Long-Term Management of Moderate-to-Severe Atopic Dermatitis (AD) With Dupilumab and Concomitant Topical Corticosteroids (TCS): A 1-Year, Randomized, Placebo-Controlled Phase 3 Trial (CHRONOS)

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Disclosures and Acknowledgments

Disclosures

- **Blauvelt A:** AbbVie, Amgen, Boehringer Ingelheim, Celgene, Dermira, Genentech, GlaxoSmithKline, Janssen, Lilly, Merck, Novartis, Pfizer, Regeneron Pharmaceuticals, Inc., Sandoz, Sanofi Genzyme, Sun Pharma, UCB, Valeant − scientific adviser and clinical study investigator; Lilly, Regeneron Pharmaceuticals, Inc., Sanofi Genzyme − paid speaker.
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- **Pirozzi G**: Sanofi − employee, may hold stock and/or stock options in the company.

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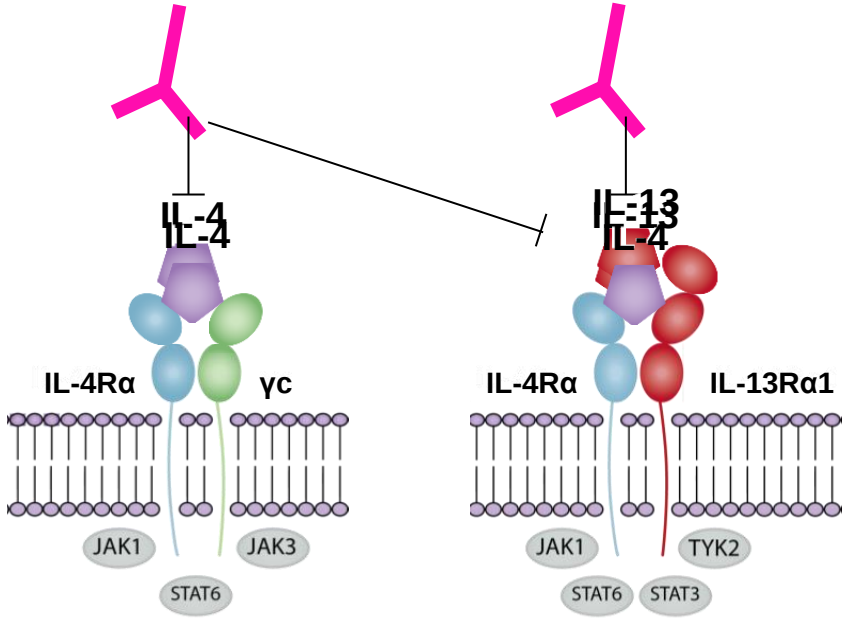
Dupilumab is not currently approved for labeling or advertising by the FDA

Background

- **Dupilumab is a potent blocker of IL-4 and IL-13 pathways**
- **IL-4 and IL-13 are type 2 (Th2) cytokines that mediate many features of AD as well as asthma and other atopic and allergic diseases**
- **In previous phase 3 studies (SOLO 1 and SOLO 2), dupilumab monotherapy for 16 weeks significantly improved AD signs and symptoms[1]**



