Clinical trials were conducted at different timepoints and Lebrikizumab 250mg Q2W had more favorable Pruritus NRS response than baseline risk (100mg QD and 200mg QD). This NMA focused on a short treatment period of 16 weeks to evaluate the relative efficacy between CrIs for abrocitinib (2mg QD and 4mg QD), dupilumab (300mg Q2W), upadacitinib (100mg and 200mg), baricitinib (2mg QD and 4mg QD), tralokinumab, and lebrikizumab and Janus kinase (JAK) inhibitors (e.g., abrocitinib, upadacitinib, and baricitinib). However, the efficacy of many treatments has not been compared in head-to-head trials.

**BACKGROUND**

- **Atopic dermatitis (AD)** is a chronic inflammatory skin disease affecting 3–9% of adults globally, with 30% experiencing moderate-to-severe disease.
- **Treatments** for moderate-to-severe AD include biologics (e.g., dupilumab, tralokinumab, and lebrikizumab) and Janus kinase (JAK) inhibitors (e.g., abrocitinib, upadacitinib, and baricitinib).

**OBJECTIVE**

- To evaluate the relative efficacy between lebrikizumab, an emerging biologic, and approved systemic AD treatments using a network meta-analysis (NMA).

**METHODS**

**Study Design**

- The NMA was based on the results of a systematic literature review and included randomized clinical trials of targeted systemic therapies (monotherapy only, published before April 2023), before any treatment is switched:
  - Abrocitinib, baricitinib, dupilumab, lebrikizumab, tralokinumab, and upadacitinib.
- Studies with a high proportion of patients who withdrew consent or that were terminated prematurely were excluded.
- Population: Adults (≥18 years) and adolescents (12–18 years) with moderate-to-severe AD.
- Time range of interest: 4–16 weeks.

**Outcome Assessments**

- Eczema Area and Severity Index (EASI): 25%, 75%, and 90% improvement in EASI scores from baseline: (EASI 25, EASI 50, EASI 75, and EASI 90).
- Investigator’s Global Assessment (IGA) of 0 (clear) or 1 (almost clear).
- Pruritus Numeric Rating Scale (NRS): 24-point improvement from baseline.

**Statistical Analysis**

- As recommended for decision-making based on evidence synthesis analyses, Bayesian methods were used to conduct analysis.
- Base-case NMA models were preferred over unadjusted models if the baseline risk coefficient was statistically significant, indicated by the 95% credible interval (CrI) that does not contain zero.
- Both fixed and random-effects (RE) models were fitted. The RE model was preferred unless the fixed-effects model had a decisively better fit, induced by a deviance information criterion of 10 points.

**RESULTS**

- Analyses of all endpoints used non-response imputation methodology.
- Meta-regression was performed to adjust for baseline severity in analysis of EASI and IGA outcomes.
- A risk of bias was evaluated using the Cochrane Collaboration’s Risk of Bias Assessment Tool.**

**Efficacy Comparison of Targeted Systemic Monotherapies Including Lebrikizumab for Moderate-to-Severe Atopic Dermatitis: a Network Meta-Analysis**

**Figure 1. Network Meta-Analysis Diagram**

**Table 1. Number Needed to Treat (Baseline-Risk Adjusted RE model)**

**Figure 2. IGA 0/1 Absolute Response Rate Estimates (Baseline-Risk Adjusted RE model)**

**Figure 3. Odds Ratios for IGA 0/1 Relative to Lebrikizumab (Baseline-Risk Adjusted RE model)**

**Figure 4. EASI-50, EASI-75, and EASI-90 Absolute Response Rate Estimates (Baseline-Risk Adjusted RE model)**

**Figure 5. Pruritus NRS at Weeks 4 and 16 After Treatment (Baseline-Risk Adjusted RE model)**

**DISCLOSURES**

- The authors have no financial or personal relationships with other people or organizations that could influence or bias their work. All authors have no conflicts of interest.

