used in combination with TCS treatment compared with placebo in combination with TCS treatment for moderate-to-severe AD.

Eligible adult and adolescent patients (≥12 to <18 years and weighing ≥40 kg) with moderate-to-severe AD for at least one year, defined according to the American Academy of Dermatology Consensus Criteria, an Eczema Area and Severity Index Score (EASI) of ≥16, an Investigator Global Assessment (IGA) score of ≥3 and a body surface area (BSA) of ≥10% will be enrolled.

During the 16-week treatment period, approximately 225 patients will be stratified and randomized (2:1, active: placebo) to treatment with either 250 mg lebrikizumab (loading dose of 500 mg given at Baseline and Week 2) or placebo by subcutaneous (SC) injection every 2 weeks (Q2W). All study drug injections will be administered in the clinic. TCS treatment will be initiated at Baseline in all patients and may be tapered or stopped, as needed, based on treatment response.

Efficacy will be measured through IGA, EASI, SCORing Atopic Dermatitis (SCORAD), BSA, Pruritus and Sleep-loss scores and, TCS/TCI use.

Safety will be assessed in all patients by monitoring adverse events, serum chemistry, hematology and urinalysis laboratory testing, physical examination, pulse and blood pressure. Additionally, adolescents will be monitored for hormones. An independent Data Safety Monitoring Board will monitor patient safety by conducting formal reviews of accumulated safety data periodically throughout the trial.

Quality of life and impact of disease will be assessed using the Patient Oriented Eczema Measure (POEM), Dermatology Life Quality Index/Children's Dermatology Life Quality Index (DLQI/CDLQI), standardized instrument developed by the EuroQol Group (EQ-5D), and Patient-Reported Outcomes Measurement Information System (PROMIS®) Anxiety and Depression measures. Patients reporting comorbid asthma at study entry will complete the Asthma Control Questionnaire (ACQ-5).

Serum samples will be collected for pharmacokinetic analysis and immunogenicity.

After completion of the Week 16 visit, patients will be offered the option of continued treatment in a separate long-term extension study (DRM06-AD07).

Patients who early terminate or choose not to enter the long-term extension study will undergo a safety follow-up visit approximately 12 weeks after the last study drug injection.

A patient is considered to have completed the study if he/she has completed all required phases of the study including the last visit as shown in the Schedule of Visits and Procedures.

The end of the study is defined as the date of the last visit of the last patient in the study shown in the Schedule of Visits and Procedures.

FDA	EMA
• Change from Baseline to Week 16 in percent BSA • Percentage of patients achieving EASI-90 at Week 4 • Percentage change in Sleep-loss score from Baseline to Week 16 • Change from Baseline in Sleep-loss score at Week 16 • Percentage of patients with a Pruritus NRS of ≥4-points at Baseline who achieve a ≥4-point reduction from Baseline to Week 4 • Percentage of patients with a Pruritus NRS of ≥4-points at Baseline who achieve a ≥4-point reduction from Baseline to Week 2 • Percentage of patients with a Pruritus NRS of ≥4-points at Baseline who achieve a ≥4-point reduction from Baseline to Week 1 • Proportion of TCS / TCI-free days from Baseline to Week 16 • Time (days) to TCS / TCI-free use from Baseline to Week 16	• Percentage of patients achieving EASI-90 at Week 4 • Change from baseline in DLQI at Week 16 • Percentage of patients achieving ≥4-point improvement in DLQI from baseline to Week 16 • Percentage change in Sleep-loss score from Baseline to Week 16 • Change from Baseline in Sleep-loss score at Week 16 • Proportion of TCS / TCI-free days from Baseline to Week 16 • Time (days) to TCS / TCI-free use from Baseline to Week 16 • Percentage of patients with a Pruritus NRS of ≥4-points at Baseline who achieve a ≥4-point reduction from Baseline to Weeks 1, 2 and 4 • Percentage of patients with a Pruritus NRS of ≥5-points at Baseline who achieve a ≥4-point reduction from Baseline to Weeks 1, 2 and 4

2.3. Other Secondary Endpoints

- Proportion of patients with EASI-75, EASI-90 and EASI-50 by visit
- Proportion of patients with IGA Score of 0 or 1 and a reduction ≥2 points from Baseline by visit
- Percentage change from Baseline in EASI Score by visit
- Percentage change from Baseline in Pruritus NRS by visit
- Percentage of patients with Pruritus NRS change of ≥4 from Baseline by visit
- Percentage of patients with a Pruritus NRS score of ≥4 points at Baseline who achieve a ≥4-point reduction from Baseline by visit
- Change from Baseline in Sleep-Loss score by visit
- Change from Baseline in DLQI/CDLQI by visit
- Change from Baseline in EQ5D by visit
- Change from Baseline in POEM by visit
- Change from Baseline in PROMIS Anxiety measure by visit

