# Supplementary Online Content

Guttman-Yassky E, Blauvelt A, Eichenfield LF, et al. Efficacy and safety of lebrikizumab, a high-affinity interleukin 13 inhibitor, in adults with moderate to severe atopic dermatitis: a phase 2b randomized clinical trial. *JAMA Dermatol*. Published online February 26, 2020. doi:10.1001/jamadermatol.2020.0079



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

**eMethods. Supplemental Methods**

**Additional Study Design Information**

Patients were required to apply over-the-counter moisturizer for ≥7 days prior to Baseline. Study drug was allowed to warm to room temperature prior to administration, was not left at room temperature for >4 hours (protocol amendment January 22, 2018), and could be injected subcutaneously in the abdomen, upper arm, or thigh. Injections administered at a single visit were to be given in the same area (may be administered in different areas for Week 0 and Week 2, where 4 injections/visit occurred; protocol amendment March 7, 2018), spaced ≥10 cm apart, and if possible, not administered through lesional skin. Patients received all injections in the clinic. The 57 US centers where the trial was conducted were: Keck School of Medicine of University of Southern California (Los Angeles, CA), Total Vein and Skin (Boynton Beach, FL), TCR Medical Corporation (San Diego, CA), Oregon Medical Research Center (Portland, OR), Lynn Health Science Institute/Elite Research Network (Oklahoma City, OK), JDR Dermatology Research (Las Vegas, NV), Center for Dermatology Clinical Research (Fremont, CA), The GW Medical Faculty Associates (Washington, DC), Schweiger Dermatology Group (New York, NY), International Clinical Research - Tennessee LLC (Murfreesboro, TN), International Clinical Research (Sanford, FL), Clinical Partners, LLC (Johnston, RI), Dawes Fretzin Clinical Research Group (Indianapolis, IN), Westlake Dermatology Clinical Research Center (Austin, TX), Wilmington Dermatology Center (Wilmington, NC), Dundee Dermatology (West Dundee, IL), Tennessee Clinical Research Center (Nashville, TN), ActivMed Practices & Research, Inc. (Beverly, MA), The Indiana Clinical Trials Center PC (Plainfield, IN), Ichan School of Medicine at Mount Sinai (New York, NY), Meridian Clinical Research, LLC (Baton Rouge, LA), UCSD Dermatology-Clinical Trials Unit (San Diego, CA), UT Health Science Center Houston (Houston, TX), Northwest Arkansas Clinical Trials Center, PLLC (Rogers, AR), ActivMed Research (Portsmouth, NH), Dermatology Associates Seattle (Seattle, WA), Skin Sciences, PLLC (Louisville, KY), Marietta Dermatology Clinical Research, Inc. (Marietta, GA), Stanford University - Stanford Medicine Outpatient Center (Redwood City, CA), University Hospitals Cleveland Medical Center (Cleveland, OH), Integrated Clinical Research (West Palm Beach, FL), Clear Dermatology & Aesthetics Center (Scottsdale, AZ), Progressive Clinical Research (San Antonio, TX), Derm Associates, PC; Dermatology and Skin Cancer Specialists, LLC (Rockville, MD), Rivergate Dermatology Clinical Research Center (Goodlettsville, TN), Kansas City Dermatology (Overland Park, KS), PMG Research of Charlotte (Charlotte, NC), Menter Dermatology Research Institute (Dallas, TX), Arlington Center for Dermatology (Arlington, TX), Somerset Skin Centre/DermCenter (Troy, MI), Wake Research (Raleigh, NC), Virginia Clinical Research, Inc. (Norfolk, VA), Tufts Medical Center (Boston, MA), Sadick Research Group (New York, NY), Clinical Research Center of the Carolinas (Charleston, SC), Dermatology Research Associates (Los Angeles, CA), Dermatology Trial Asssociates (Bryant, AR), Tory Sullivan, MD (North Miami Beach, FL), Center for Dermatology and Laser Surgery (Sacramento, CA), Bellaire Dermatology Associates (Bellaire, TX), Academic Dermatology Associates (Albuquerque, NM), Center for Clinical Studies, LTD LLP (Webster, TX), Advanced Medical Research (Atlanta, GA), Premier Clinical Research; Spokane Dermatology Clinic (Spokane, WA), Clinical Science Institute, Santa (Monica, CA), Olympian Clinical Research (Largo, FL), FL Academic Centers Research Educ (Coral Gables, FL).

