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ORIGINAL RESEARCH

Short-Term Efficacy of Lebrikizumab Versus Dupilumab in Combination with Topical Corticosteroids in Adults with Moderate-to-Severe Atopic Dermatitis: Matching-Adjusted Indirect Comparison

Raj Chovatiya · April Armstrong · Leon Kircik · Lluís Puig · Mark G. Kirchhof · Tiago Torres · Yousef Binamer · Gleison Duarte · Bülent Akmaz · Martin Dossenbach · Gaia Gallo · Chao Yang · Lucia Seminario-Vidal · Yuxin Ding · Jonathan I. Silverberg

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ABSTRACT

Introduction: A matching-adjusted indirect comparison evaluated the short-term efficacy of lebrikizumab plus topical corticosteroids (TCS) versus dupilumab plus TCS in adults with moderate-to-severe atopic dermatitis (AD).

Methods: Individual patient data from the ADhere trial (lebrikizumab 250 mg every 2 weeks [Q2W] plus TCS) and aggregate data from the CHRONOS trial (dupilumab 300 mg Q2W plus TCS) were matched using the method of moments approach to adjust baseline differences. Matching was done at the study level (primary analysis) and at the study arm level (sensitivity analysis). Efficacy endpoints up to week 16 included the proportion of patients achieving an Investigator's Global Assessment of 0 or 1 (IGA 0/1); a ≥ 50%, ≥ 75%, and ≥ 90% improvement from baseline in the Eczema Area and Severity Index (EASI 50/75/90); a ≥ 4-point improvement from baseline in the Pruritus

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R. Chovatiya (✉)
Chicago Medical School, Rosalind Franklin University of Medicine and Science, North Chicago, USA
e-mail: raj.chovatiya@gmail.com

R. Chovatiya
Center for Medical Dermatology + Immunology Research, Chicago, USA

A. Armstrong
Department of Dermatology, Keck School of Medicine, University of Southern California, Los Angeles, California, USA

L. Kircik
Icahn School of Medicine at Mount Sinai, New York, NY, USA

L. Kircik
Indiana University School of Medicine, Indianapolis, IN, USA

L. Puig
Department of Dermatology, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

M. G. Kirchhof
Division of Dermatology, Faculty of Medicine, University of Ottawa and The Ottawa Hospital, Ottawa, Canada

T. Torres
Centro Hospitalar Universitário de Santo António, University of Porto, Porto, Portugal

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Numerical Rating Scale score (PNRS ≥ 4); and a ≥ 4-point improvement from baseline in the Dermatology Life Quality Index score (DLQI ≥ 4). Placebo-adjusted efficacy outcomes were compared using odds ratios (ORs), risk ratios (RRs), and risk differences (RDs) with 95% confidence intervals (CIs).

Results: At week 16, lebrikizumab plus TCS had comparable odds to dupilumab plus TCS of achieving EASI 75 (OR 1.14, 95% CI 0.42–3.09), IGA 0/1 (OR 1.39, 95% CI 0.42–4.59), PNRS ≥ 4 (OR 0.48, 95% CI 0.17–1.37), and DLQI ≥ 4 (OR 0.89, 95% CI 0.29–2.69). At earlier timepoints, lebrikizumab plus TCS had comparable odds to dupilumab plus TCS of achieving PNRS ≥ 4 at week 2 (OR 2.04, 95% CI 0.24–17.05) and week 4 (OR 3.59, 95% CI 0.90–14.36). RR and RD estimates were consistent with OR estimates of efficacy. Sensitivity analyses confirmed the findings of the primary analysis.

Conclusion: Lebrikizumab plus TCS was comparable to dupilumab plus TCS across all efficacy endpoints at week 16.

Keywords: Atopic dermatitis; Combination therapy; Eczema Area and Severity Index; Investigator Global Assessment; Dermatology Life Quality Index; Dupilumab; Lebrikizumab; Matching-adjusted indirect comparison; Pruritus Numeric Rating Scale; Topical corticosteroids

Y. Binamer
King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia

Y. Binamer
Alfaisal University, Riyadh, Saudi Arabia

G. Duarte
Instituto Bahiano de Imunoterapia-IBIS, Salvador, Brazil

B. Akmaz
Almirall S.A., Barcelona, Spain

M. Dossenbach · G. Gallo · C. Yang · L. Seminario-Vidal · Y. Ding
Eli Lilly and Company, Indianapolis, IN, USA

J. I. Silverberg
Department of Dermatology, The George Washington University School of Medicine and Health Sciences, Washington, DC, USA

Key Summary Points

Why carry out this study?

Moderate-to-severe atopic dermatitis (AD) often requires systemic therapy with biologics such as lebrikizumab or dupilumab when topical therapies alone are insufficient.

Although both lebrikizumab plus topical corticosteroids (TCS) and dupilumab plus TCS were effective in separate phase 3 clinical trials, they were not directly compared in head-to-head trials.

This study aimed to evaluate the short-term efficacy of lebrikizumab plus TCS versus dupilumab plus TCS in adults with moderate-to-severe AD using a placebo-anchored matching-adjusted indirect comparison (MAIC).

What was learned from this study?

Lebrikizumab every 2 weeks (Q2W) plus TCS and dupilumab Q2W plus TCS had comparable efficacy up to week 16 across multiple endpoints for disease severity, itch, and quality of life.

This anchored MAIC suggests that both lebrikizumab and dupilumab, in combination with TCS, provide similar clinical benefits after 16 weeks of treatment in real-world settings where TCS are commonly used along with these biologics.

