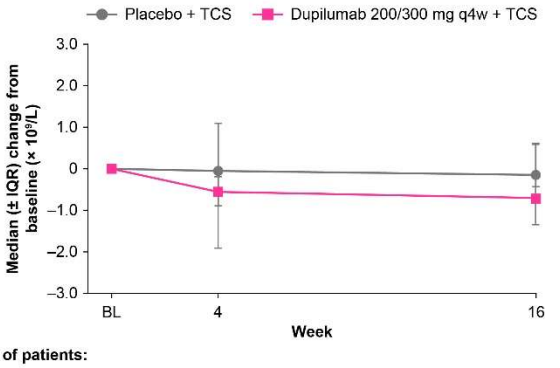
No. of patients:			
Placebo + TCS	62	58	56
Dupilumab + TCS	62	57	54

(b)

Neutrophil count



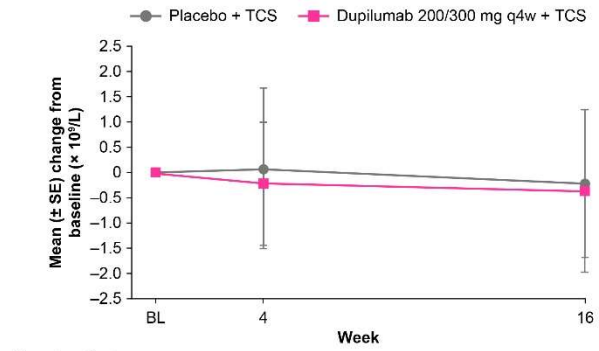
No. of patients:			
Placebo + TCS	62	58	56
Dupilumab + TCS	61	56	53



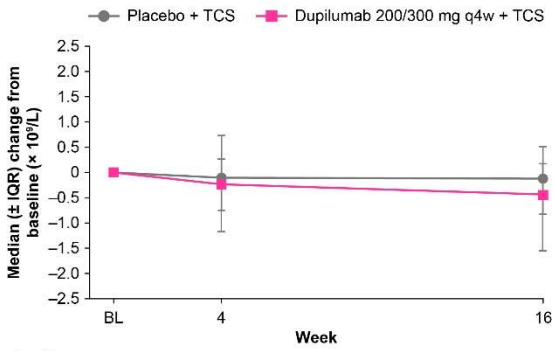
No. of patients:			
Placebo + TCS	62	58	56
Dupilumab + TCS	61	56	53

(c)

Lymphocyte count



No. of patients:			
Placebo + TCS	62	58	56
Dupilumab + TCS	62	57	54



No. of patients:			
Placebo + TCS	62	58	56
Dupilumab + TCS	62	57	54

(d)

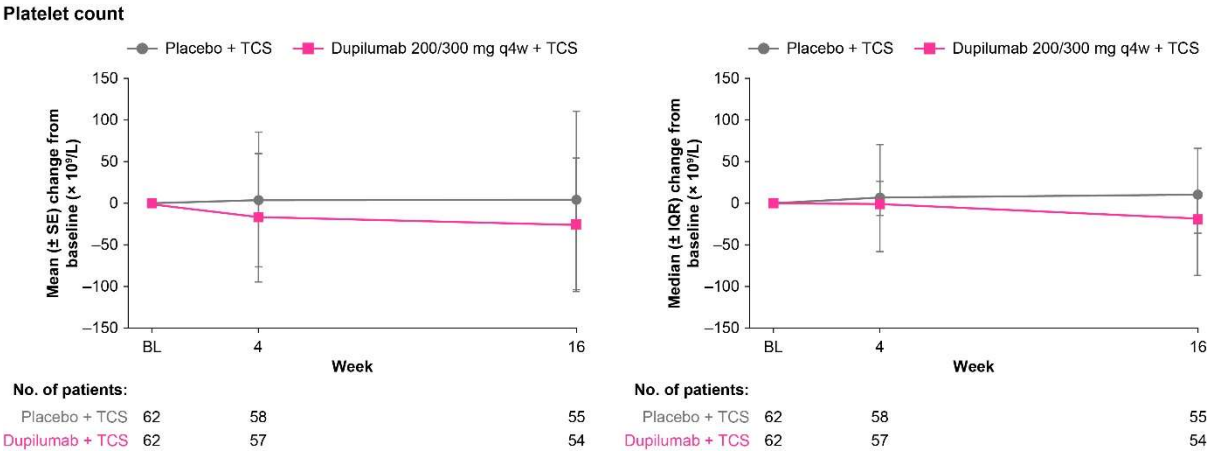
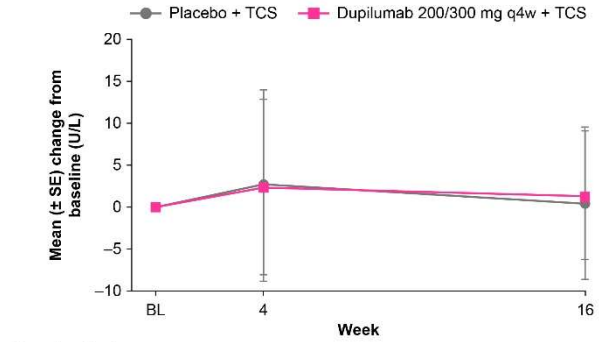


