

SUPPLEMENTARY MATERIAL

Three-Year Efficacy and Safety of Lebrikizumab in Patients with Moderate-to-Severe Atopic Dermatitis: A Long-Term Extension (ADjoin)

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Scale Descriptions

IGA:

The Investigator's Global Assessment (IGA) is a static assessment and rates the severity of the participant's AD. The IGA is comprised of a 5-point scale ranging from 0 (clear) to 4 (severe), and a score is selected using descriptors that best describe the overall appearance of the lesions at a given time point¹.

EASI:

The Eczema Area and Severity Index (EASI) is used to assess the severity and extent of AD. It is a composite index with scores ranging from 0 to 72, with the higher values indicating more severe and/or extensive disease^{2,3}.

POEM:

Patient Oriented Eczema Measure (POEM) is a participant-reported, 7-item scale that assesses disease severity in children and adults. Participants respond to questions about the frequency of 7 symptoms (itching, sleep disturbance, bleeding, weeping/oozing, cracking, flaking, and dryness/roughness) over the past week. Response categories include "No days," "1-2 days," "3-4 days," "5-6 days," and "Every day," with corresponding scores of 0, 1, 2, 3, and 4, respectively. Scores range from 0-28, with higher total scores indicating greater disease severity⁴.

Participant disposition

A total of 181 Week 16 lebrikizumab responders from ADvocate1&2 (ADvocate RES) entered ADjoin and were assigned to treatment groups consistent with treatment in the parent studies (Figure S1). In total, 82 lebrikizumab Q2W participants from ADvocate1&2 entered ADjoin, and 99 lebrikizumab Q4W participants from

ADvocate1&2 entered ADjoin. Moreover, 19 participants (23.2%) in the lebrikizumab Q2W arm discontinued ADjoin, and 63 participants (76.8%) completed 152 weeks of treatment (52 weeks in ADvocate1&2 and 100 weeks in ADjoin). In addition, 28 participants (28.3%) in the lebrikizumab Q4W arm discontinued ADjoin, and 71 participants (71.7%) completed 152 weeks of treatment (52 weeks in ADvocate1&2 and 100 weeks in ADjoin).

A total of 86 ADhere W16 lebrikizumab responders (ADhere RES) entered ADjoin and were re-randomized 2:1 to receive lebrikizumab 250 mg Q2W (N=57) or Q4W (N=29), respectively. Seventeen participants (29.8%) in the lebrikizumab Q2W arm discontinued treatment, and 40 participants (70.2%) completed 116 weeks of treatment. Seven participants (24.1%) in the lebrikizumab Q4W arm discontinued treatment, and 22 participants (75.9%) completed 116 weeks of treatment.

Table S1: Study Design⁵⁻¹⁰

	ADvocate1	ADvocate2	ADhere	ADore	ADopt-VA	ADjoin LTE^a
Regions	Global	Global	Global	Global	US	Global
N	424	427	211	206	254	1153
Background	Monotherapy	Monotherapy	+ TCS	TCS/TCI/ PDE4i optional	TCS/TCI optional	TCS/TCI/ PDE4i optional
Study population(s)	Adults and adolescents ^b	Adults and adolescents ^b	Adults and adolescents ^b	Adolescents ^b	Adults (≥18 yrs–≤55 yrs)	Adults and adolescents ^b
Dosing arms	PBO LEB 250 mg Q2W LEB 250 mg Q4W	PBO LEB 250 mg Q2W LEB 250 mg Q4W	PBO LEB 250 mg Q2W	Open-label LEB 250 mg Q2W	PBO LEB 250 mg Q2W	LEB 250 mg Q2W LEB 250 mg Q4W
Primary outcome (week)	16	16	16	52	16	100
Treatment duration (week)	52	52	16	52	16	100

LEB=Lebrikizumab; LTE=Long-Term Extension; N=Number of Participants in the Analysis Population; PBO=Placebo; PDE4i=Phosphodiesterase-4 Inhibitor; Q2W=Every 2 Weeks; Q4W=Every 4 Weeks; Q8W=Every 8 Weeks; TCI=Topical Calcineurin Inhibitor; TCS=Topical Corticosteroid.