INTRODUCTION

Atopic dermatitis (AD) is a chronic, inflammatory skin disease characterized by skin lesions and pruritus, which can markedly impair quality of life [1]. Although mild AD can often be controlled with emollients and topical corticosteroids (TCS), moderate-to-severe cases may require systemic treatment to achieve symptom control [2–4]. Targeted biologic therapy with lebrikizumab, dupilumab, or tralokinumab is commonly used as a first-line systemic therapy. These biologics were effective in clinical trials

when used as monotherapy [5–7] and when combined with TCS [8–13] and were approved for use in adolescents and adults with moderate-to-severe AD [14–19]. In real-world clinical practice, patients with moderate-to-severe AD frequently use biologics in combination with topical therapies; however, lebrikizumab plus TCS and dupilumab plus TCS were not directly compared in head-to-head clinical trials.

In the absence of head-to-head trials, indirect treatment comparisons (ITCs) can be used to assess the relative efficacy of alternative interventions [20]. A recent study applied Bucher's ITC to compare the efficacy of lebrikizumab plus TCS in the ADhere trial with dupilumab plus TCS in the CHRONOS trial at week 16 [21]. However, Bucher's ITC method does not account for differences in baseline characteristics that may modify treatment effects between trial populations [22]. Consequently, if there are baseline differences in trial populations, Bucher's ITC method may introduce bias into the safety and efficacy comparisons. In contrast, a matching-adjusted indirect comparison (MAIC) adjusts for imbalances in baseline differences between trial populations, providing a more reliable method for assessing the relative efficacy of alternative interventions [20, 22]. To address the lack of direct comparative data, the objective of this study was to assess the short-term comparative efficacy of lebrikizumab plus TCS versus dupilumab plus TCS using an anchored MAIC.

METHODS

Data Sources

Individual patient data from the ADhere trial (NCT04250337) [13] and published aggregate patient data from the CHRONOS trial (NCT02260986) were used [8, 23]. The trials were assessed for similarity of trial designs, eligibility criteria, treatment protocols, outcome definitions, and baseline characteristics of the trial populations. The ADhere trial evaluated the efficacy of lebrikizumab 250 mg every 2 weeks (Q2W) or placebo in combination with TCS for 16 weeks in adolescent and adult patients. The CHRONOS trial assessed the efficacy of dupilumab 300 mg once weekly (QW), dupilumab 300 mg Q2W, or placebo QW in combination with TCS for 52 weeks in adult patients. For this analysis, efficacy data up to week 16 were included from the dupilumab 300 mg Q2W plus TCS arm and placebo arm to align with the ADhere trial's duration and frequency of drug administration. Moreover, dupilumab 300 mg given Q2W is the only dosing frequency approved by the US Food and Drug Administration (FDA) for adults [17]. Additionally, to be consistent with CHRONOS inclusion criteria, only the adult subsample from the ADhere trial was included in the MAIC. Both trials included patients with moderate-to-severe AD, defined by an Eczema Area and Severity Index (EASI) score of 16 or higher, an Investigator's Global Assessment (IGA) score of 3 or higher, and a history of inadequate response to topical treatments. Both trials required the use of low- or medium-potency TCS, which could be tapered, stopped, or resumed depending on disease activity. Topical calcineurin inhibitors were permitted for sensitive skin areas where TCS would be inadvisable.

Ethical Approval

The ADhere and CHRONOS trials were conducted in accordance with the Declaration of Helsinki and were approved by the ethics committees of the respective institutions. Written informed consent was obtained from all patients enrolled in the trials; however, informed consent for this analysis was not required because it used anonymized data from previously published studies and did not involve primary data collection.

Efficacy Endpoints

Week-16 efficacy endpoints included the proportion of patients with an IGA 0/1 with a ≥2-point improvement from baseline [24]; the proportion of patients achieving a ≥50%, ≥75%, and ≥90% improvement from baseline in the EASI (EASI 50, EASI 75, and EASI 90) [25]; the proportion of patients achieving a ≥4-point improvement

from baseline in the Pruritus Numerical Rating Scale score (PNRS ≥ 4) among those with baseline scores ≥ 4 [26]; and the proportion of patients achieving a ≥ 4-point improvement from baseline in the Dermatology Life Quality Index score (DLQI ≥ 4) among those with baseline scores ≥ 4 [27]. Week-2 and week-4 efficacy endpoints included the proportion of patients achieving PNRS ≥ 4 among those with baseline scores ≥ 4.

Statistical Methods

Individual patient data from the ADhere trial [13] were aligned with aggregate patient data from the CHRONOS trial [8, 23] to minimize bias due to baseline differences. Baseline characteristics available for comparison in both trials and known to be potential treatment-effect modifiers were selected for adjustment, including demographic factors (age, sex, race) and disease severity (mean EASI score and proportion of patients with an IGA of 4) [28–32]. Differences in baseline characteristics were adjusted using the method of moments reweighting approach [33]. This reweighting matches the distribution of baseline characteristics in the ADhere trial to closely resemble those in the CHRONOS trial. Matching was performed at both the study level (primary analysis) and study arm level (sensitivity analysis), with the effective sample sizes (ESS) of the CHRONOS-like ADhere population reported for both analyses. After population matching, a placebo-anchored comparison of treatment effects for lebrikizumab Q2W plus TCS and dupilumab Q2W plus TCS was performed. Relative treatment effects of the CHRONOS-like ADhere population and CHRONOS population were quantified using odds ratios (ORs), risk ratios (RRs), and risk difference with 95% confidence intervals (CIs). Two-sided p values < 0.05 were considered statistically significant. All analyses were performed using R version 4.4.2 [34]. For both trials, data after the use of rescue medication or treatment discontinuation were handled using non-responder imputation.

RESULTS

Baseline Characteristics

Differences in baseline characteristics were observed between the ADhere and CHRONOS populations (Table S1). The CHRONOS study included a higher proportion of male and white patients, as well as a higher proportion of patients with more severe disease than the ADhere study. Additionally, the subsample of adult patients in the ADhere study was older on average than patients in the CHRONOS study. After reweighting, the baseline characteristics of the ADhere population were matched to the CHRONOS population at the study level (Table 1, Fig. S1) and at the study arm level (Table S2, Fig. S2). The ESS of the ADhere population was 99 after study-level matching and 94 after study arm-level matching.

