

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

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Table S1. Baseline demographics and clinical characteristics for parent studies

	ADvocate1&2 > ADjoin		ADhere > ADjoin	
	LEB 250 mg Q4W (N=99)	LEB 250 mg Q2W (N=82)	LEB 250 mg Q4W (N=29)	LEB 250 mg Q2W (N=57)
Age, years	35.8 (17.2)	35.5 (16.2)	29.8 (15.9)	37.0 (19.9)
Adolescent (≥12 to <18), n (%)	14 (14.1)	11 (13.4)	10 (34.5)	15 (26.3)
Adult (≥18), n (%)	85 (85.9)	71 (86.6)	19 (65.5)	42 (73.7)
Female, n (%)	60 (60.6)	42 (51.2)	15 (51.7)	27 (47.4)
Region, n (%)				
USA	41 (41.4)	32 (39.0)	22 (75.9)	38 (66.7)
Europe	33 (33.3)	32 (39.0)	6 (20.7)	13 (22.8)
Rest of the world ^a	25 (25.3)	18 (22.0)	1 (3.4)	6 (10.5)
BMI, kg/m ²	26.4 (6.3)	26.4 (6.2)	25.2 (6.9)	26.3 (6.6)
Disease duration since AD onset, years	22.4 (14.2)	23.6 (14.7)	21.7 (14.1)	21.6 (18.2)
IGA, n (%)				
3 (Moderate)	63 (63.6)	50 (61.0)	20 (69.0)	39 (68.4)
4 (Severe)	36 (36.4)	32 (39.0)	9 (31.0)	18 (31.6)
EASI	28.9 (12.2)	29.2 (11.2)	26.2 (7.8)	28.2 (11.1)
Pruritus NRS				
<4, n (%)	9 (9.2)	3 (3.7)	2 (7.4)	3 (5.5)
≥4, n (%)	89 (90.8)	79 (96.3)	25 (92.6)	52 (94.5)

Note: Data are mean (SD) unless stated.

^a Rest of the world includes Australia, Canada, South Korea, Mexico, Singapore, Taiwan

AD=atopic dermatitis; BMI=body mass index; EASI=Eczema Area and Severity Index; IGA=Investigator's Global Assessment; LEB=lebrikizumab; NRS=Numeric Rating Scale; Q2W=every 2 weeks; Q4W=every 4 weeks; SD=standard deviation.

Table S2. Efficacy outcomes achieved by Week 16 per-protocol responders [patients achieving IGA (0,1) or EASI 75 without rescue] during the ADjoin treatment period up to 104 Weeks of total lebrikizumab treatment analyzed by NRI/MI

	ADvocate1&2 > ADjoin		ADhere > ADjoin	
	LEB 250 mg Q4W (N=99)	LEB 250 mg Q2W (N=82)	LEB 250 mg Q4W (N=29)	LEB 250 mg Q2W (N=57)
IGA (0,1)				
Week 0 ^a	76 (76.8)	59 (72.0)	16 (55.2)	37 (64.9)
Week 52/88 ^b	72 (73.1)	57 (69.1)	19 (65.8)	39 (67.8)
EASI 75				
Week 0 ^a	93 (93.9)	79 (96.3)	29 (100)	56 (98.2)
Week 52/88 ^b	93 (94.3)	77 (94.5)	28 (96.3)	47 (82.7)
EASI 90				
Week 0 ^a	81 (81.8)	66 (80.5)	16 (55.2)	34 (59.6)
Week 52/88 ^b	78 (79.1)	64 (77.5)	21 (70.9)	41 (71.4)
Pruritus NRS ≥4-point improvement ^c				
Week 0 ^a	64 (71.9)	61 (77.2)	16 (64.0)	30 (57.7)
Week 52 ^{b,d}	66 (74.6)	59 (75.0)	18 (73.8)	31 (59.2)

Data are n (%). The number of responders, i.e. n's, are not the observed values but are estimated from the responder proportion of the multiple imputation results multiplied by the number of patients in the analysis population.

^aWeek 0 of ADjoin. For patients entering ADjoin from ADvocate1&2, ADjoin entry followed 52 Weeks of lebrikizumab treatment. For patients entering ADjoin from ADhere, ADjoin entry followed 16 Weeks of lebrikizumab treatment.

