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ORIGINAL RESEARCH

Matching-Adjusted Indirect Comparison of the Efficacy at Week 32 of Tralokinumab and Dupilumab in the Treatment of Moderate-to-Severe Atopic Dermatitis

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ABSTRACT

Introduction: Tralokinumab and dupilumab are biological agents licensed for the treatment of moderate-to-severe atopic dermatitis (AD) in adult patients who are candidates for systemic treatment. However, no head-to-head studies of their efficacy have been conducted. This study indirectly compared the efficacy of tralokinumab and dupilumab, both in combination with topical corticosteroids (TCS), at week 32.

Methods: An unanchored matching-adjusted indirect comparison was conducted using individual patient data (IPD) from the ECZTRA 3 tralokinumab trial and aggregate data from the LIBERTY AD CHRONOS dupilumab trial. IPD were selected by applying inclusion criteria from LIBERTY AD CHRONOS and weighting to match summary baseline characteristics—age, sex, race, body mass index, disease duration, Eczema Area and Severity Index (EASI), Investigator's Global Assessment (IGA), Dermatology Life Quality Index (DLQI) and SCORing Atopic Dermatitis index—of patients treated with dupilumab. Week 32 outcomes of interest were 50%, 75% or 90% improvements in EASI (EASI-50, EASI-75 and EASI-90), IGA scores of 0 or 1 (IGA 0/1), ≥ 4-point improvement in worst daily pruritus numerical rating scale (NRS) score, and mean improvements in DLQI and the Patient Oriented Eczema Measure (POEM).

Results: After matching, tralokinumab and dupilumab, both in combination with TCS, showed similar efficacy across clinical response endpoints at week 32 (IGA 0/1, tralokinumab 49.9% vs dupilumab 39.3%; EASI-50, 78.9% vs 77.5%; EASI-75, 71.5% vs 71.9%; EASI-90, 53.3% vs 56.2%). The mean change from baseline in DLQI was statistically significantly larger in the matched tralokinumab plus TCS population than in the dupilumab plus TCS arm (− 12.1 vs − 10.4, $p = 0.005$). Changes in POEM and worst daily pruritus NRS were similar in the two groups.

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Conclusion: The results of this analysis demonstrate that, in combination with TCS, tralokinumab and dupilumab have similar efficacy in the treatment of moderate-to-severe AD at 32 weeks of therapy.

Keywords: Atopic dermatitis; Dupilumab; Matching-adjusted indirect comparison; Topical corticosteroids; Tralokinumab

Key Summary Points

Why carry out this study?

There are no head-to-head studies comparing the efficacy of tralokinumab and dupilumab, two biological agents licensed for the treatment of moderate-to-severe atopic dermatitis (AD).

In this study, we conducted a matching-adjusted indirect comparison of the efficacy at week 32 of tralokinumab and dupilumab in combination with topical corticosteroids (TCS).

What was learned from the study?

The results of the analysis show that tralokinumab and dupilumab, both in combination with TCS, have similar efficacy at 32 weeks.

These results may help inform treatment choices for individual patients with moderate-to-severe AD.

INTRODUCTION

Atopic dermatitis (AD) is a chronic, relapsing–remitting, inflammatory skin condition characterised by pruritus and eczematous lesions [1, 2]. For adults with moderate-to-severe AD, the effect on health-related quality of life can be considerable, with the disease impacting sleep, mental health and both physical and social functioning [3–6]. Long-term control of disease and safety of treatment are key considerations for patients.

In recent years, targeted biological therapies have become available for patients whose AD does not respond to topical therapies or systemic immunosuppressants [7]. Tralokinumab and dupilumab are two biological agents licensed for the treatment of moderate-to-severe AD in adult patients who are candidates for systemic treatment [7]. AD pathophysiology is driven by the activity of the interleukin (IL)-13 cytokine [8]. Tralokinumab binds specifically and with high affinity to IL-13, while dupilumab inhibits both IL-4- and IL-13-mediated signalling [9]. In addition to their use as monotherapy, combination therapy with tralokinumab or dupilumab plus topical corticosteroids (TCS) is well established in guidelines as a standard treatment for AD [7]. As AD is brought under control, the amount of TCS used greatly diminishes [7, 10].