^aThis includes all ADjoin participants from parent studies (ADvocate1&2, ADhere, ADore, ADopt-VA) and participants that enrolled directly into ADjoin.

^bAdolescent participants were aged ≥12 to <18 with a body weight of at least 40 kg.

The regimen assigned to each ADjoin participant was based on the treatment received in the participant's respective parent trial. Participants who enrolled directly into ADjoin received open-label lebrikizumab 250 mg Q2W (after loading dose of 500 mg at W0 and W2).

Table S2: Population Definitions

Population	Definition
ADvocate1&2 W16 lebrikizumab responders (ADvocate RES) and ADhere W16 lebrikizumab responders (ADhere RES)	Participants who achieved IGA 0/1 with 2-point improvement from baseline or EASI 75 response at Week 16 in their parent studies without rescue medication use. Efficacy data is presented separately for W16 IGA 0/1 responders and W16 EASI 75 responders.
Per-protocol responders	Participants who achieved IGA 0/1 with 2-point improvement from baseline or EASI 75 at Week 16 in their parent studies without rescue medication use. Efficacy data is presented as a combined population of W16 IGA 0/1 responders and W16 EASI 75 responders.
ADjoin Overall Population	All participants entering ADjoin from parent studies ADvocate1&2, ADhere, ADore, ADOpt-VA, and entering ADjoin directly.
Modified Intent-to-Treat Population	Following the findings of directed site audits, data from participants at 2 sites were excluded from analyses, resulting in the creation of a modified intent-to-treat (mITT) population, data from which were used for the efficacy analyses of the ADjoin Overall population.
Modified Safety Population	Includes all participants receiving at least 1 dose of lebrikizumab in the ADjoin Overall population, except for participants from 2 study sites who were excluded due to site audit findings.

EASI=Eczema Area and Severity Index; IGA=Investigator's Global Assessment

Table S3: Safety Summary for ADjoin Overall Population (Modified Safety Population)^a

	LEB 250 mg Q4W (N=141)	LEB 250 mg Q2W (N=1012)	Any LEB (N=1153)
Participants with ≥1 TEAE	89 (63.1)	646 (63.8)	735 (63.7)
Mild	39 (27.7)	291 (28.8)	330 (28.6)
Moderate	43 (30.5)	315 (31.1)	358 (31.0)
Severe	7 (5.0)	40 (4.0)	47 (4.1)
Serious AE	5 (3.5)	41 (4.1)	46 (4.0)
Death	0	2 (0.2) ^b	2 (0.2)
Discontinuation from study treatment due to AE	3 (2.1)	46 (4.5)	49 (4.2)
Conjunctivitis cluster^c	9 (6.4)	66 (6.5)	75 (6.5)
Keratitis cluster^d	1 (0.7)	4 (0.4)	5 (0.4)
Infections^e	59 (41.8)	393 (38.8)	452 (39.2)
Potential opportunistic infections^f			
Broad	2 (1.4)	20 (2.0)	22 (1.9)
Narrow	1 (0.7)	12 (1.2)	13 (1.1)
Skin infections	4 (2.8)	31 (3.1)	35 (3.0)
Herpes infections	4 (2.8)	45 (4.4)	49 (4.2)
Parasitic infections	1 (0.7)	1 (0.1)	2 (0.2)
Injection site reactions^g	1 (0.7)	20 (2.0)	21 (1.8)
Malignancies^h	0	8 (0.8)	8 (0.7)
Hypersensitivity	2 (1.4)	36 (3.6)	38 (3.3)
Eosinophiliaⁱ	1 (0.7)	16 (1.6)	17 (1.5)
Suicide/self-injury	0	2 (0.2)	2 (0.2)

^aModified safety population from Week 0 of ADjoin through to data cut-off of 25 February 2025, 1153 participants (mSAF) from ADvocate1&2, ADhere, ADore, ADopt-VA, and ADjoin direct entry. Following the findings of 2 directed site audits, data from participants at 2 sites were excluded from analyses, resulting in the

creation of a modified Safety Population, data from which were used for the safety analyses.

^bAs reported by the Investigator, one participant died of natural causes on ADjoin Study Day 348 (462 days of total lebri exposure). A second participant died due to pancreatic cancer on ADjoin Study Day 496 (608 days of total lebrikizumab exposure).