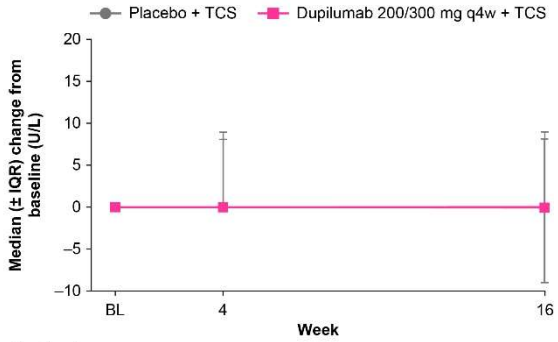
Figure S3 Mean and median change from baseline in haematologic laboratory parameters through week 16. (a) Eosinophil count. (b) Neutrophil count. (c) Lymphocyte count. (d) Platelet count. BL, baseline; IQR, interquartile range; q4w, every 4 weeks; SE, standard error; TCS, topical corticosteroids.

(a)

Creatinine



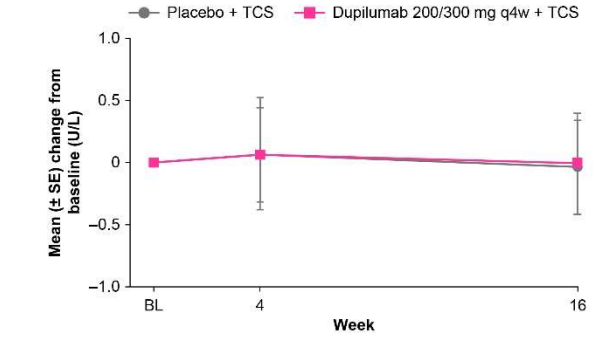
No. of patients:			
Placebo + TCS	62	58	59
Dupilumab + TCS	62	58	61



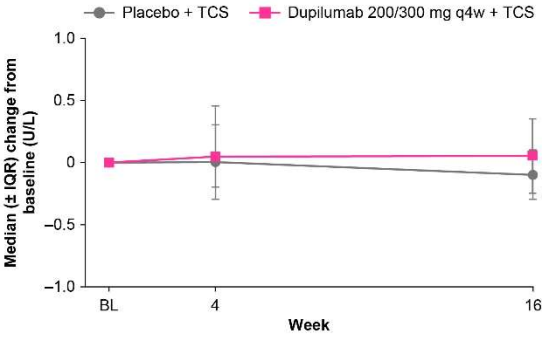
No. of patients:			
Placebo + TCS	62	58	59
Dupilumab + TCS	62	58	61

(b)

Potassium



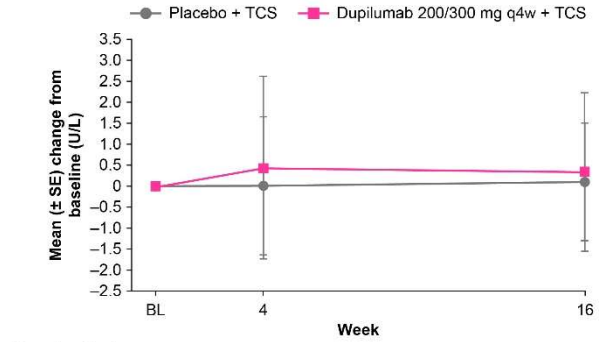
No. of patients:			
Placebo + TCS	62	58	59
Dupilumab + TCS	61	56	58



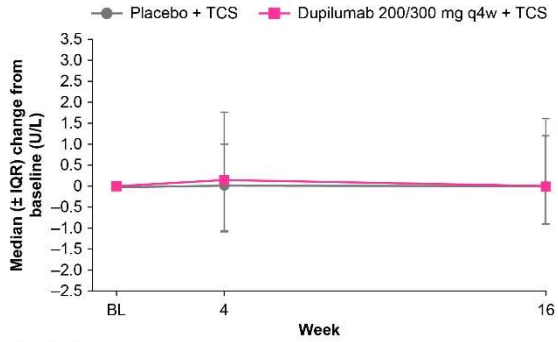
No. of patients:			
Placebo + TCS	62	58	59
Dupilumab + TCS	61	56	58