Type I receptor

B cells, T cells, monocytes, eosinophils, fibroblasts

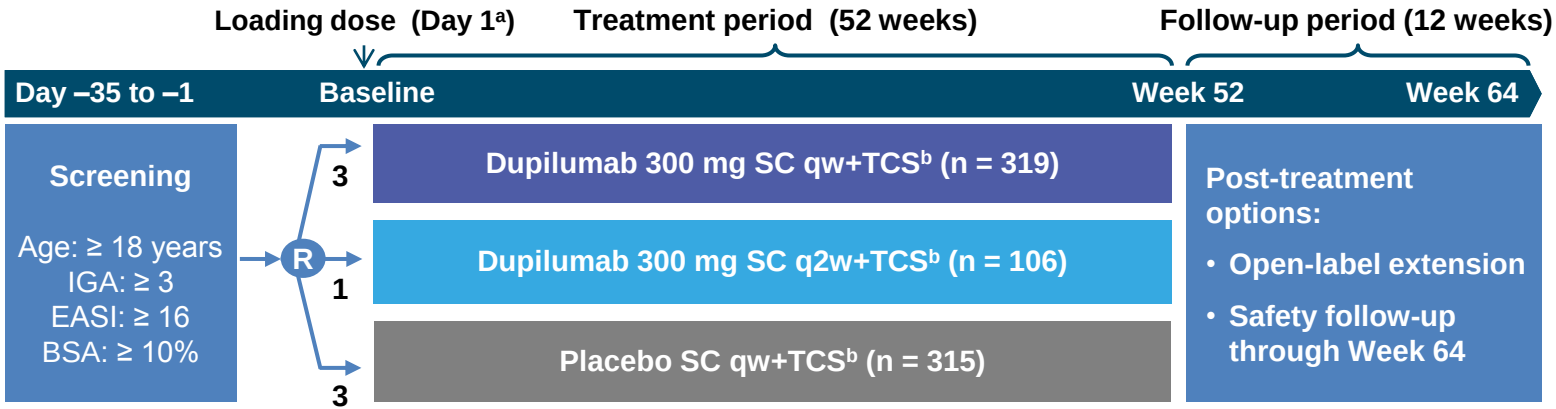
Type II receptor

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

1. Simpson EL, et al. N Engl J Med. 2016;375:2335-48. 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.

CHRONOS: Study Design and Endpoints

First Large Study Evaluating Efficacy and Safety of Dupilumab with Concomitant TCS



- **Objectives**
  - Primary: efficacy of dupilumab+TCS at Week 16 (FAS; N = 740)
  - Secondary: efficacy (FAS-52; N = 623) and safety (SAF; N = 740) of dupilumab with TCS at Week 52
- **Co-primary endpoints**
  - IGA score 0 or 1 and ≥ 2-point improvement from baseline at Week 16
  - EASI-75 at Week 16 (co-primary in Japan/EU; key secondary in USA)

85% of patients in the dupilumab qw+TCS group and 86% in the dupilumab q2w+TCS groups completed 52 weeks of treatment, vs 67% on placebo+TCS

[a] Dupilumab 600 mg or matching placebo. [b] TCI were allowed and used for areas where TCS are generally not advisable. BSA, body surface area; EASI-75, 75% improvement in Eczema Area and Severity Index; FAS, full analysis set; FAS-52, full analysis set at time of FDA cut-off; IGA, Investigator's Global Assessment; q2w, every 2 weeks; qw, weekly; R, randomization; SAF, safety analysis set; SC, subcutaneous; TCI, topical calcineurin inhibitors.

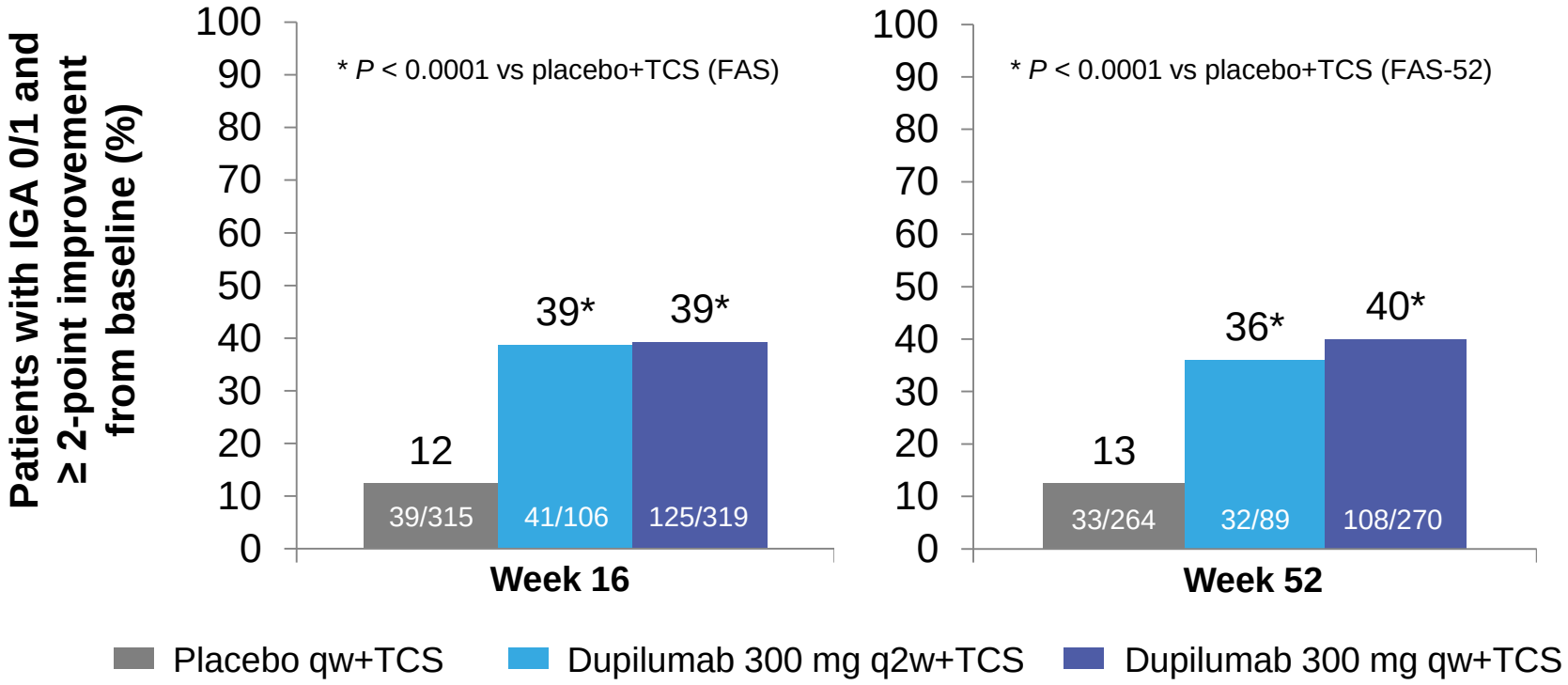
Baseline Demographics and Disease Characteristics

