Accepted Manuscript

Efficacy and safety of lebrikizumab (an anti-IL-13 monoclonal antibody) in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical corticosteroids: A randomized, placebo-controlled phase II trial (TREBLE)

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PII: S0190-9622(18)30102-6

DOI: 10.1016/j.jaad.2018.01.017

Reference: YMJD 12267

To appear in: *Journal of the American Academy of Dermatology*

Received Date: 6 November 2017

Revised Date: 21 December 2017

Accepted Date: 9 January 2018

Please cite this article as: Simpson EL, Flohr C, Eichenfield LF, Bieber T, Sofen H, Taïeb A, Owen R, Putnam W, Castro M, DeBusk K, Lin C-Y, Voulgari A, Yen K, Omachi TA, Efficacy and safety of lebrikizumab (an anti-IL-13 monoclonal antibody) in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical corticosteroids: A randomized, placebo-controlled phase II trial (TREBLE), *Journal of the American Academy of Dermatology* (2018), doi: 10.1016/j.jaad.2018.01.017.

Target journal: *Journal of the American Academy of Dermatology*

Article type: Original article

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IRB approval status: All study documents and procedures were approved by the appropriate institutional review boards and ethics committees at each study site, and each patient provided written informed consent before study participation. An internal monitoring committee was incorporated to monitor patient safety throughout the study.

Clinical Trials Registry number: NCT02340234 and EudraCT Number 2014-000049-56.

Funding: This study was funded by Genentech, a member of the Roche Group. Editorial assistance was provided by Wemimo Omotosho, PhD, of MediTech Media, funded by Genentech. The study was undertaken in accordance with Good Clinical Practice guidelines and adhered to the Declaration of Helsinki.

Disclosures:

ES reports grants, personal fees, and non-financial support from Roche-Genentech during the conduct of the study; personal fees from AbbVie, Celgene, Dermira, Galderma, LEO Pharma, Menlo Therapeutics, Sanofi Genzyme, and Valeant Pharmaceutical; grants and personal fees from Anacor Pharma, GlaxoSmithKline, and Regeneron Pharmaceuticals; grants from MedImmune, Novartis, Roivant Sciences, Tioga Pharmaceuticals, and Vanda Pharmaceuticals; and grants and personal fees from Eli Lilly outside the submitted work. CF reports personal fees from Sanofi Regeneron outside the submitted work. CF is funded through a National Institute for Health Research (NIHR) Career Development Fellowship (CDF-2014-07-037), and also supported by the NIHR Biomedical Research Centre based at Guy's and St Thomas' NHS Foundation Trust and King's College London. The views expressed are those of the author(s), and not necessarily those of the UK NIHR or the UK Department of Health. LE reports personal fees and non-financial support from Roche-Genentech during the conduct of the study; and activities including Sanofi Regeneron (investigator, consultant, and speaker), Cutanea (consultant), Dermavant (investigator), Eli Lilly (consultant), Galderma (investigator, consultant), Anacor/Pfizer (investigator, consultant), Novartis (consultant), LEO (investigator, consultant), Medimetriks (consultant), and Valeant (investigator, consultant). TB has the following declaration of interests: Roche (consultant), Sanofi Regeneron (investigator, consultant and speaker), Eli Lilly (investigator, consultant and speaker), Galderma (investigator, consultant), Pfizer (investigator, consultant), Novartis (investigator, consultant), GlaxoSmithKline (consultant and speaker), LEO (investigator, consultant and speaker), and AbbVie (consultant). HS reports personal fees from Genentech during the conduct of the study; and personal fees from Regeneron and LEO outside the

submitted work. AT has nothing to disclose. RO is an employee of Genentech, a member of the Roche Group. In addition, RO has a patent pending, and Genentech, a member of the Roche Group, has developed lebrikizumab in atopic dermatitis. WP is an employee and stockholder of Roche. WP has a patent pending on anti-IgE antibodies and methods, and a patent on diagnosis and treatments relating to Th2 inhibition. MC is an employee of Genentech, a member of the Roche group. KD, C-YL, KY and TAO are employees of Genentech, a member of the Roche group, and have patents pending. AV is an employee of Roche Products Ltd.

Data from this study have been presented at the European Academy of Dermatology and Venereology in Vienna, Austria on October 1st, 2016.

Manuscript word count [limit 2500]: 2571

Abstract word count [word limit 200 including five paragraphs: Background, Objectives, Methods, Results, Limitations and Conclusions]: word count: 200

Capsule summary word count [word limit 50]: 39

References [No limit]: 31

Tables and/or figures [No limit]: 4

Attachments

Redacted protocol

Copy of Institutional Review Board approval

Capsule Summary

- IL-13 is overexpressed in patients with atopic dermatitis (AD).
- Lebrikizumab, an anti-IL-13 monoclonal antibody, was superior to placebo in patients with AD when administered subcutaneously every 4 weeks along with topical corticosteroids.
- IL-13 inhibition with lebrikizumab could reduce the need for oral immunosuppressive therapy for patients with AD.

Abstract

Background: Interleukin (IL)-13 plays a key role in type 2 inflammation and is an emerging pathogenic mediator in atopic dermatitis.

Objective: We investigated the efficacy and safety of lebrikizumab, an anti-IL-13 monoclonal antibody, as add-on to topical corticosteroid (TCS).

Methods: A randomized, placebo-controlled, double-blind, phase II study. Adults with moderate-to-severe AD were required to use twice-daily TCS, and randomized (1:1:1:1) to lebrikizumab 125 mg single dose (SD), 250 mg SD, 125 mg once every 4 weeks (Q4W), or placebo Q4W for 12 weeks, after 2-week TCS run-in. Primary endpoint was percentage of patients achieving Eczema Area and Severity Index (EASI)-50 at Week 12.

Results: 209 patients received study drug. At Week 12, significantly more patients achieved EASI-50 with lebrikizumab 125 mg Q4W (82.4%; p=0.026) versus placebo (62.3%); patients receiving lebrikizumab SD showed no statistically significant improvements in EASI-50 versus placebo. Adverse events were similar between groups (66.7% all lebrikizumab vs 66.0% placebo), mostly mild or moderate.

***Limitations*:** Protocol-mandated twice-daily TCS limits understanding of lebrikizumab efficacy as monotherapy. Short study duration did not allow long-term efficacy or safety evaluation.

Conclusions: Lebrikizumab 125 mg Q4W led to significant improvement in patients with moderate-to-severe AD, when added to TCS, and was well tolerated.

Keywords: atopic dermatitis; lebrikizumab; anti-IL-13; topical corticosteroids; EASI; pruritus

Introduction

Atopic dermatitis (AD) is a chronic skin disorder characterized by intensely pruritic, eczematous lesions accompanied by a disrupted skin barrier and type 2 inflammation.[1] AD is one of the most common dermatologic diagnoses worldwide and its burden is multidimensional, impacting sleep, psychosocial activities and health-related quality of life (HRQoL).[2-4] In moderate-to-severe AD, potent topical corticosteroids (TCS), calcineurin inhibitors, phototherapy, and conventional immunosuppressive medications (e.g. cyclosporine) are often required. However, efficacy of topical therapies can be limited, and their frequent use is cumbersome and carries the risk of side effects.[5] Traditional systemic treatments used for moderate-to-severe disease also carry significant risks.[6]

Interleukin (IL)-13 plays a central role in type 2 inflammation, and its gene polymorphisms are associated with increased risk of AD.[7] There is increased expression of IL-13 mRNA in skin biopsy specimens from patients with AD, relative to healthy controls, and levels of IL-13 mRNA expression correlate with AD disease severity.[8,9] Furthermore, overexpression of IL-13 has been shown to reduce epithelial integrity by down-regulation of key skin barrier components.[10,11] Treatment of AD with systemic agents such as cyclosporine can decrease skin IL-13 levels,[12] and recent trials have reported improved clinical responses in patients with moderate-to-severe AD treated with dupilumab, an anti-IL-4Rα monoclonal antibody inhibiting IL-13/IL-4 signaling.[13,14] Together, these data support IL-13 as a key mediator in AD.

In theory, targeting the most central pathologic mediators in AD may maximize efficacy and limit toxicity. Lebrikizumab is a monoclonal antibody that binds specifically to soluble IL-13 with high affinity, preventing IL-13Rα1/IL-4Rα heterodimerization and subsequent signaling.[15,16] Lebrikizumab has previously been investigated for the treatment of asthma, and data have accumulated from 11 randomized clinical trials involving 4,411 individuals.[15,17-20] Following promising phase IIb data in uncontrolled asthma, only one of the two phase III studies in severe adult asthma, showed a statistically significant reduction in asthma exacerbations in the primary analysis population. Nonetheless, based on IL-13's involvement

in multiple pathways important to AD pathogenesis, lebrikizumab may represent a novel targeted therapy in AD.

In this proof-of-concept phase II study, we investigated the efficacy and safety of lebrikizumab, compared to placebo, as add-on to TCS in adults with moderate-to-severe AD.

Methods

Study design

TREBLE was a randomized, placebo-controlled, double-blind, phase II study conducted at 62 centers. It included a 2-week TCS run-in period prior to the 12-week treatment period. Patients were instructed, with daily e-Diary reminders, to apply medium-potency TCS (0.1% triamcinolone acetonide) to all lesional skin during run-in and study treatment. For lesions affecting the face or intertriginous areas, 2.5% hydrocortisone could be used. TCS was included in the regimen as, historically, studies of biologic therapies in a monotherapy setting have led to high dropout/imputed patient failure rates, in particular due to disease severity. In addition, add-on TCS treatment reflects 'real-life' clinical practice in patients with moderate-to-severe AD. Further details about study design, pharmacokinetics (PK), outcome measures, and statistical analyses are provided in the online supplement.

Patients

Eligible patients were aged 18–75 years, and had a diagnosis of moderate-to-severe AD with an inadequate response to TCS (≥1-month history within 3 months prior to screening) and regular emollient. Other key inclusion criteria were: Eczema Area and Severity Index (EASI) ≥14 and Investigator Global Assessment (IGA) score ≥3 at screening and end of the run-in period, as well as AD involvement of ≥10% of body surface area (BSA) and Pruritus Visual Analog Scale (VAS) score ≥3 (measured as part of SCORing Atopic Dermatitis [SCORAD]) at screening.

Exclusion criteria included: use of topical calcineurin inhibitors; recent systemic immunosuppressive therapies or phototherapy; and evidence of other skin conditions, including T-cell lymphoma or allergic contact dermatitis.

Randomization

Patients were randomized 1:1:1:1 to receive lebrikizumab 125 mg single dose (SD) at baseline, 250 mg SD at baseline, 125 mg once every 4 weeks (Q4W), or placebo Q4W for 12 weeks.

Procedures

The 12-week treatment period was followed by an 8-week safety follow-up period, during which patients could apply TCS as needed.

Disease severity assessments included EASI, IGA, and SCORAD; patient-reported outcome (PRO) data were collected using the Dermatology Life Quality Index (DLQI) and AD Impact Questionnaire (ADIQ).[21]

Outcomes

The primary endpoint was the percentage of patients achieving a 50% reduction in EASI score from baseline (EASI-50) at Week 12. This EASI-50 also equates to a minimum of a 7-point improvement from the required baseline score ≥14 in this study, which is above the minimum clinically important difference of 6.6 points.[22] Key secondary endpoints included the percentages of patients achieving EASI-75, IGA score of 0/1, and SCORAD-50 at Week 12. Safety outcomes, including treatment-emergent adverse events (AEs) and serious AEs (SAEs), were monitored at each visit from baseline to Week 20. Eosinophil-associated AEs were also monitored.

