Dupilumab With Concomitant Topical Corticosteroids in Adult Patients With Atopic Dermatitis who are not Adequately Controlled With or are Intolerant to Cyclosporine A, or When This Treatment is Medically Inadvisable: A Placebo-Controlled, Randomized Phase 3 Clinical Trial (LIBERTY AD CAFÉ)

Marjolein de Bruin-Weller[1], Diamant Thaçi[2], Catherine Smith[3], Kristian Reich[4], Michael Cork[5], Allen Radin[6], Rick Zhang[7], Bolanle Akinlade[6], Abhijit Gadkari[6], Laurent Eckert[8], Thomas Hultsch[9], Zhen Chen[6], Gianluca Pirozzi[10], Neil MH Graham[6], Brad Shumel[6]

[1]University Medical Center Utrecht, Utrecht, Netherlands; [2]University of Lübeck, Lübeck, Germany; [3]St. John's Institute of Dermatology, London, UK; [4]Dermatologikum Hamburg, Hamburg, Germany; [5]University of Sheffield, Sheffield, UK; [6]Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA; [7]Regeneron Pharmaceuticals, Inc., Basking Ridge, NJ, USA; [8]Sanofi, Chilly-Mazarin, France; [9]Sanofi, Cambridge, MA, USA; [10]Sanofi, Bridgewater, NJ, USA

Marjolein de Bruin-Weller, MD, PhD

University Medical Center Utrecht, Utrecht, Netherlands

#4310 Dupilumab With Concomitant Topical Corticosteroids in Adult Patients With Atopic Dermatitis who are not Adequately Controlled With or are Intolerant to Cyclosporine A, or When This Treatment is Medically Inadvisable: A Placebo-Controlled, Randomized Phase 3 Clinical Trial (LIBERTY AD CAFÉ)

Disclosures

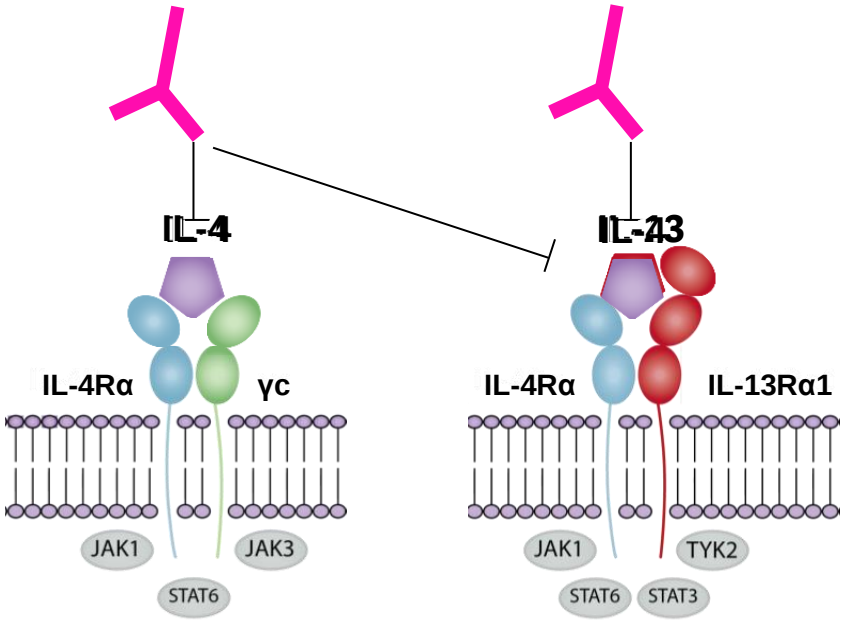
- Principal investigator, advisory board member – Regeneron Pharmaceuticals, Inc., Sanofi Genzyme
- Principal investigator, advisory board member, and consultant – AbbVie

Acknowledgments

- Research sponsored by Sanofi and Regeneron Pharmaceuticals, Inc. ClinicalTrials.gov Identifier: NCT02755649. Medical writing/editorial support provided by Ferdinando Giacco, PhD, of Excerpta Medica, funded by Sanofi Genzyme and Regeneron Pharmaceuticals, Inc.

Background

- **Atopic dermatitis (AD) is a chronic inflammatory skin disease often associated with atopic comorbidities[1]**
- **IL-4 and IL-13 are type 2/Th2 cytokines that mediate many features of AD[2]**
- **Dupilumab is a fully human monoclonal antibody directed against the IL-4Rα subunit of the IL-4 and IL-13 receptors**
- **Dupilumab is approved by the US FDA for treatment of adult patients with moderate-to-severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable, and can be used with or without topical corticosteroids (TCS)**



