Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

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eMethods. Supplemental Methods

Prohibited Medications and Procedures

- Live (attenuated) vaccine: If a live vaccine was necessary, study treatment was to be stopped, optimally ≥ 12 weeks before vaccine administration, and might not be resumed for 12 weeks following vaccine administration
- Immunomodulating biologics (other than dupilumab) might not be administered concomitantly with the study drug. If a biologic agent was administered during the study, study treatment was to be immediately discontinued. In these cases, study treatment discontinuation was permanent, unless otherwise approved by the medical monitor
- Investigational drug (other than dupilumab) might not be administered concomitantly with the study drug. If an investigational drug was administered during the study, study treatment was to be immediately discontinued. In these cases, study treatment discontinuation was permanent, unless otherwise approved by the medical monitor
- Topical corticosteroids (TCS) or topical calcineurin inhibitors (TCIs) except if required for atopic dermatitis (AD) rescue. If TCS, TCIs, or both were used during the study, study treatment could continue as planned
- Systemic corticosteroids or nonsteroidal systemic immunosuppressive drugs (e.g., ciclosporin, methotrexate, mycophenolate mofetil, azathioprine) might be used during the study only if required for AD rescue or if medically needed to treat concurrent conditions (e.g., asthma). If these medications were used during the study, study treatment was to be discontinued and might not be resumed sooner than 5 half-lives after the last dose of the respective corticosteroid or non-steroidal immunosuppressive product
- Any other medication or procedure intended to treat AD was prohibited, except those specifically permitted, (i.e., basic skin care, cleansing and bathing [including bleach baths]), emollients (required as background treatment), topical anesthetics, antihistamines, and topical and systemic anti-infective medications

The following concomitant procedures were prohibited during study participation:

- Major elective surgical procedures
- Phototherapy
- Tanning in a bed/booth

Patient Eligibility

Inclusion Criteria

- Completed the treatment phase in one of the two 16-week initial-treatment studies (SOLO 1 [R668-AD-1334] or SOLO 2 [R668-AD-1416])
- Achieved ≥ 1 of the following two treatment success criteria:
  - Investigator's Global Assessment (IGA) = 0 or 1 (clear or almost clear) at week 16, or
  - EASI-75; ≥ 75% reduction in Eczema Area and Severity Index (EASI) score from baseline to week 16
- Willing and able to comply with all clinic visits and study-related procedures

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- Provided signed informed consent
- Able to understand and complete study-related questionnaires

Exclusion Criteria

- Receipt of rescue medication for AD in the initial-treatment study (i.e., the parent studies SOLO 1 or SOLO 2)
- Any conditions that required permanent discontinuation of study treatment in either initial-treatment study
- Planned or anticipated major surgical procedures during the patient's participation in this study
- Pregnant or breastfeeding women or women planning to become pregnant or breastfeed during this study
- Women unwilling to use adequate birth control, if of reproductive potential[a] and sexually active. Adequate birth control was defined as agreement to consistently practice an effective and accepted method of contraception, whenever engaging in heterosexual intercourse, throughout the duration of the study and for 120 days after last dose of study drug. These included hormonal contraceptives, intrauterine device, or double barrier contraception (e.g., condom plus diaphragm), or a male partner with documented vasectomy. Additional requirements for acceptable contraception might apply in certain countries, based on local regulations. Investigators in these countries were to be notified accordingly in a protocol clarification letter

  [a]For women, menopause was defined as ≥12 consecutive months without menses; if in question, a follicle stimulating hormone level of ≥ 25 mU/mL was to be documented. Hysterectomy, bilateral oophorectomy, or bilateral tubal ligation was to be documented, as applicable; if documented, women with these conditions were not required to use additional contraception.

Primary, Key Secondary, Other Secondary, and Post Hoc Endpoints

- Primary
  - The continuous co-primary endpoint, based on percent change in EASI from SOLO baseline, assessed the difference between SOLO-CONTINUE week 36 and baseline (i.e., week 36 minus week 0)
  - The categorical co-primary endpoint was the percentage of patients with EASI-75 from SOLO at week 36 among patients with EASI-75 (from SOLO baseline) at baseline
- Key secondary endpoints
  - Percentage of patients with week 36 IGA maintained within 1 point of baseline
  - Percentage of patients with week 36 IGA 0/1 among patients with IGA 0/1 at baseline
  - Percentage of patients with ≥ 3-point increase (worsening) of peak pruritus Numerical Rating Scale (NRS) score (baseline to week 35) among patients with baseline pruritus NRS score ≤ 7
  - Due to a technical issue with the interactive voice monitoring system (IVRS) system used for pruritus data, IVRS accounts were closed prematurely for patients who transitioned into the open-label extension (OLE) study[1] at week 36, before they could report their last pruritus score, which resulted in considerable missing pruritus data at week 36. Because pruritus NRS scores were stable for all dose groups by week 35, this was determined to be a reasonable and suitable end-of-treatment timepoint for all pruritus NRS analyses
- Other secondary endpoints
  - Time to first IGA ≥ 2-point increase from baseline
  - Percentage of patients with week 36 IGA of 3/4 among patients with IGA 0/1 at baseline

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  - Percentage of patients with 50% improvement in EASI score from SOLO baseline (EASI-50) through week 36
  - Change from baseline through week 36 in EASI
  - Change from baseline through week 36 in SCORing Atopic Dermatitis (SCORAD)
  - Change from baseline through week 36 in percent body surface area (BSA) affected by AD
  - Change from baseline through week 36 in Peak Pruritus NRS (week 35)
  - Change from baseline through week 36 in Patient-Oriented Eczema Measure (POEM)
  - Change from baseline through week 36 in Dermatology Life Quality Index (DLQI)
  - Change from baseline through week 36 in Hospital Anxiety and Depression Scale (HADS)
  - Difference between baseline and time points through week 36 in percent change from SOLO baseline in SCORAD
  - Difference between baseline and time points through week 36 in percent change from SOLO baseline in pruritus NRS (week 35)
  - Annualized event rates during the treatment period of flares (defined as receipt of rescue treatment and latest EASI or pruritus NRS prior to rescue worsened vs baseline)
  - Skin infection treatment-emergent adverse events (TEAEs; excluding herpetic infections)
  - Proportion of well-controlled weeks, defined as the proportion of patients who responded "yes" to the question: "Has your eczema been well-controlled over the last week?" and for whom no rescue treatment was administered during that week
- Post-hoc analyses
  - Percentage of patients at week 36 (pruritus, week 35) with:
    - ≥ 3- and ≥ 4-point improvement (reduction) in pruritus NRS from SOLO baseline
    - 90% improvement from SOLO baseline in EASI (EASI-90)
    - No sleep disturbance in the past 7 days (POEM Item 2)
    - No pain/discomfort (Euro-QoL 5-Dimensional Scale [EQ-5D] pain item)
  - Mean change from SOLO baseline in SCORAD sleep visual analog scale (VAS)
  - Percent change in EASI from SOLO baseline to SOLO-CONTINUE week 36 in 2 subgroups
    - (1) patients with both IGA = 0/1 at SOLO-CONTINUE baseline and IGA > 1 at week 36
    - (2) patients with EASI-75 at SOLO-CONTINUE baseline and < 75% improvement in EASI (from SOLO baseline) at week 36
  - Post-hoc comparisons between dupilumab dose groups were conducted for the primary and key secondary endpoints

Hierarchy of Co-Primary and Key Secondary Endpoints

To control for multiplicity for the comparisons of dupilumab treatment groups versus placebo, a hierarchical 2-sided testing procedure with an alpha level of 0.05 was assessed in a hierarchical manner for the co-primary and key secondary endpoints. The prespecified order is as follows:

1. Difference between baseline (week 0) and week 36 in percent change in EASI from the baseline in the parent study (SOLO 1 or SOLO 2) for all randomized patients
2. Percentage of patients with EASI-75 at week 36 in randomized patients with EASI-75 at baseline
3. Percentage of patients whose IGA response at week 36 was maintained within 1 point of baseline in the subset of patients with IGA 0 or 1 at baseline

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4. Percentage of patients with IGA 0 or 1 at week 36 in the subset of patients with IGA 0 or 1 at baseline
5. Percentage of patients whose pruritus NRS increased by 3 or more points from baseline to week 36 in the subset of patients with pruritus NRS ≤ 7 at baseline

If an endpoint was significant at a 2-sided 0.05 level, the sequential analysis continued for the next endpoint until the significance level was no longer met.

The tests were conducted in the following order of treatment group comparisons:

1. High-dose group continued from the parent study (dupilumab 300 mg qw or q2w) versus placebo; tests conducted in the order of 5 endpoints shown above
2. Middle-dose group (300 mg q4w) versus placebo; tests conducted in the order of 5 endpoints shown above
3. Low-dose group (300 mg q8w) versus placebo; tests conducted in the order of 5 endpoints shown above

If all tests from the co-primary to key secondary endpoints were significant for dupilumab 300 mg qw/q2w versus placebo, the same hierarchical testing procedure was applied to the next group comparison, dupilumab 300 mg q4w versus placebo, and then dupilumab 300 mg q8w versus placebo.

Sensitivity Analyses of Co-Primary Endpoints

Continuous Co-Primary Endpoint

1. Mixed-effect model repeated measures (MMRM): The model included the following factors (fixed effects) and covariate (current study baseline):
    a. Treatment group
    b. Treatment regimen in parent studies
    c. Randomization strata (disease severity: baseline IGA = 0 vs 1 vs > 1; and region: Americas, Europe, and Asia Pacific including Japan)
    d. Visit
    e. Current study baseline value
    f. Treatment-by-visit interaction
    g. Baseline-by-visit interaction as covariates

    An unstructured covariance matrix was used to model the within-patient errors. Denominator degrees of freedom were estimated using approximation of SATTERTH. The efficacy data were set to missing after rescue medication was used. Afterwards no imputation was made. The MMRM model provided least-squares (LS) means at week 36 and at other time points for each treatment group with the corresponding standard error (SE), confidence interval (CI), and the *P*-value for treatment comparisons. The graph of LS mean ± SE by visit was provided
2. Last-observation-carried-forward (LOCF) method of sensitivity analysis: A sensitivity analysis using the analysis of covariance (ANCOVA) model, including the treatment group, treatment

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regimen in parent studies, current study baseline value, and the randomization strata. The efficacy data were set to missing after rescue medication was used. The post-baseline LOCF method was then used to impute missing values

3. Worst-observed-case-forward (WOCF) method of sensitivity analysis: A sensitivity analysis using the ANCOVA model, including the treatment group, treatment regimen in parent studies, current study baseline value, and the randomization strata. The efficacy data were set to missing after rescue medication was used. The post-baseline WOCF method was then used to impute missing values
4. ANCOVA model based on all observed data regardless of whether rescue medication was used; missing data were imputed using multiple imputation (MI)
5. ANCOVA model based on all observed data regardless of whether rescue medication was used; missing data were not imputed

Categorical Co-Primary Endpoint

1. Post-baseline LOCF: This approach was used after rescue medication use or study withdrawal to determine a patient's status at week 36 and was conducted to assess the robustness of the primary analysis with regards to handling of missing data
2. All observed data with missing value counted as a nonresponder: All observed data, regardless if rescue medication was used or if data were collected after study withdrawal, were included in the analysis. Patients with a missing value at a particular time point were counted as a nonresponder at that time point
3. All observed data with no imputation for missing value: All observed data, regardless if rescue treatment was used or if data were collected after study withdrawal, were included in the analysis. No imputation was conducted

Treatment-Emergent Antidrug Antibodies

Treatment-emergent antidrug antibodies (TE-ADAs) were assessed with a validated electrochemiluminescence bridging immunoassay in serum collected at SOLO baseline and SOLO-CONTINUE week 36. Patients were considered to have a TE-ADA response if their antidrug antibody (ADA) assay was positive after the first SOLO-CONTINUE study treatment and their SOLO baseline results were negative or missing. TE-ADA incidence is defined as the proportion of patients with either treatment-emergent or treatment-boosted response within the ADA analysis population.

Analysis Sets

- Full analysis set (FAS): All randomized patients; based on the treatment allocated by the IVRS at randomization (as randomized)
- Per protocol set (PPS): All patients in the FAS except those who were excluded because of major efficacy-related protocol violations (defined as one that might have affected the interpretation of study results). Examples of such violations could include:
  - A patient who did not receive treatment as randomized
  - Any major violations of efficacy-related entry criteria (e.g., inclusion criterion 2)
  - The percentage of a patient's compliance with study drug injection was < 90% or > 120% of the scheduled doses during the study treatment period
- Safety analysis set (SAF): All randomized patients who received any amount of study drug, based on the treatment received (as treated)

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- Pharmacokinetic analysis set (PKAS): All treated patients who received any study drug and who had ≥ 1 nonmissing postbaseline measurement of functional dupilumab available for statistical analysis
- ADA analysis set (AAS): All treated patients who received any amount of study drug and also had ≥ 1 post-first dose nonmissing ADA result in the ADA assay

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eTable 1. Atopic/Allergic Comorbidities at SOLO Baseline (Safety Analysis Set)

Patients With ≥ 1 Adverse Event, n (%):	**Placebo (n = 82)**	**Dupilumab 300 mg q8w (n = 84)**	**Dupilumab 300 mg q4w (n = 87)**	**Dupilumab 300 mg qw/q2w (n = 167)**
Allergies other than food allergy	52 (63.4)	49 (58.3)	56 (64.4)	108 (64.7)
Allergic rhinitis	42 (51.2)	35 (41.7)	37 (42.5)	81 (48.5)
Asthma	31 (37.8)	38 (45.2)	34 (39.1)	72 (43.1)
Food allergy	37 (45.1)	26 (31.0)	29 (33.3)	59 (35.3)
Allergic conjunctivitis	23 (28.0)	13 (15.5)	20 (23.0)	41 (24.6)
Hives	7 (8.5)	10 (11.9)	10 (11.5)	33 (19.8)
Chronic rhinosinusitis	8 (9.8)	2 (2.4)	5 (5.7)	10 (6.0)
Atopic keratoconjunctivitis	4 (4.9)	3 (3.6)	5 (5.7)	6 (3.6)
Nasal polyps	1 (1.2)	0	1 (1.1)	2 (1.2)
Eosinophilic esophagitis	1 (1.2)	0	2 (2.3)	0

Abbreviations: q2w, every 2 weeks; q4w, every 4 weeks; q8w, every 8 weeks; qw, weekly.

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eTable 2. *P* values (Nominal) From Post Hoc Analysis of Comparisons Between Dupilumab High- and Low-Dose Regimens for Co-Primary and Key Secondary Endpoints

	Percent change in EASI from SOLO baseline during SOLO-CONTINE: Difference between SOLO-CONTINUE baseline and Week 36—FAS[a]	**Proportion of patients with EASI-75 at week 36—FAS with EASI-75 at baseline[b]**	**Proportion of patients with IGA 0/1 at week 36—FAS with IGA 0/1 at baseline[b]**	**Proportion of patients with IGA maintaining within 1 point from baseline at week 36—FAS with IGA 0/1 at baseline[b]**	**Proportion of patients with Peak Pruritus NRS increase ≥3 at week 36—FAS with pruritus NRS ≤7 at baseline[c]**
qw/q2w vs q4w	.198	.045	.225	.257	.020
qw/q2w vs q8w	.025	.010	.009	.007	.002

Abbreviations: EASI, Eczema Area and Severity Index; EASI-75, 75% improvement in EASI from SOLO baseline; FAS, full analysis set; IGA, Investigator's Global Assessment; NRS, numerical rating scale; q2w, every 2 weeks; q4w, every 4 weeks; q8w, every 8 weeks; qw, weekly.
The number in each cell represents the nominal *P* value. *P* values for proportion endpoints were based on a Cochran–Mantel–Haenszel test without taking any stratification factors into account.