Statistical analyses

Primary and secondary efficacy analyses included all patients who were randomized and received at least one dose of study drug, and were analyzed according to the treatment assigned at randomization. Safety analyses included all patients who received at least one dose of study drug, and were analyzed according to the treatment received. The Cochran-Mantel–Haenszel χ^2 test was used to compare the proportions of patients with EASI-50 at Week 12 in each of the lebrikizumab groups versus placebo, stratified by randomization stratification factor geographic region (US/Canada, Europe, and other). Patients missing an EASI score at Week 12 were considered non-responders.

Results

Trial patients

Overall, 209 patients received study drug (n=53 placebo; n=156 lebrikizumab) (Figure S1). Baseline characteristics of patients were similar across treatment groups (Table I). There was a high compliance rate of TCS use amongst all treatment groups, with TCS used on 86.8% (125 mg SD), 86.7% (250 mg SD), 91.9% (125 mg Q4W), and 88.2% (placebo) of days on average from baseline to Week 12. Further details of the results are provided in the online supplement.

Primary outcome

At Week 12, significantly more patients in the lebrikizumab 125 mg Q4W group achieved EASI-50 compared with placebo (82.45 vs 62.3%; p=0.026) (Figure 1A). However, the response in the lebrikizumab SD groups was not statistically significant at Week 12. In the Q4W arm, the response curve showed an upward sloping trajectory in the final weeks of treatment (Figure 2A). Notably, patients in the placebo group, with protocol-mandated twice-daily TCS application, showed a high response rate, with 62.3% of patients exhibiting an EASI-50 response at Week 12.

Other AD severity measures

The proportion of patients achieving an EASI-75 response was significantly greater in the 125 mg Q4W group (54.9%; p=0.036) compared with placebo (34.0%), but did not achieve statistical significance in the 125 mg and 250 mg SD groups at Week 12 (Figure 1B). As with EASI-50 response, patients in the 125 mg Q4W group showed continued improvement in EASI-75 over the final weeks of the treatment period (Figure 2B).

The percentage of patients who achieved IGA 0/1 at Week 12 was higher in all lebrikizumab groups compared with placebo, but while there was a trend toward statistical significance with the 125 mg Q4W group (33.3% vs 18.9%; p=0.098), single doses clearly did not achieve statistical significance (Table S2).

For SCORAD-50, more patients in the lebrikizumab 125 mg Q4W group (51.0%; p=0.012) and 250 mg SD group (47.2%; p=0.030) achieved this endpoint compared with placebo (26.4%) at Week 12 (Figure 1D). The greatest reduction in BSA affected at Week 12 was observed in the lebrikizumab 125 mg Q4W group (57.7% reduction). There were also improvements in the placebo group (47.4%), and placebo-corrected efficacy for BSA was not statistically significant (p=0.38).

Patient-reported symptoms and quality of life

There were adjusted mean percent reductions from baseline pruritus VAS of 34.9%, 32.8%, and 40.7% in the lebrikizumab 125 mg SD, 250 mg SD, and 125 mg Q4W groups, respectively (Figure 3). The placebo group also showed reductions from baseline pruritus VAS (27.5%), and placebo-corrected efficacy was not statistically significant (p=0.40 [125 mg SD], p=0.54 [250 mg SD], and p=0.13 [125 mg Q4W]) (Table S1). Improvements in pruritus VAS during the 2-week TCS run-in were quantitatively larger, in percentage terms, than improvements in overall disease severity measures (Table S2).

There were also improvements in sleep loss VAS, with mean reduction from baseline in the lebrikizumab 125 mg SD (53.1%; p=0.029), 250 mg SD (47.2%; p=0.076), and 125 mg Q4W (53.6%; p=0.023) groups compared with the placebo group (22.6%) (Table S1).

Lebrikizumab groups showed numerical improvements, relative to placebo, in ADIQ and DLQI scores from baseline to Week 12, with ADIQ showing borderline statistical significance for the 125 mg Q4W group (p=0.057), but results were otherwise not statistically significant (Table S1).

Safety

Lebrikizumab was well tolerated, and there were no imbalances in proportions of patients reporting AEs, SAEs, events leading to discontinuation, and overall infections when comparing all lebrikizumab-treated patients with placebo (Table S5). There were no dose-response relationships in adverse events. Three (2%) patients in the lebrikizumab group (all doses combined) and one (2%) patient in placebo experienced an AE that led to withdrawal

from study. There were no deaths, anaphylactic reactions, malignancies, or protocol-defined parasitic or targeted intracellular infections of interest. Injection-site reactions occurred infrequently (1.3% all lebrikizumab groups and 1.9% placebo); all events were non-serious and lasted a median of 1–3 days.

Discussion

Lebrikizumab provided treatment benefit on top of rigorous TCS therapy in patients with moderate-to-severe AD who had an inadequate response to TCS. The study met its primary endpoint, with a statistically greater proportion of patients in the lebrikizumab 125 mg Q4W group achieving an EASI-50 response, compared with placebo. The upward sloping response curves over the final weeks of the treatment period suggest that the response plateau might not have been reached by Week 12 for lebrikizumab 125 mg Q4W, and that a longer treatment duration may lead to improved efficacy. Although improvements with the single doses were not statistically significant at Week 12, the significant responses observed with the highest lebrikizumab dose (125 mg Q4W) may indicate a dose-response relationship.

Dosing within this study was based largely on experience from the lebrikizumab asthma program and the objective of characterizing both dose-response relationships and dosing frequency requirements in AD. The dose-response relationships observed across multiple endpoints, and the trends towards improved efficacy with increasing dose and duration, suggest that further increases in the dose and/or treatment duration may have resulted in improved efficacy. Notably, the lebrikizumab 250 mg SD group showed numerically higher responses at earlier time points for several outcomes, suggesting the potential benefit of either higher dosing (e.g. 250 mg Q4W) and/or a loading dose. The observed differences in the lebrikizumab dose-response relationship between forced expiratory volume in 1 second in asthma patients[17] and EASI/IGA endpoints in AD patients suggest that AD may require higher doses of lebrikizumab to achieve a response plateau. This would suggest a higher IL-13 burden in AD than in asthma. Further studies in AD will be required to confirm whether additional clinical benefit can be observed with tailored dosing.

Lebrikizumab was generally well tolerated, and AE rates were similar between treatment groups. This safety profile is consistent with that observed in the extensive asthma program.[15,17-20,23] Previously reported increases in peripheral blood eosinophil counts with lebrikizumab treatment are possibly due to decreased eosinophil trafficking from blood to the airways as a result of reduced chemotaxis by blocking IL-13 activity.[15,20] In the TREBLE study,

although eosinophil-associated AEs occurred only among lebrikizumab-treated patients, they were reported infrequently (n=5 [3.2%]), all events were non-serious, and none were associated with clinical signs or symptoms, or resulted in dose reductions or treatment discontinuation.

The study protocol required twice-daily TCS during the 2-week run-in period, and patients were only eligible for randomization if they manifested sufficient AD severity after this run-in. Although patients included in this study had a history of inadequate control by TCS, this TCS run-in nonetheless led to disease improvement, with lower baseline AD severity scores, especially itch. Although there is rationale for such a design, it does potentially leave less room for disease improvement than without a run-in period.

During the treatment period, patients continued twice-daily application of TCS, with daily e-Diary reminders, achieving an 88% compliance rate. TCS application may explain the substantial response observed in placebo and may also have attenuated placebo-corrected efficacy. Prolonged and frequent TCS use has been shown to result in progressive improvements in AD, but most guidelines suggest limiting daily use to avoid AEs.[24-26] However, while daily TCS use is typically recommended for acute lesions, rather than chronically,[5] this proof-of-concept study sought to understand the potential efficacy of lebrikizumab in addition to continuous TCS, and not to assess TCS sparing. The chosen regimen is consistent with TCS labeling, and also considers regulatory concerns regarding off-label usage at a lower frequency than mandated by product labeling. It was also recognized that alternate designs could lead to substantial patient dropout and/or imputed patient failure within the control arm. Indeed, studies of biologic therapies in a monotherapy setting have led to dropout/imputed patient failure rates of approximately 50% within the control arm,[13] in contrast to the dropout rate of 13% for the placebo arm in this study. Nonetheless, despite the relatively high efficacy of prolonged and frequent TCS use, there were still significant improvements, particularly in AD signs (EASI) and global scores (SCORAD) after addition of lebrikizumab.

Dupilumab, an anti-IL-4Rα monoclonal antibody, demonstrated efficacy in patients with moderate-to-severe AD and has been recently approved in AD. IL-4Rα is a receptor subunit for both IL-4 and IL-13 signaling. Studies of dupilumab in AD patients provide insight into the potential of IL-13 blockade to treat AD, with the caveat that the relative importance of IL-4 compared with IL-13 in AD has not been established. Both IL-13 and IL-4 share overlapping biology and effector functions.[27,28] Given such high overlap in biology, blockade of IL-13 alone could potentially provide comparable improvements in AD to blockade of IL-13 and IL-4 in combination, with a more specific targeted action.

Targeting a soluble cytokine such as IL-13 may also offer the advantage of a linear PK profile with resulting improvements in sustained target coverage and dosing frequency. This linear PK, combined with the long half-life of lebrikizumab (19–22 days), in part explains the ability to dose lebrikizumab Q4W, and may allow for less frequent dosing during maintenance. Indeed, the fact that single-dose groups showed improving placebo-corrected efficacy through Week 8 suggests the potential for such a dosing regimen. In contrast, receptor targeting is associated with target-mediated drug clearance that may lead to rapid declines in concentration after drug discontinuation or interruption, as with dupilumab, which is dosed every 2 weeks.[29]

The results of this proof-of-concept study, using doses based on experience in asthma, suggest that IL-13-mediated signaling pathways play an important role in the pathogenesis of AD, and the blockade of this cytokine could lead to significant clinical benefit. Patients with moderate-to-severe AD showed improvements with lebrikizumab treatment, even with single doses and twice-daily TCS use. However, the twice-daily use of TCS before and during this trial in all study groups impaired the ability to fully assess the efficacy of lebrikizumab in AD, and monotherapy studies may be needed to assess the efficacy of lebrikizumab. The dose-response relationships and kinetics of response observed in this study suggest that future studies of longer duration, with loading, higher, and potentially less frequent dosing, and in a larger population on different (or without) background regimens will help clarify the role of targeting IL-13 with lebrikizumab in AD.

Acknowledgments

We thank Jingyuan Chen and Simon Luo for their support with statistical programming of the data in this manuscript. We thank Nicholas Vlahakis for his support in the design and conduct of the TREBLE study. We also thank the patients who participated in this study, as well as the investigators and staff at all study sites. A complete list of sites from the trial is provided in the appendix. Editorial assistance was provided by Wemimo Omotosho, PhD, of MediTech Media, funded by Genentech.

Contributors

All authors contributed to the analysis and interpretation of the data, and the critical revision of the report; are accountable for the accuracy and integrity of the report; and provided final approval to submit.