^bFor patients entering ADjoin from ADvocate1&2, Week 104 of lebrikizumab treatment was Week 52 of ADjoin. For patients entering ADjoin from ADhere, Week 104 of lebrikizumab treatment was Week 88 of ADjoin.

^cPruritus Numeric Rating Scale (NRS) ≥4-point improvement from baseline in those with a parent study baseline Pruritus NRS ≥4. For ADvocate 1&2 > ADjoin, Q4W N=89 and Q2W N=79. For ADhere > ADjoin, Q4W N=25 and Q2W N=52.

^dPruritus NRS was recorded through Week 52 of ADjoin, and therefore is only reported up to Week 68 of lebrikizumab treatment for patients originating from the ADhere study.

For data collected during ADjoin, patients who discontinued treatment due to lack of efficacy had values set to their baseline value (parent study baseline for patients from ADvocate1&2, Week 0 of ADjoin for patients from ADhere) subsequent to this time and MI was used to handle the remaining missing data.

EASI=Eczema Area and Severity Index; EASI 75=75% improvement in EASI; EASI 90=90% improvement in EASI;

IGA=Investigator's Global Assessment; LEB=lebrikizumab; NRI=non-responder imputation; NRS= Numeric Rating Scale;

MI=multiple imputation; Q2W=every 2 weeks; Q4W=every 4 weeks.

Table S3. IGA (0,1) in patients who received lebrikizumab Q2W or Q4W during ADvocate1 and ADvocate2

IGA (0,1) (NRI/MI), n (%)	ADvocate1&2 > ADjoin	
	LEB 250 mg Q4W (N=77)	LEB 250 mg Q2W (N=77)
Week 16	77 (100)	77 (100)
Week 20	60 (78.1)	67 (86.6)
Week 24	66 (85.4)	63 (81.4)
Week 28	61 (79.3)	59 (77.2)
Week 32	61 (79.3)	58 (75.7)
Week 36	59 (76.9)	54 (70.1)
Week 40	64 (83.2)	56 (73.2)
Week 44	60 (77.7)	53 (68.7)
Week 48	63 (81.4)	56 (72.9)
Week 52	59 (76.9)	55 (71.2)

For NRI/MI analysis of data collected during Weeks 16–52 of ADvocate1 and ADvocate2, patients who received systemic rescue medication, discontinued treatment due to lack of efficacy, or transferred to the escape arm, had values set to their baseline value (Week 0 of ADvocate1 and ADvocate2) subsequent to this time; patients who received topical rescue medication or discontinued treatment for any other reasons had values set to missing subsequent to this time through to Week 52 and MI was used to handle the missing data.

IGA=Investigator's Global Assessment; LEB=lebrikizumab; Nx=number of patients in the analysis population; Q2W=every 2 weeks; Q4W=every 4 weeks.

Table S4. EASI 75 and EASI 90 in patients who received lebrikizumab Q2W or Q4W during ADvocate1 and ADvocate2

EASI (NRI/MI), n (%)	ADvocate1&2 > ADjoin	
Timepoint	LEB 250 mg Q4W (N=115)	LEB 250 mg Q2W (N=112)
EASI 75 (NRI/MI)		
Week 16	115 (100)	112 (100)
Week 20	101 (88.1)	107 (95.5)
Week 24	99 (86.1)	99 (88.4)
Week 28	102 (89.0)	100 (89.0)
Week 32	102 (88.9)	97 (86.6)
Week 36	100 (87.3)	94 (84.3)
Week 40	103 (89.8)	91 (81.1)
Week 44	100 (87.0)	88 (79.0)
Week 48	97 (84.4)	89 (79.9)
Week 52	94 (81.7)	88 (78.4)
EASI 90 (NRI/MI)		
Week 16	69 (60)	69 (61.6)
Week 20	65 (56.3)	70 (62.8)
Week 24	77 (67.4)	70 (62.1)
Week 28	76 (65.8)	72 (63.9)
Week 32	82 (71.1)	75 (66.6)
Week 36	79 (68.8)	70 (62.6)
Week 40	83 (72.0)	71 (63.2)
Week 44	81 (70.9)	67 (60.1)
Week 48	75 (65.3)	74 (65.8)
Week 52	76 (66.4)	72 (64.0)

For NRI/MI analysis of data collected during Weeks 16–52 of ADvocate1 and ADvocate2, patients who received systemic rescue medication, discontinued treatment due to lack of efficacy, or transferred to the escape arm, had values set to their baseline value (Week 0 of ADvocate1 and ADvocate2) subsequent to this time; patients who received topical rescue medication or discontinued treatment for any other reasons had values set to missing subsequent to this time through to Week 52 and MI was used to handle the missing data.