Type I receptor

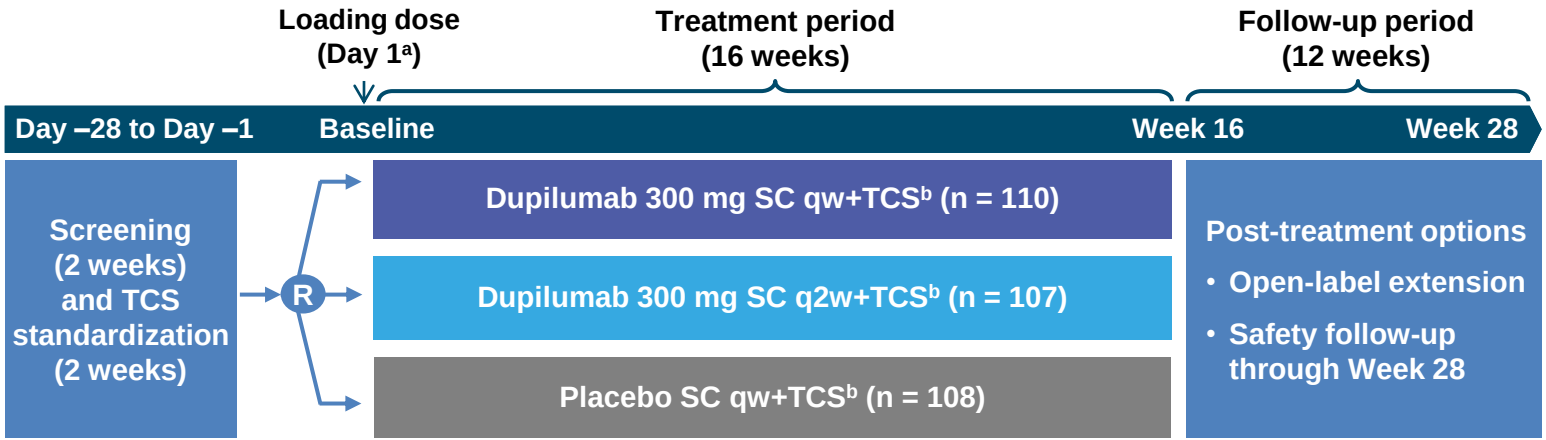
B cells, T cells, monocytes, eosinophils, fibroblasts

Type II receptor

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

[1]Silverberg J. Clin Dermatol.2017;35:360-6. [2]Gandhi N, et al. Nature Rev Drug Disc.2016;15:35-50. γc, common gamma chain; IL, interleukin; IL-4Rα, IL-4 receptor alpha; IL-13Rα, IL-13 receptor alpha; JAK, Janus kinase; STAT, signal transducer and activator of transcription; TYK2, tyrosine kinase type 2.

CAFÉ: Dupilumab With Concomitant TCS in Patients With AD Inadequately Controlled With or Intolerant to CsA, or for Whom CsA was not Advisable



[a]Dupilumab 600 mg or matching placebo. [b]Patients were required to use medium-potency TCS for the entire treatment period. CsA, cyclosporine A; q2w, every 2 weeks; qw, every week; R, randomization; SC, subcutaneous.

Key Inclusion Criteria

- **Age ≥ 18 years; EASI ≥ 20; IGA = 3 or 4**
- **Documented history (within 6 months before screening visit) of inadequate response to treatment with TCS**

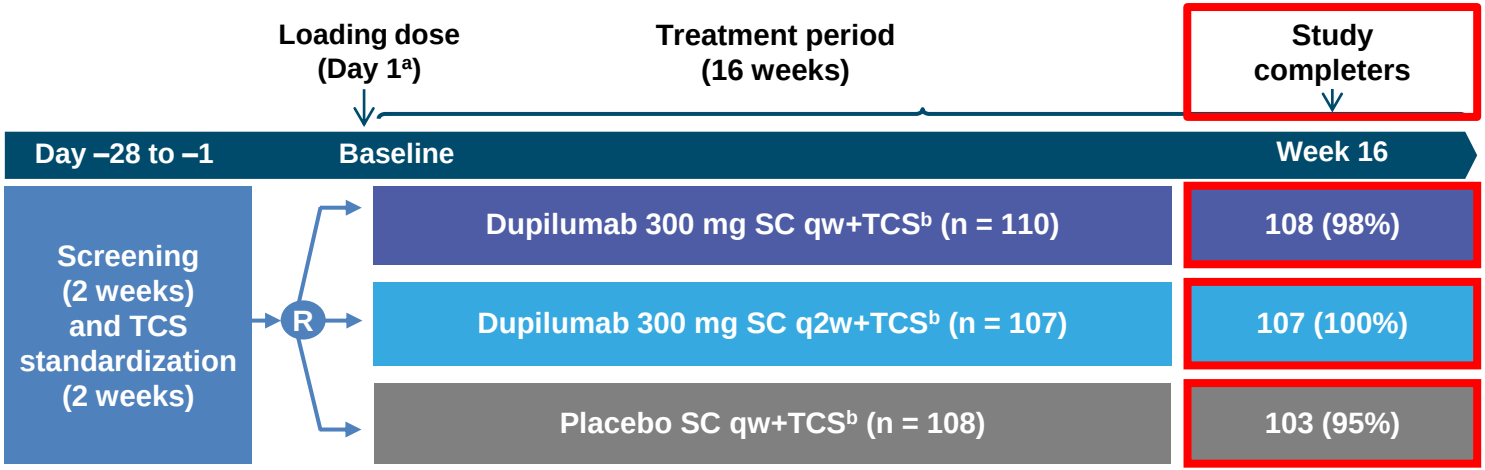
Acceptable documentation included contemporaneous chart notes that recorded CSA and treatment outcome, or investigator documentation based on communication with the patient's treating physician