(c)

Total birilubin



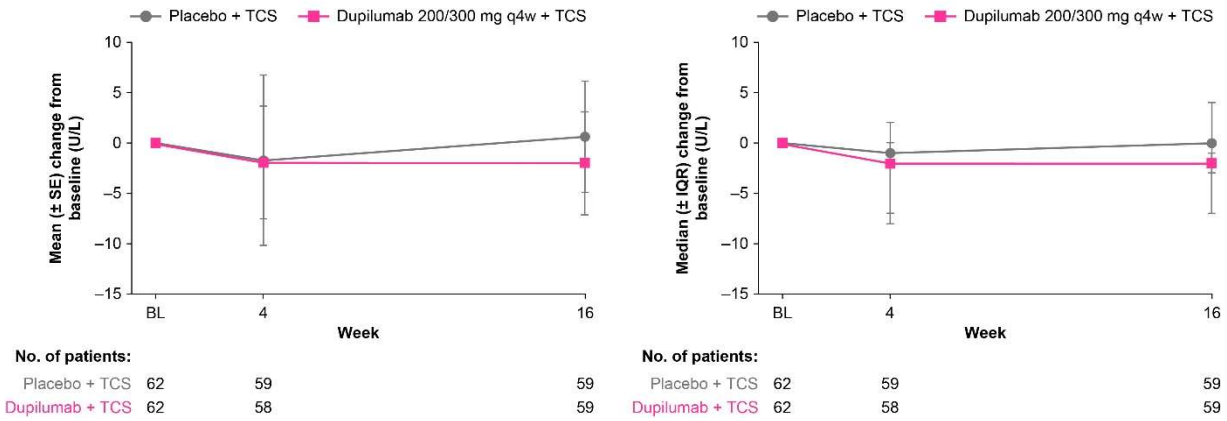
No. of patients:			
Placebo + TCS	62	59	59
Dupilumab + TCS	62	58	59



No. of patients:			
Placebo + TCS	62	59	59
Dupilumab + TCS	62	58	59

(d)

Aspartate aminotransferase

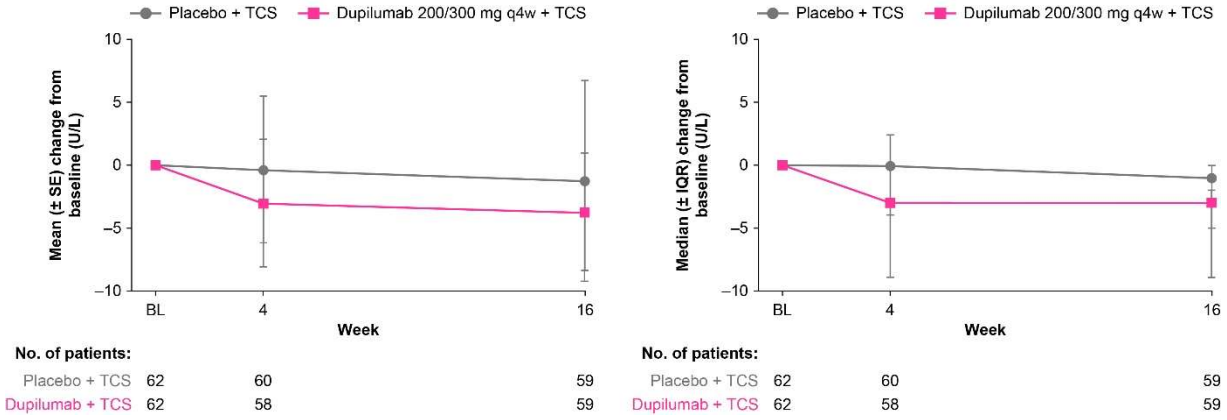


No. of patients:			
Placebo + TCS	62	59	59
Dupilumab + TCS	62	58	59

No. of patients:			
Placebo + TCS	62	59	59
Dupilumab + TCS	62	58	59

(e)

