Supplementary Appendix

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

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Drug Administration

Study drug (dupilumab or placebo) was administered subcutaneously weekly for 16 weeks (baseline [week 0] to week 15) following a 35-day screening and washout period. Patients assigned to receive dupilumab every other week alternated dupilumab injections with matching placebo in order to preserve the blind. Patients could choose to self-administer study drug (or have it administered by a caregiver) outside the clinic off-site during the weeks in which no clinic visits were scheduled. Patients and/or caregivers were trained by study staff; study staff administered the first dose and the patient or caregiver administered the second under the supervision of the study staff, followed by supervised self-administration at visits 2–4 in the clinic. Patients who preferred to have the study drug administered by study staff could have all doses administered in the clinic.

Post-Treatment Follow-Up

During the 16-week treatment period, patients had weekly study visits (some visits could be conducted by telephone). Clinical assessments were performed, safety was assessed, and blood samples were collected at specified clinic visits. At the end of the treatment period, eligible patients (who had achieved an Investigator's Global Assessment [IGA] score of 0 or 1 or ≥75% improvement from baseline in the Eczema Area Severity Index score [EASI-75] at week 16 with no rescue therapy) could enter a maintenance study (LIBERTY AD SOLO-CONTINUE; R668-AD-1415; NCT02395133); if they chose not to participate in the maintenance study, they could opt to enroll in an open-label extension study (LIBERTY AD MAINTAIN; R668-AD-1225; NCT01949311) but no earlier than 36 weeks after week 16. Patients ineligible for the maintenance study entered a safety follow-up period of at least 4 weeks after week 16 through week 28. Starting at week 20 they were eligible to enroll in the open-label extension study if

they had an IGA score of ≥3; patients with an IGA score of <3 continued follow-up to week 28 or until they had an IGA score of 3 or 4, whichever occurred first.

Rescue Treatments

If medically necessary (i.e., to control unacceptable atopic dermatitis symptoms), rescue treatment for atopic dermatitis with otherwise prohibited medications could be provided to study patients at the discretion of the investigator. For the purpose of efficacy analysis, patients who received rescue treatment during the study treatment period were considered treatment failures, but they could continue study treatment if rescue treatment consisted of topical medications (e.g., topical corticosteroids, topical calcineurin inhibitors). Topical calcineurin inhibitors were to be reserved for problem areas only, e.g., face, neck, intertriginous and genital areas, etc. If possible, investigators were to attempt to limit the first step of rescue therapy to topical medications, and escalate to systemic medications only in patients who did not respond adequately after at least 7 days of topical treatment. If a patient received rescue treatment with systemic corticosteroids or nonsteroidal systemic immunosuppressive drugs (e.g., cyclosporine, methotrexate, mycophenolate mofetil, azathioprine, etc.), study treatment was to be immediately discontinued. After treatment with these medications was completed, study treatment could be resumed if deemed appropriate by the investigator and the medical monitor, but no earlier than 5 half-lives after the last dose of systemic rescue medication. All patients were to complete the schedule of study visits and assessments whether or not they completed study treatment, and whether or not they received rescue treatment for atopic dermatitis. Investigators were to make every attempt to conduct efficacy and safety assessments (e.g., disease severity scores, safety labs) immediately before administering any rescue treatment. An unscheduled visit could be used for this purpose if necessary.

Detailed Inclusion Criteria

- Male or female, ≥18 years of age
- Chronic atopic dermatitis (according to American Academy of Dermatology Consensus Criteria[1]) that has been present for ≥3 years before screening
- EASI score of ≥16 at screening and baseline
- IGA score of ≥3 (on a scale of 0–4, in which 3 is moderate and 4 is severe) at screening and baseline
- ≥10% body-surface area of atopic dermatitis involvement at screening and baseline
- Baseline pruritus numerical rating scale average score for maximum itch intensity of ≥3, based on the average of daily pruritus numerical rating scale scores for maximum itch intensity reported during the 7 days prior to randomization
- Documented recent history (within 6 months prior to screening) of inadequate response to treatment with topical medications, or patients for whom topical treatments are otherwise medically inadvisable (e.g., because of important side effects or safety risks)
    - Inadequate response is defined as failure to achieve and maintain remission or a low disease activity state (comparable to an IGA score of 0 [indicating clear] to 2 [indicating mild] despite treatment with a daily regimen of topical corticosteroids of medium to higher potency (with or without topical calcineurin inhibitors as appropriate), applied for ≥28 days or for the maximum duration recommended by the product prescribing information (e.g., 14 days for super-potent topical corticosteroids), whichever is shorter
    - Patients with documented systemic treatment for atopic dermatitis in the preceding 6 months are also considered to be inadequate responders to topical treatments and are potentially eligible for treatment with dupilumab after appropriate washout

  - Important side effects or safety risks are those that outweigh the potential treatment benefits and include: intolerance to treatment, hypersensitivity reactions, significant skin atrophy, and systemic effects, as assessed by the investigator or by the patient's treating physician
  - Acceptable documentation includes contemporaneous chart notes that record topical medication prescription and treatment outcome, or investigator documentation based on communication with the patient's treating physician. If documentation is inadequate, potential patients may be re-screened after such documentation is obtained (i.e., patients are shown to fail a 28-day course of mid-to-higher potency topical corticosteroids [with or without topical calcineurin inhibitors]).
- Has applied a stable dose of topical emollient (moisturizer) twice daily for ≥7 consecutive days immediately before the baseline visit
- Is willing and able to comply with all clinic visits and study-related procedures
- Is able to understand and complete study-related questionnaires
- Provides signed informed consent

Detailed Exclusion Criteria

- Participation in a prior dupilumab study
- Treatment with an investigative drug within 8 weeks or within 5 half-lives (if known), whichever is longer, before baseline
- Treatment with immunosuppressive/immunomodulatory drugs or phototherapy for atopic dermatitis within 4 weeks of baseline, or any condition that, in the opinion of the investigator, was likely to require such treatment(s) during the first 4 weeks of study treatment
- Treatment with topical corticosteroids or topical calcineurin inhibitors within 1 week of baseline
- Treatment with biologics as follows:
  - Any cell-depleting agents including, but not limited to, rituximab: within 6 months prior to baseline visit, or until lymphocyte count returns to normal, whichever is longer
  - Other biologics: within 5 half-lives (if known) or 16 weeks prior to baseline visit, whichever is longer
- Initiation of treatment of atopic dermatitis with prescription moisturizers or moisturizers containing additives such as ceramide, hyaluronic acid, urea, or filaggrin degradation products during the screening period (patients may continue to use stable doses of such moisturizers if initiated before the screening visit)
- Regular use (≥2 visits per week) of a tanning booth/parlor within 4 weeks of the baseline visit
- Planned or anticipated use of any prohibited medications and procedures during study treatment
- Treatment with a live (attenuated) vaccine within 12 weeks prior to the baseline visit
- Active chronic or acute infection requiring treatment with systemic antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals within 2 weeks prior to the baseline visit, or

superficial skin infections within 1 week prior to the baseline visit. NOTE: patients may be rescreened after infection resolves

- Known or suspected history of immunosuppression, including history of invasive opportunistic infections (e.g., tuberculosis, histoplasmosis, listeriosis, coccidioidomycosis, pneumocystis, aspergillosis) despite infection resolution; or unusually frequent, recurrent, or prolonged infections, per investigator judgment
- History of human immunodeficiency virus (HIV) infection or positive HIV serology at screening
- Positive for hepatitis B surface antigen, hepatitis B core antibody, or hepatitis C antibody at the screening visit
- At baseline, presence of any conditions listed as criteria for study drug discontinuation
- Presence of skin comorbidities that may interfere with study assessments
- History of malignancy within 5 years before the screening visit, except completely treated in situ carcinoma of the cervix, and completely treated and resolved nonmetastatic 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 assessments have ruled out active infection before randomization
- History of alcohol or drug abuse within 2 years before the screening visit
- Severe concomitant illness(es) that, in the investigator's judgment, would adversely affect the patient's participation in the study
- Any other medical or psychological condition (including relevant laboratory abnormalities at screening) that, in the opinion of the investigator, may suggest a new and/or insufficiently understood disease, may present an unreasonable risk to the study patient as a result of his/her participation in the study, may make patient's participation unreliable, or may interfere with

study assessments. The specific justification for patients excluded under this criterion will be noted in study documents (chart notes, case report forms, etc.)

- Planned or anticipated major surgical procedure during the patient's participation in this study
- Membership of the investigational team or his/her immediate family
- Pregnant or breastfeeding women, or women planning to become pregnant or breastfeed during the study
- Women unwilling to use adequate birth control, if of reproductive potential and sexually active
- For further details, please see the study protocol posted at NEJM.org

Prohibited Concomitant Medications and Procedures

- Treatment with the following concomitant medications is prohibited during the study
  - Treatment with a live (attenuated) vaccine
  - Treatment with immunomodulating biologics
  - Treatment with an investigational drug (other than dupilumab)
  - Treatment with topical corticosteroids or topical calcineurin inhibitors; such agents could be administered during the study only if required for atopic dermatitis rescue. If topical corticosteroids and/or topical calcineurin inhibitors were used during the study, study treatment could continue as planned
  - Treatment with systemic corticosteroids or nonsteroidal systemic immunosuppressive drugs (e.g., cyclosporine, methotrexate, mycophenolate-mofetil, azathioprine, etc.), except if required for atopic dermatitis rescue, or if critically medically needed to treat concurrent medical conditions (e.g., asthma)
- Study drug will be discontinued if any of the following are used through week 16
  - Treatment with a live (attenuated) vaccine
  - Treatment with an investigational drug (other than dupilumab)
  - Treatment with systemic corticosteroids or nonsteroidal systemic immunosuppressive drugs (e.g., cyclosporine, methotrexate, mycophenolate-mofetil, azathioprine, etc.)

NOTE: If a patient receives treatment with systemic corticosteroids or other systemic immunosuppressive drugs (e.g., cyclosporine, methotrexate, mycophenolate-mofetil, azathioprine, etc.), study treatment will be discontinued immediately. After treatment with these medications is completed, study treatment may be 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 concomitant procedures are prohibited during study participation
  - Major elective surgical procedures
  - Phototherapy
  - Tanning in a bed/booth

Efficacy Outcomes to the Studies

- Key secondary end points
  - Proportion of patients with EASI-75 at week 16 (in countries in which this is not a coprimary end point)
  - Proportion of patients with ≥4-point improvement (reduction) of weekly average of peak daily pruritus numerical rating scale score from baseline to week 16
  - Proportion of patients with ≥3-point improvement (reduction) of weekly average of peak daily pruritus numerical rating scale score from baseline to week 16
  - Percent change from baseline to week 16 in weekly average of peak daily pruritus numerical rating scale score
  - Proportion of patients with ≥4-point improvement (reduction) of weekly average of peak daily pruritus numerical rating scale score from baseline to week 4
  - Proportion of patients with ≥4-point improvement (reduction) of weekly average of peak daily pruritus numerical rating scale score from baseline to week 2
- Other secondary end points
  - Change in weekly average of peak daily pruritus numerical rating scale score from baseline to week 16
  - Percent change in EASI score from baseline to week 16
  - Proportion of patients with improvement from baseline of ≥50% in EASI score (EASI-50) at week 16
  - Proportion of patients with improvement from baseline of ≥90% in EASI score (EASI-90) at week 16
  - Change from baseline to week 16 in percent body-surface area affected

  - Percent change from baseline to week 16 in Scoring Atopic Dermatitis (SCORAD) score
  - Change from baseline to week 16 in Dermatology Life Quality Index (DLQI) total score
  - Change from baseline to week 16 in Patient-Oriented Eczema Measure (POEM) total score
  - Change from baseline to week 16 in Hospital Anxiety and Depression Scale (HADS) total score
  - Percent change from baseline to week 16 in Global Individual Signs Score (GISS)
  - Percent change from baseline to week 2 in weekly average of peak daily pruritus numerical rating scale score
  - Incidence of skin infection adverse events requiring systemic treatment from baseline through week 16
  - Incidence of serious adverse events from baseline through week 16
  - Incidence of adverse events leading to treatment discontinuation from baseline through week 16
- Additional secondary end points
  - Proportion of patients with HADS anxiety (HADS-A) and HADS depression (HADS-D) subscores of <8 at week 16, among patients with HADS-A or HADS-D score of ≥8 at baseline
  - Proportion of patients with ≥4-point improvement in POEM total score
  - Proportion of patients with ≥4-point improvement in DLQI total score
- Additional efficacy end points
  - Change and percent change from baseline to week 16 in EuroQol 5-Dimension Health Questionnaire score[2]

- Proportion of patients who respond “absence of pruritus” or “mild pruritus” in the Pruritus Categorical Scale at week 16[3]
- Proportion of patients who respond “very good” or “excellent” in the Patient Global Assessment of Disease Status at week 16
- Proportion of patients who respond “very good” or “excellent” in the Patient Global Assessment of Treatment Effect at week 16
- Proportion of patients who achieve a reduction in the IGA score of ≥2 from baseline to week 16
- Proportion of patients who achieve a reduction in the IGA score of ≥3 from baseline to week 16
- Assessment of sick leave/missed school days

Additional Statistical Methods

Multiple imputation analyses

Multiple imputation with an analysis of covariance (ANCOVA) model was the primary analysis for continuous variables. Patients' efficacy data through week 16 after rescue medication usage were set to missing first, and then were imputed by the multiple imputation method. Missing data from the full analysis set were imputed 50 times to generate 50 complete data sets by using the Statistical Analysis System (SAS) procedure "MI" following the two steps below:

Step 1: The monotone missing pattern was induced by Markov Chain Monte Carlo (MCMC) method in the "MI" procedure. The monotone missing pattern means that if a patient had a missing value for a variable at a visit, then the values at all subsequent visits for the same variable are all missing for the patient.