Efficacy at Week 16

For EASI and IGA 0/1, the analysis population included 421 patients from the CHRONOS trial and 99 patients from the ADhere trial after study-level matching. For PNRS ≥ 4, the analysis population included 401 CHRONOS patients and 93 ADhere patients with baseline PNRS scores ≥ 4 after study-level matching. For DLQI ≥ 4, the analysis population included 400 CHRONOS patients and 94 ADhere patients with baseline DLQI scores ≥ 4 after study-level matching. After matching the ADhere population to the CHRONOS population, lebrikizumab Q2W plus TCS and dupilumab Q2W plus TCS showed similar efficacy at week 16 across all evaluated endpoints (Fig. 1, Table 2). Specifically, at week 16, lebrikizumab Q2W plus TCS had similar odds relative to dupilumab Q2W plus TCS of achieving EASI 50 (OR 1.50, 95% CI 0.54–4.20), EASI 75 (OR 1.14, 95% CI 0.42–3.09), EASI 90 (OR 0.99, 95% CI 0.31–3.21), IGA 0/1 (OR 1.39, 95% CI 0.42–4.59), PNRS ≥ 4 (OR 0.48, 95% CI 0.17–1.37), and DLQI ≥ 4 (OR 0.89, 95% CI 0.29–2.69). An analysis of RR also showed similar likelihoods for lebrikizumab Q2W plus TCS compared to dupilumab Q2W plus TCS in

Table 1 Baseline characteristics used in study-level matching of the ADhere and CHRONOS trial populations

	CHRONOS trial	ADhere trial	
	Target population	Before matching	After matching
Age in years, mean (SD)	37.4 (13.3)	43.6 (17.0)	37.4 (13.4)
% male	61	52	61
% white	67	58	67
EASI, mean (SD)	32.9 (13.0)	27.1 (11.2)	32.9 (13.1)
% with IGA = 4	48	33	48
N	421	165	–
Effective sample size	–	–	99

Data based on the weights when the whole ADhere adult population was used in the analysis. IGA = 4 indicates severe atopic dermatitis

EASI Eczema Area and Severity Index, *IGA* Investigator Global Assessment, *SD* standard deviation

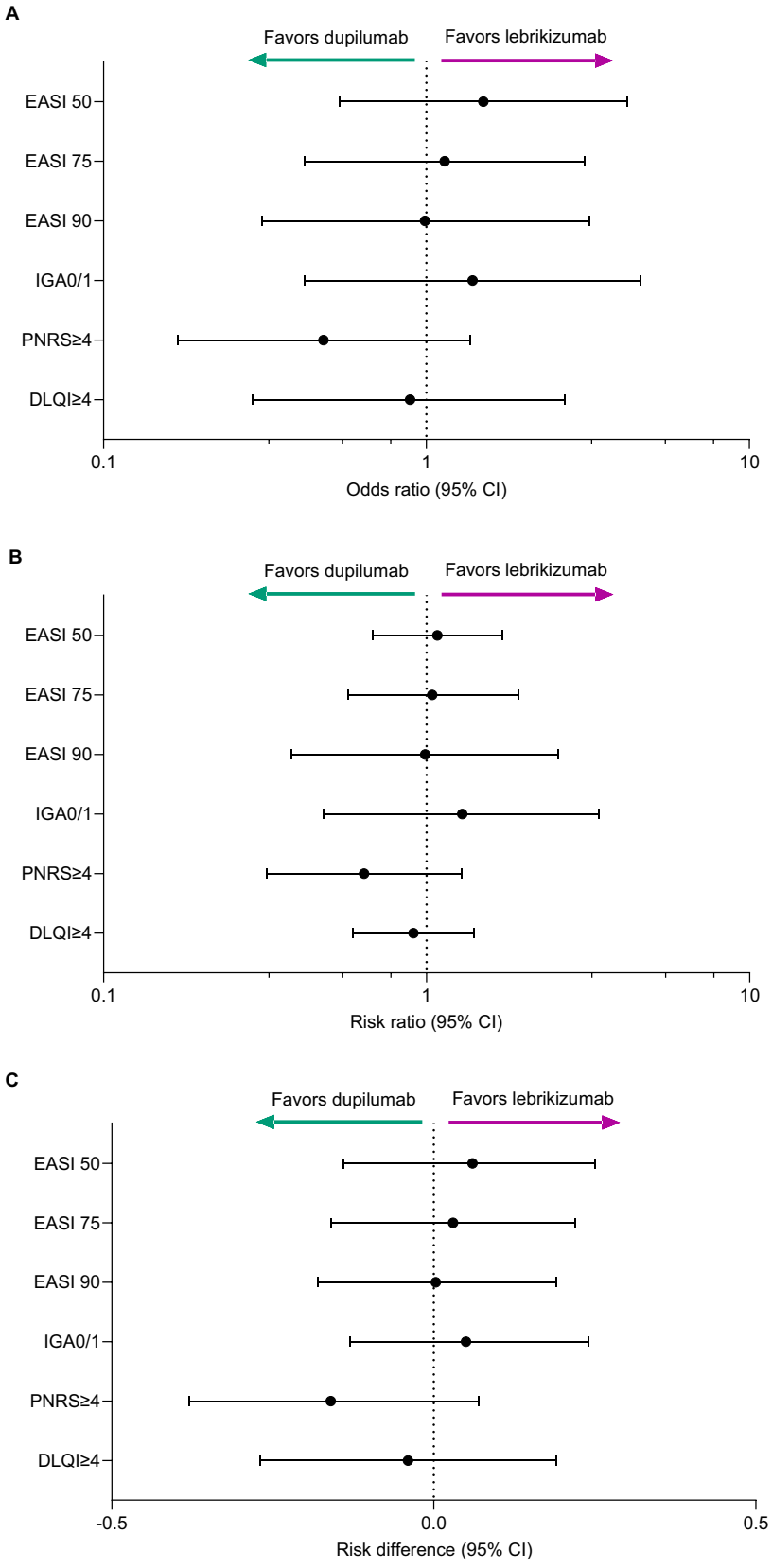
achieving EASI 50 (RR 1.08, 95% CI 0.68–1.71), EASI 75 (RR 1.04, 95% CI 0.57–1.92), EASI 90 (RR 0.99, 95% CI 0.38–2.55), IGA 0/1 (RR 1.29, 95% CI 0.48–3.42), PNRS ≥ 4 (RR 0.64, 95% CI 0.32–1.28), and DLQI ≥ 4 (RR 0.91, 95% CI 0.59–1.40). Furthermore, the risk differences (RDs) between these combination treatments were minimal across efficacy endpoints: EASI 50 (RD 0.06, 95% CI – 0.14 to 0.25), EASI 75 (RD 0.03, 95% CI – 0.16 to 0.22), EASI 90 (RD 0.003, 95% CI – 0.18 to 0.19), IGA 0/1 (RD 0.05, 95% CI – 0.13 to 0.24), PNRS ≥ 4 (RD – 0.16, 95% CI – 0.38 to 0.07), and DLQI ≥ 4 (RD – 0.04, 95% CI – 0.27 to 0.19). Although numerical differences in efficacy endpoints were observed, these differences were not statistically significant, indicating that the efficacy of lebrikizumab Q2W plus TCS was comparable to dupilumab Q2W plus TCS after 16 weeks of treatment.