**REFERENCES**


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Efficacy Comparison of Targeted Systemic Monotherapies Including Lebrikizumab For Moderate-to-Severe Atopic Dermatitis: a Network Meta-Analysis

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Almirall, S.A. has licensed the rights to develop and commercialize lebrikizumab for the treatment of dermatology indications, including atopic dermatitis, in Europe. Lilly has exclusive rights for development and commercialization of lebrikizumab in the United States and the rest of the world outside of Europe.
INTRODUCTION

- Atopic dermatitis (AD) is a chronic inflammatory skin disease affecting 2–7% of adults globally,\(^1\) with 30% experiencing moderate-to-severe disease\(^2\)

- Treatments for moderate-to-severe AD are currently available including biologics (e.g., dupilumab, tralokinumab, and lebrikizumab) and Janus kinase (JAK) inhibitors (e.g., abrocitinib, upadacitinib, and baricitinib)\(^3,4\)

- However, the efficacy of many treatments has not been compared in head-to-head trials
To evaluate the relative efficacy between lebrikizumab, an emerging biologic, and approved targeted systemic AD treatments using a network meta-analysis (NMA)
METHODS

Study design
- The NMA was based on the results of a systematic literature review and included randomized clinical trials of targeted systemic therapies (monotherapy-only, published before April 2023), before any treatment switch:
  - Abrocitinib, baricitinib, dupilumab, lebrikizumab, tralokinumab, and upadacitinib
- Studies with a high proportion of patients that withdrew consent or that were terminated prematurely were excluded
- Population: Adults (≥18 years) and adolescents (≥12 to <18 years) with moderate-to-severe AD
- Time range of interest: 4–16 weeks

Outcome Assessments

Efficacy Outcomes
- Eczema Area and Severity Index (EASI): ≥50%, ≥70%, and ≥90% improvement in EASI scores from baseline:
  - EASI-50, EASI-75, and EASI-90
- Investigator Global Assessment (IGA) of 0 (clear) or 1 (almost clear)

Patient-Reported Outcome
- Pruritus Numeric Rating Scale (NRS): ≥4-point improvement from baseline

Statistical Analysis
- As recommended for decision-making based on evidence synthesis analyses, Bayesian methods were used to conduct both primary and secondary analyses.
- Baseline risk-adjusted models were preferred over unadjusted models if the baseline risk coefficient was statistically significant, indicated by a credible interval (CrI) that did not contain zero.
- Both fixed and random-effects (RE) models were fitted. The RE model was preferred unless the fixed effects model had a decisively better fit, indicated by a deviance information criterion of ≥5 points.
- Analyses of all endpoints used non-response imputation methodology.
- Meta-regression was performed to assess baseline EASI & IGA severity.
- Risk of bias was evaluated using The Cochrane Collaboration's Risk of Bias Assessment Tool, and NMA feasibility assessments were performed for each outcome of interest.
RESULTS

NMA results

■ The NMA analyzed 22 phase II and III randomized clinical trials of targeted systemic therapies which used the approved dosing schemes (Figure 1)

■ Goodness-of-fit statistics supported the baseline risk-adjusted RE model to analyze all outcomes

■ The estimated treatment effect did not depend on baseline severity for either EASI or IGA outcomes. This was determined through a meta-regression model which included a term that modelled the relationship between baseline severity and treatment (i.e., an interaction) in the model, however, this did not decisively improve model fit

■ All targeted systemic monotherapies for AD were more efficacious than placebo for all outcomes

■ At 12–16 weeks, the estimated response rates for the efficacy outcomes of EASI (50/75/90) and IGA 0/1 were most favorable for upadacitinib (30mg QD and 15mg QD)
RESULTS

- Lebrikizumab 250 mg Q2W had higher estimates for IGA 0/1 (Figure 2), EASI (50/75/90) (Figure 4), and lower number needed to treat (NNT) (Table 1) compared to abrocitinib 100mg QD, tralokinumab 300mg Q2W, and baricitinib (2mg QD and 4mg QD).

- The IGA 0/1 estimates for lebrikizumab 250mg Q2W were statistically comparable to dupilumab 300mg Q2W, the most widely used treatment for AD (Figure 2).

