Supplemental Online Content

Simpson EI, Gooderham M, Wollenberg A, et al. Efficacy and safety of lebrikizumab in combination with topical corticosteroids in adolescents and adults with moderate-to-severe atopic dermatitis: a randomized clinical trial (ADhere). *JAMA Dermatol.* Published online January 11, 2023. doi:10.1001/jamadermatol.2022.5534

This supplemental material has been provided by the authors to give readers additional information about their work.

eMethods

Inclusion Criteria

To be eligible for the study, a patient must have

- been an adult or an adolescent (≥12 to <18 years weighing ≥40 kg),
- had a diagnosis of chronic atopic dermatitis (AD), as defined by the American Academy of Dermatology Consensus Criteria, for at least 1 year before the screening visit,
- had moderate-to-severe AD, defined as having all the following at the Baseline visit:
    - Eczema Area and Severity Index ≥16
    - Investigator's Global Assessment for AD ≥3
    - body surface area ≥10%, and
- been a candidate for systemic therapy.

Exclusion Criteria

Due to the required use of topical corticosteroids (TCS) during ADhere, a notable exclusion criterion for the study was having had an important side effect to TCS such as

- intolerance to treatment,
- hypersensitivity reactions,
- significant skin atrophy, or
- systemic effects

as assessed by the investigator or treating physician that would prevent further use.

Statistical Analyses

Primary and Secondary Estimands

Three types of estimands were used to handle missing data in the analyses. The primary estimand was used for all primary and major secondary endpoints. Two secondary estimands were also used, 1 for all categorical endpoints and 1 for all continuous endpoints. All estimands were used in the modified intent-to-treat population.

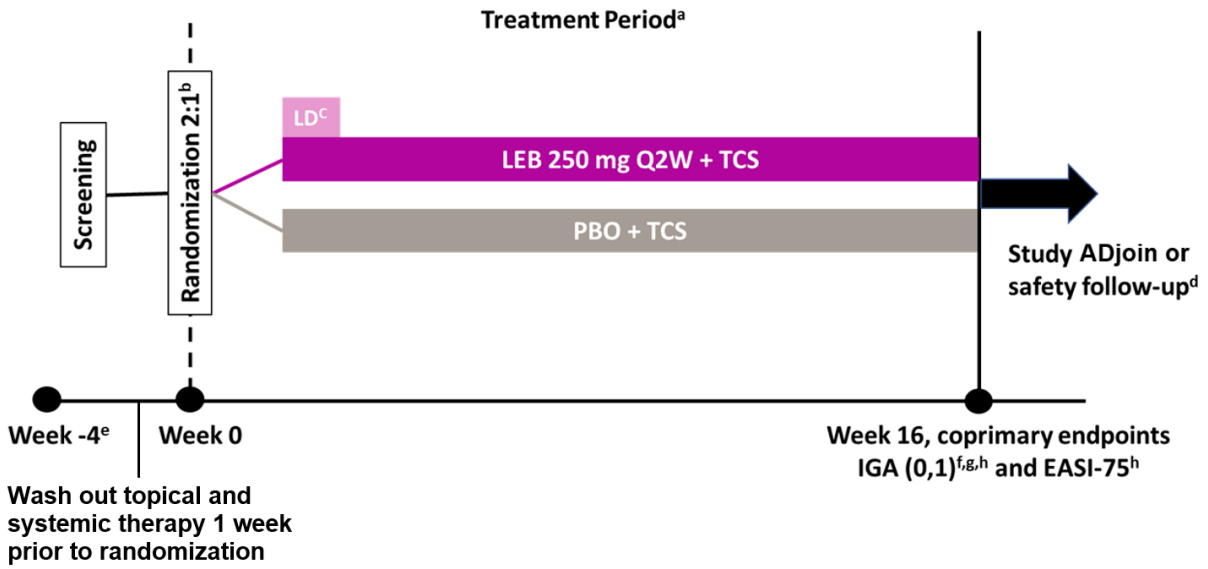
Description of Primary and Supportive Estimands