EASI=Eczema Area and Severity Index; EASI 75=75% improvement in EASI; EASI 90=90% improvement in EASI; LEB=lebrikizumab; Nx=number of patients in the analysis population; Q2W=every 2 weeks; Q4W=every 4 weeks.

Table S5. Pruritus NRS in patients who received lebrikizumab Q2W or Q4W during ADvocate1 and ADvocate2

Pruritus NRS (NRI/MI), n (%)	ADvocate1&2 > ADjoin	
Timepoint	LEB 250 mg Q4W (N=65)	LEB 250 mg Q2W (N=61)
Week 16	65 (100)	61 (100)
Week 20	58 (89.2)	55 (90.1)
Week 24	56 (86.0)	55 (90.2)
Week 28	55 (83.9)	52 (84.7)
Week 32	55 (85.3)	55 (89.6)
Week 36	58 (90.0)	51 (82.9)
Week 40	56 (86.6)	52 (84.7)
Week 44	57 (88.0)	52 (84.7)
Week 48	56 (86.7)	53 (86.4)
Week 52	55 (84.7)	52 (84.6)

For NRI/MI analysis of data collected during Weeks 16–52 of ADvocate1 and ADvocate2, patients who received systemic rescue medication, discontinued treatment due to lack of efficacy, or transferred to the escape arm, had values set to their baseline value (Week 0 of ADvocate1 and ADvocate2) subsequent to this time; patients who received topical rescue medication or discontinued treatment for any other reasons had values set to missing subsequent to this time through to Week 52 and MI was used to handle the missing data.

LEB=lebrikizumab; NRS=Numeric Rating Scale; Nx=number of patients in the analysis population; Q2W=every 2 weeks; Q4W=every 4 weeks.

Table S6. Summary of rescue and concomitant medication use during ADjoin

	ADvocate1&2 > ADjoin		ADhere > ADjoin	
	LEB 250 mg Q4W (N=99)	LEB 250 mg Q2W (N=82)	LEB 250 mg Q4W (N=29)	LEB 250 mg Q2W (N=57)
≥1 Rescue/concomitant medication ^a	20 (20.2)	10 (12.2)	23 (79.3)	42 (73.7)
Topical therapy ^b	15 (15.2)	8 (9.8)	23 (79.3)	40 (70.2)
Topical corticosteroids	12 (12.1)	7 (8.5)	23 (79.3)	40 (70.2)
Low- Moderate potency	7 (7.1)	4 (4.9)	22 (75.9)	40 (70.2)
High potency	6 (6.1)	4 (4.9)	3 (10.3)	1 (1.8)
Systemic therapy	5 (5.1)	2 (2.4)	1 (3.4)	6 (10.5)

Note: Data are n (%).

^aFor patients from ADhere, only high potency topical corticosteroids and systemic therapy are considered rescue medications

^bTopical therapy includes topical corticosteroids and topical calcineurin inhibitors.

LEB=lebrikizumab; Q2W=every 2 weeks; Q4W=every 4 weeks.

Figure S1. Study design showing re-randomized populations originating from parent studies (A) ADvocate1 and ADvocate 2 and (B) ADhere and subsequent entry into the long-term extension study ADjoin