^cConjunctivitis cluster includes MedDRA preferred terms of conjunctivitis, conjunctivitis allergic, conjunctivitis bacterial, conjunctivitis viral, giant papillary conjunctivitis.

^dKeratitis cluster includes MedDRA preferred terms of keratitis, atopic keratoconjunctivitis, allergic keratitis, ulcerative keratitis, vernal keratoconjunctivitis.

^eInfections are defined using the MedDRA preferred terms from the Infections and Infestations System Organ Class.

^fAll potential opportunistic infections were assessed based on the Winthrop criteria (2015) and updated MedDRA terms¹¹ and 2 events in the lebrikizumab Q2W group have been confirmed as opportunistic and both recovered (Herpes zoster with reversible facial paralysis and oesophageal candidiasis).

^gInjection site reactions are defined using MedDRA High-Level Term of injection site reactions, excluding joint-related preferred terms.

^hIncludes both NMSC and malignancies excluding NMSC. All malignancies were reported in the lebrikizumab Q2W group: basal cell carcinoma, prostate cancer (n=2), endometrial adenocarcinoma, gastrointestinal stromal tumor, invasive breast carcinoma, neuroendocrine tumor, pancreatic carcinoma metastatic.

ⁱEosinophilia is defined as 2 preferred terms of eosinophilia and allergic eosinophilia and the following preferred terms under the high-level term of white blood cell analysis: eosinophil count abnormal eosinophil count increased, and eosinophil percentage increased. No eosinophilic-related disorders were reported.

Notes: Data are presented as n (%). A TEAE is defined as an event that first occurred or worsened in severity after baseline and on or prior to the date of the last visit within the ADjoin treatment period. Participants with multiple occurrences of these categories are counted once for each category. Participants may be counted in more than one category. Deaths are also included as serious AEs and discontinuations due to AEs. MedDRA Version 27.1.

AE=adverse event; LEB=lebrikizumab; MedDRA=Medical Dictionary for Regulatory Activities; mITT=modified intent-to-treat; NMSC=non-melanoma skin cancer; Q2W=every 2 weeks; Q4W=every 4 weeks; TEAE=treatment-emergent adverse event; W=Week.

Table S4: Efficacy Outcomes Summary for ADjoin Overall Population (mITT)^a

Efficacy Endpoints Week 100^b	LEB 250 mg Q4W (N=141)	LEB 250 mg Q2W (N=1012)	Total LEB (N=1153)
IGA 0/1 (NRI-MI)			
Response, n (%)	113 (80.1)	613 (60.6)	726 (63.0)
95% CI ^c	(72.3, 87.8)	(57.2, 64.0)	(59.8, 66.1)
IGA 0/1 (Observed)			
Nx ^d	101	672	773
Response, n (%) ^d	84 (83.2)	433 (64.4)	517 (66.9)
95% CI ^c	(75.9, 90.5)	(60.8, 68.1)	(63.6, 70.2)
EASI 75 (NRI-MI)			
Response, n (%)	127 (90.4)	803 (79.4)	930 (80.7)
95% CI ^c	(84.8, 95.9)	(76.5, 82.2)	(78.1, 83.3)
EASI 75 (Observed)			
Nx ^d	101	672	773
Response, n (%) ^d	95 (94.1)	599 (89.1)	694 (89.8)
95% CI ^c	(89.4, 98.7)	(86.8, 91.5)	(87.6, 91.9)
EASI 90 (NRI-MI)			
Response, n (%)	112 (79.6)	615 (60.8)	728 (63.1)
95% CI ^c	(71.6, 87.7)	(57.2, 64.4)	(59.8, 66.4)
EASI 90 (Observed)			
Nx ^d	101	672	773
Response, n (%) ^d	88 (87.1)	471 (70.1)	559 (72.3)
95% CI ^c	(80.6, 93.7)	(66.6, 73.6)	(69.2, 75.5)

^amITT population from Week 0 of ADjoin through to data cut-off of 25 February 2025, 1153 participants from ADvocate1&2, ADhere, ADore, ADopt-VA, and ADjoin direct entry. Following the findings of 2 directed site audits, data from participants at 2 sites were excluded from analyses, resulting in the creation of an mITT population, data from which were used for the efficacy analyses.