Alanine aminotransferase

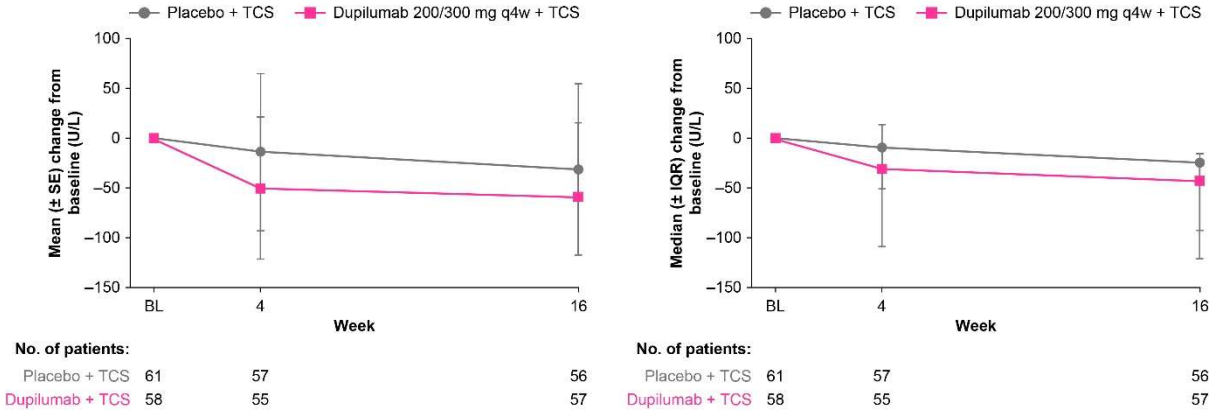


No. of patients:			
Placebo + TCS	62	60	59
Dupilumab + TCS	62	58	59

No. of patients:			
Placebo + TCS	62	60	59
Dupilumab + TCS	62	58	59

(f)

Lactate dehydrogenase



No. of patients:			
Placebo + TCS	61	57	56
Dupilumab + TCS	58	55	57

No. of patients:			
Placebo + TCS	61	57	56
Dupilumab + TCS	58	55	57

Figure S4 Mean and median change from baseline in serum chemistry analyses through week 16. (a) Creatinine. (b) Potassium. (c) Total bilirubin. (d) Aspartate aminotransferase. (e) Alanine aminotransferase. (f) Lactate dehydrogenase. BL, baseline; IQR, interquartile range; q4w, every 4 weeks; SE, standard error; TCS, topical corticosteroids.