[a] Multiple imputation censored after rescue treatment use.

[b] Patients were considered nonresponders after rescue treatment use.

[c] Considered an event after rescue treatment use.

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eTable 3. Sensitivity Analyses of Co-Primary Endpoints

Endpoint Method of Analysis	**Placebo (n = 83)**	**Dupilumab 300 mg q8w (n = 84)**	**Dupilumab 300 mg q4w (n = 86)**	**Dupilumab 300 mg qw/q2w (n = 169)**
Percent change in EASI from SOLO baseline during SOLO-CONTINE: Difference between SOLO-CONTINUE baseline and Week 36				
Sensitivity analyses				
MMRM, data after rescue set to missing, no imputation for missing data, LS mean % change (SE)	−20.23 ± 2.649	−5.35 ± 2.374*	−3.60 ± 2.301*	0.54 ± 1.554*
ANCOVA, data after rescue set to missing, LOCF for missing data, LS mean % change ± SE	−24.21 ± 2.503	−8.64 ± 2.468*	−5.66 ± 2.424*	−0.32 ± 1.865*
ANCOVA, data after rescue set to missing, WOCF for missing data, LS mean % change ± SE	−25.18 ± 2.589	−10.78 ± 2.552*	−6.98 ± 2.507*	−1.10 ± 1.928*
ANCOVA, no imputation for rescue, MI for missing data, LS mean % change ± SE	−23.74 ± 2.508	−5.06 ± 2.461*	−5.28 ± 2.393*	−0.74 ± 1.846*
ANCOVA, no imputation for rescue, no imputation for missing data (all observed), LS mean % change ± SE	−23.03 ± 2.458	−4.43 ± 2.462*	−4.99 ± 2.404*	0.99 ± 1.854*
Proportion of patients who achieved EASI-75 from SOLO baseline at week 36 (among patients with EASI-75 at baseline)				
Sensitivity analyses				
LOCF with censoring after rescue treatment use, n/N1 (%)	40/79 (50.6)	64/82 (78.0)*	62/84 (73.8)†	142/162 (87.7)*
All observed values regardless of rescue treatment use, missing considered as non-responder, n/N1 (%)	41/79 (51.9)	67/82 (81.7)*	67/84 (79.8)*	145/162 (89.5)*
All observed values regardless of rescue treatment use, n/N2 (%)	41/74 (55.4)	67/75 (89.3)*	67/78 (85.9)*	145/153 (94.8)*

Abbreviations: ANCOVA, analysis of covariance; EASI, Eczema Area and Severity Index; EASI-75, proportion of patients with ≥ 75% improvement in EASI from SOLO baseline; LOCF, last observation carried forward; LS, least squares; MMRM, mixed-effect model with repeated measures; N1, number of patients with EASI-75 at baseline; N2, number of patients with EASI score at week 36; q2w, every 2 weeks; q4w, every 4 weeks; q8w, every 8 weeks; qw, weekly; SE, standard error; WOCF, worst observation carried forward.

All *P*-values are vs placebo.

* Nominal $P < .001$.

† Nominal $P = .002$.

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eTable 4. Rescue Medication Use (Full Analysis Set)

Patients, n (%):	**Placebo (n = 83)**	**Dupilumab 300 mg q8w (n = 84)**	**Dupilumab 300 mg q4w (n = 86)**	**Dupilumab 300 mg qw/q2w (n = 169)**
Patients using ≥1 rescue medication during the 36-week treatment period	40 (48.2)	28 (33.3)	26 (30.2)	33 (19.5)
Corticosteroids, dermatologic preparations	37 (44.6)	26 (31.0)	23 (26.7)	30 (17.8)
Corticosteroids, potent (group III)	22 (26.5)	15 (17.9)	14 (16.3)	15 (8.9)
Corticosteroids, moderately potent (group II)	20 (24.1)	10 (11.9)	11 (12.8)	17 (10.1)
Corticosteroids, very potent (group IV)	3 (3.6)	3 (3.6)	1 (1.2)	2 (1.2)
Corticosteroids, weak (group I)	2 (2.4)	3 (3.6)	1 (1.2)	3 (1.8)
Corticosteroids, potent, combinations with antibiotics	1 (1.2)	2 (2.4)	1 (1.2)	2 (1.2)
Other dermatologic preparations	4 (4.8)	4 (4.8)	8 (9.3)	5 (3.0)
Agents for dermatitis, excluding corticosteroids	4 (4.8)	4 (4.8)	8 (9.3)	5 (3.0)
Corticosteroids for systemic use	6 (7.2)	2 (2.4)	4 (4.7)	3 (1.8)
Glucocorticoids	6 (7.2)	2 (2.4)	4 (4.7)	3 (1.8)
Immunosuppressants	1 (1.2)	0	0	0
Calcineurin inhibitors	1 (1.2)	0	0	0

Abbreviations: q2w, every 2 weeks; q4w, every 4 weeks; q8w, every 8 weeks; qw, weekly.

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eTable 5. Patients With ≥ 1 Adverse Event per 100 Patient-years During the 36-Week Treatment Period (Safety Analysis Set)

Patients, n per 100 patient-years	Placebo (n = 82)	Dupilumab 300 mg q8w (n = 84)	Dupilumab 300 mg q4w (n = 87)	Dupilumab 300 mg qw/q2w (n = 167)
Overall				
≥ 1 TEAE	304.79	226.46	230.69	219.52
TEAE leading to permanent study treatment discontinuation	5.32[a]	0.00	3.39[b]	0.00
TEAE leading to temporary study treatment discontinuation	17.58	11.90	11.69	5.16
Death[c]	0	0	1.72	0
Treatment-emergent SAE[d]	1.84	5.35	6.95	5.51
MedDRA PTs occurring in ≥ 2% of patients in any treatment group				
Dermatitis atopic	105.69	57.25	66.86	35.31
Nasopharyngitis	21.98	20.97	20.05	32.34
Upper respiratory tract infection	11.38	13.10	8.91	12.31
Headache	3.71	5.35	8.88	7.36
Herpes simplex	0.00	7.33	1.74	6.40
Asthma	5.55	7.18	3.46	3.61
Back pain	1.84	5.36	1.73	5.45
Oral herpes	5.65	9.18	3.49	2.71
Influenza	1.85	0.00	8.85	3.62
Bronchitis	1.84	0.00	8.85	2.72
Urticaria	1.84	3.55	1.73	4.55
Arthralgia	1.84	0.00	3.50	4.52
Pharyngitis	0.00	3.57	3.49	2.70
Diarrhea	5.61	1.76	1.73	3.63
Pruritus	3.69	1.78	3.52	2.70
Sinusitis	3.74	0.00	0.00	5.49
Blood creatine phosphokinase increased	3.70	1.77	5.20	0.89
Cough	1.84	0.00	1.73	3.62
Insomnia	1.84	1.77	0.00	3.60

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Nasal congestion	0.00	0.00	1.73	3.63
Dermatitis contact	3.70	3.57	1.73	0.90
Gastroenteritis	3.68	1.76	0.00	2.70
Ligament sprain	0.00	3.56	0.00	1.79
Toothache	0.00	0.00	0.00	3.61
Abdominal pain	1.84	3.57	1.74	0.00
Basal cell carcinoma	0.00	3.56	1.72	0.00
Contusion	1.85	3.55	0.00	0.90
Folliculitis	1.84	5.40	0.00	0.00
Hordeolum	1.84	0.00	5.30	0.00
Hypertension	3.72	1.78	0.00	1.80
Proteinuria	1.85	0.00	3.48	0.90
Rhinitis	3.68	1.76	1.73	0.89
Seasonal allergy	0.00	3.58	1.72	0.00
Tonsillitis	0.00	0.00	3.45	0.90
Urinary tract infection	3.72	1.76	0.00	1.80
Viral infection	5.60	1.77	0.00	1.80
Colitis	0.00	0.00	3.50	0.00
Eye allergy	0.00	0.00	3.48	0.00
Herpes ophthalmic	3.71	1.77	0.00	0.90
Musculoskeletal pain	3.69	1.78	0.00	0.90
Vulvovaginal candidiasis	3.70	0.00	0.00	1.79
Fall	3.69	0.00	0.00	0.90
Eye disorder with the PT conjunctivitis[e]	**7.45**	**5.39**	**7.01**	**8.34**
Nonherpetic skin infection[f]	**15.44**	**9.12**	**1.72**	**3.61**
Injection-site reaction[g]	**14.03**	**13.09**	**11.37**	**17.67**

Abbreviations: HLT, high-level term; MedDRA, Medical Dictionary for Regulatory Activities; PT, Preferred Term; q2w, every 2 weeks; q4w, every 4 weeks; q8w, every 8 weeks; qw, weekly; SAE, serious adverse event; SOC, system organ class; TEAE, treatment-emergent adverse event.

[a] Two patients discontinued due to AD and 1 patient discontinued due to dacryostenosis acquired.

[b] One patient discontinued due to glioblastoma, disorientation, and brain edema, and 1 patient discontinued due to atopic dermatitis.

[c] One death occurred during the 36-week treatment period (on study day 187) in a 21-year-old man in the dupilumab q4w group due to a gunshot wound (homicide). The event was considered by the investigator to be unrelated to the study drug.

[d] The only SAE (PT and SOC) with incidence ≥ 2% in a treatment group was basal cell carcinoma in the SOC of Neoplasms Benign, Malignant and Unspecified (including cysts and polyps), which occurred in 2 patients in the dupilumab q8w group but none in other treatment groups.

[e] Includes any PTs that included the term “conjunctivitis”: conjunctivitis, conjunctivitis bacterial, conjunctivitis viral, conjunctivitis allergic, and atopic keratoconjunctivitis (for all conjunctivitis PTs, see Supplemental Table S10).

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[f] Adjudicated; includes the following PTs: tinea versicolor, folliculitis, impetigo, skin bacterial infection, skin infection, abscess limb, localized infection, staphylococcal skin infection, subcutaneous abscess, tinea cruris (Supplemental Table S8).
[g] MedDRA HLT, see Supplemental Table S7 for all PTs).

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eTable 6. Treatment-Emergent Serious Adverse Events During the 36-Week Treatment Period (Safety Analysis Set)

	Placebo (n = 82)	**Dupilumab 300 mg q8w (n = 84)**	**Dupilumab 300 mg q4w (n = 87)**	**Dupilumab 300 mg qw/q2w (n = 167)**
Patients with ≥ 1 event, n (%)[a]				
Treatment-emergent serious adverse event	1 (1.2)	3 (3.6)	4 (4.6)	6 (3.6)
Road traffic accident	0	0	0	2 (1.2)
Gunshot wound	0	0	1 (1.1)	0
Muscle injury	0	1 (1.2)	0	0
Open fracture	0	0	0	1 (0.6)
Basal cell carcinoma	0	2 (2.4)	0	0
Glioblastoma	0	0	1 (1.1)	0
Squamous cell carcinoma of skin	0	0	0	1 (0.6)
Deep venous thrombosis	0	0	1 (1.1)	0
Hypertension	0	0	0	1 (0.6)
Atrial fibrillation	0	0	1 (1.1)	0
Tachycardia induced cardiomyopathy	0	0	1 (1.1)	0
Anaphylactic reaction	0	0	0	1 (0.6)
Biochemical pregnancy	0	0	0	1 (0.6)
Pulmonary embolism	0	0	1 (1.1)	0
Abortion induced	0	0	1 (1.1)	0
Dermatitis atopic	1 (1.2)	0	0	0

Abbreviations: q2w, every 2 weeks; q4w, every 4 weeks; q8w, every 8 weeks; qw, weekly.

[a] At each level of summarization, a patient is counted once if the patient reported ≥ 1 event.

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eTable 7. Injection-Site Reactions During the 36-Week Treatment Period (Safety Analysis Set)

	Placebo (n = 82)	**Dupilumab 300 mg q8w (n = 84)**	**Dupilumab 300 mg q4w (n = 87)**	**Dupilumab 300 mg qw/q2w (n = 167)**
Patients with ≥ 1 injection-site event by MedDRA PT, n (%)	**7 (8.5)**	**6 (7.1)**	**6 (6.9)**	**18 (10.8)**
Injection site reaction	2 (2.4)	3 (3.6)	2 (2.3)	10 (6.0)
Injection site erythema	1 (1.2)	1 (1.2)	3 (3.4)	4 (2.4)
Injection site swelling	0	0	0	4 (2.4)
Injection site hemorrhage	1 (1.2)	0	1 (1.1)	2 (1.2)
Injection site pruritus	0	2 (2.4)	0	1 (0.6)
Injection site bruising	1 (1.2)	0	0	1 (0.6)
Injection site discomfort	0	0	0	1 (0.6)
Injection site exfoliation	0	0	0	1 (0.6)
Injection site inflammation	0	0	0	1 (0.6)
Injection site nodule	0	0	0	1 (0.6)
Injection site edema	0	0	0	1 (0.6)
Injection site ulcer	0	0	0	1 (0.6)
Injection site hematoma	2 (2.4)	0	0	0
Injection site pain	2 (2.4)	0	0	0
Number of patients with ≥ 1 event by MedDRA PT per 100 patient-years	**14.03**	**13.09**	**11.37**	**17.67**
Injection site reaction	3.73	5.45	3.51	9.41
Injection site erythema	1.85	1.77	5.33	3.63
Injection site swelling	0	0	0	3.64
Injection site hemorrhage	1.84	0	1.73	1.79
Injection site pruritus	0	3.56	0	0.89
Injection site bruising	1.85	1.76	0	0.90
Injection site discomfort	0	0	0	0.90
Injection site exfoliation	0	0	0	0.89
Injection site inflammation	0	0	0	0.89
Injection site nodule	0	0	0	0.89
Injection site edema	0	0	0	0.89
Injection site ulcer	0	0	0	0.89

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Injection site hematoma	3.71	0	0	0
Injection site pain	3.73	0	0	0

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; q2w, every 2 weeks; q4w, every 4 weeks; q8w, every 8 weeks; qw, weekly.

At each level of summarization, a patient is counted once if the patient reported ≥ 1 event.

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eTable 8. Skin Infections (Excluding Herpetic Skin Infections) During the 36-Week Treatment Period (Safety Analysis Set)

	Placebo (n = 82)	**Dupilumab 300 mg q8w (n = 84)**	**Dupilumab 300 mg q4w (n = 87)**	**Dupilumab 300 mg qw/q2w (n = 167)**
Patients with ≥ 1 event by MedDRA PT, n (%)	**8 (9.8)**	**5 (6.0)**	**1 (1.1)**	**4 (2.4)**
Tinea versicolor	0	0	1 (1.1)	3 (1.8)
Folliculitis	1 (1.2)	3 (3.6)	0	0
Impetigo	1 (1.2)	1 (1.2)	0	1 (0.6)
Skin bacterial infection	0	1 (1.2)	0	0
Skin infection	1 (1.2)	1 (1.2)	0	0
Abscess limb	1 (1.2)	0	0	0
Localized infection	1 (1.2)	0	0	0
Staphylococcal skin infection	3 (3.7)	0	0	0
Subcutaneous abscess	1 (1.2)	0	0	0
Tinea cruris	1 (1.2)	0	0	0
Number of patients with ≥ 1 event by MedDRA HLT per 100 patient-years				
Bacterial infection NEC	1.84	7.24	0	0
Infection NEC	3.72	0	0	0
Skin structures and soft-tissue infection	5.57	1.77	0	0.89
Staphylococcal infection	5.61	0	0	0
Tinea infection	1.84	0	1.72	2.71
Number of patients with ≥ 1 event per 100 patient-years by MedDRA PT				
Tinea versicolor	0	0	1.72	2.71
Folliculitis	1.84	5.40	0	0
Impetigo	1.84	1.77	0	0.89
Skin bacterial infection	0	1.77	0	0
Skin infection	1.84	1.77	0	0.89
Abscess limb	1.84	0	0	0
Localized infection	1.85	0	0	0.89
Staphylococcal skin infection	5.61	0	0	0
Subcutaneous abscess	1.83	0	0	0
Tinea cruris	1.84	0	0	0

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Abbreviations: HLT, High-Level Term; MedDRA, Medical Dictionary for Regulatory Activities; PT, Preferred Term; q2w, every 2 weeks; q4w, every 4 weeks; q8w, every 8 weeks; qw, weekly.
At each level of summarization, a patient is counted once if the patient reported ≥ 1 event.