Itch Efficacy at Weeks 2 and 4

Data from the CHRONOS trial were available for earlier timepoints for PNRS ≥ 4 at weeks 2 and 4 (Fig. 2, Table 3). At week 2, lebrikizumab Q2W plus TCS and dupilumab Q2W plus TCS showed similar itch efficacy. Specifically, lebrikizumab Q2W plus TCS had similar odds relative to dupilumab Q2W plus TCS of achieving PNRS ≥ 4 at week 2 (OR 2.04, 95% CI 0.24–17.05). RR also showed similar likelihoods for lebrikizumab Q2W plus TCS compared to dupilumab Q2W plus TCS in achieving PNRS ≥ 4 at week 2 (RR 2.08, 95% CI 0.28–15.68). The risk difference between these combination treatments was also comparable at week 2 (RD – 0.01, 95% CI – 0.13 to 0.11). At week 4, lebrikizumab Q2W plus TCS had similar odds relative to dupilumab Q2W plus TCS of achieving PNRS ≥ 4 (OR 3.59, 95% CI 0.90–14.36). Notably, the RR of achieving PNRS ≥ 4 at week 4 was significantly higher for lebrikizumab Q2W plus TCS as compared to dupilumab Q2W plus TCS (RR 3.61, 95% CI 1.04–12.61; $p = 0.04$). The risk difference in itch at week 4 was comparable for these combination treatment (RD 0.03, 95% CI – 0.13 to 0.18). Although numerical differences in PNRS ≥ 4 at weeks 2 and 4 favored lebrikizumab, these differences were generally not statistically significant.

Sensitivity Analysis

Sensitivity analyses based on arm-level matching were generally consistent with the primary analyses (Table S3–S4, Figs. S3–S4). Lebrikizumab Q2W plus TCS continued to show comparable efficacy to dupilumab Q2W plus TCS across all endpoints. As in the primary analysis, the only statistically significant difference was observed for the RR of achieving PNRS ≥ 4 at week 4 (RR


A
Favors dupilumab
Favors lebrikizumab
EASI 50
EASI 75
EASI 90
IGA0/1
PNRS≥4
DLQI≥4
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Odds ratio (95% CI)
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Favors dupilumab
Favors lebrikizumab
EASI 50
EASI 75
EASI 90
IGA0/1
PNRS≥4
DLQI≥4
0.1
1
10
Risk ratio (95% CI)
C
Favors dupilumab
Favors lebrikizumab
EASI 50
EASI 75
EASI 90
IGA0/1
PNRS≥4
DLQI≥4
-0.5
0.0
0.5
Risk difference (95% CI)

◂**Fig. 1** Efficacy at week 16 of lebrikizumab Q2W plus TCS versus dupilumab Q2W plus TCS after matching the study populations from the ADhere and CHRONOS trials. ORs (**a**), RR, (**b**), and RD (**c**) comparing the efficacy of lebrikizumab Q2W plus TCS to dupilumab Q2W plus TCS. Panels **a** and **b** use a logarithmic scale; panel **c** uses a linear scale. Error bars represent 95% confidence intervals. For PNRS4 and DLQI4, available patients with baseline values ≥ 4 points from the two trials were used in analysis. The analysis population in the target CHRONOS study was assumed to have the same baseline characteristics as the whole CHRONOS population. Differences in baseline characteristics (age, sex, race, mean EASI score, and proportion of patients with an IGA of 4) at the study level were adjusted to create comparable populations as described in the Methods. *CI* confidence interval, *DLQI ≥ 4* Dermatology Life Quality Index score ≥ 4-point improvement from baseline, *EASI 75* ≥ 75% improvement in Eczema Area and Severity Index score from baseline, *IGA0/1* Investigator Global Assessment score of 0/1, *PNRS ≥ 4* Pruritus Numerical Rating Scale score ≥ 4-point improvement from baseline, *Q2W plus TCS* every 2 weeks plus topical corticosteroids

3.95, 95% CI 1.11–14.11; $p = 0.03$). These findings indicate that the primary analyses were not biased by potential intra-study heterogeneity between placebo and treatment arms.