**Additional Inclusion Criteria**

1. Willing and able to comply with all clinic visits and study-related procedures and questionnaires
2. Provide signed informed consent

**Detailed Exclusion Criteria**

1. History of anaphylaxis
2. Participation in a prior lebrikizumab clinical study
3. Treatment with any of the following agents within 4 weeks prior to the Baseline visit:
    - Immunosuppressive/immunomodulating drugs (eg, systemic corticosteroids, cyclosporine, mycophenolate-mofetil, IFN-γ, Janus kinase inhibitors, azathioprine, methotrexate, etc.)
    - Phototherapy and photochemotherapy (PUVA) for AD
4. Treatment with topical corticosteroids (TCS) or topical calcineurin inhibitors (TCI) within 1 week prior to the Baseline visit
5. Treatment with biologics as follows:
    - Treatment with an investigational drug within 8 weeks or within 5 half-lives (if known), whichever is longer, prior to the Baseline visit
    - Dupilumab within 3 months of Baseline visit

    - Cell-depleting biologics, including to rituximab, within 6 months prior to the Baseline visit
    - Biologics within 5 half-lives (if known) or 16 weeks prior to Baseline visit, whichever is longer
6. Use of prescription moisturizers within 7 days of the Baseline visit
7. Regular use (more than 2 visits per week) of a tanning booth/parlor within 4 weeks of the screening visit
8. Treatment with a live (attenuated) vaccine within 12 weeks before the Baseline visit
9. Active chronic or acute infection requiring treatment with systemic antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals within 2 weeks before the Baseline visit, or superficial skin infections within 1 week before the Baseline visit (patients may be rescreened after infection resolves)
10. Known or suspected history of immunosuppression, including history of invasive opportunistic infections (eg, tuberculosis [TB], histoplasmosis, listeriosis, coccidioidomycosis, pneumocystosis, and aspergillosis) despite infection resolution; or unusually frequent, recurrent, or prolonged infections, per the Investigator's judgment
11. History of human immunodeficiency virus (HIV) infection or positive HIV serology at screening
12. Positive with hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), or hepatitis C antibody at the screening visit
13. In the Investigator's opinion, any clinically significant laboratory results from the chemistry, hematology or urinalysis tests obtained at the screening visit
14. Presence of skin comorbidities that may interfere with study assessments
15. 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
16. 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 because of his/her participation in this clinical trial, may make patient's participation unreliable, or may interfere with study assessments; pregnant or breastfeeding women, or women planning to become pregnant or breastfeed during the study
17. Women of reproductive potential* who are sexually active and unwilling to use adequate birth control; adequate birth control is 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

*The following are considered women who are not of reproductive potential: Menopausal women, defined as ≥12 consecutive months without menses (if in question, a follicle stimulating hormone level of ≥25 mU/mL); women surgically sterilized (history of hysterectomy, bilateral oophorectomy, or bilateral tubal ligation)

†Includes abstinence, oral/implant/injectable/transdermal hormonal contraceptives, intrauterine device, double-barrier contraception (ie, condom+diaphragm), same sex partner, or a male partner with vasectomy

**Detailed Description of Sensitivity Efficacy Analyses**

1. Sensitivity using non-response imputation (NRI)
    - Used NRI to impute missing values
    - Secondary endpoints of investigator's global assessment (IGA) and ≥75% improvement from Baseline in Eczema Area and Severity Index (EASI75) at Week 16 were analyzed using the same method as their corresponding secondary endpoint
2. Repeated measures analyses on observed data
    - Primary endpoint was analyzed with a repeated measures analysis of covariance (ANCOVA), with treatment, visit (Weeks 4, 8, 12, and 16), and treatment by visit interaction as factors, and a covariate of baseline EASI score
    - The two binary secondary endpoints of IGA and EASI75 at Week 16 were each analyzed with a repeated measures logistic regression model (generalized estimating equations), with the binary endpoint as the dependent variable and treatment, visit (Weeks 4, 8, 12, and 16), and treatment by visit interaction as factors
3. Repeated measures analysis adjusting for rescue medications
    - Used NRI and last-observation-carried-forward (LOCF) to impute missing values
    - The secondary endpoints of IGA and EASI75 at Week 16 were analyzed using the same method as their corresponding repeated measures analyses on observed data