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eTable 9. Herpes Viral Infections During the 36-Week Treatment Period (Safety Analysis Set)

	Placebo (n = 82)	**Dupilumab 300 mg q8w (n = 84)**	**Dupilumab 300 mg q4w (n = 87)**	**Dupilumab 300 mg qw/q2w (n = 167)**
Patients with ≥ 1 event, n (%)	**6 (7.3)**	**8 (9.5)**	**4 (4.6)**	**9 (5.4)**
Herpes simplex virus	0	4 (4.8)	1 (1.1)	7 (4.2)
Oral herpes	3 (3.7)	5 (6.0)	2 (2.3)	3 (1.8)
Herpes ophthalmic	2 (2.4)	1 (1.2)	0	1 (0.6)
Genital herpes	0	1 (1.2)	0	0
Herpes virus infection	0	0	0	1 (0.6)
Herpes zoster virus	1 (1.2)	0	1 (1.1)	0
Ophthalmic herpes simplex virus	0	0	1 (1.1)	0
Nasal herpes	1 (1.2)	0	0	0
Number of patients with ≥ 1 event per 100 patient-years	**15.87**	**19.11**	**9.26**	**11.35**
Herpes simplex virus	0	7.33	1.74	6.40
Oral herpes	5.65	9.18	3.49	2.71
Herpes ophthalmic	3.71	1.77	0	0.90
Genital herpes	0	1.78	0	0
Herpes virus infection	0	0	0	0.89
Herpes zoster virus	1.83	0	1.73	0
Ophthalmic herpes simplex virus	0	0	1.74	0
Nasal herpes	1.84	0	0	0

Abbreviations: q2w, every 2 weeks; q4w, every 4 weeks; q8w, every 8 weeks; qw, weekly.
At each level of summarization, a patient is counted once if the patient reported ≥ 1 event.

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eTable 10. Conjunctivitis[a] During the 36-Week Treatment Period (Safety Analysis Set)

	Placebo (n = 82)	**Dupilumab 300 mg q8w (n = 84)**	**Dupilumab 300 mg q4w (n = 87)**	**Dupilumab 300 mg qw/q2w (n = 167)**
Patients with ≥ 1 event, n (%)[a]	**4 (4.9)**	**3 (3.6)**	**4 (4.6)**	**9 (5.4)**
Conjunctivitis	2 (2.4)	2 (2.4)	2 (2.3)	6 (3.6)
Conjunctivitis allergic	1 (1.2)	1 (1.2)	2 (2.3)	2 (1.2)
Conjunctivitis bacterial	1 (1.2)	0	0	1 (0.6)
Number of patients with ≥ 1 event per 100 patient-years [a]	**7.45**	**5.39**	**7.01**	**8.34**
Conjunctivitis	3.71	3.59	3.45	5.47
Conjunctivitis allergic	1.83	1.76	3.49	1.81
Conjunctivitis bacterial	1.84	0	0	0.90

Abbreviations: q2w, every 2 weeks; q4w, every 4 weeks; q8w, every 8 weeks; qw, weekly.

[a] Events with the following Medical Dictionary for Regulatory Activities Preferred Terms were included: conjunctivitis, conjunctivitis allergic, adenovirus conjunctivitis, conjunctivitis bacterial, and conjunctivitis viral. At each level of summarization, a patient is counted once if the patient reported ≥ 1 event.

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eFigure 1. Study Design

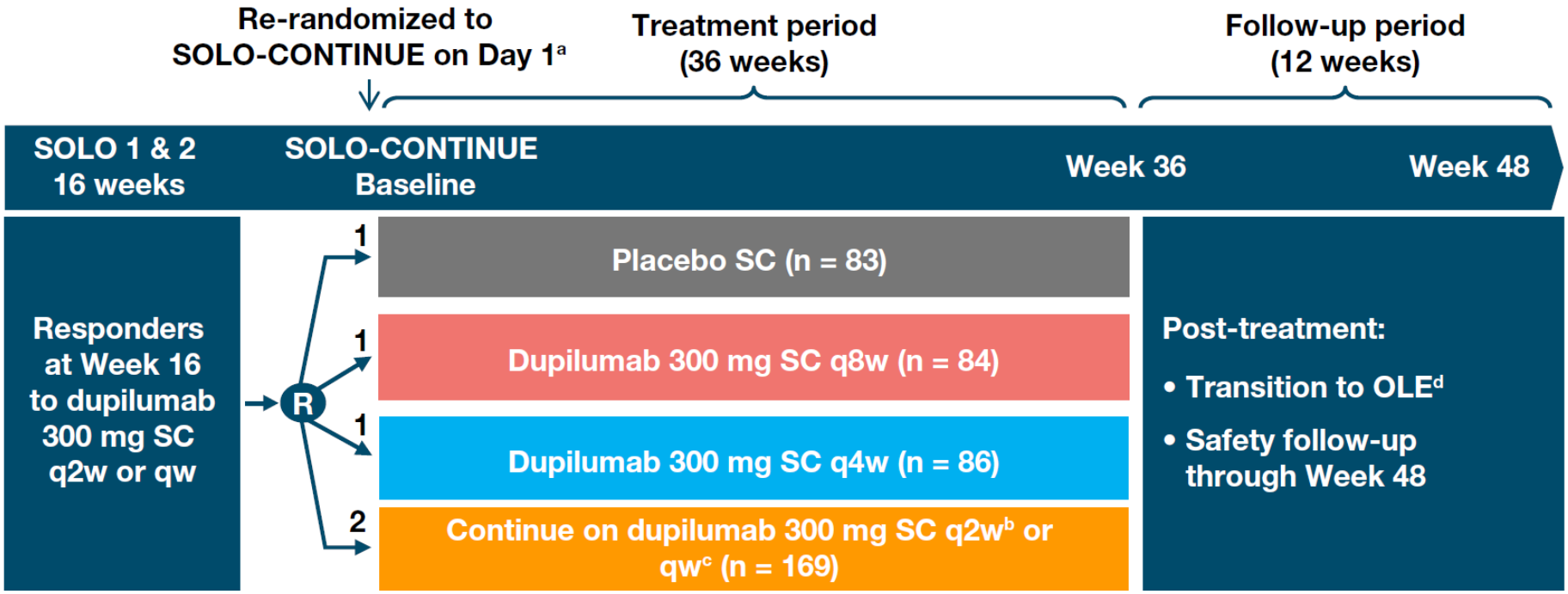
Abbreviations: EASI, Eczema Area and Severity Index; EASI-75, proportion of patients with ≥ 75% improvement in EASI from baseline; IGA, Investigator's Global Assessment; OLE, open-label extension; q2w, every 2 weeks; q4w, every 4 weeks; qw, weekly; R, randomization; SC, subcutaneous.

[a] Day 1 of SOLO-CONTINUE is in week 16 of SOLO 1 & 2.

[b] Patients originally randomized to dupilumab 300 mg q2w in SOLO 1 or SOLO 2.

[c] Patients originally randomized to dupilumab 300 mg qw in SOLO 1 or SOLO 2.

[d] Open-label extension study.[1]



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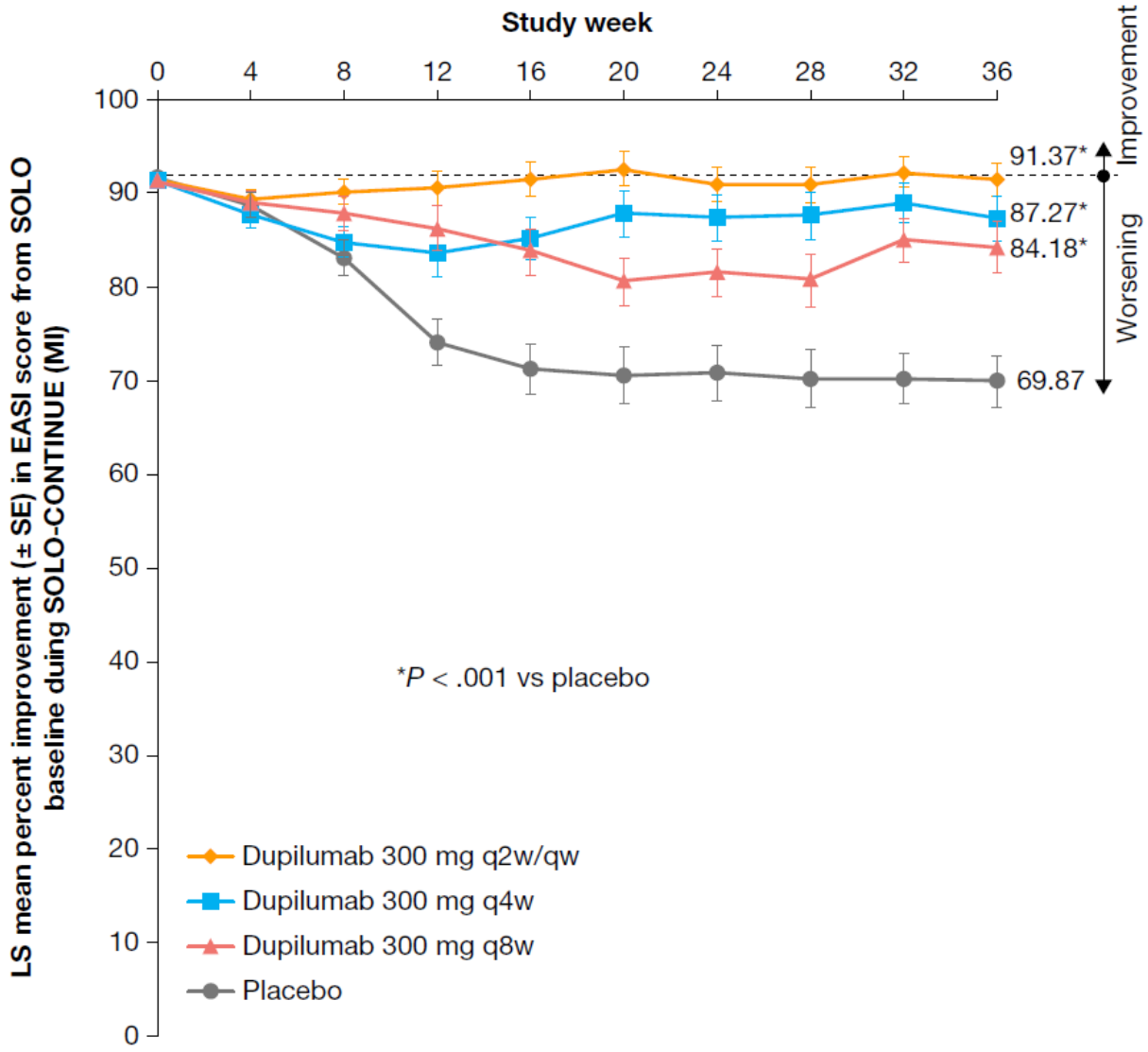
eFigure 2. Percent Change in Improvement in EASI From SOLO Baseline During the SOLO-CONTINUE Study

A. Percent change (improvement) in EASI from SOLO baseline during the SOLO-CONTINUE study (MI).
B. Percent change (improvement) in EASI from SOLO baseline during the SOLO-CONTINUE study in the subgroups of patients originally treated with dupilumab 300 mg qw and the subgroups of patients originally treated with dupilumab 300 mg q2w in SOLO (MI) (post hoc).
Abbreviations: EASI, Eczema Area and Severity Index; LS, least squares; MI, multiple imputation; q2w, every 2 weeks; q4w, every 4 weeks; q8w, every 8 weeks; qw, weekly; SE, standard error.

Error bars are ± SE.

A



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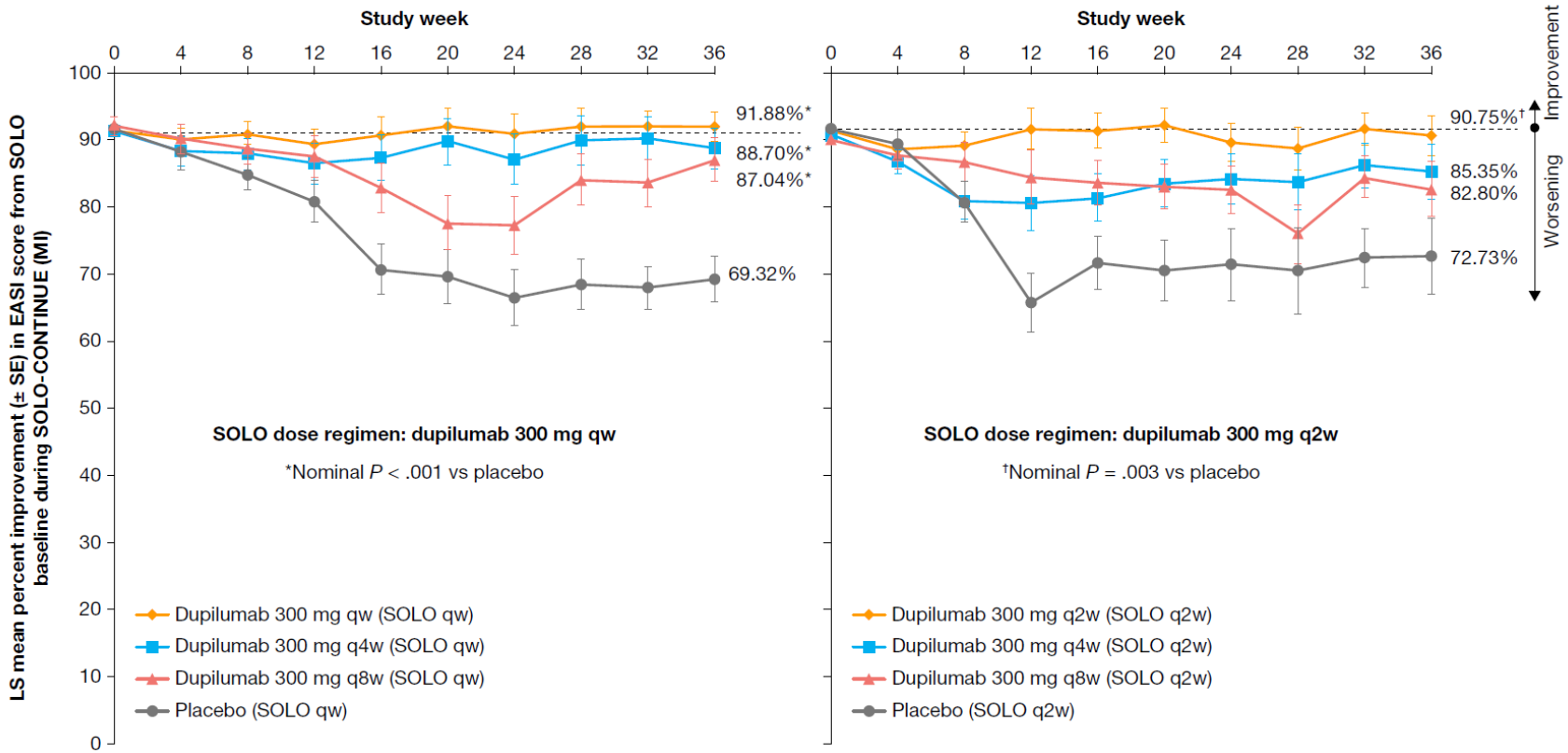