Key Inclusion Criteria

- **Age ≥ 18 years; EASI ≥ 20; IGA = 3 or 4**
- **Documented history (within 6 months before screening visit) of inadequate response to treatment with TCS**
- **Documented history by a physician of either**
  - No prior CsA exposure and not currently a candidate for CsA treatment due to
    - medical contraindications (e.g. uncontrolled hypertension on medication), or
    - use of prohibited concomitant medications, or
    - increased susceptibility to CsA-induced renal damage (elevated creatinine) and/or liver damage (elevated function tests), or
    - increased risk of serious infections, or
    - hypersensitivity to CsA active substance or excipients, or
  - Previously exposed to CsA, and CsA treatment should not be continued or restarted due to
    - intolerance and/or unacceptable toxicity, or
    - inadequate response to CsA (defined as flare of AD on CsA tapering after a maximum of 6 weeks of high dose [5 mg/kg/day] to maintenance dose [2–3 mg/kg/day] or a flare after a minimum of 3 months on maintenance dose), or
    - requirement for CsA at doses > 5 mg/kg/day, or duration beyond those specified in the prescribing information (> 1 year)

Acceptable documentation included contemporaneous chart notes that recorded CSA and treatment outcome, or investigator documentation based on communication with the patient's treating physician. EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment.

Study Completers



[a]Dupilumab 600 mg or matching placebo. [b]Patients were required to use medium-potency TCS for the entire treatment period.

Baseline Characteristics (1)

	Score range	Placebo qw + TCS (n = 108)	Dupilumab 300 mg q2w + TCS (n = 107)	Dupilumab 300 mg qw + TCS (n = 110)
Age, years, median (IQR)	--	37.5 (29.0, 49.0)	38.0 (25.0, 47.0)	38.0 (29.0, 48.0)
Male, n (%)	--	68 (63)	65 (61)	66 (60)
EASI, median (IQR)	0–72	31.7 (24.2, 40.7)	31.6 (25.2, 39.2)	31.1 (24.5, 39.0)
SCORAD, median (IQR)	0–102	67.5 (58.5, 76.6)	66.7 (61.1, 76.2)	66.1 (55.4, 75.4)
Weekly average of peak pruritus NRS, median (IQR)	0–10	6.9 (4.9, 8.1)	7.0 (5.4, 8.0)	6.4 (5.2, 7.7)
Patients with IGA = 4, n (%)	0–4	52 (48.1)	50 (46.7)	52 (47.3)
Prior cyclosporine treatment[a], n (%)	--			
Yes	--	72 (66.7)	69 (64.5)	69 (62.7)
No	--	36 (33.3)	38 (35.5)	41 (37.3)

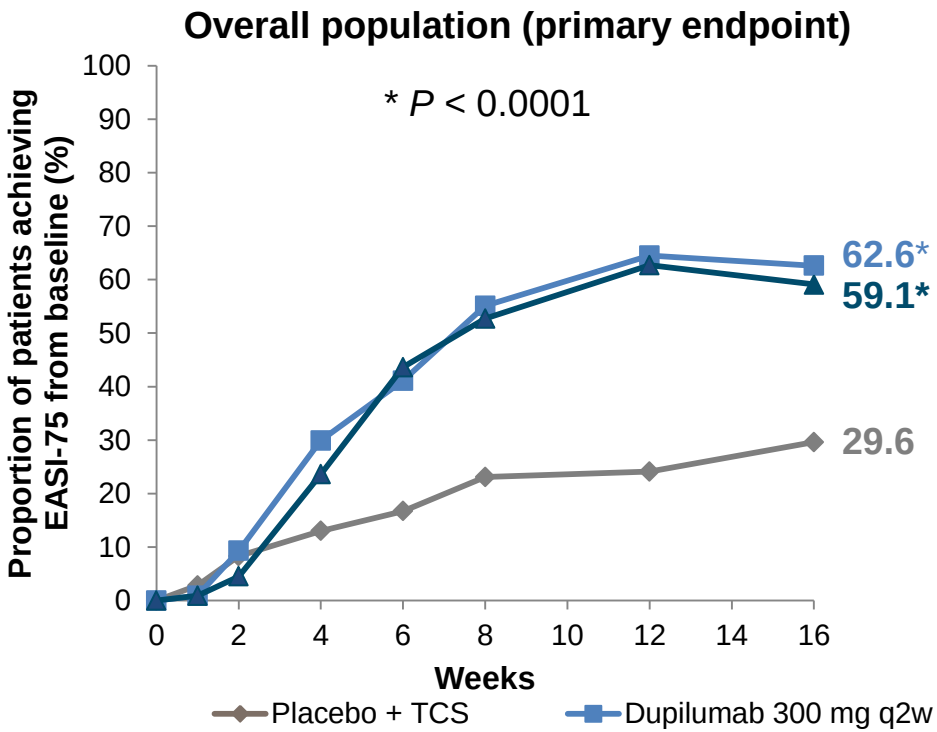
[a]Ratio of Prior CsA use/CsA naive patients was required by trial stratification. DLQI, Dermatology Life Quality Index; HADS-A, HADS Anxiety subscale; HADS-D, HADS Depression subscale; HADS, Hospital Anxiety and Depression scale; IQR, interquartile range; NRS, Numerical Rating Scale; SCORAD, Scoring Atopic Dermatitis.