Step 2: The missing data at subsequent visits were imputed using the regression method for the monotone pattern with adjustment for covariates including treatment groups, randomization strata (region, disease severity), and relevant baseline.

The week-16 data of each of the 50 complete data sets were analyzed using an ANCOVA model with treatment, randomization strata (region, disease severity), and relevant baseline values included in the model, and the SAS MIANALYZE procedure was used to generate valid statistical inferences by combining results from the 50 analyses using Rubin's formula.

The multiple imputation model included:

- the covariates included in the ANCOVA model, including treatment group, baseline values, and randomization strata
- measured end point values from every clinic visit up to week 16

Categorical variables included in the above model (i.e., treatment group and randomization strata) were not expected to be missing.

To account for the impact of rescue medication on the efficacy effect for continuous end points, the data collected after rescue medication was initiated were treated as missing.

Methods for sensitivity analysis of efficacy outcomes

For binary outcomes, prespecified sensitivity analyses were all performed using the Cochran–Mantel–Haenszel test after various missing data-handling approaches described as follows:

1. Last observation carried forward (LOCF) for imputation of missing data, with patients after rescue treatment or patients withdrawing from the study considered as non-responders
2. All observed values regardless of rescue treatment or study withdrawal; patients with missing data treated as non-responders
3. All observed values regardless of rescue treatment or study withdrawal; missing data were not imputed

For continuous end points, prespecified sensitivity analyses were as follows:

1. Multiple imputation using all observed data regardless of rescue medication use or if data were collected after withdrawal

2. Mixed-effect repeated-measures model with data collected after rescue medication use treated as missing. The model included factors (fixed effects) for treatment, baseline strata, visit, baseline value, treatment-by-visit interaction, and baseline-by-visit interaction as covariates. An unstructured covariance matrix was used to model the within-patient errors. Denominator degrees of freedom were estimated using approximation of SATTERTH. The efficacy data were set to missing after rescue medication was used. No imputation was made
3. Data collected after rescue medication use treated as missing, followed by the LOCF method and ANCOVA model, using the treatment group, baseline value, and randomization strata
4. Data collected after rescue medication use treated as missing, followed by worst observation carried forward method and ANCOVA using the treatment group, baseline value, and randomization strata
5. ANCOVA model using study, treatment group, baseline value, and randomization strata; efficacy data were based on all observed values, regardless of rescue medication use, without imputation.

Sample size and power

To detect a 29% difference between dupilumab and placebo treatment in the proportion of patients achieving the primary end point of the proportion of patients achieving an IGA score of 0 or 1 at week 16, assuming the percentages are 38% and 9% for dupilumab and placebo, respectively, the enrollment of 55 patients per group provided 90% power. However, to provide sufficient safety data and ensure sufficient responders for the maintenance study, the sample size was increased to 600 patients in total for each study, with a randomization ratio of 1:1:1 dupilumab 300 mg weekly:dupilumab 300 mg every other week:placebo. It was estimated that with 200 patients per group, this would provide 99% power in both comparisons (between dupilumab 300 mg weekly and placebo, and between dupilumab 300 mg

every other week and placebo). The same number of patients can also provide 99% power to detect a difference of 43% in the percentages of patients achieving EASI-75 response at week 16, assuming that the percentages are 58% and 15% for dupilumab and placebo, respectively.

To control for the overall type-1 error rate at 0.05 for primary and secondary end points across dose regimens, in consideration of multiplicity, a significance level of 0.025, two-sided, was used for comparisons of each dupilumab dose group with placebo, according to a prespecified hierarchical order. Statistical significance of differences between the dose groups was not investigated.

An additional power calculation was based on the secondary end point "proportions of patients with improvement of weekly average of peak daily pruritus numerical rating scale score of ≥4 from baseline to week 16"; as the analysis includes patients with baseline peak pruritus numerical rating scale score of ≥4, and assuming that 180 such patients would be randomized into each treatment group, with responder rates of 39% and 9% for dupilumab and placebo, respectively, the analysis can provide 99% power at a level of 0.025 from each comparison.

Analysis sets

Efficacy analyses were carried out using the full analysis set, which included all randomized patients. For the proportion of patients with a 3- or 4-point improvement in peak pruritus numerical rating scale score, the analysis was conducted only in patients with baseline pruritus numerical rating scale score of ≥3 or numerical rating scale score of ≥4, respectively. For the proportions of patients achieving a ≥4-point improvement in DLQI or POEM score from baseline, the analysis was carried out only in patients with baseline DLQI or POEM total score of ≥4. For the proportion of patients achieving a HADS-A and HADS-D score of <8, the analysis was carried out only in patients with baseline HADS-A or HADS-D score

of ≥8. Safety analyses were carried out using the safety analysis set, which included all randomized patients who received a dose of any study drug.

Narratives of Patient Deaths

Overview: There were two deaths in the dupilumab groups in SOLO 2. The detailed patient narratives are provided here.

Patient 1: Female patient, 49 years of age

DESCRIPTION OF EVENTS QUALIFYING FOR REPORTING IN THE NARRATIVE

On study day 170 (October 23, 2015), the patient had serious adverse events of severe intensity, reported as asthma attack (asthma), anoxic encephalopathy (hypoxic-ischemic encephalopathy), and respiratory failure (respiratory failure). The events were serious because they required hospitalization, were considered life-threatening, and resulted in death. The patient died on November 11, 2015 (study day 189) due to these events. The investigator's assessment of causality was "not related" to study drug.

NARRATIVE

The investigational product (IP subcutaneous) had been started on May 7, 2015. The most recent dose of IP before the event was on August 19, 2015 (study day 105). At that time, the patient had received a total of 16 doses of study drug (8 doses of 300 mg dupilumab every other week and 8 doses of placebo every other week on alternate weeks). At the time of the event, the patient was in follow-up and no longer receiving IP.

The patient had a history of asthma since 1990. The only recorded therapy for asthma until October 22, 2015, was an albuterol inhaler and albuterol as a nebulizer at home. The patient had taken two

nonsteroidal anti-inflammatory drugs for sciatica since July 2015; naproxen was taken constantly and ibuprofen as needed. Valproic acid was started in 1990 for bipolar disorder. The patient had been a smoker for 30 years.

On October 22, 2015, the patient received a Benadryl® (diphenhydramine) injection for itching from her primary care physician. The patient had an asthma attack flare-up at this time. During the visit, the patient was coughing and wheezing and received Qvar® (beclomethasone dipropionate HFA). The patient was seen for follow-up for eczema but complained of cough for 5 days. The patient had used her albuterol nebulizer at home without any effect.

On October 23, 2015 (study day 170), 5 months after the first IP administration (and approximately 2 months after the last IP administration), the patient experienced serious adverse events of asthma, hypoxic–ischemic encephalopathy, and respiratory failure, all of severe intensity. The events were considered life-threatening and eventually resulted in death. On that day, the patient awoke very short of breath with a cough and had no improvement with the use of an inhaler. The patient stood up to breathe better and became pale, turned blue, and lost consciousness. The patient was apneic for 2 minutes prior to emergency-personnel arrival. The patient lost pulse twice. Epinephrine was administered twice. The patient had an initial gain of pulse but was found in asystole in the emergency room. The patient was admitted to the hospital because of a life-threatening asthma attack. The patient arrived intubated and ventilated. The patient was experiencing the events asthma attack, cardiac arrest, and respiratory arrest, all considered severe in intensity.

The patient developed seizures and was in a medically induced coma because she was fighting the ventilator.

During hospitalization, the patient was treated with saline, norepinephrine, glucose, insulin, famotidine, valproate semisodium, fentanyl, acetylsalicylic acid, white petrolatum ophthalmic ointment, pantoprazole sodium, fentanyl-NS, ipratropium bromide/salbutamol sulfate, methylprednisolone sodium succinate, vecuronium, and propofol.

On October 25, 2015, 2 days after the onset of the asthma attack, the following tests were reported: urine analysis — 3 white blood cells and 7 epithelial cells; chest X-ray — no acute infiltrate; venous Doppler — no evidence of deep-vein thrombosis (DVT); methicillin-resistant *Staphylococcus aureus* screen — negative; computed tomography (CT) — no obvious infarct or mass; respiratory culture from endotracheal aspirate — heavy growth of *S. aureus*; moderate positive cocci.

On October 27, 2015, the following tests were reported: transthoracic echocardiogram — normal left ventricular size with mildly reduced systolic function with estimated ejection fraction of 45–50%; hypokinesia of the apex and apical septum; no hemodynamically significant valvular pathology appreciated.

On October 28, 2015, the following test was reported: CT head — no intracranial hemorrhage.

On November 2, 2015, the following test was reported: abdomen ultrasound — hepatomegaly.

On unspecified dates, a duplex ultrasound was negative for DVT, a chest X-ray was negative for cardiopulmonary disease, and an echocardiogram showed overall normal size of left ventricle with severely reduced ejection fraction of 30% and severe hypokinesis of anterior and anteroseptal wall, posterior wall, and akinetic apex.

On November 11, 2015 (study day 189), the patient died due to anoxic encephalopathy, respiratory failure, asthma exacerbation, and asthma.

The investigator considered the events to be not related to IP. The investigator's alternative explanation for the events was underlying/concomitant illness.

Relationship to IP according to Company for all events: excluded.

Patient 2: Male patient, 31 years of age

DESCRIPTION OF EVENTS QUALIFYING FOR REPORTING IN THE NARRATIVE

On study day 93 (August 6, 2015), the patient had a serious adverse event of severe intensity, reported as suicide (completed suicide). The event was serious because it resulted in death. The patient died on August 6, 2015, due to this event. The investigator's assessment of causality was "not related" to study drug.

NARRATIVE

On April 29, 2015, during the screening visit, the investigator reported that the patient made no mention of a history of depression, suicide attempt, or suicidal ideation during the medical history or concomitant medication review. On May 5, 2015, at the baseline visit, the patient was questioned about his mental health history, and he reported that depression had been present since autumn 2014 and was primarily caused by his severe atopic dermatitis. Medical records obtained from the patient's primary physician indicated a history of new depression and suicidal ideation (November 14, 2014). It was also noted that the patient had a family history of suicide (grandmother). The patient reported a brief hospitalization for acute worsening of depression and a request for a referral for mental health counseling during a visit to his primary physician on November 26, 2014 (dates of hospitalization not provided, and patient reported he was doing much better).

The first dose of IP (subcutaneous) was on May 6, 2015. The most recent dose of IP before the event was on July 29, 2015 (study day 85). At that time, the patient had received a total of 13 doses of 300 mg dupilumab weekly.

On August 11, 2015, the patient's sister called to inform the site that the patient died from an intentional overdose of drugs on August 6, 2015 (study day 93), 3 months after the first IP administration, and 8 days after the last dose administration. The event was assessed as an adverse event of special interest and was considered severe in intensity.

The death certificate noted the cause of death as acute mixed-drug intoxication due to the combined effects of valproic acid and diphenhydramine. Another condition contributing to death was noted as dilated cardiomyopathy (noted in the death certificate). The description of how the injury occurred was noted as an intentional acute drug intoxication. In addition, the death certificate specified that there was no injury at work and tobacco use did not contribute to death.

Action taken with study drug was reported as "dose not applicable".

The investigator considered the event to be not related to IP. The causality rationale was noted, as the patient's family attributed the depression and suicide to lifelong, severe chronic atopic dermatitis. Based on statements made by the patient (to the investigator at the baseline visit) and discussion with the patient's family, the investigator believed the patient's severe, chronic atopic dermatitis was the primary contributing factor to his depression and suicide.

Relationship to IP according to Company: not related to study drug or study procedure, but likely related to patient's past medical history of depression.