DISCUSSION

This anchored MAIC suggests that lebrikizumab 250 mg Q2W plus TCS was associated with comparable disease severity, itch, and quality-of-life outcomes as dupilumab Q2W plus TCS after 16 weeks of treatment. Lebrikizumab Q2W plus TCS showed a numerical advantage over dupilumab Q2W plus TCS for EASI 75 and IGA 0/1 outcomes at week 16 and for PNRS ≥ 4 at weeks 2 and 4. Conversely, dupilumab Q2W plus TCS was favored numerically over lebrikizumab Q2W plus TCS for PNRS ≥ 4 and DLQI ≥ 4 outcomes at week 16. Although no statistically significant differences in EASI 75, IGA 0/1, PNRS ≥ 4, and DLQI ≥ 4 were observed at week 16, patients treated with lebrikizumab Q2W plus TCS had a significantly higher likelihood of achieving PNRS ≥ 4 at week 4 compared to patients treated with dupilumab Q2W plus TCS. These findings indicate that both lebrikizumab and dupilumab in combination with TCS provide similar clinical benefits after 16 weeks of treatment and that lebrikizumab plus TCS may offer superior early itch relief compared to dupilumab plus TCS.

When individual patient data are available, MAIC is generally considered superior to Bucher's ITC [35]. MAIC adjusts for population differences, reduces bias due to population heterogeneity, and controls for confounding. In our analysis, an anchored MAIC was used to account for population heterogeneity between the CHRONOS and ADhere trials. However, in a recently published analysis, Bucher's ITC, which does not account for between-trial population heterogeneity, was used to compare outcomes in the ADhere and CHRONOS trials [21]. This study found that dupilumab plus TCS had a significantly higher likelihood of achieving EASI 75 and PNRS ≥ 4 at week 16 compared to lebrikizumab plus TCS. However, baseline differences between the CHRONOS and ADhere populations were ignored, even though age, sex, race, and disease severity were shown to be potential treatment-effect modifiers in patients with AD [28–32]. For example, the CHRONOS trial had a higher proportion of patients with severe disease at baseline compared to the ADhere trial. This difference could potentially influence treatment effects, especially in the CHRONOS and ADhere trials where all patients, including placebo patients, received TCS. Previous studies showed that less severe AD at baseline is associated with greater placebo response and less use of rescue medications in placebo arms [36]. In the CHRONOS trial, placebo plus TCS responses were lower for EASI 75, IGA 0/1, PNRS ≥ 4, and DLQI ≥ 4 at week 16 than placebo plus TCS responses in the ADhere trial [8, 13]. Such baseline differences in trial populations may result in bias when comparing treatment effects without first adjusting for them. Our population-adjusted MAIC addressed these baseline differences by reweighting patients in ADhere to match the characteristics of the target CHRONOS population, providing a more accurate assessment of the relative treatment effects of lebrikizumab Q2W plus TCS vs dupilumab Q2W plus TCS.

Table 2 Efficacy at week 16 for lebrikizumab Q2W plus TCS versus dupilumab Q2W plus TCS after matching the study populations from the ADhere and CHRONOS trials

	CHRONOS trial		ADhere trial				Odds ratio (95% CI)	*p* value	Risk ratio (95% CI)	*p* value	Risk difference (95% CI)	*p* value
	Target population % response		Before matching % response		After matching % response							
	PBO	Dupi	PBO	Lebri	PBO	Lebri						
EASI 50[a]	37	80	52	77	37	86	1.50 (0.54–4.20)	0.44	1.08 (0.68–1.71)	0.75	0.06 (−0.14 to 0.25)	0.56
EASI 75[a]	23	69	35	62	23	72	1.14 (0.42–3.09)	0.80	1.04 (0.57–1.92)	0.89	0.03 (−0.16 to 0.22)	0.78
EASI 90[a]	11	40	17	35	11	40	0.99 (0.31–3.21)	0.99	0.99 (0.38–2.55)	0.98	0.003 (−0.18 to 0.19)	0.98
IGA 0/1[a]	12	39	17	35	10	42	1.39 (0.42–4.59)	0.59	1.29 (0.48–3.42)	0.62	0.05 (−0.13 to 0.24)	0.59
PNRS ≥ 4[b]	20	59	30	46	26	49	0.48 (0.17–1.37)	0.17	0.64 (0.32–1.28)	0.21	−0.16 (−0.38 to 0.07)	0.17
DLQI ≥ 4[c]	43	81	51	76	48	82	0.89 (0.29–2.69)	0.84	0.91 (0.59–1.40)	0.66	−0.04 (−0.27 to 0.19)	0.74

CI confidence interval, *DLQI ≥ 4* Dermatology Life Quality Index score ≥ 4-point improvement from baseline, *Dupi* dupilumab Q2W plus TCS, *EASI 75* ≥ 75% improvement in Eczema Area and Severity Index score from baseline, *IGA0/1* Investigator Global Assessment score of 0/1, *Lebri* lebrikizumab Q2W plus TCS, *MAIC* matching-adjusted indirect comparison, *PBO* placebo Q2W plus TCS, *PNRS ≥ 4* Pruritus Numerical Rating Scale score ≥ 4-point improvement from baseline, *Q2W + TCS* every 2 weeks plus topical corticosteroids

[a]CHRONOS: $N = 315$ in the placebo group and $N = 106$ in the dupilumab group; ADhere (pre-matching): $N = 52$ in the placebo group and $N = 113$ in the lebrikizumab group; ADhere (post-matching): ESS = 34 in the placebo group and ESS = 65 in the lebrikizumab group

[b]CHRONOS: $N = 299$ in the placebo group and $N = 102$ in the dupilumab group; ADhere (pre-matching): $N = 46$ in the placebo group and $N = 106$ in the lebrikizumab group; ADhere (post-matching): ESS = 30 in the placebo group and ESS = 63 in the lebrikizumab group

[c]CHRONOS: $N = 300$ in the placebo group and $N = 100$ in the dupilumab group; ADhere (pre-matching): $N = 47$ in the placebo group and $N = 104$ in the lebrikizumab group; ADhere (post-matching): ESS = 30 in the placebo group and ESS = 64 in the lebrikizumab group