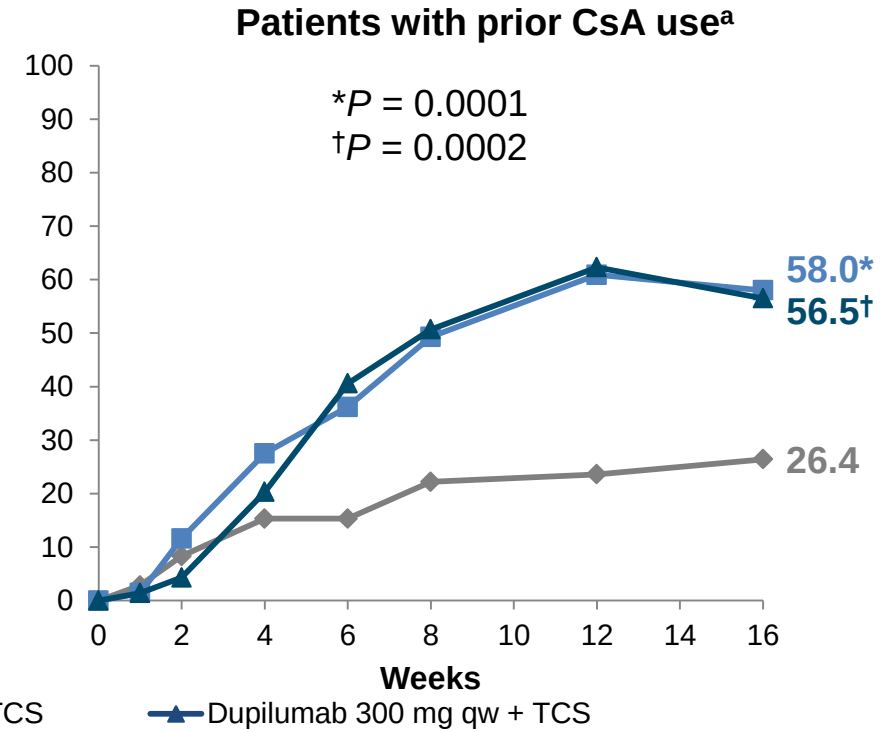
Baseline Characteristics (2)

	Score range	Placebo qw + TCS (n = 108)	Dupilumab 300 mg q2w + TCS (n = 107)	Dupilumab 300 mg qw + TCS (n = 110)
DLQI, median (IQR)	0–30	13.0 (7.0, 19.5)	14.0 (8.0, 22.0)	13.0 (7.0, 21.0)
POEM, median (IQR)[a]	0–28	19.0 (14.0, 24.0)	20.0 (15.0, 24.0)	19.0 (14.0, 24.0)
Patients with HADS-A or HADS-D ≥ 8, n (%)	0–21[b]	60 (55.6)	56 (52.3)	56 (50.9)
EQ-5D pain/discomfort domain, n (%):	--			
"I have no pain or discomfort"	--	26 (24.1)	29 (27.1)	25 (22.7)
"I have moderate pain or discomfort"	--	73 (67.6)	69 (64.5)	75 (68.2)
"I have extreme pain or discomfort"	--	9 (8.3)	9 (8.4)	10 (9.1)
SCORAD VAS sleep domain, median (IQR)	0–10	3.8 (1.4, 7.0)	4.5 (1.6, 7.6)	4.3 (1.3, 7.2)

[a]Placebo + TCS: n =107; [b]For each of the subscores (HADS-A, HADS-D). EQ-5D, 3-level EUROQOL five dimensions questionnaire; VAS, Visual Analogue