Table S1. Efficacy End Points[4]

End Point	Description	Range	MCID
Eczema Area and Severity Index (EASI)[5,6]	Assesses severity and body surface area affected by erythema, induration/papulation/edema, excoriations, and lichenification, which are graded systematically for each anatomical region and assembled in a composite score	0–72*	6.6
Investigator's Global Assessment (IGA)[7]	Determines severity of AD and clinical response to treatment based on a 5-point scale ranging from 0 (clear) to 4 (severe)	0–4*	n/a
Pruritus numerical rating scale (NRS)[8]	Two single-item 11-point scales that assess maximum and average intensity of itch within the previous 24 hours. Psychometric validation data submitted to the US Food and Drug Administration (FDA) provide evidence that this is a well-defined, reliable, sensitive, and valid scale (data on file). Responder analyses submitted to the FDA suggest that the most appropriate definition of a responder on the	0–10*	n/a

	peak pruritus numerical rating scale is in the range of 3 to 4 points		
Scoring Atopic Dermatitis (SCORAD)[6,9]	The extent and severity of atopic dermatitis over the body area (A) and the severity of 6 specific symptoms (erythema, edema/papulation, excoriations, lichenification, oozing/crusts, and dryness) (B) are assessed and scored by the investigator. Subjective assessment of itch and sleeplessness is scored by the patient (C). The SCORAD score is a combined score (A/5 + 7B/2 + C) of body area affected, and investigator and patient symptom scoring, with a maximum of 103	0–103*	8.7
Global Individual Signs Score (GISS)	Individual components of the atopic dermatitis lesions (erythema, infiltration/papulation, excoriations, and lichenification) were rated globally (i.e., each assessed for the whole body, not by anatomical region) on a 4-point scale (from 0 [none] to 3 [severe]) using the EASI severity grading criteria. The cumulative score, which ranges from 0 to 12, is the sum of the four components	0–12*	n/a
Patient-Oriented Eczema Measure	A 7-item, validated questionnaire used in clinical practice and clinical	0–28*	4

(POEM)[6,10]	trials to assess time spent with disease symptoms in children and adults, and their impact on sleep		
Dermatology Life Quality Index (DLQI)[11,12]	A 10-item, validated questionnaire used in clinical practice and clinical trials to assess the impact of skin conditions on quality of life	0–30*	4
Hospital Anxiety and Depression Scale (HADS)[13,14]	A general Likert scale used to detect states of anxiety and depression; anxiety and depression subscales each with 7 items	0–42 for total score; 0–21 for each subscale*	n/a

* Higher scores indicate greater severity/worsened state.
MCID, minimum clinically important difference; n/a, not applicable.
Adapted from: The Lancet, Vol. 387, Thaçi D, Simpson EL, Beck LA, et al., Efficacy and safety of dupilumab in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical treatments: a randomised, placebo-controlled, dose-ranging phase 2b trial, Pages 40-52, Copyright (2016), with permission from Elsevier.

Table S2. Additional Baseline Characteristics

	SOLO 1			SOLO 2		
Variable	Placebo (n = 224)	Dupilumab 300 mg every other week (n = 224)	Dupilumab 300 mg weekly (n = 223)	Placebo (n = 236)	Dupilumab 300 mg every other week (n = 233)	Dupilumab 300 mg weekly (n = 239)
Peak pruritus numerical rating scale score ≥3 — no. (%)	221 (99)	220 (98)	211 (95)*	226 (96)	231 (99)*	234 (98)
Peak pruritus numerical rating scale score ≥4 — no. (%)	212 (95)	213 (95)	201 (90)	221 (94)	225 (97)	228 (95)

Peak pruritus numerical rating scale score is a patient-reported measure which assesses maximum itch intensity in the previous 24 hours using a 10-point scale (from 0 [no itch] to 10 [worst itch imaginable]).[8]

* P<0.05 vs. placebo.

Table S3. Prior Systemic Medication Ended Prior to Baseline (Safety Analysis Set)

	SOLO 1			SOLO 2		
Prior systemic therapy — no. (%)	Placebo (n = 222)	Dupilumab 300 mg every other week (n = 229)	Dupilumab 300 mg weekly (n = 218)	Placebo (n = 234)	Dupilumab 300 mg every other week (n = 236)	Dupilumab 300 mg weekly (n = 237)
Systemic corticosteroids	78 (35)	77 (34)	65 (30)	82 (35)	80 (34)	73 (31)
Immunosuppressants	52 (23)	60 (26)	61 (28)	70 (30)	77 (33)	75 (32)
Calcineurin inhibitors	40 (18)	47 (21)	49 (23)	53 (23)	60 (25)	52 (22)
Selective immunosuppressants	8 (4)	14 (6)	9 (4)	4 (2)	10 (4)	9 (4)
Other immunosuppressants	20 (9)	24 (11)	23 (11)	25 (11)	27 (11)	28 (12)
Interleukin inhibitors	3 (1)	2 (1)	0	0	0	1 (<1)
Tumor necrosis factor-	1 (1)	2 (1)	0	0	1 (<1)	0

	SOLO 1			SOLO 2		
Prior systemic therapy — no. (%)	Placebo (n = 222)	Dupilumab 300 mg every other week (n = 229)	Dupilumab 300 mg weekly (n = 218)	Placebo (n = 234)	Dupilumab 300 mg every other week (n = 236)	Dupilumab 300 mg weekly (n = 237)
alpha inhibitors						

Table S4. Additional Efficacy Outcomes (Not Included in Hierarchical Testing)

	SOLO 1			SOLO 2		
End Point	Placebo (n = 224)	Dupilumab 300 mg every other week (n = 224)	Dupilumab 300 mg weekly (n = 223)	Placebo (n = 236)	Dupilumab 300 mg every other week (n = 233)	Dupilumab 300 mg weekly (n = 239)
DLQI score, ≥4-point improvement from baseline to week 16 — no. (%)*	65 (31)	134 (64) †	122 (58) †	62 (28)	163 (73) †	145 (62) †
POEM score, ≥4-point improvement from baseline to week 16 — no. (%)‡	60 (27)	150 (68) †	140 (63) †	57 (24)	167 (72) †	153 (64) †
HADS-A and HADS-D score <8 at week 16 — no./N (%)§	12/97 (12)	41/100 (41) †	37/102 (36) †	7/115 (6)	51/129 (40) †	56/136 (41) †

* In the subset of patients with DLQI ≥4 at baseline.

† Nominal P<0.001 vs. placebo.

‡ In the subset of patients with POEM ≥4 at baseline.

§ In the subset of patients with HADS-A or HADS-D ≥8 at baseline, representing the cutoff for identifying patients with anxiety or depression, respectively.

Scores on the DLQI range from 0 to 30, with higher scores indicating greater impact on quality of life; a change of 4 has been estimated as the minimal clinically important difference (MCID).[11,12] Scores on the POEM range from 0 to 28, with higher scores indicating greater symptom burden; a change of 4 has been estimated as the MCID.[6,10] HADS total score ranges from 0 to 42 (HADS-A and HADS-D subscale scores range from 0 to 21)[13,14] with higher scores indicating greater burden of anxiety and depression symptoms; the MCID for this scale has not been determined. Based on Bjelland et al.,[13] an optimal balance between sensitivity and specificity for HADS as a screening instrument was achieved most frequently at a cutoff score of ≥8 for both HADS-A and HADS-D, giving sensitivities and specificities for both subscales of approximately 0.80. Receiver-operator characteristic curves also identified scores of ≥8 to be an optimal cutoff score for caseness for both anxiety disorders and depression based on the International Classification of Diseases, Ninth Revision (ICD-9). Most outcomes were assessed at scheduled study visits. DLQI, Dermatology Life Quality Index; HADS, Hospital Anxiety and Depression Scale; HADS-A, HADS anxiety subscore; HADS-D, HADS depression subscore; N, number of patients in baseline subgroup; POEM, Patient-Oriented Eczema Measure.

Table S5. Proportion of Patients Receiving Rescue Therapy at Week 16 (Full Analysis Set)

	SOLO 1			SOLO 2		
	Placebo (n = 224)	Dupilumab 300 mg every other week (n = 224)	Dupilumab 300 mg weekly (n = 223)	Placebo (n = 236)	Dupilumab 300 mg every other week (n = 233)	Dupilumab 300 mg weekly (n = 239)
Rescue therapy — no. (%)						
Any rescue therapy	115 (51)	47 (21)	52 (23)	123 (52)	35 (15)	49 (21)
Systemic corticosteroids	17 (8)	2 (1)	5 (2)	30 (13)	3 (1)	6 (3)
Immunosuppressants	5 (2)	3 (1)	2 (1)	16 (7)	1 (<1)	2 (1)
Calcineurin inhibitors	4 (2)	2 (1)	1 (<1)	13 (6)	1 (<1)	2 (1)
Selective immunosuppressants	0	1 (<1)	1 (<1)	0	0	0
Other	1 (<1)	0	0	4 (2)	0	0

	SOLO 1			SOLO 2		
	Placebo (n = 224)	Dupilumab 300 mg every other week (n = 224)	Dupilumab 300 mg weekly (n = 223)	Placebo (n = 236)	Dupilumab 300 mg every other week (n = 233)	Dupilumab 300 mg weekly (n = 239)
immunosuppressants						

Table S6. Sensitivity Analyses of Primary Outcome and Key Secondary Outcomes

	SOLO 1			SOLO 2		
End Point	Placebo (n = 224)	Dupilumab 300 mg every other week (n = 224)	Dupilumab 300 mg weekly (n = 223)	Placebo (n = 236)	Dupilumab 300 mg every other week (n = 233)	Dupilumab 300 mg weekly (n = 239)
Primary analysis						
IGA score of 0 or 1 and ≥2-point improvement from baseline at week 16 — no. (%)	23 (10)	85 (38)*	83 (37)*	20 (8)	84 (36)*	87 (36)*
EASI-75 at week 16 — no. (%)†	33 (15)	115 (51)*	117 (52)*	28 (12)	103 (44)*	115 (48)*
Sensitivity analysis 1: All observed values regardless of rescue treatment; missing considered as non-responder						
IGA score of 0 or 1 and ≥2-point improvement from baseline at week 16 — no. (%)	29 (13)	91 (41)*	85 (38)*	25 (11)	87 (37)*	91 (38)*
EASI-75 at week 16 — no. (%)	50 (22)	133 (59)*	136 (61)*	37 (16)	116 (50)*	138 (58)*
Sensitivity analysis 2: Last observation carried forward; patient considered as non-responder after rescue treatment						
IGA score of 0 or 1 and ≥2-point improvement from baseline at week 16 — no. (%)	25 (11)	85 (38)*	88 (39)*	22 (9)	86 (37)*	91 (38)*

	SOLO 1			SOLO 2		
End Point	Placebo (n = 224)	Dupilumab 300 mg every other week (n = 224)	Dupilumab 300 mg weekly (n = 223)	Placebo (n = 236)	Dupilumab 300 mg every other week (n = 233)	Dupilumab 300 mg weekly (n = 239)
EASI-75 at week 16 — no. (%)	38 (17)	122 (54)*	126 (57)*	32 (14)	108 (46)*	132 (55)*
Sensitivity analysis 3: All observed values regardless of rescue treatment; missing data not imputed						
IGA score of 0 or 1 and ≥2-point improvement from baseline at week 16 — n/N1 (%)	29/205 (14)	91/216 (42)*	85/207 (41)*	25/219 (11)	87/224 (39)*	91/224 (41)*
EASI-75 at week 16 — no./N1 (%)	50/205 (24)	133/216 (62)*	136/207 (66)*	37/219 (17)	116/224 (52)*	138/224 (62)*

* P<0.001 vs. placebo.

† Co-primary outcome in EU and Japan. EASI, Eczema Area and Severity Index; EASI-75, ≥75% improvement in EASI score from baseline; IGA, Investigator's Global Assessment; n, number of patients; N1, number of patients without missing data at week 16.