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Abbreviations

AD	Atopic dermatitis
ADIQ	Atopic Dermatitis Impact Questionnaire
AE	Adverse event
BSA	Body surface area
DLQI	Dermatology Life Quality Index
EASI	Eczema Area and Severity Index
HRQoL	Health-related quality of life
IGA	Investigator Global Assessment
IL-4	Interleukin-4
IL-13	Interleukin-13
PK	Pharmacokinetic
PRO	Patient-reported outcome
Q4W	Once every 4 weeks
SAE	Serious adverse events
SCORAD	SCORing Atopic Dermatitis
SD	Single dose
SDv	Standard deviation
TCS	Topical corticosteroids
VAS	Visual Analog Scale

Figure legends

Figure 1. Atopic dermatitis. Proportion of patients achieving (A) EASI-50, (B) EASI-75, (C) IGA 0/1, and (D) SCORAD-50 at Week 12

EASI=Eczema Area Severity Index; IGA=Investigator Global Assessment; Q4W=once every 4 weeks; SCORAD=SCORing Atopic Dermatitis; SD=single dose.

Figure 2. Atopic dermatitis. Proportion of patients achieving (A) EASI-50, (B) EASI-75, (C) IGA 0/1, and (D) SCORAD-50 over time

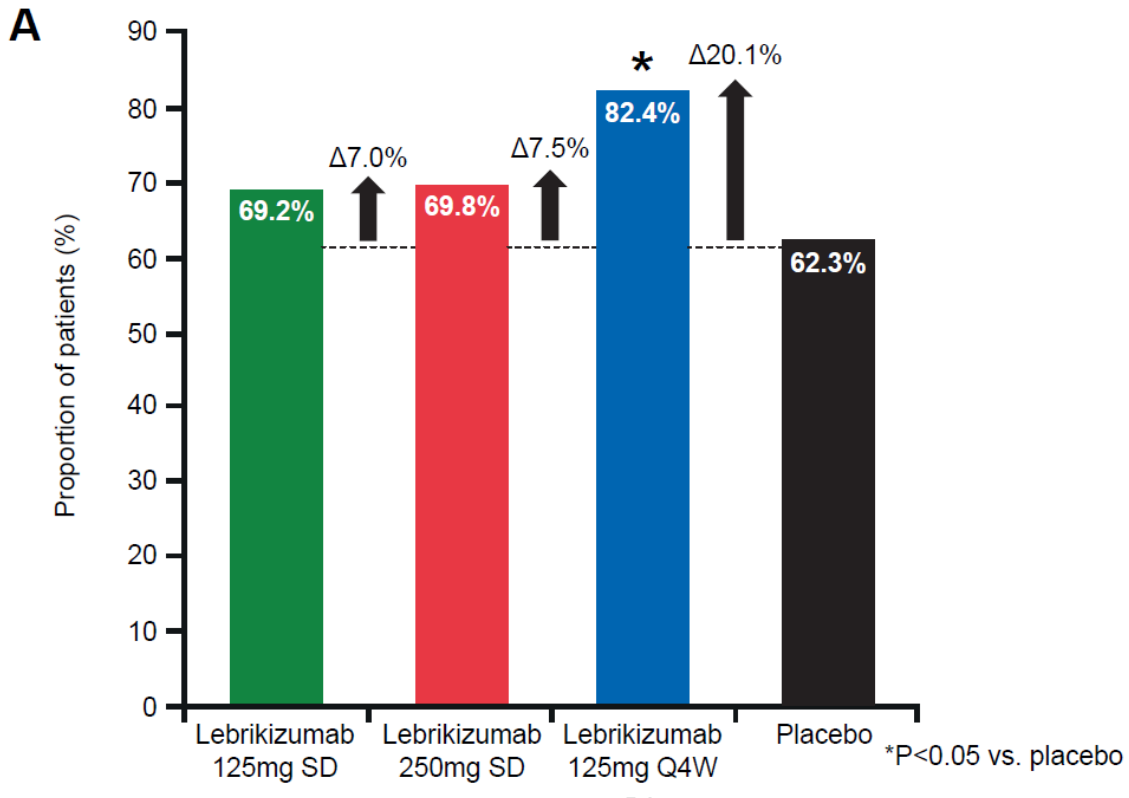
EASI=Eczema Area Severity Index; IGA=Investigator Global Assessment; Q4W=once every 4 weeks; SCORAD=SCORing Atopic Dermatitis; SD=single dose

Figure 3. Atopic dermatitis. Adjusted mean percent change from baseline in (A) pruritus VAS, (B) sleep loss VAS, (C) ADIQ, and (D) DLQI over time

ADIQ=Atopic Dermatitis Impact Questionnaire; DLQI=Dermatology Life Quality Index; Q4W=once every 4 weeks; SD=single dose; VAS=Visual Analog Scale.

458 **Figure 1. Atopic dermatitis. Proportion of patients achieving (A) EASI-50, (B) EASI-75,**

459 **(C) IGA 0/1, and (D) SCORAD-50 at Week 12**



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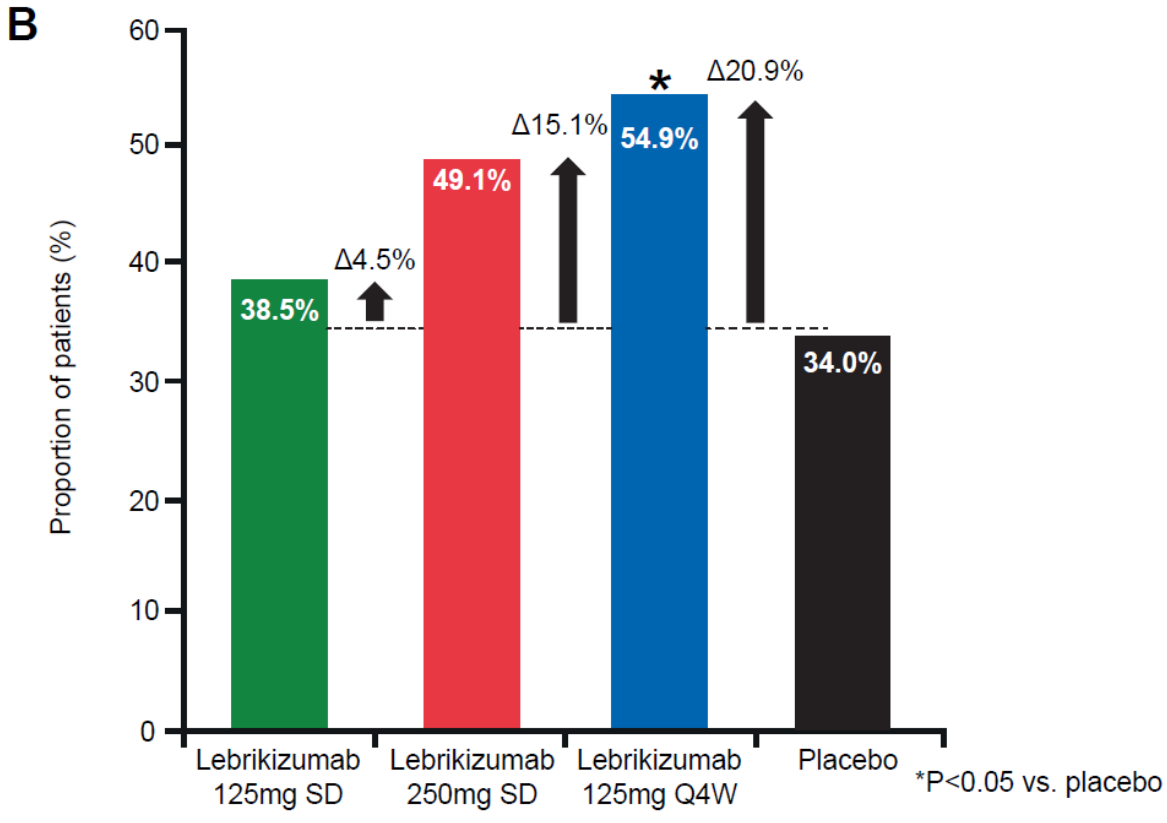

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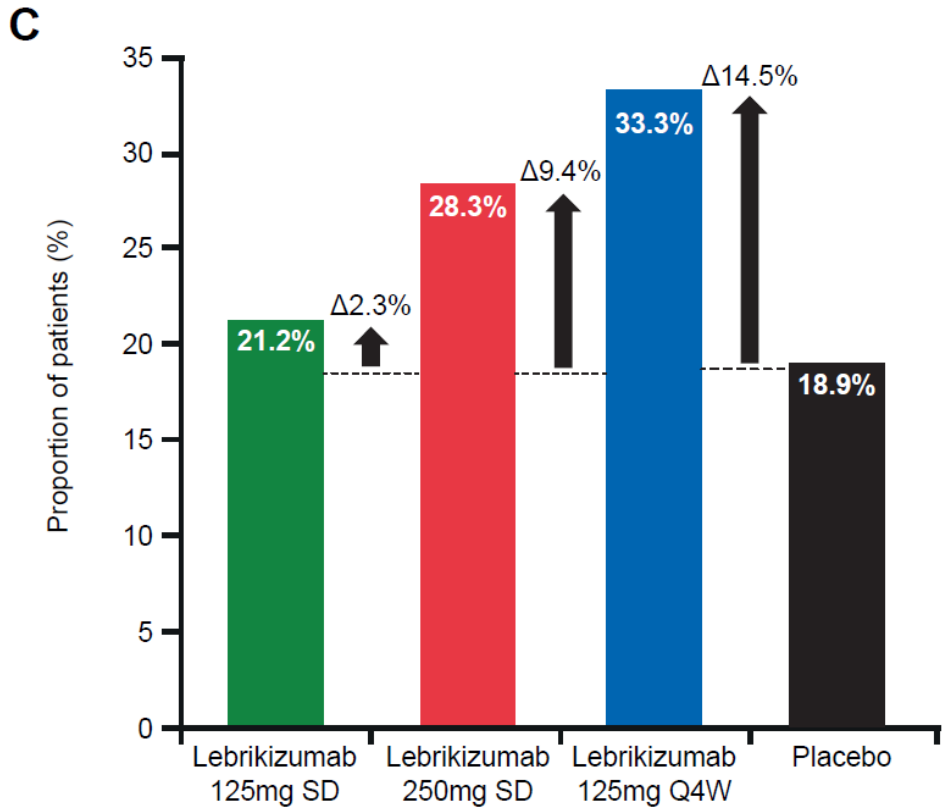