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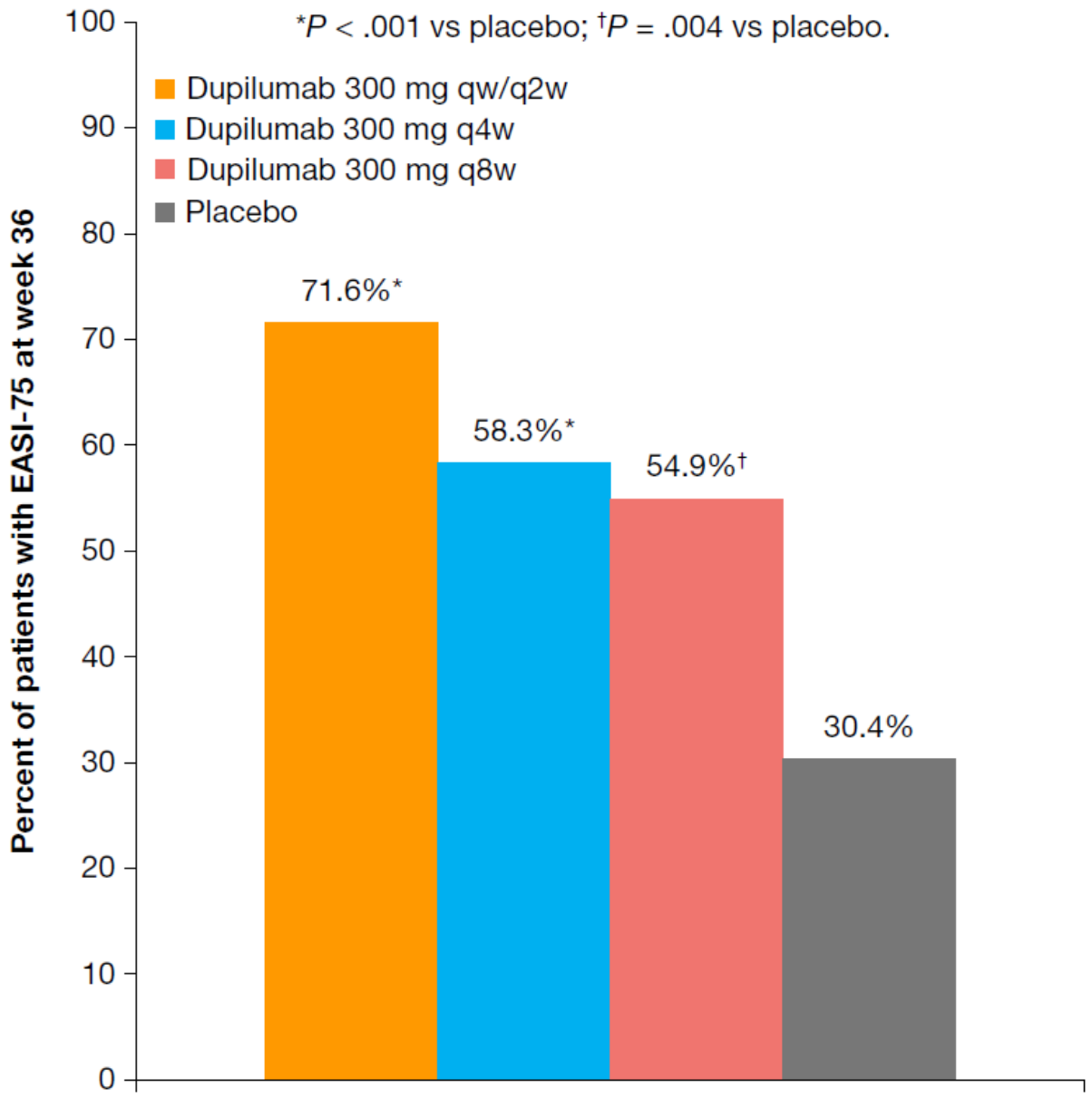
eFigure 3. Percentage of Patients With EASI-75 at Week 36, Among Patients With EASI-75 at SOLO-CONTINUE Baseline (Co-Primary Endpoint)
Abbreviations: EASI, Eczema Area and Severity Index; EASI-75, proportion of patients with ≥ 75% improvement in EASI from SOLO baseline; q2w, every 2 weeks; q4w, every 4 weeks; q8w, every 8 weeks; qw, weekly.

Higher percentages indicate maintenance of improvement, or further improvement from the SOLO-CONTINUE baseline.



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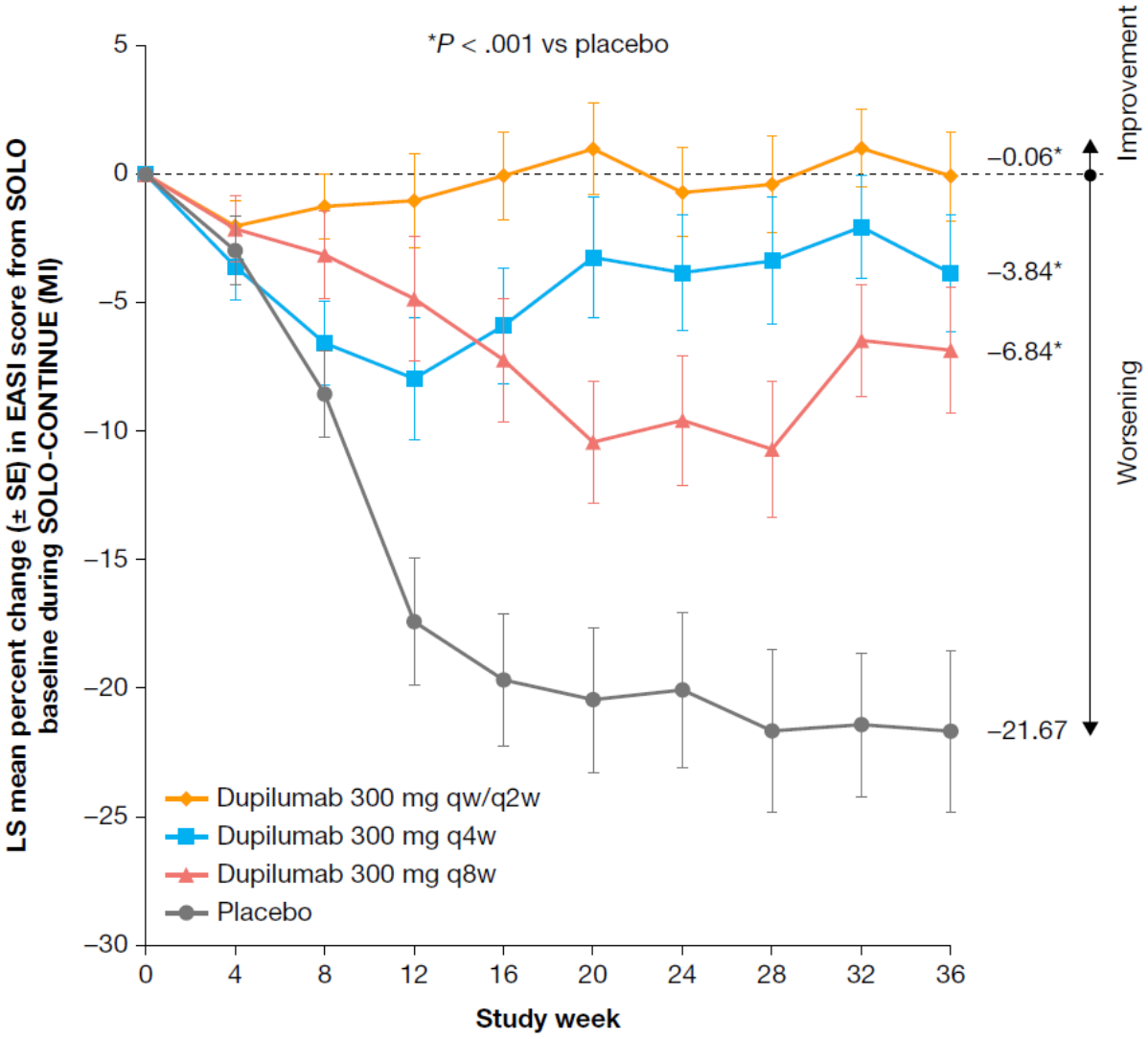
eFigure 4. Percent Change (Improvement) in EASI From Parent Study Baseline During the SOLO-CONTINUE Study: difference between SOLO-CONTINUE baseline and week 36 — primary and sensitivity analyses

A. MI analysis. B. LOCF analysis. C. All observed values.

Abbreviations: EASI, Eczema Area and Severity Index; LOCF, last observation carried forward; LS, least squares; MI, multiple imputation; q2w, every 2 weeks; q4w, every 4 weeks; q8w, every 8 weeks; qw, weekly; SE, standard error.

Error bars are ± SE.

A



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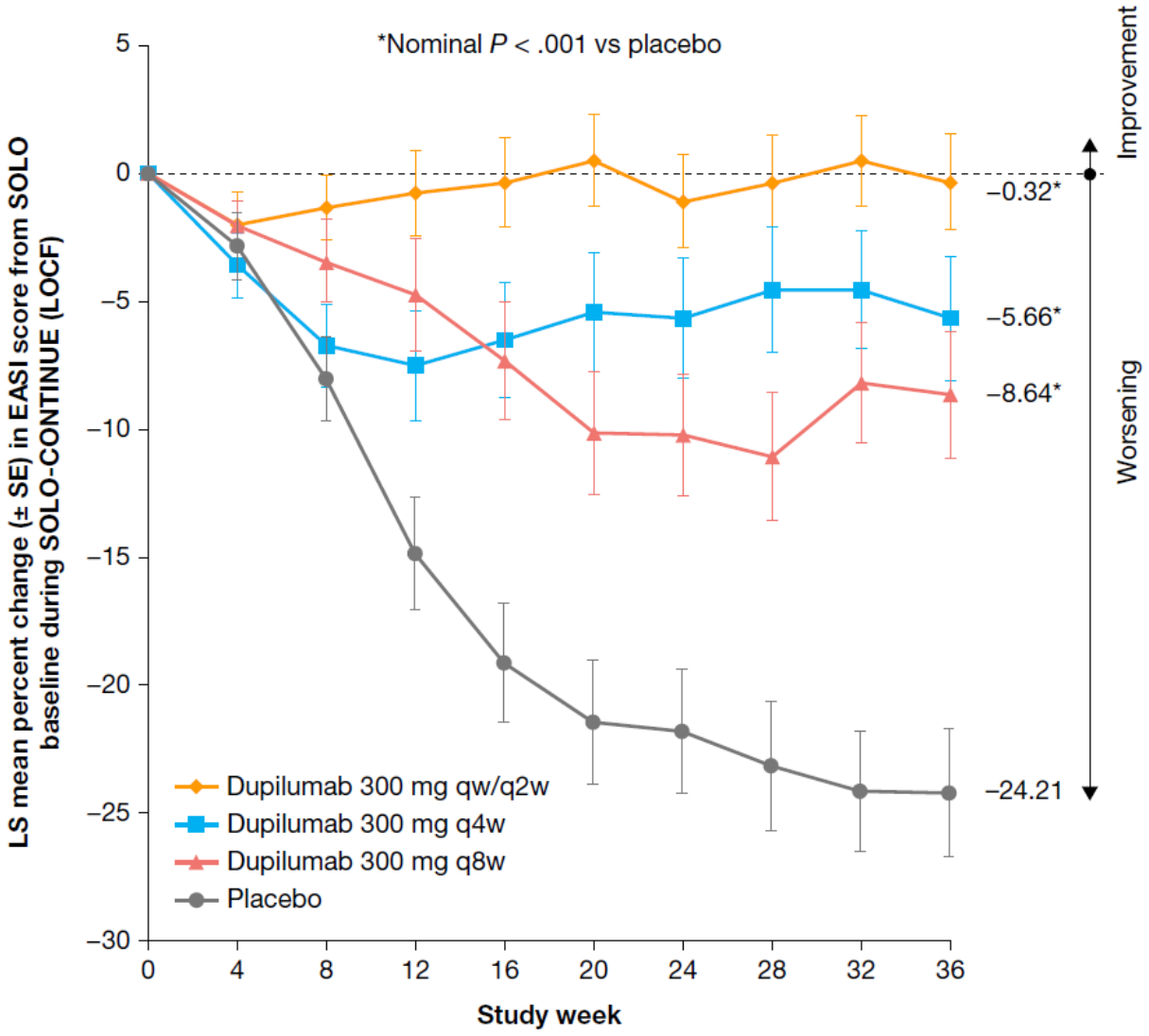

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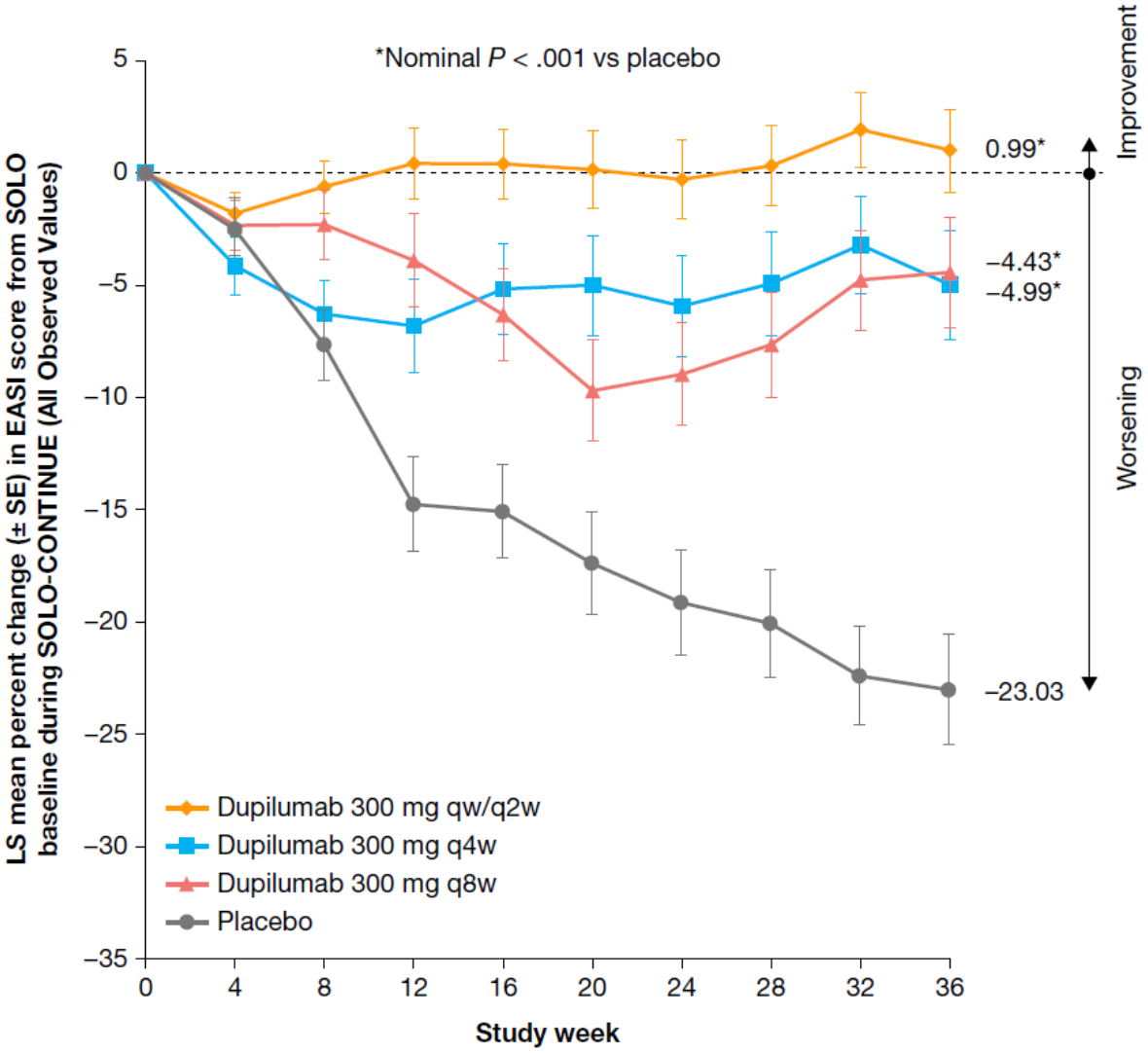

