Supplementary Material

Safety of lebrikizumab in adults and adolescents with moderate-to-severe atopic dermatitis: an integrated analysis of eight clinical trials

Linda Stein Gold[1], Diamant Thaçi[2], Jacob P Thyssen[3], Melinda Gooderham[4], Vivian Laquer[5], Angela Moore[6] Chitra R. Natalie[7], Fangyi Zhao[7], Eric Meskimen[7], Hany Elmaraghy[7], Sonia Montmayeur[7], Gaia Gallo[7], Gemma Jimenez[8], Marjolein de Bruin-Weller[9]

[1]Henry Ford Health System, Detroit, USA; [2] Institute and Comprehensive Center for Inflammation Medicine University of Lübeck, Lübeck, DE; [3]Bispebjerg Hospital, University of Copenhagen, Copenhagen, DK; [4]Skin Centre for Dermatology and Queen's University, Ontario, CA; [5]University of California, Irvine, Irvine, CA, USA; [6] Arlington Research Center, Arlington, TX, USA; Baylor University Medical Center, Dallas, TX, USA; [7]Eli Lilly and Company, Indianapolis, IN, USA; [8]Almirall, S.A., Barcelona, ESP; [9]University Medical Center Utrecht, Utrecht, NL

Corresponding author:
Linda Stein Gold, MD
Director of Clinical Research
Department of Dermatology
Henry Ford Health
Detroit, MI
lstein1@hfhs.org
Office: 248-661-8764
Cell: 248-884-5356

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Supplemental Table 1. Lebrikizumab trials included in the integrated analysis

Study	Treatments	Patients	Analysis dataset Lebrikizumab therapy Treatment period (weeks) Randomization	Study status Data cutoff for this analysis
		PHASE 2		
ARBAN (NCT02465606)	LEB 125mg Q4W (N=28) TCS (N=27)	Adult patients (18-75 years) with moderate-to-severe AD with inadequate response to TCS	All-LEB Monotherapy 12 1:1 (open-label)	Completed July 26, 2016
TREBLE (NCT02340234)	LEB 250mg single dose + TCS (N=53) LEB 125mg single dose + TCS (N=53) LEB 125mg Q4W + TCS (N=52) PBO Q4W + TCS (N=54)	Adult patients (18-75 years) with moderate-to-severe AD with inadequate response to TCS	All-LEB In combination with TCS 12 1:1:1:1	Completed June 29, 2016
Phase 2b KGAF (NCT03443024)	LEB 125mg Q4W[h] (N=73) LEB 250mg Q4W[i] (N=80) LEB 250mg Q2W[a] (N=75) PBO Q2W (N=52)	Adult patients (≥18 years) with moderate-to-severe AD for whom topical treatment was inadequate or inadvisable	Placebo-controlled, All-LEB Monotherapy 16 3:3:3:2	Completed May 23, 2019
		PHASE 3		

Study	Treatments	Patients	Analysis dataset Lebrikizumab therapy Treatment period (weeks) Randomization	Study status Data cutoff for this analysis
ADvocate1 NCT04146363	*Induction period* LEB 250mg Q2W[a] (N=283) PBO (N=141) *Maintenance blinded period* LEB 250mg Q2W (N=72) LEB 250mg Q4W (N=73) PBO (N=36) *Maintenance escape period* LEB 250 mg Q2W (N=202)	Adults and adolescents (≥12 to <18 years and ≥40 kg weight) with moderate-to-severe AD for whom topical treatment was inadequate or inadvisable	Placebo-controlled, All-LEB Monotherapy *Monotherapy Induction period* 16 weeks 2:1 *Maintenance period* 36 weeks 2:2:1	Completed April 29, 2022
ADvocate2[b] NCT04178967	*Induction period* LEB 250mg Q2W[a] (N=281) PBO (N=146) *Maintenance blinded period* LEB 250mg Q2W (N=61) LEB 250mg Q4W (N=63) PBO (N=32) *Maintenance escape period* LEB 250mg Q2W (N=233)	Adults and adolescents (≥12 to <18 years and ≥40 kg weight) with moderate-to-severe AD for whom topical treatment was inadequate or inadvisable	Placebo-controlled, All-LEB Monotherapy *Monotherapy Induction period* 16 weeks 2:1 *Maintenance period* 36 weeks 2:2:1	Completed May 3, 2022