- Figure 3 shows the odds of achieving an IGA 0/1 response for all treatments versus lebrikizumab 250mg Q2W.
  - Crls for abrocitinib (100mg QD and 200mg QD), dupilumab 300 mg Q2W, and upadacitinib 15mg QD overlapped with lebrikizumab 250mg Q2W, indicating that their IGA 0/1 response rates were not statistically different.

- Figure 5 shows the Pruritus NRS response rates for all treatments at weeks 4 and 16.
  - Lebrikizumab 250mg Q2W had higher Pruritus NRS response rates among all biologics.
  - Lebrikizumab 250mg Q2W had more favorable Pruritus NRS response rates compared to JAK inhibitors baricitinib 2mg QD and abrocitinib 100mg QD.
RESULTS

Figure 1. Network Meta-Analysis Diagram

List of studies included in the NMA:
- Abrocitinib (100mg and 200mg): NCT02780167, NCT03349060, NCT03575871, and NCT03915496
- Baricitinib (2mg and 4mg): NCT03334396, NCT03334422, and NCT03435081
- Dupilumab 300mg, NCT03912259, NCT03054428, NCT02277743, NCT02277769, and NCT01859988
- Lebrikizumab 250mg: NCT04146363, NCT04178967, and NCT03443024
- Tralokinumab 300mg: NCT03131648, NCT03160885, NCT03562377, and NCT03526861
- Upadacitinib (15mg and 30mg), NCT02925117, NCT03569293, and NCT03607422

For each intervention, line weightings denote the number of studies and node weightings denote the number of patients. Abbreviations: Q2W, once every 2 weeks; QD, once daily.
RESULTS

For each trial, endpoints were measured at the primary endpoint timepoint (i.e., week 12 for abrocitinib and week 16 for all other treatments). Abbreviations: CrI, credible interval; IGA 0/1, Investigator’s Global Assessment score of 0 (clear) or 1 (almost clear); Q2W, once every 2 weeks; QD, once daily; RE, random-effects.
RESULTS

Figure 3. Odds Ratios for IGA 0/1 Relative to Lebrikizumab (Baseline-Risk Adjusted RE model)

Forest plot derived from Bayesian NMA. For each trial, endpoints were measured at the primary endpoint timepoint (i.e., week 12 for abrocitinib and week 16 for all other treatments). Abbreviations: CrI, credible interval; IGA 0/1, Investigator’s Global Assessment score of 0 (clear) or 1 (almost clear); Q2W, once every 2 weeks; QD, once daily; RE, random-effects.
For each trial, endpoints were measured at the primary endpoint timepoint (i.e., week 12 for abrocitinib and week 16 for all other treatments). Abbreviations: CrI, credible interval; EASI, Eczema Area and Severity Index; EASI-50, ≥50% improvement from baseline in the EASI score; EASI-75, ≥75% improvement from baseline in the EASI score; EASI-90, ≥90% improvement from baseline in the EASI score; Q2W, once every 2 weeks; QD, once daily; RE, random-effects.
RESULTS

Figure 5. Pruritus NRS at Weeks 4 and 16* After Treatment (Baseline-Risk Adjusted RE model)

For each trial, endpoints were measured at the primary endpoint timepoint (i.e., week 12 for abrocitinib and week 16 for all other treatments). *Primary endpoint timepoint was ≥4-Point improvement in the Pruritus NRS score between baseline and week 16. Abbreviations: CrI, credible interval; NRS, Numeric Rating Scale; Q2W, once every 2 weeks; QD, once daily; RE, random-effects.
# RESULTS