	Placebo qw+TCS (n = 315)	Dupilumab 300 mg q2w+TCS (n = 106)	Dupilumab 300 mg qw+TCS (n = 319)
Age in years, median (Q1, Q3)	34.0 (25.0, 45.0)	40.5 (28.0, 49.0)	34.0 (26.0, 45.0)
Male sex, **%** (n)	61 (193)	58 (62)	60 (191)
Disease duration in years, median (Q1, Q3)	26.0 (17.0, 38.0)	28.0 (20.0, 44.0)	26.0 (18.0, 39.0)
BSA %, median (Q1, Q3)	55.0 (40.0, 75.0)	58.8 (43.5, 78.5)	52.0 (36.0, 71.5)
EASI score, median (Q1, Q3)	29.6 (22.2, 40.8)	30.9 (22.3, 41.6)	29.0 (21.6, 40.7)
IGA score, **%** (n)			
4 (severe)	47 (147)	50 (53)	46 (147)
3 (moderate)	53 (168)	50 (53)	54 (172)
Peak pruritus NRS score, median (Q1, Q3)	7.6 (6.3, 8.6)	7.7 (6.6, 8.5)	7.4 (6.0, 8.6)
POEM score, median (Q1, Q3)	20.0 (16.0, 25.0)	21.0 (16.0, 25.0)	20.0 (16.0, 25.0)
DLQI score, median (Q1, Q3)	14.0 (9.0, 20.0)	13.5 (8.0, 20.0)	14.0 (8.0, 20.0)
Comorbid type 2 immune diseases, % (n/N)[a]	81 (256/315)	84 (92/110)	84 (264/315)