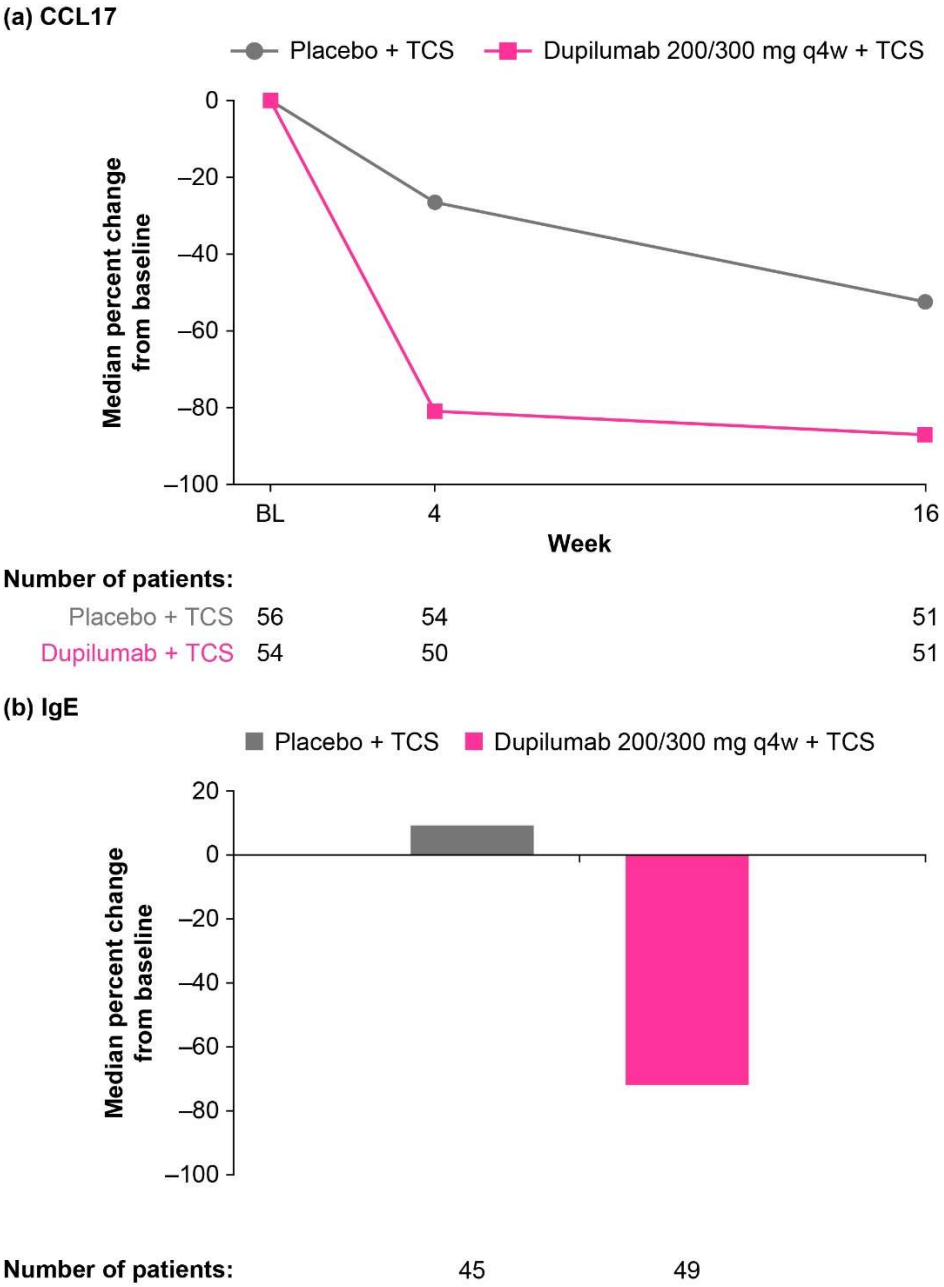


Figure S5 Median % change from baseline in serum CCL17 and serum total IgE. CCL17, CC chemokine ligand 17; IgE, immunoglobin E; q4w, every 4 weeks; TCS, topical corticosteroids.

Tables

Table S1 Efficacy in co-primary and key secondary endpoints at week 4

	Placebo + TCS (N = 62)	**Dupilumab 200/300 mg q4w + TCS (N = 63)**	**Δ vs. placebo (95% CI)**	**Nominal *P*-value vs. placebo**
Patients with IGA ≤ 1 (score range 0–4), *n* (%)	0	3 (4.8)	4.8 (−0.5, 10.0)	0.0850
Patients with IGA ≤ 2 (score range 0–4), *n* (%)	1 (1.6)	17 (27.0)	25.3 (13.9, 36.8)	< 0.0001
Patients with EASI-75 (score range 0–72), *n* (%)	3 (4.9)	17 (27.0)	22.1 (9.8, 34.3)	0.0009
Percent change from baseline in EASI, LS mean (SE)	−14.6 (3.8)	−49.7 (3.8)	−35.1 (−45.3, −25.0)	< 0.0001
Percent change from baseline in Worst Scratch/Itch NRS (score range 0–10), LS mean (SE)	0.1 (5.1)	−32.0 (5.0)	−32.1 (−45.27, −18.86)	< 0.0001
Patients with improvement of weekly average of daily Worst Scratch/Itch NRS ≥ 4, *n* (%)	3 (5.2)	15 (24.2)	19.0 (6.9, 31.1)	0.0041
Patients with improvement of weekly average of daily Worst Scratch/Itch NRS ≥ 3, *n* (%)	6 (10.3)	28 (45.2)	34.8 (20.2, 49.5)	< 0.0001
Patients with EASI-50, *n* (%)	12 (20.0)	38 (60.3)	40.3 (24.6, 56.1)	< 0.0001
Patients with EASI-90, *n* (%)	0	4 (6.4)	6.4 (0.3, 12.4)	0.0523
Change from baseline in percent BSA affected by AD, LS mean (SE)	−8.6 (1.8)	−26.2 (1.8)	−17.5 (−22.4, −12.7)	< 0.0001
Change from baseline in POEM (scale range 0–28), LS mean (SE)	−2.7 (0.6)	−11.2 (0.6)	−8.4 (−10.1, −6.7)	< 0.0001
Percent change from baseline in SCORAD (score range 0–103), LS mean (SE)	−15.2 (2.1)	−38.1 (2.1)	−22.9 (−28.4, −17.3)	< 0.0001
Change from baseline in patient's sleep quality NRS* (0–10), LS mean (SE)	0.6 (0.2)	1.6 (0.2)	1.0 (0.6, 1.4)	< 0.0001

Change from baseline in patient's skin pain NRS (range 0–10), LS mean (SE)	−0.8 (0.2)	−2.9 (0.2)	−2.1 (−2.7, −1.6)	< 0.0001
Change from baseline in DFI (Dermatitis Family Index) (0–30), LS mean (SE)	−20.7 (3.8)	−43.3 (3.7)	−22.5 (−32.5, −12.5)	< 0.0001
Change from baseline in CDLQI (Child Dermatology Life Quality Index) (0–30), LS mean (SE)**	−4.2 (1.0)	−8.8 (1.0)	−4.5 (−6.8, −2.3)	0.0001
Change from baseline in IDQOL (Infant Dermatitis Quality of Life Index) (0–30), LS mean (SE)***	−2.8 (0.9)	−10.3 (1.0)	−7.4 (−10.1, −4.8)	< 0.0001

