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Dupilumab with concomitant topical corticosteroids in adult patients with atopic dermatitis who are not adequately controlled with or are intolerant to ciclosporin A, or when this treatment is medically inadvisable: a placebo-controlled, randomized phase 3 clinical trial (LIBERTY AD CAFÉ)

Running head: Dupilumab in adults with AD: a phase 3 trial (LIBERTY AD CAFÉ)

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Conflicts of interest

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Statements

- **What's already known about this topic: (word limit: 70 words; word count: 70 words)**
  - Patients with atopic dermatitis (AD) inadequately controlled with topical therapy have few systemic treatment options
  - Ciclosporin A (CsA) is a systemic immunosuppressant approved for AD in most European countries and Japan, but not all patients respond, and side effects limit its use
  - Dupilumab (monoclonal antibody against interleukin-4 receptor-alpha) with/without topical corticosteroids (TCS) is approved in the U.S.A. and E.U. for the treatment of adults with moderate-to-severe AD
- **What does this study add: (word limit: 70 words; word count: 56 words)**
  - In this 16-week trial in adults with AD and history of inadequate response to/intolerance of/medically inadvisable for CsA, dupilumab administered weekly or every 2 weeks with concomitant TCS significantly improved signs and symptoms and quality of life, with no new safety signals
  - These data support the use of dupilumab in this difficult-to-treat population

SUMMARY

Background: Atopic dermatitis (AD) is a chronic inflammatory skin disease that may require systemic therapy. Ciclosporin A (CsA) is a widely-used, potent immunosuppressant for AD. CsA is not effective in all patients, and side effects limit its use. Dupilumab, a fully human anti-interleukin (IL)-4 receptor-alpha monoclonal antibody, inhibits signaling of IL-4 and IL-13, key drivers of type 2/Th2-mediated inflammation, and is approved in the U.S.A. and the E.U. for the treatment of adults with moderate-to-severe AD.

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Objectives: To evaluate efficacy and safety of dupilumab with concomitant topical corticosteroids (TCS) in adults with AD with inadequate response to/intolerance of CsA, or for whom CsA was medically inadvisable.

Methods: In this 16-week, double-blind, randomized, placebo-controlled, phase 3 trial, patients were randomized 1:1:1 to subcutaneous dupilumab 300 mg weekly (qw):every two weeks (q2w):placebo. All received concomitant medium-potency TCS from Week −2 through Week 16; dosage could be tapered if lesions cleared, or stopped for adverse reactions to TCS.

Results: 390 patients were screened; 325 were randomized and 318 completed the trial. Treatment groups had similar baseline characteristics. Significantly more patients on dupilumab qw+TCS/q2w+TCS achieved ≥75% improvement from baseline in Eczema Area and Severity Index at Week 16 vs placebo+TCS (primary endpoint) (59.1%/62.6% vs 29.6%; *P*<0.0001 vs placebo+TCS, both doses). Dupilumab qw+TCS/q2w+TCS significantly improved other clinical outcomes and AD symptoms, including pruritus, pain, sleep disturbance, symptoms of anxiety and depression, and quality of life (QOL). Treatment groups had similar overall rates of adverse events (69.1%/72.0%/69.4%; qw+TCS/q2w+TCS/placebo+TCS) and serious adverse events (1.8%/1.9%/1.9%). Conjunctivitis was more frequent with dupilumab+TCS; skin infections were more frequent with placebo+TCS.

Conclusions: Dupilumab+TCS significantly improved signs and symptoms of AD and QOL in adults with history of inadequate response to/intolerance of CsA, or for whom CsA treatment was medically inadvisable. No new safety signals were identified. (ClinicalTrials.gov Identifier: NCT02755649; EudraCT: 2015-002653-35)

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INTRODUCTION

Atopic dermatitis (AD) is a chronic pruritic inflammatory skin disease that features activation of type 2/T-helper (Th2) immune responses, and altered skin barrier and skin microbiome.[1–7] For patients with inadequate response or intolerance to topical therapies, guidelines recommend systemic immunosuppressants (e.g. ciclosporin A [CsA], methotrexate, azathioprine, or mycophenolic acid), although these treatments show variable efficacy/effectiveness and tolerability, and may be complicated by adverse effects and adverse medication interactions both in the short and long term.[8–17] Phototherapy is also recommended, but cannot be used as long-term treatment and has risks including burning, skin aging, adverse medication interactions, and skin cancer.[8–17]

Unlike other systemic immunosuppressants, CsA is approved in many European countries and Japan for severe AD when systemic therapy is required. CsA suppresses Th1, Th2, and Th17/22, affecting both humoral and cellular immune responses.[18,19] Long-term use (beyond 1 year) of CsA, as may be required in AD, is limited by risk of side effects, although off-label use beyond 1 year has been reported.[16,20–38] Side effects associated with CsA include hypertension, nephrotoxicity, and subjective side effects (e.g. headache, paresthesia in fingers and toes, fatigue).[16,20–38] Its use is also limited by contraindications due to other medical conditions. Thus, patients with AD who are unresponsive to or who are unable to use topical medications or CsA have few treatment options. Given the chronicity of AD and the need for long-term pharmacologic therapy, new treatment options with better benefit-risk profiles are needed.

Dupilumab, a fully human monoclonal antibody directed against the interleukin (IL)-4 receptor-alpha, is a targeted agent that selectively inhibits signalling of IL-4 and IL-13, key cytokines of type 2/Th2 inflammation.[39] Dupilumab is approved in the U.S.A. for the treatment of adults with moderate-to-severe AD whose disease is inadequately controlled by topical therapies, or when such treatments are not advisable, and can be used with or without topical corticosteroids (TCS).[40] Dupilumab has also been approved by the European Medicines Agency for use in adults with

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moderate-to-severe AD who are candidates for systemic therapy.[41] In patients with moderate-to-severe AD who had inadequate response to topical medications, dupilumab alone or with TCS significantly improved clinical signs and symptoms of AD.[42–47] In these studies, adverse events (AEs) that were more frequent with dupilumab included conjunctivitis and injection-site reactions, but there was no increase in infections or serious AEs (SAEs) compared with placebo.[42–46] In addition, dupilumab is being investigated in other type 2/Th2 diseases. Positive data have been reported in clinical trials with dupilumab in patients with asthma,[48–50] chronic rhinosinusitis with nasal polyposis (CRsNP),[51] and eosinophilic esophagitis,[52] providing evidence of a common type 2/Th2 mechanism underlying these diseases.

The present study expands upon previous studies of dupilumab in patients with moderate-to-severe AD by evaluating the efficacy and safety of dupilumab with concomitant TCS in patients with AD and a history of inadequate response or intolerance to CsA, or CSA-naive patients for whom CsA treatment was medically inadvisable.

METHODS

Study design

LIBERTY AD CAFÉ (ClinicalTrials.gov Identifier: NCT02755649; EudraCT: 2015-002653-35) was a randomised, double-blind, placebo-controlled, parallel-group, phase 3 clinical study (Fig. 1). Patients were enrolled at academic institutions, hospitals, and clinics in 10 European countries in which systemic CsA has been approved for AD (Table S1). Patients were recruited by individual sites, based on reviews of patient databases, referrals, and advertising.

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Patients

Main inclusion criteria were: ≥18 years of age with chronic AD according to American Academy of Dermatology consensus criteria;[1] treatment with potent TCS indicated; inadequate response to TCS (as defined by investigator) within 6 months before screening; history of (1) prior CsA exposure and either inadequate response to CsA, requirement for CsA at doses or durations beyond those specified in prescribing information, or intolerance and/or unacceptable toxicity, or (2) CsA-naive and not eligible for CsA due to medical contraindications (e.g. uncontrolled hypertension on medication), use of prohibited concomitant medications, increased susceptibility to CsA-induced renal damage (elevated creatinine) and/or liver damage (elevated liver function tests), increased risk of serious infection, or hypersensitivity to CsA active substance or excipients; Eczema Area Severity Index (EASI) score ≥20 at screening and baseline; Investigator's Global Assessment (IGA) score ≥3 (scale 0 [clear] to 4 [severe]) at screening and baseline; ≥10% body surface area (BSA) of AD involvement at screening and baseline. See Supporting Information for full inclusion/exclusion criteria.

Ethics

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and are consistent with International Council for Harmonisation guidelines for Good Clinical Practice and applicable regulatory requirements. All patients provided signed written informed consent prior to any study procedure. Prior to study initiation, Institutional Review Boards (Table S1) and Independent Ethics Committees reviewed and approved the protocol, informed consent form, and patient information. An independent data monitoring committee (IDMC) monitored patient safety.

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Study procedures, randomization, and treatments

The screening period ran from Day −28 to baseline, and included a TCS standardization period, which ran from Day −14 to baseline (Fig. 1). At baseline, patients were randomized (1:1:1) to receive 16 weeks of subcutaneous dupilumab 300 mg weekly (qw):every 2 weeks (q2w):placebo, using a central interactive voice/web response randomization system, stratified by baseline IGA score (3 or 4) and prior CsA exposure (yes/no). At baseline, patients received a loading dose of 600 mg dupilumab or matching placebo, followed thereafter by subcutaneous dupilumab 300 mg qw or q2w, or placebo. For blinding purposes, patients assigned to dupilumab q2w+TCS received placebo on weeks when dupilumab was not administered. Blinded study drug (dupilumab or placebo) was provided in coded kits with a medication numbering system. Except for the statistician who provided the randomization sequence, the IDMC statistician, and IDMC members, the study remained blinded to all individuals until prespecified unblinding. Emergency unblinding was permitted for a medical emergency, a SAE that was unexpected or for which a causal relationship to study drug could not be ruled out, or for any other significant medical event. During Weeks 17–28, patients were followed for safety or could enter an open-label extension study (R668-AD-1225; ClinicalTrials.gov: NCT01949311; EudraCT: 2013-001449-15).

During the initial two weeks of the screening period, patients could use TCS at investigator discretion. Starting at Day −14, and during the study treatment period, all eligible patients applied medium-potency TCS once daily to active lesion areas, or low-potency TCS on areas of thin skin (e.g. face, neck, intertriginous and genital areas) or where continued treatment with medium-potency TCS was considered unsafe. Patients could stop TCS upon adverse reaction to TCS. Patients achieving IGA=0 by Weeks 4, 8, or 12 could taper TCS to every other day. After Week 4, patients remaining at IGA=0 for 4 weeks could switch TCS to twice per week; if they did not remain at IGA=0 they would revert to daily dosing. Patients with clear skin continued to apply TCS to lesion-prone areas at intervals of every other day (if prior to Day 57) or twice weekly (after Day 57), as described above.

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During the safety follow-up, patients could remain on TCS at investigator discretion. Patients recorded TCS use in a medication diary; tubes were weighed at each visit through Week 16. Patients were instructed to apply emollients twice daily for the 7 days prior to randomization and throughout the study; stable doses of prescription moisturizers or moisturizers containing additives were permitted if initiated before screening.

Patients could receive rescue medication, including potent or very potent TCS, topical calcineurin inhibitors, or systemic medication, if medically necessary (e.g. to control intractable AD symptoms), at investigator discretion. Patients who received rescue medication were considered treatment failures, but continued study visits and assessments; those on topical rescue medication could continue study treatment, while those on systemic rescue medication discontinued study treatment (see Supporting Information: prohibited concomitant medications).

Endpoints

The primary endpoint was the proportion of patients with ≥75% improvement from baseline in EASI score (EASI-75) at Week 16. Secondary endpoints were the following (all at Week 16, unless otherwise indicated): percent change from baseline in EASI, SCORing AD (SCORAD), weekly average of peak daily pruritus numerical rating scale (NRS) (Weeks 2 and 16), and Global Individual Sign Score (GISS); change from baseline in percent BSA affected by AD, Dermatology Life Quality Index (DLQI), Patient Oriented Eczema Measure (POEM), and Hospital Anxiety and Depression Scale (HADS); mean weekly dose of TCS during the treatment period; proportions of patients with ≥50% or ≥90% improvement from baseline in EASI score (EASI-50 or EASI-90), EASI-75 (among patients with prior CsA exposure), ≥4-point reduction in weekly average of peak daily pruritus NRS score (among patients with baseline pruritus NRS score ≥4), ≥50% improvement from baseline in SCORAD (SCORAD-50), and both IGA 0 or 1 (clear or almost clear) and 2-point reduction in IGA from baseline.

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Post hoc analyses included: mean change from baseline in EASI, SCORAD, and pruritus NRS scores; mean change from baseline in SCORAD visual analogue scale for sleep; and proportions of patients reporting "no problem" on the pain/discomfort subscale on the generic 5-dimension 3-level EuroQoL scale (among patients reporting moderate-to-severe pain/discomfort at baseline), reporting "no days" or "1–2 days" for number of nights sleep was disturbed in the past week (POEM item 2) (among patients reporting 3–7 nights missed sleep the previous week at baseline), achieving ≥4-point improvement in DLQI score (minimal clinically important difference [MCID]) (among patients with baseline DLQI ≥4),[53] achieving ≥4-point improvement in POEM score (MCID) (among patients with baseline POEM ≥4),[54] and achieving HADS anxiety (HADS-A) and depression (HADS-D) scores <8 (among patients with HADS-A or HADS-D ≥8 at baseline).[55]

Statistical analyses

Approximately 110 patients were planned for each treatment group – approximately 70 with previous exposure to CsA and 40 with no exposure (see Supporting Information). Target accrual was approximately 330 patients (110 per arm, including 70 with prior CsA exposure and 40 with no prior CsA exposure); this provided 99% power for the primary endpoint, assuming EASI-75 rates of 60.1% in the dupilumab arms and 26.4% in the placebo group, based on results of a 16-week phase 2b study[43] and a 12-week phase 2a study[42] in patients with moderate-to-severe AD, by prior CSA use and CSA-naive patients.

Significance was set to *P*=0.05, two-sided. To account for multiplicity arising from comparison of each of the dupilumab+TCS dose groups with placebo+TCS, efficacy analyses were carried out in sequential order, following an endpoint hierarchy for each dupilumab dose regimen (see Supporting Information). The study was not powered for comparison of the two dupilumab dose regimens. Significance values were considered nominal for post hoc analyses.

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For the primary efficacy endpoint and other binary endpoints, the Cochran-Mantel-Haenszel test adjusted by randomization strata (disease severity [IGA 3 or 4] and prior CsA use [yes/no], was used to compare each dupilumab+TCS group with placebo+TCS. Patients were specified as non-responders at rescue medication initiation. Continuous endpoints were analysed using multiple imputation with analysis of covariance (ANCOVA); data after rescue medication usage was set to missing, and imputed by multiple imputation. For post hoc responder analyses, values after first rescue treatment were set to missing; patients with missing scores at Week 16 were considered non-responders (see Supporting Information).

Safety assessments are reported for the 16-week treatment period, and include AEs, treatment-related AEs, SAEs, and AEs leading to discontinuation or death.

Efficacy assessments were based on the full analysis set, which included all randomized patients, based on the treatment allocated as randomized (intention-to-treat). Safety analyses were based on the safety population, which included all randomized patients who received any study drug, based on the treatment received.

Analyses used SAS® version 9.2 (SAS Institute Inc., Cary, NC, U.S.A.) or above.

RESULTS

Patient disposition and baseline characteristics

Between January and December 2016, 390 patients were screened and 325 randomized to 300 mg dupilumab qw+TCS (n=110), 300 mg dupilumab q2w+TCS (n=107), or placebo+TCS (n=108) (Fig. S1, Table S2; see Supporting Information).

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Baseline characteristics were similar among treatment groups overall (**Table 1**), and in subgroups based on prior CsA use (Table S3; see Supporting Information). Median AD duration was 30 years. At baseline, median EASI score was 31.1–31.7, 75% of patients reported moderate or severe pain/discomfort, 59% reported sleep disruption in 3–7 nights over the past week, and 65% had previously received CsA. Most patients completed study treatment (98.2%, 100%, and 95.4%; qw+TCS, q2w+TCS, and placebo+TCS, respectively) by data cut-off (5 January 2017); 3 (3%) in the placebo+TCS group withdrew from study treatment due to lack of efficacy, and 2 (2%) each in the placebo+TCS and dupilumab qw+TCS groups withdrew due to AEs.

Efficacy

Primary endpoint

The proportion of patients achieving EASI-75 at Week 16 was significantly higher in the dupilumab qw+TCS and q2w+TCS groups vs placebo+TCS (59.1% and 62.6% vs 29.6%, respectively; *P*<0.0001, each dose group vs placebo+TCS) (Table 2, Fig. 2a**)**.

Secondary endpoints

Significantly more patients receiving dupilumab+TCS achieved EASI-50 and EASI-90 at Week 16 than placebo+TCS (Table 2; Fig. 2b,c)**.** Among patients with prior exposure to CsA, significantly more receiving dupilumab+TCS achieved EASI-75 vs placebo+TCS (Table 2, Fig. 2d). Dupilumab+TCS significantly improved EASI and SCORAD scores from baseline to Week 16 vs placebo+TCS (Table 2, Fig. 3a,b; Table S4, Figs S2, S3), and significantly improved all other measures of clinical efficacy vs placebo+TCS (Table 2, Fig. S4).

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Dupilumab+TCS significantly improved weekly average peak pruritus NRS from baseline to Week 16 vs placebo+TCS, with significant improvement by Week 2 (Table 2, Fig. 4a, Table S4, Fig. S5). Significantly more patients receiving dupilumab+TCS achieved ≥4-point reduction in pruritus NRS by Week 16 vs placebo+TCS (Table 2, Fig. 4b).

Dupilumab+TCS significantly improved health-related quality of life (HRQOL), symptoms of AD, pain/discomfort, sleep, and symptoms of anxiety and depression vs placebo+TCS (Table 2, Table S4, Figs S6–8). Significantly higher proportions of patients on dupilumab+TCS achieved ≥4-point improvement (MCID) in DLQI and POEM scores by Week 16 vs placebo+TCS (Table 2, Fig 5a,b). The proportion of patients who achieved HADS-A and HADS-D subscores <8 (among patients with HADS-A or HADS-D ≥8 at baseline) by Week 16 was significantly higher in the dupilumab q2w+TCS group, but not the qw+TCS group, vs placebo+TCS (Table 2, Fig. 5c).

Results of sensitivity analyses were similar to the primary analyses (Table S5; Figs S2–5, 6b, 7b, 8b).

Medication use

The dupilumab+TCS groups used a lower mean weekly dose by weight of TCS vs placebo+TCS (Table 2). Fewer patients receiving dupilumab+TCS vs placebo+TCS used rescue medication (Table 3). The most frequently-used rescue medication was potent TCS.

Safety

Similar proportions of patients in the dupilumab qw+TCS, q2w+TCS, and placebo+TCS groups reported AEs (Table 4). Few patients permanently discontinued treatment due to AEs. Two patients in each treatment group experienced SAEs; none were considered related to study treatment. No deaths occurred during the study.

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The dupilumab+TCS groups had higher rates of conjunctivitis and injection-site reactions than the placebo+TCS group, while the placebo+TCS group had higher rates of non-herpetic skin infections and AD exacerbations (Table 4, Tables S6, S7). There were no clinically meaningful differences in laboratory values between treatment groups (data not shown).

Conjunctivitis (including Medical Dictionary for Regulatory Activities Preferred Terms [MedDRA PTs] conjunctivitis, conjunctivitis allergic, conjunctivitis bacterial, conjunctivitis viral, and atopic keratoconjunctivitis) was reported in 16%, 28%, and 11% of patients in the dupilumab qw+TCS, q2w+TCS, and placebo+TCS groups, respectively; all but one event were mild or moderate (Table S6). Most conjunctivitis events (89%, 62%, and 87%, respectively) were recovered/resolved or recovering/resolving by end of treatment (Table S6).

Herpes viral infections were reported in 7%, 5%, and 6% of patients in the dupilumab qw+TCS, q2w+TCS, and placebo+TCS groups, respectively (Table S8). The more serious forms of herpes viral infections (e.g. eczema herpeticum, ophthalmic herpes simplex, and ophthalmic herpes zoster) occurred only in the placebo+TCS group. No localized herpes infections were severe and all but one had recovered/resolved by the end of treatment visit.

DISCUSSION

Treatment options are limited for patients with AD who previously failed to respond to CsA or experienced CsA-related AEs, or for whom CsA use is inadvisable because of concomitant medical conditions or risk of drug interactions. This study demonstrates that dupilumab+TCS significantly improves skin lesions, pruritus and other symptoms of AD including pain/discomfort and sleep disruption, symptoms of anxiety and depression, and HRQOL in this difficult-to-treat patient population. No new safety signals were identified in this study. Significantly more patients receiving

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dupilumab+TCS achieved EASI-75 at Week 16 (primary efficacy endpoint) vs placebo+TCS. Among patients receiving dupilumab+TCS, 85% achieved a 50% reduction from baseline in EASI at Week 16 – a clinically meaningful response in this patient population with high baseline burden of disease. Results in the subgroup of patients with prior exposure to CsA were consistent with the overall population. Outcomes for the two dupilumab dose regimens were generally similar. These results are consistent with those of previous studies of dupilumab in patients with moderate-to-severe AD inadequately controlled with topical medications.[42–47]

This study expands upon the previous studies in two principal ways: first, unlike previous studies, the patients in this study were candidates for systemic treatment, and had either not responded to or had experienced intolerance to CsA, or were medically inadvisable to be treated with CsA; and second, this study evaluated dupilumab on a background of treatment with TCS and could not discontinue TCS, unless for safety reasons, unlike in previous studies of dupilumab with concomitant TCS, in which TCS could be stopped if lesions cleared.[42–47]

Patients with moderate-to-severe AD who need systemic therapy experience significant burden of disease.[56–60] AD symptoms can profoundly affect sleep, daily functioning, mental/emotional state, concomitant medication use, and HRQOL, particularly in patients with untreated or inadequately-treated AD.[56–60] Improvement in patient-reported outcomes was significant in both dupilumab+TCS treatment groups, except for the proportion of patients who achieved HADS-A and HADS-D scores <8 (among patients with HADS-A or HADS-D ≥8 at baseline), which was significantly greater with dupilumab q2w+TCS, but not qw+TCS; however, both dupilumab+TCS dose regimens showed significant improvement in mean change in HADS score from baseline. Improvement in pruritus was rapid; divergence between dupilumab+TCS and placebo+TCS was significant by Week 2. By significantly improving a wide range of AD symptoms (including pruritus, pain/discomfort, and sleep), as well as aspects of mental health and HRQOL, dupilumab+TCS improved not only skin

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lesions but also the broader burden associated with moderate-to-severe AD in this patient population, consistent with previous studies.[42–47]

The choice of TCS background therapy as a control was consistent with European guidelines for patients eligible for systemic CsA,[10,11,15] and reflects real-world practice. Patients receiving placebo+TCS used significantly more background TCS and rescue medication than the dupilumab+TCS groups, another indicator of better disease control with dupilumab+TCS compared with background TCS alone.

Several factors may help to account for the effect of placebo+TCS treatment on efficacy. Some "placebo+TCS effect" may appear because of the natural waxing and waning clinical course of AD. In addition, the protocol requirement for patients with inadequate response to TCS is not the same as no response to TCS. As noted, patients in the placebo group applied TCS and emollients in a continuous manner in a controlled setting under the supervision of a principal investigator. This alone may be responsible for an approximate 10% improvement in the percent change in EASI score, as can be seen by comparing the Week 16 placebo response in LIBERTY AD CHRONOS (−48.4%)[46] to the Week 16 response in the monotherapy LIBERTY AD SOLO 1 (−37.6%) and LIBERTY AD SOLO 2 (−30.9%) trials.[45] The effect would be expected to be greater in a trial requiring continuous use of TCS (unlike CHRONOS, in which patients could stop TCS if their lesions cleared). This suggests that even patients who were candidates for systemic therapy could still obtain some benefit of continuous treatment with TCS. Nonetheless, in CAFÉ the significantly greater efficacy of dupilumab+TCS compared with placebo+TCS demonstrates that dupilumab provides clinically meaningful improvement over any improvement provided by background therapy with TCS in this patient population.

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Treatment groups had similar overall rates of AEs and SAEs; no new safety signals were identified. Dupilumab+TCS was not associated with increased overall risk of infections. Conjunctivitis and injection-site reactions were more frequent with dupilumab+TCS, while skin infections and AD exacerbations were more frequent with placebo+TCS, consistent with previous studies of dupilumab in AD.[42,43,45,46] Decreased incidence of non-herpetic skin infections in dupilumab-treated patients in this study, as in previous studies, adds to the body of evidence suggesting that dupilumab may restore skin barrier function.

Conjunctivitis rates in this study, especially MedRA PTs of conjunctivitis and allergic conjunctivitis, were higher in all treatment groups compared to previous studies.[43,45,46] In addition, more patients in this study reported a history of allergic conjunctivitis at baseline (36.4%, 41.1%, and 54.6% [dupilumab qw+TCS, q2w+TCS, and placebo+TCS, respectively]) compared to previous studies (e.g. LIBERTY AD CHRONOS, 21.6–28.2%).[43,45,46] This may partly be due to an increased awareness of conjunctivitis following publication of previous studies, as well as the regional distribution of study sites (most patients were from Germany and Poland), compared with previous studies, which were conducted not only in Europe, but also in countries from North America and Asia-Pacific. However, most conjunctivitis events were of mild or moderate severity and resolved while patients were still on treatment. No patient withdrew from study treatment because of an AE of conjunctivitis. Interestingly, dupilumab is not associated with increased conjunctivitis rates in studies in other diseases, including asthma[48–50] and CRsNP,[51] suggesting that the increased rates of conjunctivitis in AD studies may reflect a unique interaction between AD- and dupilumab-related mechanisms. Further evaluations of conjunctivitis are ongoing to better characterize the etiology, clinical features, and most effective treatments.

As a chronic disease, AD requires long-term treatment options. In the present study, dupilumab+TCS was evaluated for 16 weeks. Safety and efficacy of dupilumab+TCS in the present study are similar to those observed at 52 weeks in a subset of patients in the CHRONOS study (n/N=126/623) with

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baseline characteristics similar to the patient population in the present study.[46,61] Safety of dupilumab beyond 1 year is being evaluated in the open-label extension study.

Oral CsA is a broad immunosuppressant prescribed for patients with severe AD whose disease warrants systemic treatment. While it may be effective in the short term in patients with severe AD, use of CsA is limited because of the risk of several types of side effects, and the label restricts use to one year.[20–38] In addition, cessation of CsA treatment can lead to disease rebound, which is difficult to manage. Concern about these issues has led to reluctance among some physicians to initiate CsA therapy. The data from this 16-week clinical trial show that dupilumab is highly efficacious and well tolerated among patients not adequately controlled with or intolerant to CsA, or when this treatment is medically inadvisable, giving physicians an important new treatment option. No blood monitoring is required for dupilumab;[40,41] however, blood monitoring may be required in some regions based on local guidelines.