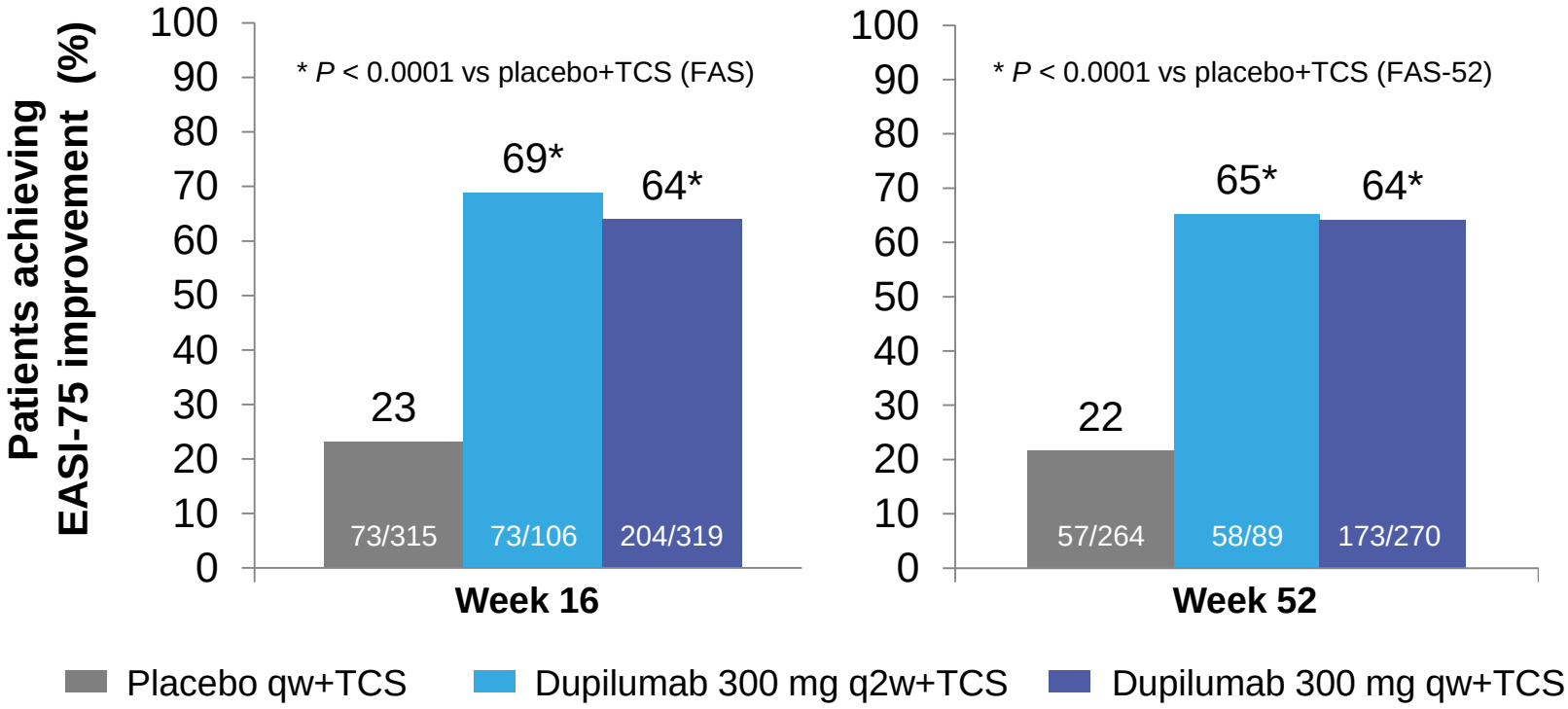
[a] Including: allergic rhinitis, asthma, food allergy, allergic conjunctivitis, hives, chronic rhinosinusitis, nasal polyps, and eosinophilic esophagitis. DLQI, Dermatology Life Quality Index; NRS, Numerical Rating Scale; POEM, Patient-Oriented Eczema Measure; Q1, first quartile; Q3, third quartile.