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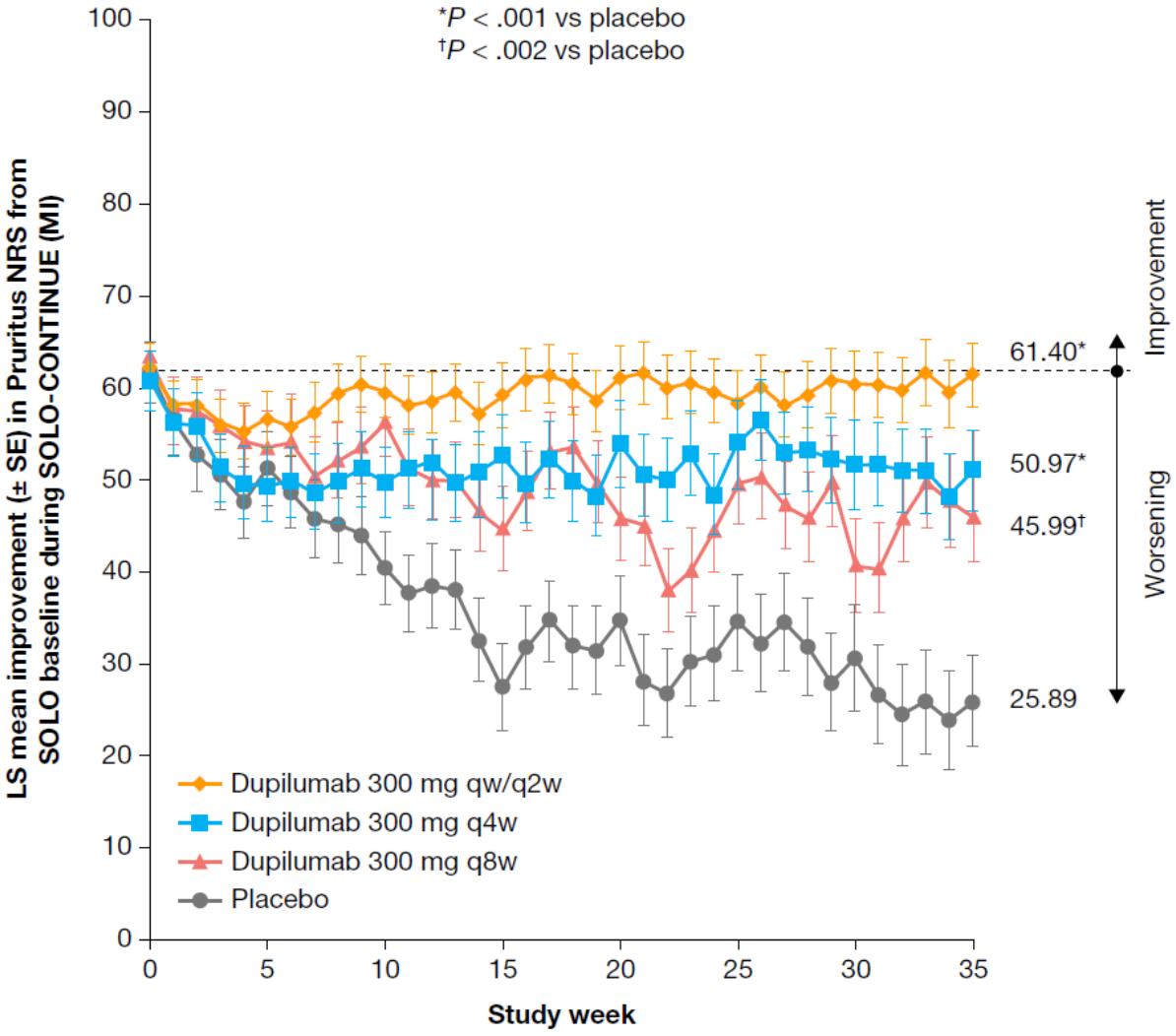
eFigure 5. Percent Change (Improvement) in Peak Pruritus NRS From Parent Study Baseline During the SOLO-CONTINUE Study in Patients Originally Treated in SOLO 1 or SOLO 2 (MI Analysis)

Abbreviations: LS, least squares; MI, multiple imputation; NRS, numerical Rating Scale; q2w, every 2 weeks; q4w, every 4 weeks; q8w, every 8 weeks; qw, weekly; SE, standard error.

Error bars are ± SE.



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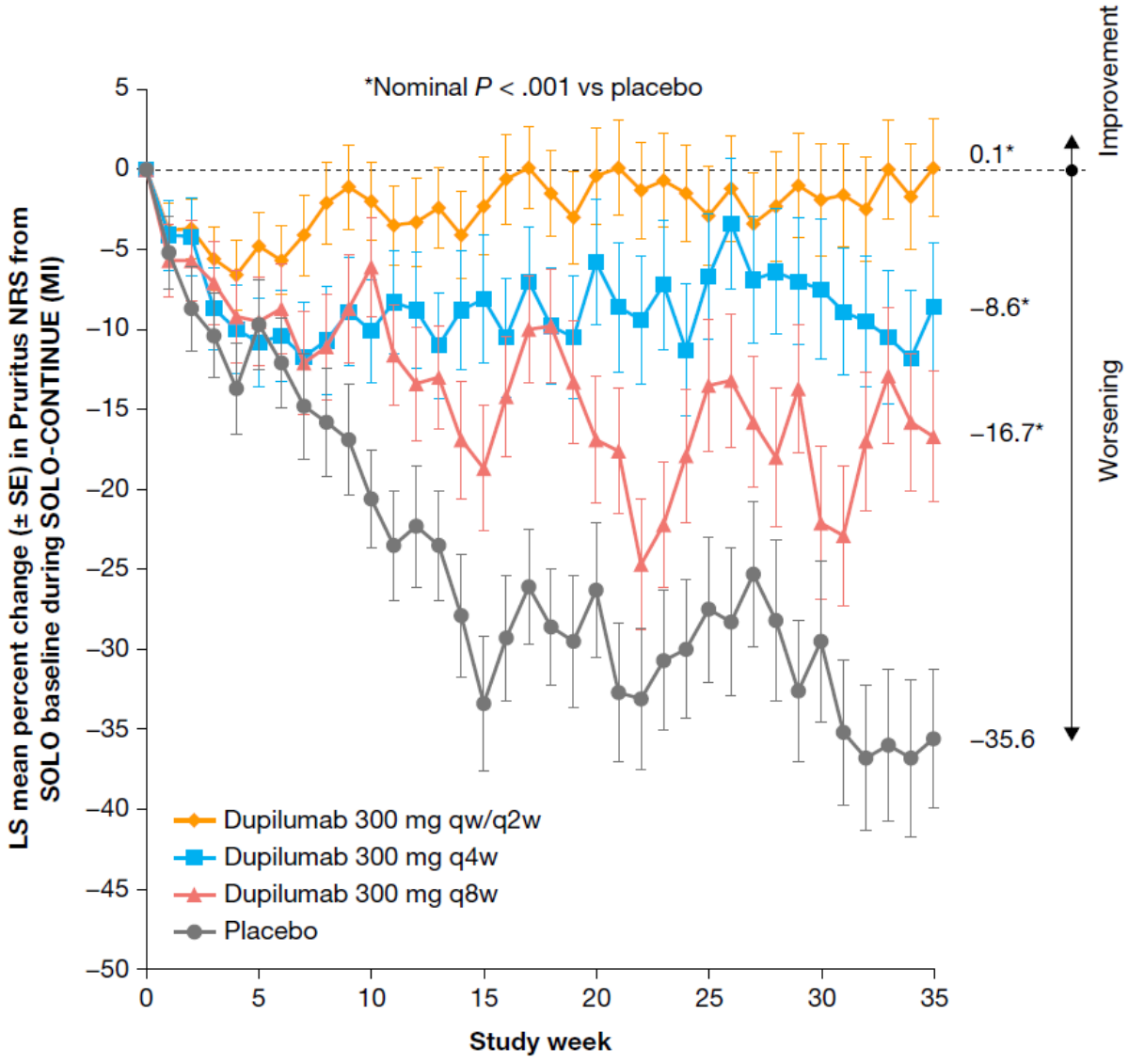
eFigure 6. Percent Change (Improvement) in Peak Pruritus NRS From Parent Study Baseline During the SOLO-CONTINUE Study: difference between SOLO-CONTINUE baseline and week 35
A. MI analysis. B. LOCF analysis. C. All observed values regardless of rescue medication use.
Abbreviations: LOCF, last observation carried forward; LS, least squares; MI, multiple imputation; NRS, numerical rating scale; q2w, every 2 weeks; q4w, every 4 weeks; q8w, every 8 weeks; qw, weekly; SE, standard error.

Error bars are ± SE.

A



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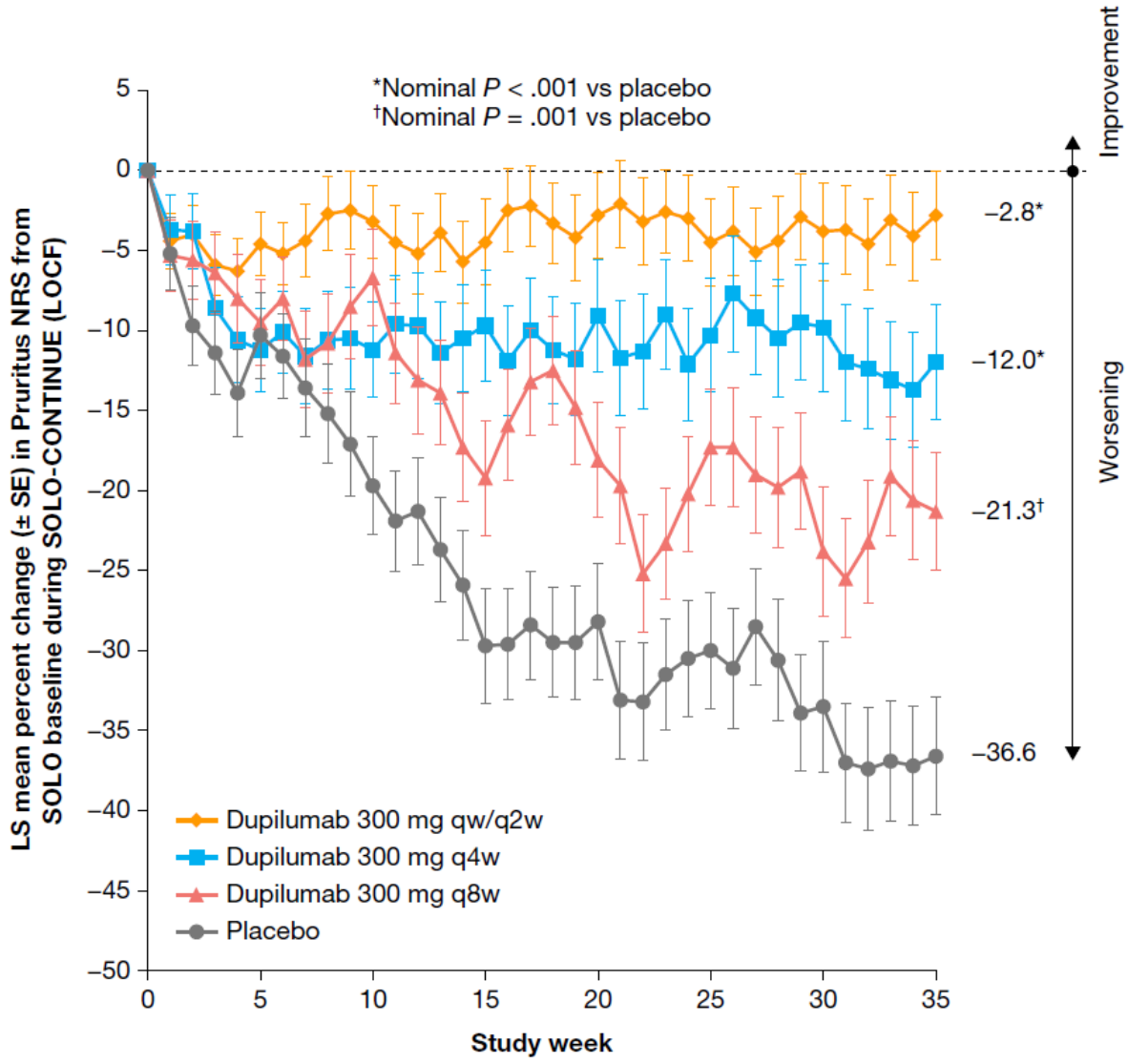