Study	Treatments	Patients	Analysis dataset Lebrikizumab therapy Treatment period (weeks) Randomization	Study status Data cutoff for this analysis
ADhere[b] NCT04250337	LEB 250mg Q2W[a] + TCS (N=145) PBO + TCS (N=66)	Adults and adolescents (≥12 to <18 years and ≥40 kg weight) with moderate-to-severe AD for whom topical treatment was inadequate	Placebo-controlled, All-LEB In combination with TCS 16 weeks 2:1	Completed December 16, 2021
ADore NCT04250350	LEB 250mg Q2W[a] (N=206)	Adolescents (≥12 to <18 years and ≥40 kg weight) with moderate-to-severe AD for whom topical treatment was inadequate or inadvisable	All-LEB Monotherapy[j] 52 weeks N/A	Completed May 12, 2022
LTE				
ADjoin[b] NCT04392154	LEB 250mg Q2W[c,d,e,f] LEB 250mg Q4W	Adult and adolescent patients with moderate-to-severe AD including those that completed studies ADvocate 1, ADvocate 2, ADhere, ADore, and ADopt-VA[g].	All-LEB Monotherapy[j] 100 weeks	Ongoing July 6, 2022

[a]Loading dose: lebrikizumab 500 mg SC at baseline and Week 2.
[b]Modified safety population as defined in Methods section. 228 patients enrolled, 211 patients analyzed
[c]Treatment assignment is based on treatment regimen in the parent study, except for participants who are enrolled into the open-label addendum.
[d]Patients who were receiving placebo in the parent study prior to rolling over to Study Adjoin received lebrikizumab 250 mg Q2W with a loading dose of 500 mg at the time of enrollment (baseline) and at Week 2.
[e]Patients in Study Adjoin addendum (1) received open-label 250 mg lebrikizumab Q2W with a loading dose of 500 mg at baseline and Week 2.
[f]Includes participants from the Study Adjoin addendum (2).
[g]Note, data from Study KGAK participants included in Study KGAA is not part of the integrated database.
[h]Loading dose: lebrikizumab 250mg SC at baseline
[i]Loading dose: lebrikizumab 500mg SC at baseline
jIntermittent use of topical rescue medications (e.g., low- and mid-potency TCS, TCIs and PDE4 inhibitors) for AD is permitted for the treatment of disease flares during the trial.
Abbreviations: AD, atopic dermatitis; LEB, lebrikizumab; LTE, long-term extension; N/A, not applicable; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks; TCS, topical corticosteroids

Supplemental Table 2. Safety outcomes definitions

Safety Outcome	Definition/Assessment
TEAEs (AEs were classified based on the MedDRA, version 25.0)	
TEAE	A TEAE was defined as an event that first occurred or worsened in severity after the first dose of study treatment and on or prior to the last visit date during the analysis period)
SAE	An SAE was any event meeting the 21 Code of Federal Regulations (CFR) 312.21 (a) (CFR 2010) and International Conference on Harmonisation (ICH) E2A criteria (ICH 1994) and included any AE that resulted in • death • initial or prolonged inpatient hospitalization • a life-threatening experience (that is, immediate risk of dying) • persistent or significant disability or incapacity • congenital anomaly or birth defect, and • other important medical events at the discretion of the investigator
TEAE leading to permanent discontinuation of study drug	When study drug was permanently discontinued because of an adverse event either as defined in the study protocol or determined by the investigator
Special Safety Topics	
Infections	Infections were defined using all the PTs with primary mapping from the Infections and infestations SOC as defined in MedDRA. Serious infections were defined as all infections that met the SAE criteria.
Herpes infections including herpes zoster	Herpes infections were defined using the high-level term herpes viral infection, with herpes OIs defined based on MedDRA (both narrow and broad terms)
Parasitic infection	Parasitic (helminth) infections were defined based on the MedDRA high-level terms: cestode infections, helminthic infections NEC, nematode infections, and trematode infections. In addition, parasitic OIs were defined using MedDRA PT (both narrow and broad terms) under the following categories: Trypanosoma cruzi infection (Chagas' Disease) (progression of chronic and disseminated disease only); Cryptosporidium species (chronic disease only); Leishmaniasis (Visceral only); Strongyloides (hyperinfection syndrome and disseminated forms only); and Toxoplasmosis (myocarditis, pneumonitis, or characteristic retinochoroiditis only).
Potential Opportunistic infections (OIs)	Potential OIs were identified using a list of MedDRA PTs created to align with the consensus recommendations for reporting OIs in clinical trials and postmarketing surveillance of drugs used to treat immune-mediated

	inflammatory diseases. For this analysis, OIs were defined according to Winthrop et al. 2015, with the following Modification
	
	• Localized herpes zoster infections were not considered opportunistic. Only multidermatomal infections, disseminated infections, or a combination of these were considered opportunistic.
	