This study had limitations. It was not designed to compare the two dupilumab dose regimens; however, results were similar for both regimens. In addition, the study was not designed to compare the CsA-experienced and CsA-naive subgroups. In both subgroups, patients had been considered for CsA treatment, but CsA-naive patients did not receive CsA because it was considered medically inadvisable (e.g. due to pre-existing hypertension, or use of statins).

In conclusion, 16 weeks of dupilumab+TCS compared with placebo+TCS significantly improved signs and symptoms of AD and HRQOL, reduced use of concomitant TCS and rescue medications, and had an acceptable safety profile in adults with AD with history of inadequate response or intolerance to CsA, or for whom CsA was medically inadvisable. These data support the use of dupilumab+TCS as a targeted biologic therapy in this difficult-to-treat population.

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Table 1. Baseline demographics and disease characteristics

	Placebo+TCS (n=108)	**Dupilumab q2w+TCS (n=107)**	**Dupilumab qw+TCS (n=110)**
Age, median (IQR), years	37.5 (29.0–49.0)	38.0 (25.0–47.0)	38.0 (29.0–48.0)
Race, n (%)			
White	104 (96.3)	104 (97.2)	105 (95.5)
Asian	2 (1.9)	2 (1.9)	2 (1.8)
Black	0	0	2 (1.8)
Other	2 (1.9)	0	1 (0.9)
Not reported/missing	0	1 (0.9)	0
Male, n (%)	68 (63.0)	65 (60.7)	66 (60.0)
Duration of AD, median (IQR), years	28.5 (19.5–40.0)	29.0 (19.0–43.0)	32.0 (21.0–42.0)
EASI score, median (IQR)	31.7 (24.2–40.7)	31.6 (25.2–39.2)	31.1 (24.5–39.0)
IGA score			
Median (IQR)	3.0 (3.0–4.0)	3.0 (3.0–4.0)	3.0 (3.0–4.0)
Patients with IGA 4 (severe), n (%)	52 (48.1)	50 (46.7)	52 (47.3)
Peak weekly averaged pruritus NRS, median (IQR)	6.9 (4.9–8.1)	7.0 (5.4–8.0)	6.4 (5.2–7.7)
BSA, median (IQR)	53.0 (38.3–69.3)	55.0 (44.0–66.0)	55.8 (41.5–68.0)
SCORAD score, median (IQR)	67.5 (58.5–76.6)	66.7 (61.1–76.2)	66.1 (55.4–75.4)
DLQI total score, median (IQR)	13.0 (7.0–19.5)	14.0 (8.0–22.0)	13.0 (7.0–21.0)
POEM score, median (IQR)	19.0 (14.0–24.0)	20.0 (15.0–24.0)	19.0 (14.0–24.0)
HADS total score, median (IQR)	13.0 (6.0–18.5)	13.0 (6.0–19.0)	12.0 (6.0–19.0)

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	Placebo+TCS (n=108)	Dupilumab q2w+TCS (n=107)	Dupilumab qw+TCS (n=110)
GISS, median (IQR)	9.0 (8.0–11.0)	9.0 (8.0–11.0)	9.0 (8.0–10.0)
EQ5D-pain/discomfort, n (%)			
I have no pain/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 sleep VAS, median (IQR)	3.8 (1.4–7.0)	4.5 (1.6–7.6)	4.25 (1.3–7.2)
POEM item 2: in last week nights sleep has been disturbed, n (%)			
Number of patients reporting	107	107	110
0=no Days	12 (11.2)	17 (15.9)	24 (21.8)
1=1–2 Days	35 (32.7)	24 (22.4)	19 (17.3)
2=3–4 Days	19 (17.8)	21 (19.6)	15 (13.6)
3=5–6 Days	18 (16.8)	12 (11.2)	22 (20.0)
4=every Day	23 (21.5)	33 (30.8)	30 (27.3)
Atopic/allergic conditions, n (%)			
Food allergy	41 (38.0)	51 (47.7)	54 (49.1)
Other allergy*	71 (65.7)	76 (71.0)	76 (69.1)
Allergic rhinitis	61 (56.5)	60 (56.1)	63 (57.3)
Allergic conjunctivitis	59 (54.6)	44 (41.1)	40 (36.4)
Asthma	50 (46.3)	41 (38.3)	44 (40.0)
Chronic rhinosinusitis	10 (9.3)	7 (6.5)	8 (7.3)
Urticaria	9 (8.3)	8 (7.5)	10 (9.1)
Atopic keratoconjunctivitis	6 (5.6)	8 (7.5)	11 (10.0)
Nasal polyps	6 (5.6)	0	9 (8.2)
Eosinophilic oesophagitis	0	1 (0.9)	1 (0.9)

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	Placebo+TCS (n=108)	Dupilumab q2w+TCS (n=107)	Dupilumab qw+TCS (n=110)
Previous use of systemic immunosuppressants for AD, n (%)†	84 (77.8)	84 (78.5)	84 (76.4)
Previous use of MTX, n (%)	7 (6.5)	10 (9.3)	13 (11.8)
Previous use of AZA, n (%)	6 (5.6)	7 (6.5)	13 (11.8)
CsA exposure, n (%)			
Yes	72 (66.7)	69 (64.5)	69 (62.7)
Reasons for stopping the most recent CsA treatment			
CsA worked well	2 (2.8)	4 (5.8)	2 (2.9)
Inadequate efficacy	35 (48.6)	40 (58.0)	38 (55.1)
Because of important side effects	45 (62.5)	32 (46.4)	34 (49.3)
To avoid important side effects	7 (9.7)	5 (7.2)	7 (10.1)
Patient intolerance, discomfort, or inconvenience	9 (12.5)	9 (13.0)	12 (17.4)
Other	4 (5.6)	9 (13.0)	8 (11.6)
Unknown	1 (1.4)	0	0
No	36 (33.3)	38 (35.5)	41 (37.3)
Reasons for no prior CsA			
Medical contraindication	27 (75.0)	27 (71.1)	24 (58.5)
Treatment with CsA is otherwise inappropriate	12 (33.3)	14 (36.8)	15 (36.6)
Risk of important side effects is generally too high	5 (13.9)	5 (13.2)	6 (14.6)
CsA treatment is difficult to manage	0	0	1 (2.4)
Other	1 (2.8)	3 (7.9)	1 (2.4)

*Includes allergies to medications, animals, plants, mould, dust mites, and other. †Patients may have used more than one type of immunosuppressant prior to study entry. AZA, azathioprine; BSA, body

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surface area; CsA, ciclosporin A; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; EQ-5D, 5-dimension EuroQoL scale; HADS, Hospital Anxiety and Depression Scale; IGA, Investigator's Global Assessment; IQR, interquartile range; MTX, methotrexate; NRS, numerical rating scale; q2w, every 2 weeks; qw, weekly; SCORAD, SCORing atopic dermatitis; SD, standard deviation; TCS, topical corticosteroids; VAS, visual analogue scale of 0–10 (higher numbers represent worse scores).

Table 2. Efficacy outcomes.

	Placebo+TCS (n=108)	**Dupilumab q2w+TCS (n=107)**	**Dupilumab qw+TCS (n=110)**
Primary efficacy outcome			
Proportion of patients who achieved EASI-75 at Week 16, n (%)	32 (29.6)	67 (62.6)*	65 (59.1)*
Secondary efficacy outcomes			
EASI score: LS mean percent change from baseline at Week 16, % (SE)	−46.6% (2.76)	−79.8% (2.59)*	−78.2% (2.55)*
Weekly average of peak pruritus NRS score: LS mean percent change from baseline at Week 16, % (SE)	−25.4% (3.39)	−53.9% (3.14)*	−51.7% (3.09)*
SCORAD score: LS mean percent change from baseline at Week 16 (SE)	−29.5 (2.55)	−62.4 (2.48)*	−58.3 (2.45)*
Weekly average of peak pruritus NRS score: proportion of patients who achieved improvement (reduction) ≥4-point from baseline to Week 16, n/N1 (%)‡	13/91 (14.3)	43/94 (45.7)*	38/94 (40.4)*
Percent BSA affected: LS mean change from baseline at Week 16 (SE)	−19.6 (1.80)	−39.2 (1.72)*	−37.5 (1.69)*
IGA: Proportion of patients who achieved both IGA 0 or 1 and reduction from baseline of ≥2 points at Week 16, n (%)	15 (13.9)	43 (40.2)*	43 (39.1)*
DLQI: LS mean change from baseline (SE)	−4.5 (0.49)	−9.5 (0.46)*	−8.8 (0.45)*

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	Placebo+TCS (n=108)	Dupilumab q2w+TCS (n=107)	Dupilumab qw+TCS (n=110)
POEM: LS mean change from baseline (SE)	−4.3 (0.62)	−11.9 (0.60)*	−11.4 (0.59)*
Proportion of patients with prior history of CsA who achieved EASI-75 at Week 16, n (%)	19 (26.4)	40 (58.0)†	39 (56.5)†
Mean weekly dose (g) of TCS use (SE)	25.1 (1.48)	15.0 (1.51)*	17.5 (1.49)†
HADS: LS mean change from baseline (SE)	−2.3 (0.56)	−6.1 (0.54)*	−5.2 (0.53)†
Other secondary efficacy outcomes			
Proportion of patients who achieved SCORAD-50 at Week 16, n (%)	28 (25.9)	71 (66.4)*	61 (55.5)*
GISS: LS mean change from baseline at Week 16 (SE)	−29.0 (2.75)	−55.2 (2.66)*	−53.3 (2.65)*
Weekly average of peak pruritus NRS score: LS mean percent change from baseline at Week 2, % (SE)	−10.0% (2.24)	−17.2% (2.25)§	−19.7% (2.21)¶
Post hoc efficacy outcomes‖			
Proportion of patients who achieved EASI-50 at Week 16, n (%)	47 (43.5)	91 (85.0)*	94 (85.5)*
Proportion of patients who achieved EASI-90 at Week 16, n (%)	13 (12.0)	49 (45.8)*	41 (37.3)*
Proportion of patients with ≥4-point improvement in DLQI score at Week 16, n/N2 (%)	42/95 (44.2)	85/97 (87.6)*	77/99 (77.8)*
Proportion of patients with ≥4-point improvement in POEM score at Week 16, n/N3 (%)	45/107 (42.1)	89/106 (84.0)*	84/109 (77.1)*
Proportion of patients with HADS-A and HADS-D <8, n/N4 (%)	22/60 (36.7)	35/56 (62.5)¶	26/56 (46.4)NS
EQ-5D item 4 (pain/discomfort): proportion of patients reporting “no problem” at Week 16, n (%)	40 (37.0)	75 (70.1)*	69 (62.7)†

*P<0.0001 vs placebo+TCS; †P<0.001 vs placebo+TCS; ‡analysis was conducted in the population of patients with peak pruritus NRS score ≥4 at baseline; §P<0.05 vs placebo+TCS; ¶P<0.01 vs

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placebo+TCS; ‖all *P*-values for po st hoc outcomes are nominal. BSA, body surface area; CsA, ciclosporin A; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; EASI-50, ≥50% improvement from baseline in EASI score; EASI-75, ≥75% improvement from baseline in EASI score; EASI-90, ≥90% improvement from baseline in EASI score; EQ-5D, 5-dimension EuroQoL scale; HADS, Hospital Anxiety and Depression Scale; IGA, Investigator's Global Assessment; LS, least squares; N1, number of patients with peak pruritus NRS score ≥4 at baseline; N2, number of patients with DLQI score ≥4 at baseline; N3, number of patients with POEM score ≥4 at baseline; N4, number of patients with HADS anxiety (HADS-A) or depression (HADS-D) ≥8 at baseline; NRS, numerical rating scale; NS, not significant; POEM, Patient Oriented Eczema Measure; q2w, every 2 weeks; qw, weekly; SCORAD, Scoring Atopic Dermatitis; SCORAD-50, ≥50% improvement from baseline in SCORAD score; SE, standard error; TCS, topical corticosteroids; VAS, visual analogue scale of 0–10 (higher numbers represent worse scores).

Table 3. Use of rescue medication during the study

	Placebo+TCS (n=108)	**Dupilumab q2w+TCS (n=107)**	**Dupilumab qw+TCS (n=110)**
Patients requiring ≥1 rescue medication, n (%)	19 (17.6)	4 (3.7)	5 (4.5)
TCS	16 (14.8)	3 (2.8)	4 (3.6)
Potent (group III)	11 (10.2)	3 (2.8)	2 (1.8)
Very potent (group IV)	7 (6.5)	0	2 (1.8)
Immunosuppressants	3 (2.8)	0	1 (0.9)
Oral CsA	3 (2.8)	0	0
Selective immunosuppressants	0	0	1 (0.9)
Non-TCS topical preparations (e.g. TCI)	0	1 (0.9)	0
Systemic glucocorticoids	2 (1.9)	0	0

CsA, ciclosporin A; q2w, every 2 weeks; qw, weekly; TCI, topical calcineurin inhibitors; TCS, topical corticosteroids.

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Table 4. Adverse events

Number (%) of patients with	**Placebo+TCS (n=108)**	**Dupilumab q2w+TCS (n=107)**	**Dupilumab qw+TCS (n=110)**
≥1 AE	75 (69.4)	77 (72.0)	76 (69.1)
Any drug-related AE	20 (18.5)	36 (33.6)	37 (33.6)
Any AE causing discontinuation of study drug permanently	1 (0.9)	0	2 (1.8)
Any death	0	0	0
Any SAE*	2 (1.9)	2 (1.9)	2 (1.8)
Any drug-related SAE	0	0	0
Any SAE causing discontinuation of study drug permanently	0	0	1 (0.9)
AEs (MedDRA PTs) reported by ≥2% of patients in any treatment group			
Infections and infestations†	44 (40.7)	49 (45.8)	47 (42.7)
Nasopharyngitis‡	18 (16.7)	22 (20.6)	17 (15.5)
Conjunctivitis‡	3 (2.8)	12 (11.2)	8 (7.3)
Oral herpes‡	0	3 (2.8)	5 (4.5)
Gastroenteritis‡	1 (0.9)	2 (1.9)	3 (2.7)
Respiratory tract infection viral‡	1 (0.9)	0	4 (3.6)
Upper respiratory tract infection‡	1 (0.9)	1 (0.9)	3 (2.7)
Pharyngitis‡	3 (2.8)	1 (0.9)	2 (1.8)
Respiratory tract infection‡	0	0	3 (2.7)
Herpes simplex‡	3 (2.8)	1 (0.9)	1 (0.9)
Skin and subcutaneous tissue disorders†	21 (19.4)	22 (20.6)	21 (19.1)
Dermatitis atopic‡	16 (14.8)	8 (7.5)	9 (8.2)
Eye disorders†	15 (13.9)	21 (19.6)	18 (16.4)
Allergic conjunctivitis‡	7 (6.5)	16 (15.0)	10 (9.1)
Lacrimation increased‡	1 (0.9)	1 (0.9)	3 (2.7)
Eye pruritus‡	0	0	3 (2.7)
General disorders and administration site conditions†	12 (11.1)	9 (8.4)	21 (19.1)

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Number (%) of patients with	**Placebo+TCS (n=108)**	**Dupilumab q2w+TCS (n=107)**	**Dupilumab qw+TCS (n=110)**
Fatigue‡	1 (0.9)	4 (3.7)	3 (2.7)
Injection-site reaction‡	0	1 (0.9)	4 (3.6)
Injection-site erythema‡	1 (0.9)	1 (0.9)	3 (2.7)
Injection-site swelling‡	1 (0.9)	0	3 (2.7)
Oedema peripheral‡	3 (2.8)	0	2 (1.8)
Nervous system disorders†	12 (11.1)	14 (13.1)	14 (12.7)
Headache‡	9 (8.3)	10 (9.3)	10 (9.1)
Respiratory, thoracic, and mediastinal disorders†	14 (13.0)	14 (13.1)	14 (12.7)
Rhinitis allergic‡	1 (0.9)	7 (6.5)	4 (3.6)
Cough‡	1 (0.9)	4 (3.7)	3 (2.7)
Oropharyngeal pain‡	2 (1.9)	3 (2.8)	1 (0.9)
Rhinorrhoea‡	3 (2.8)	0	3 (2.7)
Asthma‡	3 (2.8)	1 (0.9)	1 (0.9)
Gastrointestinal disorders†	16 (14.8)	9 (8.4)	9 (8.2)
Diarrhoea‡	2 (1.9)	3 (2.8)	2 (1.8)
Abdominal pain‡	4 (3.7)	0	4 (3.6)
Musculoskeletal and connective tissue disorders†	12 (11.1)	4 (3.7)	10 (9.1)
Myalgia‡	0	0	4 (3.6)
Back pain‡	3 (2.8)	1 (0.9)	2 (1.8)
Vascular disorders†	1 (0.9)	4 (3.7)	3 (2.7)
Hypertension‡	1 (0.9)	1 (0.9)	3 (2.7)
Blood and lymphatic system disorders†	4 (3.7)	4 (3.7)	1 (0.9)
Lymphadenopathy‡	4 (3.7)	2 (1.9)	0
Skin infections (adjudicated; excluding herpetic infections)	9 (8.3)	2 (1.9)	4 (3.6)
Treatment-emergent conjunctivitis, n (%)	12 (11.1)	30 (28.0)	18 (16.4)
Conjunctivitis	3 (2.8)	12 (11.2)	8 (7.3)
Conjunctivitis allergic	7 (6.5)	16 (15.0)	10 (9.1)

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Number (%) of patients with	**Placebo+TCS (n=108)**	**Dupilumab q2w+TCS (n=107)**	**Dupilumab qw+TCS (n=110)**
Adenovirus conjunctivitis	0	1 (0.9)	0
Conjunctivitis bacterial	2 (1.9)	1 (0.9)	0
Conjunctivitis viral	1 (0.9)	1 (0.9)	0

*SAEs were acute pancreatitis and hepatotoxicity (1 patient each in the dupilumab q2w+TCS group), ureteric calculus and AD (1 patient each in the dupilumab qw+TCS group), and hemiparesis and emphysema (1 patient each in the placebo+TCS group). †MedDRA SOC; SOCs listed are those for which at least 1 associated PT was reported in ≥2% of patients in any treatment group. ‡MedDRA PT. AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; q2w, every 2 weeks; qw, weekly; SAE, serious AE; SOC, system organ class; TCS, topical corticosteroids.

Figure legends

Fig 1. Study design.

[a]Dupilumab 600 mg or matching placebo. [b]Patients were required to use TCS for the entire treatment period. CsA, ciclosporin A; q2w, every 2 weeks; qw, weekly; R, randomization (1:1:1); SC, subcutaneous; TCS, topical corticosteroids.

Fig 2. (a) Proportion of patients achieving EASI-75 (primary endpoint); (b) Proportion of patients achieving EASI-50; (c) Proportion of patients achieving EASI-90; (d) Proportion of patients with prior CsA use achieving EASI-75.

CsA, ciclosporin A; EASI, Eczema Area and Severity Index; EASI-50, ≥50% improvement in EASI score; EASI-75, ≥75% improvement in EASI score; EASI-90, ≥90% improvement in EASI score; q2w, every 2 weeks; qw, weekly; TCS, topical corticosteroids.

Fig 3. (a) EASI: LS mean percent change from baseline, multiple imputation with censoring after rescue treatment use; (b) SCORAD: LS mean percent change from baseline, multiple imputation with censoring after rescue treatment use

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Error bars are ±SE. EASI, Eczema Area and Severity Index; LS, least squares; MI, multiple imputation; q2w, every 2 weeks; qw, weekly; SCORAD, SCORing Atopic Dermatitis; SD, standard deviation; SE, standard error; TCS, topical corticosteroids.

Fig 4. Weekly average of peak pruritus NRS: (a) LS mean percent change from baseline, multiple imputation with censoring after rescue treatment use; (b) proportion of patients achieving ≥4-point reduction (improvement) from baseline

Error bars are ±SE. LS, least squares; MI, multiple imputation; NRS, numerical rating scale; q2w, every 2 weeks; qw, weekly; SD, standard deviation; SE, standard error; TCS, topical corticosteroids.

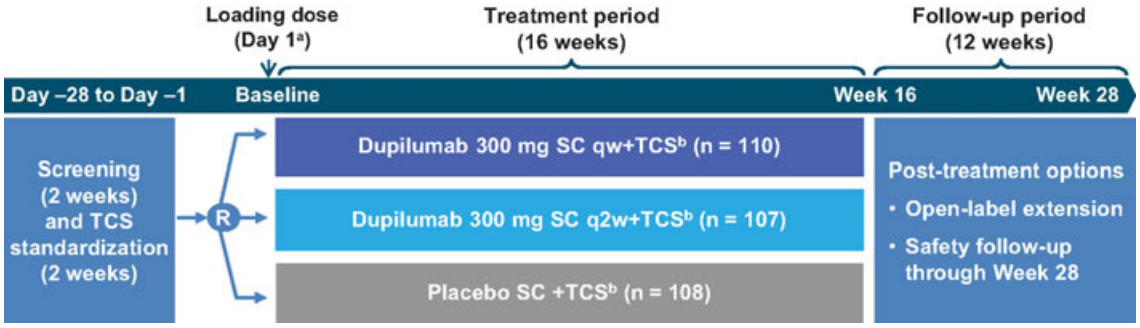
Fig 5. (a) DLQI: proportion of patients achieving ≥4-point reduction (improvement) from baseline (among patients with DLQI ≥4 at baseline); (b) POEM: proportion of patients achieving ≥4-point reduction (improvement) from baseline (among patients with POEM ≥4 at baseline); and (c) proportion of patients with HADS anxiety (HADS-A) and depression (HADS-D) <8 at Week 16 among patients with HADS-A or HADS-D ≥8 at baseline

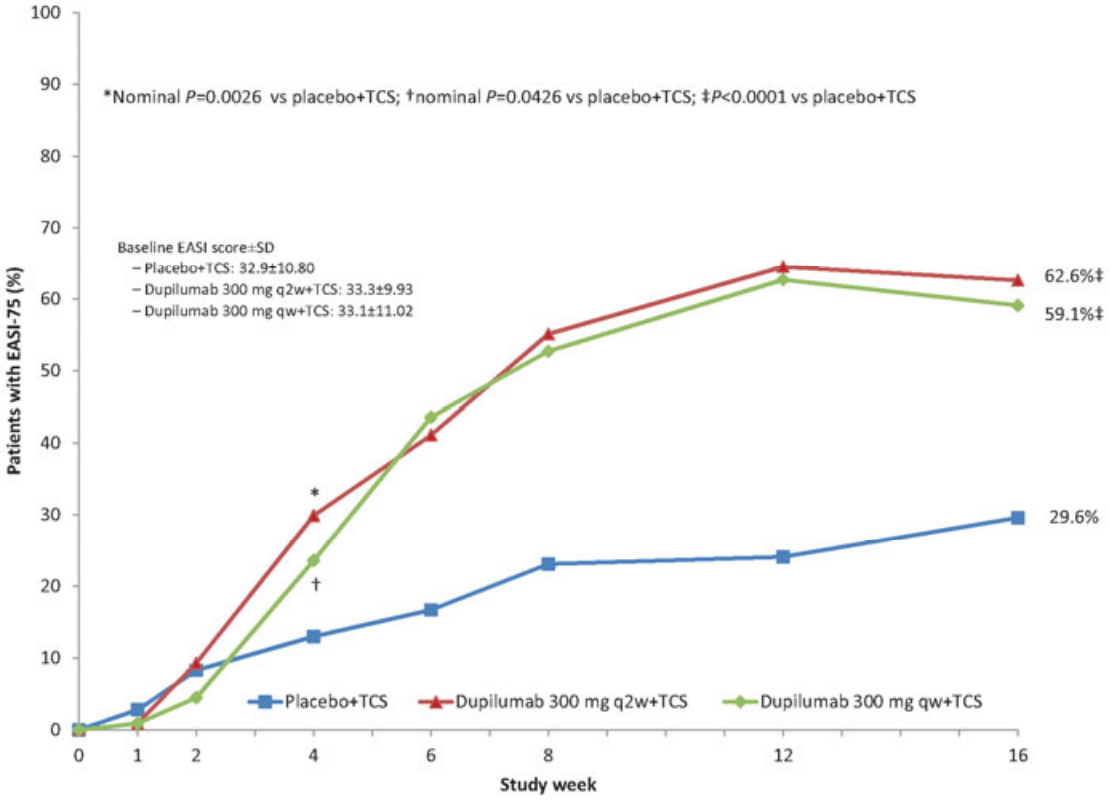
DLQI, Dermatology Life Quality Index; HADS, Hospital Anxiety and Depression Scale; POEM, Patient-Oriented Eczema Score; q2w, every 2 weeks; qw, weekly; SE, standard error; TCS, topical corticosteroids.