Estimand	Analysis Strategy for Intercurrent Events			Missing Data Imputation Method
	ICE: Rescue Medication	ICE: Treatment Discontinuation		
		Due to Lack of Efficacy	Due to Any Other Reasons	
Primary estimand (Hybrid)	Composite: Set to baseline	Composite: Set to baseline	Hypothetical: Set to missing	Primary analysis: MCMC-MI Sensitivity analysis: Tipping point analysis
Supportive estimand for categorical endpoints (Composite)	Composite: Set to nonresponder	Composite: Set to nonresponder	Composite: Set to nonresponder	NRI
Supportive estimand for continuous endpoints (Hypothetical)	Hypothetical: Set to missing	Hypothetical: Set to missing	Hypothetical: Set to missing	MMRM, LOCF

Abbreviations: ICE, intercurrent event; LOCF, last observation carried forward; MCMC-MI, Markov Chain Monte Carlo multiple imputation; MMRM, mixed-model repeated measures; NRI, nonresponder imputation.

More details about estimands and missing value imputation analysis are described in the statistical analysis protocols. Outcomes based on supportive estimands are shown in **eTable 1.**

eFigure: Study Design



Abbreviations: AD, atopic dermatitis; EASI-75, 75% reduction in the Eczema Area and Severity Index; EMA, European Medicines Agency; FDA, Food and Drug Administration; IGA, Investigator's Global Assessment; LD, loading dose; LEB, lebrikizumab; LTE, long-term extension; PBO, placebo; Q2W, every 2 weeks; TCS, topical corticosteroid; W, Week.

[a] Use of TCS was required at Baseline but could be used, tapered, stopped, and resumed as needed after that.
[b] A total of 228 participants with moderate-to-severe AD, including 53 adolescent participants.
[c] 500 mg loading dose at W0 and W2.
[d] Participants who completed ADhere had the option to enroll in ADjoin long-term extension. Otherwise, participants entered a safety follow-up period for 12 weeks after their last dose.
[e] ≤30-day screening period.
[f] IGA (0,1) with ≥2-point improvement from Baseline.
[g] FDA primary endpoint.
[h] EMA co-primary endpoint.