Table S7. Serious Adverse Events (MedDRA PTs) (Safety Analysis Set)

	SOLO 1			SOLO 2		
Event	Placebo (n = 222)	Dupilumab 300 mg every other week (n = 229)	Dupilumab 300 mg weekly (n = 218)	Placebo (n = 234)	Dupilumab 300 mg every other week (n = 236)	Dupilumab 300 mg weekly (n = 237)
Patients with — no. (%)						
≥1 Serious adverse event	11 (5.0)	7 (3.1)	2 (0.9)	13 (5.6)	4 (1.7)	8 (3.4)
Acute myocardial infarction	0	1 (0.4)	0	0	0	1 (0.4)
Myocardial infarction	0	0	1 (0.5)	0	0	0
Coronary artery disease	1 (0.5)	0	0	0	0	0
Cardiac failure, congestive	0	0	0	0	0	1 (0.4)
Abdominal pain	0	0	0	0	0	1 (0.4)
Colonic pseudo-obstruction	0	0	0	0	0	1 (0.4)
Abscess sweat gland	0	1 (0.4)	0	0	0	0
Kidney infection	0	0	1 (0.5)	0	0	0
Mastitis	1 (0.5)	0	0	0	0	0

	SOLO 1			SOLO 2		
Event	Placebo (n = 222)	Dupilumab 300 mg every other week (n = 229)	Dupilumab 300 mg weekly (n = 218)	Placebo (n = 234)	Dupilumab 300 mg every other week (n = 236)	Dupilumab 300 mg weekly (n = 237)
Urinary tract infection bacterial	1 (0.5)	0	0	0	0	0
Cellulitis	0	0	0	0	0	1 (0.4)
Erysipelas	0	0	0	0	0	1 (0.4)
Endocarditis bacterial	0	0	0	1 (0.4)	0	0
Sepsis	0	0	0	2 (0.9)	0	0
Septic embolus	0	0	0	1 (0.4)	0	0
Skin infection	0	0	0	1 (0.4)	0	0
Dermatitis atopic	3 (1.4)	2 (0.9)	0	5 (2.1)	0	1 (0.4)
Dermatitis exfoliative	0	0	0	0	1 (0.4)	0
Clavicle fracture	0	1 (0.4)	0	0	0	0
Laceration	0	1 (0.4)	0	0	0	0
Concussion	0	0	0	1 (0.4)	0	0

	SOLO 1			SOLO 2		
Event	Placebo (n = 222)	Dupilumab 300 mg every other week (n = 229)	Dupilumab 300 mg weekly (n = 218)	Placebo (n = 234)	Dupilumab 300 mg every other week (n = 236)	Dupilumab 300 mg weekly (n = 237)
Fall	0	0	0	0	1 (0.4)	0
Ligament sprain	0	0	0	1 (0.4)	0	0
Radius fracture	0	0	0	0	1 (0.4)	0
Cerebrovascular accident	0	0	0	1 (0.4)	0	0
Headache	0	0	0	0	1 (0.4)	0
Subarachnoid hemorrhage	0	0	0	0	1 (0.4)	0
Completed suicide	0	0	0	0	0	1 (0.4)
Delirium	0	0	0	0	0	1 (0.4)
Confusional state	0	0	0	1 (0.4)	0	0
Psychotic disorder	0	0	0	1 (0.4)	0	0
Depression	1 (0.5)	0	0	0	0	0
Suicidal ideation	2 (0.9)	0	0	1 (0.4)	0	0

	SOLO 1			SOLO 2		
Event	Placebo (n = 222)	Dupilumab 300 mg every other week (n = 229)	Dupilumab 300 mg weekly (n = 218)	Placebo (n = 234)	Dupilumab 300 mg every other week (n = 236)	Dupilumab 300 mg weekly (n = 237)
Lipoma	0	1 (0.4)	0	0	0	0
Hodgkin's disease	0	0	0	0	0	1 (0.4)
Nephrolithiasis	0	0	1 (0.5)	0	0	0
Limb operation	0	1 (0.4)	0	0	0	0
Anemia	1 (0.5)	0	0	0	0	0
Thrombocytopenia	0	0	0	1 (0.4)	0	0
Hyperglycemia	1 (0.5)	0	0	0	0	0
Failure to thrive	0	0	0	1 (0.4)	0	0
Intervertebral disc protrusion	1 (0.5)	0	0	0	0	0
Bursitis	0	0	0	1 (0.4)	0	0
Aortic stenosis	1 (0.5)	0	0	0	0	0
Abortion, spontaneous	0	0	0	0	0	1 (0.4)

	SOLO 1			SOLO 2		
Event	Placebo (n = 222)	Dupilumab 300 mg every other week (n = 229)	Dupilumab 300 mg weekly (n = 218)	Placebo (n = 234)	Dupilumab 300 mg every other week (n = 236)	Dupilumab 300 mg weekly (n = 237)
Angle-closure glaucoma	0	0	0	1 (0.4)	0	0
Acute kidney injury	0	0	0	2 (0.9)	0	0

Serious adverse events were defined as any untoward medical occurrence that results in death; is life-threatening; requires in-patient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect; or is an important medical event. Safety analyses were carried out using the safety analysis set, which included all randomized patients who received a dose of any study drug. MedDRA, Medical Dictionary for Regulatory Activities; PT, Preferred Term.

Table S8. Adverse Events (MedDRA PTs) Leading to Discontinuation (Safety Analysis Set)

	SOLO 1			SOLO 2		
Event	Placebo (n = 222)	Dupilumab 300 mg every other week (n = 229)	Dupilumab 300 mg weekly (n = 218)	Placebo (n = 234)	Dupilumab 300 mg every other week (n = 236)	Dupilumab 300 mg weekly (n = 237)
Patients with — no. (%)						
AEs leading to discontinuation	2 (0.9)	4 (1.7)	4 (1.8)	5 (2.1)	2 (0.8)	3 (1.3)
Dermatitis atopic	1 (0.5)	2 (0.9)	1 (0.5)	2 (0.9)	1 (0.4)	0
Dermatitis allergic	0	0	1 (0.5)	0	0	0
Lymphocytosis	0	0	1 (0.5)	0	0	0
Neutropenia	0	0	0	0	1 (0.4)	0
Diarrhea	0	0	0	0	0	1 (0.4)
Acute myocardial infarction	0	1 (0.4)	0	0	0	0
Conjunctivitis allergic	0	0	1 (0.5)	0	0	0
Angle-closure glaucoma	0	0	0	1 (0.4)	0	0

	SOLO 1			SOLO 2		
Event	Placebo (n = 222)	Dupilumab 300 mg every other week (n = 229)	Dupilumab 300 mg weekly (n = 218)	Placebo (n = 234)	Dupilumab 300 mg every other week (n = 236)	Dupilumab 300 mg weekly (n = 237)
Folliculitis	0	0	1 (0.5)	0	0	0
Eczema, impetiginous	0	0	0	0	1 (0.4)	0
Endocarditis bacterial	0	0	0	1 (0.4)	0	0
Sepsis	0	0	0	1 (0.4)	0	0
Septic embolus	0	0	0	1 (0.4)	0	0
Hodgkin disease	0	0	0	0	0	1 (0.4)
Lethargy	0	0	0	0	0	1 (0.4)
Cerebrovascular accident	0	0	0	1 (0.4)	0	0
Clavicle fracture	0	1 (0.4)	0	0	0	0
Laceration	0	1 (0.4)	0	0	0	0
Suicidal ideation	2 (0.9)	0	0	0	0	0
Psychotic disorder	0	0	0	1 (0.4)	0	0

	SOLO 1			SOLO 2		
Event	Placebo (n = 222)	Dupilumab 300 mg every other week (n = 229)	Dupilumab 300 mg weekly (n = 218)	Placebo (n = 234)	Dupilumab 300 mg every other week (n = 236)	Dupilumab 300 mg weekly (n = 237)
Abortion, spontaneous	0	0	0	0	0	1 (0.4)
Acute kidney injury	0	0	0	1 (0.4)	0	0

Safety analyses were carried out using the safety analysis set, which included all randomized patients who received a dose of any study drug. AE, adverse event, MedDRA, Medical Dictionary for Regulatory Activities; PT, Preferred Term.

Table S9. Infections: Skin and non-Skin (MedDRA PTs) (Safety Analysis Set)

	SOLO 1			SOLO 2		
Event	Placebo (n = 222)	Dupilumab 300 mg every other week (n = 229)	Dupilumab 300 mg weekly (n = 218)	Placebo (n = 234)	Dupilumab 300 mg every other week (n = 236)	Dupilumab 300 mg weekly (n = 237)
Patients with — no. (%)						
Skin infections*	18 (8.1)	13 (5.7)	14 (6.4)	26 (11.1)	14 (5.9)	15 (6.3)
Eczema herpeticum	2 (0.9)	1 (0.4)	1 (0.5)	1 (0.4)	2 (0.8)	0
Impetigo	4 (1.8)	1 (0.4)	2 (0.9)	3 (1.3)	2 (0.8)	0
Skin infection	2 (0.9)	2 (0.9)	1 (0.5)	5 (2.1)	1 (0.4)	1 (0.4)
Infected dermal cyst	0	1 (0.4)	1 (0.5)	0	0	0
Abscess sweat gland	0	1 (0.4)	0	0	0	0
Acne pustular	0	0	1 (0.5)	0	0	0
Rash pustular	0	0	0	1 (0.4)	0	1 (0.4)
Paronychia	1 (0.5)	0	0	1 (0.4)	0	0

	SOLO 1			SOLO 2		
Event	Placebo (n = 222)	Dupilumab 300 mg every other week (n = 229)	Dupilumab 300 mg weekly (n = 218)	Placebo (n = 234)	Dupilumab 300 mg every other week (n = 236)	Dupilumab 300 mg weekly (n = 237)
Soft tissue infection	1 (0.5)	0	0	0	0	0
Folliculitis	4 (1.8)	2 (0.9)	3 (1.4)	4 (1.7)	2 (0.8)	3 (1.3)
Cellulitis	2 (0.9)	1 (0.4)	1 (0.5)	2 (0.9)	0	2 (0.8)
Eczema impetiginous	0	0	1 (0.5)	1 (0.4)	3 (1.3)	1 (0.4)
Furuncle	0	2 (0.9)	1 (0.5)	1 (0.4)	0	0
Staphylococcal impetigo	0	1 (0.4)	0	0	0	0
Staphylococcal skin infection	0	1 (0.4)	0	2 (0.9)	0	1 (0.4)
Molluscum contagiosum	1 (0.5)	1 (0.4)	1 (0.5)	1 (0.4)	0	2 (0.8)
Otitis externa	0	0	1 (0.5)	0	2 (0.8)	0
Eyelid infection	0	0	1 (0.5)	0	0	0
Otitis externa fungal	0	0	1 (0.5)	0	0	0
Wound infection	0	0	1 (0.5)	0	1 (0.4)	0

	SOLO 1			SOLO 2		
Event	Placebo (n = 222)	Dupilumab 300 mg every other week (n = 229)	Dupilumab 300 mg weekly (n = 218)	Placebo (n = 234)	Dupilumab 300 mg every other week (n = 236)	Dupilumab 300 mg weekly (n = 237)
Tinea versicolor	1 (0.5)	1 (0.4)	0	0	0	1 (0.4)
Tinea pedis	2 (0.9)	0	0	0	0	0
Body tinea	0	0	0	0	0	1 (0.4)
Tinea manuum	0	0	0	1 (0.4)	0	0
Erysipelas	1 (0.5)	0	0	0	0	1 (0.4)
Skin bacterial infection	0	0	0	2 (0.9)	0	0
Subcutaneous abscess	0	0	0	3 (1.3)	1 (0.4)	0
Abscess limb	0	0	0	0	0	1 (0.4)
Non-skin infections	49 (22.1)	69 (30.1)	67 (30.7)	57 (24.4)	58 (24.6)	61 (25.7)
Nasopharyngitis	17 (7.7)	22 (9.6)	25 (11.5)	22 (9.4)	20 (8.5)	20 (8.4)
Upper respiratory tract infection	5 (2.3)	6 (2.6)	11 (5.0)	5 (2.1)	7 (3.0)	9 (3.8)
Conjunctivitis	2 (0.9)	11 (4.8)	7 (3.2)	1 (0.4)	9 (3.8)	9 (3.8)

	SOLO 1			SOLO 2		
Event	Placebo (n = 222)	Dupilumab 300 mg every other week (n = 229)	Dupilumab 300 mg weekly (n = 218)	Placebo (n = 234)	Dupilumab 300 mg every other week (n = 236)	Dupilumab 300 mg weekly (n = 237)
Conjunctivitis bacterial	1 (0.5)	2 (0.9)	4 (1.8)	1 (0.4)	4 (1.7)	4 (1.7)
Oral herpes	4 (1.8)	9 (3.9)	4 (1.8)	4 (1.7)	8 (3.4)	9 (3.8)
Cystitis	0	1 (0.4)	3 (1.4)	0	2 (0.8)	0
Bacteriuria	0	0	2 (0.9)	1 (0.4)	1 (0.4)	0
Herpes simplex	3 (1.4)	7 (3.1)	2 (0.9)	1 (0.4)	0	1 (0.4)
Influenza	1 (0.5)	1 (0.4)	2 (0.9)	1 (0.4)	2 (0.8)	1 (0.4)
Otitis media	1 (0.5)	0	2 (0.9)	0	0	0
Pharyngitis	2 (0.9)	1 (0.4)	2 (0.9)	2 (0.9)	0	1 (0.4)
Tonsillitis	1 (0.5)	1 (0.4)	2 (0.9)	0	0	0
Asymptomatic bacteriuria	0	0	1 (0.5)	0	0	0
Bronchitis	2 (0.9)	2 (0.9)	1 (0.5)	2 (0.9)	1 (0.4)	2 (0.8)
Eye infection	0	2 (0.9)	1 (0.5)	0	0	1 (0.4)