No head-to-head studies comparing the efficacy of tralokinumab and dupilumab, either as monotherapy or combination therapy with TCS, have been conducted. In the absence of head-to-head data, indirect comparison methods can be used to compare therapies [11]. To date, indirect comparisons assessing the relative efficacy of tralokinumab and dupilumab have been reported up to 16 weeks of treatment [12, 13]. However, a comparison at 16 weeks may be too early in the course of treatment to fully assess the benefits of these therapies, given that response to treatment may continue to improve with additional time, and that AD is a chronic disease [14]. Accordingly, it is important to investigate the comparative efficacy of tralokinumab and dupilumab beyond 16 weeks.

In this study, we conducted an indirect comparison of tralokinumab and dupilumab in combination with TCS beyond 16 weeks of treatment. Because the relevant phase 3 trials had differences in the design of their placebo arms, it was not possible to use an anchored indirect comparison method [14, 15]. In such circumstances, a matching-adjusted indirect comparison (MAIC) can be used. MAIC uses individual patient data (IPD) from a clinical trial of one intervention and aggregate data from a trial of another [11, 16]. These IPD are weighted

such that potential prognostic variables and treatment effect modifiers are matched to the mean characteristics of the second trial population, in order to compare outcomes across balanced trial populations [11, 16]. In particular, unanchored MAIC analysis allows the relative efficacy of therapies for which no common comparator is available to be evaluated [11, 16].

We used MAIC methodology to indirectly compare the efficacy of tralokinumab and dupilumab, both in combination with TCS, at 32 weeks of treatment, in adult patients with moderate-to-severe AD. The objectives of the analysis were to compare the efficacy of tralokinumab and dupilumab, in combination with TCS, as measured by the Investigator's Global Assessment (IGA) and the Eczema Area and Severity Index (EASI), and to compare patient-reported outcomes (PROs) among patients treated with tralokinumab or dupilumab plus TCS.

METHODS

MAIC Methods and Source Data

A MAIC analysis was conducted as described by Signorovitch et al. [16, 17]. The randomised controlled trials (RCTs) included in the analysis are summarised in Fig. 1.

An unanchored MAIC was conducted using IPD from adult patients treated with tralokinumab in combination with TCS in the ECZTRA 3 trial, which were compared with aggregate data from the LIBERTY AD CHRONOS trial of dupilumab in combination with TCS [14, 15]. Indirect comparisons were performed using data at week 32, the duration of ECZTRA 3, from both trials.

ECZTRA 3 was a 32-week, double-blind phase 3 trial of tralokinumab every 2 weeks (Q2W) versus placebo, for an initial 16-week treatment period, both in combination with TCS [14]. Patients receiving tralokinumab who had a clinical response at 16 weeks (an IGA score of 0 or 1 [IGA 0/1] or a 75% improvement in EASI [EASI-75]) were re-randomised 1:1 to tralokinumab Q2W or every 4 weeks (Q4W), with TCS as needed, for a further 16 weeks. Those without a response to tralokinumab at 16 weeks continued to receive tralokinumab Q2W in combination with TCS. IPD from all patients initially randomised to tralokinumab Q2W, regardless of clinical response at week 16, were included in the analysis (Fig. 1).

LIBERTY AD CHRONOS was a 52-week double-blind phase 3 trial of dupilumab weekly or Q2W versus placebo, both in combination with TCS [15]. Patients received the same treatment for the 52-week duration of the trial, regardless of clinical response. LIBERTY AD CHRONOS reported results at week 32 for four outcomes: the proportions of patients achieving IGA 0/1, EASI-75, and 50% or 90% improvements in EASI (EASI-50 or EASI-90). Data for PROs and other clinical endpoints in LIBERTY AD CHRONOS were digitised from figures in the published paper using PlotDigitizer.

Only LIBERTY AD CHRONOS patients treated with dupilumab Q2W were included in this analysis (Fig. 1). The published week 32 results for dupilumab Q2W are from a data cut before the conclusion of the trial and were reported for 89 patients out of the 106 randomised [15].