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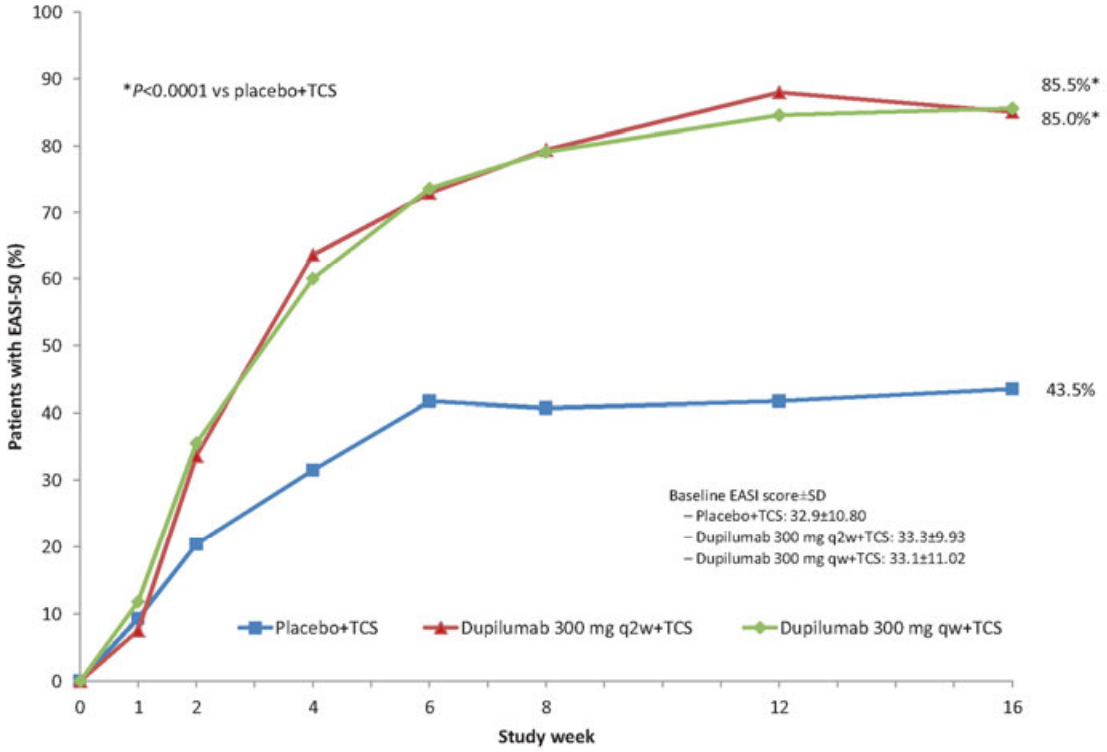
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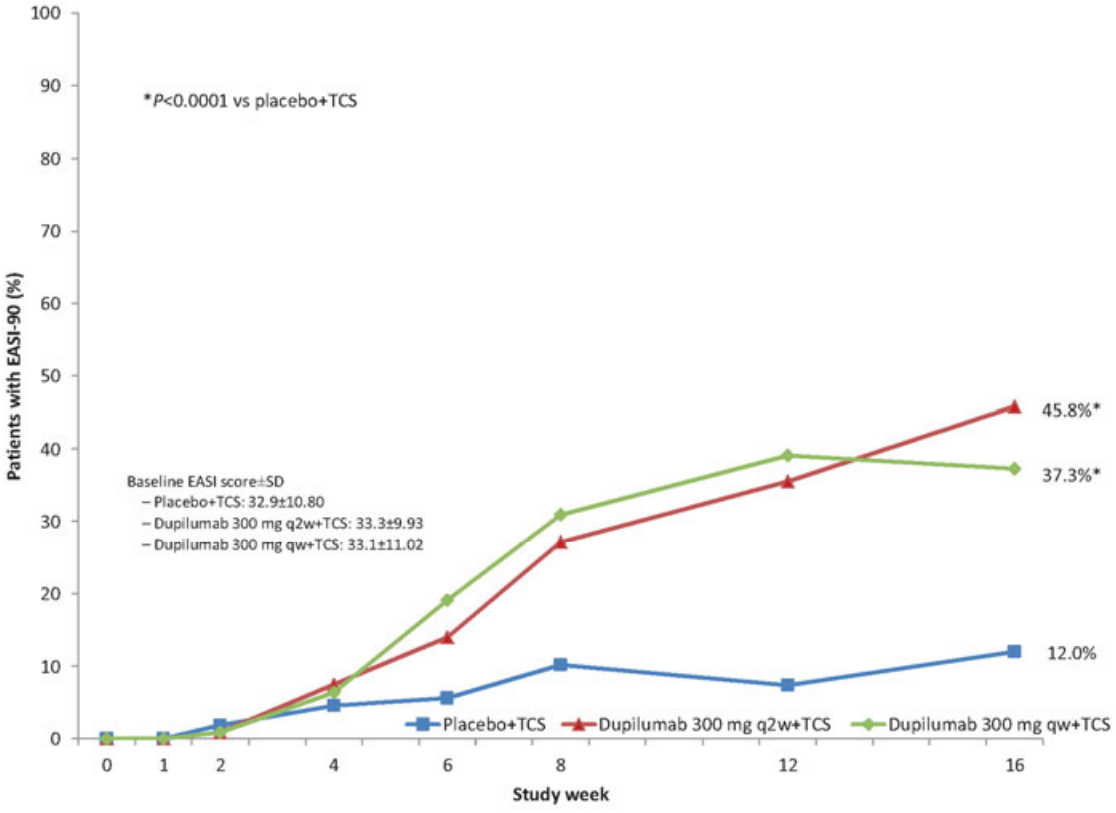




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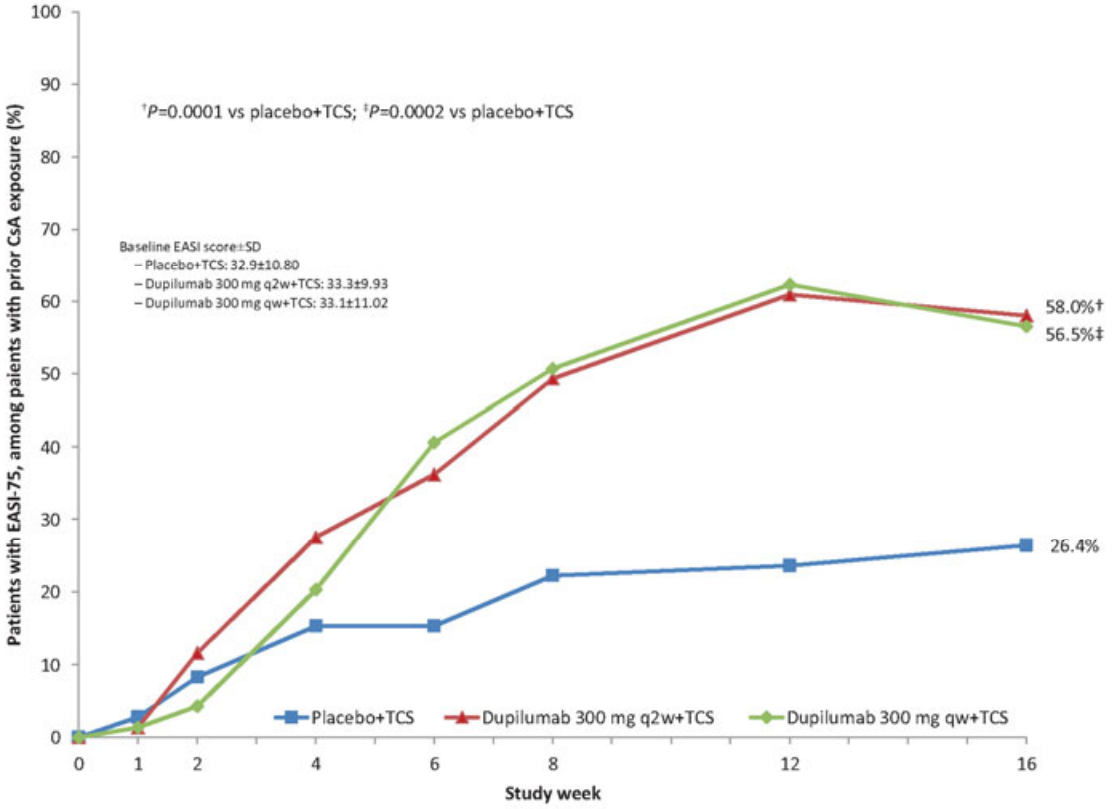
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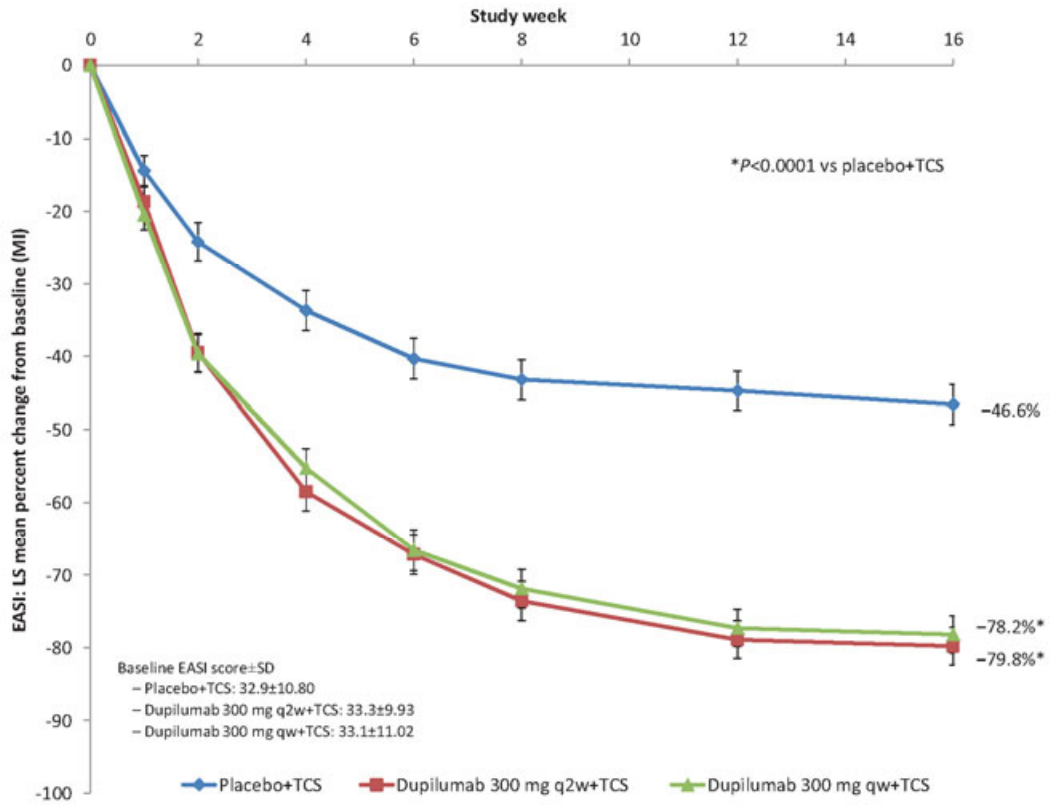




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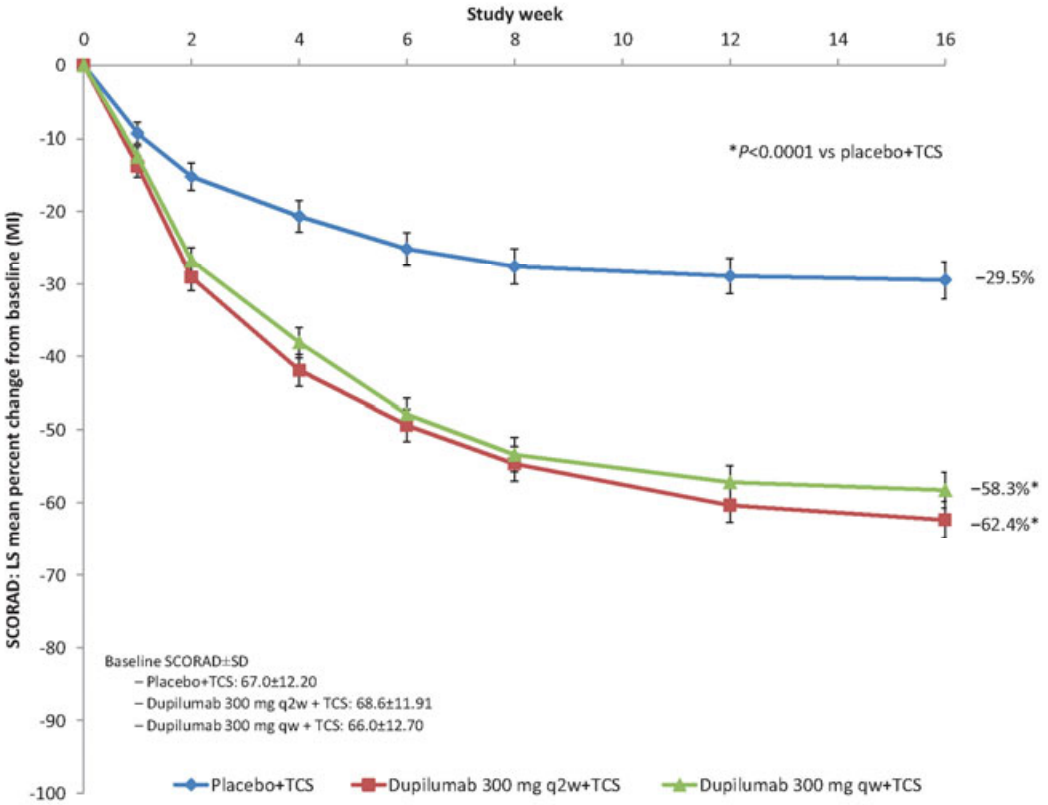
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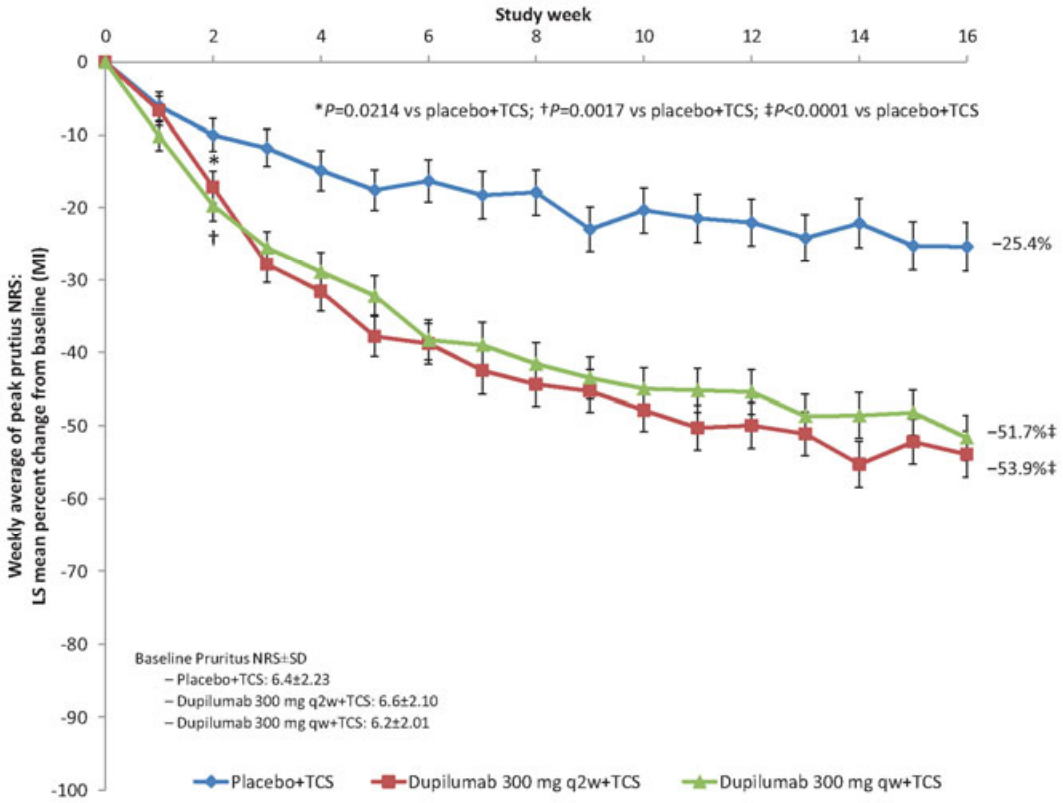
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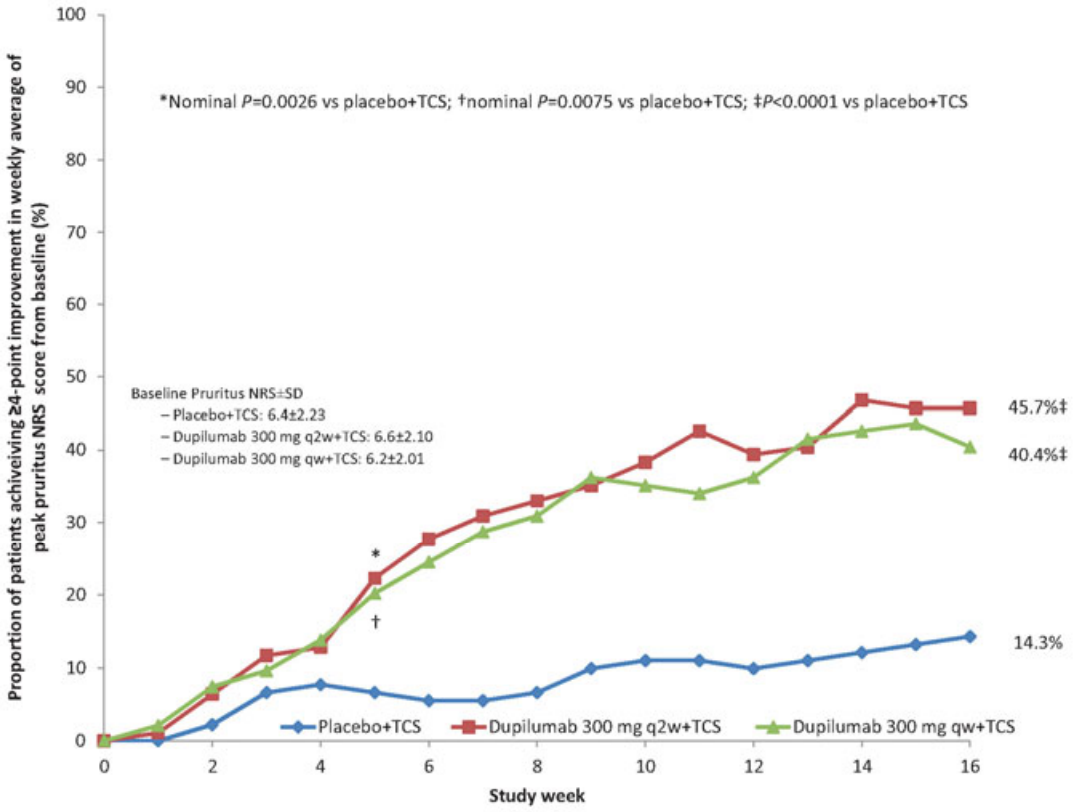
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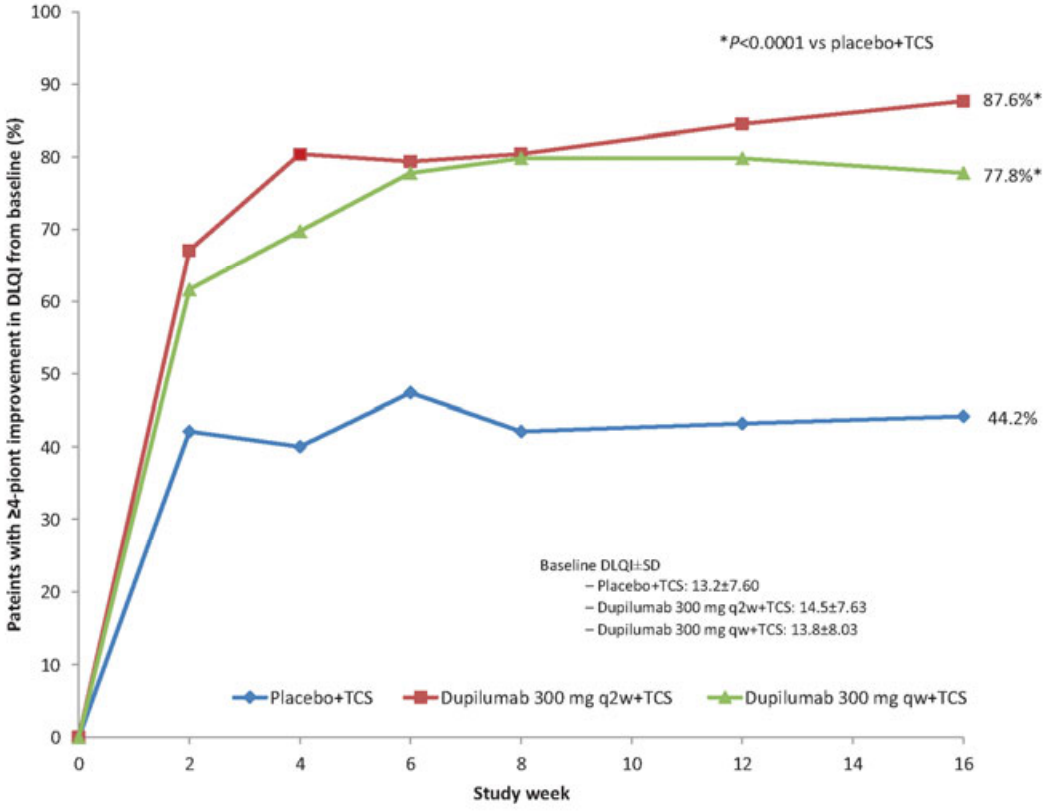
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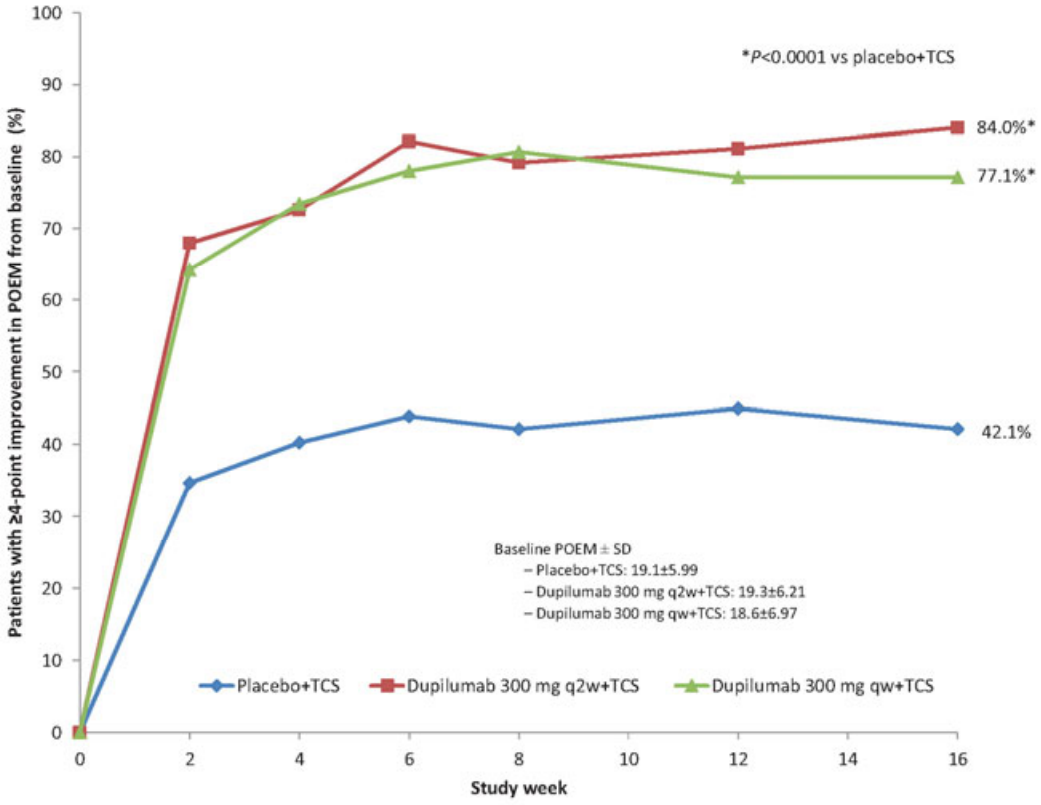
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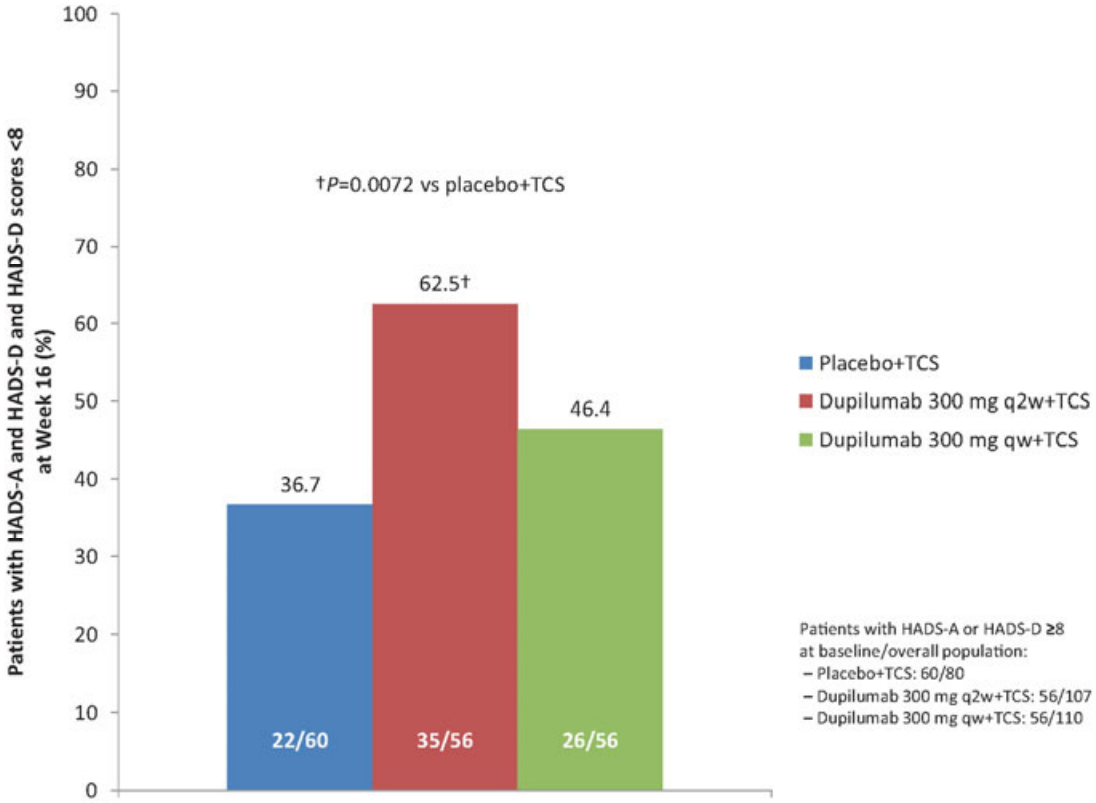
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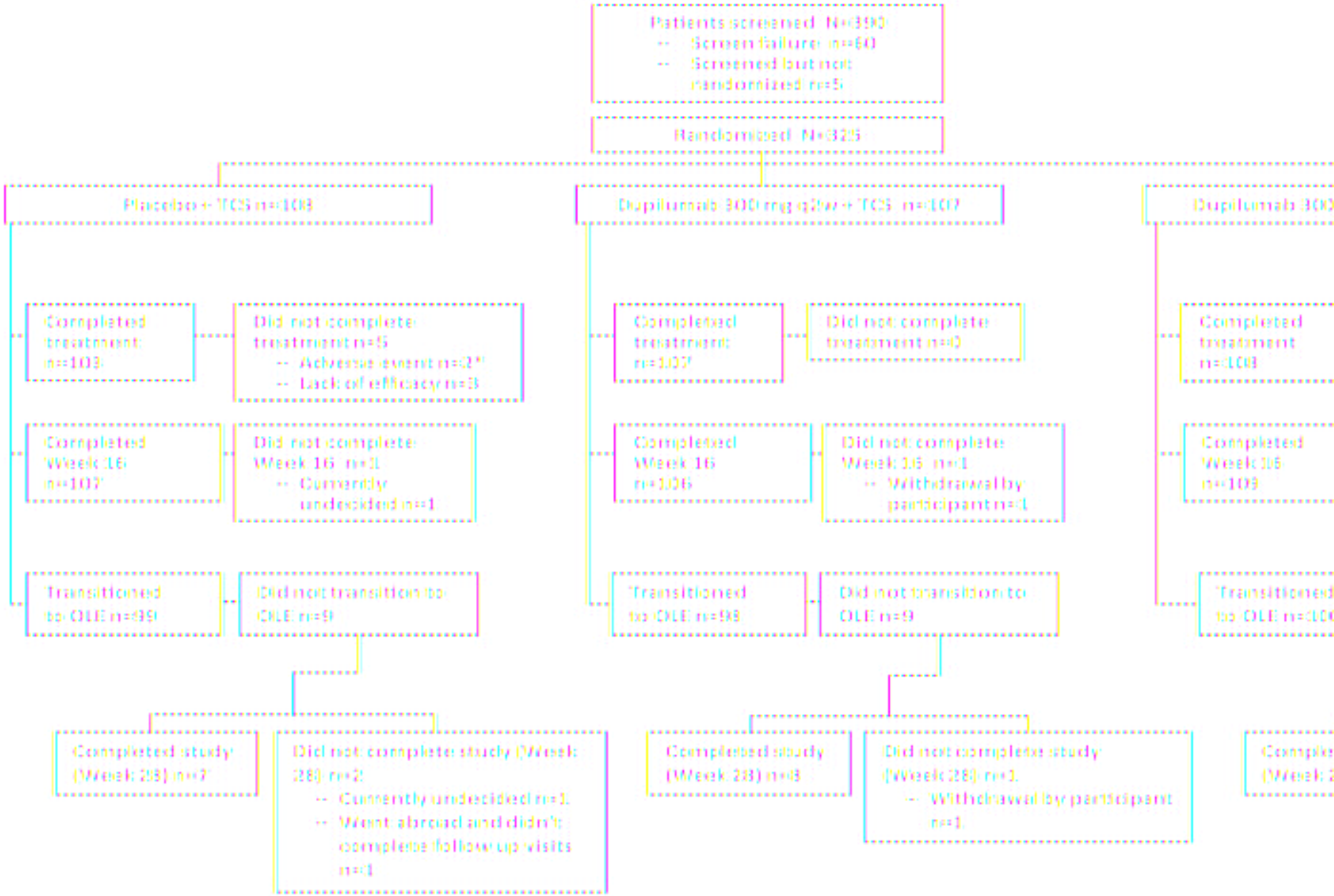