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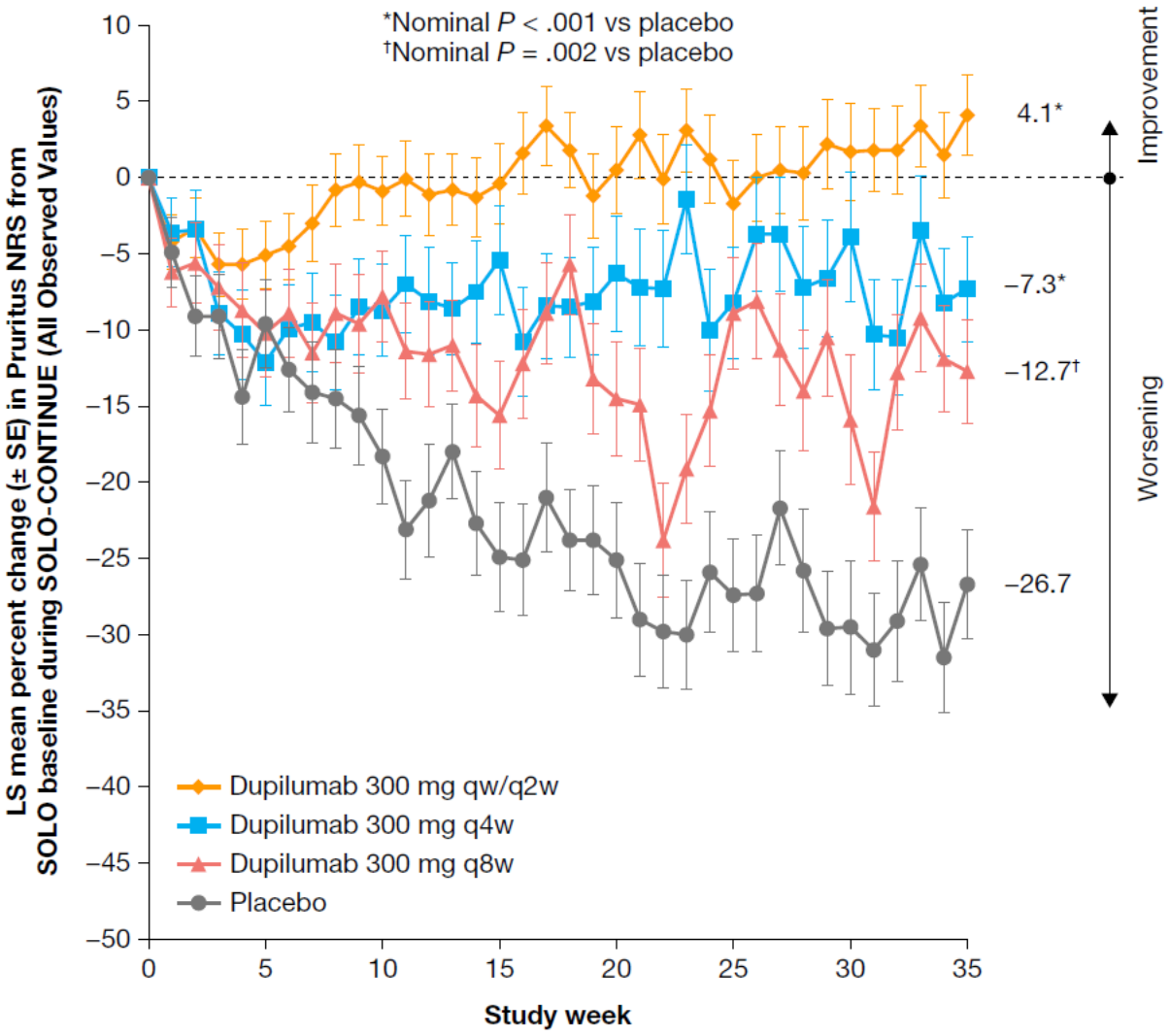

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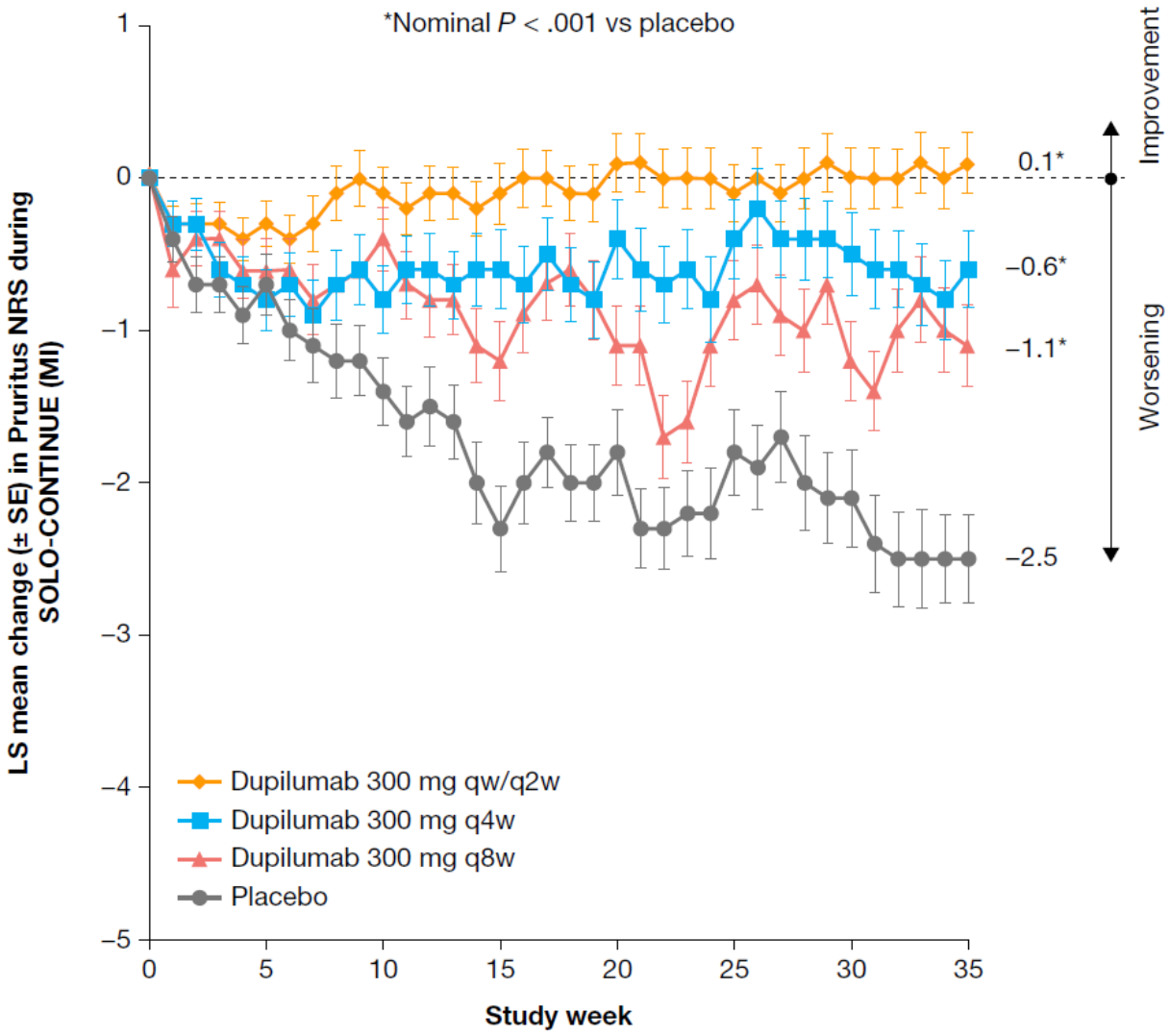
eFigure 7. Change (Improvement) in Peak Pruritus NRS From Baseline Through Week 35 During the SOLO-CONTINUE Study

A. MI analysis. B. All observed values regardless of rescue medication use.

Abbreviations: LS, least squares; MI, multiple imputation; NRS, Numerical Rating Scale; q2w, every 2 weeks; q4w, every 4 weeks; q8w, every 8 weeks; qw, weekly; SE, standard error.

Error bars are ± SE.

A



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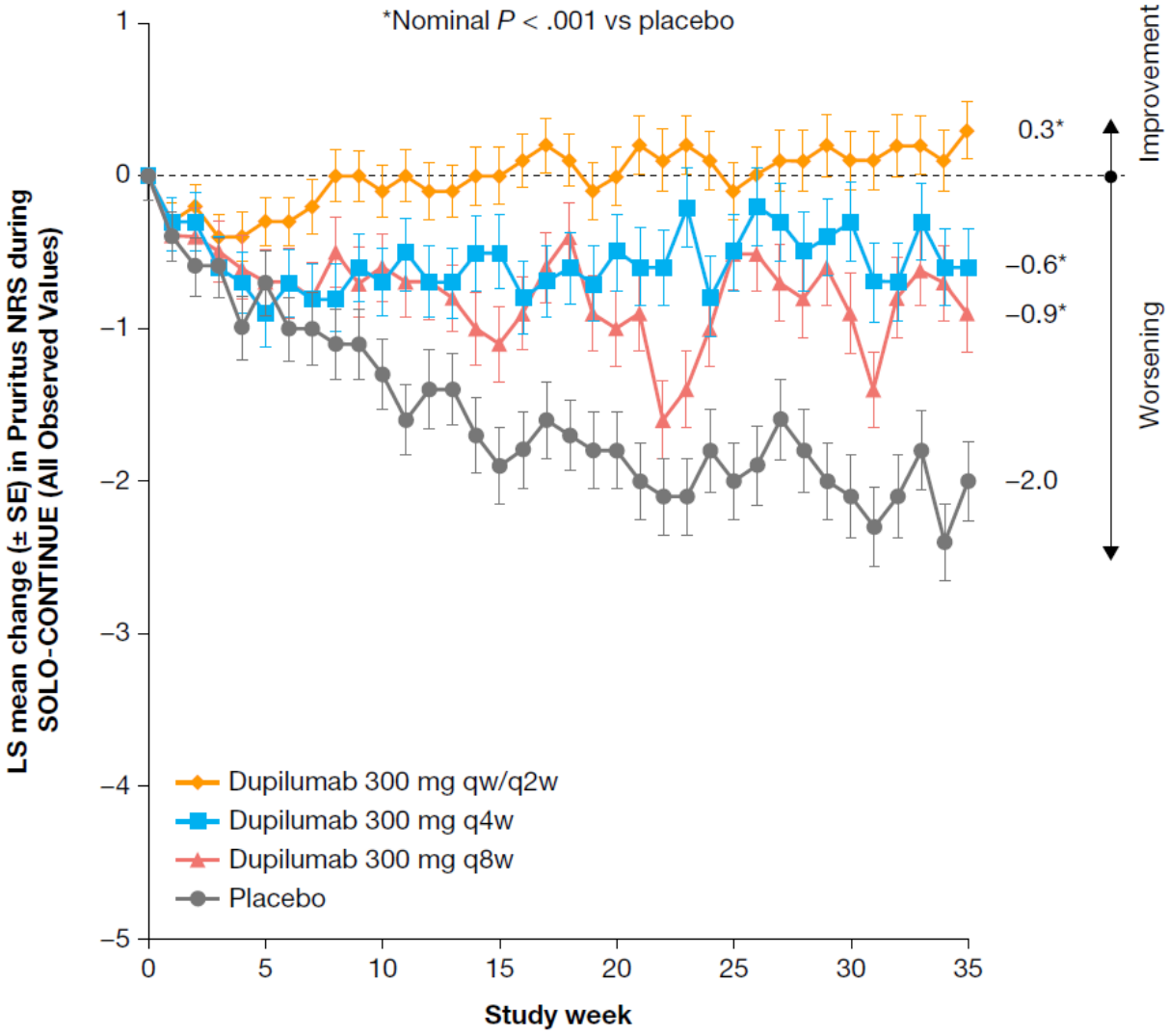

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eFigure 8: Change (Improvement) in EASI From Baseline of the SOLO-CONTINUE Study Through Week 36

A. MI analysis. B. All observed values.

Abbreviations: EASI, Eczema Area and Severity Index; LS, least squares; MI, multiple imputation; q2w, every 2 weeks; q4w, every 4 weeks; q8w, every 8 weeks; qw, weekly; SE, standard error.

Error bars are ± SE.

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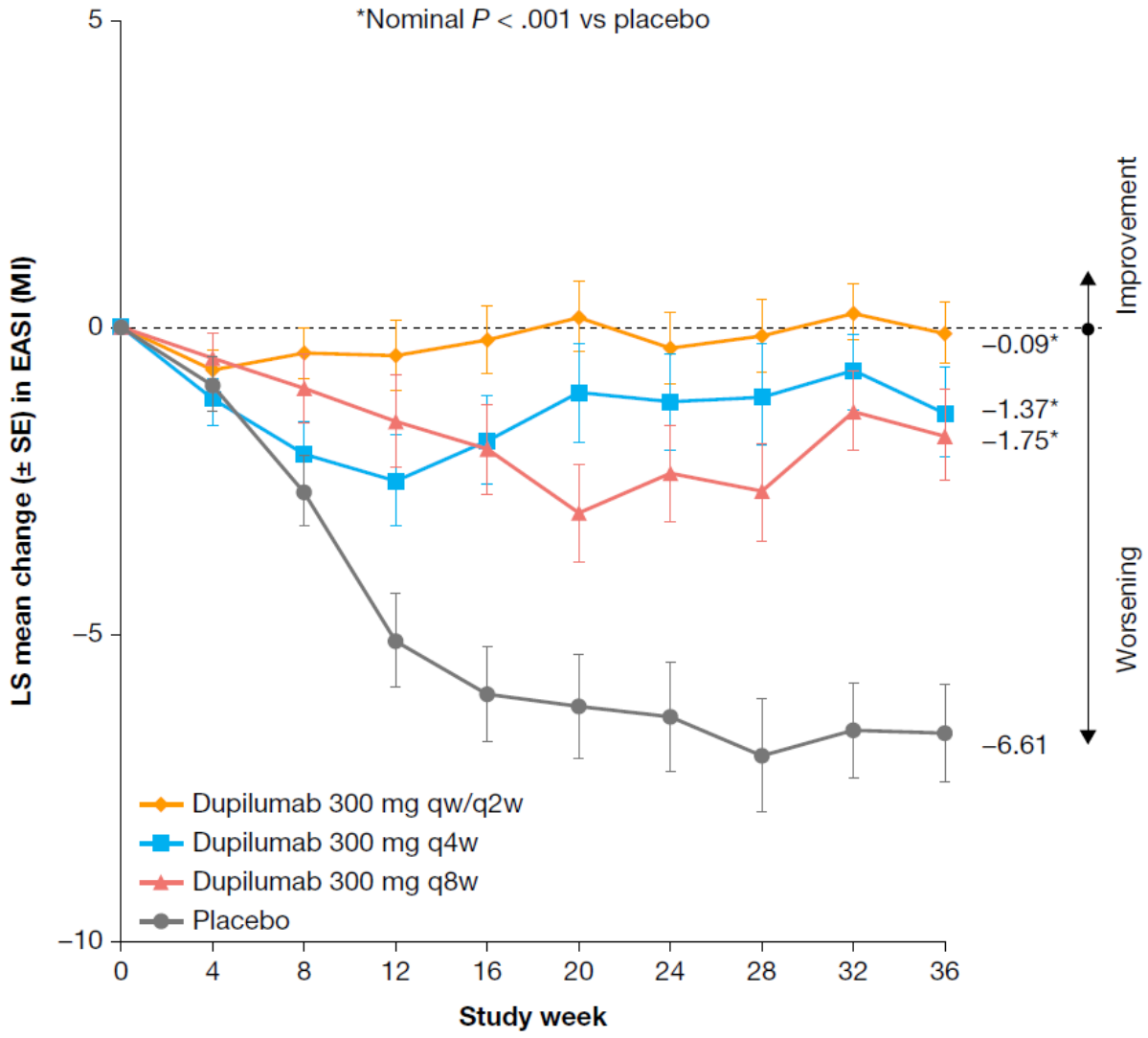