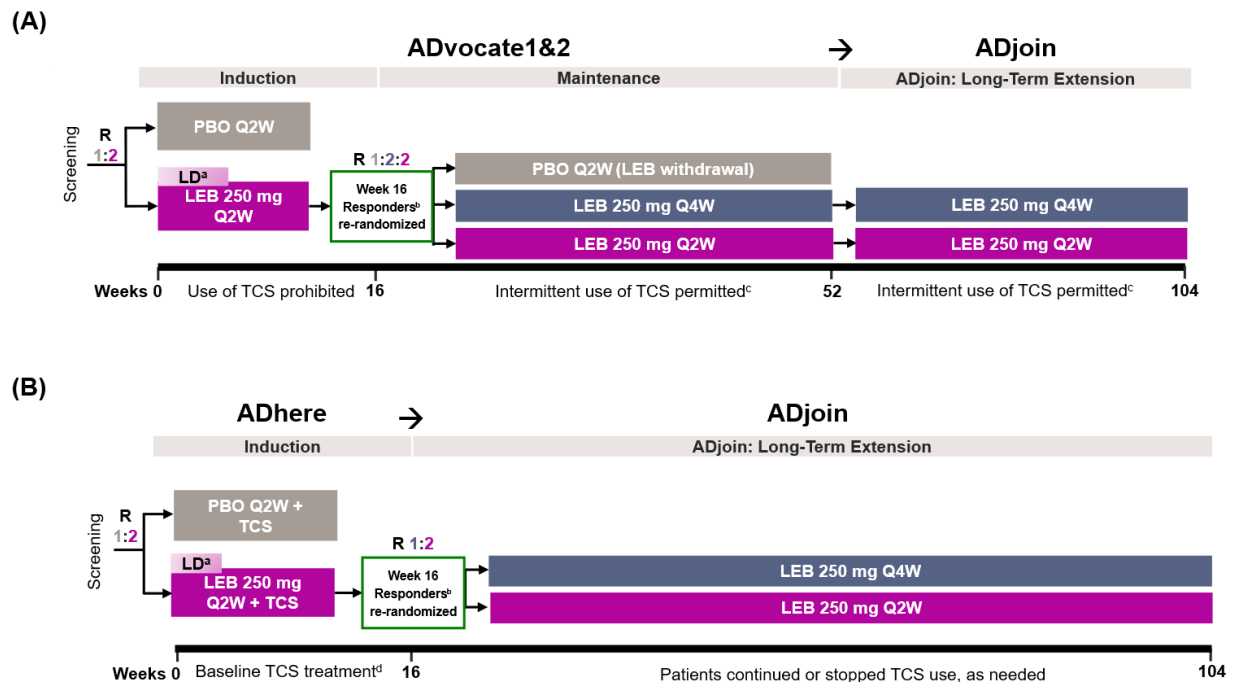


Figure shows only parent study Week 16 lebrikizumab responders who were re-randomized, entered into ADjoin, and received lebrikizumab. All patients who completed final visit of the respective parent study could enter ADjoin.

^aLebrikizumab-treated patients received a 500 mg loading dose at Weeks 0 and 2.

^bResponders in ADvocate1&2 and ADhere were defined as patients who achieved either EASI 75 or IGA (0,1) following 16 weeks of lebrikizumab 250 mg Q2W treatment without use of rescue therapy.

^cPatients who required short-term systemic treatment for AD in the ADvocate1&2 Maintenance Period and ADjoin were assessed on a case-by-case basis.

^dTCS treatment was initiated at baseline in all patients and was tapered or stopped, as needed, based on treatment response.

EASI 75=at least 75% improvement from baseline in Eczema Area and Severity Index; IGA=Investigator's Global Assessment;

LD=loading dose; LEB=lebrikizumab; PBO=placebo; Q2W=every 2 weeks; Q4W=every 4 weeks; R=randomization;

TCS=topical corticosteroids.

Figure S2. Disposition of patients from ADvocate1 and ADvocate2 who entered ADjoin
Disposition of patients who achieved clinical response following 16 Weeks of lebrikizumab treatment in ADvocate1 and ADvocate2 and entered ADjoin (ADvocate1&2 re-randomized population).