IGA 0/1 and ≥ 2-Point Improvement from Baseline

All Patients Required Entry IGA Score of 3 or 4

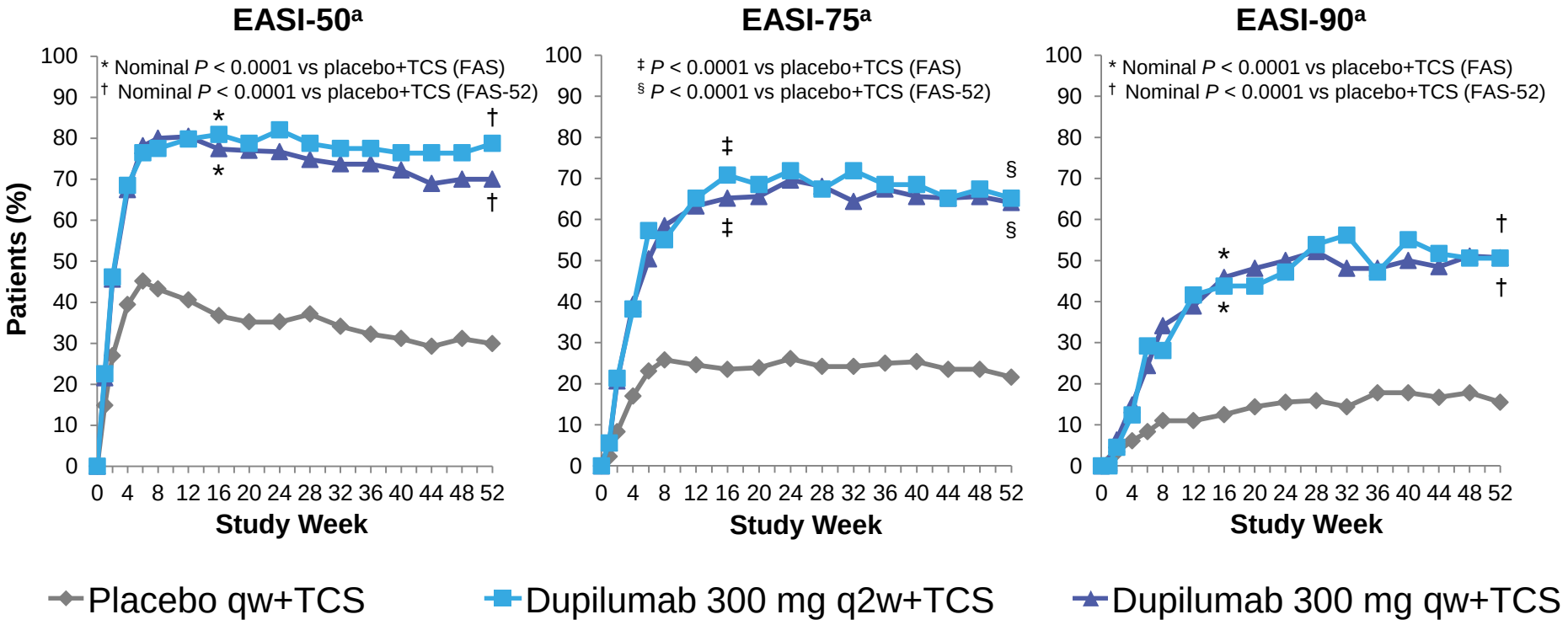


EASI-75



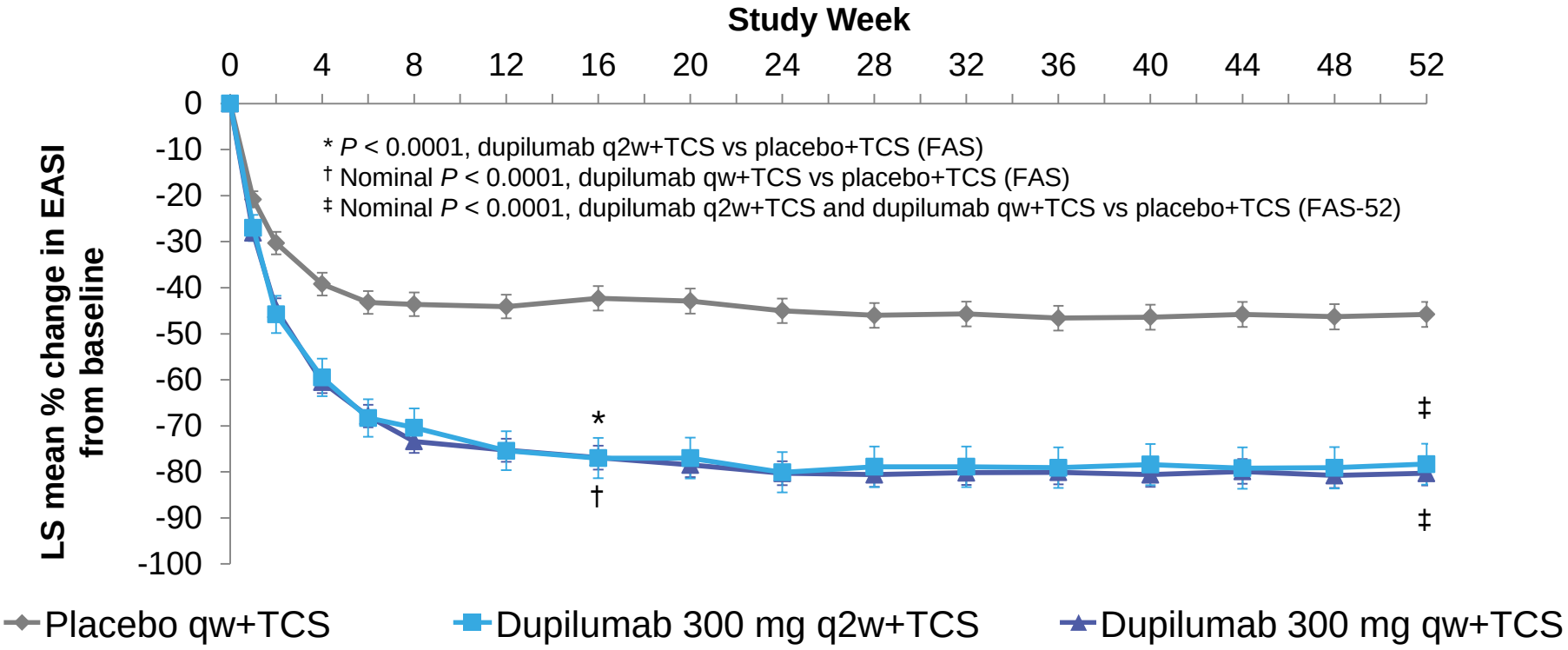
Baseline EASI median scores (Q1, Q3): placebo+TCS, dupilumab 300 mg q2w+TCS, and dupilumab 300 mg qw+TCS were 29.6 (22.2, 40.8), 30.9 (22.3, 41.6), and 29.0 (21.6, 40.7), respectively.