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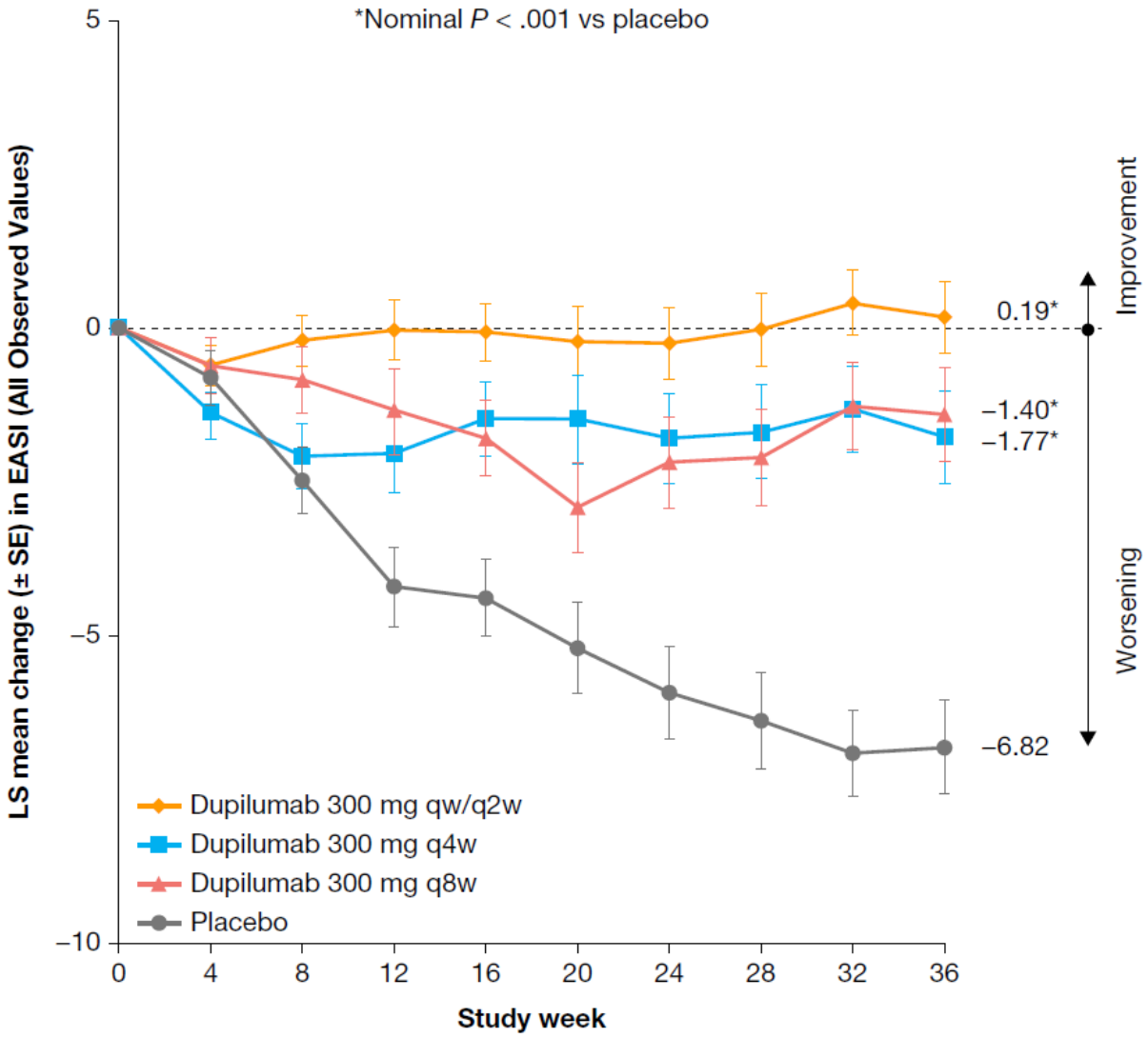

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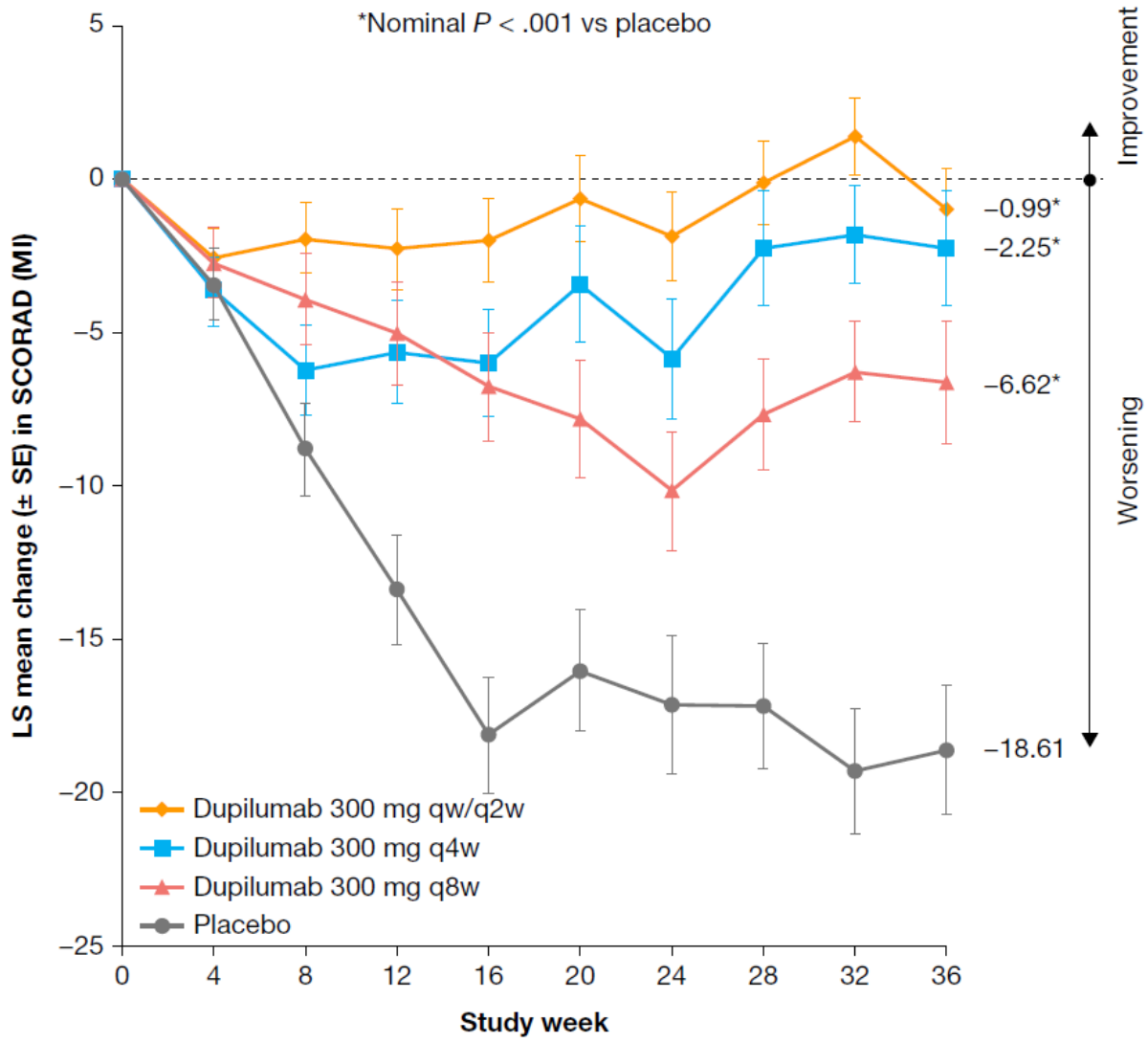
eFigure 9. Change (Improvement) in SCORAD From Baseline During the SOLO-CONTINUE Study Through Week 36

A. MI analysis. B. All observed values. C. Percent change (improvement) in SCORAD from parent SOLO baseline (difference between baseline of SOLO-CONTINUE and time points through week 36: MI analysis).

Abbreviations: LS, least squares; MI, multiple imputation; q2w, every 2 weeks; q4w, every 4 weeks; q8w, every 8 weeks; qw, weekly; SCORAD, SCORing Atopic Dermatitis; SE, standard error.

Error bars are ± SE.

A



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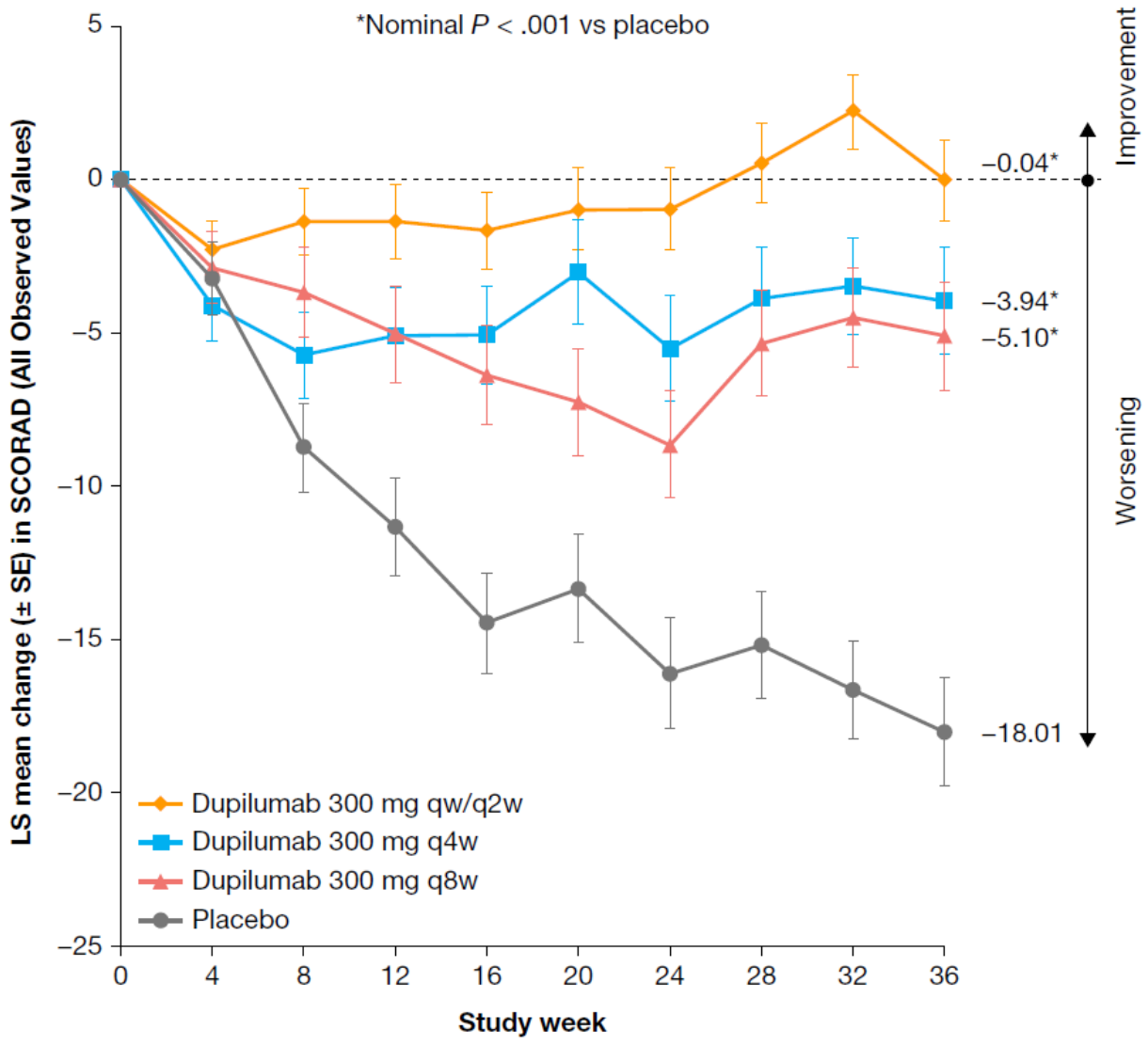

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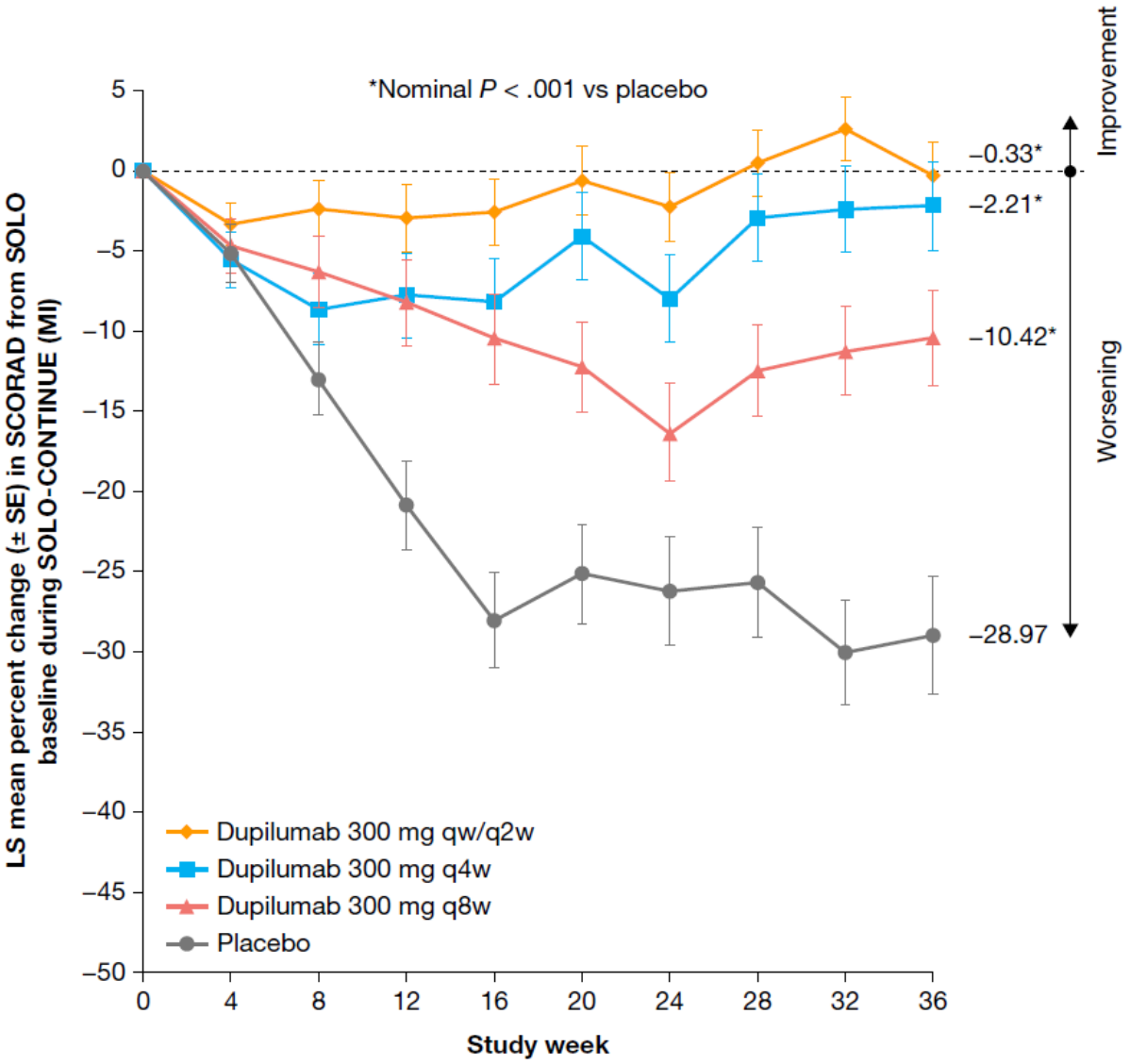

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eFigure 10. Percent BSA Affected by AD
A. Change (improvement) from baseline of SOLO-CONTINUE through week 36: MI analysis. B. All observed values.
Abbreviations: AD, atopic dermatitis; BSA, body surface area; LS, least squares; MI, multiple imputation; q2w, every 2 weeks; q4w, every 4 weeks; q8w, every 8 weeks; qw, weekly; SE, standard error.

Error bars are ± SE.