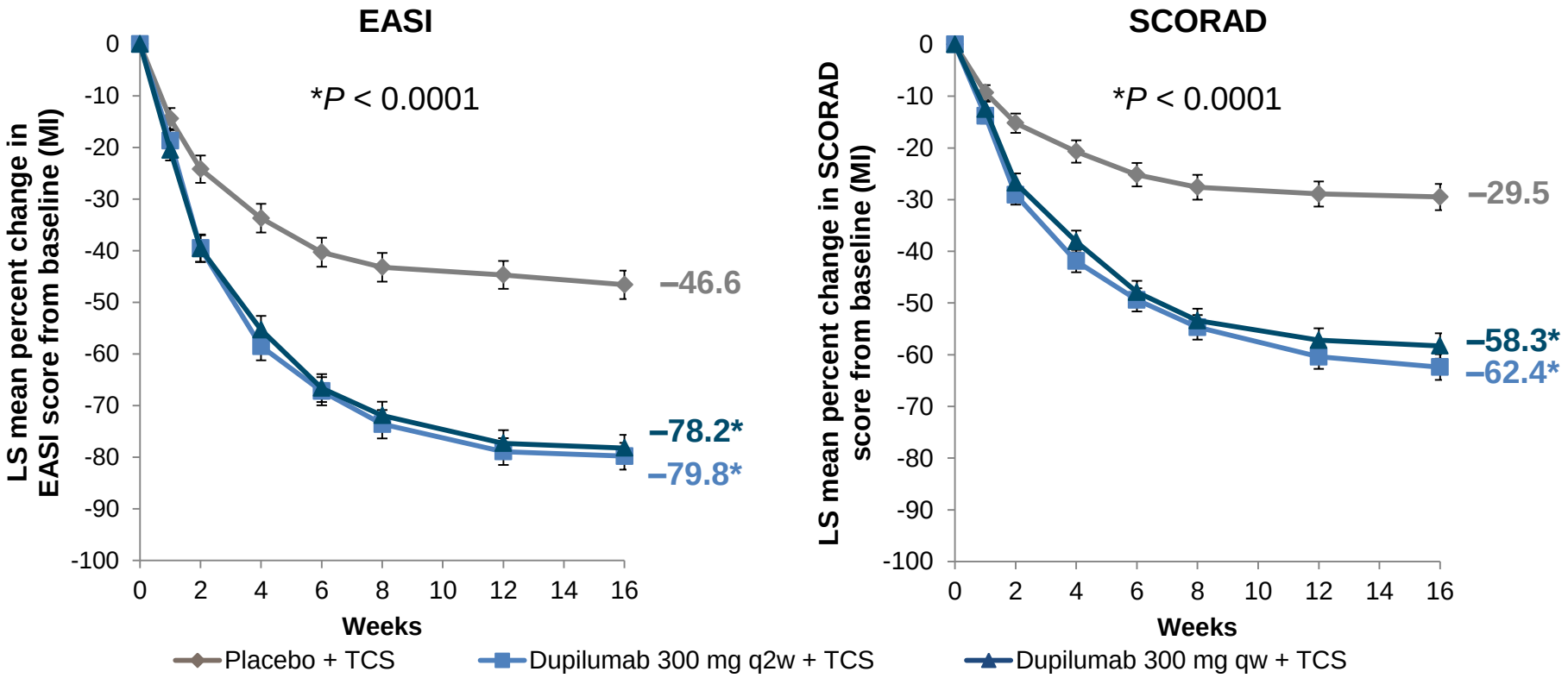
Significantly Higher Number of Patients Treated With Dupilumab + TCS Achieved EASI-75 at Week 16 vs Placebo + TCS