Ethical approval was not required for this study because the analysis is based on previously conducted studies and does not contain data from any new studies with human participants or animals.

Matching Trial Populations

IPD for patients treated with tralokinumab in combination with TCS were selected by applying the inclusion criteria from LIBERTY AD CHRONOS to the ECZTRA 3 trial population. ECZTRA 3 IPD were analysed as in the published LIBERTY AD CHRONOS analysis [15]. For binary outcomes, IPD were analysed using non-responder imputation after use of rescue therapy or withdrawal. For continuous endpoints the last observation carried forward method was used after use of rescue therapy or withdrawal. ECZTRA 3 IPD were then weighted to match the baseline summary statistics reported for patients treated with dupilumab Q2W plus TCS in LIBERTY AD CHRONOS.

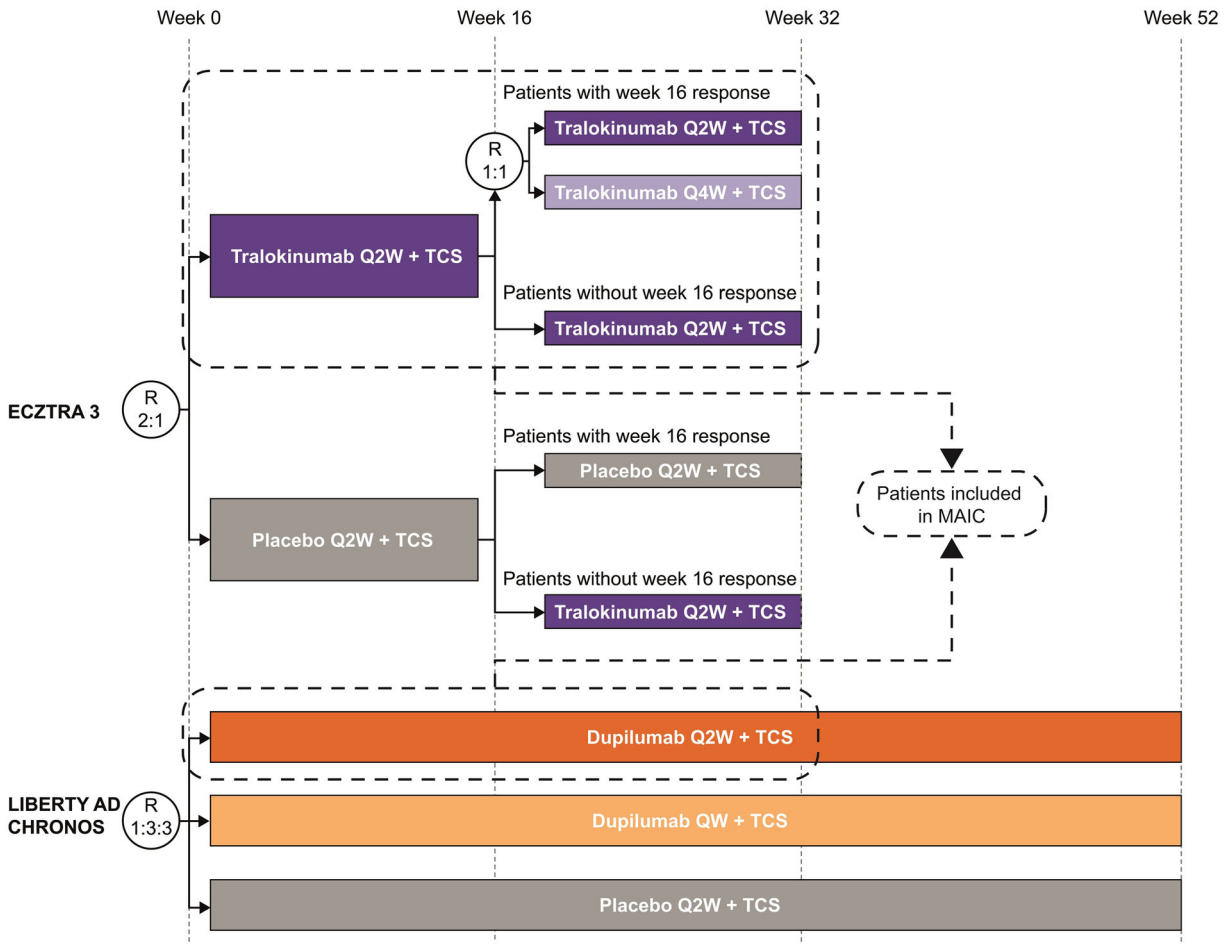

Fig. 1 Design of included randomised controlled trials. *MAIC* matching-adjusted indirect comparison, *QW* weekly, *Q2W* every 2 weeks, *Q4W* every 4 weeks, *R* randomisation, *TCS* topical corticosteroids