- Change from Baseline in PROMIS Depression measure by visit
- Change in ACQ-5 score from Baseline to Week 16 in patients who have self-reported comorbid asthma
- Percentage change from Baseline to Week 16 in SCORAD

3. STUDY DESIGN

This is a randomized, double-blind, placebo-controlled, parallel-group study which is 16 weeks in duration. The study is designed to evaluate the safety and efficacy of lebrikizumab when used in combination with TCS treatment compared with placebo in combination with TCS treatment for moderate-to-severe AD (Figure 1).

Eligible adult and adolescent patients (≥12 to <18 years and weighing ≥40 kg) with moderate-to-severe AD for at least one year, defined according to the American Academy of Dermatology Consensus Criteria, an EASI of ≥16, an IGA score of ≥3 and a BSA of ≥10% will be enrolled.

During the 16-week treatment period, approximately 225 patients will be stratified and randomized 2:1 to treatment with either 250 mg lebrikizumab (loading dose of 500 mg given at Baseline and Week 2) or placebo by subcutaneous (SC) injection every 2 weeks (Q2W). All study drug injections will be administered in the clinic. TCS will be initiated at Baseline in all patients and may be tapered or stopped, as needed, based on treatment response.

Efficacy will be measured through IGA, EASI, SCORAD, BSA, Pruritus and Sleep-loss scores and, TCS/TCI use.

Safety will be assessed by monitoring adverse events, serum chemistry, hematology and urinalysis laboratory testing, physical examination, pulse and blood pressure. An independent Data Safety Monitoring Board will monitor patient safety by conducting formal reviews of accumulated safety data periodically throughout the trial.

Quality of life and impact of disease will be assessed using the POEM, DLQI/CDLQI, EQ-5D, and PROMIS® Anxiety and Depression measures. Patients reporting comorbid asthma at study entry will complete the ACQ-5.

Serum samples will be collected for pharmacokinetic analysis and immunogenicity.

After completion of the Week 16 visit, patients will be offered the option to continue treatment in a separate long-term extension study (DRM06-AD07).

Patients who early terminate or choose not to enter the long-term extension study will receive a safety follow-up approximately 12 weeks after the last study drug injection.

Completion of Patient Participation: A patient is considered to have completed the study if he/she has completed the last scheduled visit:

- For subjects continuing into LTE, upon completion of week 16 visit and rolling into LTE study
- For subjects not continuing into LTE, when subject had either week 16 or ET visit, and safety follow up visit (12 weeks after last IP administration)

The end of the study is defined as the date of the last visit of the last patient in the study shown in the Schedule of Visits and Procedures.

Figure 1: Study Schema

3.1. Duration of the Study

The total duration of a patient's participation in this study, if enrolling in the LTE, will be approximately 20 weeks (Screening: maximum duration of 30 days; Treatment Period: 16 weeks).

The total duration of a patient's participation in this study if not enrolling in the long-term extension will be approximately 30 weeks (Screening: maximum duration of 30 days; Treatment Period: 16 weeks; Post-Treatment Follow-up: 12 weeks from last dose).

3.2. Study Population and Number of Patients

Approximately 225 patients with moderate to severe atopic dermatitis, including approximately 50 adolescent patients (≥12 to <18 years, weighing ≥40 kg).

4. SELECTION OF PATIENTS

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

4.1. 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 (see Appendix 2).
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 (see Section 8.2.1).
5. ≥10% body surface area (BSA) of AD involvement at the baseline visit

8.1.2. Medical History

A complete medical history will be collected and include immunization record (for adolescent patients), clinically relevant medical conditions or surgeries, including more specific information on a history of conjunctivitis and herpes infection/zoster. Information on the patient's AD and comorbidities (past history of asthma, allergic rhinitis, food allergies, alopecia) will be collected and include the date of onset, extent of involvement and past treatments for AD and comorbidities.

8.2. Assessment of Efficacy

Each patient's AD will be assessed as specified in the Schedule of Visits and Procedures. Whenever possible, the same assessor should perform all assessments on a given patient over the course of the study. The sponsor will administer training on the required efficacy assessments, detail on the specific instruments and training given are recorded in the study training materials.

8.2.1. Investigator Global Assessment

The IGA is a static assessment and rates the severity of the patient'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 point. It is not necessary that all characteristics under Morphological Description be present. Assessors must be trained and certified by the Sponsor prior to conducting this assessment. The IGA must be conducted prior to conducting the EASI and BSA assessments. A single assessor should be assigned to each individual patient for as many visits as possible, to avoid inter-assessor variability in scoring.