^bImprovement measured from parent study baseline for participants from a parent study. For the participants directly enrolled in ADjoin, baseline is ADjoin Visit 1.

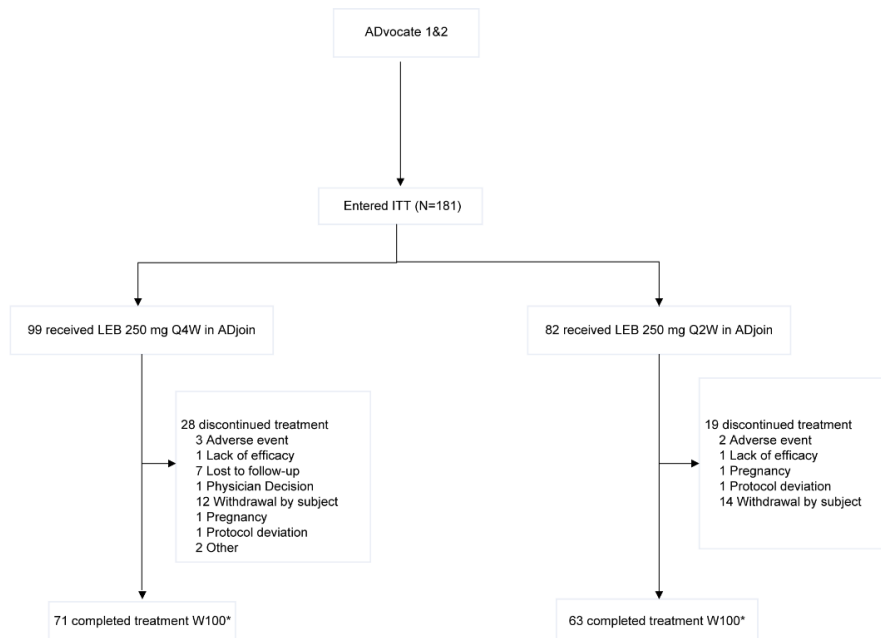
^cCI_s are calculated using asymptotic method without continuity correction, that is, normal approximation to the binomial distribution.

^dPercentage of response is calculated by $n/N_x \times 100$.

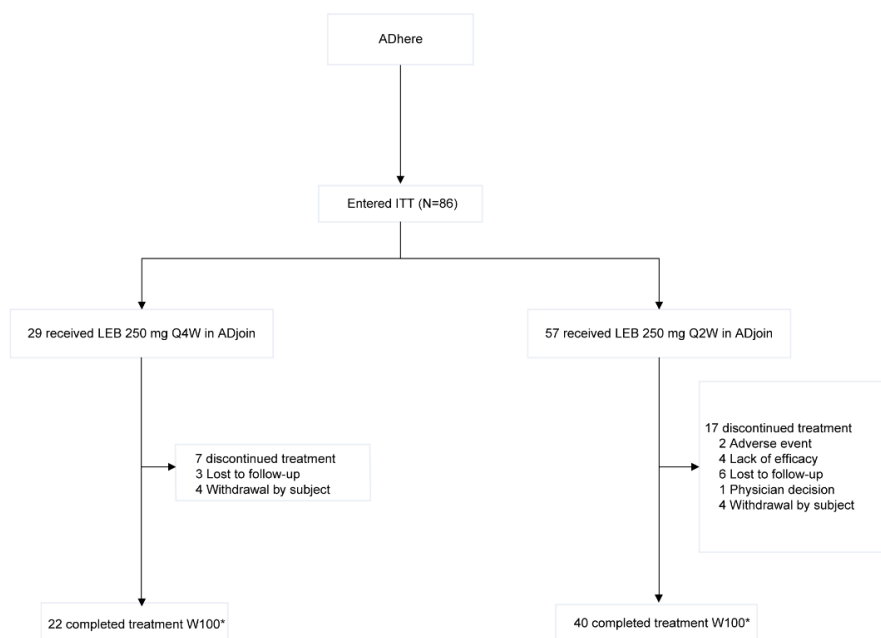
CI=confidence interval; EASI=Eczema Area and Severity Index; EASI 75=75% reduction from baseline in EASI; EASI 90=90% reduction in EASI; IGA 0/1=Investigator's Global Assessment score of 0 or 1; LEB=lebrikizumab; mITT=modified intent-to-treat; NRI/MI=non-responder imputation/multiple imputation; n=number of participants in the specified category; N=number of participants in the analysis population; Nx=number of participants with non-missing values; Q2W=every 2 weeks; Q4W=every 4 weeks; W=Week.