- Patients with missing IGA or EASI75 values at Week 16 were treated as non-responders for analysis purposes
- Any patient with rescue mediation use or who discontinued treatment before the Week 16 study drug administration were treated as non-responders; other missing values before Week 16 used the LOCF method
- Patients that completed treatment but had a missing binary IGA success or EASI score success used the LOCF method

**eTable 1. Investigator's Global Assessment (IGA)**

| Score | Grade | Definition |
|---|---|---|
| 0 | Clear | Minor, residual discoloration; no erythema or induration/papulation; no oozing/crusting; no edema. |
| 1 | Almost clear | Trace, faint pink erythema with barely perceptible induration/papulation and no oozing/crusting; no edema. |
| 2 | Mild | Faint-pink erythema with papulation and edema perceptible upon palpation and no oozing/crusting; minimal induration. |
| 3 | Moderate | Pink-red erythema with definite edema of skin papules and plaques; there may be some oozing/crusting; palpable induration. |
| 4 | Severe | Deep/bright red erythema with significant swelling and obvious raised borders of papules and plaques with oozing/crusting; significant induration. |

## eTable 2. Schedule of Assessments

| | Study Period and Week | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Screening | Baseline | Treatment Period | | | | | | | | Follow-Up/End of Study | | | Early Termination[a] |
| Study Procedure | -30 to -7 | Wk 0 | Wk 2 | Wk 4 | Wk 6 | Wk 8 | Wk 10 | Wk 12 | Wk 14 | Wk 16 | Wk 20 | Wk 24 | Wk 32 (phone call) | |
| Informed consent | X | | | | | | | | | | | | | |
| Inclusion/exclusion | X | X | | | | | | | | | | | | |
| Weight | X | X | | | | | | | | X | | | | X |
| Vital signs | X | X | X | X | X | X | X | X | X | X | X | X | | X |
| Physical examination | X | | | | | | | | | X | | | | X |
| Adverse events | | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Concomitant medications | X | X | X | X | X | X | X | X | X | X | X | X | | X |
| 12-lead electrocardiogram | | X | | | | | | | | X | | | | |
| Hematology, chemistry | X | X | | X | | X | | X | | X | | X | | X |
| Urinalysis | X | X | | X | | X | | X | | X | | X | | X |
| IGA | X | X | | X | | X | | X | | X | X | X | | X |
| EASI | X | X | | X | | X | | X | | X | X | X | | X |
| BSA | X | X | | X | | X | | X | | X | | X | | X |
| Pruritus (daily)[b] | | X | X | X | X | X | X | X | X | X | | | | X |
| POEM | | X | | | | | | | | X | | | | X |
| DLQI | | X | | | | X | | | | X | | | | X |
| Sleep-loss (daily)[b] | | X | X | X | X | X | X | X | X | X | | | | X |

Abbreviations: BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment (5-point scale); POEM, Patient Oriented Eczema Measure; Wk, Week

[a]If applicable

[b]Completed on an electronic tablet issued to the patient at the Baseline visit

**eTable 3. Summary of Rescue Medication Use (Modified Intent-to-Treat Population)**

| | Placebo every 2 wk (n = 52) | Lebrikizumab 125 mg every 4 wk (n = 73) | Lebrikizumab 250 mg every 4 wk (n = 80) | Lebrikizumab 250 mg every 2 wk (n = 75) |
|---|---|---|---|---|
| Any use of rescue medication, no. (%) | 18 (34.6) | 9 (12.3) | 10 (12.5) | 10 (13.3) |
| Topical only | 15 (28.8) | 9 (12.3) | 3 (3.8) | 6 (8.0) |
| Systemic only | 3 (5.8) | 0 | 6 (7.5) | 4 (5.3) |
| Topical and systemic | 0 | 0 | 1 (1.3) | 0 |
| Topical rescue medication duration, days | | | | |
| Mean (SD) | 8.0 (12.6) | 4.9 (5.2) | 1.0 (0.0) | 2.5 (3.2) |