EASI-50/75/90



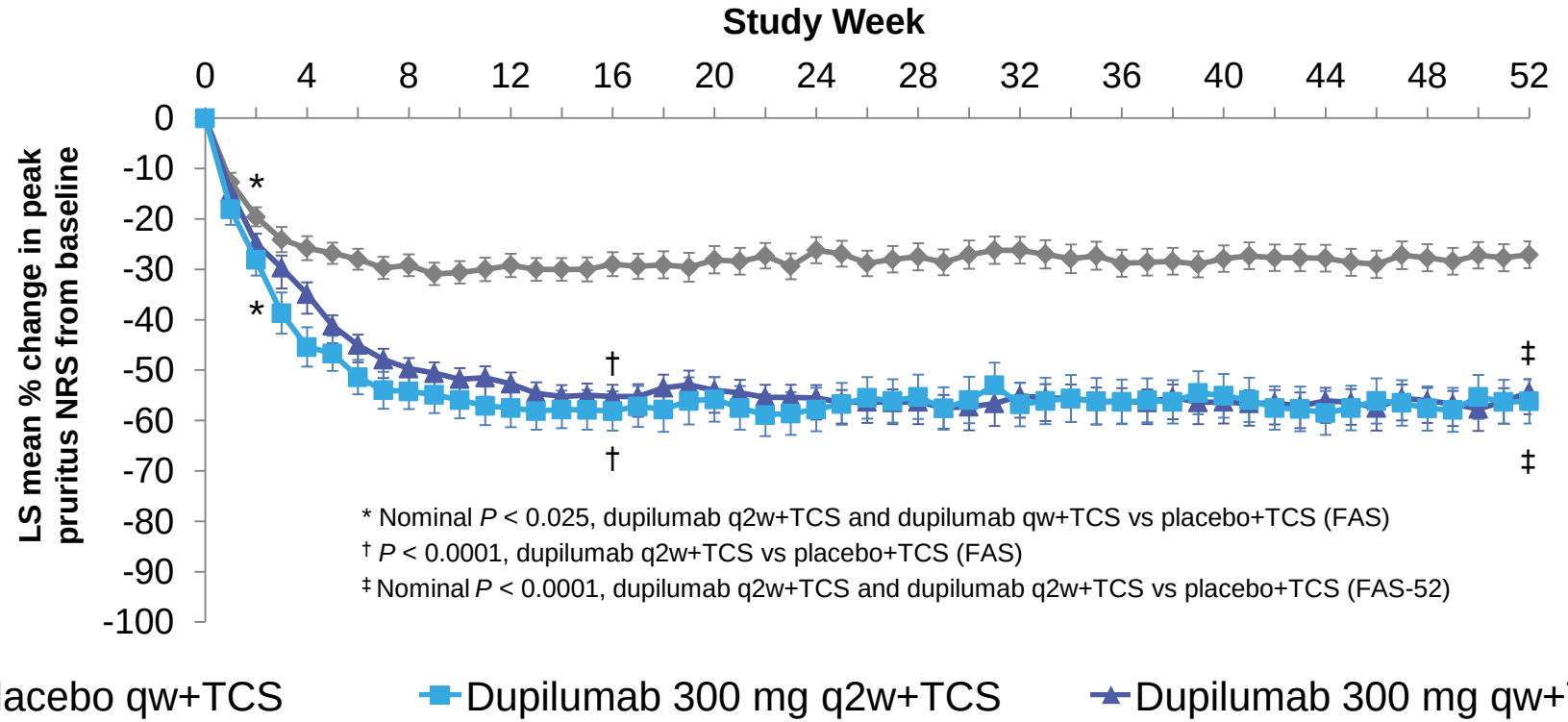
[a] Baseline EASI median scores (Q1, Q3) for placebo+TCS, dupilumab 300 mg q2w+TCS, and dupilumab 300 mg qw+TCS were 29.6 (22.2, 40.8), 30.9 (22.3, 41.6), and 29.0 (21.6, 40.7), respectively. EASI-50/75/90, proportion of patients with ≥ 50%/75%/90% improvement in EASI score from baseline.