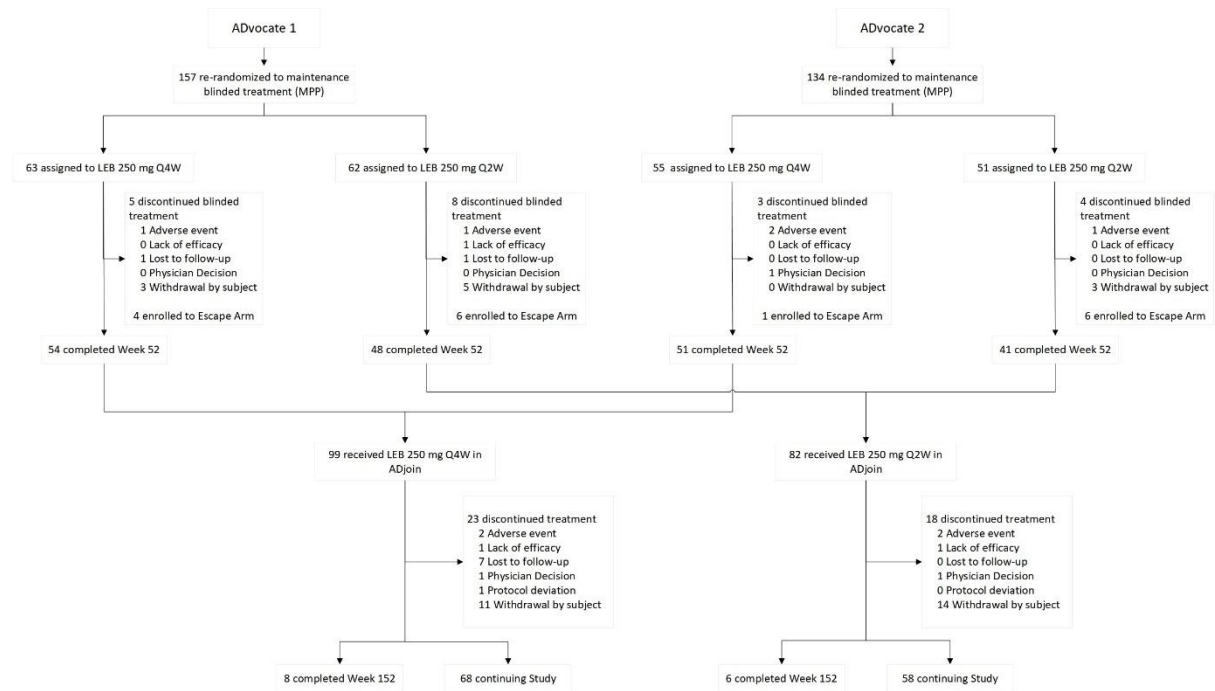
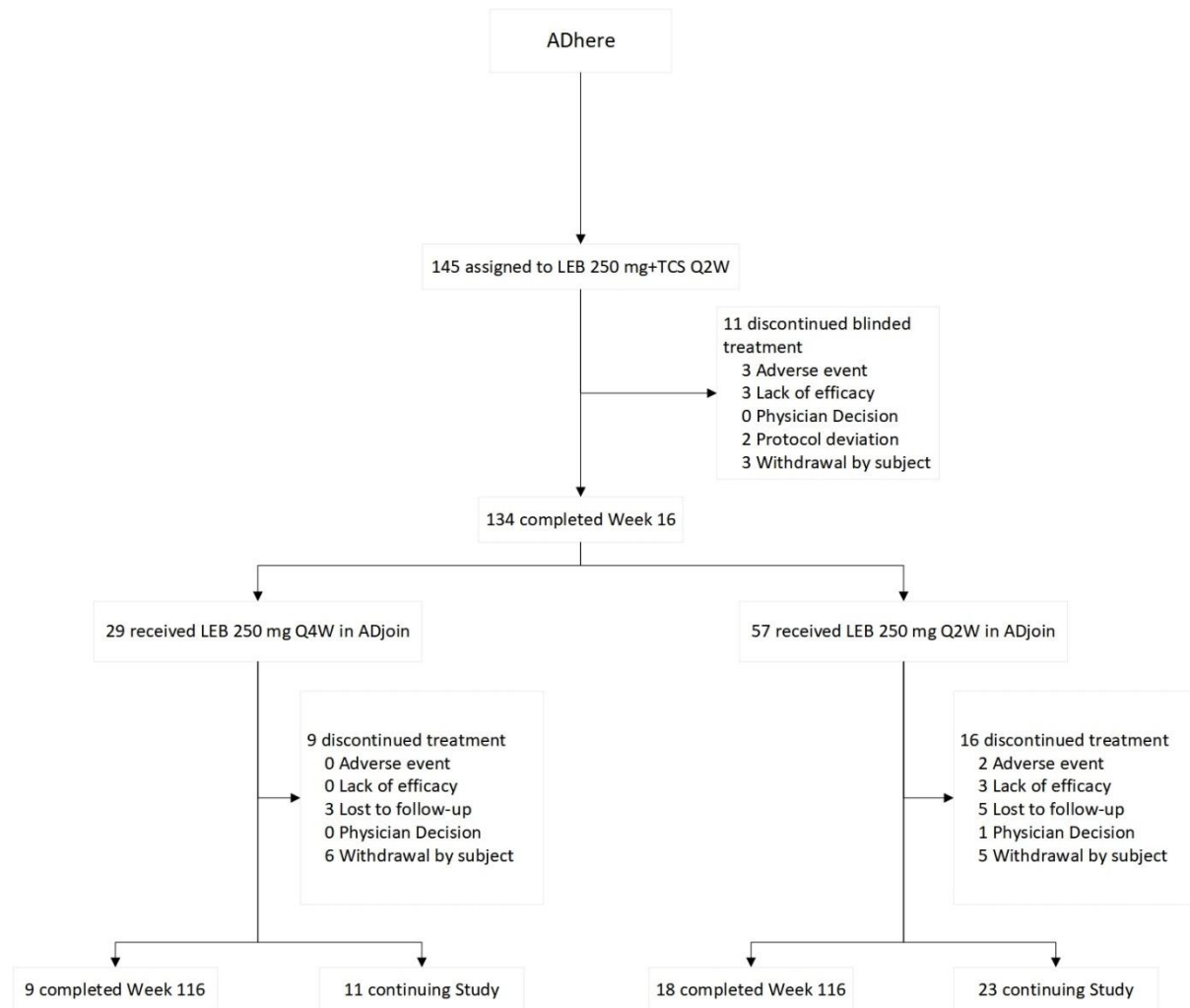