Figure S1: Disposition of W16 Lebrikizumab Responders in Participants from ADvocate1&2 (A) and ADvocate2 (B) Who Entered ADjoin

(A)



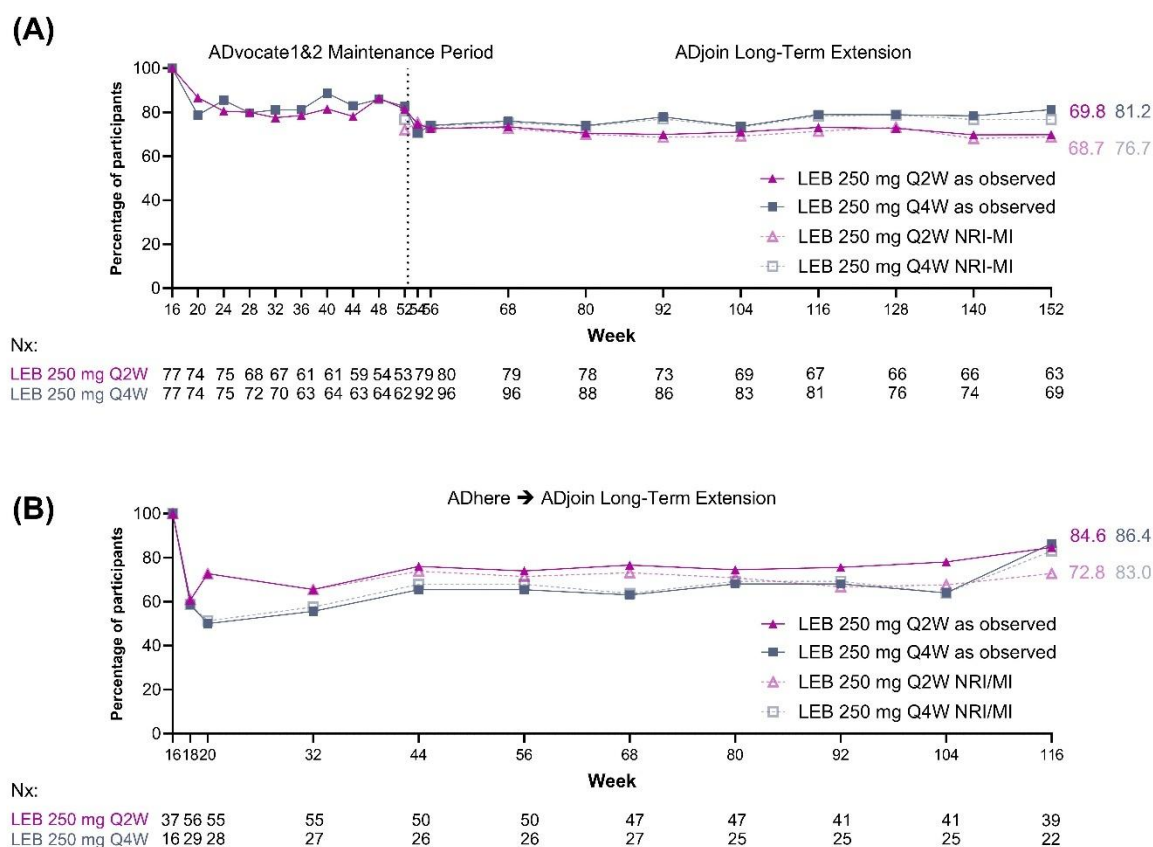
(B)



(A) Disposition of W16 lebrikizumab responders (IGA 0/1 or EASI 75 at W16 of parent study) in ADvocate1&2 who completed maintenance period of ADvocate1&2 and entered ADjoin.

(B) Disposition of W16 lebrikizumab responders (IGA 0/1 or EASI 75 at W16 of parent study) in ADhere who completed 16 weeks of treatment in ADhere and entered ADjoin
ITT=intent-to-treat; LEB=lebrikizumab; mITT=modified intent-to-treat; Q2W=every 2 weeks; Q4W=every 4 weeks; W=Week.