Abbreviations: mITT, modified intent-to-treat; SD, standard deviation

## eTable 4. Post Hoc Sensitivity Analysis (Modified Intent-to-Treat Population)

| | Placebo every 2 wk (n = 52) | Lebrikizumab 125 mg every 4 wk (n = 73) | Lebrikizumab 250 mg every 4 wk (n = 80) | Lebrikizumab 250 mg every 2 wk (n = 75) |
|---|---|---|---|---|
| **Sensitivity Analysis 1: NRI for all missing values** | | | | |
| n | 52 | 73 | 80 | 75 |
| EASI75, no. (%) | 8 (15.4) | 27 (37.0) | 38 (47.5) | 38 (50.7) |
| *P* value versus placebo[a] | --- | .008 | <.001 | <.001 |
| IGA 0/1 response, no. (%) | 5 (9.6) | 16 (21.9) | 22 (27.5) | 28 (37.3) |
| *P* value versus placebo[a] | --- | .07 | .013 | <.001 |
| **Sensitivity Analysis 2: Repeated measures analyses on observed data** | | | | |
| n | 24 | 59 | 62 | 59 |
| LS mean (SD) percent change from Baseline in EASI | -45.1 (26.9) | -63.8 (30.3) | -70.0 (30.1) | -71.2 (30.0) |
| *P* value versus placebo[b] | -- | .006 | <.001 | <.001 |
| EASI75, no. (%) | 8 (33.3) | 27 (45.8) | 38 (61.3) | 38 (64.4) |
| *P* value versus placebo[c] | --- | .10 | .004 | .002 |
| IGA 0/1 response, no. (%) | 5 (20.8) | 16 (27.1) | 22 (35.5) | 28 (47.5) |
| *P* value versus placebo[c] | --- | .34 | .12 | .014 |
| **Sensitivity Analysis 3: NRI for rescue medication use and LOCF for other missing values[d]** | | | | |
| N | 52 | 73 | 80 | 75 |
| EASI75, no. (%) | 6 (11.5) | 26 (35.6) | 34 (42.5) | 36 (48.0) |
| *P* value versus placebo[e] | --- | .004 | <.001 | <.001 |
| IGA 0/1 response, no. (%) | 4 (7.7) | 15 (20.5) | 19 (23.8) | 26 (34.7) |
| *P* value versus placebo[f] | --- | .06 | .02 | .001 |

Abbreviations: CMH, Cochran-Mantel-Haenszel; EASI, Eczema Area and Severity Index; EASI75, ≥75% improvement from Baseline in EASI; IGA, Investigator's Global Assessment (5-point scale); IGA 0/1, score of 0 'clear' or 1 'almost clear'; LOCF, last-observation-carried-forward; LS, least squares; mITT, modified intent-to-treat; NRI, non-responder imputation; SD, standard deviation

[a] *P* value from pairwise CMH tests

[b] Least squares mean, standard deviation, and contrast *P* values from an analysis of covariance with factors of treatment, visit, treatment by visit interaction, and Baseline EASI as a covariate

[c] Contrast *P* values from a repeated measures logistic regression with factors of treatment, visit, and treatment by visit interaction

[d] Patients who used rescue medication or discontinued treatment before Week 16 had Week 16 imputed as a non-responder, with all other missing data handled using LOCF imputation

[e] Contrast *P* values and overall *P* value from a repeated measures logistic regression with factors of treatment, visit, and treatment by visit interaction

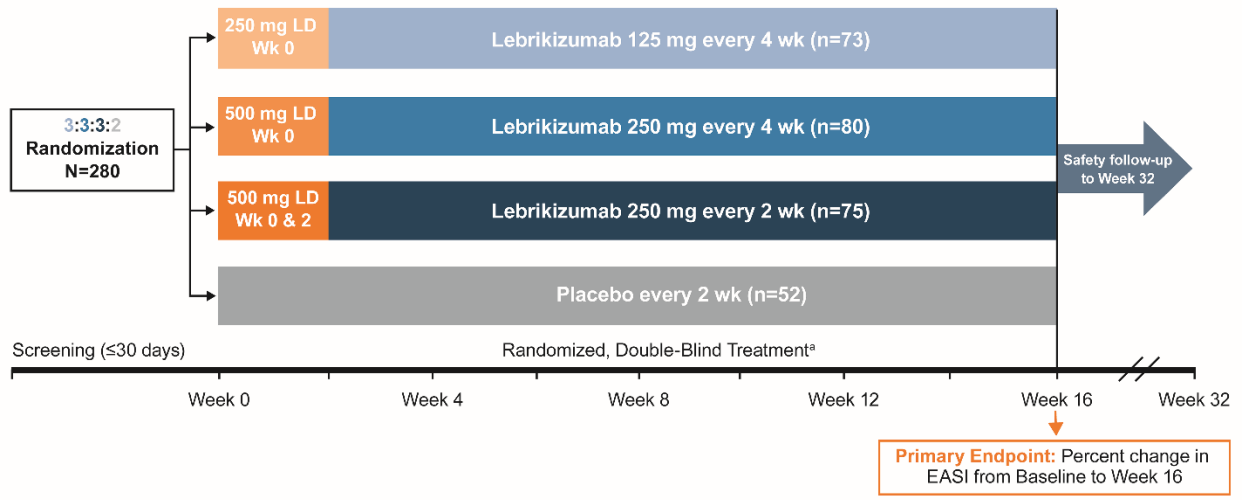
[f] Contrast *P* values from a repeated measures logistic regression with factors of treatment, visit (Week 8, 12, and 16), and treatment by visit interaction; Week 4 was removed from the model due to no successes at Week 4 in the placebo group