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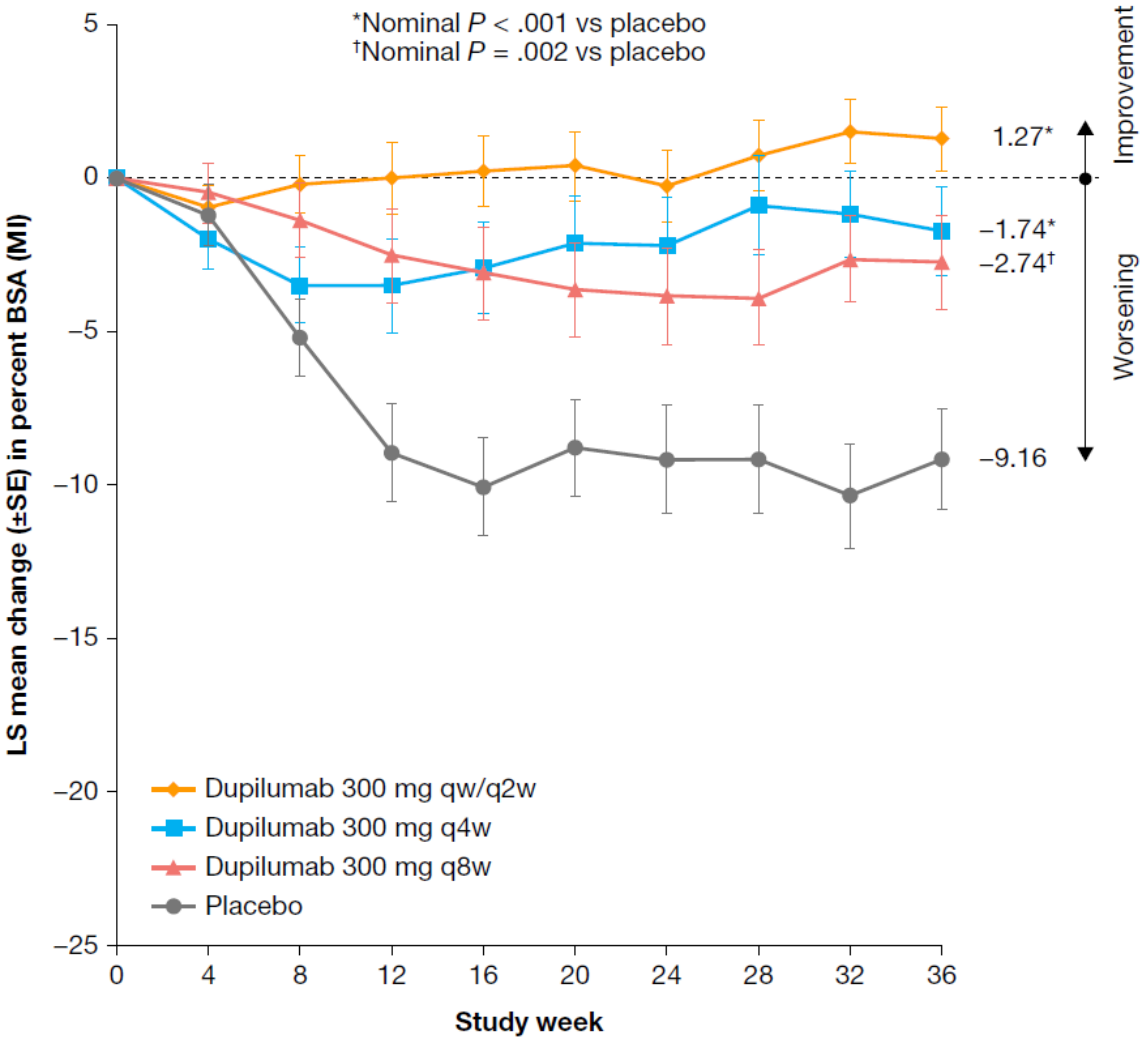

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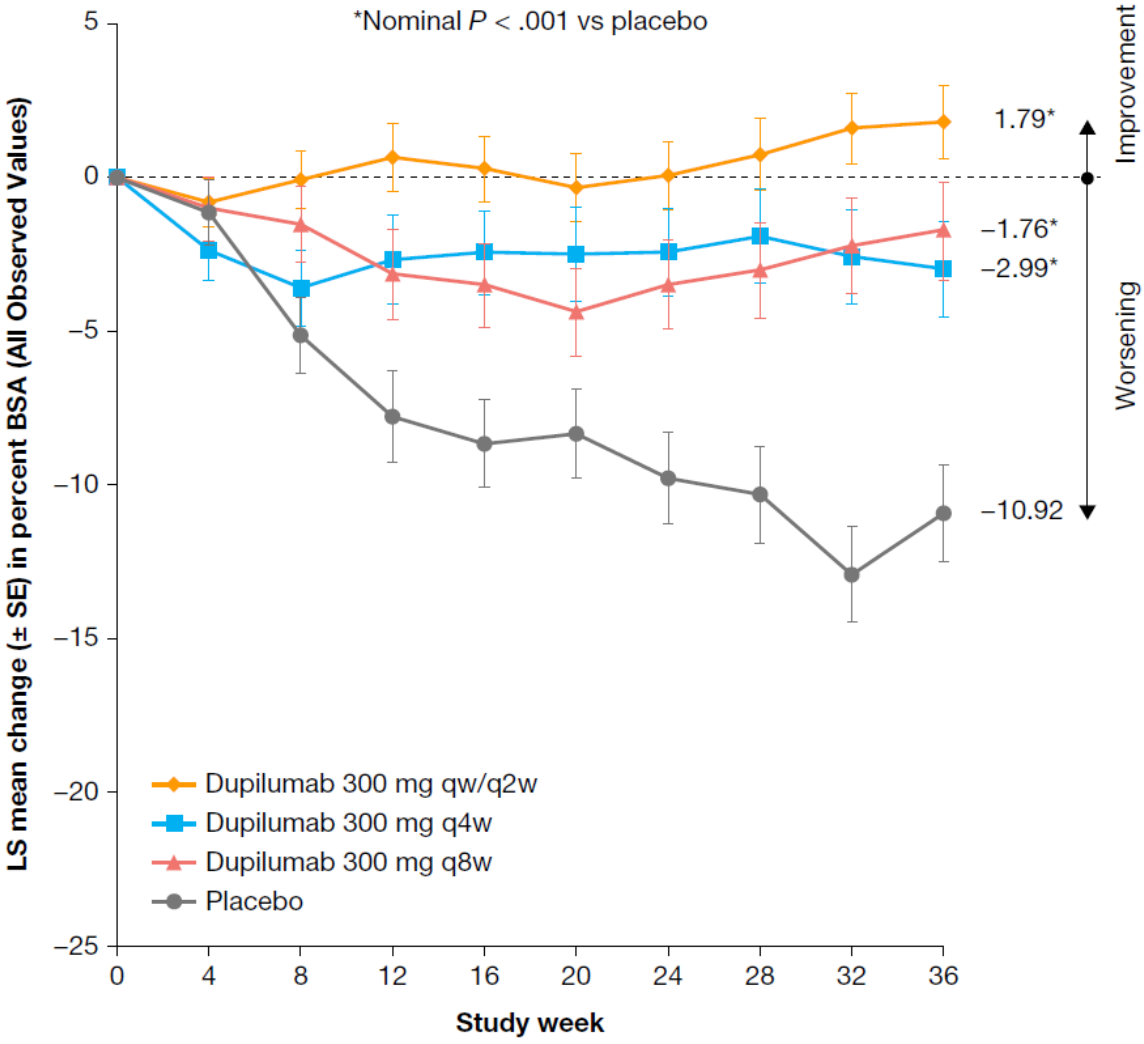

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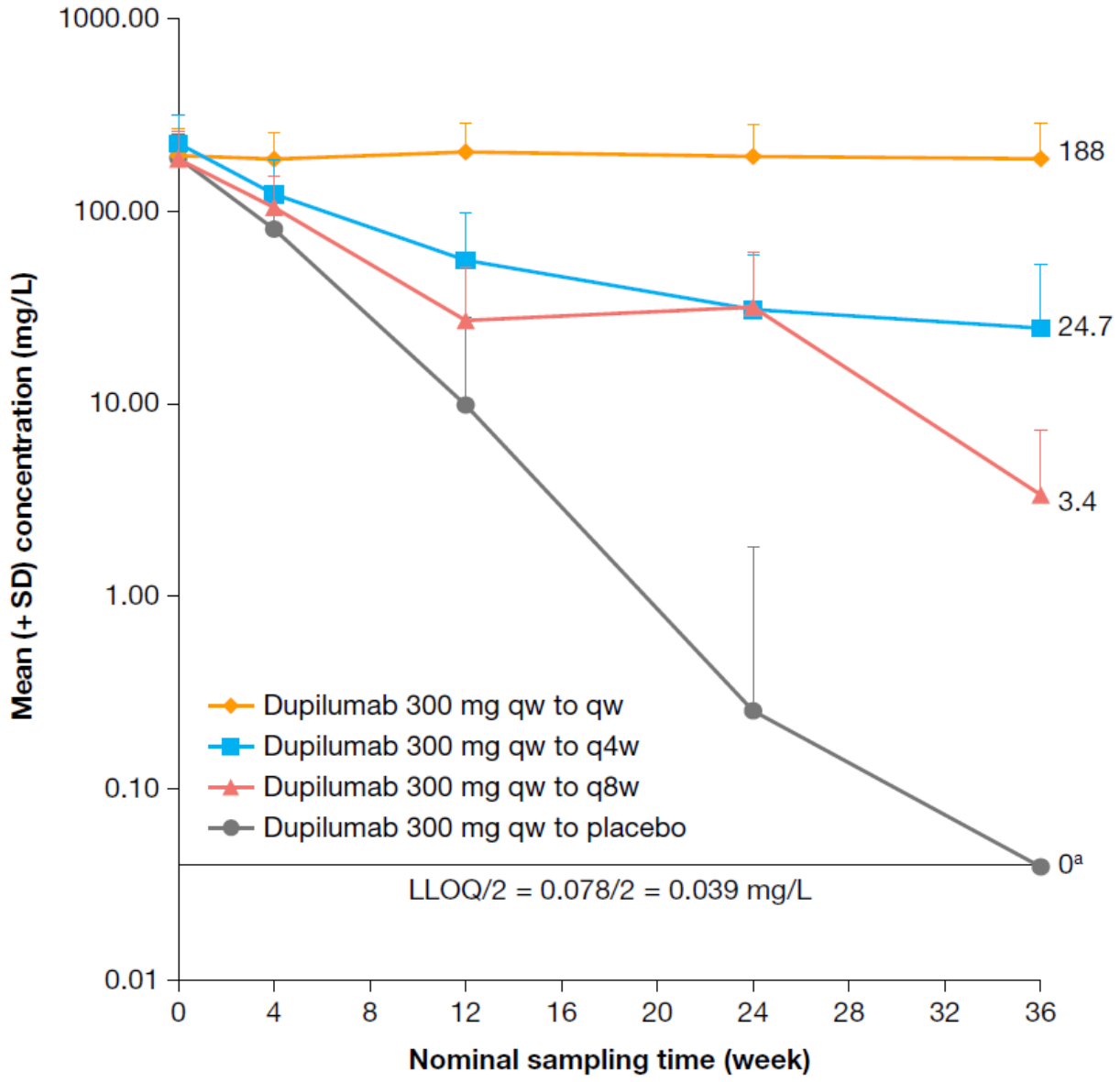
eFigure 11. Log-Scaled Mean Functional Dupilumab Concentrations (+ SD) Over Time in SOLO-CONTINUE

A. In patients who received dupilumab 300 mg qw in SOLO. B. In patients who received dupilumab 300 mg q2w in SOLO.

Abbreviations: LLOQ, lower limit of quantification; q2w, every 2 weeks; q4w, every 4 weeks; q8w, every 8 weeks; qw, weekly; SD, standard deviation.

[a] Concentrations below the lower limit of quantification (LLOQ, horizontal dotted line = 0.0780 mg/L) are imputed as LLOQ/2 = 0.0390 mg/L. For the dupilumab q8w group, the second dose was given 7 weeks after the first dose; therefore, doses for the dupilumab q8w group were given at weeks 0, 7, 15, 23, and 31.

A



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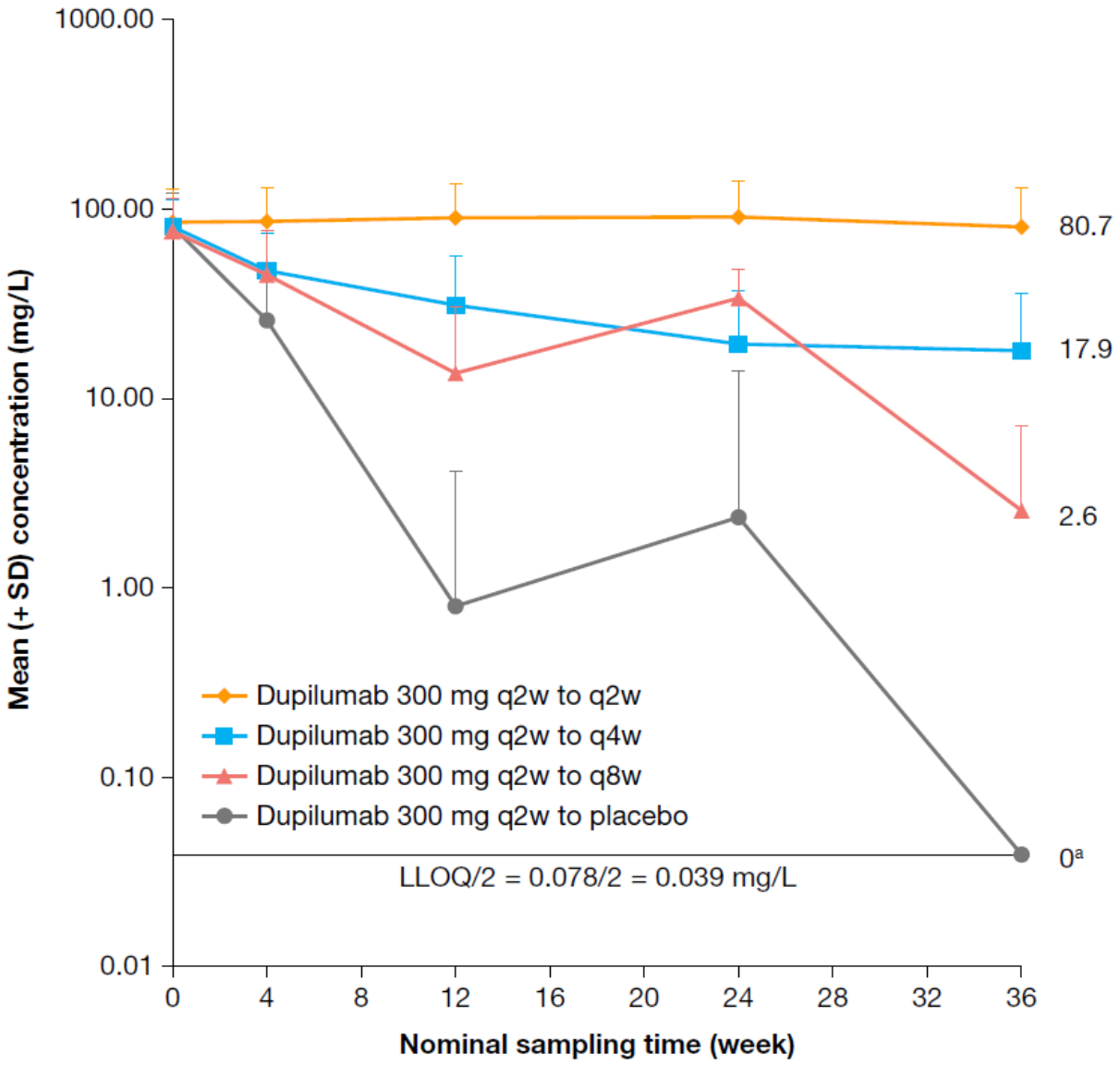

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