	SOLO 1			SOLO 2		
Event	Placebo (n = 222)	Dupilumab 300 mg every other week (n = 229)	Dupilumab 300 mg weekly (n = 218)	Placebo (n = 234)	Dupilumab 300 mg every other week (n = 236)	Dupilumab 300 mg weekly (n = 237)
Gastroenteritis	0	2 (0.9)	1 (0.5)	0	0	2 (0.8)
Herpes virus infection	0	0	1 (0.5)	1 (0.4)	0	0
Hordeolum	0	0	1 (0.5)	1 (0.4)	0	2 (0.8)
Kidney infection	0	0	1 (0.5)	0	0	0
Esophageal candidiasis	0	0	1 (0.5)	0	0	0
Ophthalmic herpes simplex	0	0	1 (0.5)	0	0	0
Sinusitis	1 (0.5)	2 (0.9)	1 (0.5)	5 (2.1)	0	0
Staphylococcal infection	0	0	1 (0.5)	0	0	0
Viral infection	0	0	1 (0.5)	0	0	0
Bacterial infection	0	1 (0.4)	0	0	0	0
Bacterial sepsis	0	1 (0.4)	0	0	0	0
Conjunctivitis viral	0	2 (0.9)	0	1 (0.4)	2 (0.8)	0

	SOLO 1			SOLO 2		
Event	Placebo (n = 222)	Dupilumab 300 mg every other week (n = 229)	Dupilumab 300 mg weekly (n = 218)	Placebo (n = 234)	Dupilumab 300 mg every other week (n = 236)	Dupilumab 300 mg weekly (n = 237)
Diverticulitis	0	1 (0.4)	0	0	0	0
Ear infection	0	1 (0.4)	0	0	0	0
Gastroenteritis norovirus	1 (0.5)	0	0	0	0	0
Gastroenteritis viral	2 (0.9)	0	0	1 (0.4)	1 (0.4)	0
Gastrointestinal infection	1 (0.5)	0	0	0	0	0
Genital herpes	1 (0.5)	0	0	0	0	1 (0.4)
Gingivitis	0	1 (0.4)	0	0	0	0
Herpes zoster	1 (0.5)	1 (0.4)	0	1 (0.4)	0	0
Mastitis	1 (0.5)	1 (0.4)	0	0	0	0
Pharyngitis streptococcal	0	2 (0.9)	0	0	0	3 (1.3)
Respiratory tract infection	0	1 (0.4)	0	1 (0.4)	0	1 (0.4)
Rhinitis	2 (0.9)	1 (0.4)	0	0	2 (0.8)	1 (0.4)

	SOLO 1			SOLO 2		
Event	Placebo (n = 222)	Dupilumab 300 mg every other week (n = 229)	Dupilumab 300 mg weekly (n = 218)	Placebo (n = 234)	Dupilumab 300 mg every other week (n = 236)	Dupilumab 300 mg weekly (n = 237)
Sialoadenitis	0	1 (0.4)	0	0	0	0
Urinary tract infection	4 (1.8)	2 (0.9)	0	4 (1.7)	2 (0.8)	2 (0.8)
Urinary tract infection bacterial	1 (0.5)	0	0	0	0	0
Viral upper respiratory tract infection	1 (0.5)	0	0	1 (0.4)	2 (0.8)	0
Ear infection bacterial	0	0	0	0	1 (0.4)	1 (0.4)
Herpes ophthalmic	0	0	0	1 (0.4)	0	1 (0.4)
Tooth infection	0	0	0	0	0	1 (0.4)
Acarodermatitis	0	0	0	1 (0.4)	0	0
Chronic tonsillitis	0	0	0	0	1 (0.4)	0
Dental gangrene	0	0	0	1 (0.4)	0	0
Endocarditis bacterial	0	0	0	1 (0.4)	0	0

	SOLO 1			SOLO 2		
Event	Placebo (n = 222)	Dupilumab 300 mg every other week (n = 229)	Dupilumab 300 mg weekly (n = 218)	Placebo (n = 234)	Dupilumab 300 mg every other week (n = 236)	Dupilumab 300 mg weekly (n = 237)
Herpes simplex otitis externa	0	0	0	0	1 (0.4)	0
Onychomycosis	0	0	0	1 (0.4)	0	0
Oral candidiasis	0	0	0	1 (0.4)	0	0
Periorbital abscess	0	0	0	1 (0.4)	0	0
Peritonsillar abscess	0	0	0	1 (0.4)	1 (0.4)	0
Sepsis	0	0	0	2 (0.9)	0	0
Septic embolus	0	0	0	1 (0.4)	0	0
Tooth abscess	0	0	0	1 (0.4)	0	0
Vaginal infection	0	0	0	1 (0.4)	0	0
Viral pharyngitis	0	0	0	1 (0.4)	0	0
Vulvovaginal candidiasis	0	0	0	2 (0.9)	0	0
Vulvovaginal mycotic infection	0	0	0	1 (0.4)	0	0

*Skin infections were adjudicated by the medical director for each study. Infections are listed as MedDRA PTs. Safety analyses were carried out using the safety analysis set, which included all randomized patients who received a dose of any study drug. MedDRA, Medical Dictionary for Regulatory Activities; PT, Preferred Term.

Table S10. Serious Infections, Severe Infections, and Opportunistic Infections (MedDRA PTs) (Safety Analysis Set)

	SOLO 1			SOLO 2		
Event	Placebo (n = 222)	Dupilumab 300 mg every other week (n = 229)	Dupilumab 300 mg weekly (n = 218)	Placebo (n = 234)	Dupilumab 300 mg every other week (n = 236)	Dupilumab 300 mg weekly (n = 237)
Patients with — no. (%)						
Serious infections and infestations	2 (0.9)	1 (0.4)	1 (0.5)	3 (1.3)	0	2 (0.8)
Kidney infection	0	0	1 (0.5)	0	0	0
Abscess sweat gland	0	1 (0.4)	0	0	0	0
Mastitis	1 (0.5)	0	0	0	0	0
Bacterial urinary tract infection	1 (0.5)	0	0	0	0	0
Cellulitis	0	0	0	0	0	1 (0.4)
Erysipelas	0	0	0	0	0	1 (0.4)
Endocarditis bacterial	0	0	0	1 (0.4)	0	0

	SOLO 1			SOLO 2		
Event	Placebo (n = 222)	Dupilumab 300 mg every other week (n = 229)	Dupilumab 300 mg weekly (n = 218)	Placebo (n = 234)	Dupilumab 300 mg every other week (n = 236)	Dupilumab 300 mg weekly (n = 237)
Sepsis	0	0	0	2 (0.9)	0	0
Septic embolus	0	0	0	1 (0.4)	0	0
Skin infection	0	0	0	1 (0.4)	0	0
Severe infections and infestations	4 (1.8)	3 (1.3)	1 (0.5)	4 (1.7)	1 (0.4)	0
Abscess sweat gland	0	1 (0.4)	0	0	0	0
Conjunctivitis	0	1 (0.4)	0	0	0	0
Herpes simplex	0	1 (0.4)	0	0	0	0
Kidney infection	0	0	1 (0.5)	0	0	0
Mastitis	1 (0.5)	0	0	0	0	0
Nasopharyngitis	1 (0.5)	0	0	0	0	0
Pharyngitis	1 (0.5)	0	0	0	0	0
Soft tissue infection	1 (0.5)	0	0	0	0	0

	SOLO 1			SOLO 2		
Event	Placebo (n = 222)	Dupilumab 300 mg every other week (n = 229)	Dupilumab 300 mg weekly (n = 218)	Placebo (n = 234)	Dupilumab 300 mg every other week (n = 236)	Dupilumab 300 mg weekly (n = 237)
Conjunctivitis bacterial	0	0	0	0	1 (0.4)	0
Endocarditis bacterial	0	0	0	1 (0.4)	0	0
Folliculitis	0	0	0	2 (0.9)	0	0
Sepsis	0	0	0	2 (0.9)	0	0
Septic embolus	0	0	0	1 (0.4)	0	0
Opportunistic infections	3 (1.4)	2 (0.9)	1 (0.5)	2 (0.9)	2 (0.8)	0
Eczema herpeticum	2 (0.9)	1 (0.4)	1 (0.5)	1 (0.4)	2 (0.8)	0
Herpes zoster	1 (0.5)	1 (0.4)	0	1 (0.4)	0	0

Serious adverse events were defined as any untoward medical occurrence that results in death; is life-threatening; requires in-patient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect; or is an important medical event. Severe adverse events were defined as those that produce significant impairment of functioning or incapacitation and are a definite hazard to the patient's health. Opportunistic infections were determined based on the 2015 consensus guidance by Winthrop et al.[15] Safety analyses were carried out using the safety analysis set, which included all randomized patients who received a dose of any study drug. MedDRA, Medical Dictionary for Regulatory Activities; PT, Preferred Term.

Table S11. Mean and Median Changes From Baseline in Eosinophils (Safety Analysis Set)

	SOLO 1			SOLO 2		
Event	Placebo (n = 222)	Dupilumab 300 mg every other week (n = 229)	Dupilumab 300 mg weekly (n = 218)	Placebo (n = 234)	Dupilumab 300 mg every other week (n = 236)	Dupilumab 300 mg weekly (n = 237)
Change from baseline (10^9 per liter)						
Week 4						
N	205	217	207	222	220	222
Mean (SD)	0 (0.495)	0.07 (0.584)	0.07 (0.525)	–0.02 (0.547)	0.11 (0.568)	0.13 (0.650)
Median	0	0	0	0	0	0
Q1, Q3	−0.15, 0.10	−0.10, 0.20	−0.10, 0.20	–0.20, 0.20	−0.10, 0.20	−0.20, 0.20
Week 8						
N	194	215	201	208	216	216
Mean (SD)	−0.13 (0.484)	0.06 (0.675)	0.02 (0.538)	–0.09 (0.620)	0.07 (0.596)	0.12 (0.853)