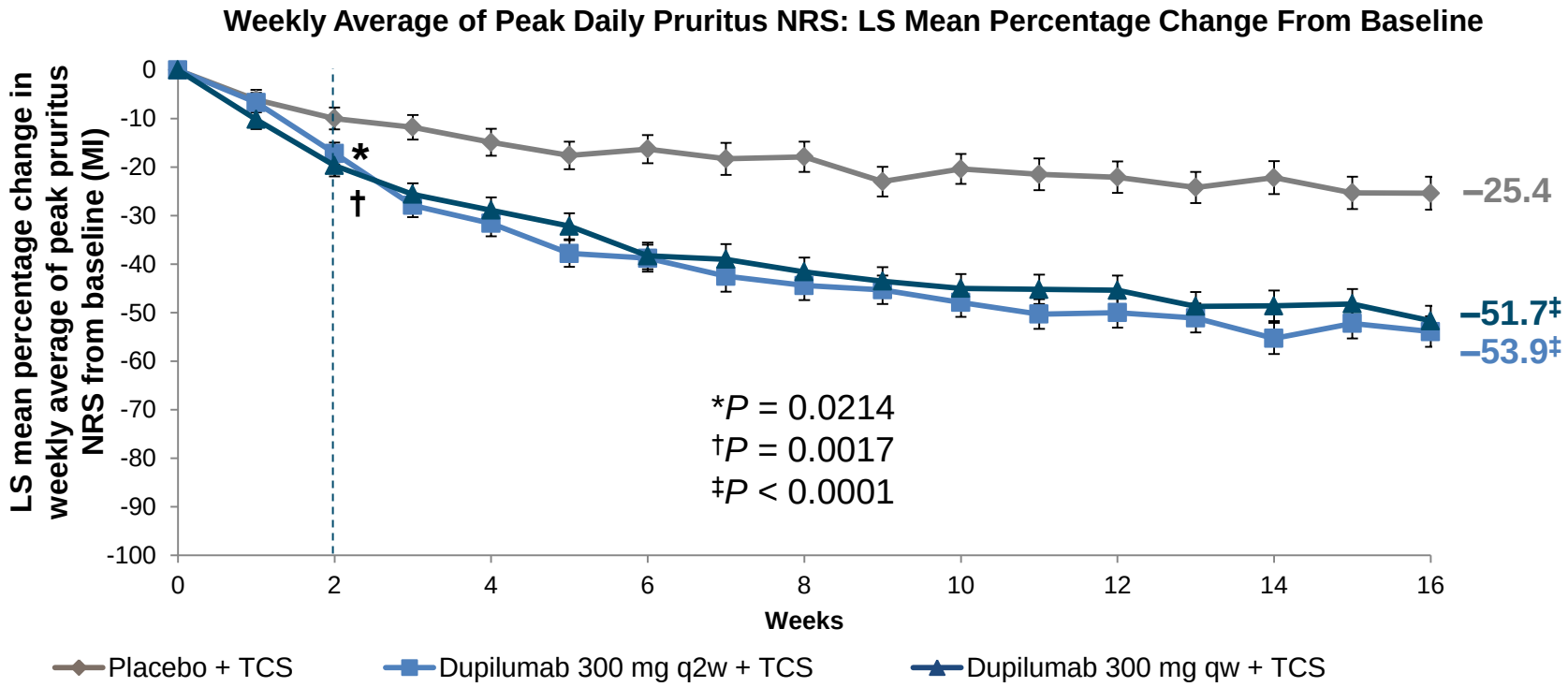
Values after first rescue treatment used were set to missing (censoring). Patients with missing values at Week 16 were considered as non-responders.
[a]Placebo, n/N1 = 19/72; dupilumab 300 mg qw, n/N1 = 39/69; dupilumab 300 mg q2w, n/N1 = 40/69. EASI-75, 75% improvement in EASI score from baseline; n, number of patients with EASI-75; N1, number of patients in treatment group with prior CsA use.

Dupilumab + TCS Induced Significantly Greater Reduction From Baseline in EASI and SCORAD vs Placebo + TCS



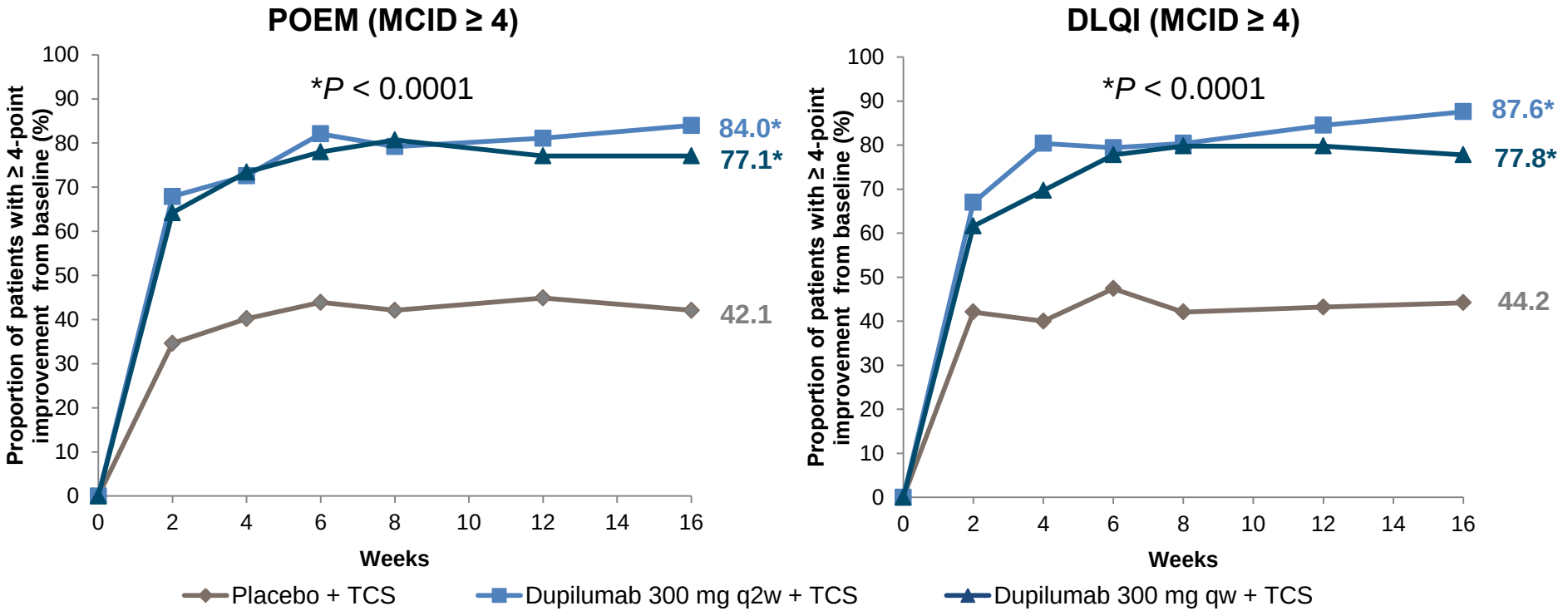
Error bars are ± SE. LS, least squares; MI, multiple imputation method with censoring after rescue treatment use; SE, standard error.