**eTable 5. Summary of Treatment-Emergent Adverse Events Leading to Study Discontinuation Through End of Study[a] (Safety Population)**

| | Placebo every 2 wk (n = 52) | Lebrikizumab 125 mg every 4 wk (n = 73) | Lebrikizumab 250 mg every 4 wk (n = 80) | Lebrikizumab 250 mg every 2 wk (n = 75) | All Lebrikizumab (n = 228) |
|---|---|---|---|---|---|
| Patients who discontinued study due to TEAE[b], no. (%) | 1 (1.9) | 2 (2.7) | 4 (5.0) | 3 (4.0) | 9 (3.9) |
| Dermatitis atopic | 1 (1.9) | 1 (1.4) | 0 | 0 | 1 (0.4) |
| Dermatitis allergic | 0 | 0 | 0 | 1 (1.3) | 1 (0.4) |
| Dermatitis exfoliative | 0 | 0 | 0 | 1 (1.3) | 1 (0.4) |
| Eczema | 0 | 0 | 1 (1.3) | 0 | 1 (0.4) |
| Skin irritation | 0 | 0 | 1 (1.3) | 0 | 1 (0.4) |
| Injection site dermatitis | 0 | 0 | 0 | 1 (1.3) | 1 (0.4) |
| Injection site erythema | 0 | 0 | 1 (1.3) | 0 | 1 (0.4) |
| Injection site edema | 0 | 0 | 1 (1.3) | 0 | 1 (0.4) |
| Injection site pain | 0 | 0 | 1 (1.3) | 0 | 1 (0.4) |
| Injection site pruritus | 0 | 0 | 1 (1.3) | 0 | 1 (0.4) |
| Skin infection | 0 | 0 | 1 (1.3) | 0 | 1 (0.4) |
| Alanine aminotransferase increased | 0 | 0 | 1 (1.3) | 0 | 1 (0.4) |
| Aspartate aminotransferase increased | 0 | 0 | 1 (1.3) | 0 | 1 (0.4) |
| Back pain | 0 | 1 (1.4) | 0 | 0 | 1 (0.4) |