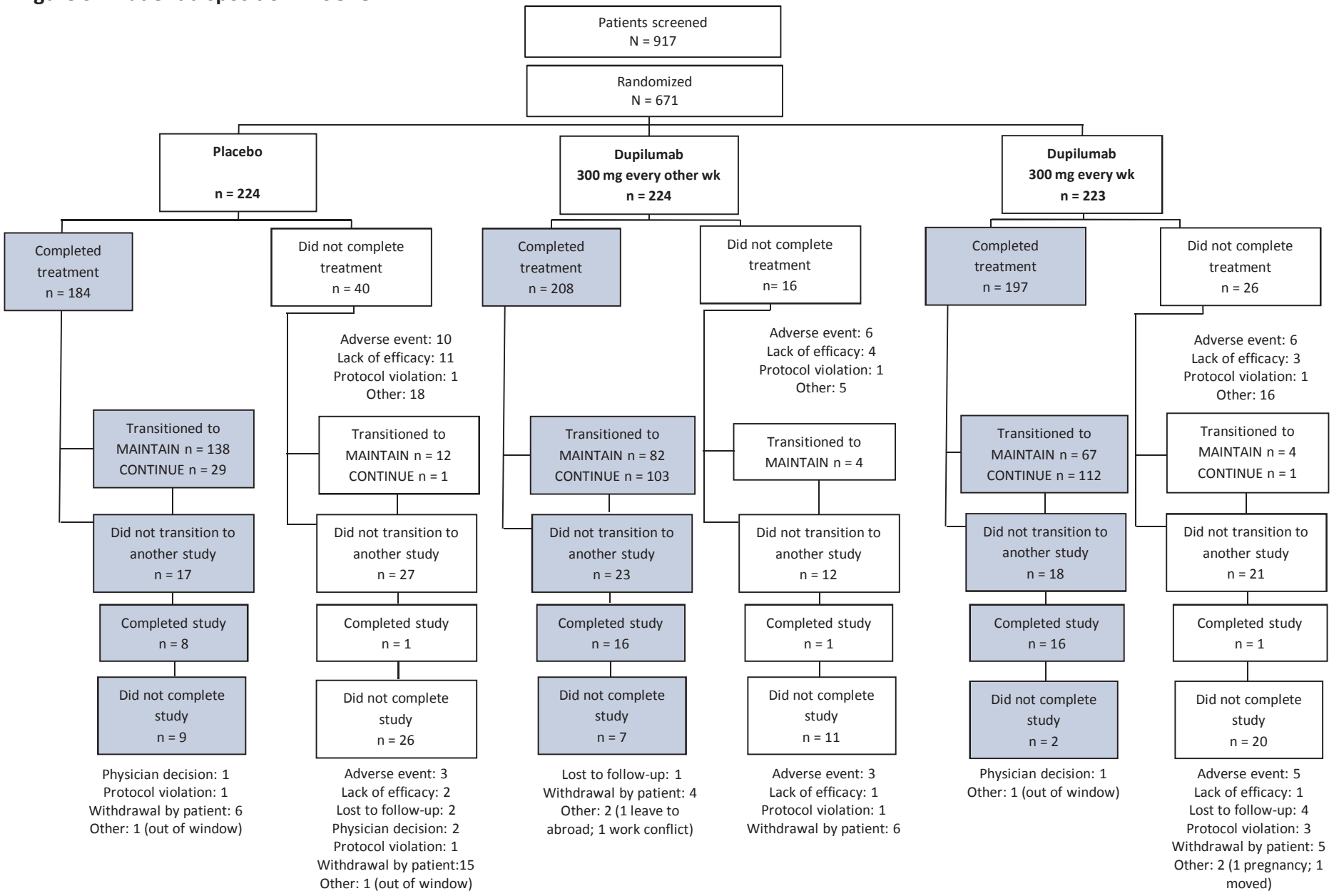
	SOLO 1			SOLO 2		
Event	Placebo (n = 222)	Dupilumab 300 mg every other week (n = 229)	Dupilumab 300 mg weekly (n = 218)	Placebo (n = 234)	Dupilumab 300 mg every other week (n = 236)	Dupilumab 300 mg weekly (n = 237)
Median	−0.10	0	0	−0.05	0	0
Q1, Q3	−0.30, 0.10	−0.20, 0.20	−0.20, 0.20	−0.20, 0.10	−0.20, 0.20	−0.20, 0.20
Week 12						
N	191	212	196	207	219	218
Mean (SD)	−0.12 (0.443)	−0.01 (0.606)	0.01 (0.581)	−0.13 (0.675)	0.03 (0.545)	0.05 (0.591)
Median	−0.10	0	0	0	0	0
Q1, Q3	−0.30, 0.10	−0.20, 0.20	−0.20, 0.20	−0.20, 0.10	−0.20, 0.20	−0.20, 0.20
Week 16						
N	198	216	201	214	218	214
Mean (SD)	−0.16 (0.444)	−0.06 (0.568)	−0.01 (0.612)	−0.14 (0.591)	0.01 (0.641)	0.02 (0.573)
Median	−0.10	0	0	−0.10	0	0

	SOLO 1			SOLO 2		
Event	Placebo (n = 222)	Dupilumab 300 mg every other week (n = 229)	Dupilumab 300 mg weekly (n = 218)	Placebo (n = 234)	Dupilumab 300 mg every other week (n = 236)	Dupilumab 300 mg weekly (n = 237)
Q1, Q3	−0.30, 0	−0.25, 0.10	−0.20, 0.20	−0.30, 0.10	−0.20, 0.20	−0.30, 0.20

Q1, first quartile; Q3, third quartile; SD, standard deviation.

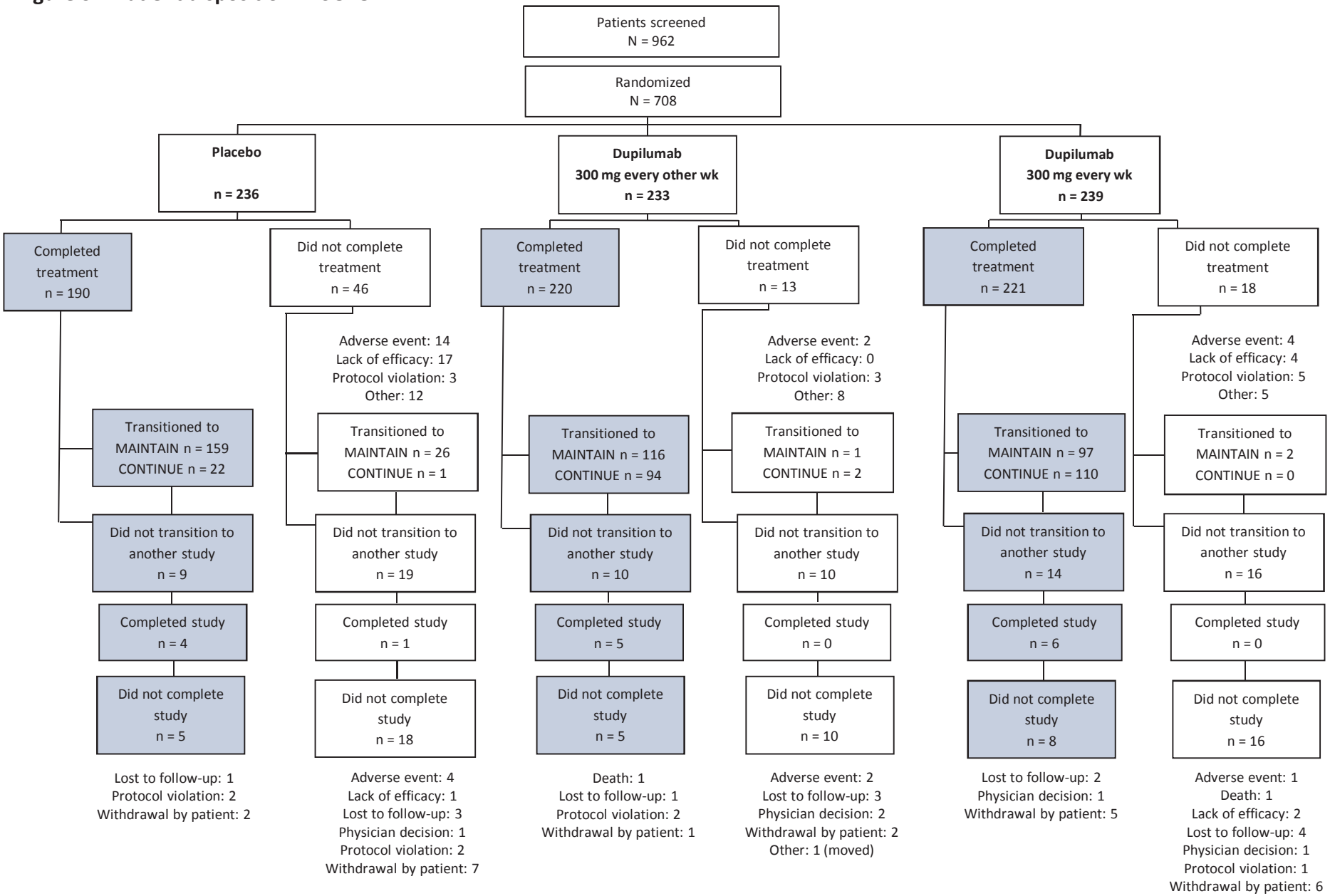
Supplemental figures

Figure S1. Patient disposition in SOLO 1



LIBERTY AD SOLO-CONTINUE, NCT02395133; LIBERTY AD MAINTAIN, NCT01949311.

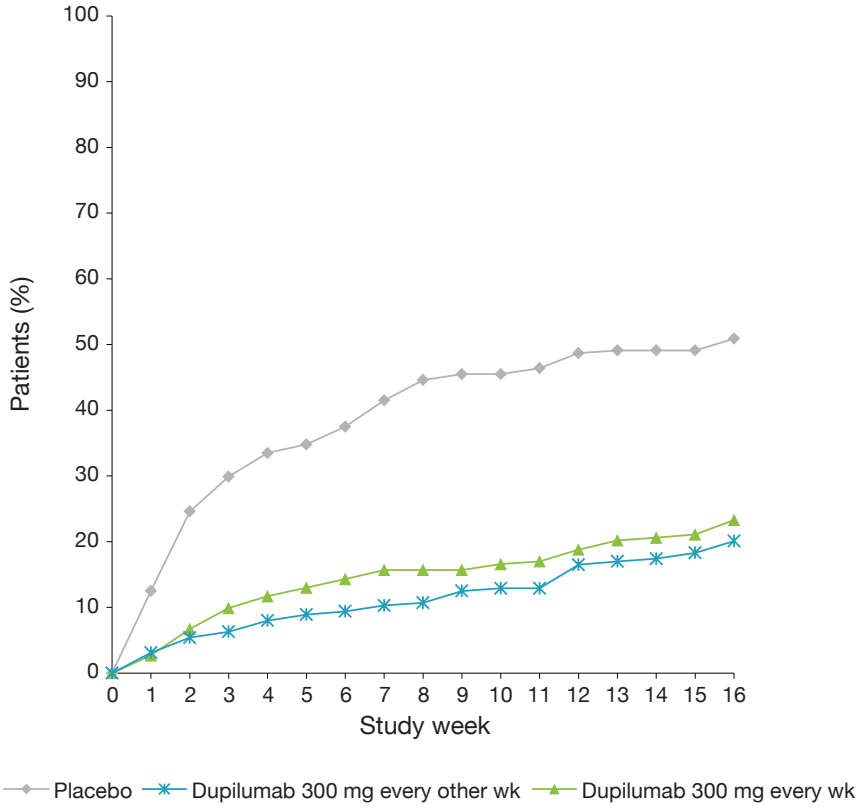
Figure S2. Patient disposition in SOLO 2



LIBERTY AD SOLO-CONTINUE, NCT02395133; LIBERTY AD MAINTAIN, NCT01949311.

Figure S3. Cumulative Proportion of Patients Receiving Rescue Therapy During the Treatment Period