eTable 1: Summary of Efficacy Outcomes in the mITT Population

Variable	Observed Values: n, Mean (SD) for continuous endpoints n/N, (%) (95% CI) for categorical endpoints		Analysis Results: N, LS Mean (SE) for continuous endpoints n/N, % (95% CI) for categorical endpoints		
	PBO + TCS (N=66)	LEB + TCS (N=145)	PBO + TCS (N=66)	LEB + TCS (N=145)	Treatment Difference
Primary Endpoints					
IGA (0,1) and ≥2-point improvement from Baseline at Week 16	13/53 (24.5) (12.9, 36.1)	57/130 (43.8) (35.3, 52.4)	15/66, (22.1) (11.6, 32.7)	60/145, (41.2) (33.0, 49.4)	18.3 (5.1, 31.5)*
Key Secondary Endpoints					
EASI-75 at Week 16 [a]	26/53 (49.1) (35.6, 62.5)	97/130 (74.6) (67.1, 82.1)	28/66, (42.2) (30.1, 54.4)	101/145, (69.5) (61.9, 77.2)	26.4 (12.1, 40.8)***
EASI-90 at Week 16	13/53 (24.5) (12.9, 36.1)	57/130 (43.8) (35.3, 52.4)	14/66, (21.7) (11.4, 32.0)	60/145, (41.2) (33.0, 49.3)	18.9 (6.1, 31.7)**
EASI %CFB at Week 16, LSM (SE)	53, -59.4 (44.0)	130, -81.1 (20.3)	66, -53.1 (5.1)	145, -76.8 (4.1)	-23.6 (5.1) (-33.6, -13.7)***
Pruritus NRS ≥4-point improvement from Baseline at Week 16 [b]	15/41 (36.6) (21.8, 51.3)	59/107 (55.1) (45.7, 64.6)	18/57, (31.9) (19.3, 44.4)	66/130, (50.6) (41.8, 59.4)	19.2 (4.3, 34.1)*
Pruritus NRS %CFB at Week 16, LSM (SE)	45, -41.2 (38.6)	113, -55.4 (29.4)	63, -35.5 (6.4)	139, -50.7 (4.5)	-15.2 (6.4) (-27.7, -2.7)*
EASI-75 and Pruritus NRS ≥4-point improvement from Baseline at Week 16 [b]	6/41 (14.6) (3.8, 25.5)	45/106 (42.5) (33.0, 51.9)	10/57, (16.8) (6.7, 27.0)	50/130, (38.3) (29.8, 46.9)	21.6 (8.3, 35.0)**
Sleep-Loss Scale CFB at Week 16, LSM (SE)	45, -0.8 (0.8)	113, -1.3 (0.9)	63, -0.8 (0.1)	139, -1.1 (0.1)	-0.3 (0.1) (-0.6, -0.0)*
DLQI ≥4-point improvement from Baseline at Week 16 [c]	24/38 (63.2) (47.8, 78.5)	80/96 (83.3) (75.9, 90.8)	28/48, (58.7) (44.1, 73.2)	81/105, (77.4) (69.3, 85.5)	17.2 (0.1, 34.3)*
DLQI CFB at Week 16, LSM (SE)	40, -5.4 (7.4)	99, -9.8 (7.4)	51, -6.5 (1.9)	109, -9.8 (1.8)	-3.33 (1.0) (-5.3, -1.3)**
Other Secondary Endpoints					
Proportion of TCS/TCI-free days from Baseline to Week 16, LSM (SE)	53, 27.3 (32.8)	131, 34.0 (33.8)	53, 23.9 (4.8)	131, 31.2 (3.5)	7.3 (5.1) (-2.78, 17.4)
SCORAD %CFB at Week 16 [d]	52, -42.6 (30.7)	122, -63.0 (20.7)	65, -37.4 (4.4)	140, -55.0 (3.5)	-17.7 (4.4) *** (-26.4, -9.0)
Change in EQ-5D-5L (VAS) at Week 16	53, 5.0 (23.9)	126, 8.6 (19.3)	65, 6.5 (2.4)	143, 10.1 (1.8)	3.6 (2.4) (-1.1, 8.3)
Change in EQ-5D-5L (UK Health Index) at Week 16	53, 0.04 (0.2)	126, 0.2 (0.2)	65, 0.1 (0.0)	143, 0.2 (0.0)	0.1 (0.00) (0.1, 0.2)***
Change in EQ-5D-5L (US Health Index) at Week 16	53, 0.03 (0.2)	126, 0.1 (0.2)	65, 0.0 (0.0)	143, 0.1 (0.0)	0.07 (0.00) (0.00, 0.1)***
Change in POEM at Week 16	40, -6.3 (7.6)	101, -10.2 (7.5)	40, -6.2 (1.04)	101, -10.2 (0.7)	-4.0 (1.1) (-6.3, -1.7)***

Change in PROMIS Adults Anxiety at Week 16	26, -0.6 (10.0)	74, -3.5 (9.0)	43, -1.1 (1.4)	101, -1.9 (1.0)	-0.8 (1.4) (-3.6, 2.0)
Change in PROMIS Adults Depression at Week 16	26, -0.4 (7.6)	74, -2.2 (7.4)	43, -1.2 (1.1)	101, -1.4 (0.8)	-0.2 (1.1) (-2.4, 2.1)
Change in CDLQI at Week 16	11, -3.2 (5.4)	24, -8.8 (7.1)	11, -4.7 (1.2)	24, -9.3 (0.9)	-4.6 (1.3) (-7.2, -2.0)**

For primary or key secondary endpoints, analyses are based on data imputed with (1) non-responder imputation for patients who use rescue medication or discontinue study drug due to lack of efficacy; (2) MCMC-MI for all other missing data. For other secondary endpoints, analyses are based on LOCF if data is planned to be collected once during the treatment period; analyses are based on MMRM model if data is planned to be collected multiple times during the treatment period.

Abbreviations: CFB, change from Baseline; CDLQI, Children Dermatology Life Quality Index; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; EMA, European Medicines Agency; IGA, Investigator's Global Assessment; LEB, lebrikizumab; LSM, least squares mean; mITT, modified intent-to-treat; NRS, numeric rating scale; PBO, placebo; POEM, Patient Oriented Eczema Measure; PROMIS, Patient-Reported Outcomes Measurement Information System; SE, standard error; TCS, topical corticosteroid; TCI, topical calcineurin inhibitor; VAS, visual analogue scale.