Figure S2: IGA 0/1 Response Rates Were Maintained in W16 Per-Protocol Responders (either EASI 75 or IGA 0/1) Receiving Lebrikizumab Q4W and Q2W Through 152 Weeks



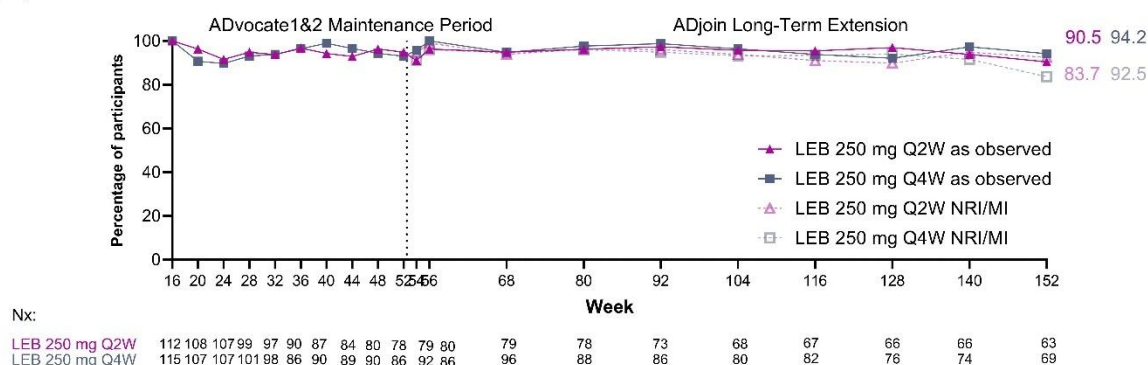
Data from W16 lebrikizumab responders achieving IGA 0/1 or EASI 75 at Week 16 of parent study.

Data presented at Week 52 are the results and participant numbers of ADvocate1&2 Week 52 and not ADjoin baseline data. ADjoin data are reflected in the graph from Week 54 onward (Figure S2A).

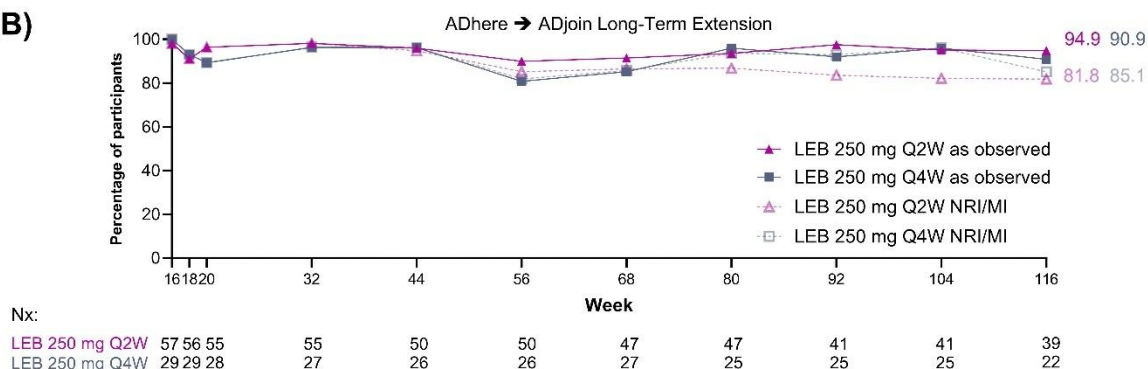
IGA 0/1=Investigator's Global Assessment response of clear or almost clear;
LEB=lebrikizumab; NRI/MI=non-responder imputation/multiple imputation;
Nx=number of participants with non-missing values; Q2W=every 2 weeks;
Q4W=every 4 weeks; W=Week.