A. SOLO 1



B. SOLO 2

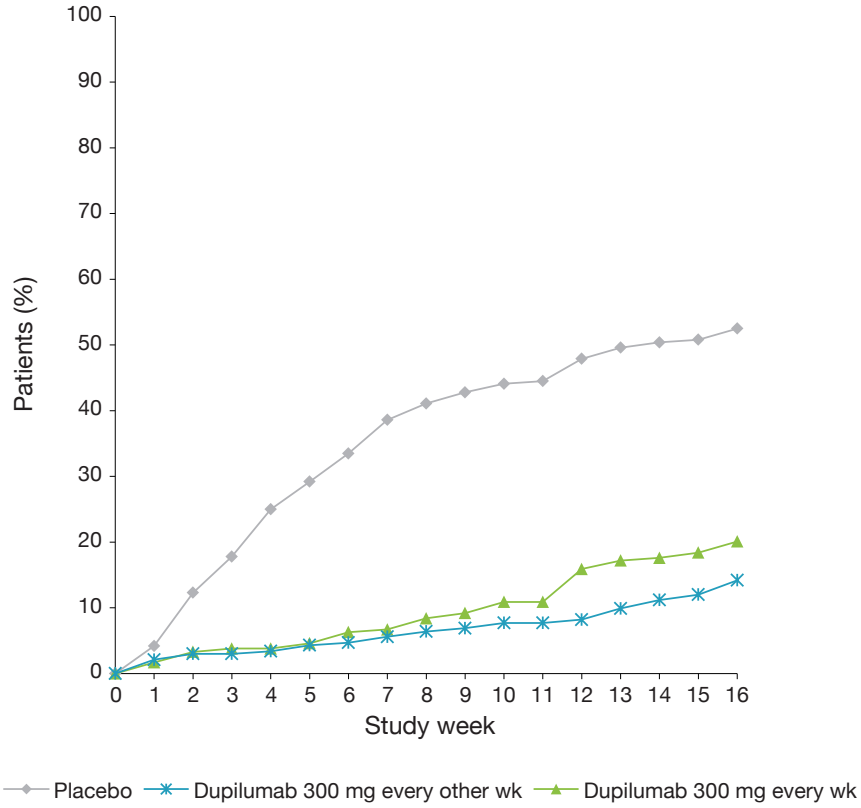
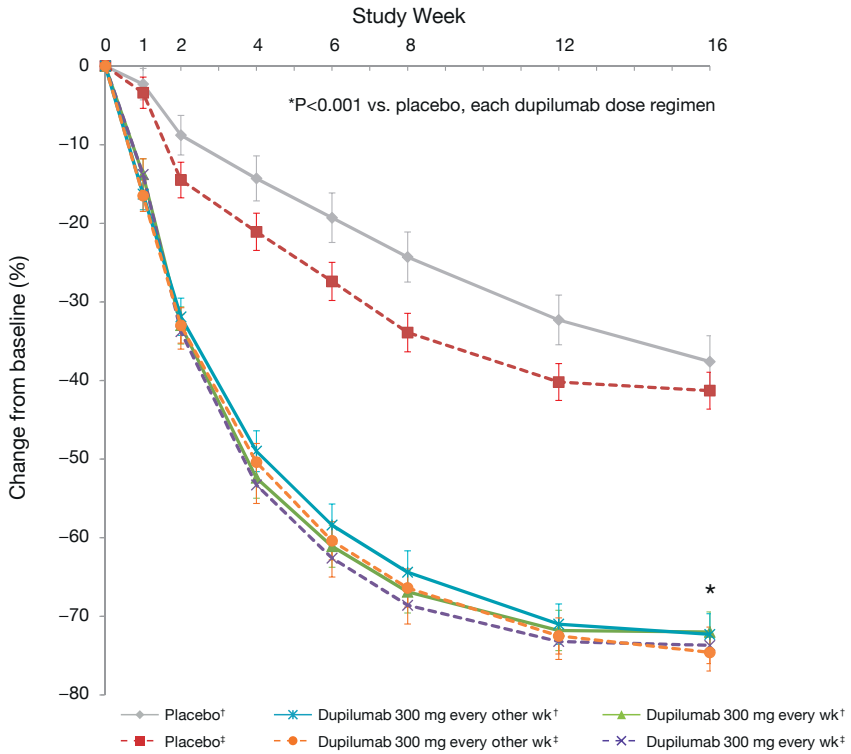
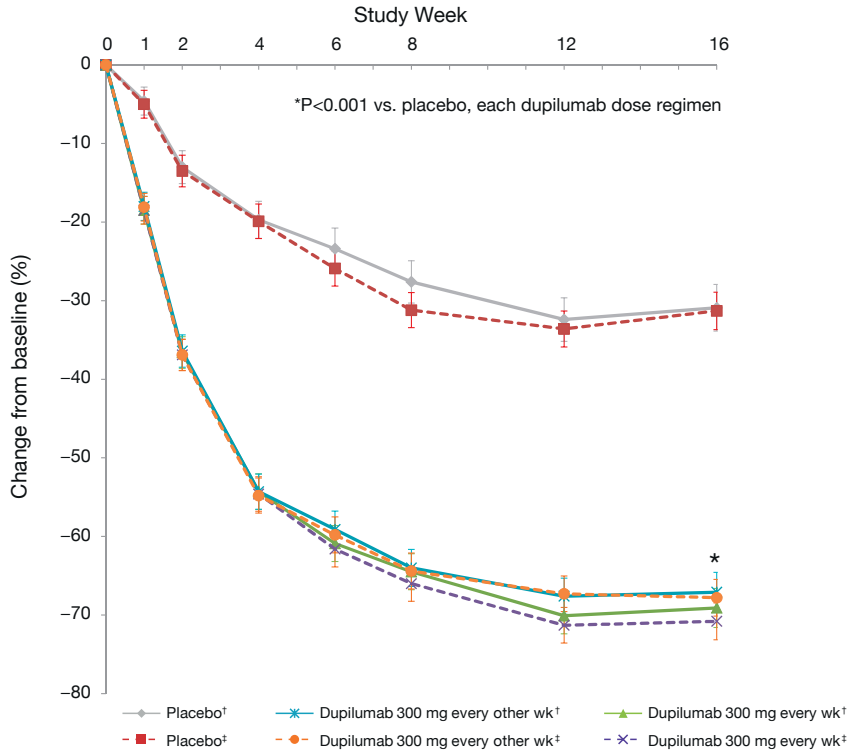


Figure S4. EASI: Least Squares Mean Percent Change Over Time, Primary Analysis, and Sensitivity Analysis

A. SOLO 1



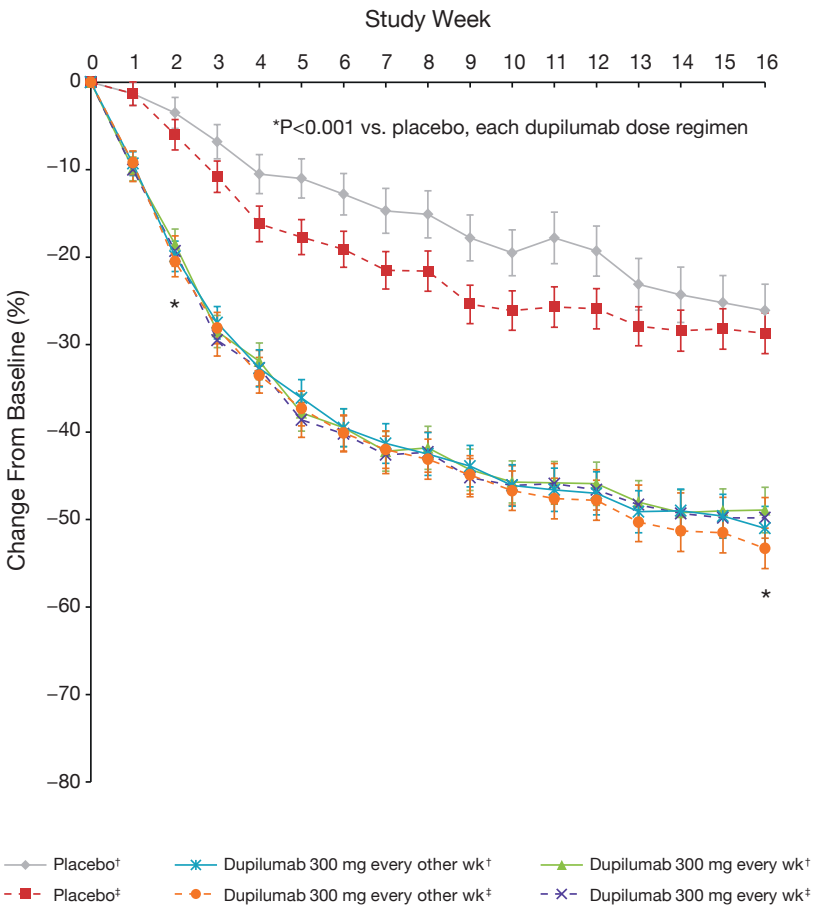
B. SOLO 2



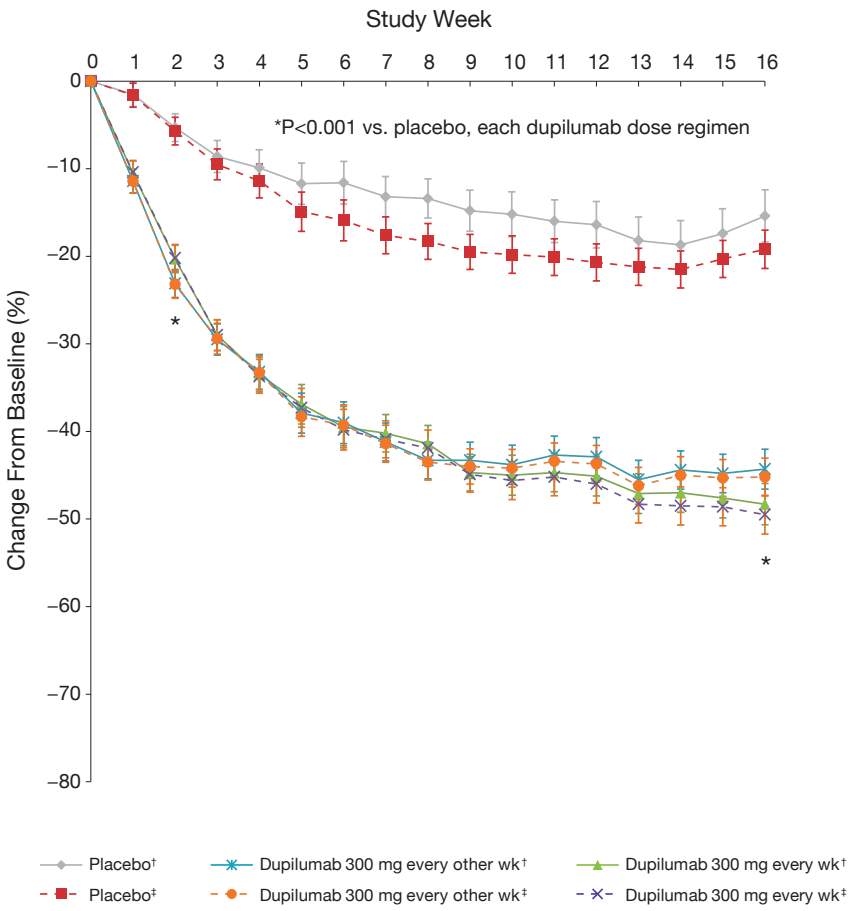
† Data from patients who received rescue medications were categorized as "missing" at all time points subsequent to rescue medication use; for the primary analysis of continuous end points, missing data were imputed using a multiple imputation approach.
‡All observed data, regardless of rescue medication use; missing data were imputed using multiple imputation.
EASI, Eczema Area and Severity Index.

Figure S5. Pruritus Numerical Rating Scale: Least Squares Mean Percent Change Over Time, Primary Analysis, and Sensitivity Analysis

A. SOLO 1



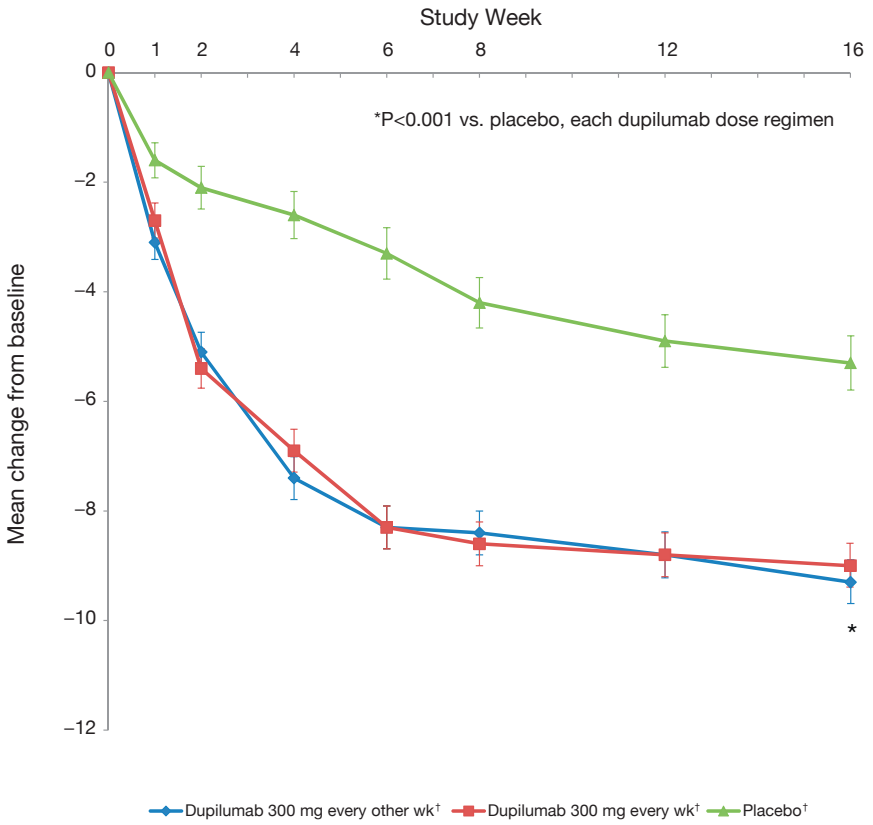
B. SOLO 2



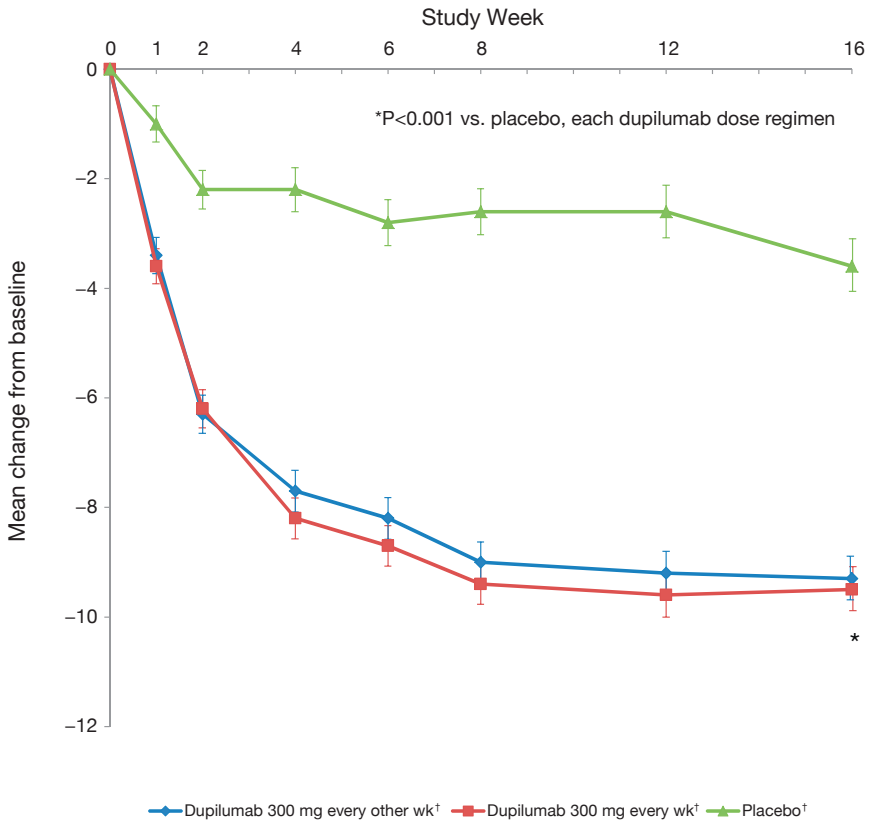
†Data from patients who received rescue medications were categorized as "missing" at all time points subsequent to rescue medication use; for the primary analysis of continuous end points, missing data were imputed using a multiple imputation approach.
‡All observed data, regardless of rescue medication use; missing data were imputed using multiple imputation.