[a] Co-primary endpoint for EMA.

[b] Patients with Baseline Pruritus NRS score ≥4.

[c] Patients with Baseline DLQI ≥4.

[d] ADhere used a modified version of the SCORAD with a maximum point score of 101 rather than 103. Due to a system setup error in the electronic data collection tool, the actual maximum score for each of the symptoms in Part C was 9 instead of 10, which resulted in the total maximum SCORAD score of 101 instead of 103. While this error directly impacted only Part C of the SCORAD, the measure is calculated as one total score, so the total SCORAD score collected could have been up to 2% lower than would have been expected if the error had not occurred.

Patients (>16 years of age) who answered DLQI at Baseline: [e] n=48; [f] n=105.

*p-value <0.05; **p-value <0.01; ***p-value <0.001

eTable 2: Supportive Analysis of Primary and Secondary Efficacy Outcomes

Variable, %	Placebo + TCS Q2W (N=66)	LEB + TCS Q2W (N=145)
Primary Endpoint		
IGA (0,1) and ≥2-point improvement from Baseline at Week 16	19.7	39.3**
Key Secondary Endpoints		
EASI-75 at Week 16 [a]	39.4	66.9***
EASI-90 at Week 16	19.7	39.3**
EASI %CFB at Week 16, LSM (SE)	-55.7 (4.3)	-80.0 (3.2) ***
Nx	53	130
Pruritus NRS ≥4-point improvement from Baseline at Week 16 [b]	26.3	45.4*
Pruritus NRS %CFB at Week 16, LSM (SE)	-39.2 (5.5)	-51.8 (3.7) *
Nx	45	113
EASI-75 and Pruritus NRS ≥4-point improvement from Baseline at Week 16 [b]	10.5	34.6***
Sleep-Loss Scale CFB at Week 16, LSM (SE)	-1.0 (0.1)	-1.2 (0.1) *
Nx	45	113
DLQI ≥4-point improvement from Baseline at Week 16 [c]	50.0 [d]	76.2** [e]
DLQI CFB at Week 16, LSM (SE)	-7.1 (1.5)	-10.5 (1.4) ***
Nx	40	99

The supportive analyses were performed using Cochran-Mantel-Haenszel with NRI for categorical endpoints and MMRM for continuous endpoints.
Abbreviations: CFB, change from baseline; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; EMA, European Medicines Agency; IGA, Investigator's Global Assessment; LEB, lebrikizumab; LSM, least squares mean; MMRM, mixed-model repeated measure; NRI, nonresponder imputation; NRS, numeric rating scale; Nx, number of patients with non-missing values; Q2W, every 2 weeks; SE, standard error; TCS, topical corticosteroid.
[a] Co-primary endpoint for EMA.
[b] Patients with Baseline Pruritus NRS score ≥4.
[c] Patients with Baseline DLQI score ≥4.
Patients (>16 years of age) who answered DLQI at baseline: [d] n=48; [e] n=105.
*p-value <0.05; **p-value <0.01; ***p-value <0.001

eTable 3. Summary of Time (days) to TCS/TCI-Free Use from Baseline

Percentile of Patients	Placebo + TCS Q2W (N=66)	LEB + TCS Q2W (N=145)
25th Percentile	94	86
50th Percentile	-	121
75th Percentile	-	-
Minimum	1	2
Maximum	112	121

Abbreviations: LEB, lebrikizumab; Q2W, every 2 weeks; TCS, topical corticosteroid; TCI, topical calcineurin inhibitor.