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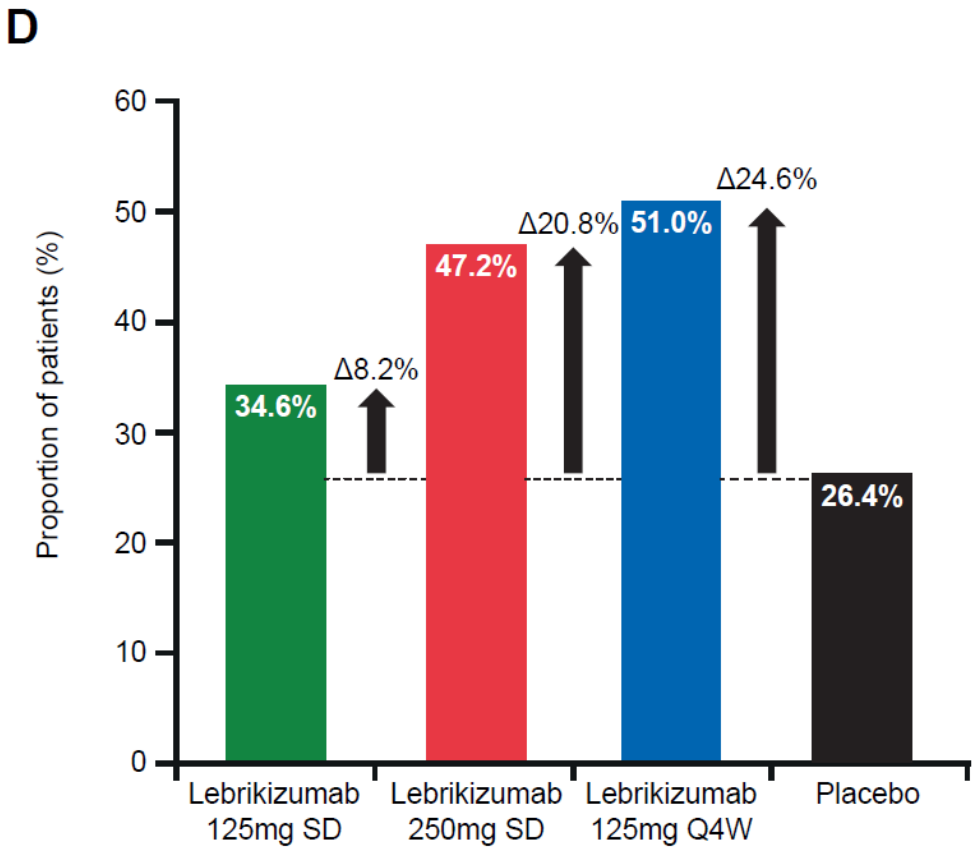

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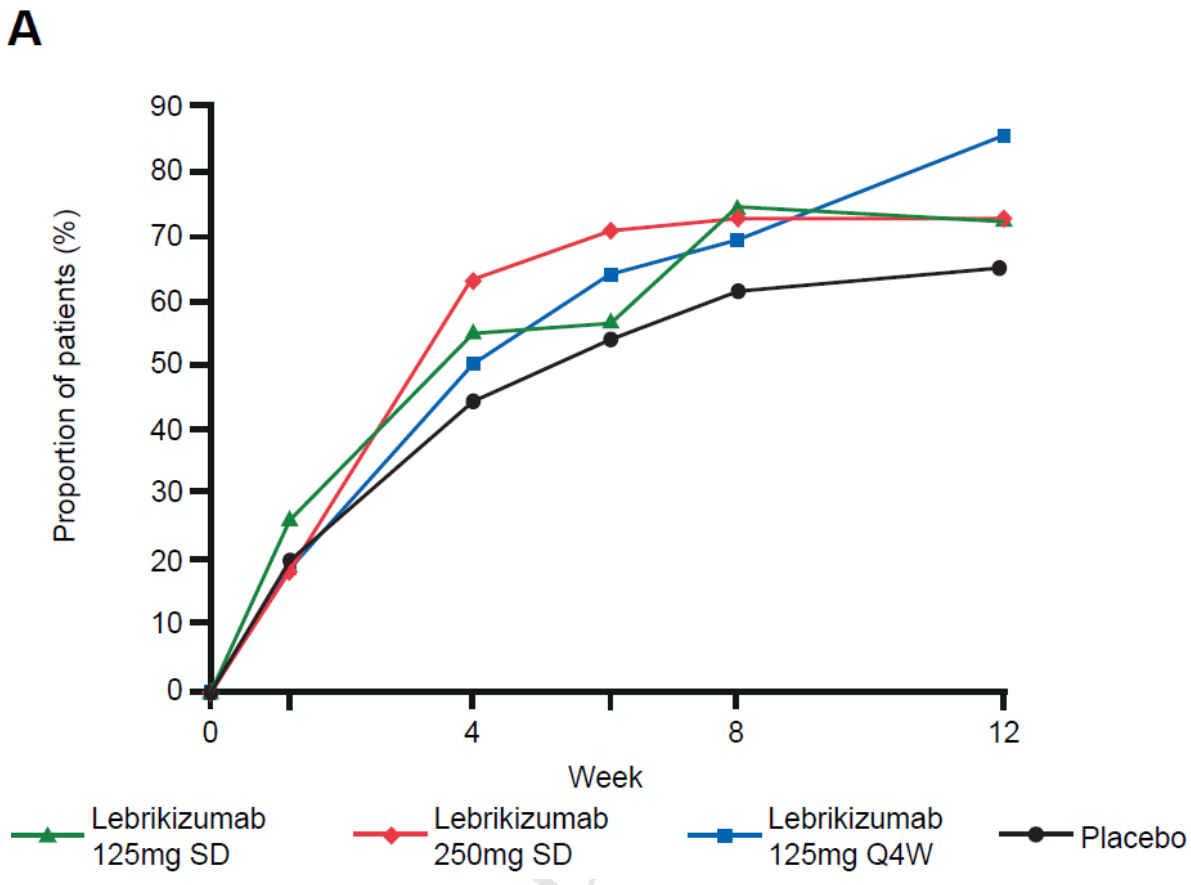
464 EASI=Eczema Area Severity Index; IGA=Investigator Global Assessment; Q4W=once every
465 4 weeks; SCORAD=SCORing Atopic Dermatitis; SD=single dose.

Figure 2. Atopic dermatitis. Proportion of patients achieving (A) EASI-50, (B) EASI-75, (C) IGA 0/1, and (D) SCORAD-50 over time



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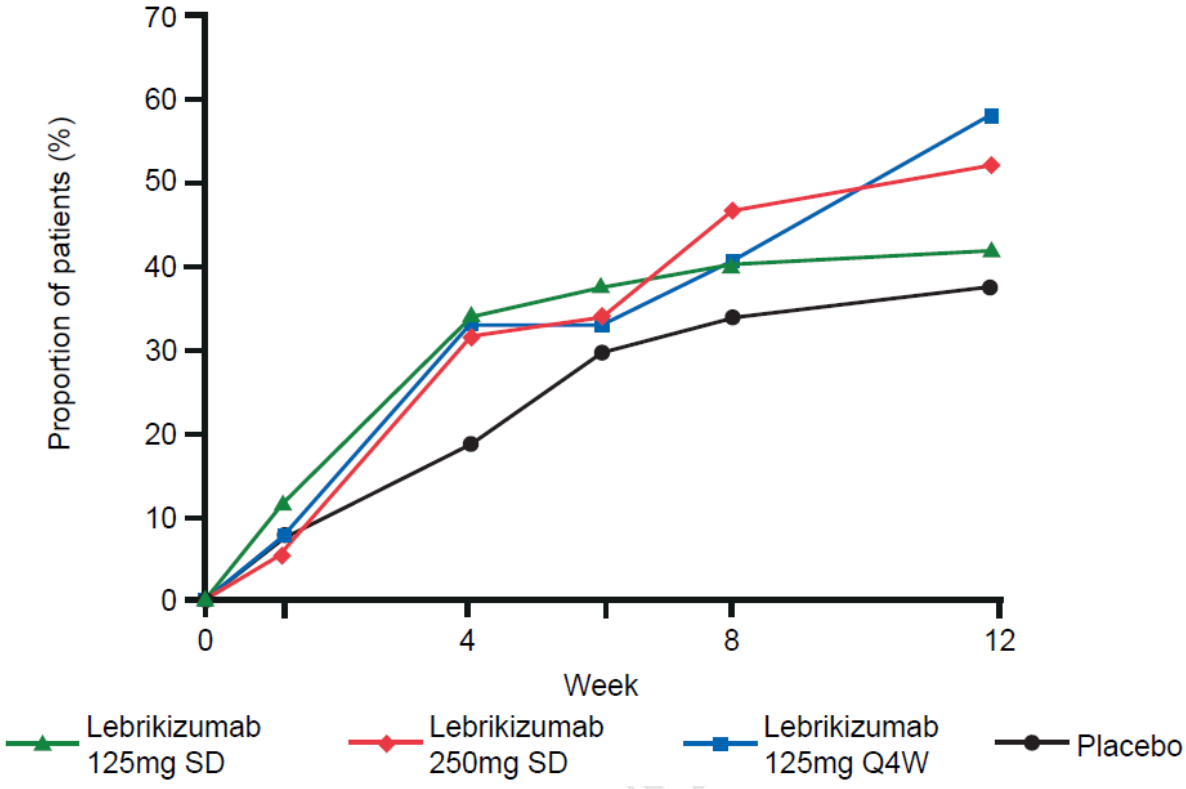
Proportion of patients (%)
70
60
50
40
30
20
10
0
0
4
8
12
Week
Lebrikizumab 125mg SD
Lebrikizumab 250mg SD
Lebrikizumab 125mg Q4W
Placebo

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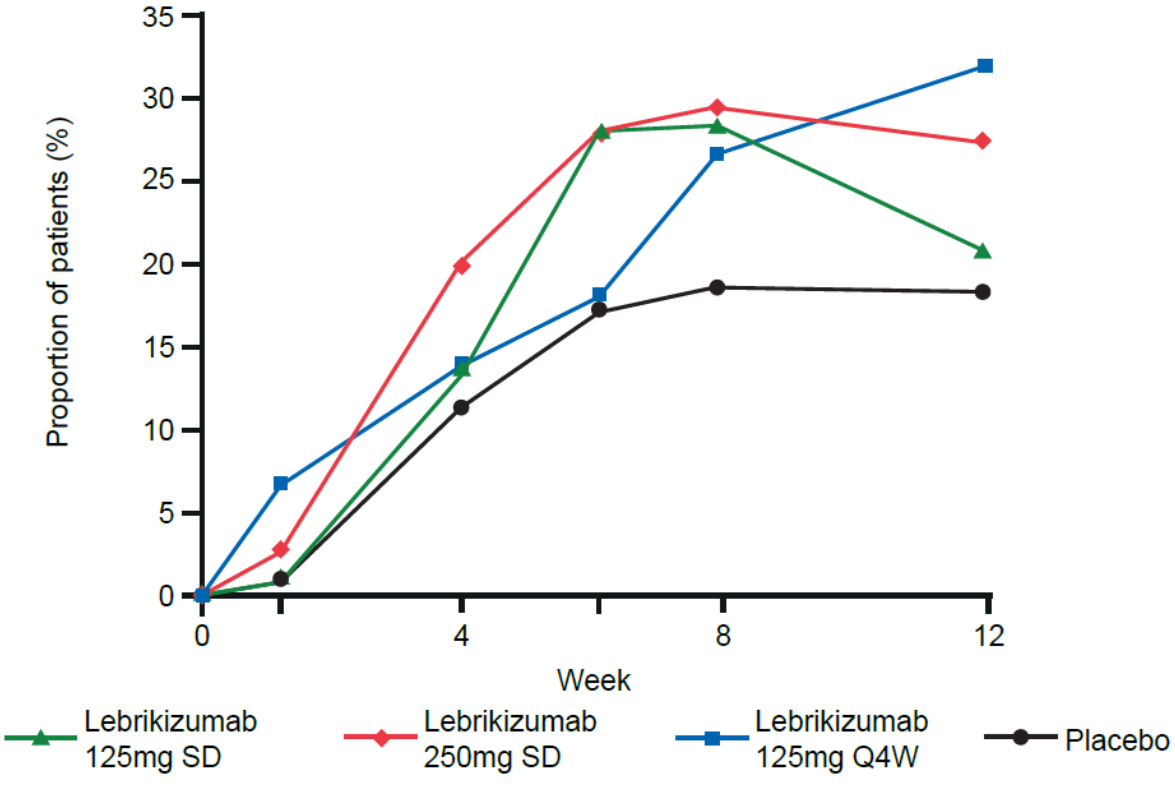
C