Dupilumab + TCS Induced a Significantly Greater Reduction in Weekly Average of Peak Daily Pruritus NRS From Baseline vs Placebo +TCS



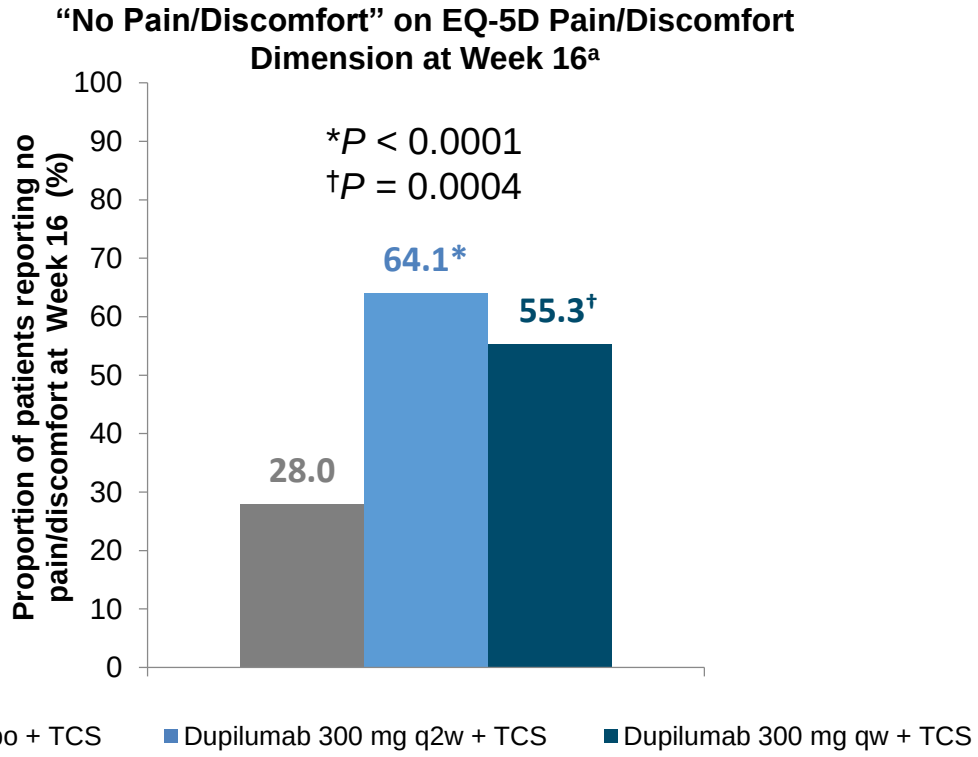
MI, multiple imputation method with censoring after rescue treatment use; SE, standard error. Error bars are ± SE.

Dupilumab + TCS Induced Significant Improvement in POEM and DLQI at Week 16 vs Placebo + TCS



All observed values. Values after first rescue treatment used were set to missing (censoring). Patients with missing values at Week 16 were considered as non-responders.

Dupilumab + TCS Improved EQ-5D Pain/Discomfort Score at Week 16 vs Placebo + TCS



[a]Among patients who reported moderate or severe pain/discomfort at baseline. Values after first rescue treatment used were set to missing (censoring). Patients with missing scores at week 16 were considered non-responders.