For [b] and [c], patients with baseline PNRS or DLQI values ≥ 4 points from the two trials were used in the analysis. This subset of the target CHRONOS population was assumed to have the same baseline characteristics at the study level as the whole CHRONOS population (i.e., without restricting for baseline values ≥ 4 points)

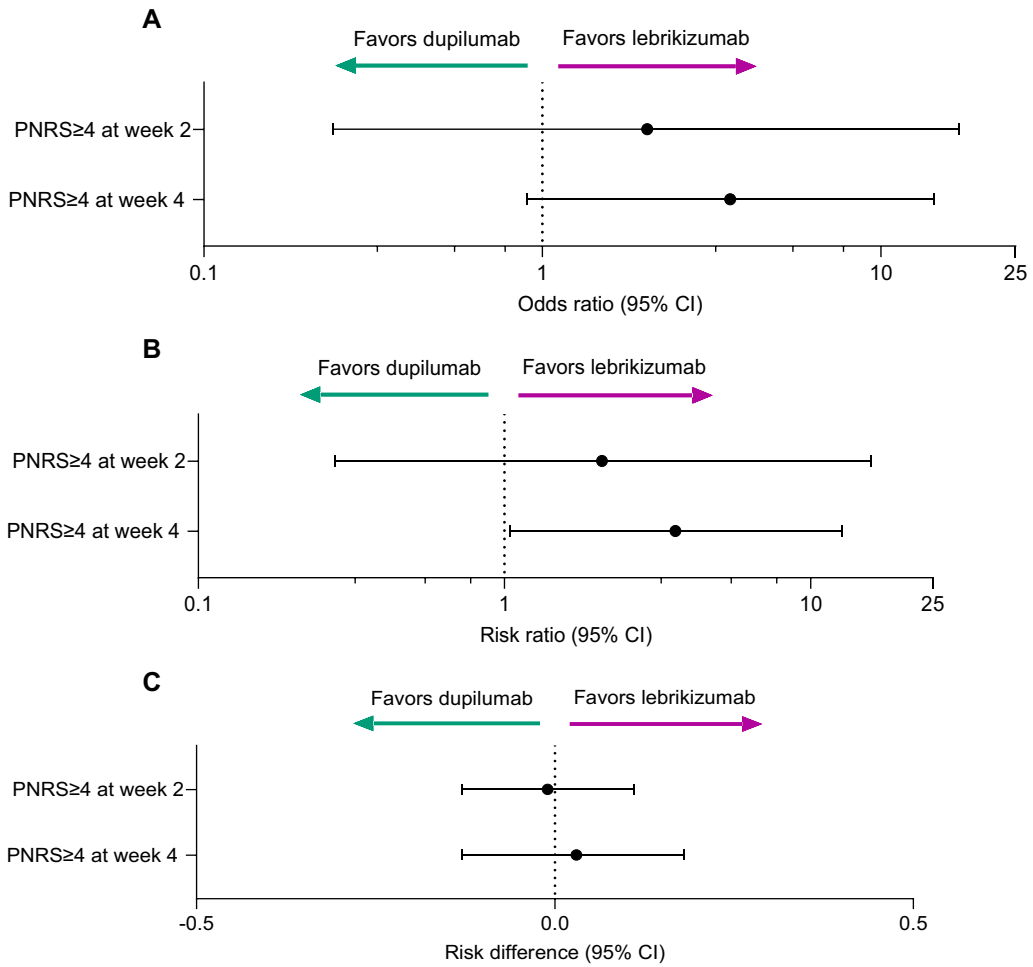

Fig. 2 Itch efficacy at weeks 2 and 4 of lebrikizumab Q2W plus TCS versus dupilumab Q2W plus TCS after matching the study populations from the ADhere and CHRONOS trials. ORs (**a**), RR, (**b**), and RD (**C**) comparing itch efficacy of lebrikizumab Q2W plus TCS to dupilumab Q2W plus TCS. Panles **a** and **b** use a logarithmic scale; panel **c** uses a linear scale. Error bars represent 95% confidence intervals. Available patients with baseline values ≥ 4 points from the two trials were used in analysis. The analysis population in the target CHRONOS study was assumed to have the same baseline characteristics as the whole CHRONOS population. Differences in baseline characteristics (age, sex, race, mean EASI score, and proportion of patients with an IGA of 4) at the study level were adjusted to create comparable populations as described in the Methods. *CI* confidence interval, *PNRS ≥ 4* Pruritus Numerical Rating Scale score ≥ 4-point improvement from baseline, *Q2W plus TCS* every 2 weeks plus topical corticosteroids

Our anchored MAIC is the first ITC to use a robust methodology to demonstrate that lebrikizumab plus TCS has comparable response rates to dupilumab plus TCS after 16 weeks of induction treatment [8, 13]. Although data on the efficacy of AD combination therapies are limited, many studies evaluated the efficacy of AD monotherapies in adults at week 16 [37–43]. A recent network meta-analysis (NMA) comparing monotherapy with lebrikizumab 250 mg Q2W and dupilumab 300 mg Q2W found that these biologics have comparable efficacy in terms of EASI 75, IGA 0/1, and PNRS ≥ 4 at week 16 [43]. Another NMA combining data from both monotherapy and combination therapy trials found that lebrikizumab was similarly effective to

Table 3 Itch efficacy at weeks 2 and 4 for lebrikizumab Q2W plus TCS versus dupilumab Q2W plus TCS after matching the study populations from the ADhere and CHRONOS trials