The baseline characteristics matched were age, sex, race, body mass index, disease duration and baseline Dermatology Life Quality Index (DLQI), EASI, IGA and SCORing Atopic Dermatitis index (SCORAD).

Study Outcomes

The clinical outcomes assessed in the MAIC were the proportion of patients achieving IGA 0/1 or EASI-50, EASI-75 or EASI-90, the mean percentage change from baseline in EASI and the mean percentage change from baseline in SCORAD.

The PROs analysed were the percentage change from baseline in the worst daily pruritus numerical rating scale (NRS), the change from baseline in DLQI and the change from baseline in the Patient Oriented Eczema Measure (POEM). Worst daily pruritus NRS results were also assessed as the proportion of patients with a $\geq$ 4-point improvement, which is considered to be a clinically meaningful change [18].

Results are reported as percentages and risk differences (RD) for binary outcomes, and as least squares means (LSM) and LSM differences for continuous outcomes.

RESULTS

Matching Populations

IPD for a total of 250 patients treated with tralokinumab in combination with TCS in ECZTRA 3 were included in the matching

process. After matching, the effective sample size was 123.4, corresponding to 49.4% of the original tralokinumab plus TCS arm from ECZTRA 3. The baseline characteristics of the matched ECZTRA 3 tralokinumab plus TCS arm were well balanced with the dupilumab plus TCS arm (Table 1).

Clinical Outcomes

Tralokinumab and dupilumab, both in combination with TCS, showed similar efficacy across clinical response endpoints at week 32 (Fig. 2). The matched proportion of patients achieving IGA 0/1 was numerically higher for tralokinumab (49.9%), compared with dupilumab (39.3%, RD 10.6%, 95% confidence interval [CI] − 2.9 to 24.0%). For the remaining clinical outcomes, the matched proportion of responders was similar for tralokinumab and dupilumab (EASI-50 78.9% vs 77.5% respectively, RD 1.3%, 95% CI − 9.9 to 12.6%; EASI-75 71.5% vs 71.9%, RD − 0.4%, 95% CI − 12.7 to 11.9%; EASI-90 53.3% vs 56.2%, RD − 2.9%, 95% CI − 16.4 to 10.7%).

Mean changes in EASI and SCORAD were similar for the matched tralokinumab and dupilumab groups (Fig. S1).

Patient-Reported outcomes

The mean change from baseline in DLQI in the matched tralokinumab population was statistically significantly larger than that in the dupilumab arm (− 12.1 vs − 10.4; LSM difference − 1.7, 95% CI − 2.9 to − 0.5, $p = 0.005$; Fig. 3). The mean change from baseline in POEM was similar for tralokinumab and dupilumab (− 12.4 vs − 13.6, LSM difference 1.2, 95% CI − 0.4 to 2.8). Improvements in worst daily pruritus NRS were similar in the matched tralokinumab and dupilumab groups (Figs. 2 and S1).

Table 1 Matched baseline characteristics

	Dupilumab	Tralokinumab	
		Unweighted	Weighted
	$N = 106$	$N = 250$	$N_{eff} = 123.4$
Age, years	39.6 (14.0)	39.8 (15.3)	39.6 (16.0)
Sex, % male	58.5	49.2	58.5
BMI, kg/m^2	25.5 (5.8)	27.6 (6.7)	25.5 (5.6)
Disease duration, years	30.1 (15.5)	27.9 (16.4)	30.1 (17.6)
Race, % white	69.8	80.4	69.8
EASI	33.6 (13.3)	28.7 (11.8)	33.6 (13.9)
IGA score	3.5 (0.5)	3.5 (0.5)	3.5 (0.5)
DLQI	14.5 (7.3)	17.6 (7.1)	14.5 (6.6)
SCORAD	69.3 (15.2)	67.0 (13.2)	69.3 (14.3)