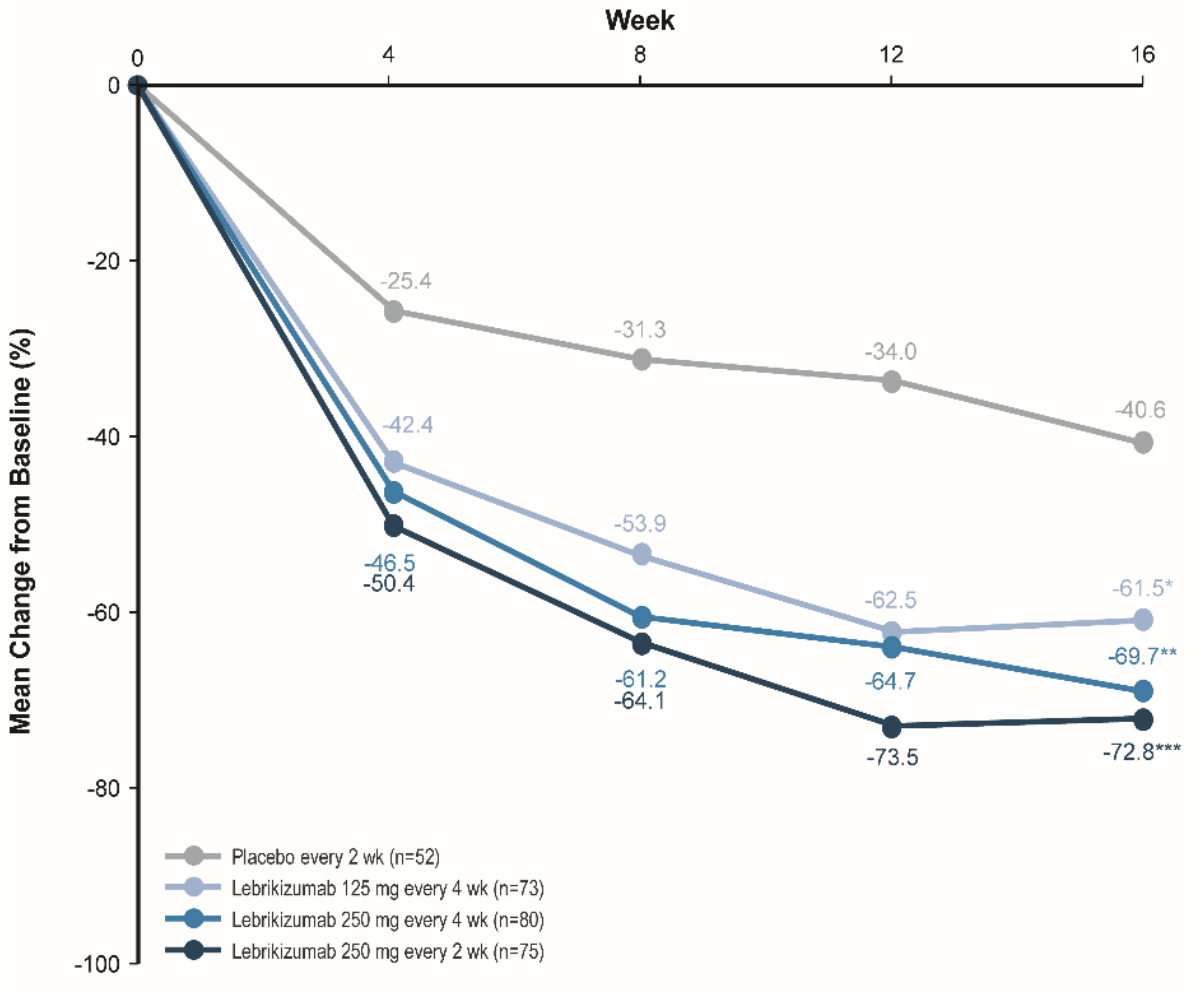
Abbreviations: TEAE, treatment-emergent adverse event
[a]Includes the off-treatment period
[b]MedDRA Version 20.1 preferred terms
TEAEs are those with an onset on or after the date of first study drug injection; percentages are based on the number of patients in the safety population