## Table 1. Number Needed to Treat (Baseline-Risk Adjusted RE model)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>EASI-50 95% CrI</th>
<th>EASI-75 95% CrI</th>
<th>EASI-90 95% CrI</th>
<th>IGA 0/1 95% CrI</th>
<th>NRS ≥4 Week 4 95% CrI</th>
<th>NRS ≥4 Week 16 95% CrI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upadacitinib 30 mg QD</td>
<td>1.665 (1.476, 1.686)</td>
<td>1.604 (1.473, 1.795)</td>
<td>1.907 (1.670, 2.253)</td>
<td>2.011 (1.735, 2.566)</td>
<td>1.736 (1.501, 2.091)</td>
<td>2.014 (1.737, 2.446)</td>
</tr>
<tr>
<td>Upadacitinib 15 mg QD</td>
<td>1.859 (1.696, 2.104)</td>
<td>2.044 (1.794, 2.426)</td>
<td>2.656 (2.209, 3.349)</td>
<td>2.836 (2.303, 3.947)</td>
<td>2.223 (1.814, 2.856)</td>
<td>2.572 (2.088, 3.265)</td>
</tr>
<tr>
<td>Abrocitinib 200 mg QD</td>
<td>1.809 (1.641, 2.039)</td>
<td>1.970 (1.713, 2.329)</td>
<td>2.529 (2.075, 3.182)</td>
<td>3.035 (2.414, 4.050)</td>
<td>2.299 (1.847, 3.124)</td>
<td>2.395 (1.941, 3.159)</td>
</tr>
<tr>
<td>Dupilumab 300 mg Q2W</td>
<td>2.263 (2.026, 2.588)</td>
<td>2.642 (2.273, 3.159)</td>
<td>3.694 (3.017, 4.667)</td>
<td>3.885 (3.114, 5.456)</td>
<td>7.450 (5.098, 11.770)</td>
<td>3.437 (2.765, 4.496)</td>
</tr>
<tr>
<td>Lebrizumab 250 mg Q2W</td>
<td>2.382 (2.030, 2.923)</td>
<td>2.819 (2.282, 3.661)</td>
<td>4.005 (3.038, 5.561)</td>
<td>3.932 (3.041, 5.327)</td>
<td>4.917 (3.420, 7.390)</td>
<td>2.928 (2.278, 3.861)</td>
</tr>
<tr>
<td>Abrocitinib 100 mg QD</td>
<td>2.653 (2.215, 3.332)</td>
<td>3.223 (2.557, 4.273)</td>
<td>4.716 (3.509, 6.678)</td>
<td>5.415 (3.897, 8.121)</td>
<td>4.382 (3.102, 7.001)</td>
<td>3.591 (2.665, 5.276)</td>
</tr>
</tbody>
</table>

For each trial, endpoints were measured at the primary endpoint timepoint (i.e., week 12 for abrocitinib and week 16 for all other treatments). For NRS, the endpoint was ≥4-point improvement in the Pruritus NRS score from baseline to weeks 4 and 16. NNT was estimated relative to placebo, with lower NNT values indicating higher efficacy. Abbreviations: CrI, credible interval; EASI, Eczema Area and Severity Index; IGA 0/1, Investigator's Global Assessment score of 0 (clear) or 1 (almost clear); NMA, network meta-analysis; NNT, number needed to treat; NRS, Numeric Rating Scale; Q2W, once every 2 weeks; QD, once daily; RE, random-effects.
LIMITATIONS

- Clinical trials were conducted at different timepoints and may have influenced the results
  - Efficacy outcomes for abrocitinib were assessed at 12 weeks rather than 16 weeks
- Absolute response estimates were influenced by placebo responses
- Slight differences in the IGA scales used between studies may have influenced the results
- The exact itch scale used in the clinical trials varied. However, the concept of itch measured by each of the scales was the same and for the comparison in the NMA they have been pooled together into one endpoint
- This NMA focused on a short treatment period of 16 weeks
This 16-week NMA shows that lebrikizumab had a similar response rate to dupilumab, the most widely used targeted systemic therapy for AD, and, if approved, may represent a valuable treatment option for moderate-to-severe AD.
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DISCLOSURES

