Safety Profile of Lebrikizumab in Adults and Adolescents with Moderate-to-Severe Atopic Dermatitis: Integrated Data Used in the US Prescribing Information

Linda Stein Gold,[1] Gaia Gallo,[2] Maria Lucia Buziqui Piruzeli,[2] Fangyi Zhao,[2] Sarah Reifeis,[2] Hany Elmaraghy,[2] Mark Lebwohl[3]

[1]Henry Ford Health System, Detroit, MI, USA; [2]Eli Lilly and Company, Indianapolis, IN, USA; [3]Mount Sinai, New York, NY, USA

Sponsored by Eli Lilly and Company

OBJECTIVE

- Lebrikizumab has recently been approved in the United States for the treatment of moderate-to-severe AD.
- Safety data have been reported in individual trial disclosures and multiple long-term integrated analyses of lebrikizumab.
- Lebrikizumab has no boxed warning on its USPI, is not an immunosuppressant or steroid, requires no laboratory monitoring, and has no expected drug–drug interactions and no significant hepatic metabolism or renal elimination.
- Here we present integrated safety data from the USPI (cutoff date: June 6, 2022).

CONCLUSIONS

- For the adverse reactions reported in the lebrikizumab USPI, the majority were mild to moderate in severity and few led to treatment discontinuation.
- The incidence of conjunctivitis and keratitis decreased with longer exposure to lebrikizumab.
- There was no imbalance between placebo and lebrikizumab in the frequency of patients reporting the preferred term of arthralgia.

Abbreviations: AD, atopic dermatitis; AE, adverse event; EAIR, exposure-adjusted incidence rate; N, number of patients in the analysis population; n, number of patients in the specified category; Q2W, every 2 weeks; Q4W, every 4 weeks; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid; TEAE, treatment-emergent adverse event; US, United States; USPI, US prescribing information.

Winter Clinical Hawaii; Big Island, Waikoloa Village, HI, USA; February 14–19, 2025

RESULTS

Adverse Reactions Occurring in ≥1% of the Lebrikizumab Monotherapy Group or the Lebrikizumab + TCS Group During the Placebo-Controlled Period (Weeks 0–16)

Patients With ≥1 Event, n (%)	Lebrikizumab Monotherapy[a]		Lebrikizumab + TCS[b]	
	Lebrikizumab 250 mg Q2W[c] (N=638)	Placebo (N=338)	Lebrikizumab 250 mg Q2W[c] + TCS (N=145)	Placebo + TCS (N=66)
Conjunctivitis cluster[d]	61 (9.6)	10 (3.0)	7 (4.8)	0 (0.0)
Injection site reactions[e]	16 (2.5)	4 (1.2)	4 (2.8)	1 (1.5)
Herpes zoster	3 (0.5)	0 (0.0)	2 (1.4)	0 (0.0)

[a] Integrated analysis of ADvocate1, ADvocate2, and the phase 2 dose-finding trial KGAF; [b] Analysis of the TCS combination therapy trial ADhere; [c] Lebrikizumab 500 mg at Week 0 and Week 2, followed by 250 mg Q2W; [d] Conjunctivitis cluster includes conjunctivitis, conjunctivitis allergic, and conjunctivitis bacterial; [e] Injection site reactions cluster includes injection site-related: pain, erythema, reaction, discomfort, dermatitis, pruritus, swelling, and rash.

- All events were nonserious.
- All conjunctivitis events were mild or moderate and the majority did not lead to treatment discontinuation.
- Most injection site reactions were mild or moderate and did not lead to treatment discontinuation.
- No events of herpes zoster were severe, and none led to treatment discontinuation. All herpes zoster cases were localized, and none were found to be opportunistic infections (multidermatomal or disseminated).

Adverse Reactions Occurring in <1% of the Lebrikizumab Monotherapy Group or the Lebrikizumab + TCS Group During the Placebo-Controlled Period (Weeks 0–16)

Eosinophilia

- Increased postbaseline blood eosinophils were observed at a higher frequency in lebrikizumab-treated patients compared to patients receiving placebo.
- During the first 16 weeks, eosinophilia (>5000 cells/µL) was observed in 0.4% of lebrikizumab-treated patients and 0.0% of patients receiving placebo.
- Blood eosinophil elevations were generally transient and did not result in discontinuation.
- No eosinophil-related AEs were reported.

Keratitis Cluster

- Monotherapy trials:
  - n=4 (0.6%) in the lebrikizumab 250 mg Q2W group and n=1 (0.3%) in the placebo group
- TCS combination therapy trial:
  - n=1 (0.7%) in the lebrikizumab 250 mg Q2W group and none in the placebo group
- All events were nonserious and mild or moderate in severity.
- Keratitis led to treatment discontinuation in 2 patients across the monotherapy and TCS combination therapy trials.