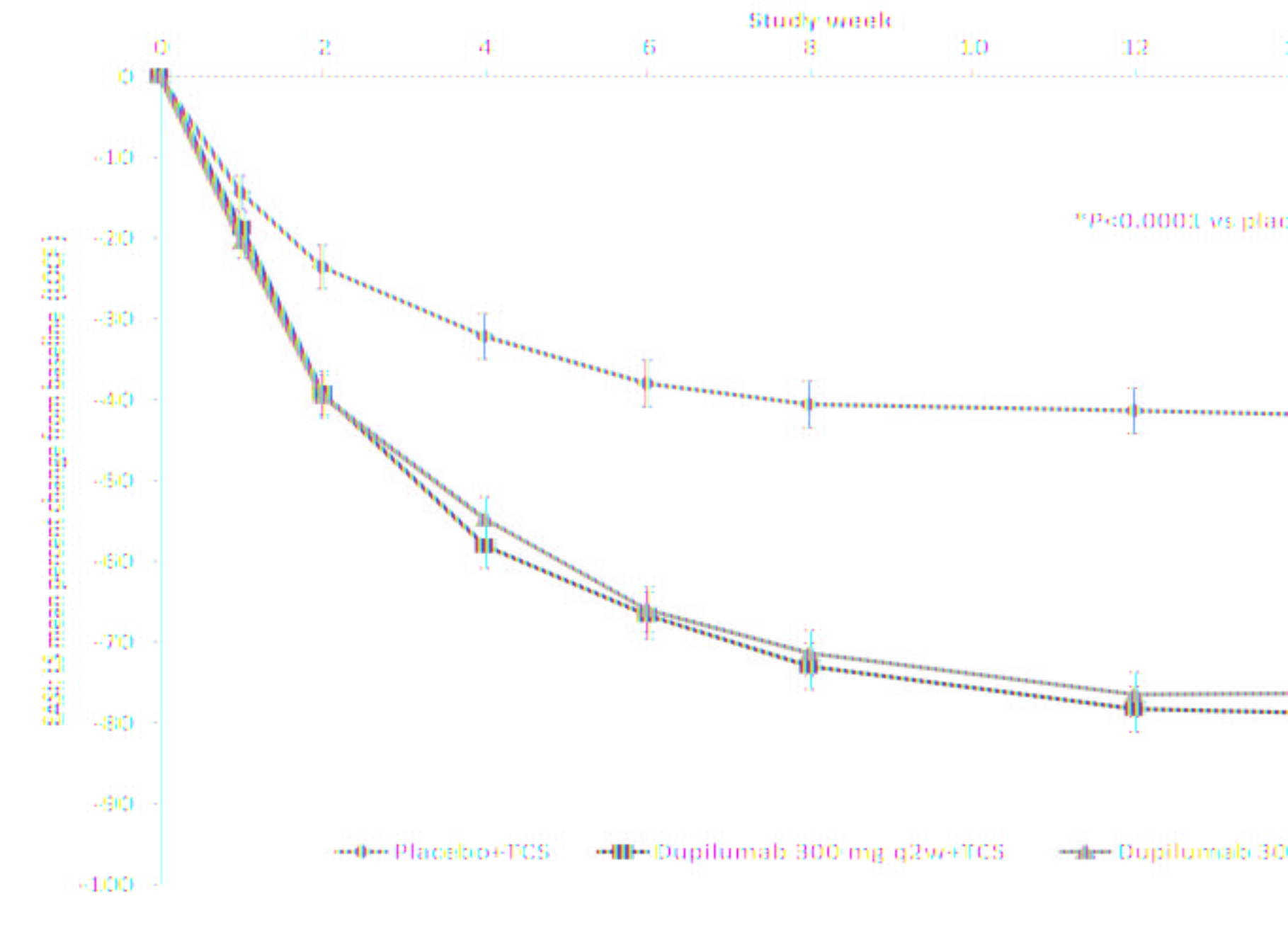
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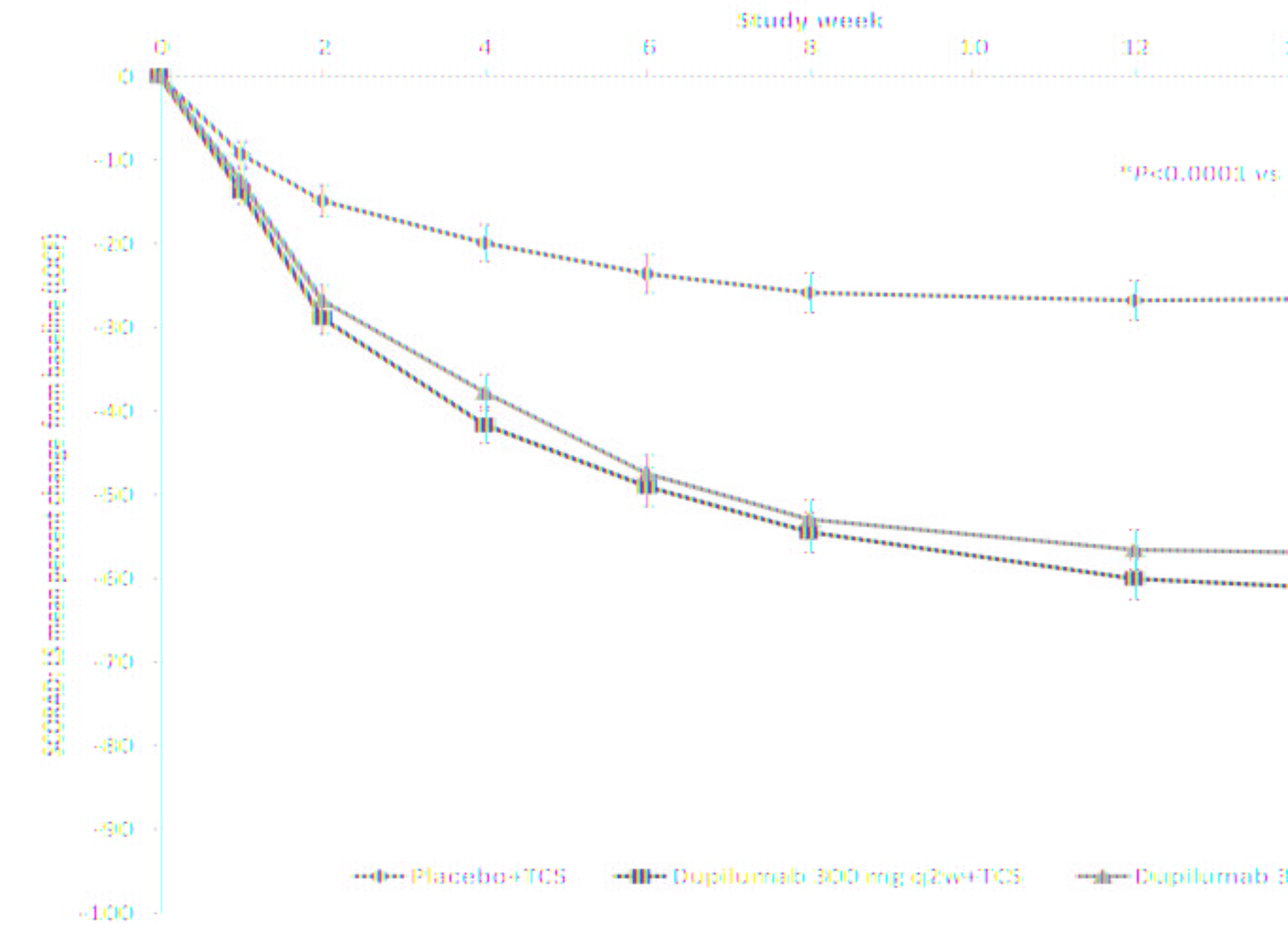
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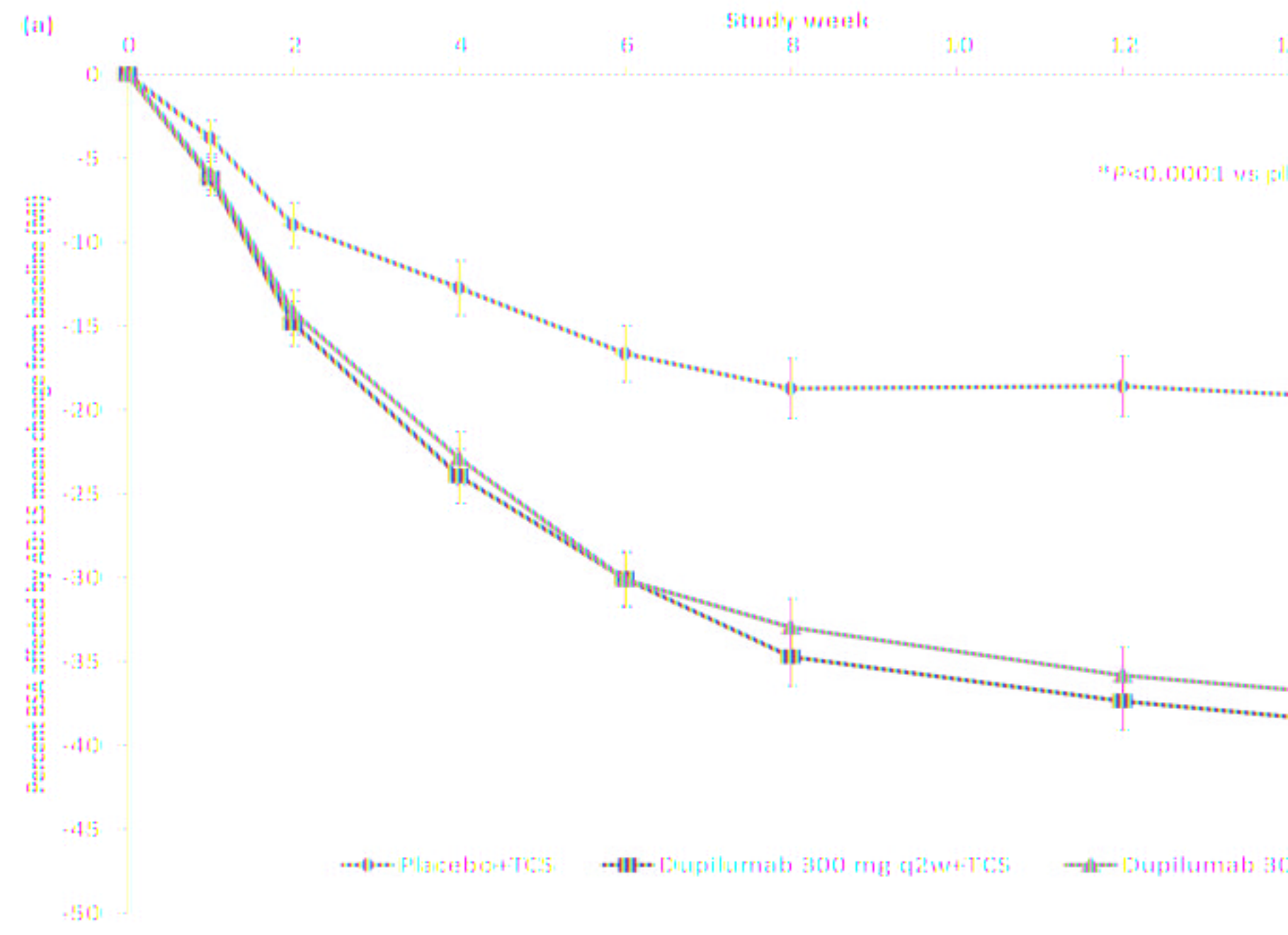


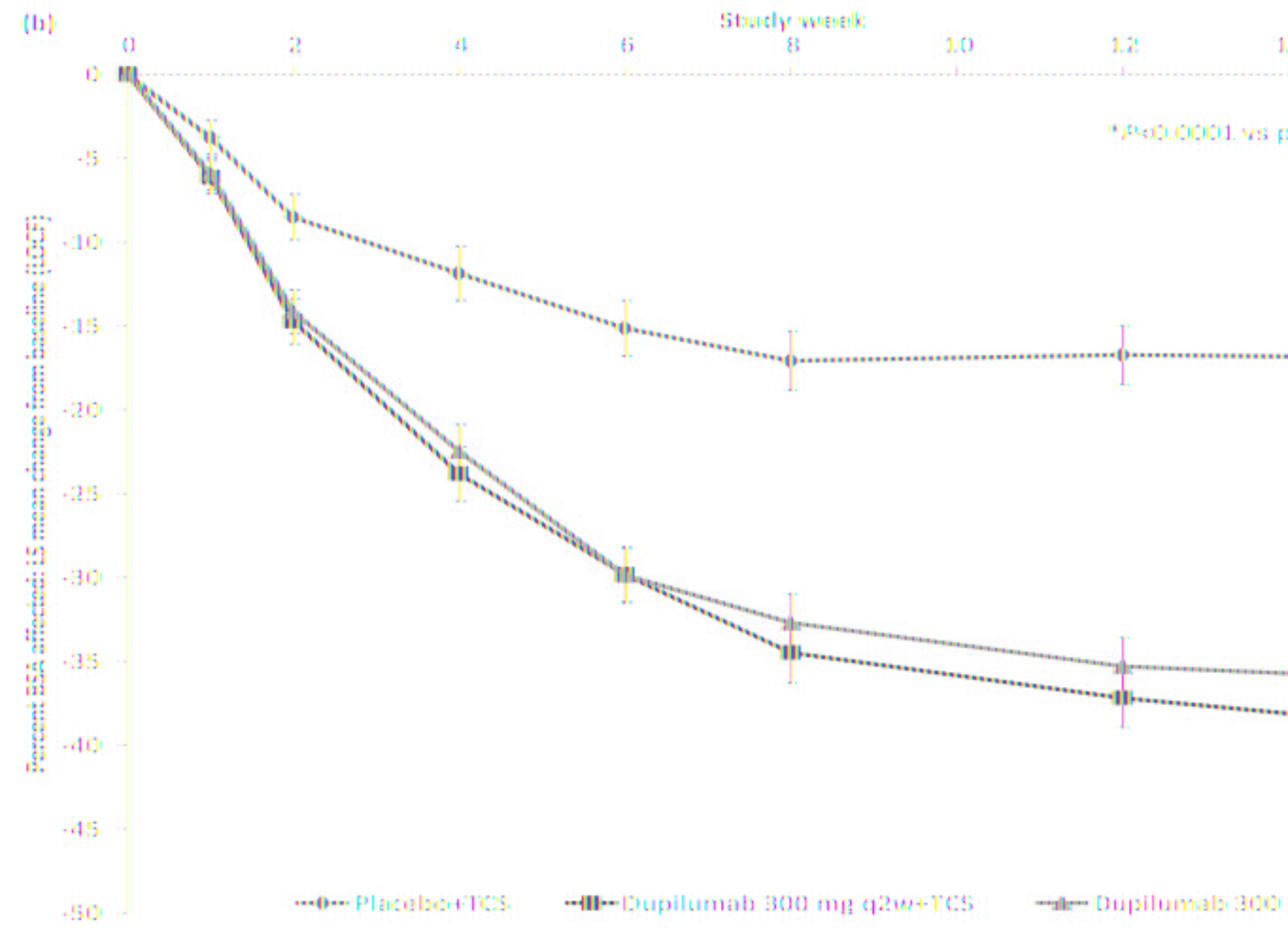
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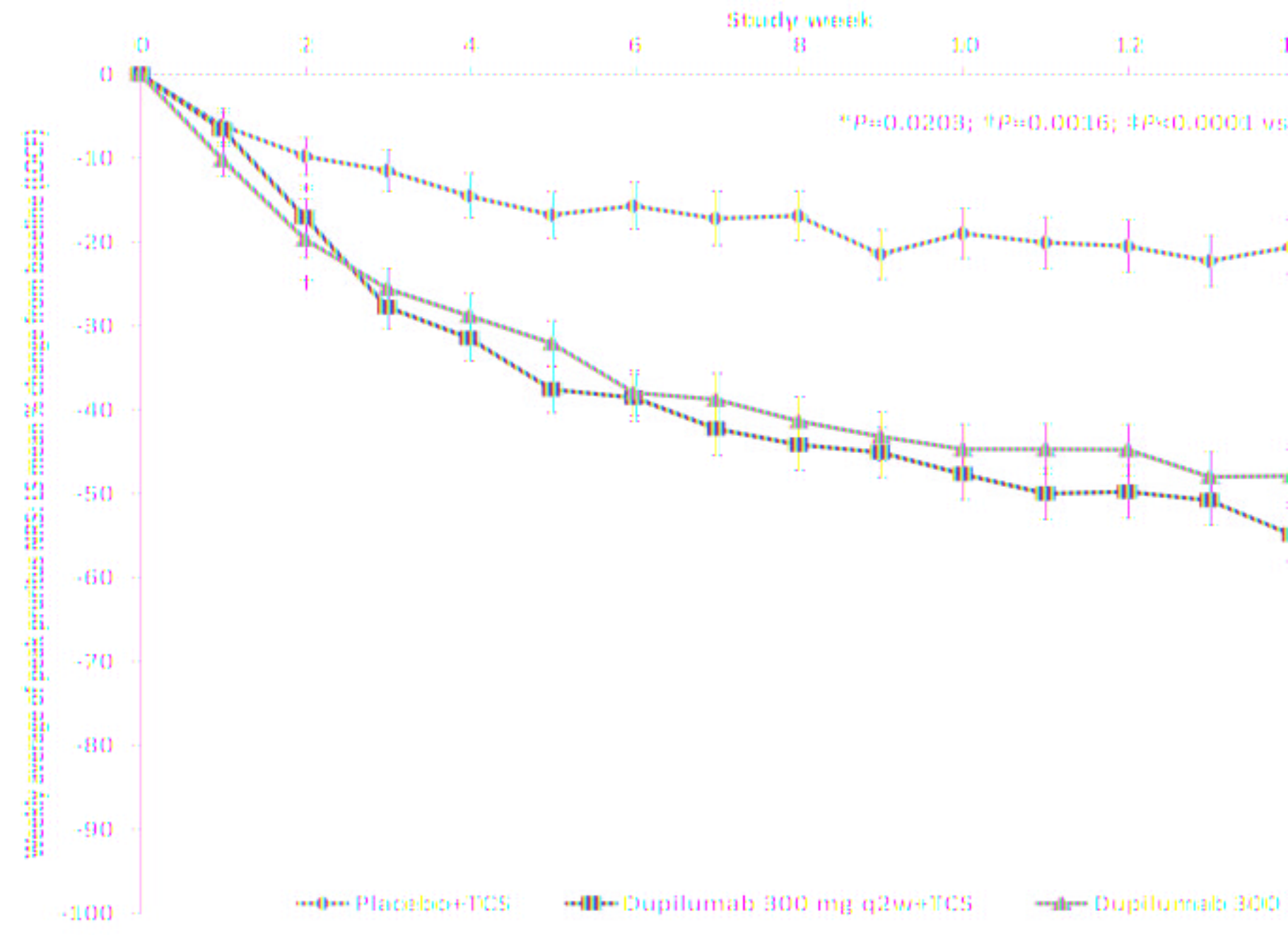

Patients screened (N=350)
-- Screen failure (n=64)
-- Screened but not randomized (n=5)
Randomized (N=322)
Placebo (n=160)
Dupilumab 300 mg q2w (n=162)
Completed treatment (n=103)
Did not complete treatment (n=5)
-- Adverse event (n=2)
-- Lack of efficacy (n=3)
Completed Week 16 (n=107)
Did not complete Week 16 (n=2)
-- Currently undecided (n=1)
Transitioned to OLE (n=89)
Did not transition to OLE (n=9)
Completed study (Week 208) (n=7)
Did not complete study (Week 208) (n=2)
-- Currently undecided (n=1)
-- Went abroad and didn't complete follow-up visits (n=1)
Completed treatment (n=153)
Did not complete treatment (n=9)
Completed Week 16 (n=152)
Did not complete Week 16 (n=1)
-- Withdrawn by participant (n=1)
Transitioned to OLE (n=138)
Did not transition to OLE (n=9)
Completed study (Week 208) (n=8)
Did not complete study (Week 208) (n=1)
-- Withdrawn by participant (n=1)
Completed treatment (n=160)
Completed Week 16 (n=160)
Completed Week 208 (n=139)

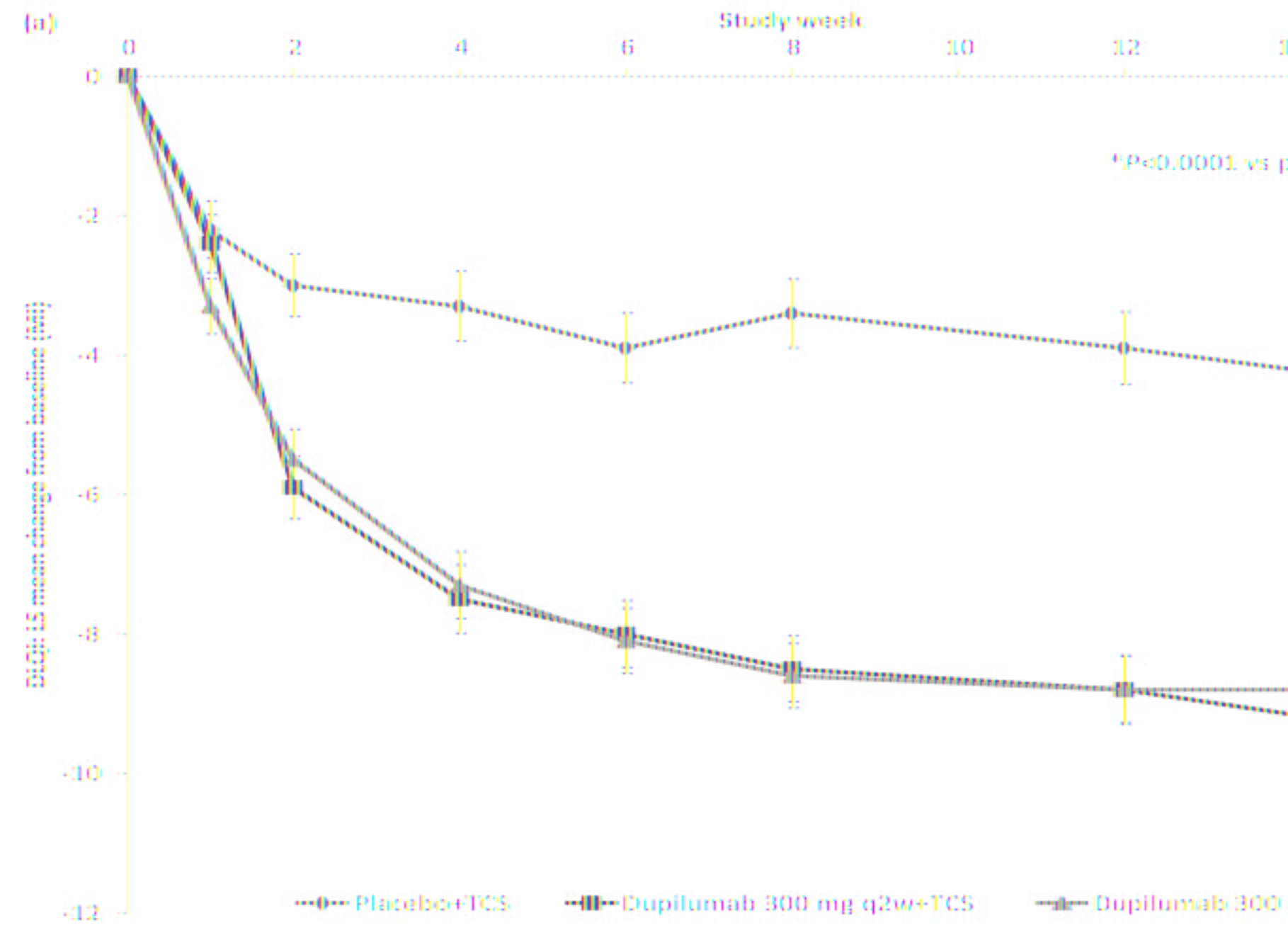

Study week
0
2
4
6
8
10
12
0
-100
-200
-300
-400
-500
-600
-700
-800
-900
-1000
Least squares mean percent change from baseline (SE)
**P<0.0001 vs. placebo
Placebo+TCS
Dupilumab 300 mg q2w+TCS
Dupilumab 300