Proportion of patients (%)
35
30
25
20
15
10
5
0
0
4
8
12
Week
Lebrikizumab 125mg SD
Lebrikizumab 250mg SD
Lebrikizumab 125mg Q4W
Placebo

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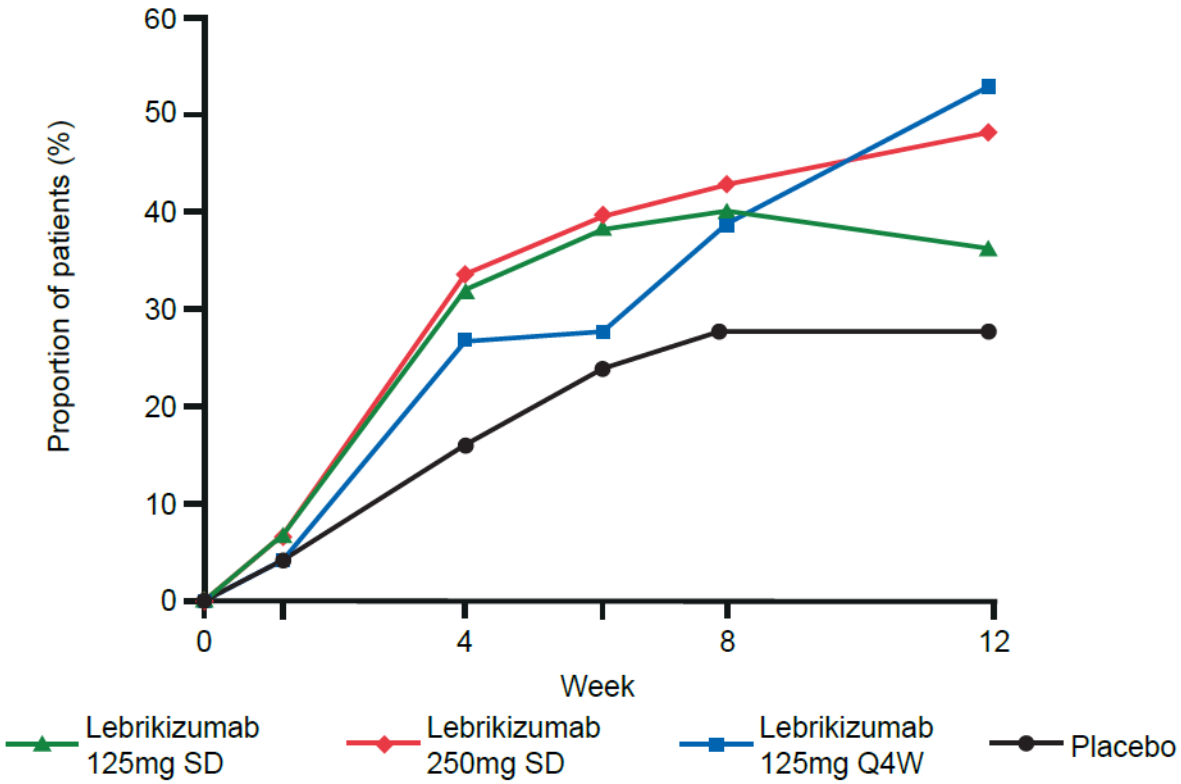
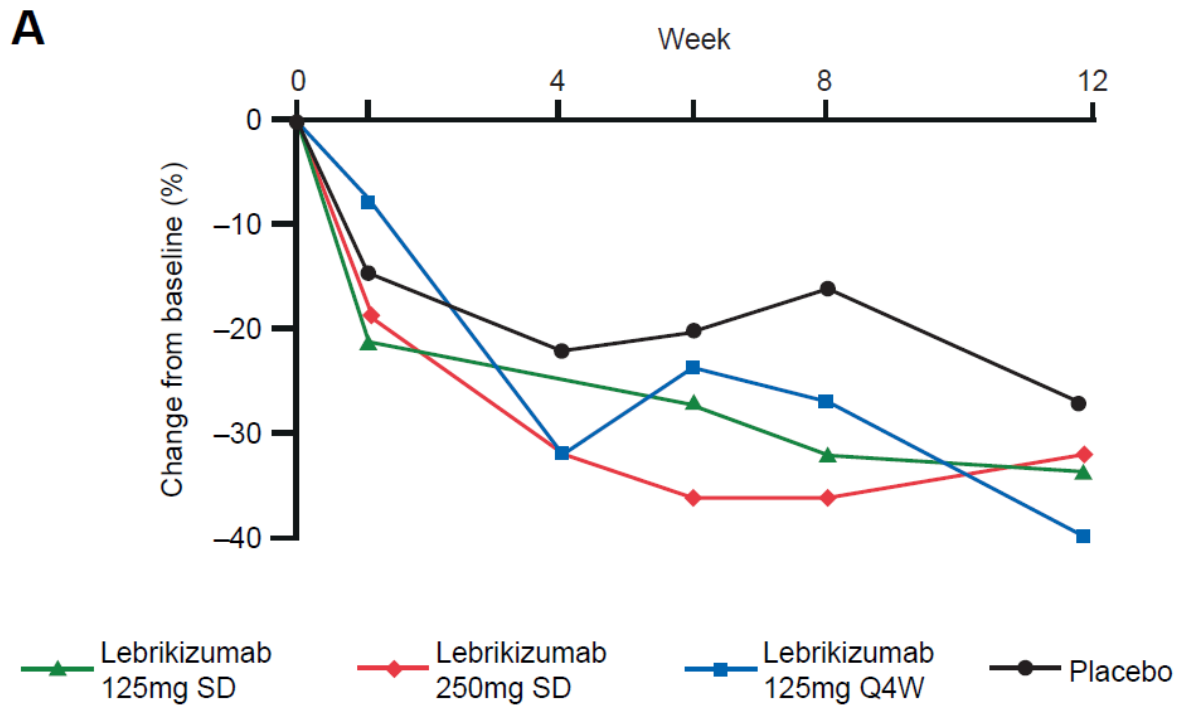
D



EASI=Eczema Area Severity Index; IGA=Investigator Global Assessment; Q4W=once every 4 weeks; SCORAD=SCORing Atopic Dermatitis; SD=single dose.

474 **Figure 3. Atopic dermatitis. Adjusted mean percent change from baseline in (A)**

475 **pruritus VAS, (B) sleep loss VAS, (C) ADIQ, and (D) DLQI over time**



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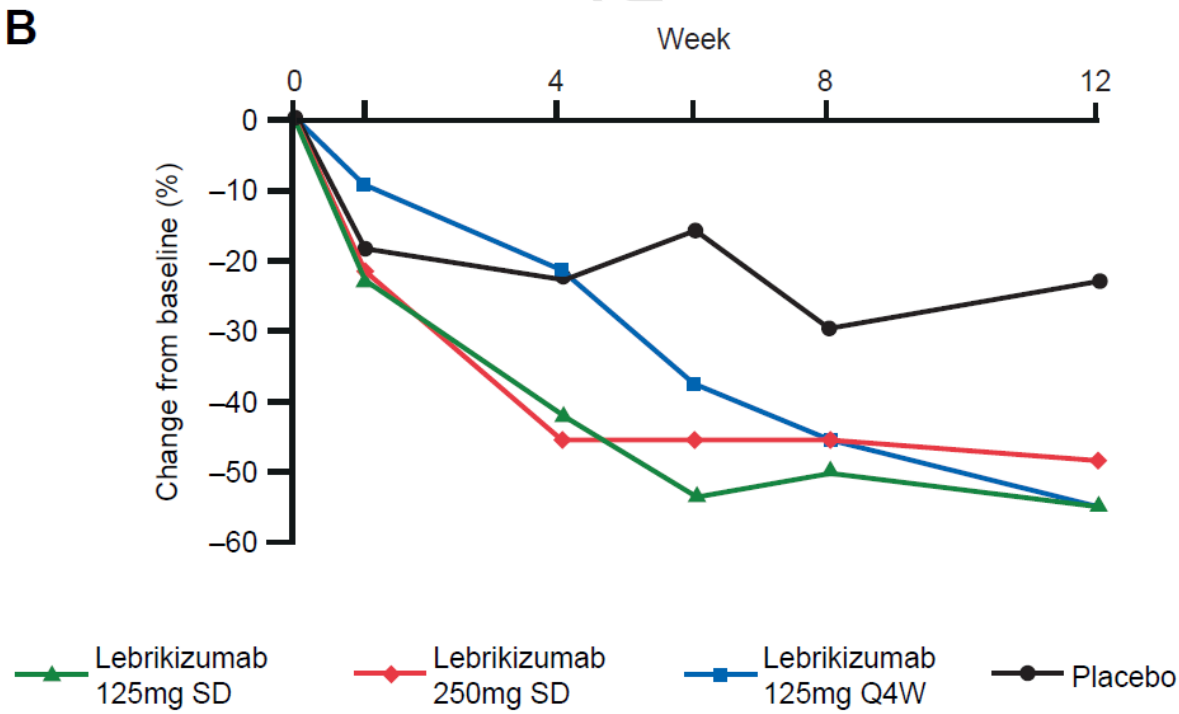

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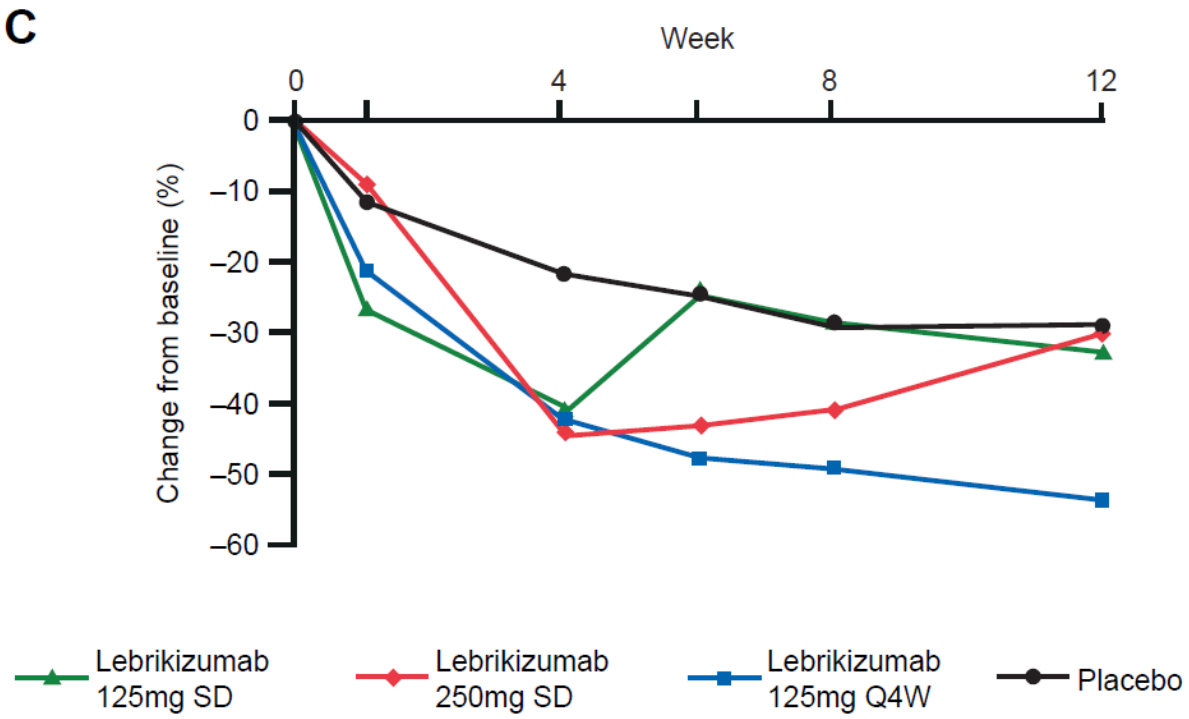