Table 2: Investigator Global Assessment

Score	Grade	Definition
0	Clear	Minor, residual discoloration; no erythema or induration/papulation; no oozing/crusting; no edema.
1	Almost Clear	Trace, faint pink erythema with barely perceptible induration/papulation and no oozing/crusting; no edema.
2	Mild	Faint-pink erythema with papulation and edema perceptible upon palpation and no oozing/crusting; minimal induration.
3	Moderate	Pink-red erythema with definite edema of skin papules and plaques; there may be some oozing/crusting; palpable induration.
4	Severe	Deep/bright red erythema with significant swelling and obvious raised borders of papules and plaques with oozing/crusting; significant induration.

8.2.2. Eczema Area and Severity Index

The 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. Assessors must be trained and certified by the Sponsor prior to conducting this assessment.

8.3.1. Patient Oriented Eczema Measure

The POEM is a 7-item, validated, questionnaire used by the patient to assess disease symptoms over the last week. The patient is asked to respond to 7 questions on skin dryness, itching, flaking, cracking, sleep loss, bleeding and weeping. All 7 answers carry equal weight with a total possible score from 0 to 28 (answers scored as: No days=0; 1– 2 days = 1; 3-4 days = 2; 5–6 days = 3; everyday = 4). A high score is indicative of a poor quality of life. POEM responses will be captured using an electronic diary and transferred into the clinical database.

8.3.2. Dermatology Life Quality Index

The DLQI is a 10-item, validated questionnaire used to assess the impact of skin disease on the quality of life of an affected person. The 10 questions cover the following topics: symptoms, embarrassment, shopping and home care, clothes, social and leisure, sport, work or study, close relationships, sex, and treatment, over the previous week. Questions are scored from 0 to 3, giving a possible total score range from 0 (meaning no impact of skin disease on quality of life) to 30 (meaning maximum impact on quality of life). A high score is indicative of a poor quality of life. Patients ≤16 years will complete the Children's Dermatology Life Quality Index (CDLQI) and should continue to complete the CDLQI for the duration of the study. DLQI/CDLQI is completed by the patient in the study clinic.

8.3.3. EQ-5D

EQ-5D comprises five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The EQ VAS records the patient's self-rated health on a vertical visual analogue scale. The scores on these five dimensions can be presented as a health profile or can be converted to a single summary index number (utility) reflecting preferability compared to other health profiles. EQ-5D is completed by the patient in the study clinic.

8.3.4. Patient-Reported Outcomes Measurement Information System: Anxiety and Depression

Patient-Reported Outcomes Measurement Information System is a set of person-centered measures that evaluates and monitors physical, mental, and social health in adults and children. Pediatric and tools for anxiety and depression. Patients ≤17 years will complete pediatric versions for the duration of the study. The PROMIS measures will be completed by the patient in the study clinic.

8.3.5. Asthma Control Questionnaire

Patients who report comorbid asthma prior to enrollment will complete the ACQ-5) in addition to other patient reported outcomes in this trial. The ACQ-5 has been shown to reliably measure asthma control and distinguish patients with well-controlled asthma (score ≤0.75 points) from those with uncontrolled asthma (score ≥1.5 points). It consists of 5 questions that are scored on a 7-point Likert scale with a recall period of 1 week. The total ACQ-5 score is the mean score of all questions; a lower score represents better asthma control. ACQ-5 is completed by the patient in the study clinic.

8.4. Assessment of Safety

8.4.1. Physical Examination

A complete physical examination will be conducted at screening and cover general appearance, dermatological, head, ears, eyes, nose, throat, respiratory, cardiovascular, abdominal, neurological, musculoskeletal, and lymphatic body systems. Height and weight will also be recorded. At subsequent study visits, a symptom-directed physical examination may be conducted at the discretion of the Investigator. Findings will be recorded as medical history or AE in the eCRF.

8.4.2. Vital Signs

Vital signs, including body temperature, respiratory rate (breath per minute), pulse (beats per minute), and blood pressure (mmHg), will be obtained with the patient in the seated position, after sitting for at least 5 minutes. Any abnormal findings which are new or worsened in severity and clinically significant, in the opinion of the Investigator, will be recorded as an AE. Vital sign measurements will be recorded in the eCRF.

8.4.3. Laboratory Evaluations

Laboratory tests will be analyzed using a central laboratory and include hematology with differential, serology, a standard chemistry panel (including liver-function tests), total cholesterol, standard urine testing, and urine pregnancy test for women who are not post-menopausal or surgically sterile. Blood and urine will be collected from each patient as specified in the Schedule of Visits and Procedures or as clinically indicated. Laboratory data will be transferred to the clinical database.