Figure S3: EASI 75 Response Rates Were Maintained in W16 Per-Protocol Responders (either EASI 75 or IGA 0/1) Receiving Lebrikizumab Q4W and Q2W Through 152 Weeks

(A)



(B)



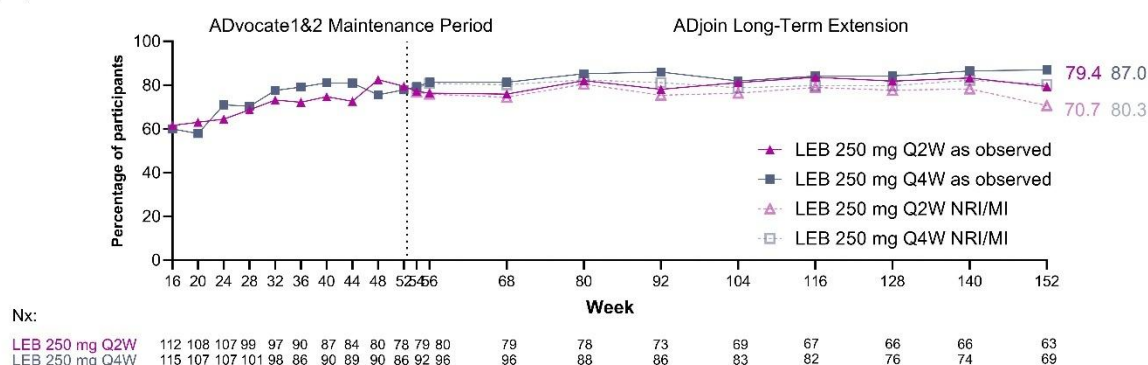
Data from W16 per-protocol responders achieving IGA 0/1 or EASI 75 at Week 16 of parent study.

Data presented at Week 52 are the results and participant numbers of ADvocate1&2 Week 52 and not ADjoin baseline data. ADjoin data are reflected in the graph from Week 54 onward (Figure S3A).

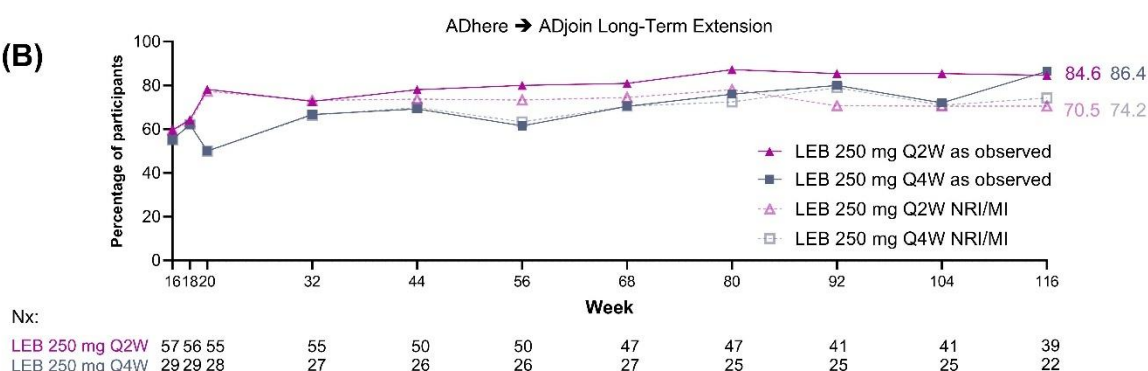
EASI 75=at least 75% improvement from parent study baseline in Eczema Area and Severity Index; LEB=lebrikizumab; NRI/MI=non-responder imputation/multiple imputation; Nx=number of participants with non-missing values; Q2W=every 2 weeks; Q4W=every 4 weeks; W=Week.

Figure S4: EASI 90 Response Rates Were Maintained in W16 Per-Protocol Responders (either EASI 75 or IGA 0/1) Receiving Lebrikizumab Q4W and Q2W Through 152 Weeks

(A)



(B)



Data from W16 per-protocol responders achieving IGA 0/1 or EASI 75 at Week 16 of parent study.

Data presented at Week 52 are the results and participant numbers of ADvocate1&2 Week 52 and not ADjoin baseline data. ADjoin data are reflected in the graph from Week 54 onward (Figure S4A).

EASI 90=at least 90% improvement from parent study baseline in Eczema Area and Severity Index; LEB=lebrikizumab; NRI/MI=non-responder imputation/multiple imputation; Nx=number of participants with non-missing values; Q2W=every 2 weeks; Q4W=every 4 weeks; W=Week.

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