Conjunctivitis and Keratitis Clusters

The Incidence of Conjunctivitis and Keratitis Decreased With Longer Exposure to Lebrikizumab

	Pooled Placebo-Controlled Period (Weeks 0–16)[a]		Weeks 0–52/56[b]	
	Lebrikizumab 250 mg Q2W (N=783)	Placebo (N=404)	Lebrikizumab 250 mg Q2W (N=844)	Lebrikizumab 250 mg Q2W/Q4W (N=147)
	EAIR/100 Patient-Years at Risk[c]			
Conjunctivitis cluster[d]	30.4	8.9	18.3	20.6
Keratitis cluster[e]	2.2	0.9	1.0	0.7

[a] Pooled analysis of the monotherapy trials (ADvocate1, ADvocate2, and the phase 2 dose-finding trial KGAF) and the TCS combination therapy trial (ADhere); [b] Pooled analysis of ADvocate1, ADvocate2, ADhere, and ADjoin; [c] EAIRs were calculated as the number of patients reporting a TEAE per 100 patient-years at risk; [d] Conjunctivitis cluster includes conjunctivitis, conjunctivitis allergic, conjunctivitis bacterial, and conjunctivitis viral; [e] Keratitis cluster includes keratitis, vernal keratoconjunctivitis, and atopic keratoconjunctivitis.

- Conjunctivitis cluster (Weeks 16-52):
  - All events were mild or moderate in severity.
  - Conjunctivitis led to treatment discontinuation in 2 patients in the lebrikizumab 250 mg Q4W group.
- Keratitis cluster (Weeks 16-52):
  - One keratitis event was severe and led to treatment discontinuation in the lebrikizumab 250 mg Q2W group.

Treatment Discontinuation Due to AEs During the Placebo-Controlled Period

Patients With ≥1 Event, n (%)	Lebrikizumab Monotherapy[a]		Lebrikizumab + TCS[b]	
	Lebrikizumab 250 mg Q2W[c] (N=638)	Placebo (N=338)	Lebrikizumab 250 mg Q2W[c] + TCS (N=145)	Placebo + TCS (N=66)
Treatment discontinuation due to AEs	15 (2.4)	6 (1.8)	3 (2.1)	0 (0.0)

[a] Integrated analysis of ADvocate1, ADvocate2, and the phase 2 dose-finding trial KGAF; [b] Analysis of the TCS combination therapy trial ADhere; [c] Lebrikizumab 500 mg at Week 0 and Week 2, followed by 250 mg Q2W.

- The most common adverse reactions leading to discontinuation of lebrikizumab versus placebo were:
  - Monotherapy trials: conjunctivitis and keratitis (0.8% vs 0.3%) and injection site reactions (0.2% vs 0.0%)
  - TCS combination therapy trial: conjunctivitis (0.7% vs 0.0%) and injection site reactions (0.7% vs 0.0%)

METHODS

Study Design

Placebo-controlled dataset (4 studies)

- Studies: ADvocate1, ADvocate2, ADhere, and KGAF
- Treatment duration: Weeks 0–16
- Treatment:
  - ADvocate1, ADvocate2, and ADhere studies: randomized 2:1 to lebrikizumab 250 mg Q2W or placebo
  - KGAF study: randomized 3:3:3:2 to lebrikizumab 125 mg Q4W, lebrikizumab 250 mg Q4W, lebrikizumab 250 mg Q2W, or placebo Q2W
- **Monotherapy studies (ADvocate1, ADvocate2, and KGAF):**
  - N=638 treated with lebrikizumab 250 mg Q2W
  - N=338 treated with placebo
- **TCS combination therapy study (ADhere):**
  - N=145 treated with lebrikizumab 250 mg Q2W
  - N=66 treated with placebo

Maintenance period (2 studies)

- Studies: ADvocate1 and ADvocate2
- Treatment duration: Weeks 16–52
- Treatment: patients treated with lebrikizumab 250 mg Q2W who responded at Week 16 were rerandomized 2:2:1 to lebrikizumab 250 mg Q2W, lebrikizumab 250 mg Q4W, or placebo (lebrikizumab withdrawal) until Week 52
  - N=113 treated with lebrikizumab 250 mg Q2W
  - N=118 treated with lebrikizumab 250 mg Q4W
  - N=60 treated with placebo

Weeks 0–52/56 dataset (4 studies)