EASI: % Change from Baseline to Week 52 (LOCF[a])



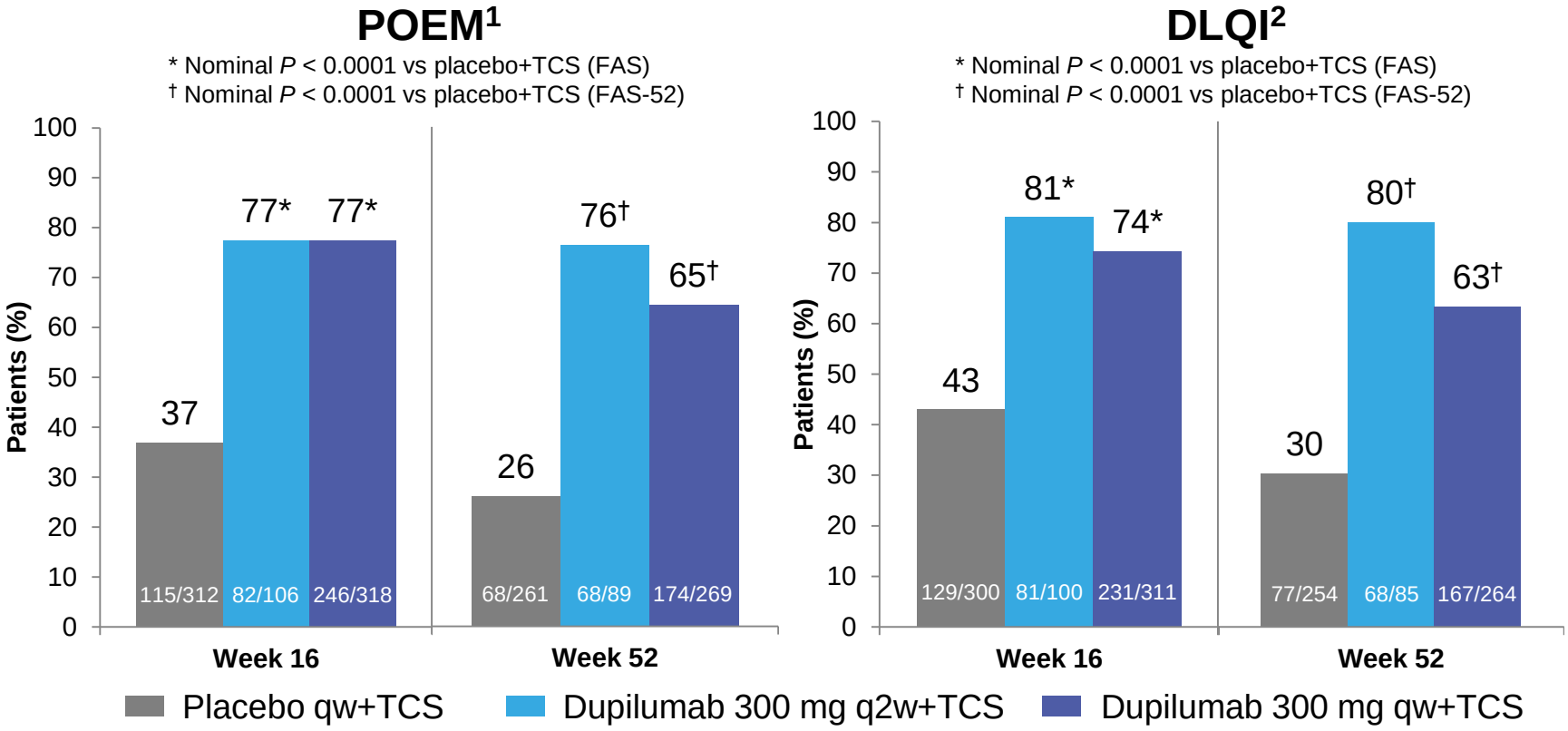
Baseline EASI median scores (Q1, Q3) for placebo+TCS, dupilumab 300 mg q2w+TCS, and dupilumab 300 mg qw+TCS were 29.6 (22.2, 40.8), 30.9 (22.3, 41.6), and 29.0 (21.6, 40.7), respectively. [a] Sensitivity analysis. LOCF, last observation carried forward. LS, least squares.