eTable 4. Proportion of TCS/TCI Free Days

Timepoint Treatment	Nx	LSM (SE)	Comparison versus placebo		
			LSM Diff (SE)	95% CI	p-value
Week 2					
Placebo + TCS Q2W	66	26.3 (4.5)	3.3 (4.7)	(-5.9, 12.6)	0.477
LEB + TCS Q2W	144	29.6 (3.4)			
Week 4					
Placebo + TCS Q2W	60	24.5 (4.7)	6.7 (4.9)	(-3.0, 16.4)	0.176
LEB + TCS Q2W	140	31.2 (3.5)			
Week 6					
Placebo + TCS Q2W	59	20.0 (4.6)	12.5 (4.8)	(3.0, 21.9)	0.010
LEB + TCS Q2W	137	32.4 (3.4)			
Week 8					
Placebo + TCS Q2W	57	23.7 (4.9)	10.7 (5.2)	(0.4, 21.0)	0.042
LEB + TCS Q2W	135	34.4 (3.6)			
Week 10					
Placebo + TCS Q2W	55	21.9 (5.0)	12.6 (5.4)	(1.9, 23.2)	0.021
LEB + TCS Q2W	132	34.5 (3.7)			
Week 12					
Placebo + TCS Q2W	55	25.8 (5.0)	6.6 (5.3)	(-3.8, 17.1)	0.211
LEB + TCS Q2W	132	32.5 (3.6)			
Week 14					
Placebo + TCS Q2W	55	26.5 (4.9)	5.9 (5.2)	(-4.5, 16.2)	0.264
LEB + TCS Q2W	129	32.3 (3.6)			
Week 16					
Placebo + TCS Q2W	53	23.9 (4.8)	7.3 (5.1)	(-2.8, 17.4)	0.155
LEB + TCS Q2W	131	31.2 (3.5)			
Combined DB period					
Placebo + TCS Q2W	66	26.0 (4.2)	7.4 (4.2)	(-0.9, 15.7)	0.079
LEB + TCS Q2W	145	33.4 (3.2)			

Abbreviations: CI, confidence interval; DB, double-blinded; LEB, lebrikizumab; LSM, least squares mean; LSM Diff, LSM difference; Nx, number of patients with non-missing values; Q2W, every 2 weeks; SE, standard error; TCS, topical corticosteroid; TCI, topical calcineurin inhibitor.

eTable 5. Use of rescue medication through Week 16 in ADhere modified safety population

Patients N (%)	Placebo + TCS Q2W (N=66)	LEB + TCS Q2W (N=145)
Use of any rescue medication	7 (10.6)	6 (4.1)
High-potency TCS	3 (4.5)	2 (1.4)
Systemic rescue medication	5 (7.6)	5 (3.4)

Abbreviations: LEB, lebrikizumab; Q2W, every 2 weeks; TCS, topical corticosteroids

eTable 6. Incidence of ADAs

Category	Placebo + TCS Q2W n (%) [a]	LEB + TCS Q2W n (%) [a]
Participants evaluable for TE ADA[b]	**64 (100)**	**143 (100)**
Participants with ADA present at Baseline	**7 (10.9)**	**9 (6.3)**
Median (range) of maximum Baseline titer	10 (10, 10)	10 (10, 80)
Neutralizing Ab present at Baseline, n (%)	1 (1.6)	4 (2.8)
Participants with postbaseline TE ADA positive [c]	**0**	**5 (3.5)**
Median (range) of maximum postbaseline titer	0	40 (20, 160)
Treatment-induced TE ADA+	0	4 (2.8)
Treatment-boosted TE ADA+	0	1 (0.7)
NAb present	0	5 (3.5)
Participants with postbaseline TE ADA negative	**64 (100)**	**138 (96.5)**

Abbreviations: Ab, antibody; ADA, antidrug antibodies; LEB, lebrikizumab; n, number of participants in the specified category; NAb, neutralizing Ab; Q2W, every 2 weeks; TCS, topical corticosteroids; TE, treatment-emergent.

[a] Percentages are relative to the total number of TE ADA-evaluable participants.

[b] A participant was TE ADA-evaluable if there was at least 1 non-missing test result for lebrikizumab ADA for each of the Baseline period and the postbaseline period.

[c] TE ADA are defined as those with a titer 2-fold (1 dilution) greater than the minimum required dilution if no ADAs were detected at baseline (treatment-induced ADA) or those with a 4-fold (2 dilutions) increase in titer compared to baseline if ADAs were detected at baseline (treatment-boosted ADA).

Note: Immunogenicity was assessed by a validated assay designed to perform in the presence of lebrikizumab. The assay used a minimum required dilution of 1:10, had a sensitivity of 13.8 ng/mL, and a drug tolerance of 250 µg/mL.