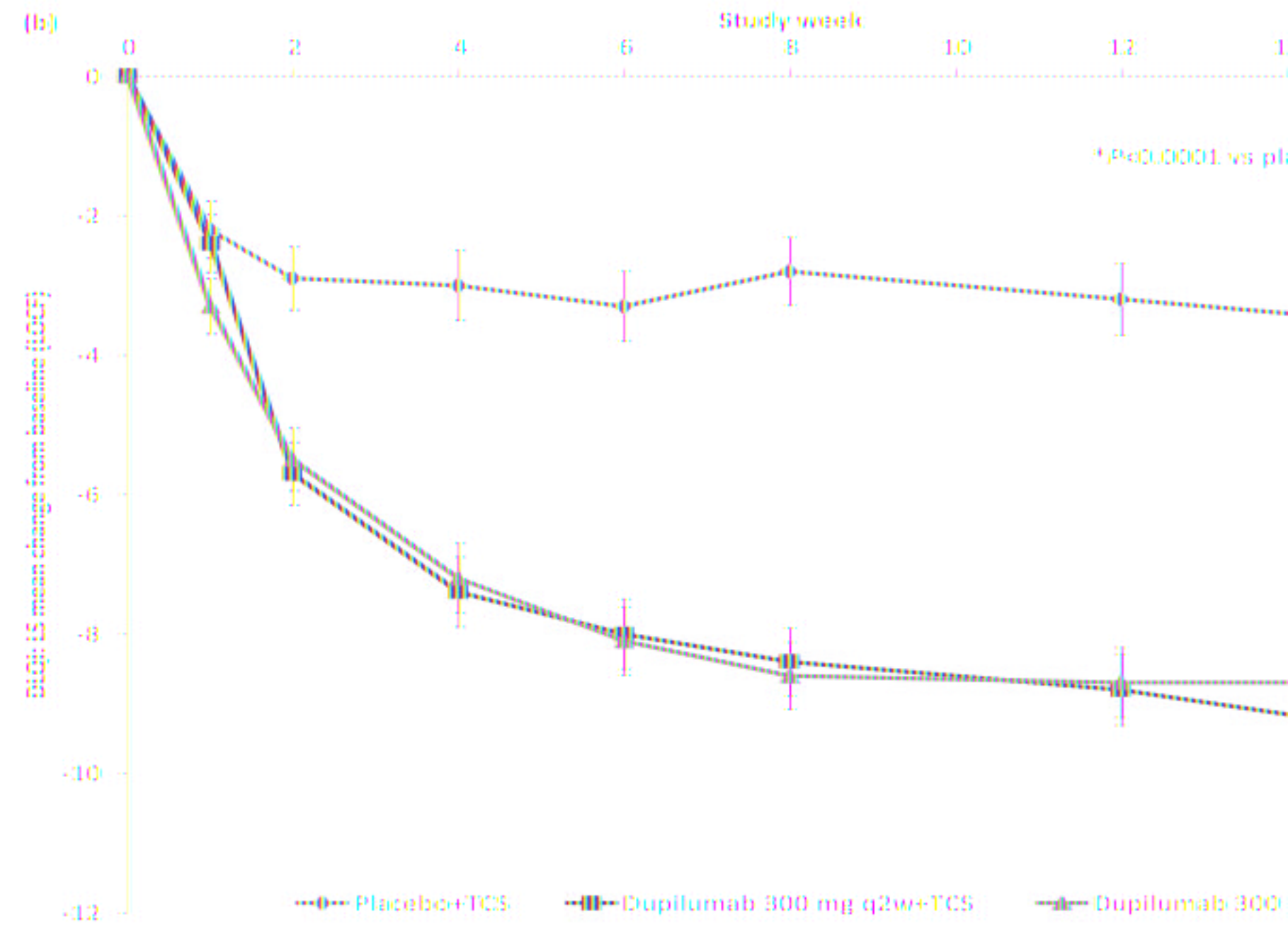

Study week
0
2
4
6
8
10
12
0
-100
-200
-300
-400
-500
-600
-700
-800
-900
-1000
**P<0.0001 vs
Placebo+TACS
Dupilumab 300D

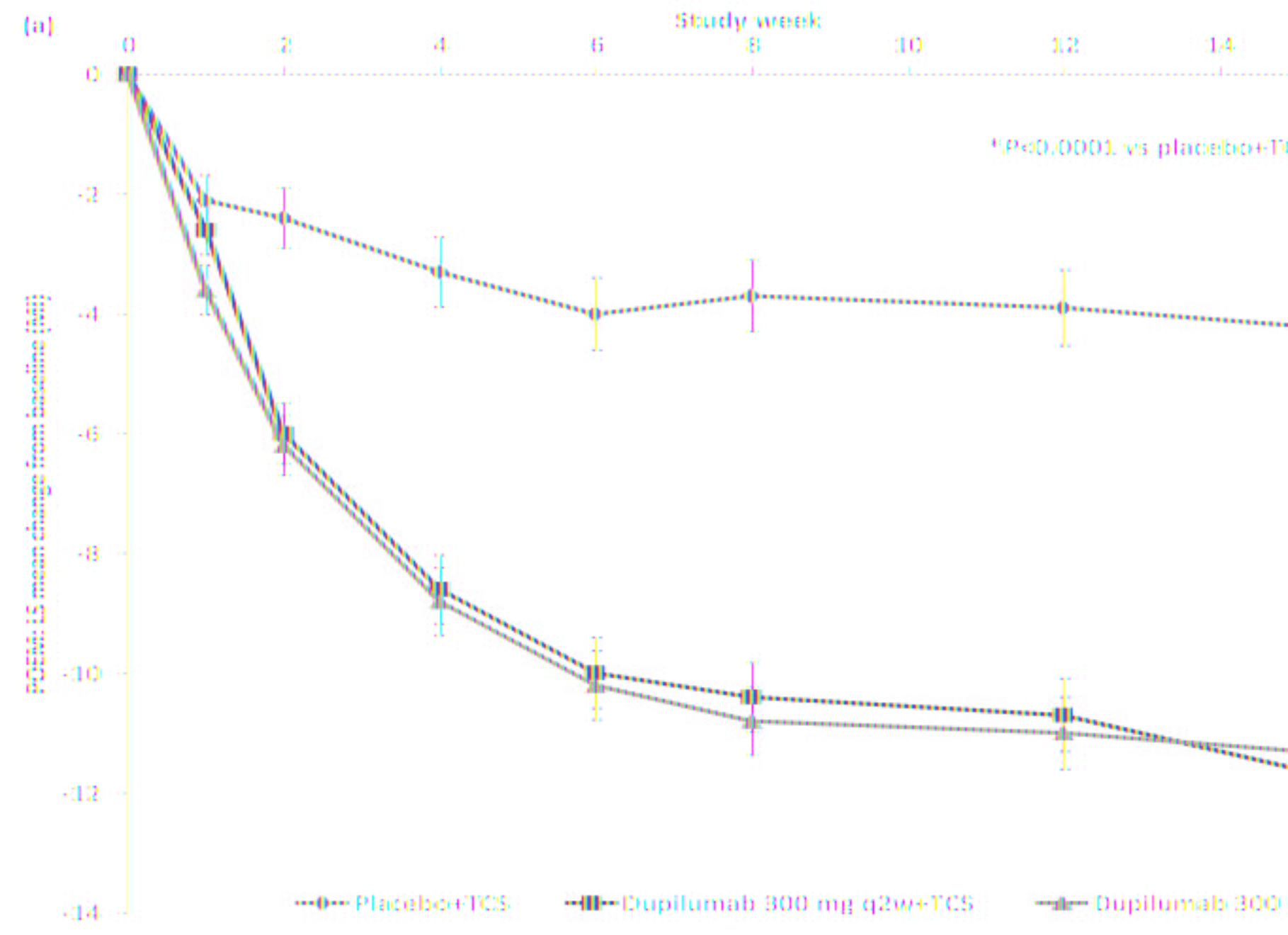

(a)
Study week
0
2
4
6
8
10
12
0
-5
-10
-15
-20
-25
-30
-35
-40
-45
-50
Percent SCORAD affected by AD: LS mean change from baseline (SE)
**P<0.0001 vs pl
Placebo+TCS
Dupilumab 300 mg q2w+TCS
Dupilumab 30

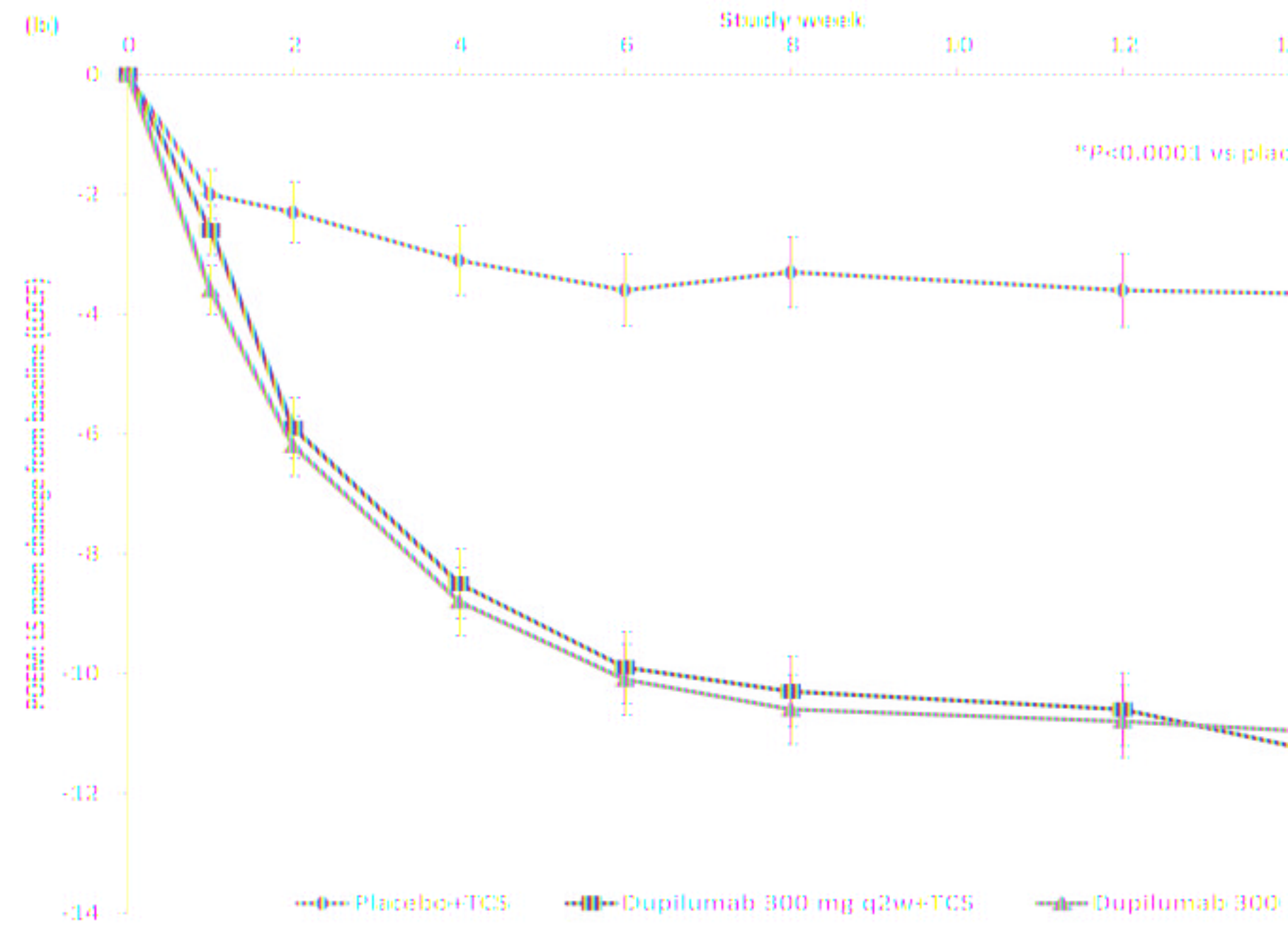

(b)
Study week
0
2
4
6
8
10
12
0
-5
-10
-15
-20
-25
-30
-35
-40
-45
-50
Placebo+TCS
Dupilumab 300 mg q2w+TCS

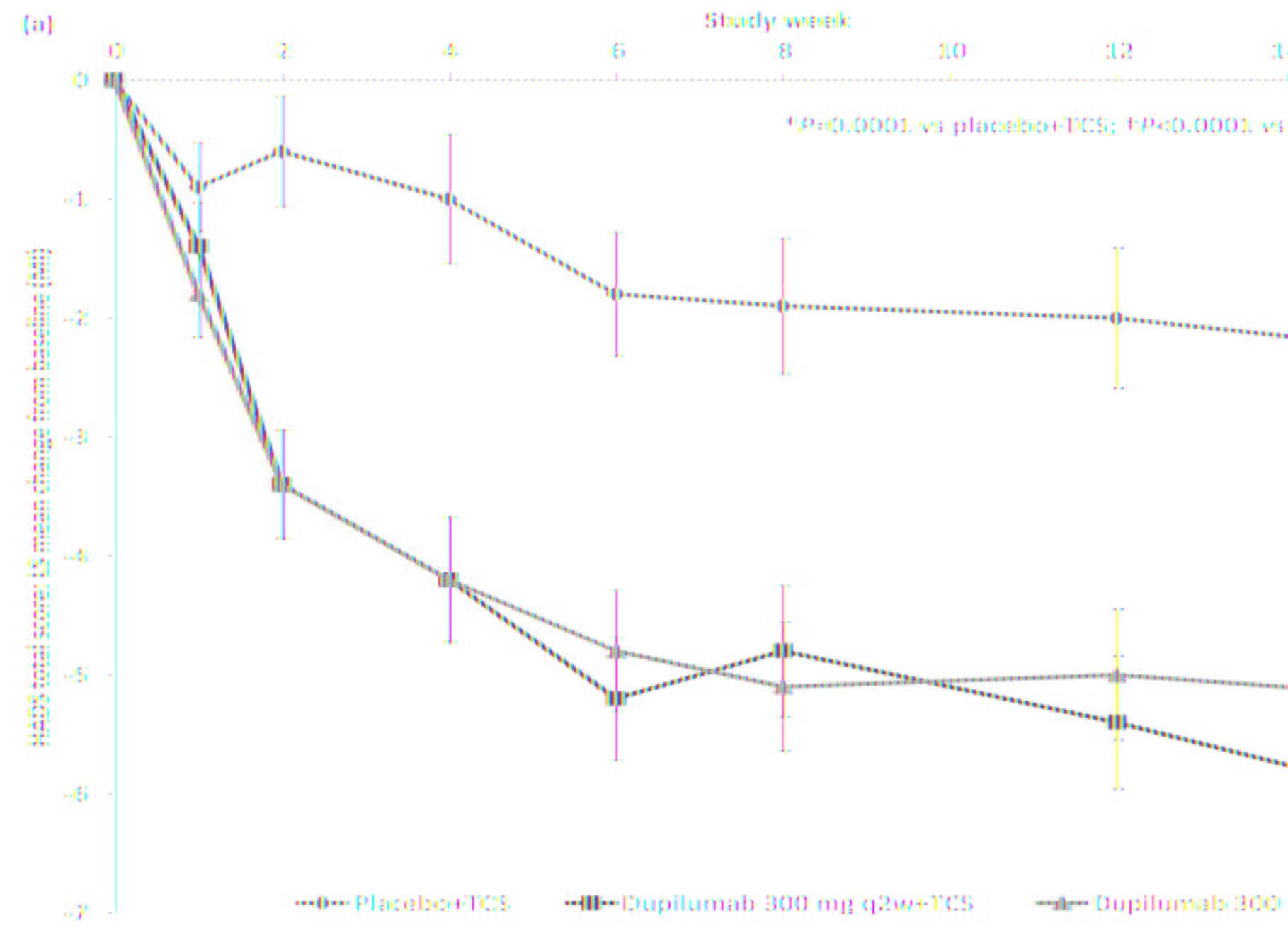

Study week
0
2
4
6
8
10
12
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
*P=0.02033; †P=0.00016; ‡P<0.00001 vs
Placebo+TCS
Dupilumab 300 mg q2w+TCS
Dupilumab 300 q

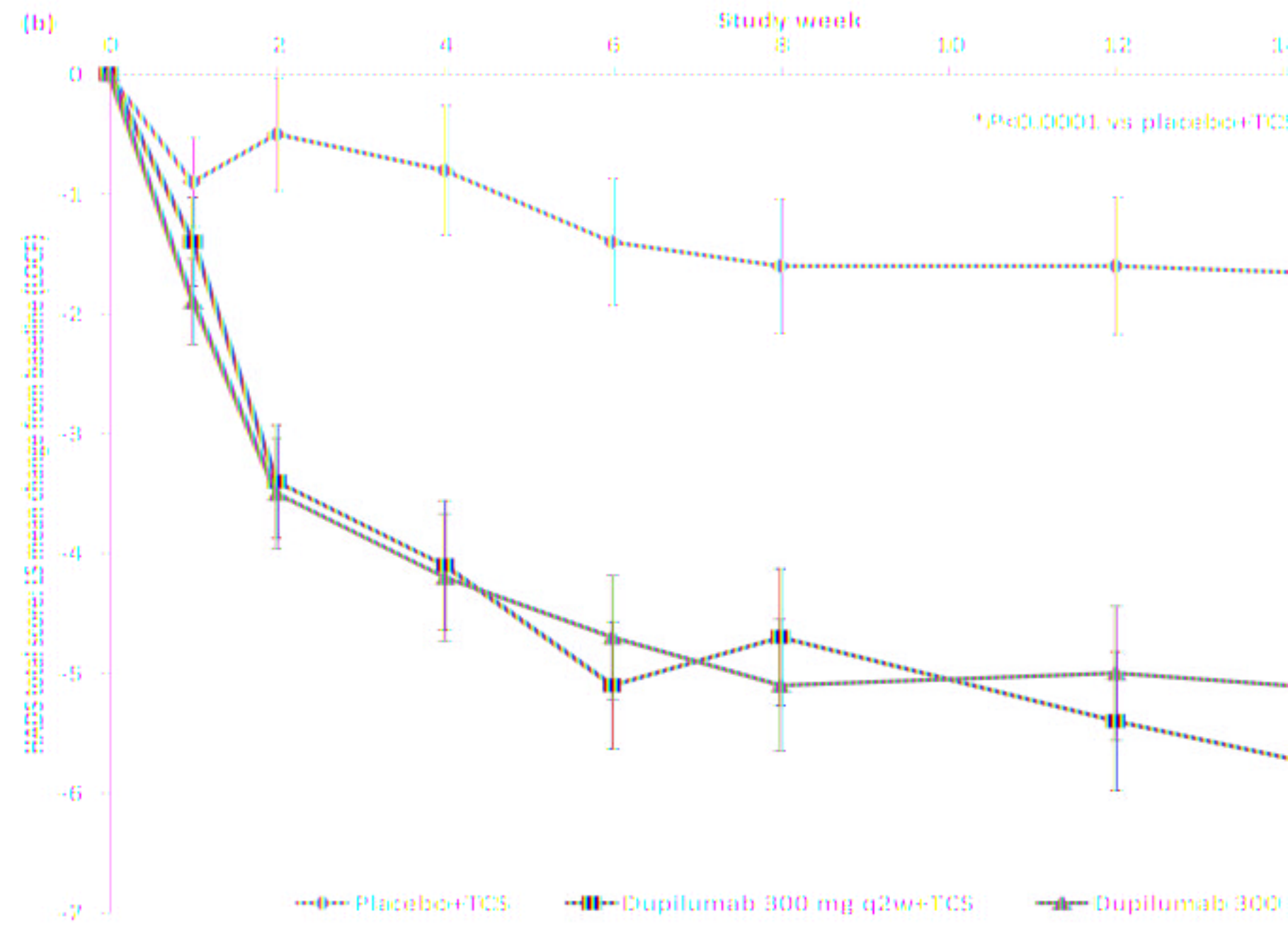

(a)
Study week
0
2
4
6
8
10
12
0
-2
-4
-6
-8
-10
-12
Placebo+TCS
Dupilumab 300 mg q2w+TCS


(b)
Study weeks
0
2
4
6
8
10
12
0
-2
-4
-6
-8
-10
-12
*p<0.000001 vs pla
Placebo+TCS
Dupilumab 300 mg q2w+TCS
Dupilumab 300


(a)
Study week
0
2
4
6
8
10
12
14
0
-2
-4
-6
-8
-10
-12
-14
*P<0.00001 vs placebo+T
Placebo+TCS
Dupilumab 300 mg q2w+TCS
Dupilumab 300


(b)
Study week
0
2
4
6
8
10
12
0
-2
-4
-6
-8
-10
-12
-14
**P<0.0001 vs plac
Placebo+TCS
Dupilumab 300 mg q2w+TCS
Dupilumab 300


(a)
Study week
0
2
4
6
8
10
12
0
-1
-2
-3
-4
-5
-6
-7
*,P<0.0001 vs placebo+TCS; †,P<0.0001 vs
Placebo+TCS
Dupilumab 300 mg q2w+TCS


(b)
Study week
0
2
4
6
8
10
12
0
-1
-2
-3
-4
-5
-6
-7
*p<0.000001 vs placebo+TCS
Placebo+TCS
Dupilumab 300 mg q2w+TCS

Supplementary Information

Dupilumab with concomitant topical corticosteroids in adult patients with atopic dermatitis who are not adequately controlled with or are intolerant to ciclosporin A, or when this treatment is medically inadvisable: a placebo-controlled, randomized phase 3 clinical trial (LIBERTY AD CAFÉ)

Submitted to British Journal of Dermatology

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ADDITIONAL METHODS

Detailed inclusion criteria

A patient must have met the following criteria to be eligible for inclusion in the study.

- Male or female, 18 years of age or older with severe chronic atopic dermatitis (AD) (according to American Academy of Dermatology Consensus Criteria[1]), for whom treatment with potent topical corticosteroids (TCS) was indicated
- Eczema Area Severity Index (EASI) score ≥20 at the screening and baseline visits
  - A single reassessment of EASI score was allowed within 48 hours of the initial screening, if EASI score at the initial screening visit was either 18 or 19
- Investigator's Global Assessment (IGA) score ≥3 (on the 0–4 IGA scale) at the screening and baseline visits
- ≥10% body surface area (BSA) of AD involvement at the screening and baseline visits
- Documented history by a physician of either
  - No prior ciclosporin A (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 (e.g. statins, digoxin, macrolide antibiotics, barbiturates, anti-seizure, nonsteroidal anti-inflammatory drugs, diuretics, angiotensin-converting-enzyme inhibitors, St John's Wort, etc.), 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 (e.g. elevated creatinine, elevated liver function tests, uncontrolled hypertension, paraesthesia, headache, nausea, hypertrichosis, etc.), 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 to 3 mg/kg/day] or a flare after a minimum of 3 months on maintenance dose). Flare is

defined as increase in signs and/or symptoms leading to escalation of therapy, which can be an increase in dose, a switch to a higher-potency class of TCS, or the start of another systemic nonsteroidal immunosuppressive drug, or

- requirement for CsA at doses >5 mg/kg/day, or duration beyond those specified in the prescribing information (>1 year)

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

- Documented recent history (within 6 months before the screening visit) of inadequate response to treatment with TCS

  NOTE: Inadequate response was defined as failure to achieve and maintain remission or a low disease activity state (comparable to IGA 0=clear to 2=mild) despite treatment with a daily regimen of TCS of medium- to higher-potency (±topical calcineurin inhibitors [TCIs] as appropriate), applied for at least 28 days or for the maximum duration recommended by the product prescribing information (e.g. 14 days for super-potent TCS), whichever was shorter.

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

- Having applied a stable dose of topical emollient (moisturizer) twice daily for at least the 7 consecutive days immediately before the baseline visit
- Willing and able to comply with clinic visits and study-related procedures
- Provided signed informed consent
- Able to understand and complete study-related questionnaires

Detailed exclusion criteria

- Participation in a prior dupilumab clinical study
- Treatment with an investigational drug within 8 weeks or within 5 half-lives (if known), whichever was longer, prior to screening

- Hypersensitivity and/or intolerance to corticosteroids or to any other ingredients contained in the TCS product used in the study
- Systemic CsA, systemic corticosteroids, or phototherapy within 4 weeks prior to screening, and azathioprine (AZA), methotrexate (MTX), mycophenolate mofetil (MMF), or Janus kinase (JAK) inhibitors within 8 weeks prior to screening
- Treatment with a TCI within 1 week prior to the screening visit
- Treatment with biologics as follows:

  – Any cell-depleting agents including but not limited to rituximab: within 6 months before the screening visit, or until lymphocyte count returned to normal, whichever was longer
  – Other biologics: within 5 half-lives (if known) or 16 weeks prior to the screening visit, whichever was longer

- At the baseline visit, ≥30% of the total lesional surface located on areas of thin skin that could not be safely treated with medium-potency TCS (e.g. face, neck, intertriginous areas, genital areas, areas of skin atrophy)
- Initiation of treatment of AD with prescription moisturizers or moisturizers containing additives such as ceramide, hyaluronic acid, urea, or filaggrin degradation products during the screening period (use of stable doses of such moisturizers could continue if initiated before the screening visit)
- Regular use (more than 2 visits per week) of a tanning booth/parlour within 4 weeks of the screening visit
- Planned or anticipated use of any prohibited medications and procedures during study treatment
- Treatment with a live (attenuated) vaccine within 12 weeks before the baseline visit
- Active chronic or acute infection requiring treatment with systemic antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals within 2 weeks before the screening-visit, or superficial skin infections within 1 week before the screening visit

  NOTE: Patients could be rescreened no sooner than 2 weeks after the infection resolved, and with permission of the sponsor's medical monitor.