	CHRONOS trial		ADhere trial				Odds ratio (95% CI)	*p* value	Risk ratio (95% CI)	*p* value	Risk difference (95% CI)	p value
	Target population % response		Before matching % response		After matching % response							
	PBO	Dupi	PBO	Lebri	PBO	Lebri						
PNRS ≥ 4 at week 2[a]	8	18	4	9	2	11	2.04 (0.24–17.05)	0.51	2.08 (0.28–15.68)	0.48	− 0.01 (− 0.13 to 0.11)	0.89
PNRS ≥ 4 at week 4[a]	16	37	9	25	3	27	3.59 (0.90–14.36)	0.07	3.61 (1.04–12.61)	0.04	0.03 (− 0.13 to 0.18)	0.73

CI confidence interval, *Dupi* dupilumab Q2W plus TCS, *Lebri* lebrikizumab Q2W plus TCS, *MAIC* matching-adjusted indirect comparison, *PBO* placebo Q2W plus TCS, *PNRS ≥ 4* Pruritus Numerical Rating Scale score ≥ 4-point improvement from baseline, *Q2W + TCS* every 2 weeks plus topical corticosteroids

[a]CHRONOS: $N = 299$ in the placebo group and $N = 102$ in the dupilumab group; ADhere (pre-matching): $N = 46$ in the placebo group and $N = 106$ in the lebrikizumab group; ADhere (post-matching): ESS = 30 in the placebo group and ESS = 63 in the lebrikizumab group. Patients with baseline PNRS values ≥ 4 points from the two trials were used in the analysis. This subset of the target CHRONOS population was assumed to have the same baseline characteristics at the study level as the whole CHRONOS population (i.e., without restricting for baseline values ≥ 4 points)

dupilumab after 16 weeks of treatment in adults with AD [42]. A limitation of this approach is that combination therapy trials do not show a drug's effect independently of the additional therapeutic agents used in the combination therapy. In the ADhere and CHRONOS trials, while the TCS approaches were similar, the frequency and amount of TCS use were not well controlled, which could have affected treatment outcomes. Despite this limitation, these findings suggest that lebrikizumab and dupilumab have similar efficacy at week 16 when used as monotherapy or in combination therapies with TCS.

AD is a chronic and relapsing inflammatory condition that requires long-term maintenance treatment for disease management. Currently, there are no head-to-head clinical trials comparing long-term maintenance treatment with lebrikizumab and dupilumab in either the monotherapy or combination therapy settings. In the ADvocate and SOLO-CONTINUE monotherapy trials, patients who responded to induction treatment (week 0–16) were enrolled in the maintenance phase (week 16–52) of these trials [5, 6]. Week-16 responders were re-randomized to receive either active treatment or placebo (treatment withdrawal) from weeks 16 to 52. Notably, response rates at week 52 in the active treatment and treatment withdrawal arms differed for lebrikizumab and dupilumab. A numerically higher proportion of week-16 responders who withdrew lebrikizumab maintained their response at week 52 compared to those who withdrew dupilumab. This difference in off-drug durability of response is an important factor to consider when comparing maintenance responses. For comparisons of these data, an anchored MAIC and Bucher's ITC are not appropriate methodologies because the placebo (treatment withdrawal) arms cannot be used as a common comparator. However, Bucher's ITC was recently used to compare week-52 outcomes in the SOLO-CONTINUE and ADvocate trials [21]. If post-withdrawal maintenance responses are ignored, this approach will lead to erroneous conclusions, as it would not account for the differences in off-drug durability of response observed in these trials. In contrast, an unanchored MAIC approach allows for indirect comparisons of treatments across trials without a common comparator. A recent unanchored MAIC used individual patient data from the ADvocate trials to match it with aggregate data from the SOLO-CONTINUE trial [44]. This study found that maintenance treatment with lebrikizumab monotherapy was more likely to maintain IGA 0/1 compared with dupilumab (RR 1.334; 95% CI 1.02–1.74; $p=0.035$). Both treatments had comparable efficacy for EASI 75 maintenance (RR 0.937; 95% CI 0.78–1.13; $p=0.490$). Taken together, these findings suggest that lebrikizumab monotherapy may have equal or superior efficacy than dupilumab monotherapy during maintenance treatment; however, further research is needed to evaluate the outcomes of long-term maintenance treatment with combination therapeutic approaches.

Our study has several strengths that contribute to the robustness and reliability of the findings. The use of individual patient data from the ADhere trial allowed for adjusting baseline differences between the ADhere and CHRONOS trial populations. The MAIC approach ensures that potential treatment-effect modifiers (e.g., age, sex, race, and disease severity) are balanced between trial populations, thereby providing a more accurate assessment of the relative efficacy of combination treatments. Although the MAIC methodology adjusts for baseline differences, there is still the possibility of residual confounding that could affect the results. Additionally, this study relied on published aggregate patient data from the CHRONOS trial, which may introduce potential biases that are less controllable compared to using individual patient data. Another strength of the study is the robustness of the conclusions of the primary analysis, which were supported by the study arm-level matching analysis; this helps reduce bias by accounting for potential differences between treatment arms within the comparator study.

This MAIC analysis has some important limitations that should be acknowledged. First, the comparative efficacy estimates derived from the MAIC are based on the population enrolled in the CHRONOS trial. Consequently, any differences between the target population in this MAIC and the general target population of interest may limit the generalizability of the findings [45]. Second, after reweighting

only a portion of the original patient cohort contributed meaningfully to the adjusted estimates, which may affect the reliability and precision of the estimates. Third, the analysis was restricted to the induction phase (16 weeks), as data beyond this time point were not available for comparison. This limits the ability to assess longer-term outcomes and the durability of treatment effects. Fourth, published aggregate data were available for only one of the studies, limiting the capacity to explore potential treatment effect modifiers across both treatment populations. As with all indirect comparisons, unmeasured or unreported treatment effect modifiers may also introduce residual bias, despite efforts to adjust for observed baseline differences.