JS has served as advisor, consultant, or speaker for AbbVie, Asana BioSciences, Dermavant, Galderma, GSK, Glenmark, Kiniksa, LEO Pharma, Eli Lilly and Company, Menlo Therapeutics, Novartis, Pfizer, Realm Pharma, and Regeneron-Sanoﬁ; and is a researcher for GSK. TB has served as consultant, investigator, or speaker for AbbVie, Affibody, Almirall, AnaptyxBio, Arena, Asana Biosciences, Aslan, Bayer Health, BioVerSys, Boehringer-Ingelheim, Bristol Myers Squibb, Connect Pharma, Dermavant, Domain Therapeutics, EQRx, Galderma, Glenmark, GSK, Incyte, Innovaderm, IQVIA, Janssen, Kirin, Kymab, LEO Pharma, LG Chem, Lilly, L’Oréal, MSD, Novartis, Numab, OM Pharma, Pfizer, Pierre Fabre, Q32bio, RAPT, Sanoﬁ/Regeneron and UCB; and is the founder and chairman of the board of Davos Biosciences. AP has served as consultant or investigator for AbbVie, Abeona, Aegeron Pharma, Azitra, BioCryst, Boehringer-Ingelheim, Bristol Myers Squibb, Castle Creek, Catawba, Dermavant, Eli Lilly, Galderma, Incyte, InMed, Janssen, Krystal, LEO Pharma, Novartis, Regeneron, Sanofi/Genzyme, Seaneergy, TWI Biotechnology, and UCB. LB has received grants and/or served as advisor, consultant, data monitoring committee member, or speaker for AbbVie, Allakos, Amgen, Arena Pharmaceuticals, AstraZeneca, Cara Therapeutics, DermTech, Evasive Pharmaceuticals, Evelo Biosciences, Genzyme, GSK, Incyte, Invea Therapeutics, Janssen, Kiniksa, LEO Pharma, Maruho/Galderma, Merck, Nektar Therapeutics, Novartis, Numab Therapeutics, Pfizer, Rapt Therapeutics, Regeneron, Ribon Therapeutics, Sanofi/Sanoﬁ-Aventis, Simpson Healthcare, Stealth BioTherapeutics, Trevi Therapeutics, UCB, Union Therapeutics, and Xencor; and owns stocks in Gilead, Medtronic, and Moderna. MK has received honoraria for lectures from AbbVie and Eli Lilly and Company. LP has received grants and/or served as consultant or speaker for AbbVie, Almirall, Amgen, Baxalta, Biogen, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Fresenius-Kabi, Janssen, JS BIOCAD, LEO Pharma, Eli Lilly and Company, Mylan, Novartis, Pfizer, Regeneron, Roche, Samsung-Bioepis, Sandoz, Sanofi, and UCB. MW has served as advisor, consultant, investigator, or speaker for AbbVie, Amgen, Arcutis, Asana BioSciences, AstraZeneca, Bausch Health, Bristol Myers Squibb, Celgene, Dermira, Eli Lilly and Company, Galderma, Glenmark, Incyte, Janssen, La Roche-Posay, LEO Pharma, Novartis, Pfizer, Principia, PRCL Research, Regeneron, Sanofi, and UCB. KE has served as consultant for AbbVie, Almirall, Bristol Myers Squibb, Incyte, La Roche-Posay, MSD, Pfizer, Pierre Fabre, and Sanofi. PF received funding/honoraria and served as advisor, consultant, investigator, or speaker for AbbVie, Amgen, ArGenx, Arcutis, Aslan, AstraZeneca, Boehringer Ingelheim, Botanix, Bristol Myers Squibb, Celgene, Celitasys, CSL, Cutanea, Dermira, Eli Lilly and Company, EVELO, Galderma, Genentech, Geneseeq, GenesisCare, GSK, Hexima, Incyte, Kymab, Janssen, LEO Pharma, Mayne Pharma, MedImmune, Merck, Novartis, Pfizer, Regeneron Pharmaceuticals, Reistone, Roche, Sanofi, Sun Pharma, Takeda, Teva, UCB, and Valeant. EJ, MD, and MC are employees of Eli Lilly and Company. BA is an employee of Almirall. AK is an employee of Costello Medical, which was funded by Eli Lilly and Company to provide analytical services for this publication. RC has served as an advisor, consultant, investigator, or speaker for AbbVie, Apogee Therapeutics, Arcutis, ArGenx, Aslan, Beiersdorf, Boehringer Ingelheim, Bristol Myers Squibb, Cara Therapeutics, Dermavant, Eli Lilly and Company, FIDE, Galderma, Genentech, Incyte, Janssen, LEO Pharma, L’Oreal, Nektar Therapeutics, Novan, Opsdiao, Pfizer, Regeneron, RAPT, Sanofi, and UCB.

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