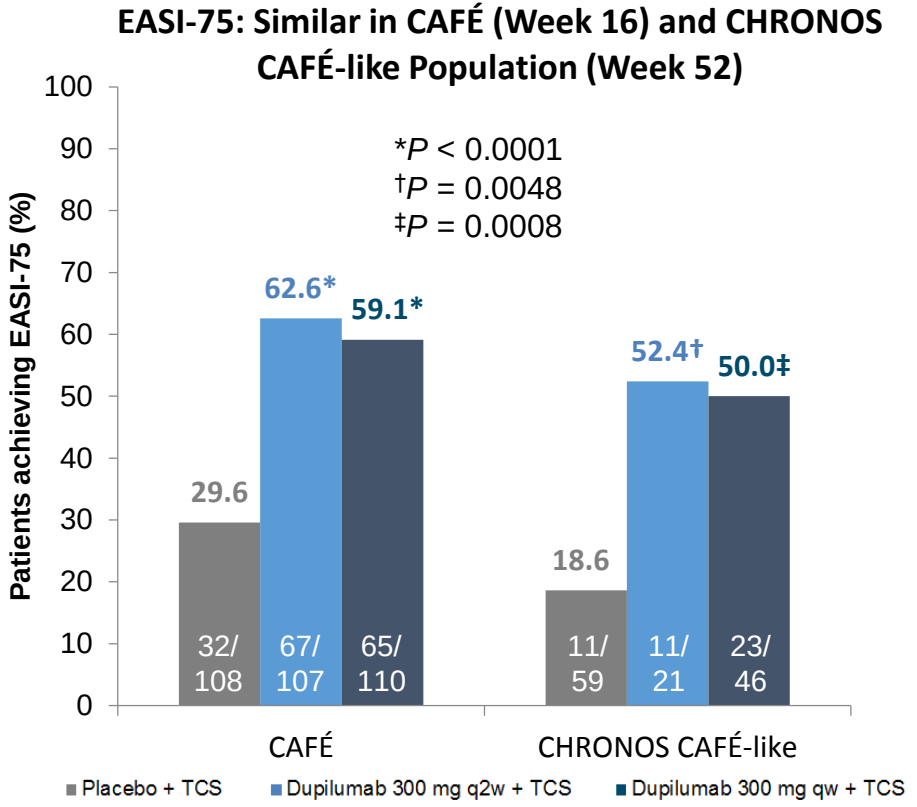
Overall Summary of Number of Patients With Adverse Events Through the 16-Week Treatment Period – SAF

Patients with, n (%):	Placebo qw + TCS (n = 108)	Dupilumab 300 mg q2w + TCS (n = 107)	Dupilumab 300 mg qw + TCS (n = 110)
Any TEAE	75 (69.4)	77 (72.0)	76 (69.1)
Any drug-related TEAE	20 (18.5)	36 (33.6)	37 (33.6)
Any TEAE causing discontinuation of study drug permanently	1 (0.9)	0	2 (1.8)
Conjunctivitis[a]	12 (11.1)	30 (28.0)	18 (16.4)
Skin infection (adjudicated)	9 (8.3)	2 (1.9)	4 (3.6)
Herpes viral infections	6 (5.6)	5 (4.7)	8 (7.3)
Any death	0	0	0
Any TE SAE	2 (1.9)	2 (1.9)	2 (1.8)
Any drug-related TE SAE	0	0	0
Any TE SAE causing discontinuation of study drug permanently	0	0	1 (0.9)
Any Severe TEAE	10 (9.3)	5 (4.7)	3 (2.7)

[a]Includes MedDRA PTs of conjunctivitis, conjunctivitis allergic, conjunctivitis bacterial, conjunctivitis viral, and atopic keratoconjunctivitis. MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; SAE, serious adverse event; SAF, safety analysis set (all randomized patients who received any study drug, was based on treatment received [as treated]); TE, treatment-emergent; TEAE, treatment-emergent adverse events.

CAFÉ confirms results of CHRONOS subgroup analysis of CAFÉ-like patients

- Outcomes were comparable to those at Week 52 for a CAFÉ-like subgroup of patients in LIBERTY AD CHRONOS (52-week randomized placebo-controlled phase 3 study of dupilumab+TCS)
- Data from the CAFÉ-like subgroup in CHRONOS show sustained treatment effect of dupilumab + TCS
- The results from both CAFÉ and the CAFÉ-like subgroup in CHRONOS support the benefit of dupilumab + TCS in this difficult-to-treat AD population



Conclusions

- 16 weeks of dupilumab with concomitant TCS significantly improved signs and symptoms of AD compared with placebo in adult patients with AD and a history of inadequate response or intolerance to TCS and CsA, or for whom CsA treatment is medically inadvisable
- In this study dupilumab was well tolerated with an acceptable safety profile
- Results in this study are similar to other phase 3 studies (16- and 52-week studies) of dupilumab with or without concomitant TCS
- These data support the use of dupilumab in adult patients with moderate-to-severe AD
  - who have previously used CsA and stopped it due to intolerance or lack of efficacy
  - who are not candidates for CsA because of medical conditions or use of contraindicated concomitant medications