*Increase in score means improvement. ** Placebo group n = 31, Dupilumab group n = 38. *** Placebo group n = 29, Dupilumab group n = 23.
BSA, body surface area; CDLQI, Child Dermatology Life Quality Index; DFI, Dermatitis Family Index; EASI, Eczema Area and Severity Index; EASI-75, 75% decrease in EASI; IDQOL, Infant Dermatitis Quality of Life Index; IGA, Investigator's Global Assessment; LS, least squares; NRS, Numerical Rating Scale; POEM, Patient Oriented Eczema Measure; q4w, every 4 weeks; SCORAD, SCORing Atopic Dermatitis; TEAE, treatment-emergent adverse event; TCS, topical corticosteroids.

Table S2 Efficacy outcomes at week 16 by baseline bodyweight: ≥ 5 to < 15 kg vs. ≥ 15 to < 30 kg

	≥ 5 to < 15 kg			≥ 15 to < 30 kg		
	Placebo + TCS	**200 mg q4w + TCS**	**Difference vs placebo (%) (95% CI)**	**Placebo + TCS**	**300 mg q4w + TCS**	**Difference vs. placebo (%) (95% CI)**
	***n* = 18**	***n* = 18**		***n* = 44**	***n* = 45**	
Patients with IGA ≤ 1 (score range 0–4), *n* (%)	0	2 (11.1)	11.1 (−3.4, 25.6)	1 (2.4)	9 (20.0)	17.6 (5.1, 30.2)
Patients with IGA ≤ 2 (score range 0–4), *n* (%)	2 (11.8)	7 (38.9)	27.1 (−0.1, 54.4)	5 (11.9)	27 (60.0)	48.1 (30.8, 65.4)
Patients with EASI-75 (score range 0–72), *n* (%)	1 (5.9)	10 (55.6)	49.7 (24.1, 75.2)	6 (14.3)	28 (62.2)	47.9 (30.3, 65.6)
Percent change in EASI score from baseline, LS mean (SE)	−42.3 (6.9)	−59.4 (6.7)	−17.0 (−35.8, 1.8)	−40.1 (4.1)	−72.1 (4.0)	−32.0 (−43.3, −20.8)
Percent change in Worst Scratch/Itch NRS from baseline (score range 0–10), LS mean (SE)	−14.2 (12.2)	−44.4 (11.9)	−30.3 (−63.8, 3.3)	−18.7 (3.7)	−52.0 (3.6)	−33.3 (−43.4, −23.2)
Patients with improvement of weekly average of daily Worst Scratch/Itch NRS ≥ 4, *n* (%)	2 (12.5)	8 (50.0)	37.5 (8.1, 66.9)	6 (16.7)	21 (53.9)	37.2 (17.4, 57.0)
Patients with improvement of weekly average of daily Worst Scratch/Itch NRS ≥ 3, *n* (%)	4 (25.0)	9 (56.3)	31.3 (−1.0, 63.5)	9 (25.0)	23 (59.0)	34.0 (13.0, 54.9)
Patients with EASI-50, *n* (%)	7 (41.2)	12 (66.7)	25.5 (−6.5, 57.4)	17 (40.5)	37 (82.2)	41.8 (23.2, 60.3)
Patients with EASI-90, *n* (%)	0	2 (11.1)	11.1 (−3.4, 25.6)	0	10 (22.2)	22.2 (10.1, 34.4)
Change in percent BSA affected by AD from baseline, LS mean (SE)	−40.1 (6.7)	−45.1 (6.5)	–4.9 (−23.1, 13.3)	−30.6 (4.4)	−62.9 (4.2)	–32.3 (–44.2, −20.5)
Change in POEM from baseline (scale range 0–28), LS mean (SE)	−30.2 (6.7)	−43.4 (6.5)	−13.2 (−31.4, 5.0)	−21.3 (4.1)	−54.3 (4.0)	–32.9 (–44.0, −21.8)
Percent change in SCORAD from baseline (score range 0–103), LS mean (SE)	−30.3 (5.0)	−45.4 (4.8)	−15.1 (−28.7, −1.4)	–26.9 (2.9)	−56.6 (2.8)	−29.8 (−37.6, −21.9)