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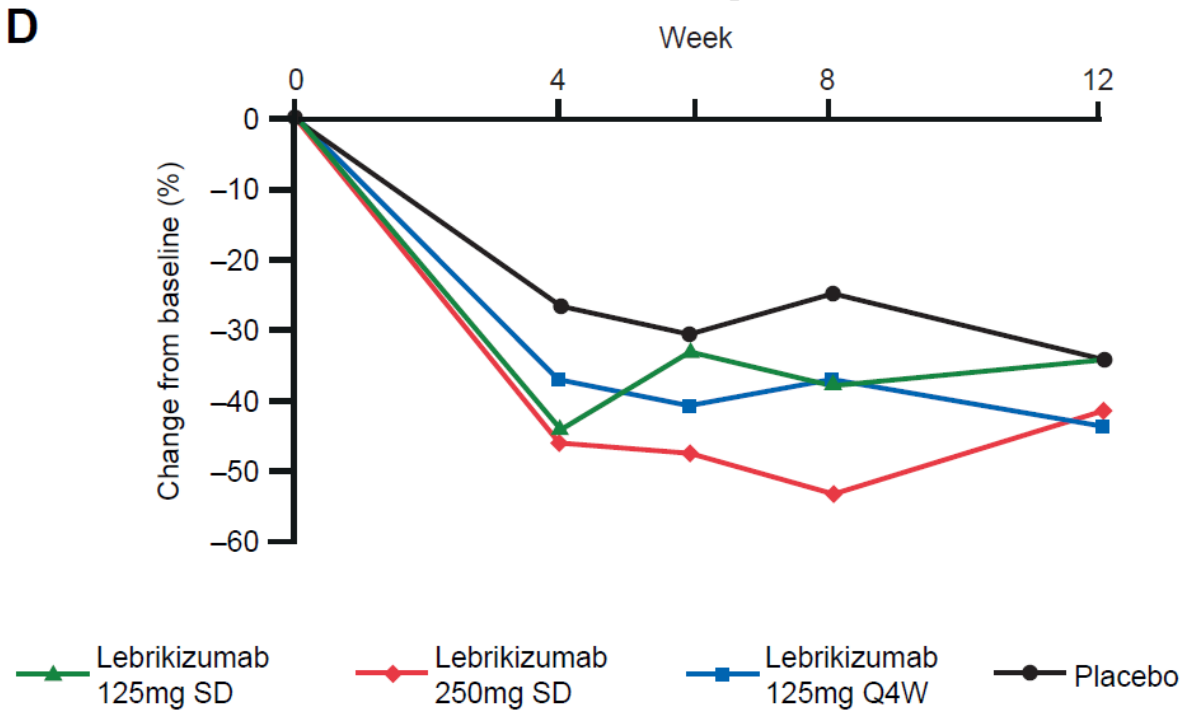

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480 ADIQ=Atopic Dermatitis Impact Questionnaire; DLQI=Dermatology Life Quality Index;

481 Q4W=once every 4 weeks; SD=single dose; VAS=Visual Analog Scale.

482 **Table I. Atopic dermatitis. Baseline characteristics and demographics**

	Lebrikizumab 125 mg single dose (n=52)	Lebrikizumab 250 mg single dose (n=53)	Lebrikizumab 125 mg Q4W (n=51)	Placebo (n=53)
Mean age, year (SDv)	**34.9 (12.7)**	**34.4 (12.3)**	**36.6 (12.3)**	**38.7 (13.2)**
Male, n (%)	**34 (65.4)**	**31 (58.5)**	**35 (68.6)**	**36 (67.9)**
Race, n (%)				
White	**36 (69)**	**43 (81)**	**36 (71)**	**35 (66)**
Asian	**13 (25)**	**9 (17)**	**15 (29)**	**16 (30)**
Other	**3 (6)**	**1 (2)**	**0**	**2 (4)**
Mean Rajka-Langeland (SDv)	**8.50 (0.73)**	**8.49 (0.67)**	**8.34 (0.87)**	**7.96 (1.06)**
Mean EASI (SDv)	**24.6 (11.1)**	**26.3 (12.2)**	**26.9 (11.7)**	**23.6 (9.2)**
Mean SCORAD (SDv)	**56.5 (13.4)**	**58.9 (13.5)**	**60.8 (13.6)**	**59.2 (12.0)**
Mean IGA (SDv)	**3.2 (0.4)**	**3.3 (0.5)**	**3.2 (0.42)**	**3.2 (0.4)**
IGA=4, n (%)	**10 (19)**	**15 (28)**	**11 (22)**	**11 (21)**
Mean % BSA affected (SDv)	**44.2 (21.3)**	**50.5 (24.7)**	**48.5 (22.7)**	**43.4 (22.0)**

483 BSA=body surface area; EASI=Eczema Area Severity Index; IGA=Investigator Global Assessment; Q4W=once

484 every 4 weeks; SCORAD=SCORing Atopic Dermatitis; SDv=standard deviation

APPENDIX

Supplementary Methods

Study design

This study included a 2-week topical corticosteroid (TCS) run-in period prior to the 12-week treatment period, with the goal of standardizing the background therapy prior to randomization and demonstrating failure to respond to TCS alone. To assess TCS adherence, patients were required to record medication use in e-Diary devices.

The study was undertaken in accordance with Good Clinical Practice guidelines and adhered to the Declaration of Helsinki.

Patients

Eligible patients had a diagnosis of moderate-to-severe AD as graded by the Rajka-Langeland criteria that had been present for at least 1 year at screening.

In addition to those stated in the manuscript, key exclusion criteria included: past and/or current use of any anti-IL-13 or anti-IL-4/IL-13 monoclonal antibody; and clinically significant abnormality on screening electrocardiogram or laboratory tests.

Randomization and masking

Three active doses were included to characterize both exposure–response relationships and dosing frequency requirements. A blocked randomization scheme stratified by region was used with a block size of four. To maintain blinding, a placebo arm was included, and all patients were administered two prefilled syringes on Day 1 (placebo patients received two 1mL placebo syringes, 125 mg patients received one 1mL syringe of lebrikizumab 125 mg/mL and one placebo syringe, and 250 mg patients received two 1mL syringes of lebrikizumab 125 mg/mL); all randomized patients received a total of four subcutaneous injections (two on Day 1, one on Day 29, and one on Day 57, i.e. three doses) of study drug (lebrikizumab or placebo) over the first 8 weeks of the 12-week blinded treatment period.

Placebo was prepared with the same formulation as lebrikizumab without addition of the active agent, and both formulations were identical in appearance.

Procedures

Assessments occurred on Weeks 1, 4, 6, 8, and 12 during the 12-week treatment period. Days 1, 29, and 57 (Weeks 1, 4, and 8) were treatment days, during which assessments were carried out prior to study drug administration. The DLQI and ADIQ questionnaires were self-administered at the study site prior to other non-PRO assessments. A study completion visit was performed at the end of Week 20.

The use of TCS other than that provided was prohibited.

As anaphylaxis, anaphylactoid, and hypersensitivity reactions are considered a potential risk with all biologic medications, all potential cases were identified and sent for adjudication by an independent lebrikizumab Anaphylaxis Adjudication Committee.

Pharmacokinetics

Serum samples for analysis of lebrikizumab PKs were obtained in all patients at Day 1 (pre-dose) and at Weeks 1, 4 (pre-dose), 6, 8 (pre-dose), 12, 16, and 20 for all dosing regimens. Serum lebrikizumab concentrations were summarized by treatment and visit using descriptive statistics for the patients that received one of the lebrikizumab treatment regimens. The reported PK parameters include the Week 1 C_{max}, C_{min} at Weeks 4, 8, and 12, and the elimination half-life.

Outcomes

In addition to those stated in the manuscript, key secondary efficacy endpoints included the percentage change from baseline in EASI score at Week 12; percentage change from baseline in SCORAD at Week 12; percentage change from baseline in total % BSA affected at Week 12; percentage change from baseline in itch as measured by SCORAD pruritus VAS at Week 12; and absolute and percentage change in DLQI and ADIQ.

Other analyses included percentage change in SCORAD sleep loss VAS, as well as percentage of patients with an absolute change in pruritus VAS ≥3 from baseline, where the threshold of 3 was based on the minimum clinically important difference for that instrument.

The ADIQ is an AD-specific measure of HRQoL for use in patients aged ≥12 years, developed by Genentech/Roche following US Food and Drug Administration PRO Guidance (2009).

Statistical analyses

Enrollment of 50 patients per treatment group was estimated to provide at least 90% power to detect a 40% difference in the proportion of patients with EASI-50 between each lebrikizumab group and the placebo group at Week 12, under the assumption of a two-sided type I error rate of 0.05, a dropout rate of 20%, and an EASI-50 rate at Week 12 in the placebo group of approximately 20%.

Statistical analyses of all endpoints related to a binary outcome used the same methodology as described for the primary endpoint. Point estimates of the proportions by treatment group, corresponding differences from placebo, and associated two-sided 95% confidence intervals (CI) for differences in proportions were provided.

Change from baseline for continuous endpoints was analyzed using a mixed-effects model for repeat measures, including fixed effects of baseline value, treatment group, visit, treatment by visit interaction, and geographic region; the variable “patient” was included in the model as random effects with unstructured covariance structure. Missing data were implicitly imputed by the model (assuming missing at random). The 95% CIs and two-sided p-values were reported for all secondary efficacy endpoints. No adjustments for multiplicity were made.

All analyses were performed using SAS.

An internal monitoring committee was incorporated to monitor patient safety throughout the study.

Supplementary Results

Trial patients

A total of 294 patients were assessed for eligibility; 82 were ineligible and 212 patients were randomized. Of the 212 patients randomized, 209 received study drug. Among enrolled and treated patients, the mean age (standard deviation) at baseline was 36.1±12.6 years; 35% were female and 72% were Caucasian. Patients had on average 47% of their BSA affected, an average SCORAD of 59, and an EASI of 25. These baseline severity scores were already improved in comparison to screening due to the 2-week run-in period with twice-daily TCS application (Online Appendix Table S2). The most common reason for screen failure (n=26 of 82 [31.7%] screen-failed patients) was patients not meeting the inclusion criterion of EASI score ≥14 due to improvements in EASI score during the run-in period.

Efficacy during safety follow-up

Overall, exploratory analyses showed that the proportion of patients maintaining EASI-50 (90.5%), EASI-75 (75.0%), and IGA 0/1 (70.6%) responses with lebrikizumab 125 mg Q4W from Week 12 to Week 20 followed a similar pattern to that observed at Week 12. Dose-dependent responses were also observed for percent change from baseline pruritus VAS at Week 20.

Pharmacokinetics

The mean PK parameters and respective standard deviations for each of the lebrikizumab dosing regimens are shown in Table S4. As expected, the PKs of lebrikizumab in AD patients were linear and dose-proportional over the dose range tested. The PK of lebrikizumab was also consistent with that of previous studies in adult asthma,[1-4] showing linear, dose-proportional characteristics with a half-life of 19–22 days.