Figure S6. Least Squares Mean Change From Baseline in DLQI in SOLO 1 and SOLO 2

A. SOLO 1



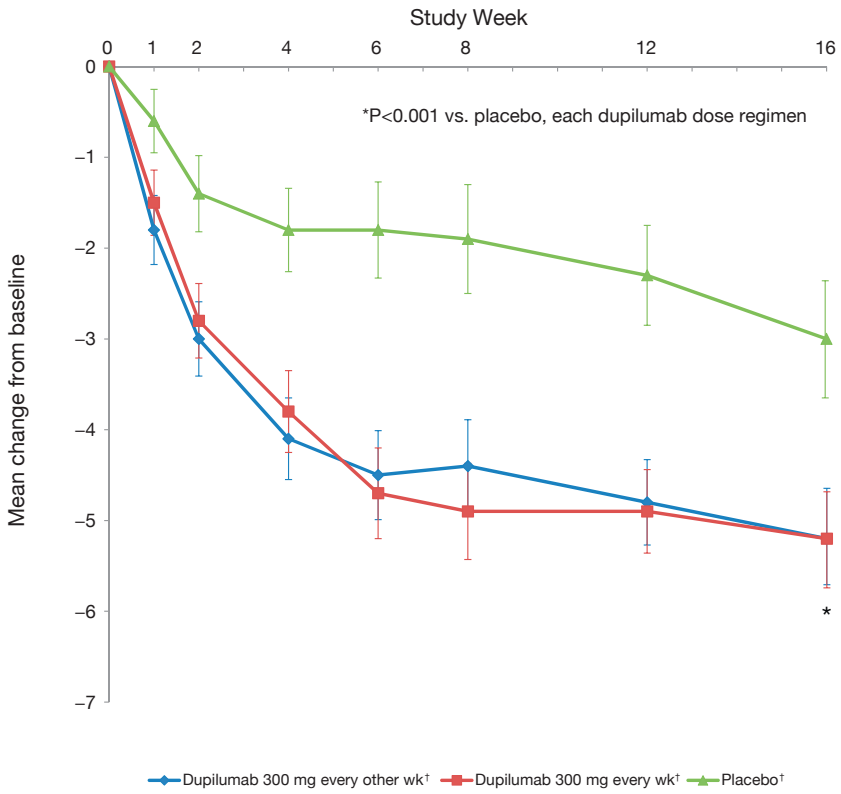
B. SOLO 2



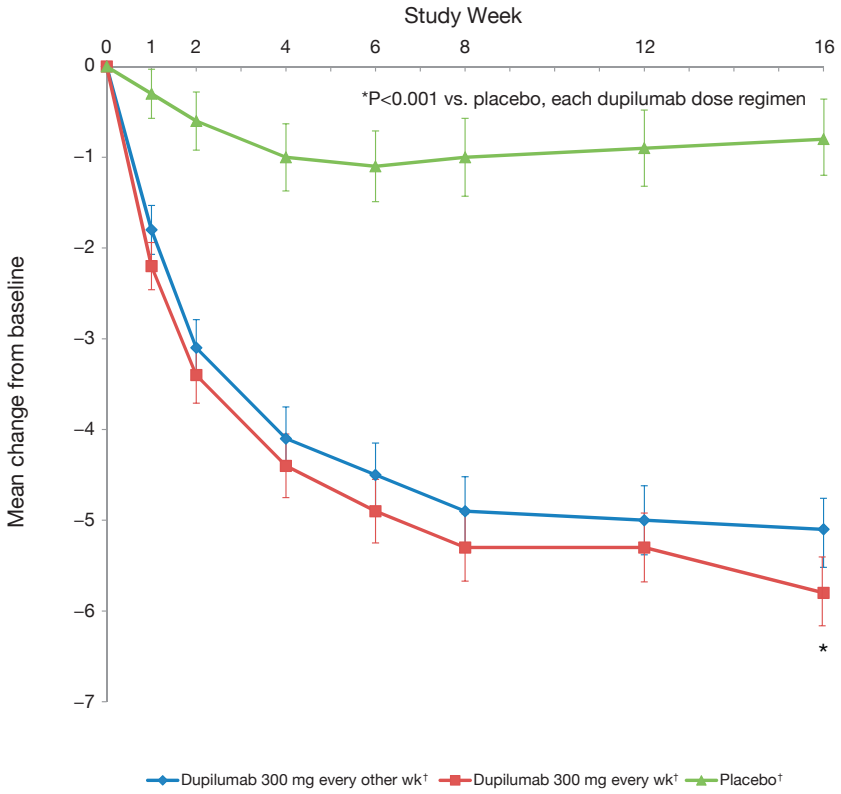
†Data from patients who received rescue medications were categorized as "missing" at all time points subsequent to rescue medication use; for the primary analysis of continuous end points, missing data were imputed using a multiple imputation approach.
‡All observed data, regardless of rescue medication use; missing data were imputed using multiple imputation.
DLQI, Dermatology Life Quality Index.

Figure S7. Least Squares Mean Change From Baseline in HADS Total Score in SOLO 1 and SOLO 2

A. SOLO 1



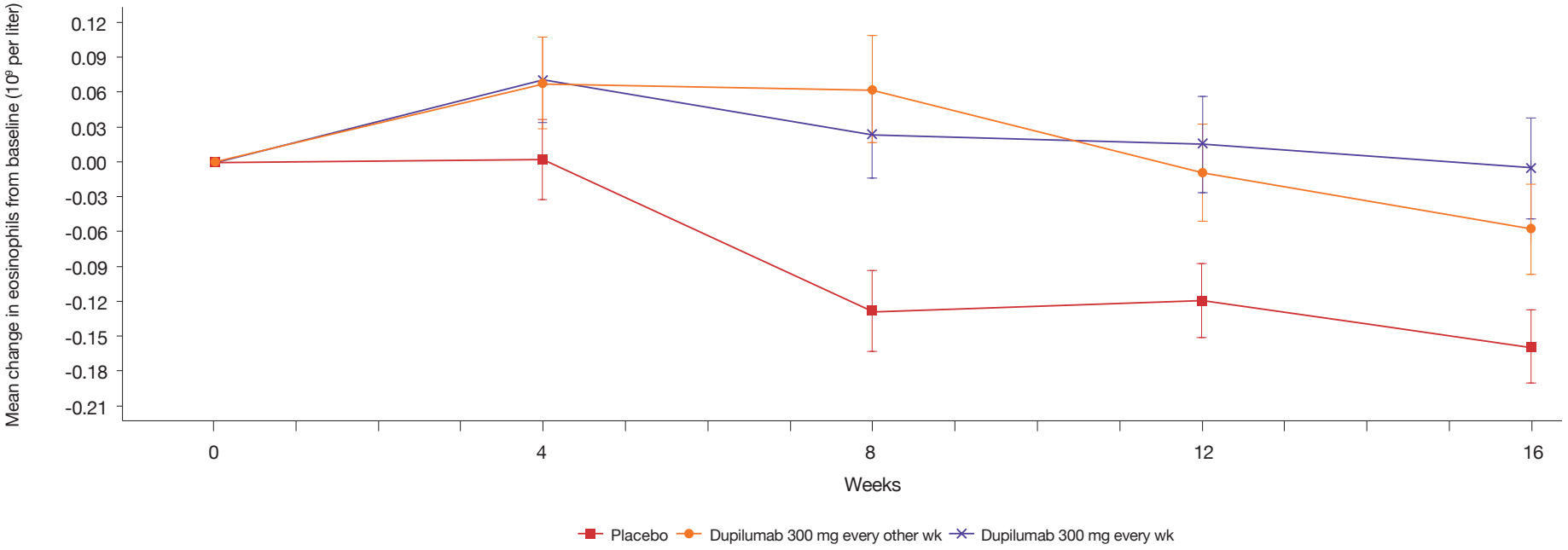
B. SOLO 2



†Data from patients who received rescue medications were categorized as "missing" at all time points subsequent to rescue medication use; for the primary analysis of continuous end points, missing data were imputed using a multiple imputation approach.
‡All observed data, regardless of rescue medication use; missing data were imputed using multiple imputation.
HADS, Hospital Anxiety and Depression Scale.

Figure S8. Change in Average Eosinophils (10^9 per Liter) From Baseline Through Week 16

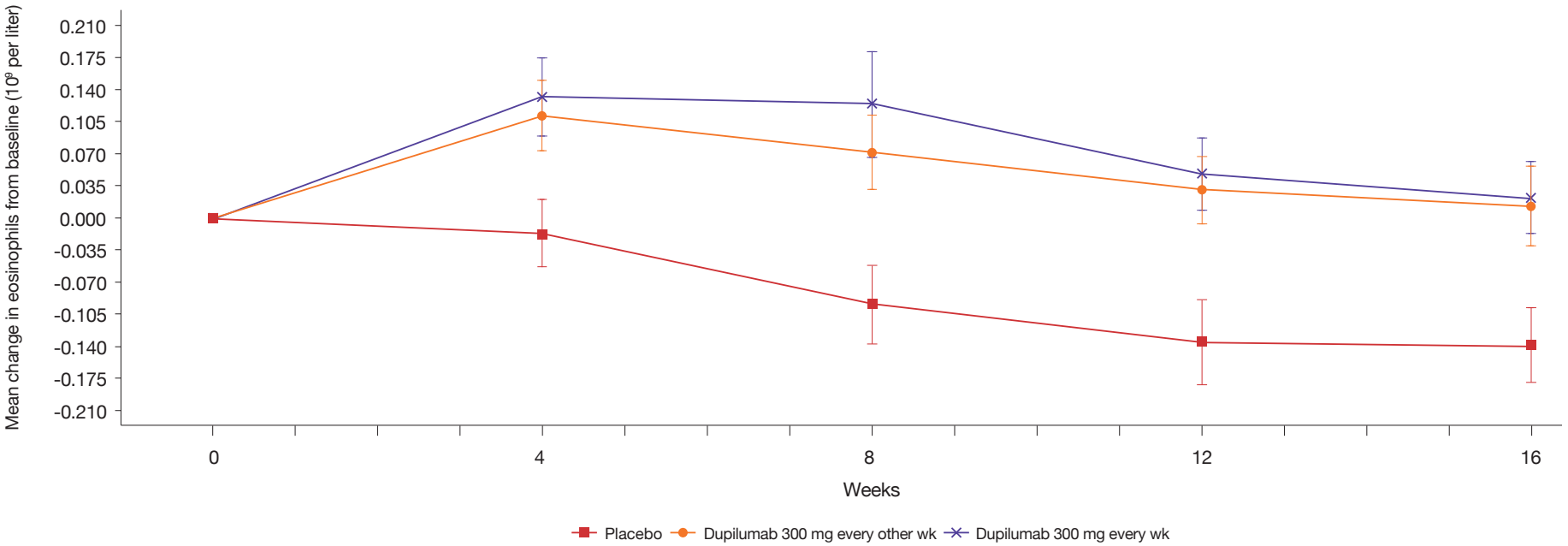
A. SOLO 1



Number of patients in each visit					
Dupilumab 300 mg qw (N=218)	216	207	200	195	199
Dupilumab 300 mg q2w (N=229)	229	217	215	212	216
Placebo qw (N=222)	221	204	194	191	197

Figure S8. Change in Average Eosinophils (10^9 per Liter) From Baseline Through Week 16

B. SOLO 2



Number of patients in each visit					
Dupilumab 300 mg qw (N=237)	237	222	216	218	214
Dupilumab 300 mg q2w (N=236)	236	220	216	219	218
Placebo qw (N=234)	233	222	208	207	214

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