Data are mean (SD) or percentage of patients
BMI body mass index, *DLQI* Dermatology Life Quality Index, *EASI* Eczema Area and Severity Index, *IGA* Investigator's Global Assessment, N_{eff} effective sample size, *SCORAD* SCORing Atopic Dermatitis, *SD* standard deviation

DISCUSSION

For adult patients with moderate-to-severe AD for whom topical therapies or systemic immunosuppressants are insufficiently effective, the available biological therapy options are tralokinumab and dupilumab, with lebrikizumab also recently approved in Europe [7]. In this study, we used a MAIC approach to compare the efficacy of tralokinumab and dupilumab, both in combination with TCS, at 32 weeks. Clinical efficacy results were similar between the treatments in terms of clinical endpoints and changes in worst daily pruritus NRS and POEM scores. Analysis of mean changes in DLQI showed a statistically significant difference, favouring tralokinumab, at week 32.

Recent network meta-analyses of tralokinumab and dupilumab phase 3 trials have analysed data at 16 weeks of treatment [12, 13]. One limitation of comparisons over 16 weeks is that differences in study design can have a particularly large impact in the early weeks of clinical trials. The washout period for prior

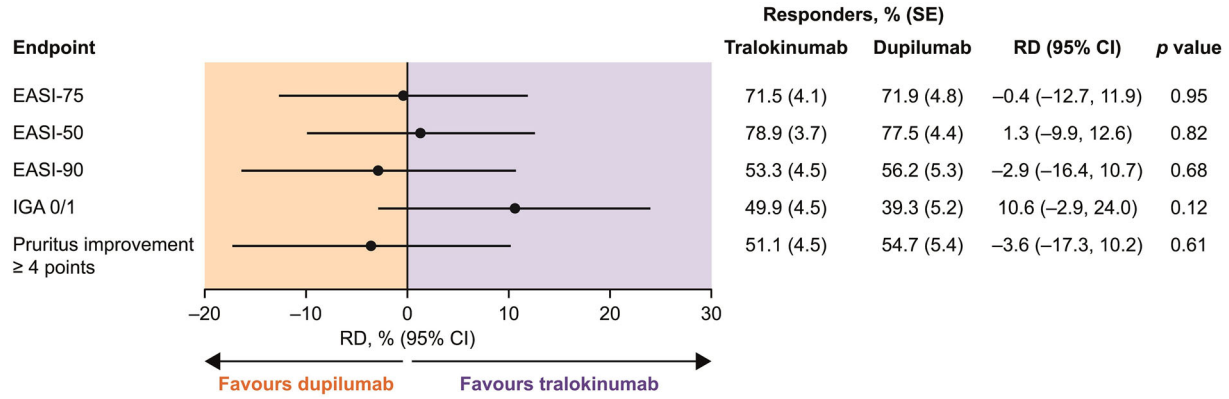

Fig. 2 Risk difference for achieving binary endpoints for tralokinumab vs dupilumab at week 32. *p* value is for 2-sided test for zero difference in proportions between tralokinumab and dupilumab. Data shown in forest plot are risk differences between tralokinumab and dupilumab; positive risk differences indicate a greater likelihood of achieving responses with tralokinumab than with dupilumab. Pruritus improvement is measured as the proportion of patients with a ≥ 4-point improvement in worst daily pruritus NRS. *CI* confidence interval, *EASI* Eczema Area and Severity Index, *IGA* Investigator's Global Assessment, *NRS* numeric rating scale, *RD* risk difference, *SE* standard error