Change in patient's sleep quality NRS* from baseline (range 0–10), LS mean (SE)	106.1 (27.8)	94.0 (28.2)	−12.1 (−89.9, 65.7)	30.4 (69.5)	206.6 (66.7)	176.2 (−11.8, 364.2)
Change in patient's skin pain NRS from baseline (range 0–10), LS mean (SE)	−19.3 (10.1)	−54.6 (9.9)	−35.3 (−63.2, −7.4)	−24.3 (4.2)	−60.3 (4.0)	−35.9 (−47.2, −24.6)
Change from baseline in DFI (range 0–30), LS mean (SE)	−38.9 (7.5)	−45.5 (7.5)	−6.6 (−27.5, 14.3)	−31.8 (5.1)	−57.3 (5.0)	−25.5 (−39.3, −11.7)
Change from baseline in CDLQI (range 0–30), LS mean (SE)**	−53.5 (14.1)	−48.1 (10.7)	5.5 (−34.7, 45.7)	−33.6 (6.0)	−54.4 (5.3)	−20.8 (−36.6, −5.0)
Change from baseline in IDQOL (range 0–30), LS mean (SE)***	−29.5 (8.2)	−49.4 (8.0)	−20.0 (−42.8, 2.8)	−15.3 (8.8)	−59.2 (11.4)	−43.9 (−71.2, −16.6)

*Increase in score means improvement. ** ≥ 5 to < 15 kg placebo group n = 3, dupilumab group n = 3; ≥ 15 to < 30 kg placebo group n = 27, dupilumab group n = 35. *** ≥ 5 to < 15 kg placebo group n = 14, dupilumab group n = 15; ≥ 15 to < 30 kg placebo group n = 12, dupilumab group n = 7. Percentages in the following endpoints are calculated based on the available assessment: Patients with IGA ≤ 1, IGA ≤ 2, EASI-75, EASI-50, EASI-90 (≥ 5 to < 15 kg placebo group n = 17, dupilumab group n = 18; ≥ 15 to < 30 kg placebo group n = 42, dupilumab group n = 45); Patients with improvement of weekly average of daily Worst Scratch/Itch NRS ≥ 4 and NRS ≥ 3 (≥ 5 to < 15 kg placebo group n = 16, dupilumab group n = 16; ≥ 15 to < 30 kg placebo group n = 36, dupilumab group n = 39). BSA, Body Surface Area; CDLQI, Child Dermatology Life Quality Index; CI, confidence interval; DFI, Dermatitis Family Index; EASI, Eczema Area and Severity Index; EASI-75, 75% decrease in EASI; IDQOL, Infant Dermatitis Quality of Life Index; IGA, Investigator's Global Assessment; LS, least squares; NRS, Numerical Rating Scale; POEM, Patient Oriented Eczema Measure; q4w, every 4 weeks; SCORAD, SCORing Atopic Dermatitis; TEAE, treatment-emergent adverse event; TCS, topical corticosteroids.

Table S3. Number of patients with treatment-emergent SAEs

MedDRA Primary System Organ Class* Preferred Term*	**Placebo + TCS (N = 61)**	**Dupilumab 200/300 mg q4w + TCS (N = 63)**
Number of such events	4	0
Number of patients with at least one such event, *n* (%)	3 (4.9)	0
Infections and infestations	3 (4.9)	0
Cellulitis staphylococcal	1 (1.6)	0
Dermatitis infected	1 (1.6)	0
Staphylococcal bacteremia	1 (1.6)	0
Skin and subcutaneous tissue disorders	1 (1.6)	0
Dermatitis atopic	1 (1.6)	0
Immune system disorders	1 (1.6)	2 (3.2)
Hypersensitivity	1 (1.6)	0

*MedDRA Version 23.1. MedDRA, Medical Dictionary for Regulatory Activities; q4w, every 4 weeks; SAE, serious adverse event; TCS, topical corticosteroids.

Table S4. Number of patients with severe TEAEs

MedDRA Primary System Organ Class*, *n* (%) **Preferred Term***	**Placebo + TCS (N = 61)**	**Dupilumab + TCS (N = 63)**
Patients with ≥ 1 event	7 (11.5)	2 (3.2)
Blood and lymphatic system disorders	0	1 (1.6)
Eosinophilia	0	1 (1.6)
Eye disorders	0	1 (1.6)
Blepharitis	0	1 (1.6)
Infections and infestations	4 (6. 6)	0
Cellulitis staphylococcal	1 (1.6)	0
Dermatitis infected	1 (1.6)	0
Staphylococcal bacteremia	1 (1.6)	0
Staphylococcal skin infection	1 (1.6)	0
Injury, poisoning, and procedural complications	1 (1.6)	0
Head injury	1 (1.6)	0
Skins and subcutaneous tissue disorders	4 (6.6)	0
Dermatitis atopic	3 (4.9)	0
Pruritus	1 (1.6)	0

*MedDRA Version 23.1. MedDRA, Medical Dictionary for Regulatory Activities; q4w, every 4weeks; TCS, topical corticosteroids; TEAE, treatment-emergent adverse event.