CONCLUSIONS

This anchored MAIC demonstrated that lebrikizumab Q2W plus TCS and dupilumab Q2W plus TCS had similar efficacy up to week 16 across multiple endpoints in adults with moderate-to-severe AD. By addressing several methodological limitations of Bucher's ITC, this MAIC provides a less biased comparison of the efficacy of combination treatments. These findings may assist clinicians and their patients in making informed treatment decisions about the short-term efficacy of lebrikizumab compared to dupilumab, especially in real-world settings where TCS is commonly used in combination with these biologics. Given lebrikizumab's long-term clinical benefits and ability to accommodate treatment interruptions as a monotherapy, further investigations are needed to determine the long-term outcomes of combination therapies and whether lebrikizumab's off-drug durability of response allows for interruptions in TCS as well.

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Data Availability. Eli Lilly and Company provides access to all individual participant data collected during the trial, after anonymisation, with the exception of pharmacokinetic or genetic data. Data are available to request 6 months after the indication studied has been approved in the USA and EU and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data proposal request form. For more on submitting a request see http://www.vivli.org sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, and blank or annotated case report forms, will be provided in a secure data

sharing environment. For details on submitting a request, see the instructions provided online.

Declarations

Conflict of Interest. Raj Chovatiya served as an advisor, consultant, speaker, and/or investigator for AbbVie, Acelyrin, Alumis, Amgen, AnaptysBio, Apogee Therapeutics, Arcutis Biotherapeutics Inc., Argenx, Astria Therapeutics Inc., Avalere Health, Beiersdorf, Boehringer Ingelheim, Bristol Myers Squibb, Cara Therapeutics, Castle Biosciences, CLn Skin Care, Dermavant, Eli Lilly and Company, EMD Serono, Formation Bio, Galderma, Genentech, GSK, Incyte, Johnson & Johnson, Kenvue, LEO Pharma, L'Oréal, Nektar Therapeutics, Novartis, Opsidio, Pfizer Inc., RAPT, Regeneron, Sanofi, Sitryx, Takeda, TRex Bio, and UCB and is an Editorial Board member of *Dermatology and Therapy* but was not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions. April Armstrong received research grants and personal fees from Bristol Myers Squibb, Eli Lilly, Janssen, Leo Pharma, and Novartis; personal fees from Boehringer Ingelheim/Parexel, Celgene, Dermavant, Genentech, GlaxoSmithKline, Menlo Therapeutics, Merck, Modernizing Medicine, Ortho Dermatologics, Pfizer, Regeneron, Sanofi Genzyme, Science 37, Sun Pharma, and Valeant; and grants from Dermira, Kyowa Hakko Kirin, and UCB, outside the submitted work. Leon Kircik received research grants from AbbVie, Allergan, Almirall, Amgen, Arcutis, Boehringer Ingelheim, Breckinridge Pharma, Bristol Myers Squibb, Celgene, Cellceutix, Centocor, Combinatrix, Connetics, Coria, Dermavant, Dermira, Dow Pharma, Dr Reddy's Laboratories, Eli Lilly, Galderma, Genentech, GlaxoSmithKline, Idera, Johnson & Johnson, Leo Pharma, Maruho, Merck, Medicis, Novartis AG, Pfizer, PharmaDerm, Promius, Stiefel, Sun Pharma, UCB, Valeant, and XenoPort and honoraria from AbbVie, Allergan, Almirall, Amgen, Arcutis, Biogen Idec, Bristol Myers Squibb, Celgene, Cipher, Connetics, Dermavant, Dermira, Dr Reddy's Laboratories, Eli Lilly, Galderma, Genentech, GlaxoSmithKline, Johnson & Johnson, Leo Pharma, Merck, Novartis AG, PharmaDerm, Promius, Serono (Merck Serono International SA), Stiefel, Sun Pharma, Taro, UCB, and Valeant. Lluís Puig received consultancy/speaker's honoraria from and/or participated in clinical trials sponsored by Abbvie, Almirall, Amgen, Biogen, Boehringer Ingelheim, Bristol Myers Squibb, Fresenius-Kabi, J&J Innovative Medicine, Leo-Pharma, Lilly, Novartis, Pfizer, STADA, Sun-Pharma, and UCB and is an Editorial Board member of *Dermatology and Therapy* but was not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions. Mark G. Kirchhof served as a consultant for AbbVie, Eli Lilly, Janssen, Novartis, Pfizer, UCB, Sanofi-Genzyme and on the speakers bureau for AbbVie, Janssen, Novartis, Pfizer, UCB, and Sanofi-Genzyme and has received grants from the Canadian Dermatology Foundation. Tiago Torres received consultancy and/or speaker's honoraria from, and/or participated in clinical trials sponsored by, AbbVie, Almirall, Amgen, Arena Pharmaceuticals, Biocad, Biogen, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Fresenius-Kabi, Janssen, LEO Pharma, Eli Lilly, MSD, Mylan, Novartis, Pfizer, Samsung-Bioepis, Sanofi-Genzyme, Sandoz and UCB and is an Editorial Board member of *Dermatology and Therapy* but was not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions. Yousef Binamer received consultancy/speaker's honoraria and travel support from AbbVie, Amgen, Eli Lilly, Janssen, Kyowa Kirin, NewBridge, Novartis, and Sanofi and research grants from AbbVie, Novartis, and Sanofi. Gleison Duarte served as a scientific consultant, speaker, or clinical trial investigator for Abbvie, Bayer, Janssen, Leo-Pharma, Galderma, Sanofi, Boehringer, Novartis, Pfizer, Amgen, Celldex, and UCB. Bülent Akmaz is an employee of Almirall. Martin Dossenbach, Gaia Gallo, Chao Yang, Lucia Seminario-Vidal, and Yuxin Ding are employees of, and own stock in, Eli Lilly and Company, which funded this research. Jonathan I. Silverberg received honoraria as a consultant and/or advisory board member for Abbvie, Aldena, Aldena, Amgen, AObiome, Apollo, Arcutis, Arena, Asana, Aslan, Attovia, Bodewell, Boehringer Ingelheim, Bristell-Meyers Squibb, Cara, Castle Biosciences, Celgene,

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