Peak Pruritus NRS: % Change from Baseline to Week 52 (LOCF[a])



Baseline median peak pruritus NRS scores (Q1, Q3) for placebo+TCS, dupilumab 300 mg q2w+TCS, and dupilumab 300 mg qw+TCS were 7.6 (6.3, 8.6), 7.7 (6.6, 8.5), and 7.4 (6.0, 8.6), respectively. [a] Sensitivity analysis.

Proportion of Patients Achieving ≥ 4-Point Improvement in POEM or DLQI Scores from Baseline (MCID)



1. Schram ME, et al. Allergy. 2012;67:99-106. 2. Basra MK, et al. Dermatology. 2015;230:27-33. MCID, minimal clinically important difference.

Overall Safety at Week 52 (SAF)

	Placebo qw+TCS (n = 315)	Dupilumab 300 mg q2w+TCS (n = 110)	Dupilumab 300 mg qw+TCS (n = 315)
Total number of adverse events, n	1,493	478	1,482
Total number of SAEs, n	22	5	10
Patients, % (n), with:			
≥ 1 AE	84 (266)	88 (97)	83 (261)
Death[a]	0 (0)	0 (0)	< 1 (1)
≥ 1 SAE	5 (16)	4 (4)	3 (9)
AEs leading to treatment discontinuation	8 (24)	2 (2)	3 (9)

[a] One patient died as a result of a motor vehicle accident; this was considered to be not related to study drug. AEs, adverse events; SAE, serious adverse event.

AEs Reported in ≥ 5% of Patients in Any Treatment Group (SAF)[a]

Patients with AEs, % (n)	Placebo qw+TCS (n = 315)	Dupilumab 300 mg q2w+TCS (n = 110)	Dupilumab 300 mg qw+TCS (n = 315)
Nasopharyngitis	19 (61)	23 (25)	19 (60)
Upper respiratory tract infection	10 (32)	10 (11)	14 (43)
Sinusitis	3 (9)	2 (2)	6 (18)
Influenza	5 (17)	4 (4)	3 (9)
Blepharitis	1 (3)	5 (6)	3 (11)
Dermatitis atopic	46 (144)	18 (20)	17 (52)
Injection-site reaction	8 (24)	15 (16)	19 (60)
Asthma	6 (19)	5 (5)	1 (2)
Headache	6 (19)	5 (5)	8 (24)
Any herpes infections[b]	8 (25)	7 (8)	7 (22)
Herpes zoster	2 (5)	1 (1)	< 1 (1)
Eczema herpeticum	2 (6)	1 (1)	0 (0)
Non-herpetic skin infections[c]	18 (56)	11 (12)	8 (26)
Conjunctivitis[b]	8 (25)	14 (15)	19 (61)

[a] The AEs included here are according to the PTs in the MedDRA hierarchy, unless otherwise specified. [b] High-level term per MedDRA hierarchy. [c] Adjudicated. MedDRA, Medical Dictionary for Regulatory Activities; PTs, Preferred Term.

Summary

- The co-primary endpoints were met:
  - IGA 0/1 and ≥ 2-point improvement from baseline: **39%** at Week 16 and **36-40%** at Week 52
  - EASI-75: **64-69%** at Week 16 and **64-65%** at Week 52
- Significant improvement in pruritus as early as Week 2 and sustained to Week 52
- Improvement in symptoms including sleep (POEM) and quality of life (DLQI) at Weeks 16 and 52
- The safety profile was generally consistent with previous phase 3 studies[1]
  - There were fewer AEs leading to discontinuation with dupilumab+TCS
  - **Conjunctivitis and injection-site reactions more frequent in dupilumab+TCS groups**
  - **AD flares and non-herpetic skin infections more frequent in placebo+TCS group**

1. Simpson EL, et al. N Engl J Med. 2016;375:2335-48.

Conclusions

- First randomized placebo-controlled study of a biologic for AD for a 1-year period
- Both dose regimens of dupilumab+TCS provided significant improvements vs placebo+TCS in multiple efficacy measures and patient-reported outcomes
- Blocking signaling of the type 2 (Th2) cytokines IL-4 and IL-13 leads to sustained control of moderate-to-severe AD during the 52-week treatment period
- Ongoing confirmatory phase 3 programs in asthma and other allergic diseases