- Studies: ADvocate1, ADvocate2, ADhere, and ADjoin
- Treatment duration: Weeks 0–52/56
- Treatment: patients treated with lebrikizumab 250 mg Q2W only or lebrikizumab 250 mg Q2W then lebrikizumab 250 mg Q4W up to 52 or 56 weeks
  - N=844 treated with lebrikizumab 250 mg Q2W
  - N=147 treated with lebrikizumab 250 mg Q2W/Q4W

Note: Data cutoff date was June 6, 2022. ClinicalTrials.gov identifiers: ADvocate1, NCT04146363; ADvocate2, NCT04178967; KGAF, NCT03443024; ADhere, NCT04250337; ADjoin, NCT04392154.
[a] Placebo controlled; [b] TCS/TCI use was permitted during the maintenance period of ADvocate1 and ADvocate2; [c] Modified safety population, defined as patients who received ≥1 dose of study treatment, excluding 38 patients from 1 study site (17 patients in ADhere who continued in ADjoin, 18 patients in ADvocate2 who continued in ADjoin, and 3 patients in ADjoin, as the patient eligibility criteria could not be confirmed); [d] Low (1% hydrocortisone) to mid (0.1% triamcinolone acetonide), potency TCS for AD symptoms and TCI were permitted for use on sensitive skin areas; [e] This study has direct entry patients in addition to patients from parent studies; [f] This study was ongoing at the time of this analysis.

Assessments and Statistical Analyses

- Study size-adjusted percentages were calculated for the pooled placebo-controlled analysis of the monotherapy studies and for the maintenance period.
- EAIRs were calculated as the number of patients reporting a TEAE per 100 patient-years at risk.
  - Time at risk was calculated as the sum of time to the first event for patients who experienced the TEAE and the time during the interval for patients who did not experience the TEAE.
- For AEs analyzed as a cluster, searches of the following preferred terms were conducted:
  - Conjunctivitis: conjunctivitis; conjunctivitis allergic; conjunctivitis bacterial; conjunctivitis viral; and giant papillary conjunctivitis
  - Keratitis: keratitis; allergic keratitis; ulcerative keratitis; vernal keratoconjunctivitis; and atopic keratoconjunctivitis

RESULTS

No Imbalance Between Placebo and Lebrikizumab for the Preferred Term of Arthralgia during Induction

Patients With ≥1 Event, n (%)	Pooled Placebo-Controlled Period (Weeks 0–16)[a]		Weeks 0–52/56[b]	
	Lebrikizumab 250 mg Q2W (N=783)	Placebo (N=404)	Lebrikizumab 250 mg Q2W (N=844)	Lebrikizumab 250 mg Q2W/Q4W (N=147)
Arthralgia	6 (0.8)	3 (0.7)	11 (1.3)	1 (0.7)

[a] Pooled analysis of the monotherapy trials (ADvocate1, ADvocate2, and the phase 2 dose-finding trial KGAF) and the TCS combination therapy trial (ADhere); [b] Pooled analysis of ADvocate1, ADvocate2, ADhere, and ADjoin.

- Continued low frequency of arthralgia in patients on lebrikizumab maintenance (Weeks 52/56).

Disclosures: LSG is an investigator, consultant, and/or speaker for AbbVie, Amgen, Arcutis, Bristol Myers Squibb (BMS), Dermavant, Eli Lilly and Company (Lilly), Galderma, Incyte, Janssen, Novartis, Ortho Dermatologics, Pfizer, Regeneron, Sanofi, and UCB Pharma. **GG**, **MLBP**, **FZ**, **SR**, and **HE** are employees and shareholders of Lilly. **ML** is an employee of Mount Sinai and receives research funds from AbbVie, Arcutis, Avotres, Boehringer Ingelheim (BI), Cara Therapeutics, Clexio Biosciences, Dermavant, Lilly, Incyte, Inozyme, Janssen, Pfizer, Sanofi-Regeneron, and UCB Pharma; and is a consultant for Almirall, AltruBio, Apogee, Arcutis, AstraZeneca, Atomwise, Avotres, BI, BMS, Castle Biosciences, Celltrion, CorEvitas, Dermavant, Dermsquared, Evommune, FIDE, Forte Biosciences, Galderma, Genentech, Incyte, LEO Pharma, Meiji Seika Pharma, Mindera, Pfizer, Sanofi-Regeneron, Seanergy, STRATA Skin Sciences, Takeda, Trevi Therapeutics, and Verrica Pharmaceuticals.

Acknowledgments: Medical writing assistance was provided by Kathy Oneacre, MA, CMPP, of Syneos Health, and was funded by Lilly.