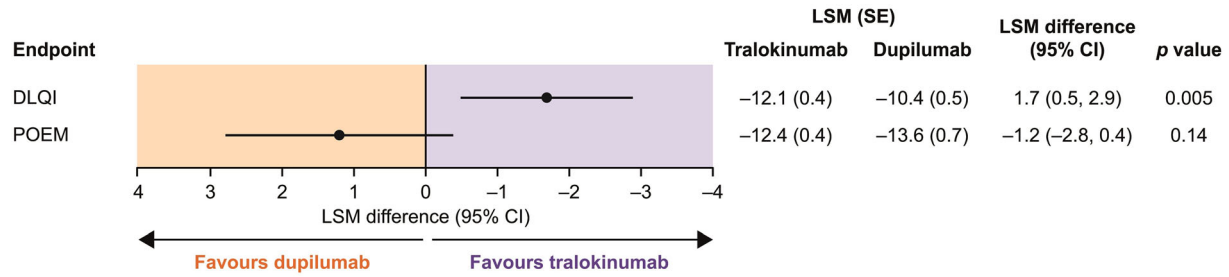

Fig. 3 Least squares mean difference in continuous endpoints for tralokinumab vs dupilumab at week 32. *p* value is for 2-sided test for zero difference between LSM changes from baseline with tralokinumab and dupilumab. Data shown in forest plot are LSM differences in changes in outcome measures; positive LSM differences indicate larger mean improvements with tralokinumab than with dupilumab. *CI* confidence interval, *DLQI* Dermatology Life Quality Index, *LSM* least squares mean, *POEM* Patient Oriented Eczema Measure, *SE* standard error

topical medication was 2 weeks in ECZTRA 3 and 1 week in LIBERTY AD CHRONOS. As suggested by Silverberg et al., a shorter washout period may lead to the severity of AD among trial participants being underestimated, skewing the enrolled population [19]. By contrast, a longer washout period may lead to some patients with relatively mild disease experiencing a flare and thereby meeting trial entry criteria they would not have met with a shorter treatment-free interval [19]. In addition, shorter washout periods may reduce the likelihood of rescue treatment being needed during the trial, due to the short time without treatment [19]. Furthermore, as recently noted by Silverberg et al., 16 weeks may be too short a time period to evaluate the full benefits of biologics in AD; clinical trials of both tralokinumab and dupilumab have found that responses continue to improve over time beyond 16 weeks of treatment [20]. AD is a chronic disease with a complex relapsing–remitting course [20], and long-term treatment is typically needed to control patients' symptoms. Together, these factors

mean that the comparative efficacy of tralokinumab and dupilumab combination therapy for treatment periods longer than 16 weeks is of considerable clinical interest.

The present analysis has shown that the two therapies, in combination with TCS, have similar efficacy at 32 weeks. It is likely that the clinical response will be close to the maximum expected by week 32, although some further increases in response rates were seen between week 32 and week 52 in the ECZTRA 1 and ECZTRA 2 trials of tralokinumab monotherapy [21]. Accordingly, these results provide valuable evidence that can help inform treatment choices for individual patients with moderate-to-severe AD.

This analysis included all patients originally randomised to tralokinumab Q2W plus TCS in ECZTRA 3, of whom approximately 30% received tralokinumab Q4W plus TCS from week 16 to week 32 [14]. This was necessary to avoid introducing bias by selecting only patients treated with tralokinumab Q2W plus TCS throughout, but may have the effect of making the results of this analysis slightly conservative with regard to the expected efficacy of 32 weeks of treatment with tralokinumab Q2W plus TCS.

MAIC, originally described by Signorovitch et al. in 2010 [16, 17], is now a well-accepted and widely used tool for the study of comparative efficacy [11]. MAIC approaches have been used in multiple disease areas [11], including a number of studies of treatments in dermatological indications. These include several comparisons of biological therapies for psoriasis [22–24], as well as a comparison of dupilumab and lebrikizumab monotherapy for AD [25]. The strength of the MAIC approach has recently been demonstrated in a study by Signorovitch et al. [26], in which the results of two MAIC analyses of psoriasis therapies were compared with those of subsequently conducted RCTs of the same pairs of therapies [26]. In both cases, comparative efficacy results were consistent between MAIC and RCT. This confirms that MAIC methods can provide valid estimates of relative treatment effects [26].