Table S5 Number of patients with TEAEs deemed related to the study drug

MedDRA Primary System Organ Class*, *n* (%) **Preferred Term***	**Placebo + TCS (N = 61)**	**Dupilumab 200/300 mg q4w + TCS (N = 63)**
Patients with ≥ 1 event	5 (8.2)	8 (12.7)
Infections and infestations (SOC)	2 (3.3)	4 (6.4)
Conjunctivitis	0	3 (4.8)
Herpes viral infection	0	1 (1.6)
Impetigo	1 (1.6)	0
Respiratory syncytial infection	1 (1.6)	0
Staphylococcal infection	1 (1.6)	0
General disorders and administration site conditions	2 (3.3)	1 (1.6)
Injection-site erythema	0	1 (1.6)
Injection-site swelling	0	0
Injection-site edema	1 (1.6)	0
Injection-site urticaria	1 (1.6)	0
Skin and subcutaneous tissue disorders	2 (3.3)	2 (3.2)
Dermatitis atopic	2 (3.3)	0
Erythema	0	1 (1.6)
Hair growth abnormal	0	1 (1.6)
Blood and lymphatic system disorders	0	1 (1.6)
Eosinophilia	0	1 (1.6)
Eye disorders	0	1 (1.6)
Blepharitis	0	1 (1.6)

*MedDRA Version 23.1. MedDRA, Medical Dictionary for Regulatory Activities; q4w, every 4 weeks; TCS, topical corticosteroids; TEAE, treatment-emergent adverse event.

Table S6 Number of patients with treatment-emergent conjunctivitis (narrow and broad CMQ) by MedDRA Preferred Term*

	Placebo + TCS (N = 61)	**Dupilumab 200/300 mg q4w + TCS (N = 63)**
Narrow conjunctivitis		
Patients with ≥ 1 such event, *n* (%)	0	4 (6.3)
Conjunctivitis	0	3 (4.8)
Conjunctivitis allergic	0	1 (1.6)
Broad conjunctivitis		
Patients with ≥ 1 such event, *n* (%)	1 (1.6)	6 (9.5)
Conjunctivitis	0	3 (4.8)
Conjunctivitis allergic	0	1 (1.6)
Blepharitis	0	2 (3.2)
Eye irritation	1 (1.6)	0

*MedDRA Version 23.1. CMQ, customised Medical Dictionary for Regulatory Activities query; MedDRA, Medical Dictionary for Regulatory Activities; q4w, every 4 weeks; TCS, topical corticosteroids.

Table S7 Number of patients with skin infections (adjudicated), excluding herpes viral infections

MedDRA Primary System Organ Class*, *n (%)* **High-Level Term*** **Preferred Term***	**Placebo + TCS (N = 61)**	**Dupilumab 200/300 mg q4w + TCS (N = 63)**
Number of patients with at least one such event, *n* (%)	16 (26.2)	9 (14.3)
Infections and infestations	16 (26.2)	9 (14.3)
Skin structures and soft tissue infections	8 (13.1)	5 (7.9)
Impetigo	5 (8.2)	2 (3.2)
Dermatitis infected	1 (1.6)	1 (1.6)
Paronychia	1 (1.6)	1 (1.6)
Skin infection	1 (1.6)	1 (1.6)
Molluscum contagiosum viral infections	2 (3.3)	4 (6.3)
Molluscum contagiosum	2 (3.3)	4 (6.3)
Bacterial infections NEC	2 (3.3)	1 (1.6)
Cellulitis	1 (1.6)	1 (1.6)
Skin bacterial infection	1 (1.6)	0
Candida infections	1 (1.6)	0
Genital candidiasis	1 (1.6)	0
Infections NEC	1 (1.6)	0
Abscess limb	1 (1.6)	0
Staphylococcal infections	6 (9.8)	0
Cellulitis staphylococcal	1 (1.6)	0

*MedDRA Version 23.1. MedDRA, Medical Dictionary for Regulatory Activities; NEC, not elsewhere classified; q4w, every 4 weeks; TCS, topical corticosteroids.

Table S8 Number of patients with herpes viral infections

MedDRA High-Level Term*, *n (%)* Preferred Term*	**Placebo + TCS (N = 61)**	**Dupilumab 200/300 mg q4w + TCS (N = 63)**
Number of patients with at least one such event, *n* (%)		
Herpes viral infections	4 (6.6)	3 (4.8)
Herpes virus infection	0	1 (1.6)
Varicella	0	2 (3.2)
Eczema herpeticum	1 (1.6)	0
Oral herpes	2 (3.3)	0
Herpes simplex	1 (1.6)	0

*MedDRA Version 23.1. MedDRA, Medical Dictionary for Regulatory Activities; q4w, every 4 weeks; TCS, topical corticosteroids.