- Known or suspected history of immunosuppression, including history of invasive opportunistic infections (e.g. tuberculosis [TB], histoplasmosis, Listeriosis, coccidioidomycosis, pneumocystosis, aspergillosis) despite infection resolution; or unusually frequent, recurrent, or prolonged infections, per investigator judgment
- TB tests were performed on a country-by-country basis according to local guidelines, only if required by regulatory authorities or ethics boards. TB tests included presence of any 1 of the following TB criteria:

  – A positive tuberculin skin test at the screening visit
  – A positive blood QuantiFERON®-TB or T-Spot test at the screening visit
  – Chest x-ray (posterior-anterior and lateral views) at screening or within 3 months before the screening visit (radiology report had to be available) with results consistent with prior TB infection (including but not limited to apical scarring, apical fibrosis, or multiple calcified granuloma). This did not include non-caseating granulomata

  NOTE: Any of these 3 TB tests were performed on a country-by-country basis according to local guidelines only if required by regulatory authorities or ethics boards.

- History of human immunodeficiency virus (HIV) infection or positive HIV serology at screening
- Positive hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), or hepatitis C antibody (HCV Ab) at the screening visit
- At baseline, presence of any conditions listed as criteria for study drug discontinuation
- Presence of skin characteristics that could interfere with study assessments
- History of malignancy within 5 years before the screening visit, except completely treated in situ carcinoma of the cervix, completely treated and resolved non-metastatic squamous or basal cell carcinoma of the skin
- Diagnosed active endoparasitic infections; suspected or high risk of endoparasitic infection, unless clinical and (if necessary) laboratory assessment had ruled out active infection before randomization
- History of alcohol or drug abuse within 2 years of the screening visit
- Severe concomitant illness(es) that, in the investigator's judgment, would adversely affect the patient's participation in the study. Examples included, but were not limited to, patients with short life expectancy, patients with uncontrolled diabetes (haemoglobin A1c ≥9%), patients with

cardiovascular conditions (e.g. stage III or IV cardiac failure according to the New York Heart Association classification), severe renal conditions (e.g. patients on dialysis), hepato-biliary conditions (e.g. Child-Pugh class B or C), neurological conditions (e.g. demyelinating diseases), active major autoimmune diseases (e.g. lupus, inflammatory bowel disease, rheumatoid arthritis, etc.), neuro-inflammatory disease, other severe endocrinological, gastrointestinal, metabolic, pulmonary or lymphatic diseases. The specific justification for patients excluded under this criterion was noted in study documents (chart notes, case report forms [CRFs], etc.).

- Any other medical or psychological condition (including relevant laboratory abnormalities at screening) that, in the opinion of the investigator, could suggest a new and/or insufficiently understood disease, could present an unreasonable risk to the study patient as a result of his/her participation in this clinical trial, could make the patient's participation unreliable, or could interfere with study assessments. The specific justification for patients excluded under this criterion was noted in study documents (chart notes, CRFs, etc.).
- Planned or anticipated major surgical procedure during the patient's participation in this study
- Patient was a member of the investigational team or his/her immediate family
- Pregnant or breastfeeding women, or women planning to become pregnant or to breastfeed during the study
- Women unwilling to use adequate birth control, if of reproductive potential* and sexually active. Adequate birth control was defined as agreement to consistently practice an effective and accepted method of contraception 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 (i.e. condom + diaphragm) or a male partner with documented vasectomy. Additional requirements for acceptable contraception could apply in certain countries, based on local regulations. Investigators in these countries were notified accordingly in a protocol clarification letter.

**For females, menopause was defined as at least 12 consecutive months without menses; if in question, a follicle stimulating hormone (FSH) 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.*

Prohibited concomitant medications

Use of the following concomitant medications was prohibited during the study from screening until the end of study visit:

- Live (attenuated) vaccine
- Immunomodulating biologics
- An investigational drug (other than dupilumab)
- Treatment with a TCI, except when used for rescue
- Treatment with high-potency TCS, except when used for rescue
- Treatment with TCS for patients who were intolerant or hypersensitive to TCS
- Systemic corticosteroids or nonsteroidal systemic immunosuppressive drugs (e.g. CsA, AZA, MTX, MMF, JAK inhibitors, etc.)

NOTE: If a patient received rescue treatment with systemic corticosteroids or other systemic immunosuppressive drugs (CsA, AZA, MTX, MMF, JAK inhibitors, etc.), study treatment was to be immediately discontinued. After treatment with these medications was completed, study treatment was resumed if deemed appropriate by the investigator and the medical monitor, but not sooner than 5 half-lives after the last dose of systemic rescue medication.

The following procedures were prohibited during study participation:

- Phototherapy
- Tanning in a bed/booth

ADDITIONAL STATISTICAL METHODS

Hierarchy of efficacy endpoints

To account for multiplicity arising from comparison of each of the two dupilumab+TCS dose groups with placebo+TCS, efficacy analyses were carried out in sequential order following a hierarchy of endpoints for each dupilumab dose regimen, such that if an endpoint did not achieve statistical significance for a dose regimen, comparisons for all subsequent endpoints were considered nominal for that dose regimen. The hierarchy is as follows:

- Proportion of patients with EASI 75 (≥75% improvement from baseline) at Week 16 at a dose of 300 mg weekly (qw)
- Proportion of patients with EASI 75 (≥75% improvement from baseline) at Week 16 at a dose of 300 mg every 2 weeks (q2w)
- Percent change in EASI score from baseline to Week 16 at a dose of 300 mg qw
- Percent change in EASI score from baseline to Week 16 at a dose of 300 mg q2w
- Percent change from baseline to Week 16 in weekly average of peak daily pruritus numerical rating scale (NRS) at a dose of 300 mg qw
- Percent change from baseline to Week 16 in weekly average of peak daily pruritus NRS at a dose of 300 mg q2w
- Percent change from baseline to Week 16 in SCORing AD (SCORAD) at a dose of 300 mg qw
- Percent change from baseline to Week 16 in SCORAD at a dose of 300 mg q2w
- Proportion of patients with improvement (reduction) of weekly average of peak daily pruritus NRS ≥4 from baseline to Week 16 at a dose of 300 mg qw
- Change from baseline to Week 16 in percent BSA at a dose of 300 mg qw
- Proportion of patients with improvement (reduction) of weekly average of peak daily pruritus NRS ≥4 from baseline to Week 16 at a dose of 300 mg q2w
- Change from baseline to Week 16 in percent BSA at a dose of 300 mg q2w
- Proportion of patients with IGA 0 or 1 (on a 5-point scale) and a reduction from baseline of ≥2 points at Week 16 at a dose of 300 mg qw
- Proportion of patients with IGA 0 or 1 (on a 5-point scale) and a reduction from baseline of ≥2 points at Week 16 at a dose of 300 mg q2w
- Change from baseline to Week 16 in Dermatology Life Quality Index (DLQI) at a dose of 300 mg qw
- Change from baseline to Week 16 in Patient-Oriented Eczema Measure (POEM) at a dose of 300 mg qw

- Proportion of patients with EASI-75 (≥75% improvement from baseline in EASI score) at Week 16 at a dose of 300 mg qw for patients with prior CsA use
- Change from baseline to Week 16 in DLQI at a dose of 300 mg q2w
- Change from baseline to Week 16 in POEM at a dose of 300 mg q2w
- Proportion of patients with EASI 75 (≥75% improvement from baseline) at Week 16 at a dose of 300 mg q2w for patients with prior CsA use
- Mean weekly dose of TCS use (grams) during the treatment period at a dose of 300 mg qw
- Mean weekly dose of TCS use during the treatment period at a dose of 300 mg q2w
- Change from baseline to Week 16 in HADS at a dose of 300 mg qw
- Change from baseline to Week 16 in HADS at a dose of 300 mg q2w

Sensitivity analyses:

- Primary endpoint and other binary endpoints
  - Last observation carried forward (LOCF) at Week 16; patients were set to missing after rescue medication use or study withdrawal
  - All observed data regardless of rescue medication use or study withdrawal; patients with missing values were counted as non-responders
  - All observed data regardless of rescue medication use or study withdrawal; patients with missing values were *not* counted as non-responders
- Continuous secondary endpoints
  - All observed data regardless of whether rescue medication was used
  - Mixed-effect model repeated measures to account for missing data; factors in the model included treatment, randomization strata, visit, baseline value, treatment-by-visit interaction, and baseline-by-visit interaction as covariates

- Analysis of covariance (ANCOVA) model using treatment group, baseline value, and randomization strata; data were set to missing after rescue medication use; LOCF was used to impute missing values
- ANCOVA model using treatment group, baseline value, and randomization strata: data were set to missing after rescue medication use; worst observation carried forward (WOCF) was used to impute missing values
- ANCOVA model using treatment group, baseline value, and randomization strata; all observed values were used regardless of rescue medication use.

Table S1. Institutional review boards and independent ethics committees.

Country and Central IRB/IEC	**Local IRB/IEC**
Austria: Ethikkommission der Stadt Wien, Wien, Austria	Ethikkommission der Stadt Wien, Wien, Austria
	Ethik-Kommission der Medizinischen Universität Wien, Wien, Austria
Belgium: Cliniques Universitaires Saint-Luc Comité d'Ethique Hospitalo-Facultaire Saint-Luc - UCL Brussels, Belgium	Cliniques Universitaires Saint-Luc Comité d'Ethique, Hospitalo-Facultaire Saint-Luc - UCL, Brussels, Belgium
	Grand Hôpital de Charleroi Comité d'Ethique, Charerloi, Belgium
	Commissie Medische, Ethiek UZ KU Leuven / Onderzoek Campus Gasthuisberg, Leuven, Belgium
Germany: Ethikkommission der Universität zu Lübeck, Lübeck, Germany	Ethikkommission der Universität zu Lübeck, Lübeck, Germany
	Ethik-Kommission Kiel der Medizinischen Fakultät der Christian-Albrechts-Universität zu Kiel Universitäts-Kinderklinik, Kiel, Germany
	Landesamt für Gesundheit und Soziales, Geschäftsstelle der Ethik-Kommission des Landes Berlin, Berlin, Germany
	Ethik-Kommission des Fachbereichs Medizin der Johann Wolfgang Goethe-Universität, Frankfurt am Main, Germany
	Ethikkommission bei der Landesärztekammer Baden-Württemberg, Stuttgart, Germany
	Landesärztekammer Brandenburg Ethikkommission, Cottbus, Germany
	Ethik-Kommission der Ärztekammer Westfalen-Lippe und der Medizinischen Fakultät der Westfälischen Wilhelms-Universität, Münster, Germany
	Ethikkommission der Med. Fakultät der Ludwig-Maximilian-Universität (LMU), München Fachbereich Medizin, München, Germany

Country and Central IRB/IEC	**Local IRB/IEC**
	Ethikkommission bei der Sächsischen Landesärztekammer, Dresden, Germany
	Ethik-Kommission der Medizinischen Fakultät der Eberhard-Karls-Universität und am Universitätsklinikum Tübingen, Tübingen, Germany
	Ethikkommission der Fakultät für Medizin der Technischen Universität München, München, Germany
	Ethikkommission Technische Universität Dresden, Dresden, Germany
	Ethikkommission der Medizinischen Fakultät Heidelberg Alte Glockengießerei, Heidelberg, Germany
	Ethik-Kommission an der Medizinischen Fakultät der Universität Leipzig Haus: Karl-Sudhoff-Institut, Leipzig, Germany
	Ethik-Kommission der Medizinischen Fakultät der Ruhr-Universität Bochum, Bochum, Germany
	Ethik-Kommission der Ärztekammer Hamburg, Hamburg, Germany
	Ethik-Kommission bei der Ärztekammer Niedersachsen Unterkommission zur Beurteilung medizinischer Forschung am Menschen, Hannover, Germany
	Ethikkommission der Landesärztekammer Rheinland-Pfalz, Mainz, Germany
	Ethik-Kommission der Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany
	Ethik-Kommission der Otto-von-Guericke-Universität an der Medizinischen Fakultät, Magdeburg, Germany
	Ethikkommission der Landesärztekammer, Mainz, Germany
Ireland: Clinical Research Ethics Committee of the Cork Teaching	n/a

Country and Central IRB/IEC	**Local IRB/IEC**
Hospitals, Cork, Ireland	
Netherlands: METC Brabant: Medical Ethics Review Committee Brabant, Tilburg, Netherlands	n/a
Poland: Komisja Bioetyczna przy Okregowej Izbie Lekarskiej, Lodz, Poland	n/a
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	SBEI of Higher Professional Education "Kazan State Medical University" of Ministry of Healthcare of Russian Federation, Kazan, Russia
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Slovakia: Etická komisia Prešovský samosprávny kraj, Prešov, Slovakia	Etická komisia Nemocnica Košice- Šaca, a.s., Košice-Šaca, Slovakia
	CEIC – Parc de Salut MAR IMIM - Institut Hospital del Mar d' Investigacions Mèdiques Parc de Recerca Biomèdica de Barcelona, Barcelona, Spain
Spain: Comité Etico Regional de la Comunidad de Madrid, Madrid, Spain	n/a
United Kingdom: Yorkshire & The	n/a

Country and Central IRB/IEC	**Local IRB/IEC**
Humber - Sheffield Research Ethics Committee, Jarrow, United Kingdom	

IRB, institutional review board; IEC, independent ethics committee; n/a, no local IRB/IECs in this country.

Table S2. Recruitment by country

Country	Number of patients enrolled	Number of patients randomized
Austria	7	7
Belgium	13	11
Germany	144	142
Ireland	2	2
Netherlands	16	16
Poland	108	107
Russia	16	16
Slovakia	4	4
Spain	3	3
United Kingdom	17	17

Table S3. Baseline characteristics: subgroups based on prior CsA use (a); subgroups based on baseline disease severity (IGA score=3 or 4) (b).

(a) Subgroups based on prior CsA use

	Prior use of CsA			**No prior use of CsA**		
	Placebo+TCS (n=72)	**Dupilumab q2w+TCS (n=69)**	**Dupilumab qw+TCS (n=69)**	**Placebo+TCS (n=36)**	**Dupilumab q2w+TCS (n=38)**	**Dupilumab qw+TCS (n=41)**
Age, median (IQR), years	37.5 (30.0–47.5)	37.0 (26.0–47.0)	36.0 (28.0–45.0)	37.5 (27.5–52.0)	38.5 (24.0–47.0)	42.0 (31.0–53.0)
Race, n (%)						
White	69 (95.8)	66 (95.7)	65 (94.2)	35 (97.2)	38 (100)	40 (97.6)
Asian	2 (2.8)	2 (2.9)	2 (2.9)	0	0	0
Black	0	0	2 (2.9)	0	0	0
Other	1 (1.4)	0	0	1 (2.8)	0	1 (2.4)
Not reported/ missing	0	1 (1.4)	0	0	0	0
Male, n (%)	43 (59.7)	40 (58.0)	42 (60.9)	25 (69.4)	25 (65.8)	24 (58.5)
Duration of AD, median (IQR), years	29.5 (20.0–40.0)	29.0 (18.0–44.0)	30.0 (20.0–40.0)	27.0 (18.5–40.5)	29.5 (19.0–41.0)	33.0 (24.0–44.0)
EASI score, median (IQR)	32.8 (24.5, 41.0)	32.7 (26.4, 38.7)	32.0 (25.0, 39.4)	27.1 (23.8, 36.7)	30.1 (25.0, 40.2)	28.0 (24.0, 37.5)
IGA score						
Median (IQR)	4.0 (3.0, 4.0)	4.0 (3.0, 4.0)	4.0 (3.0, 4.0)	3.0 (3.0, 4.0)	3.0 (3.0, 4.0)	3.0 (3.0, 4.0)
Patients with IGA 4 (severe), n (%)	38 (52.8)	35 (50.7)	35 (50.7)	14 (38.9)	15 (39.5)	17 (41.5)
Peak weekly averaged pruritus NRS, median (IQR)	7.0 (5.4, 8.3)	7.1 (6.0, 8.0)	6.3 (5.2, 7.3)	5.5 (4.3, 8.0)	6.4 (4.0, 8.2)	7.0 (4.6, 7.7)
BSA, median (IQR)	57.0 (38.3, 70.6)	55.5 (47.0, 67.8)	56.5 (44.0, 68.0)	47.8 (38.5, 60.3)	52.0 (42.5, 64.0)	55.0 (35.5, 66.0)
SCORAD score, median (IQR)	67.7 (57.2, 77.0)	68.7 (62.6, 76.6)	66.8 (55.4, 75.5)	67.4 (60.4, 74.7)	66.0 (59.5, 73.1)	66.0 (57.7, 74.7)
DLQI total score, median (IQR)	14.0 (8.0, 20.0)	15.0 (11.0, 22.0)	14.0 (7.0, 21.0)	11.5 (4.5, 16.5)	10.5 (6.0, 19.0)	12.0 (6.0, 21.0)

	Prior use of CsA			No prior use of CsA		
	Placebo+TCS (n=72)	**Dupilumab q2w+TCS (n=69)**	**Dupilumab qw+TCS (n=69)**	**Placebo+TCS (n=36)**	**Dupilumab q2w+TCS (n=38)**	**Dupilumab qw+TCS (n=41)**
POEM score, median (IQR)	20.0 (16.0, 25.0)	20.0 (17.0, 23.0)	19.0 (14.0, 23.0)	18.0 (13.0, 24.0)	19.0 (12.0, 24.0)	20.0 (14.0, 24.0)
HADS total score, median (IQR)	14.0 (6.0, 19.0)	13.0 (6.0, 19.0)	11.0 (7.0, 18.0)	10.0 (8.0, 16.0)	12.0 (5.0, 17.0)	14.0 (6.0, 22.0)
GISS, median (IQR)	9.0 (8.0, 11.0)	9.0 (8.0, 11.0)	9.0 (8.0, 10.0)	10.0 (8.0, 11.0)	9.0 (8.0, 10.0)	9.0 (8.0, 10.0)
CsA exposure, n (%)						
No	0	0	0	36 (100)	38 (100)	41 (100)
Reasons for no prior CsA						
Medical contraindication	n/a	n/a	n/a	24 (66.7)	17 (44.7)	22 (53.7)
Use of prohibited concomitant medication	n/a	n/a	n/a	13 (36.1)	16 (42.1)	18 (43.9)
Increased risk of renal damage and liver damage	n/a	n/a	n/a	1 (2.8)	7 (18.4)	6 (14.6)
Increased risk of serious infection	n/a	n/a	n/a	5 (13.9)	6 (15.8)	4 (9.8)
Yes	72 (100)	69 (100)	69 (100)	0	0	0
Reasons for stopping CsA						
Intolerance and/or unacceptable toxicity	41 (56.9)	33 (47.8)	37 (53.6)	n/a	n/a	n/a
Inadequate response	39 (54.2)	34 (49.3)	36 (52.2)	n/a	n/a	n/a
Required doses >5 mg/kg/day or treatment >1 year	8 (11.1)	12 (17.4)	8 (11.6)	n/a	n/a	n/a
Hypersensitivity to CsA active	4 (5.6)	4 (5.8)	6 (8.7)	n/a	n/a	n/a

	Prior use of CsA			No prior use of CsA		
	Placebo+TCS (n=72)	**Dupilumab q2w+TCS (n=69)**	**Dupilumab qw+TCS (n=69)**	**Placebo+TCS (n=36)**	**Dupilumab q2w+TCS (n=38)**	**Dupilumab qw+TCS (n=41)**
substance or excipients						

(b) Subgroups based on baseline disease severity (IGA=3 or 4)

	Baseline IGA=3			**Baseline IGA=4**		
	Placebo+TCS (n=56)	**Dupilumab q2w+TCS (n=57)**	**Dupilumab qw+TCS (n=58)**	**Placebo+TCS (n=52)**	**Dupilumab q2w+TCS (n=50)**	**Dupilumab qw+TCS (n=52)**
Age, median (IQR), years	37.5 (27.5, 46.0)	36.0 (26.0, 44.0)	38.5 (28.0, 46.0)	37.0 (30.0, 49.5)	39.0 (25.0, 48.0)	37.5 (29.0, 49.5)
Race, n (%)						
White	54 (96.4)	56 (98.2)	57 (98.3)	50 (96.2)	48 (96.0)	48 (92.3)
Asian	0	0	0	2 (3.8)	2 (4.0)	2 (3.8)
Black	0	0	0	0	0	2 (3.8)
Other	2 (3.6)	0	1 (1.7)	0	0	0
Not reported/ missing	0	1 (1.8)	0	0	0	0
Male, n (%)	33 (58.9)	30 (52.6)	33 (56.9)	35 (67.3)	35 (70.0)	33 (63.5)
Duration of AD, median (IQR), years	29.0 (18.5, 40.0)	27.0 (17.0, 41.0)	30.0 (21.0, 42.0)	28.0 (20.0, 39.5)	33.0 (21.0, 44.0)	33.0 (21.5, 44.0)
EASI score, median (IQR)	25.5 (21.6, 33.4)	27.4 (22.8, 35.3)	24.9 (21.7, 31.7)	38.0 (30.1, 44.5)	35.0 (30.1, 44.6)	37.3 (31.2, 46.8)
IGA score						
Median (IQR)	3.0 (3.0, 3.0)	3.0 (3.0, 3.0)	3.0 (3.0, 3.0)	4.0 (4.0, 4.0)	4.0 (4.0, 4.0)	4.0 (4.0, 4.0)
Patients with IGA 4 (severe), n (%)	0	0	0	52 (100)	50 (100)	52 (100)
Peak weekly averaged pruritus NRS, median (IQR)	5.7 (4.4, 7.6)	6.1 (5.0, 8.0)	6.3 (4.5, 7.3)	7.6 (6.2, 8.4)	7.5 (6.1, 8.0)	6.8 (5.5, 8.0)
BSA, median (IQR)	46.8 (34.5,	50.0 (39.0,	45.8 (37.0,	61.3 (44.8,	61.0 (51.0,	65.0 (54.0,

	Baseline IGA=3			Baseline IGA=4		
	Placebo+TCS (n=56)	Dupilumab q2w+TCS (n=57)	Dupilumab qw+TCS (n=58)	Placebo+TCS (n=52)	Dupilumab q2w+TCS (n=50)	Dupilumab qw+TCS (n=52)
	58.3)	59.5)	58.0)	82.0)	72.5)	78.8)
SCORAD score, median (IQR)	62.1 (52.6, 67.9)	63.2 (55.6, 72.3)	58.4 (52.4, 67.2)	75.8 (67.3, 80.9)	72.8 (65.9, 80.1)	73.3 (66.1, 79.4)
DLQI total score, median (IQR)	10.0 (5.0, 14.0)	13.0 (8.0, 21.0)	12.0 (6.0, 16.0)	16.5 (9.5, 21.0)	15.5 (9.0, 22.0)	16.0 (9.0, 24.0)
POEM score, median (IQR)	17.0 (12.0, 21.0)	20.0 (13.0, 23.0)	18.0 (11.0, 23.0)	22.0 (19.0, 26.0)	21.0 (17.0, 25.0)	22.0 (15.0, 26.0)
HADS total score, median (IQR)	10.0 (5.0, 17.0)	13.0 (6.0, 18.0)	10.5 (6.0, 17.0)	15.0 (10.0, 19.5)	12.5 (6.0, 19.0)	14.0 (8.0, 21.5)
GISS, median (IQR)	8.5 (8.0, 10.0)	8.0 (8.0, 9.0)	8.0 (8.0, 9.0)	10.0 (9.0, 11.0)	10.0 (9.0, 11.0)	10.0 (9.0, 11.0)
CsA exposure, n (%)						
No	22 (39.3)	23 (40.4)	24 (41.4)	14 (26.9)	15 (30.0)	17 (32.7)
Reasons for no prior CsA						
Medical contraindication	14 (25.0)	10 (17.5)	13 (22.4)	10 (19.2)	7 (14.0)	9 (17.3)
Use of prohibited concomitant medication	8 (14.3)	9 (15.8)	10 (17.2)	5 (9.6)	7 (14.0)	8 (15.4)
Increased risk of renal damage and liver damage	1 (1.8)	3 (5.3)	0	0	4 (8.0)	6 (11.5)
Increased risk of serious infection	3 (5.4)	5 (8.8)	2 (3.4)	2 (3.8)	1 (2.0)	2 (3.8)
Yes	34 (60.7)	34 (59.6)	34 (58.6)	37 (71.2)	34 (68.0)	35 (67.3)
Reasons for stopping CsA						
Intolerance and/or unacceptable toxicity	18 (32.1)	17 (29.8)	21 (36.2)	23 (44.2)	16 (32.0)	16 (30.8)
Inadequate response	22 (39.3)	19 (33.3)	16 (27.6)	17 (32.7)	15 (30.0)	20 (38.5)

	Baseline IGA=3			Baseline IGA=4		
	Placebo+TCS (n=56)	Dupilumab q2w+TCS (n=57)	Dupilumab qw+TCS (n=58)	Placebo+TCS (n=52)	Dupilumab q2w+TCS (n=50)	Dupilumab qw+TCS (n=52)
Required doses >5 mg/kg/day or treatment >1 year	3 (5.4)	4 (7.0)	5 (8.6)	5 (9.6)	8 (16.0)	3 (5.8)
Hypersensitivity to CsA active substance or excipients	2 (3.6)	2 (3.5)	3 (5.2)	2 (3.8)	2 (4.0)	3 (5.8)

CsA, ciclosporin A; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; GISS, Global Individual Signs Score; HADS, Hospital Anxiety and Depression Scale; IGA, Investigator's Global Assessment; IQR, interquartile range; n/a, not applicable; NRS, numerical rating scale; q2w, every 2 weeks; qw, once weekly; SCORAD, SCORing atopic dermatitis; SD, standard deviation; TCS, topical corticosteroids.

Table S4. Mean change from baseline at Week 16 in EASI, SCORAD, weekly average of peak pruritus NRS, DLQI, and POEM; multiple imputation method with censoring after rescue treatment.

	MCID	**Placebo+TCS (n=108)**	**Dupilumab q2w+TCS (n=107)**	**Dupilumab qw+TCS (n=110)**
EASI score, LS mean change from baseline at Week 16 (SE)	6.6 points[4]	−14.5 (0.98)	−26.0 (0.92)*	−25.6 (0.90)*
SCORAD score, LS mean change from baseline at Week 16 (SE)	8.7 points[5]	−19.3 (1.74)	−41.9 (1.68)*	−39.0 (1.66)*
Weekly average of peak pruritus NRS score, LS mean change from baseline at Week 16 (SE)	n/a	−1.7 (0.21)	−3.5 (0.19)*	−3.3 (0.19)*
DLQI score, LS mean change from baseline at Week 16 (SE)	4.0 points[4]	−4.5 (0.49)	−9.5 (0.46)†	−8.8 (0.45)†
POEM score, LS mean change from baseline at Week 16 (SE)	4.0 points[4]	−4.3 (0.62)	−11.9 (0.60)†	−11.4 (0.59)†

*Nominal *P*<0.0001; †*P*<0.0001. DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; LS, least squares; MCID, minimal clinically important difference; n/a, not applicable; NRS, numerical rating scale; POEM, Patient-Oriented Eczema Measure; q2w, every 2 weeks; qw, once weekly; SCORAD, Scoring atopic dermatitis; TCS, topical corticosteroids.