In ECZTRA 3, patients in the placebo group who did not achieve a clinical response received tralokinumab Q2W from week 16 [14]. By contrast, patients in the LIBERTY AD CHRONOS placebo group continued to receive placebo, regardless of clinical response, for the entire 52-week duration of the study [15]. Accordingly, an unanchored MAIC was conducted, allowing the therapies to be compared without the need for a common comparator [11, 16]. The reduction in effective sample size in the tralokinumab plus TCS arm after matching illustrates the extent of the difference between the two populations and the need for adjusted analyses. In addition to enabling an unbiased comparison of the two patient populations, an advantage of the MAIC approach is that inclusion and exclusion criteria could be matched between trials—this avoids the complication of inconsistent inclusion and exclusion criteria, which can impact the interpretation of comparisons between trials [19].

One remaining difference between the ECZTRA 3 and LIBERTY AD CHRONOS trials is that the use of TCS may not be comparable [14, 15]. First, as described above, LIBERTY AD CHRONOS used a shorter TCS washout period prior to randomisation [14, 15]. Second, the type of TCS used was different in the two studies [14, 15]. Third, in ECZTRA 3 TCS was supplied to patients during study visits, with all tubes returned and weighed to determine the amount of medication that had been used [14]. By contrast, in LIBERTY AD CHRONOS TCS was prescribed to patients but not supplied, and the amount used was not reported [15].

In addition to clinical efficacy, the comparative safety of systemic treatments for AD is also an important factor in clinical decision-making. However, for several reasons it was not possible to compare safety outcomes between ECZTRA 3 and LIBERTY AD CHRONOS. Data for LIBERTY AD CHRONOS are available only after 52 weeks of exposure, which might bias any safety comparison with the 32 weeks of data from ECZTRA 3. The trials also are not contemporaneous, meaning that adverse events, and particularly adverse events of interest, may not be recorded in the same way [21], but are dependent on the information on the safety of biological treatments that was available at the time of designing the trials.

The results of these analyses have some limitations. First, LIBERTY AD CHRONOS results are reported after week 16 only for a subset of the participants who were randomised to dupilumab Q2W (89 of 106 patients). Consequently, because matching was performed on the basis of aggregate data for the full analysis set for dupilumab Q2W, the matched tralokinumab population may not be completely representative of the dupilumab population for whom outcomes are reported. However, this is not expected to pose a challenge to the interpretability of the MAIC as the trial was randomised and systematic differences in characteristics are not expected between the reported subset and the overall population. Second, it was necessary to obtain some of the LIBERTY AD CHRONOS data used to inform the MAIC from figures in the published paper. Third, there were some differences between the trials, for which the MAIC process could not adjust. In particular, the amount of TCS used may not be comparable between the trials, as described above. Fourth, there were slight geographic discrepancies between the included trials. Although both studies included multiple centres in North America and Europe, LIBERTY AD CHRONOS, but not ECZTRA 3, also included centres in the Asia–Pacific region. Finally, as with all indirect comparisons, there may be some bias due to unobserved differences across the trials, for which it was not possible to adjust.

Indirect comparisons such as the MAIC analysis conducted here are well-accepted, useful methods of assessing comparative efficacy, and are the only options for doing so when no head-to-head trials have been conducted. Further indirect comparisons between tralokinumab and dupilumab, particularly if these could be conducted using longer-term data, might also provide useful information to support clinical decision-making.

CONCLUSION

The results of this analysis demonstrate that, in combination with TCS, tralokinumab and dupilumab have similar efficacy in the treatment of moderate-to-severe AD at 32 weeks of therapy.

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Data Availability. All data generated or analysed during this study are included in this published article.

Declarations

Conflict of Interest. Tiago Torres has received consultancy and/or speaker's honoraria from and/or participated in clinical trials sponsored by AbbVie, Amgen, Almirall, 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. Anne Sohrt Petersen, Ulla Ivens, Albert Bosch Vilaro, and John Stinson are employees of LEO Pharma. José Manuel Carrascosa has participated as PI/SI and/or invited speaker and/or adviser for LEO Pharma, Sanofi, Pfizer, Almirall, Lilly, AbbVie, AMGEN, and Galderma.

Ethical Approval. This analysis is based on previously conducted studies and does not contain data from any new studies with human participants or animals.

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