Safety

The rate of injection-site reactions was low in both the lebrikizumab-treated and placebo groups (1.3% and 1.9%, respectively). Herpes infections occurred infrequently and only

among lebrikizumab-treated patients (n=6 [3.8%]; herpes simplex in n=4 [2.6%], and herpes zoster in n=2 [1.3%]); all events were non-serious, mild in intensity, and resolved by the end of the study; there were no events of eczema herpeticum. Five (3.2%) lebrikizumab-treated patients reported eosinophil-associated AEs (3 events of "eosinophilia" and 2 events of "eosinophil count increased"); all events were non-serious and mild-to-moderate in intensity. There were no associated clinical symptoms noted with these five AEs. The maximum eosinophil count in these five patients ranged from 1.0 to 3.2 x 10^9/L; of these, three were Grade 2 eosinophilia (1,501–5,000 cell/mm^3). The increases observed were in line with what has been seen in previous lebrikizumab studies.[2,5] Given the previous imbalances reported in biologic trials in AD,[6] we evaluated conjunctivitis: a total of 15 (9.6%) patients in the pooled lebrikizumab group and four patients (7.5%) in placebo had a conjunctivitis AE; all events were non-serious, none led to treatment discontinuation, and there was not a dose-response relationship.

600 **Table S1. Atopic dermatitis. Summary of primary and secondary efficacy outcomes at**

601 **Week 12**

Efficacy endpoint	Lebrikizumab 125 mg single dose (n=52)	Lebrikizumab 250 mg single dose (n=53)	Lebrikizumab 125 mg Q4W (n=51)	Placebo (n=53)
PRIMARY ENDPOINT				
EASI-50				
% patients	**69.2**	**69.8**	**82.4**	**62.3**
Δ (95% CI)	**7.0 (–11.1, 25.1)**	**7.5 (–10.4, 25.5)**	**20.1 (3.4, 36.8)**	
p-value	**0.48**	**0.44**	**0.026**	
SECONDARY ENDPOINTS				
IGA 0/1				
% patients	**21.2**	**28.3**	**33.3**	**18.9**
Δ (95% CI)	**2.3 (–13.0, 17.6)**	**9.4 (–6.6, 25.5)**	**14.5 (–2.2, 31.2)**	
p-value	**0.77**	**0.26**	**0.098**	
EASI-75				
% patients	**38.5**	**49.1**	**54.9**	**34.0**
Δ (95% CI)	**4.5 (–13.9, 22.9)**	**15.1 (–3.4, 33.6)**	**20.9 (2.3, 39.6)**	
p-value	**0.66**	**0.12**	**0.036**	
EASI score, % change from baseline				
Adjusted mean (SE)	**–58.5 (5.36)**	**–57.7 (5.26)**	**–70.5 (5.45)**	**–53.1 (5.38)**
Δ (95% CI)	**–5.3 (–20.3, 9.7)**	**–4.6 (–19.4, 10.3)**	**–17.4 (–32.5, –2.2)**	
p-value	**0.48**	**0.55**	**0.025**	
SCORAD-50				
% patients	**34.6**	**47.2**	**51.0**	**26.4**

Δ (95% CI)	**8.2 (–9.4, 25.8)**	**20.8 (2.8, 38.7)**	**24.6 (6.4, 42.7)**	
p-value	**0.38**	**0.030**	**0.012**	
SCORAD, % change from baseline				
Adjusted mean (SE)	**–38.7 (4.14)**	**–42.6 (4.07)**	**–53.5 (4.22)**	
Δ (95% CI)	**–3.3 (–14.9, 8.3)**	**–7.2 (–18.7, 4.3)**	**–18.0 (–29.7, –6.4)**	**–35.4 (4.16)**
p-value	**0.57**	**0.22**	**0.0026**	
Total % BSA affected, % change from baseline				
Adjusted mean (SE)	**–45.2 (8.21)**	**–38.6 (8.07)**	**–57.7 (8.35)**	
Δ (95% CI)	**2.2 (–20.7, 25.1)**	**8.8 (–13.9, 31.6)**	**–10.3 (–33.4, 12.9)**	**–47.4 (8.24)**
p-value	**0.85**	**0.45**	**0.38**	
Pruritus (VAS), % change from baseline				
Adjusted mean (SE)	**–34.9 (6.14)**	**–32.8 (5.95)**	**–40.7 (6.19)**	
Δ (95% CI)	**–7.4 (–24.5, 9.7)**	**–5.3 (–22.1, 11.6)**	**–13.2 (–30.3, 4.0)**	**–27.5 (6.12)**
p-value	**0.40**	**0.54**	**0.13**	
Sleep loss (VAS), % change from baseline				
Adjusted mean (SE)	**–53.1 (9.90)**	**–47.2 (9.83)**	**–53.6 (9.49)**	
Δ (95% CI)	**–30.6 (–57.9, –3.2)**	**–24.6 (–51.8, 2.6)**	**–31.0 (–57.8, –4.2)**	**–22.6 (9.70)**
p-value	**0.029**	**0.076**	**0.023**	
ADIQ, % change from baseline				
Adjusted mean (SE)	**–33.2 (9.15)**	**–30.8 (8.99)**	**–54.3 (9.17)**	
Δ (95% CI)	**–3.7 (–29.2, 21.8)**	**–1.3 (–26.6, 24.0)**	**–24.8 (–50.3, 0.7)**	**–29.5 (9.13)**
p-value	**0.77**	**0.92**	**0.057**	
DLQI, % change from baseline				
Adjusted mean (SE)	**–34.3 (6.93)**	**–40.7 (6.69)**	**–43.1 (7.02)**	
Δ (95% CI)	**–0.8 (–20.0, 18.5)**	**–7.1 (–26.0, 11.9)**	**–9.6 (–28.9, 9.8)**	**–33.6 (6.93)**
p-value	**0.94**	**0.46**	**0.33**	

ADIQ=Atopic Dermatitis Impact Questionnaire; BSA=body surface area; CI=confidence interval; DLQI=Dermatology Life Quality Index; EASI=Eczema Area Severity Index; IGA=Investigator Global Assessment; Q4W=once every 4 weeks; SCORAD=SCORing Atopic Dermatitis; SE=standard error; VAS=Visual Analog Scale.

Table S2. Atopic dermatitis. Percent change in EASI, SCORAD, IGA, pruritus VAS, sleep loss VAS and percent BSA affected from screening to baseline (run-in)

	Lebrikizumab 125 mg single dose (n=52)	Lebrikizumab 250 mg single dose (n=53)	Lebrikizumab 125 mg Q4W (n=51)	Placebo (n=53)	All patients (n=209)
Mean % change in EASI (SDv)	**−14.3 (27.6)**	**−10.2 (29.2)**	**−9.1 (22.7)**	**−6.4 (32.2)**	**−10.0 (28.1)**
Mean absolute change in IGA (SDv)	**−0.21 (0.50)**	**−0.17 (0.51)**	**−0.14 (0.40)**	**−0.09 (0.45)**	**−0.15 (0.47)**
Mean % change in SCORAD (SDv)	**−12.2 (20.0)**	**−9.9 (14.7)**	**−7.7 (15.0)**	**−5.0 (20.3)**	**−8.7 (17.8)**
Mean % change in % BSA affected (SDv)	**−17.1 (26.7)**	**−4.3 (26.9)**	**−9.3 (27.0)**	**−6.2 (23.2)**	**−9.2 (26.3)**
Mean % change in pruritus VAS (SDv)	**−23.8 (29.6)**	**−15.5 (28.6)**	**−15.2 (39.4)**	**−12.8 (29.8)**	**−16.8 (32.1)**
Mean % change in sleep loss VAS (SDv)	**−29.0 (43.6)**	**−8.1 (81.8)**	**−12.9 (40.1)**	**−5.4 (57.2)**	**−13.9 (58.2)**

BSA=body surface area; EASI=Eczema Area Severity Index; IGA=Investigator Global Assessment; Q4W=once every 4 weeks; SCORAD=SCORing Atopic Dermatitis; SDv=standard deviation; VAS=Visual Analog Scale.

611 **Table S3. Atopic dermatitis. Summary of key efficacy outcomes at Week 20**

	Lebrikizumab 125 mg single dose	Lebrikizumab 250 mg single dose	Lebrikizumab 125 mg Q4W	Placebo
Patients maintaining EASI-50 response from Week 12 to Week 20				
N (%)	**29/36 (80.6)**	**29/37 (78.4)**	**38/42 (90.5)**	**24/33 (72.7)**
Placebo-corrected differences (SE)	**7.8**	**5.7**	**17.8**	
p-value	**0.39**	**0.58**	**0.047**	
Patients maintaining EASI-75 response from Week 12 to Week 20				
N (%)	**9/20 (45.0)**	**16/26 (61.5)**	**21/28 (75.0)**	**12/18 (66.7)**
Placebo-corrected differences (SE)	**–21.7**	**–5.1**	**8.3**	
p-value	**0.20**	**0.81**	**0.54**	
Patients maintaining IGA 0/1 response from Week 12 to Week 20				
N (%)	**6/11 (54.5)**	**9/15 (60.0)**	**12/17 (70.6)**	**6/10 (60)**
Placebo-corrected differences (SE)	**–5.5**	**0**	**10.6**	
p-value	**0.97**	**0.94**	**0.58**	
Patients maintaining SCORAD-50 response from Week 12 to Week 20				
N (%)	**11/18 (61.1)**	**16/25 (64.0)**	**13/26 (50.0)**	**11/14 (78.6)**
Placebo-corrected differences (SE)	**–17.5**	**–14.6**	**–28.6**	
p-value	**0.34**	**0.49**	**0.13**	
Percent change from baseline in EASI				
Adjusted mean % change (SE)	**–62.1 (5.43)**	**–55.9 (5.28)**	**–71.1 (5.50)**	**–54.1 (5.49)**

Placebo-corrected differences (95% CI)	**–8.1 (–23.3, 7.1)**	**–1.9 (–16.9, 13.2)**	**–17.1 (–32.4, -1.7)**	
p-value	**0.30**	**0.81**	**0.03**	
Percent change from baseline in the % BSA affected				
Adjusted mean % change (SE)	**–53.6 (6.10)**	**–46.4 (5.96)**	**–63.8 (6.19)**	**–52.0 (6.16)**
Placebo-corrected differences (95% CI)	**–1.6 (–18.7, 15.5)**	**5.6 (–11.4, 22.5)**	**–11.8 (–29.0, 5.5)**	
p-value	**0.85**	**0.52**	**0.18**	
Percent change from baseline pruritus VAS				
Adjusted mean % change (SE)	**–27.6 (7.64)**	**–30.3 (7.36)**	**–35.2 (7.68)**	**–21.5 (7.66)**
Placebo-corrected differences (95%CI)	**–6.1 (–27.5, 15.2)**	**–8.8 (–29.7, 12.2)**	**–13.8 (–35.2, 7.6)**	
p-value	**0.57**	**0.41**	**0.21**	

612 BSA=body surface area; CI=confidence interval; EASI=Eczema Area Severity Index; IGA=Investigator Global
613 Assessment; Q4W=once every 4 weeks; SCORAD=SCORing Atopic Dermatitis; SE=standard error; VAS=Visual
614 Analog Scale.