	  • Multidermatomal was defined as involvement beyond primary and adjacent dermatomes (that is, 4 or more contiguous dermatomes) or involvement of 2 or more noncontiguous dermatomes, and
	
	  • Disseminated was defined as systemic infection, visceral, or widespread cutaneous (for example, 5 or more dermatomes or from 3 to 4 dermatomes including at least 1 noncontiguous [nonadjacent]). Treatment-emergent, active tuberculosis infections were summarized separately from opportunistic infections
	
	The cases of potential OIs were medically reviewed internally by 2 physicians and clinical research scientists, prior to database locks of each study. These separate reviews were completed to determine whether any event met the definition of confirmed OIs.

Conjunctivitis	Conjunctivitis as identified for this analysis referred broadly to several ocular symptoms and disorders, including blepharitis, conjunctivitis of various etiologies (that is, bacterial, viral, allergic), keratitis, and dry eye. After review of blinded data, the following clusters were identified for conjunctivitis, keratitis and other ocular events and symptoms, defined by MedDRA preferred terms. The Conjunctivitis cluster is defined by • Conjunctivitis • Conjunctivitis allergic • Conjunctivitis bacterial • Conjunctivitis viral, and • Giant papillary conjunctivitis. The Keratitis cluster is defined by • Keratitis • Atopic keratoconjunctivitis • Allergic keratitis • Ulcerative keratitis, and • Vernal keratoconjunctivitis. The MedDRA preferred term “Blepharitis” was also analyzed.
Malignancy	Malignancies were defined using preferred terms from the Malignant tumors SMQ (SMQ 20000194), including sub-SMQs of 20000227 (Haematological malignant tumors) and 20000228 (Non-haematological malignant tumors). Malignancies were summarized separately for the

	following categories: • NMSC, and • Malignancies excluding NMSC.
Eosinophilia	TEAEs of eosinophilia and eosinophil-related disorders were summarized using the following MedDRA PTs • Eosinophil-related disorder was defined as all PTs under high-level term of eosinophil disorders except the following: o Eosinophilia o Allergic eosinophilia • Eosinophilia was defined as 2 PTs of eosinophilia and allergic eosinophilia and the following PTs under the high-level term of white blood cell analysis: o Eosinophil count abnormal o Eosinophil count increased o Eosinophil percentage increased
Laboratory analysis	
Eosinophil changes	Shifts in eosinophil increases were evaluated according to the following categories: • Normal (<500 per microliter) • Mild (500 to <1500 per microliter) • Moderate (1500 to <5000 per microliter), and • Severe (≥5000 per microliter)

Abbreviations: ICH, International Conference on Harmonisation; MedDRA, Medical Dictionary for Regulatory Activities; NMSC, nonmelanoma skin cancer; OI, opportunistic infection; PT, preferred term; SAE, serious adverse events; SMQ, standardized MedDRA queries; SOC, system organ class; TE, treatment-emergent; TEAE, treatment-emergent adverse events

Supplemental Table 3. Eosinophil changes

	All-PC Week 0-16		All-LEB
	Placebo N=404 Nx=386 n (adj %)	**LEB 250 mg Q2W** N=783 Nx=768 n (adj %)	N=1720 Nx=1681 n (%)
Shift type			
Normal to mild	49 (12.7)	122 (15.9)	322 (19.2)
Normal to moderate	2 (0.5)	3 (0.4)	18 (1.1)
Normal to severe	0	0	1 (0.1)
Mild to moderate	14 (3.6)	53 (6.9)	131 (7.8)
Mild to severe	0	1 (0.1)	4 (0.2)
Moderate to severe	0	2 (0.3)	3 (0.2)

Abbreviations: adj %, study size adjusted percentage; LEB, lebrikizumab; N, number of patients in the analysis population; n, number of patients in the specified category; Nx, number of patients with a baseline and at least 1 post baseline value; Q2W, every 2 weeks

Eosinophil categories: normal (<500 per microliter), mild (500 to <1500 per microliter), moderate (1500 to <5000 per microliter), severe (≥5000 per microliter).

Note: Percentage is calculated by n/Nx*100%.

Fig. 1 Study designs