Figure S3. Disposition of patients from ADhere who entered ADjoin

Disposition of patients in ADhere who achieved clinical response following 16 Weeks of lebrikizumab treatment and entered ADjoin (ADhere re-randomized population).



Supplementary Methods

ADvocate1 and ADvocate2 Inclusion and Exclusion criteria

Inclusion Criteria

Patients must meet all the following criteria to be eligible for this study:

1. Adults and adolescents (≥ 12 to < 18 years of age and weighing ≥ 40 kg).
2. Chronic AD (according to American Academy of Dermatology Consensus Criteria) that has been present for ≥ 1 year before the screening visit.
3. Eczema Area and Severity Index (EASI) score ≥ 16 at the baseline visit.
4. Investigator Global Assessment (IGA) score ≥ 3 (scale of 0 to 4) at the baseline visit.
5. $\geq 10\%$ body surface area (BSA) of AD involvement at the baseline visit.
6. History of inadequate response to treatment with topical medications; or determination that topical treatments are otherwise medically inadvisable.
7. Apply a stable dose of non-medicated topical moisturizer at least twice daily for ≥ 7 days prior to the baseline visit.
8. Completed electronic diary entries for pruritus and sleep-loss for a minimum of 4 of 7 days preceding randomization.
9. Willing and able to comply with all clinic visits and study-related procedures and questionnaires.
10. For women of childbearing potential: agree to remain abstinent (refrain from heterosexual intercourse) or use a highly effective contraceptive method during the treatment period and for at least 18 weeks after the last dose of lebrikizumab or placebo.
NOTE: A woman of childbearing potential (WOCBP) is defined as a postmenarcheal female, who has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause) and has not undergone surgical sterilization (removal of ovaries and/or uterus).
NOTE: The following are highly effective contraceptive methods: combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) associated with inhibition of ovulation, progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation, intrauterine device (IUD), intrauterine hormone-releasing system (IUS), bilateral tubal occlusion, vasectomized partner, or sexual abstinence. The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.
11. Male patients must agree to use an effective barrier method of contraception during the study and for a minimum of 18 weeks following the last dose of study drug if sexually active with a female of childbearing potential.
12. Provide signed informed consent/assent.