## eFigure 1. Study Design



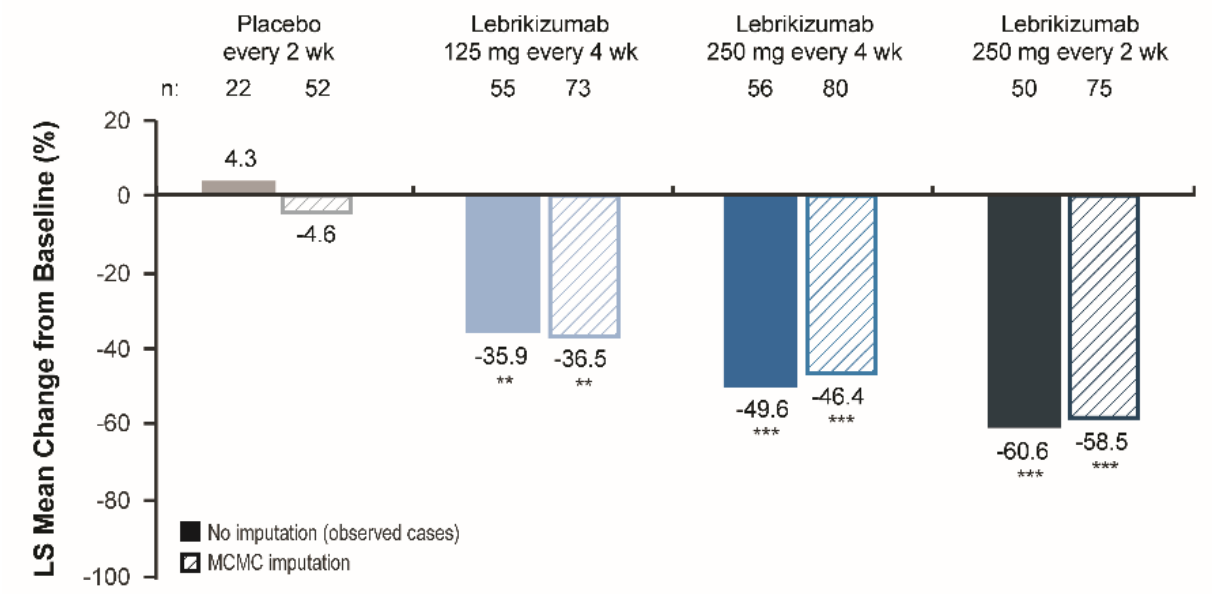

Abbreviations: EASI, Eczema Area and Severity Index; LD, loading dose
[a]Patients were seen every two weeks and received all study drug injections in the clinic
Patients received the same number of injections each week regardless of treatment group, including loading doses administered at Baseline and Week 2

**eFigure 2. Percent Change in EASI (mITT Population; Statistical Comparison at Week 16 Only)**

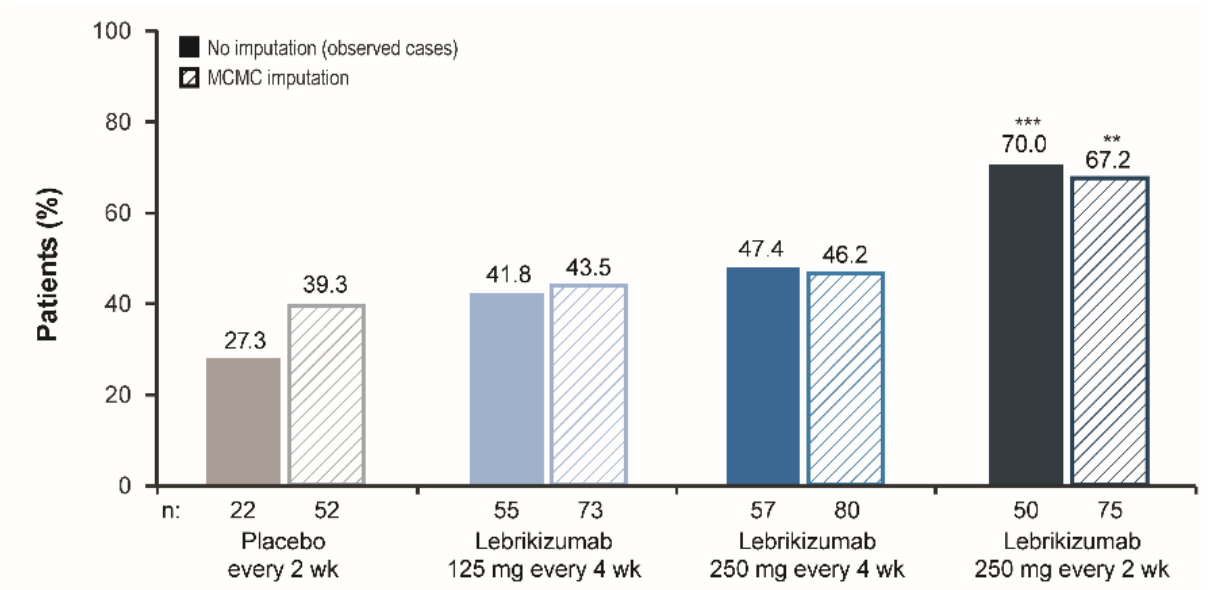



Abbreviations: EASI, Eczema Area and Severity Index; mITT, modified intent-to-treat
Mean percent change values graphed for Week 4, 8, 12, and 16
*$P$<0.05, **$P$<0.01, and ***$P$<0.001 versus placebo from least squares mean values and an analysis of covariance with a factor of treatment group and corresponding Baseline EASI as a covariate; values have been adjusted for multiple imputation
Missing data were imputed using Markov chain Monte Carlo (MCMC) multiple imputation; post-Baseline up through Week 16 visit summary statistics represent average values, obtained by averaging the summary statistics generated from each imputed dataset