615 **Table S4. Atopic dermatitis. Mean lebrikizumab pharmacokinetic parameters following**

616 **single or multiple dose subcutaneous administration**

	Lebrikizumab 125 mg single dose	Lebrikizumab 250 mg single dose	Lebrikizumab 125 mg Q4W
Mean $C_{max, wk1}$ µg/mL (SDv)	17.0 (5.22)	35.6 (10.8)	16.1 (5.19)
Mean $C_{min, wk4}$ µg/mL (SDv)	10.2 (3.00)	21.4 (6.87)	9.15 (2.99)
Mean $C_{min, wk8}$ µg/mL (SDv)	4.59 (2.12)	9.53 (3.53)	13.6 (5.34)
Mean $C_{min, wk12}$ µg/mL (SDv)	2.28 (1.72)	3.77 (2.01)	14.4 (5.69)
$t_{1/2}$, day	18.5 (5.06)	22.2 (6.18)	20.9 (4.17)

617 $C_{max, wk1}$=maximum lebrikizumab concentration at Week 1; $C_{min, wk4}$=observed minimum concentration at Week 4;

618 $C_{min, wk8}$=observed minimum concentration at Week 8; $C_{min, wk12}$=observed minimum concentration at Week 12;

619 Q4W=once every 4 weeks; SDv=standard deviation; $t_{1/2}$=elimination half-life.

620 **Table S5. Atopic dermatitis. Overview of key safety information, Weeks 0 to 20**

	Lebrikizumab 125 mg single dose (n=54)	Lebrikizumab 250 mg single dose (n=52)	Lebrikizumab 125 mg Q4W (n=50)	All lebrikizumab (n=156)	Placebo (n=53)
Patients with at least one AE, n (%)	**38 (70)**	**39 (75)**	**27 (54)**	**104 (67)**	**35 (66)**
AE leading to withdrawal from study drug[1]	**1 (2)**	**0**	**2 (4)**	**3 (2)**	**1 (2)**
AE leading to dose modification/interruption[2]	**0**	**1 (2)**	**0**	**1 (1)**	**0**
Patients with at least one SAE, n (%)	**3 (6)**	**0**	**2 (4)**	**5 (3)**	**2 (4)**
SAE leading to withdrawal from study drug, n (%)	**0**	**0**	**1 (2) (Myopathy)**	**1 (1)**	**0**
AEs of interest/events to be monitored, n (%)					
Adjudicated anaphylaxis per Sampson's criteria[3]	**0**	**0**	**0**	**0**	**0**
Infections	**24 (44)**	**20 (39)**	**12 (24)**	**56 (36)**	**24 (45)**
Injection site reactions	**0**	**0**	**2 (4)**	**2 (1)**	**1 (2)**
Malignancies	**0**	**0**	**0**	**0**	**0**
Skin infections, n (%)					
Patients with skin infection	**6 (11)**	**5 (10)**	**3 (6)**	**14 (9)**	**9 (17)**
Herpes infections, n (%)					
Total number of patients with at least one infection	**1 (2)**	**3 (6)**	**2 (4)**	**6 (4)**	**0**
Total number of infections	**0**	**0**	**0**	**0**	**0**

related to study drug*					
Herpes simplex	**1 (2)**	**2 (4)**	**1 (2.0)**	**4 (3)**	**0**
Herpes zoster	**0**	**1 (2)**	**1 (2.0)**	**2 (1)**	**0**
Conjunctival infections, irritations and inflammations, n (%)					
Total number of patients with at least one AE	**7 (13)**	**5 (10)**	**3 (6)**	**15 (10)**	**4 (8)**
Total number of events	**8**	**6**	**4**	**18**	**4**
Conjunctivitis allergic	**4 (7)**	**2 (4)**	**2 (4)**	**8 (5)**	**0**
Conjunctival hyperaemia	**0**	**1 (2)**	**0**	**1 (1)**	**0**

*Infections related to study drug were investigator-assessed.

[1]The following AEs led to withdrawal from study drug: “skin infection” in the 125 mg SD group, “anxiety” and “myopathy” in 125 mg Q4W group, and “atopic dermatitis” in the placebo group.

[2]One (1%) patient in the 250 mg SD lebrikizumab group experienced an AE (“gastrointestinal viral infection”) that led to dose interruption.

[3]Members of the lebrikizumab Anaphylaxis Adjudication Committee reviewed blinded data to adjudicate cases as anaphylaxis per Sampson’s criteria.

AE=adverse event; Q4W=every 4 weeks; SAE=serious adverse event.

629 **Table S6. Atopic dermatitis. Principal investigator sites**

Site number	Investigator	Center
267701	*Simon, Dagmar	Inselspital Bern; Dermatologie, Freiburgstrasse, 3000, Bern, Switzerland
267730	*Remitz, Anita Reitamo, Sakari	Helsinki University Central Hospital; Skin & Allergy Hospital, Meilahdentie 2, PO Box 160, 00029, Helsinki, Finland
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267732	*Lammintausta, Kaija	Turku Central University Hospital; Dermatology and Allergology, Hämeentie 11 (Post Address PL52, 20521 Turku), 20250, Turku, Finland
268162	*de Bruin, Marjolein Bruijnzeel-Koomen, C.A.F.M.	Umc Utrecht; Dermatology, Heidelberglaan 100, Huispostnr.: F02.127, 3584 Cx, Utrecht, Netherlands
268163	*Schuttelaar, M.L.A.	University Medical Center Groningen; Department of Dermatology, Hanzeplein 1, De Brug, Room 2.084. Mailcode AB21 PO Box 30.001, 9700RB, Groningen, Netherlands
268592	*Spuls, Phyllis	Academisch Medisch Centrum Universiteit Amsterdam; Dermatology and VU University Medical Center, Meibergdreef 9, 1100 DD, Amsterdam, Netherlands
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275005	*Maari, Catherine	Innovaderm Research Inc., 1851 Sherbrooke St. East, Suite

	Nigen, Simon	502, L2K 4L5, Montreal, Quebec, Canada
275031	*Raman, Mani	The Centre for Dermatology, 312 Highway 7 East, L4B 1A5, Richmond Hill, Ontario, Canada
275032	*Papp, Kim	K. Papp Clinical Research Inc., 135 Union Street East, N2J 1C4, Waterloo, Ontario, Canada
275033	*Sadick, Neil	Sadick Research Group, 911 Park Avenue, Suite 1a, New York, NY, 10075, United States
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275093	*Toth, Darryl	Xlr8 Medical Research Inc., 2425 Tecumseh Road East, Suite 210, N8W 1E6, Windsor, Ontario, Canada
275094	*Pariser, David	Virginia Clinical Research Inc., 6160 Kempsville Circle, Suite 200a, Norfolk, VA, 23502, United States
275095	*Sofen, Howard	Dermatology Research Associate, 8930 S. Sepulveda Blvd., Suite 114, Los Angeles, CA, 90045, United States
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275793	*Chu, Chia-Yu	National Taiwan University Hospital; Department of Dermatology, 2F, No.1, Changde St, Zhongzheng District, 10048, Taipei, Taiwan
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276128	*Bzdulska-Doskocz, Beata	ALERGO-MED Specjalistyczna Przychodnia Lekarska Sp. Z O. O, Ul. PCK 26, 33-100, Tarnow, Poland
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276356	*Filipovska, Olga	Masarykova Nemocnice O.Z; Kozni Oddeleni, Socialni Pece 3316/12A, 401 13, Usti Nad Labem, Czech Republic
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276373	*Arenberger, Petr	Charles University School of Medicine; Department of Dermatology, Srobarova 50, 100 34, Prague 10, Czech Republic
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277780	*Puig, Luis	Hospital de la Santa Creu I Sant Pau; Servicio de Dermatologia, Sant Antoni Maria Claret, 167, 08025, Barcelona, Spain
277784	*Vilata, Juan Jose	Hospital General Universitario de Valencia; Servicio de Dermatología, Av. Tres Cruces S/N, Pabellon B Planta Baja, 46014, Valencia, Valencia, Spain
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277804	*Perez, Bibiana	Hospital Ramon y Cajal; Servicio Dermatologia, Ctra. de Colmenar Viejo, Km. 9,100, 28034, Madrid, Madrid, Spain
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278391	*Pinter, Andreas	Klinik Johann Wolfgang von Goethe Uni; Klinik Für Dermatologie, Venerologie und Allergologie, Theodor-Stern-Kai 7, 60590, Frankfurt, Germany
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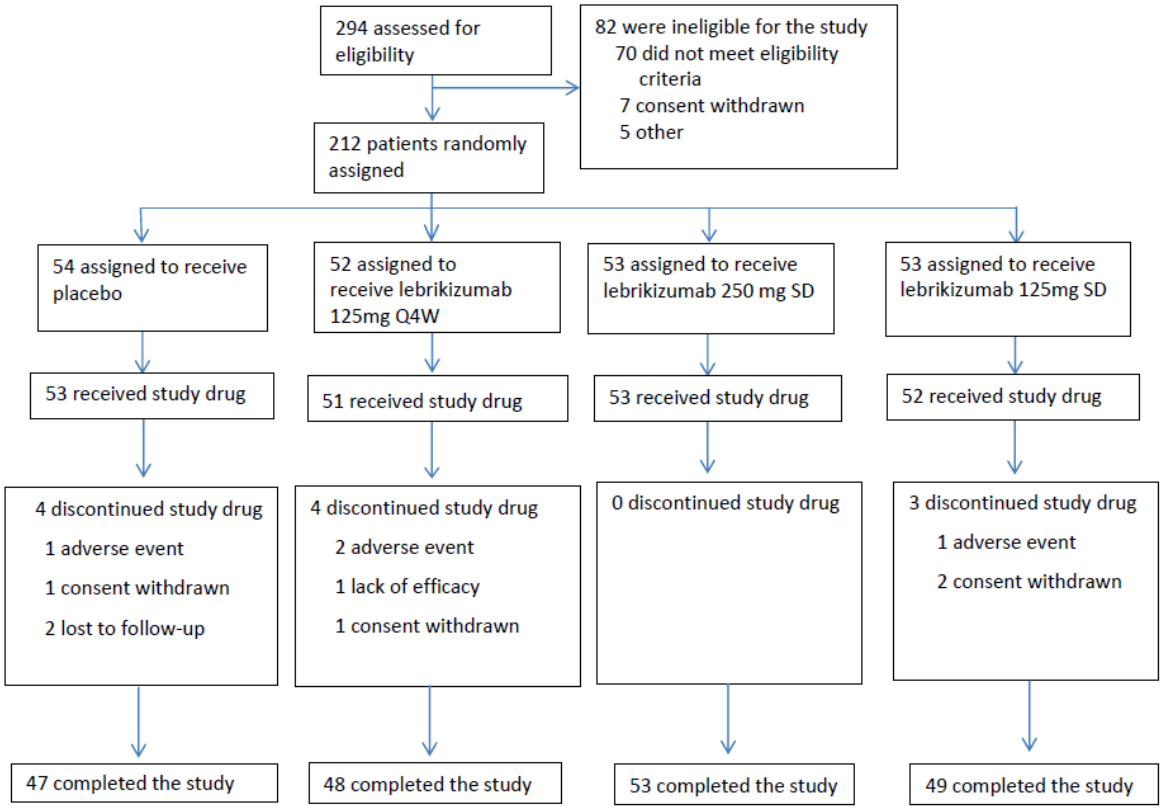
630 *Indicates the current Principal Investigator. The names of previous Principal Investigators, if any, are also listed.

631 **Figure S1. Atopic dermatitis. Patient disposition for the TREBLE study**



632
633 Q4W=once every 4 weeks; SD=single dose.

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