Table S5. Sensitivity analyses of the proportion of patients who achieved EASI-75 at Week 16 (primary endpoint).

	Placebo+TCS (n=108)	**Dupilumab q2w+TCS (n=107)**	**Dupilumab qw+TCS (n=110)**
Primary analysis, n (%)	32 (29.6)	67 (62.6)*	65 (59.1)*
Sensitivity analyses			
LOCF with patient considered non-responder after rescue treatment use, n (%)	32 (29.6)	68 (63.6)*	66 (60.0)*
All observed values regardless of rescue medication use, missing considered as non-responder, n (%)	35 (32.4)	69 (64.5)*	67 (60.9)*
All observed values regardless of rescue medication use, n/N1 (%)	35/108 (32.4)	69/107 (64.5)*	67/109 (61.5)*

**P*<0.0001. EASI-75, 75% improvement from baseline in Eczema Area and Severity Index score; LOCF, last observation carried forward; N1, number of patients with all observed data at Week 16; q2w, every 2 weeks; qw, weekly; TCS, topical corticosteroids.

Table S6. Incidence of conjunctivitis and keratitis according to treatment group.

	Placebo+TCS (n=108)	**Dupilumab q2w+TCS (n=107)**	**Dupilumab qw+TCS (n=110)**
Conjunctivitis*			
Number of events of treatment-emergent conjunctivitis*	15	37	19
Patients with at least 1 event, n (%):			
Treatment-emergent conjunctivitis*	12 (11)	30 (28)	18 (16)
Conjunctivitis†	3 (3)	12 (11)	8 (7)
Conjunctivitis allergic†	7 (6)	16 (15)	10 (9)
Adenovirus conjunctivitis†	0	1 (1)	0
Conjunctivitis bacterial†	2 (2)	1 (1)	0
Conjunctivitis viral†	1 (1)	1 (1)	0
Drug-related conjunctivitis*	5 (5)	13 (12)	7 (6)
Conjunctivitis causing permanent discontinuation of study drug*	0	0	0
Maximum intensity for any treatment-emergent event			
Mild	6 (6)	16 (15)	12 (11)
Moderate	6 (6)	13 (12)	6 (5)
Severe	0	1 (1)	0
Number of events resolved by end of treatment			
Recovered/resolved	11	14	15

	Placebo+TCS (n=108)	Dupilumab q2w+TCS (n=107)	Dupilumab qw+TCS (n=110)
Recovered/resolved with sequelae	1	1	0
Recovering/resolving	1	8	2
Not recovered/not resolved	2	13	2
Unknown	0	1	0
Keratitis:‡			
Number of keratitis adverse events‡	1	3	0
Patients with at least 1 event, n (%):			
Treatment-emergent keratitis‡	1 (1)	2 (2)	0
Keratitis†	0	2 (2)	0
Corneal infection†	0	1 (1)	0
Ophthalmic herpes simplex†	1 (1)	0	0

*Includes MedDRA PTs of conjunctivitis, conjunctivitis allergic, adenovirus conjunctivitis, conjunctivitis bacterial, and conjunctivitis viral. †MedDRA PT. ‡Includes MedDRA PTs of keratitis, corneal infection, and ophthalmic herpes simplex. MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; q2w, every 2 weeks; qw, weekly; TCS, topical corticosteroids.

Table S7. Incidence of skin infection according to treatment group (MedDRA HLTs and PTs).

Patients with, n (%)*	Placebo+TCS (n=108)	Dupilumab q2w+TCS (n=107)	Dupilumab qw+TCS (n=110)
Skin infection	9 (8)	2 (2)	4 (4)
Skin structures and soft tissue infections†	1 (1)	1 (1)	2 (2)
Dermatitis infected‡	0	1 (1)	0
Eczema infected‡	1 (1)	0	1 (1)
Skin infection‡	0	0	1 (1)
Bacterial infections NEC†	2 (2)	0	1 (1)
Folliculitis‡	1 (1)	0	1 (1)
Skin bacterial infection‡	1 (1)	0	0
Streptococcal infections†	2 (2)	0	1 (1)
Erysipelas‡	2 (2)	0	1 (1)
Tinea infections†	0	1 (1)	0
Tinea versicolour‡	0	1 (1)	0
Candida infections†	1 (1)	0	0
Skin candida‡†	1 (1)	0	0
Ear infections†	2 (2)	0	0
Otitis externa‡	2 (2)	0	0
Fungal infections NEC†	1 (1)	0	0
Fungal skin infection‡	1 (1)	0	0
Staphylococcal infections†	1 (1)	0	0
Staphylococcal skin infection‡	1 (1)	0	0

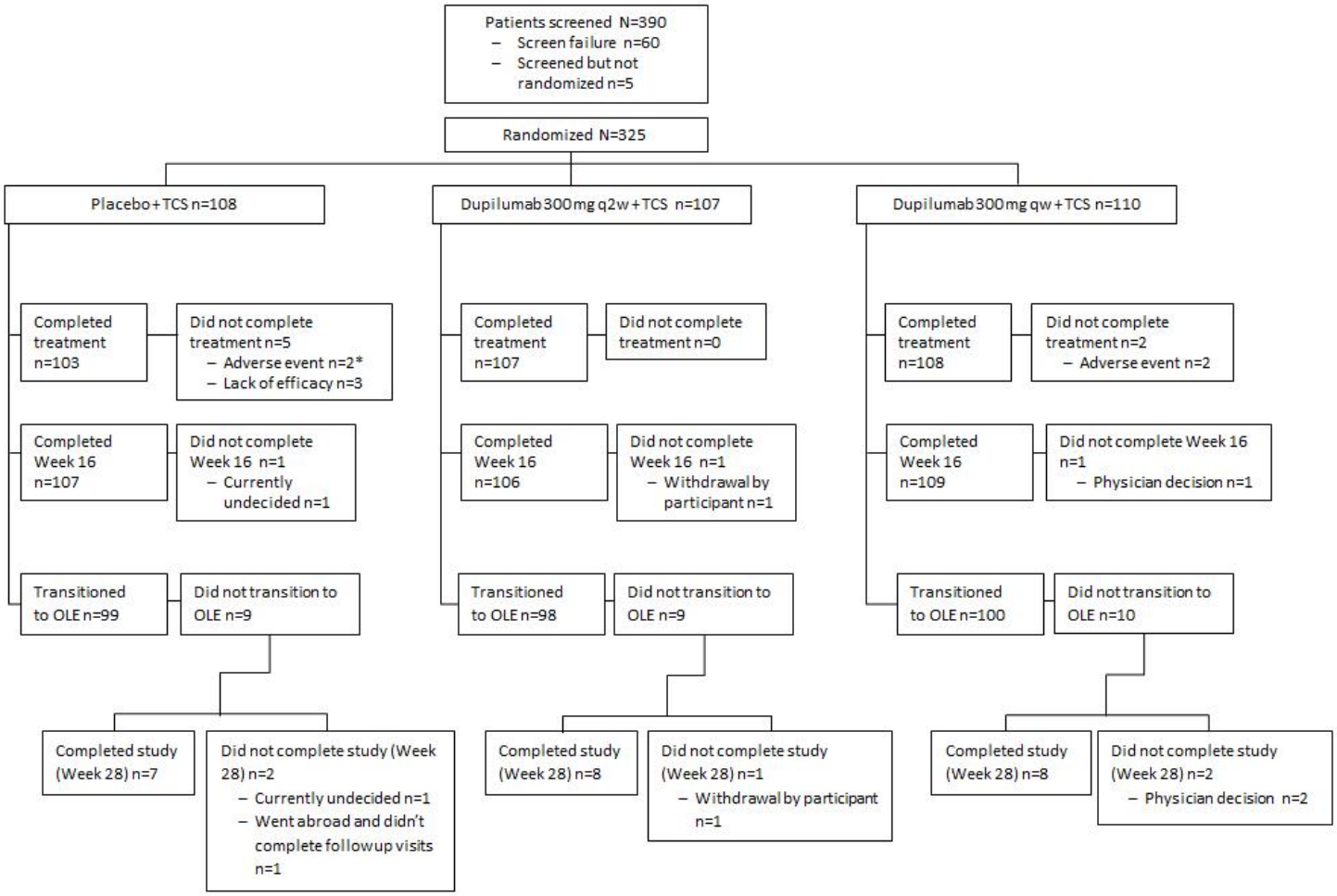
*Patients with at least one such event. †MedDRA HLT. ‡MedDRA PT. HLT, MedDRA high-level term; MedDRA, Medical Dictionary for Regulatory Activities; NEC, not elsewhere classified; PT, preferred term; q2w, every 2 weeks; qw, weekly; TCS, topical corticosteroids.

Table S8. Incidence of herpes virus infection according to treatment group.

	Placebo+TCS (n=108)	**Dupilumab q2w+TCS (n=107)**	**Dupilumab qw+TCS (n=110)**
Patients with herpes viral infections, n (%)	6 (6)	5 (5)	8 (7)
Oral herpes	0	3 (3)	5 (5)
Herpes simplex	3 (3)	1 (1)	1 (1)
Nasal herpes	0	0	2 (2)
Genital herpes	0	1 (1)	0
Herpes zoster infection neurological	0	0	1 (1)*
Eczema herpeticum	1 (1)†	0	0
Ophthalmic herpes simplex	1 (1)	0	0
Ophthalmic herpes zoster	1 (1)*	0	0

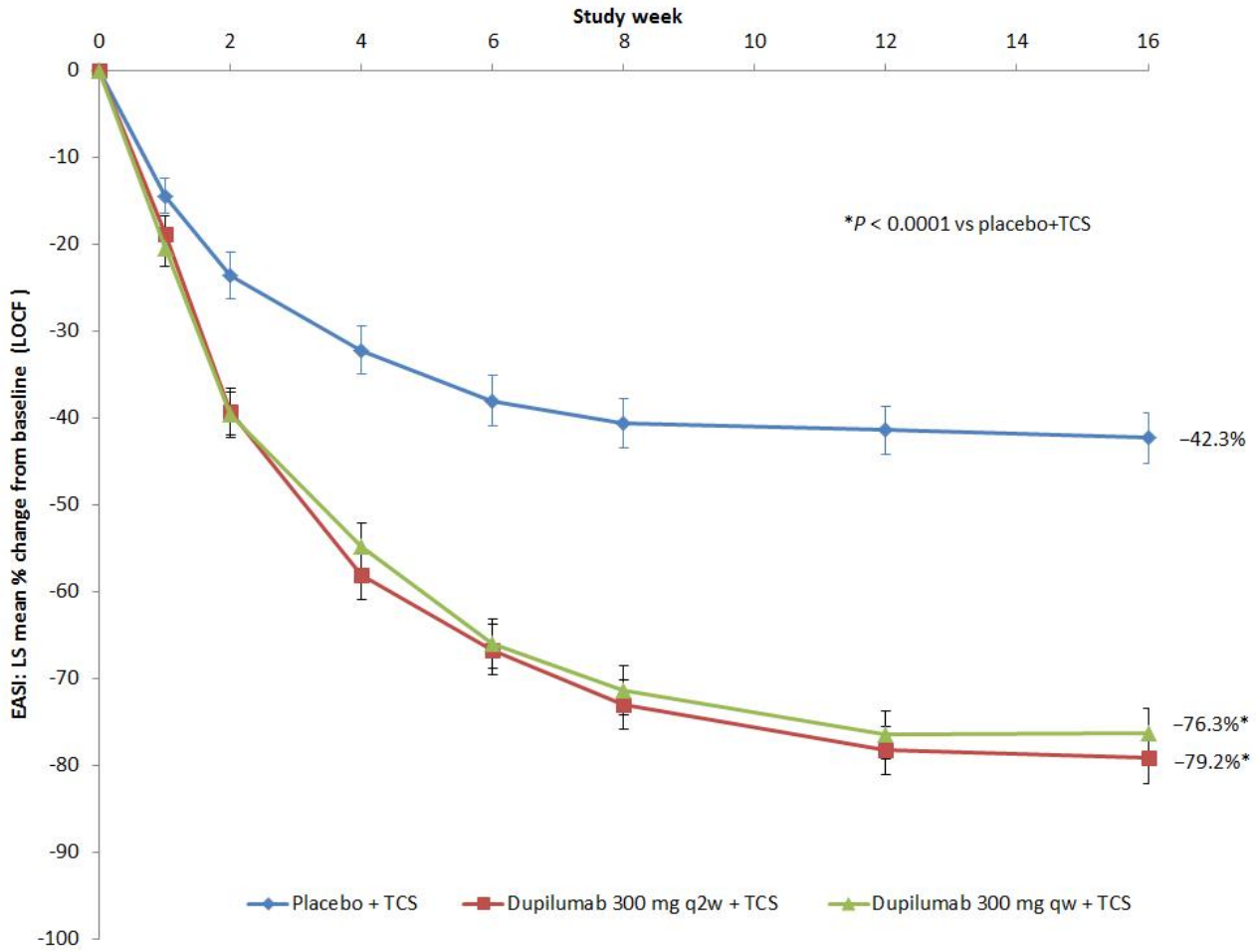
*This AE was of mild severity and considered unrelated to study drug. Pt experienced pain in the shin. PI believed this was neuropathic pain caused by herpetic reactivation, although there were no visible signs of herpetic lesions. Treated with oral acyclovir. Pain resolved after ~3 weeks. Virology tests were conducted but were all negative. †Severity was moderate, duration of ~3 weeks, and the patient also experienced a secondary bacterial skin infection. Treatment was with oral acyclovir. Treatment was temporarily discontinued; the event resolved. q2w, every 2 weeks; qw, weekly; TCS, topical corticosteroids.

Figure S1. CONSORT diagram of patient disposition.



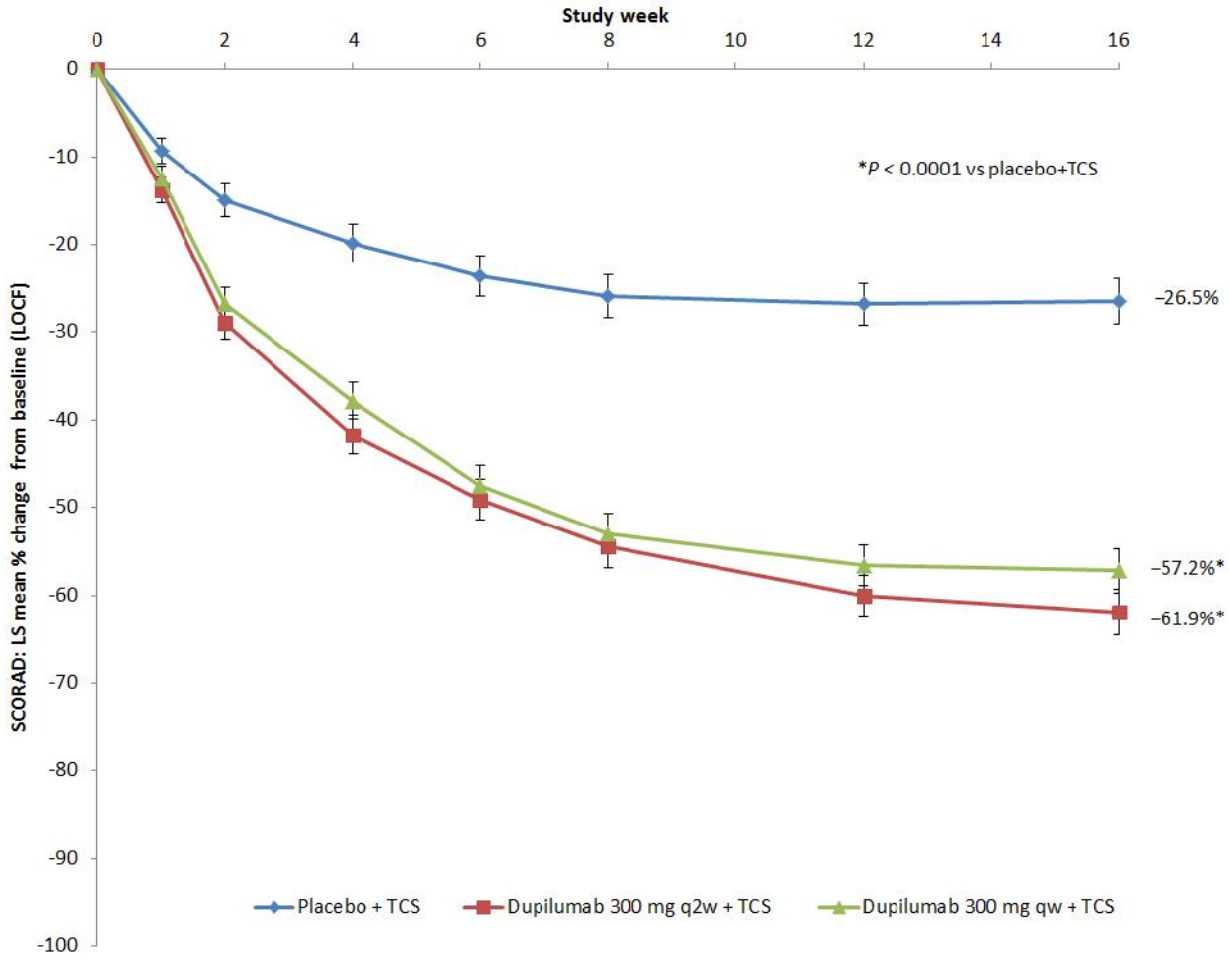
*One patient discontinued due to an adverse event that had onset 3 days prior to baseline.

Figure S2. EASI: LS mean percent change (±SE) from baseline (LOCF).



Error bars are ±SE. EASI, Eczema Area and Severity Index; LOCF, last observation carried forward; LS, least squares; q2w, every 2 weeks; qw, weekly; SE, standard error; TCS, topical corticosteroids.

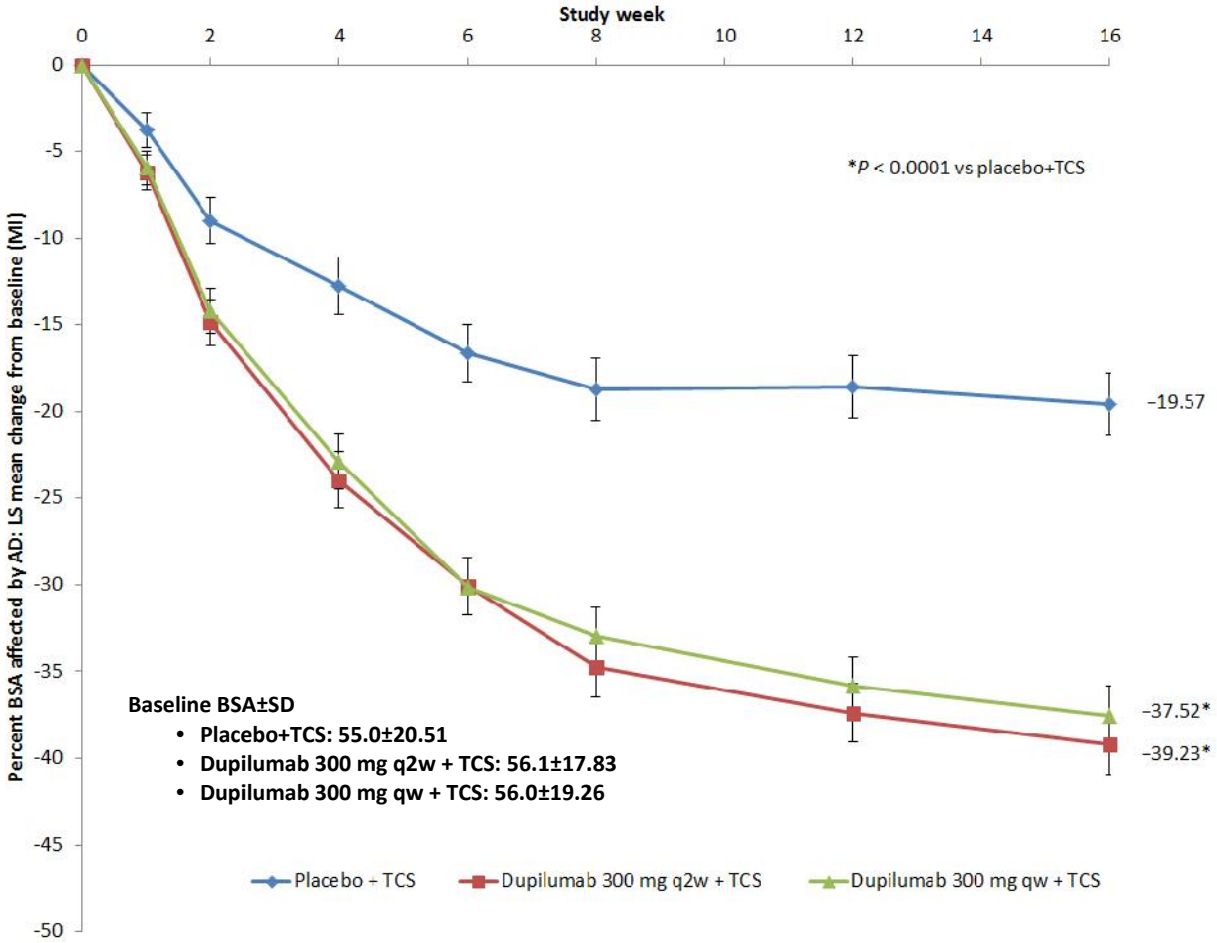
Figure S3. SCORAD: LS mean percent change in SCORAD from baseline (LOCF).



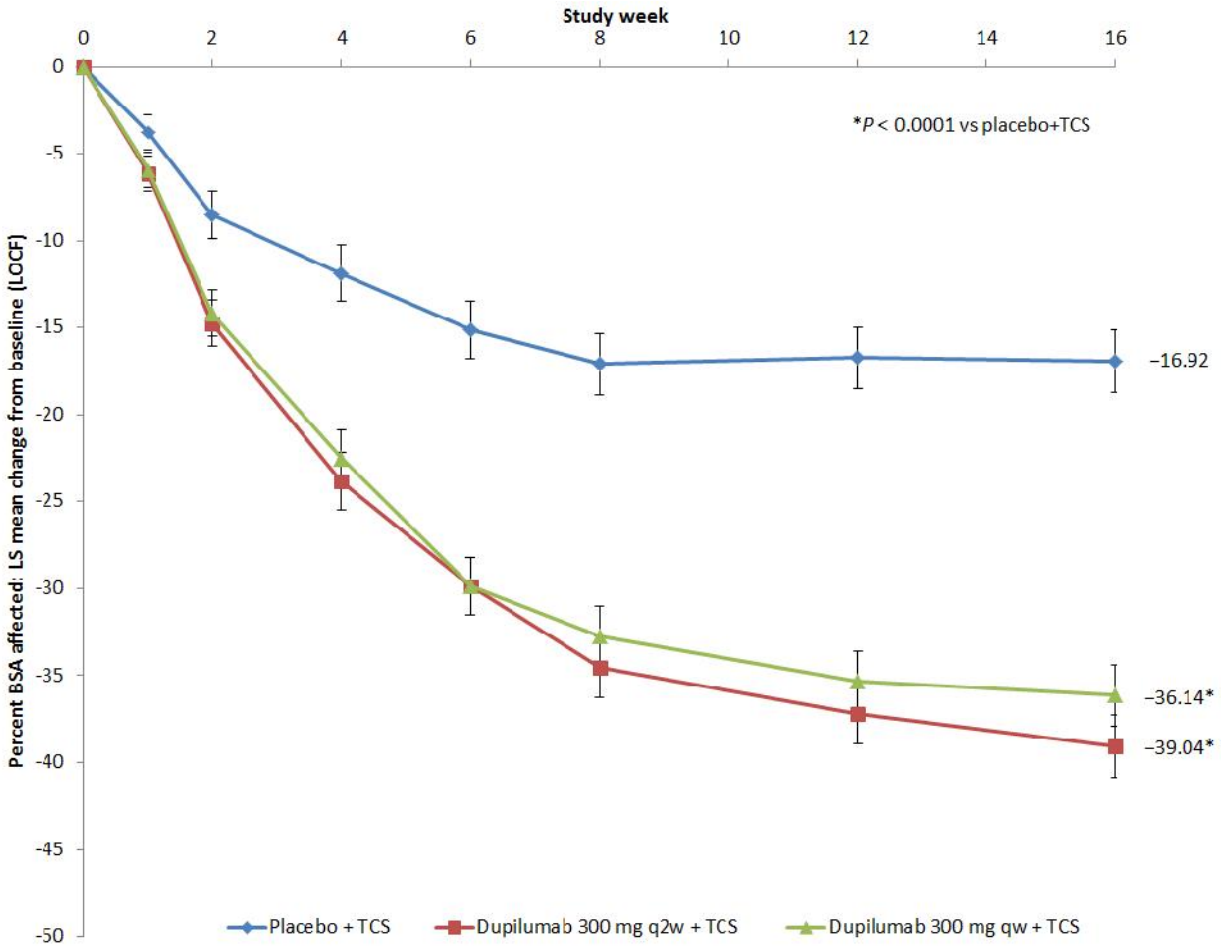
Error bars are ±SE. LOCF, last observation carried forward; LS, least squares; q2w, every 2 weeks; qw, weekly; SCORAD, SCORing Atopic Dermatitis; SE, standard error; TCS, topical corticosteroids.

Figure S4. Percent BSA affected by AD: LS mean change (±SE) from baseline: (a) multiple imputation; (b) LOCF.