Exclusion Criteria

Patients meeting any of the criteria below will be excluded from this study:

1. Participation in a prior lebrikizumab clinical study.
2. History of anaphylaxis as defined by the Sampson criteria (Sampson, 2006).
3. Treatment with topical corticosteroids, calcineurin inhibitors or phosphodiesterase-4 inhibitors such as crisaborole within 1 week prior to the baseline visit.
4. Prior treatment with dupilumab or tralokinumab.
5. Treatment with any of the following agents within 4 weeks prior to the baseline visit:
 - a. Immunosuppressive/immunomodulating drugs (e.g., systemic corticosteroids, cyclosporine, mycophenolate-mofetil, IFN- γ , Janus kinase inhibitors, azathioprine, methotrexate, etc.)
 - b. Phototherapy and photochemotherapy (PUVA) for AD.
6. Treatment with the following prior to the baseline visit:
 - a. An investigational drug within 8 weeks or within 5 half-lives (if known), whichever is longer.
 - b. B Cell-depleting biologics, including rituximab, within 6 months.
 - c. Other biologics within 5 half-lives (if known) or 16 weeks, whichever is longer.
7. Use of prescription moisturizers within 7 days of the baseline visit.
8. Regular use (more than 2 visits per week) of a tanning booth/parlor within 4 weeks of the screening visit.
9. Treatment with a live (attenuated) vaccine within 12 weeks of the baseline visit or planned during the study.
10. Uncontrolled chronic disease that might require bursts of oral corticosteroids, e.g., co-morbid severe uncontrolled asthma (defined by an ACQ-5 score ≥ 1.5 or a history of ≥ 2 asthma exacerbations within the last 12 months requiring systemic [oral and/or parenteral] corticosteroid treatment or hospitalization for > 24 hours).
11. Active chronic or acute infection requiring treatment with systemic antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals within 2 weeks before the baseline visit, or superficial skin infections within 1 week before the baseline visit.
NOTE: patients may be rescreened after infection resolves.
12. Evidence of active acute or chronic hepatitis (as defined by the Department of Health & Human Services Centers for Disease Control and Prevention) or known liver cirrhosis.
13. Diagnosed active endoparasitic infections or at high risk of these infections.
14. Known or suspected history of immunosuppression, including history of invasive opportunistic infections (e.g., tuberculosis [TB], histoplasmosis, listeriosis, coccidioidomycosis, pneumocystosis, and aspergillosis) despite infection resolution: or unusually frequent, recurrent, or prolonged infections, per the Investigator's judgment.
15. History of human immunodeficiency virus (HIV) infection or positive HIV serology at screening.
16. In the Investigator's opinion, any clinically significant laboratory results from the chemistry, hematology or urinalysis tests obtained at the screening visit.
17. Presence of skin comorbidities that may interfere with study assessments.
18. History of malignancy, including mycosis fungoides, within 5 years before the screening visit, except completely treated in situ carcinoma of the cervix, completely treated and resolved non-metastatic squamous or basal cell carcinoma of the skin.

19. Severe concomitant illness(es) that in the Investigator's judgment would adversely affect the patient's participation in the study. Any other medical or psychological condition that in the opinion of the Investigator may suggest a new and/or insufficiently understood disease, may present an unreasonable risk to the study patient because of his/her participation in this clinical trial, may make patient's participation unreliable, or may interfere with study assessments.

20. Pregnant or breastfeeding women, or women planning to become pregnant or breastfeed during the study.

ADhere Inclusion and Exclusion criteria

Inclusion Criteria

Patients must meet all the following criteria to be eligible for this study:

1. Adults and adolescents (≥ 12 to < 18 years of age and weighing ≥ 40 kg).
2. Chronic AD (according to American Academy of Dermatology Consensus Criteria) that has been present for ≥ 1 year before the screening visit.
3. Eczema Area and Severity Index (EASI) score ≥ 16 at the baseline visit.
4. Investigator Global Assessment (IGA) score ≥ 3 (scale of 0 to 4) at the baseline visit.
5. $\geq 10\%$ body surface area (BSA) of AD involvement at the baseline visit.
6. History of inadequate response to treatment with topical medications.
7. Applied a stable dose of non-medicated topical moisturizer at least twice daily for ≥ 7 days prior to the baseline visit.
8. Completed electronic diary entries for pruritus and sleep-loss for a minimum of 4 of 7 days preceding randomization.
9. Willing and able to comply with all clinic visits and study-related procedures and questionnaires.
10. For women of childbearing potential: agree to remain abstinent (refrain from heterosexual intercourse) or use a highly effective contraceptive method during the treatment period and for at least 18 weeks after the last dose of lebrikizumab or placebo.
NOTE: A woman of childbearing potential (WOCBP) is defined as a postmenarcheal female, who has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).
NOTE: The following are highly effective contraceptive methods: combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) associated with inhibition of ovulation, progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation, intrauterine device (IUD), intrauterine hormone-releasing system (IUS), bilateral tubal occlusion, vasectomized partner, or sexual abstinence. The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.
11. Male patients must agree to use an effective barrier method of contraception during the study and for a minimum of 18 weeks following the last dose of study drug if sexually active with a female of childbearing potential.
12. Provided signed informed consent/assent.