**eFigure 3. Improvement on Pruritus NRS at Week 16 (mITT Population)**
**A. LS Mean % Change From Baseline**

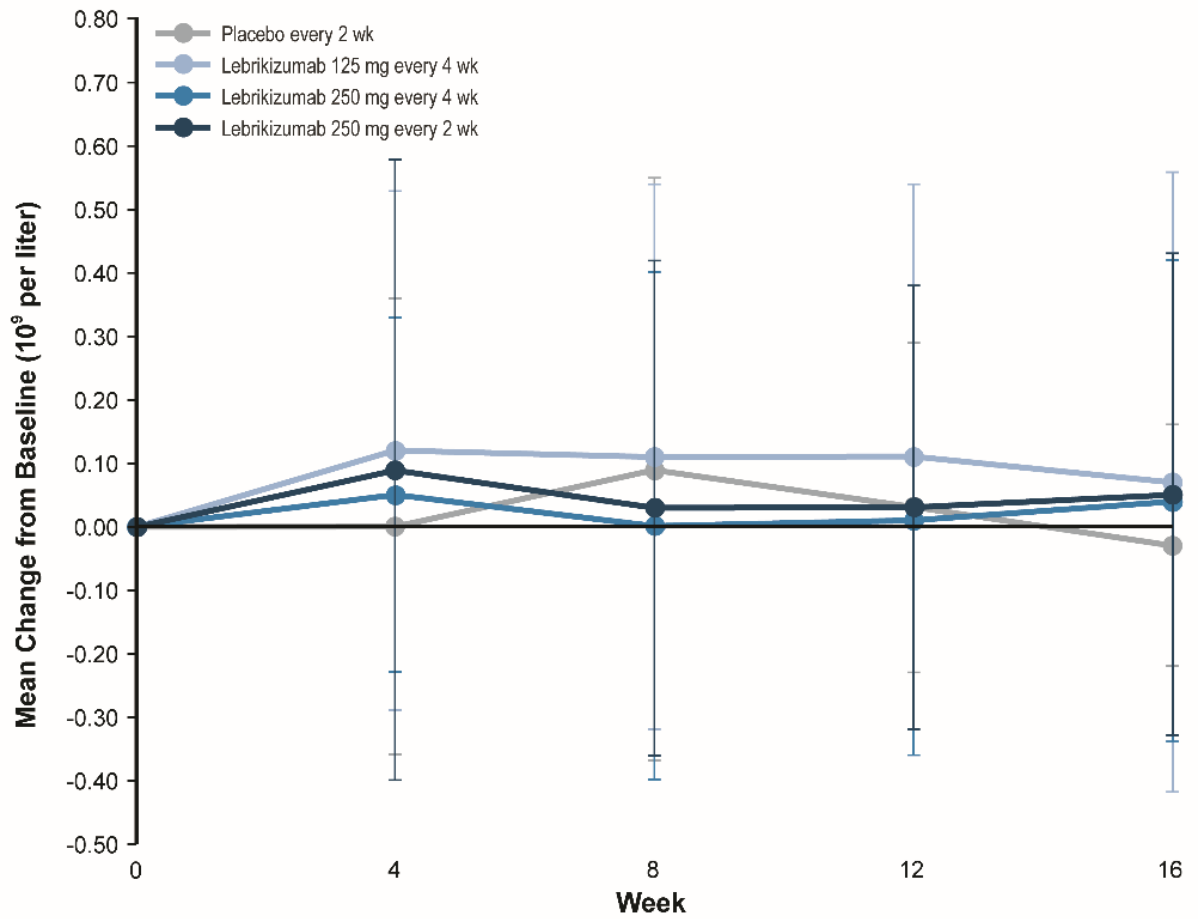



**B. Improvement of ≥4 Points**




Abbreviations: BL, Baseline; CMH, Cochran-Mantel-Haenszel; LD, loading dose; LS, least squares; MCMC, Markov chain Monte Carlo; mITT, modified intent-to-treat; NRS, numeric rating scale; SD, standard deviation
*P<0.05, **P<0.01, and ***P<0.001 versus placebo from pairwise CMH tests

## eFigure 4. Mean Change From Baseline ($10^9$/Liter) in Eosinophils (Safety Population)




Change from Baseline values calculated as post-Baseline – Baseline
Patients reporting laboratory values less than the limit of detection for that test were not included in the summary
Mean (standard deviation) of eosinophils at Baseline: placebo every 2 wk: 0.52 (0.43); lebrikizumab 125 mg every 4 wk: 0.49 (0.41); lebrikizumab 250 mg every 4 wk: 0.45 (0.48); lebrikizumab 250 mg every 2 wk: 0.46 (0.42)
Patient n values fluctuate at each visit; at Week 16: placebo every 2 wk, n=22; lebrikizumab 125 mg every 4 wk, n=57; lebrikizumab 250 mg every 4 wk, n=61; lebrikizumab 250 mg every 2 wk, n=57