(a) Percent BSA affected by AD: LS mean change from baseline (multiple imputation)

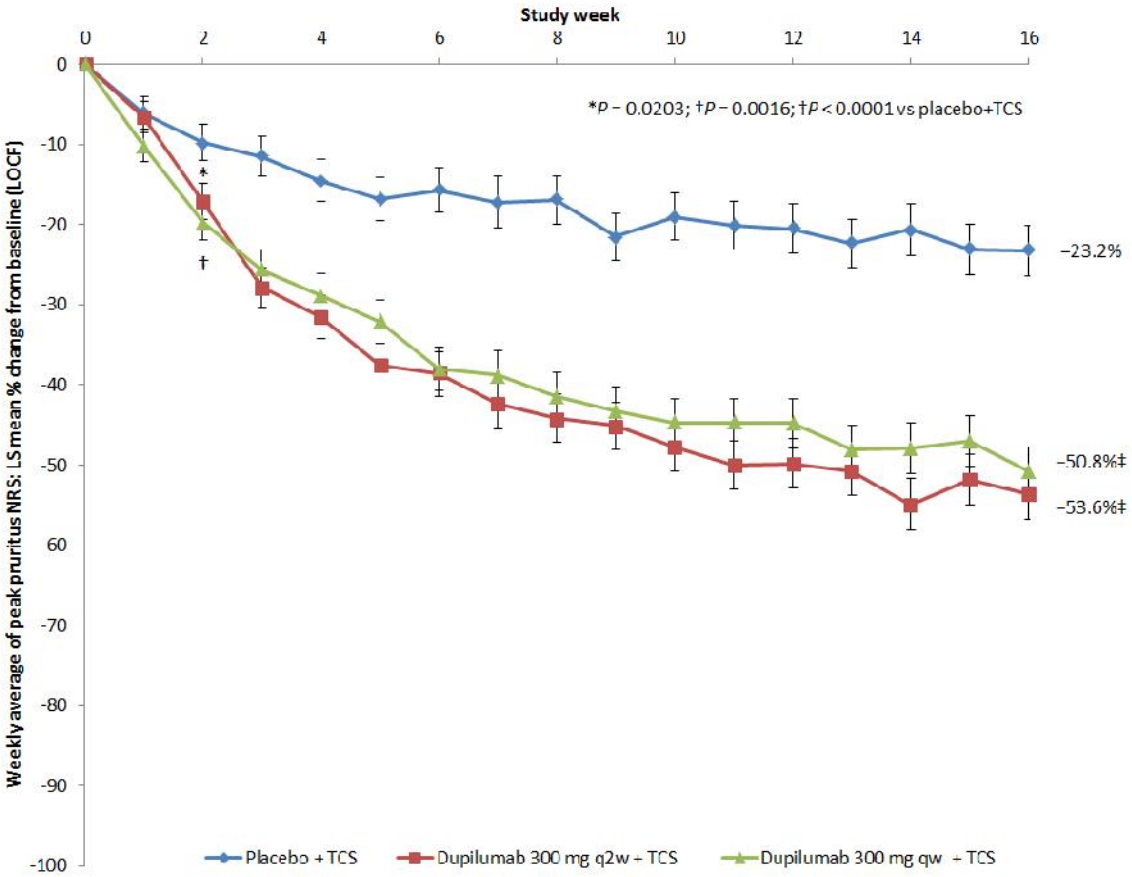


(b) Percent BSA affected by AD: LS mean change from baseline (LOCF)



Error bars are ±SE. AD, atopic dermatitis; BSA, body surface area; LOCF, last observation carried forward; LS, least squares; MI, multiple imputation; q2w, every 2 weeks; qw, weekly; SE, standard error; TCS, topical corticosteroids.

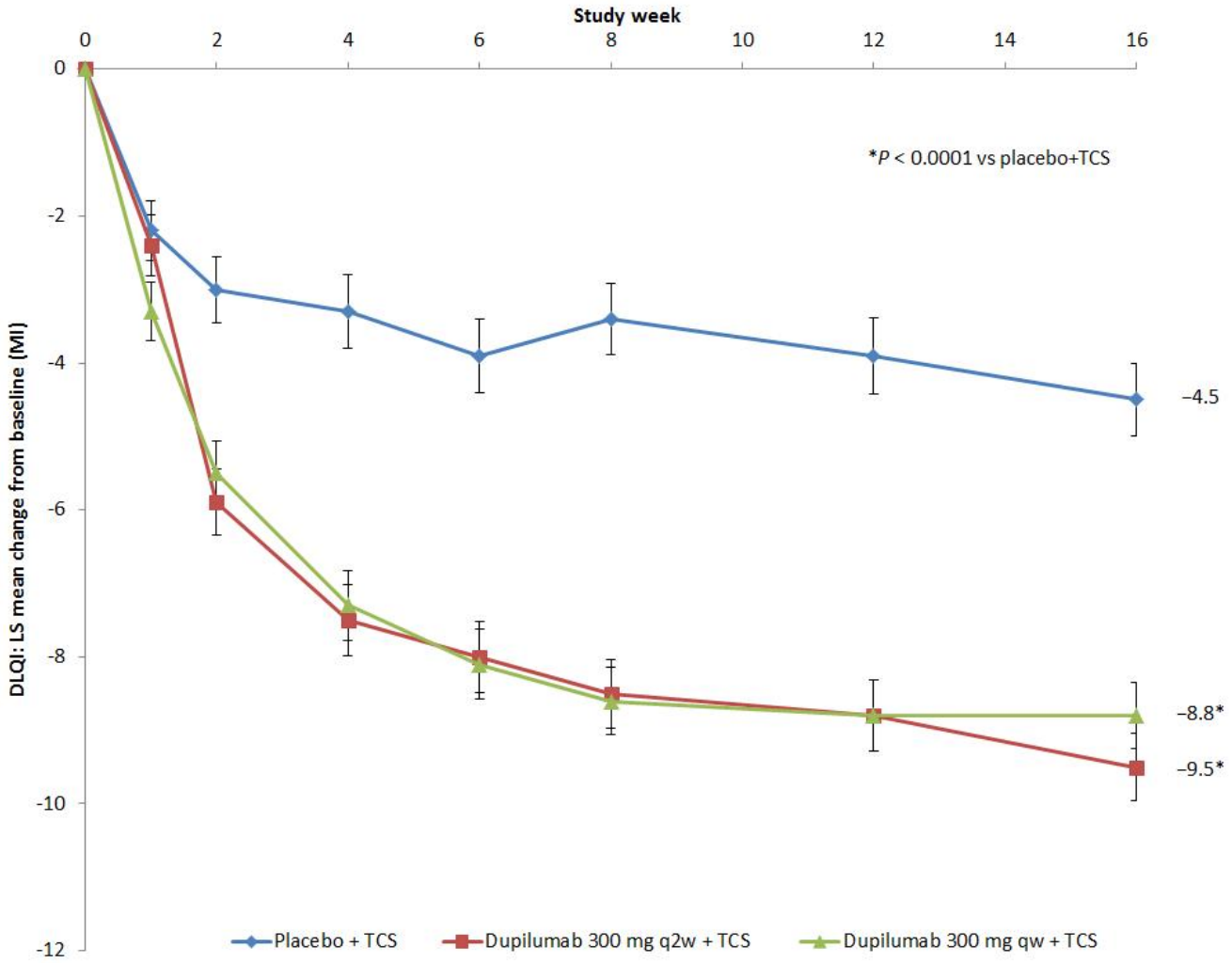
Figure S5. Peak weekly pruritus NRS: LS mean percent change (±SE) from baseline (LOCF).



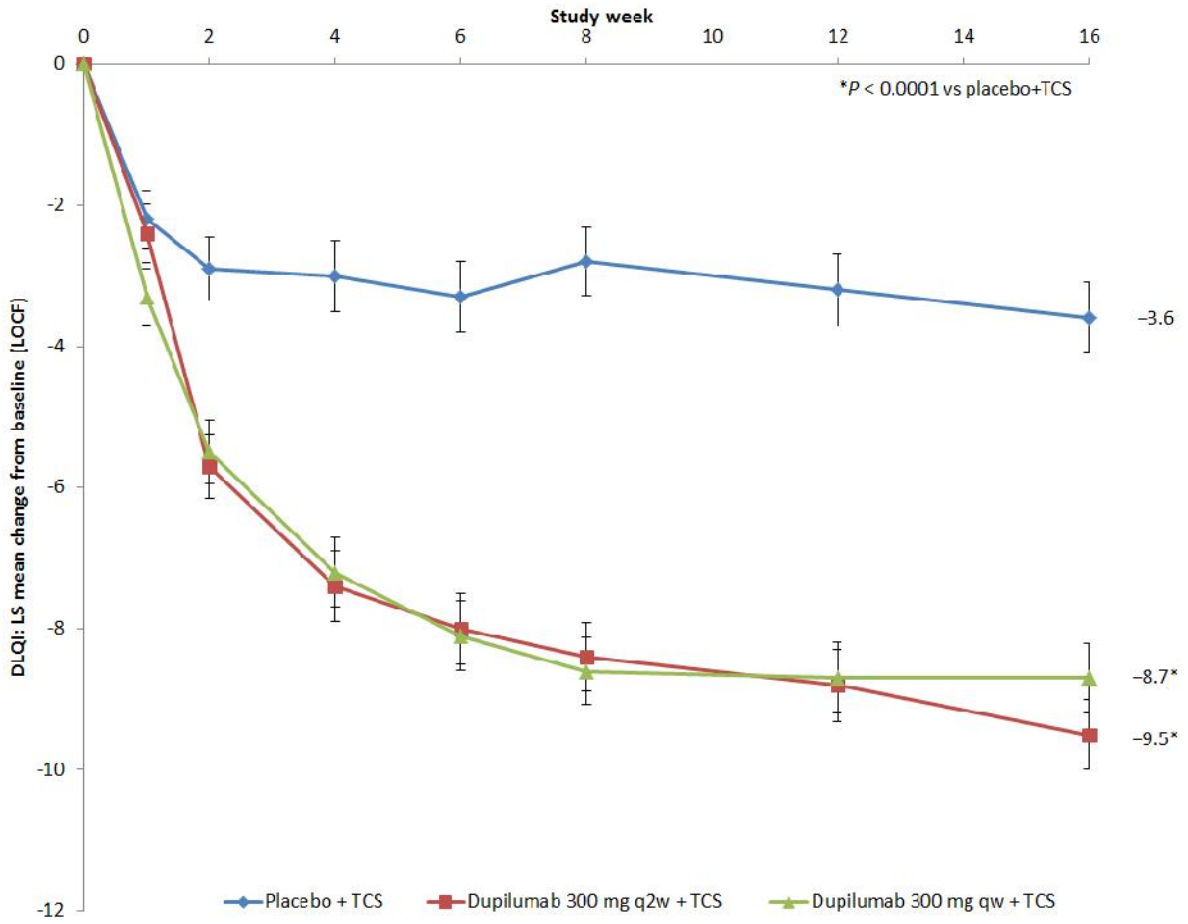
Error bars are ±SE. LOCF, last observation carried forward; LS, least squares; NRS, numerical rating scale; q2w, every 2 weeks; qw, weekly; SE, standard error; TCS, topical corticosteroids.

Figure S6. DLQI: LS mean change from baseline: (a) multiple imputation; (b) LOCF.

(a) DLQI: LS mean change from baseline (multiple imputation)



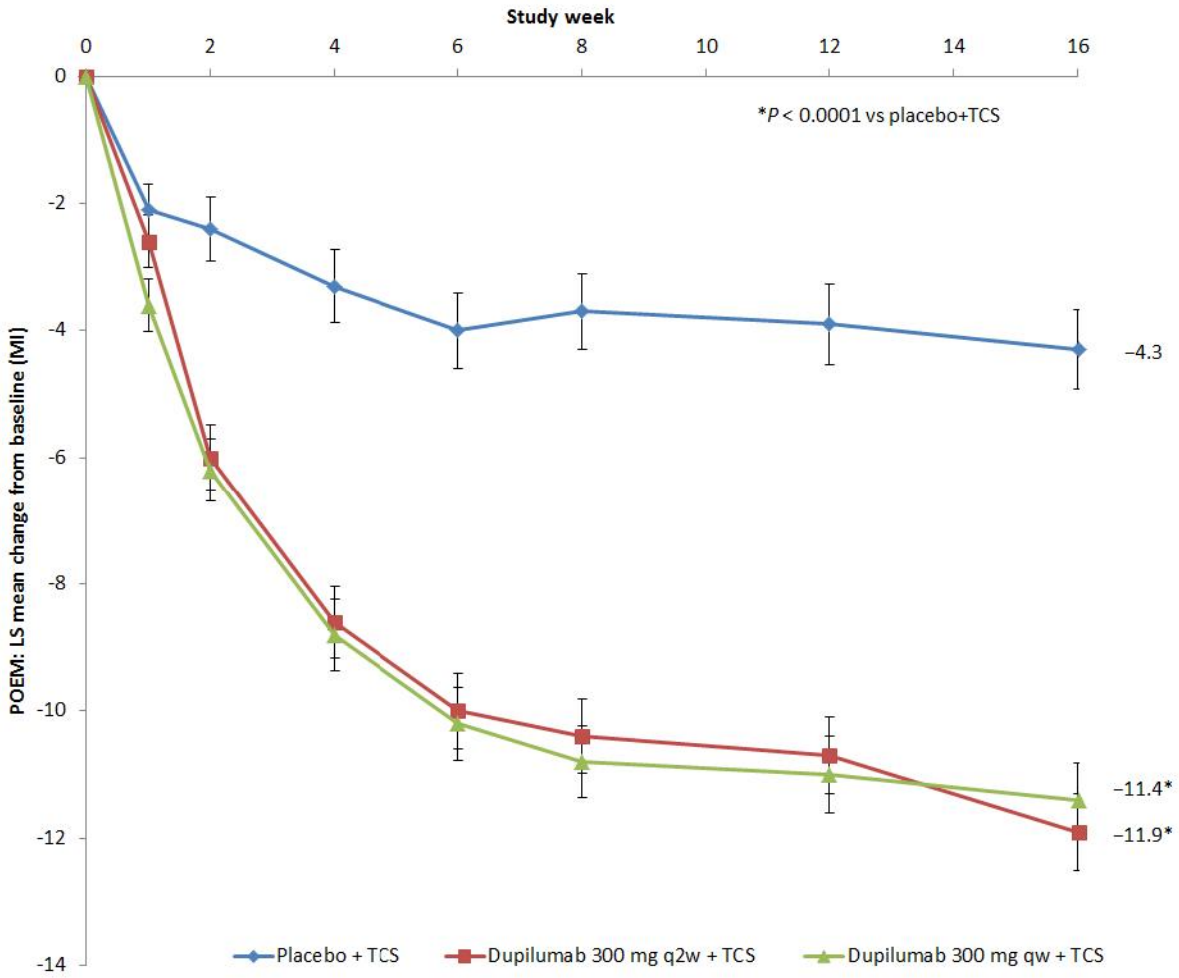
(b) DLQI: LS mean change from baseline (LOCF)



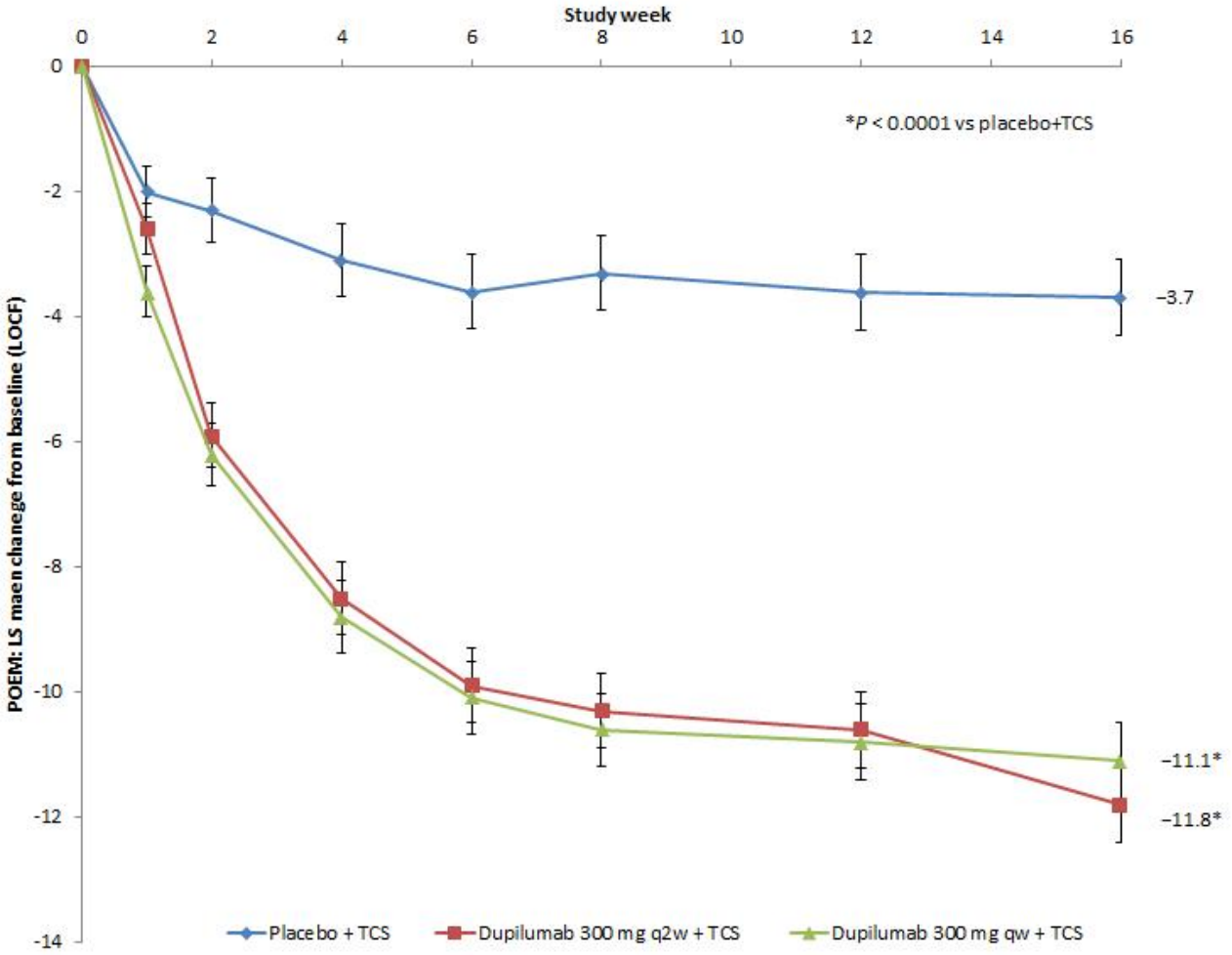
Error bars are ±SE. DLQI, Dermatology Life Quality Index; LOCF, last observation carried forward; LS, least squares; MI, multiple imputation; q2w, every 2 weeks; qw, weekly; SE, standard error; TCS, topical corticosteroids.

Figure S7. POEM: LS mean change from baseline: (a) multiple imputation; (b) LOCF.

(a) POEM: LS mean change from baseline, multiple imputation



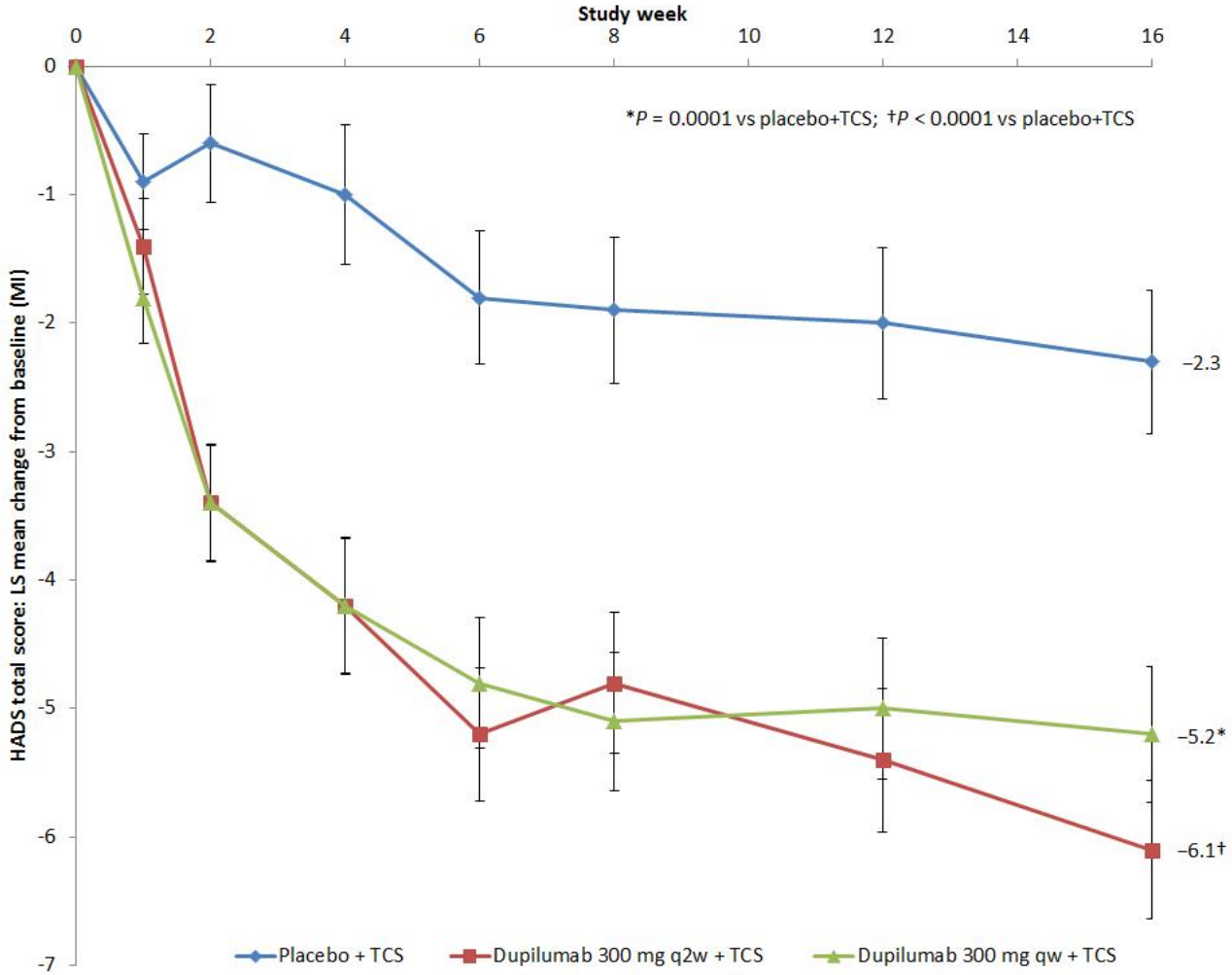
(b) POEM: LS mean change from baseline (LOCF)



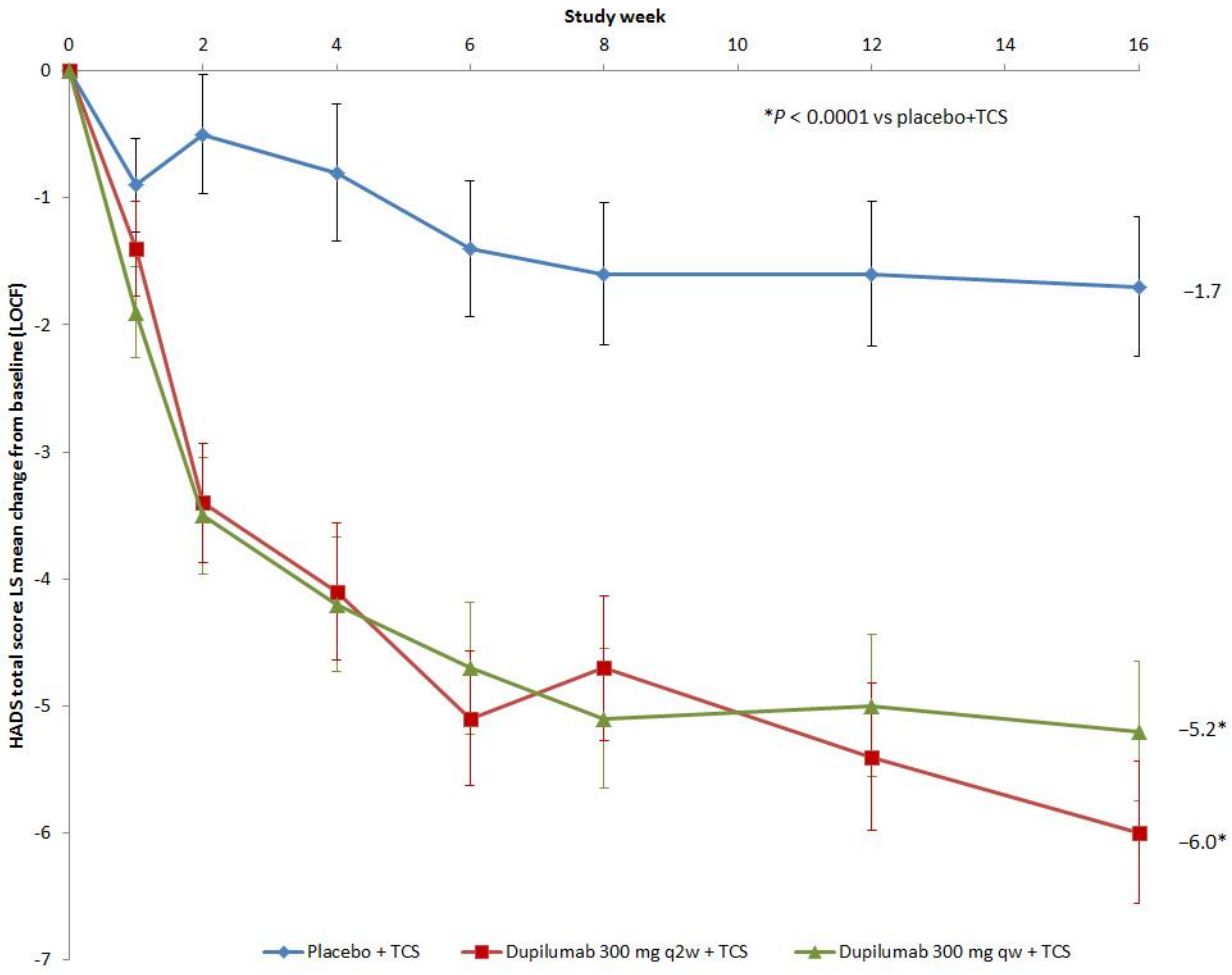
Error bars are ±SE.POEM, Patient-Oriented Eczema Measure; LOCF, last observation carried forward; LS, least squares; MI, multiple imputation; q2w, every 2 weeks; qw, weekly; TCS, topical corticosteroids.

Figure S8. HADS total score: LS mean change from baseline: (a) multiple imputation; (b) LOCF.

(a) HADS total score: LS mean change from baseline, multiple imputation



(b) HADS total score: LS mean change from baseline, LOCF



Error bars are ±SE. HADS, Hospital Anxiety and Depression Score; LOCF, last observation carried forward; LS, least squares; MI, multiple imputation; q2w, every 2 weeks; qw, weekly; SE, standard error; TCS, topical corticosteroids.

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