Exclusion Criteria

Patients meeting any of the criteria below will be excluded from this study:

1. Participation in a prior lebrikizumab clinical study.
2. History of anaphylaxis as defined by the Sampson criteria (Sampson 2006).
3. Treatment with topical corticosteroids, calcineurin inhibitors or Phosphodiesterase-4 inhibitors such as crisaborole within 1 week prior to the baseline visit.
4. Treatment with any of the following agents within 4 weeks prior to the baseline visit:
 - a. Immunosuppressive/immunomodulating drugs (e.g., systemic corticosteroids, cyclosporine, mycophenolate-mofetil, IFN- γ , Janus kinase inhibitors, azathioprine, methotrexate, etc.)
 - b. Phototherapy and photochemotherapy (PUVA) for AD.
5. Treatment with the following prior to the baseline visit:
 - a. An investigational drug within 8 weeks or within 5 half-lives (if known), whichever is longer.
 - b. Dupilumab within 8 weeks.
 - c. B Cell-depleting biologics, including rituximab, within 6 months.
 - d. Other biologics within 5 half-lives (if known) or 16 weeks, whichever is longer.
6. Use of prescription moisturizers within 7 days of the baseline visit.
7. Regular use (more than 2 visits per week) of a tanning booth/parlor within 4 weeks of the screening visit.
8. Treatment with a live (attenuated) vaccine within 12 weeks of the baseline visit or planned during the study.
9. Uncontrolled chronic disease that might require bursts of oral corticosteroids, e.g., co-morbid severe uncontrolled asthma (defined by an ACQ-5 score ≥ 1.5 or a history of ≥ 2 asthma exacerbations within the last 12 months requiring systemic [oral and/or parenteral] corticosteroid treatment or hospitalization for > 24 hours).
10. Active chronic or acute infection requiring treatment with systemic antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals within 2 weeks before the baseline visit, or superficial skin infections within 1 week before the baseline visit.
NOTE: patients may be rescreened after infection resolves.
11. Evidence of active acute or chronic hepatitis (as defined by the Department of Health & Human Services Centers for Disease Control and Prevention) or known liver cirrhosis.
12. Diagnosed active endoparasitic infections or at high risk of these infections.
13. Known or suspected history of immunosuppression, including history of invasive opportunistic infections (e.g., tuberculosis [TB], histoplasmosis, listeriosis, coccidioidomycosis, pneumocystosis, and aspergillosis) despite infection resolution: or unusually frequent, recurrent, or prolonged infections, per the Investigator's judgment.
14. History of human immunodeficiency virus (HIV) infection or positive HIV serology at screening.
15. In the Investigator's opinion, any clinically significant laboratory results from the chemistry, hematology or urinalysis tests obtained at the screening visit.
16. Presence of skin comorbidities that may interfere with study assessments.
17. History of malignancy, including mycosis fungoides, within 5 years before the screening visit, except completely treated in situ carcinoma of the cervix, completely treated and resolved non-metastatic squamous or basal cell carcinoma of the skin.

18. Severe concomitant illness(es) that in the Investigator's judgment would adversely affect the patient's participation in the study. Any other medical or psychological condition that in the opinion of the Investigator may suggest a new and/or insufficiently understood disease, may present an unreasonable risk to the study patient because of his/her participation in this clinical trial, may make patient's participation unreliable, or may interfere with study assessments.

19. Pregnant or breastfeeding women, or women planning to become pregnant or breastfeed during the study.

20. Have had an important side effect to TCS (e.g., intolerance to treatment, hypersensitivity reactions, significant skin atrophy, and systemic effects), as assessed by the Investigator or treating physician that would prevent further use.