Table 3: Laboratory Parameters

Hematology	Chemistry	Urine	Hormones
CBC with differential: Hematocrit (HCT) Hemoglobin (HGB) Red blood cells (RBC) White blood cells (WBC) Mean corpuscular hemoglobin (MCH) MCH concentration (MCHC) Mean corpuscular volume (MCV) RBC morphology Platelet count Neutrophils Lymphocytes Monocytes Eosinophils Basophils Screening Only: HIV Antibody (HIV Ab) Hepatitis B Antibody (HBcAb) Hepatitis B Antigen (HBsAg) Hepatitis C Antibody (Hep C Ab)	Sodium Potassium Chloride Calcium Phosphorus Bicarbonate Uric Acid Blood urea nitrogen (BUN) Creatinine Total Protein Albumin Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Lactic dehydrogenase (LDH) Gamma-glutamyl transpeptidase (GGT) Alkaline phosphatase Bilirubin (total and direct) Total cholesterol Non-fasting glucose For All Female Patients (WOCBP) At Screening: Serum beta human chorionic gonadotropin (β-hCG)	pH Specific gravity Protein Glucose Ketones Bilirubin Blood Nitrite Urobilinogen Leukocyte esterase At All Visits Except Screening (WOCBP only): Urine beta human chorionic gonadotropin (β-hCG)	Estradiol (for adolescent females only) Testosterone (for adolescent males only)

8.4.4. Adverse Events

Adverse events will be monitored throughout the study. Patients will be instructed to inform the Investigator and/or study staff of any AEs. At each visit, patients will be asked about AEs in a non-specific manner using open-ended questions so as not to bias the response (e.g., How have you been since the last visit?). Specific inquiry regarding reported AEs will be conducted when applicable. All AEs will be documented and recorded in the patient's eCRF.

Any patient who has an AE (serious or non-serious) will be evaluated by the Investigator and treated and followed until the symptom(s) return to normal or to clinically acceptable levels, as judged by the Investigator. A physician, either at the clinical site, or at a nearby hospital emergency room, will administer treatment for any serious AEs (SAEs), if necessary. When

appropriate, medical tests and examinations will be performed to document resolution of event(s).

8.4.4.1. Reporting

Only AEs that occur during or following study treatment with the study drug will be reported in the AE section of the eCRF. Events occurring prior to study treatment with the drug will be reported in the Medical History section of the eCRF. All AEs occurring during the study will be individually recorded in the eCRF. Any condition present prior to administration of study drug and that worsens after administration of study drug should be reported as an AE. Information regarding the onset, duration, severity, action taken, outcome, and relationship to study drug will be recorded.

New or worsening abnormal laboratory values and/or vital signs are to be recorded as AEs if they are considered to be of clinical significance by the Investigator or meet the criteria of an SAE as described in Section 8.4.4.3. Unless an overall diagnosis is described, signs and symptoms must be reported as individual AEs in the eCRF; a diagnosis is preferred.

The severity of an AE will be designated as mild, moderate or severe. The term “severe” is used to describe the intensity of an AE; the event itself, however, may be of relatively minor clinical significance (e.g., ‘severe’ upper respiratory infection). Severity is not the same as “serious”. Seriousness of AEs is based on the outcome/action of an AE. (See Section 8.4.4.3)

The relationship of the AE to the study treatment should be determined by the Investigator and will be based on the following two definitions:

Not related: The AE is judged to not be associated with the study drug and is most likely attributable to another cause.

Related: A causal relationship between the AE and the study drug is a reasonable possibility, i.e., there is evidence (e.g., dechallenge/rechallenge) or other clinical arguments to suggest a causal relationship between the AE and study treatment.

8.4.4.2. Adverse Events of Special Interest

The following treatment emergent adverse events are being designated adverse events of special interest (AESI):

- conjunctivitis
- herpes infection or zoster
- parasitic infection or an infection related to an intracellular pathogen

Adverse events of special interest should be reported to the Sponsor or designee within 48 hours of knowledge of the event. Additional data will be collected for AESIs on study-specific AESI forms will be provided to the site. Patient records must include any follow-up information regarding these AESIs.

Study drug should be discontinued if an adverse event is deemed persistent and if continuation of study drug would not be in the best interest of the patient. Discuss discontinuation of study drug or dose changes with the Sponsor or designee prior to implementation.

8.4.4.3. Serious Adverse Events

An SAE is defined as any untoward medical occurrence that,

- Results in death
- Is in the opinion of the Investigator immediately life threatening (i.e., the patient is at immediate risk of death; it does not include a reaction that, had it occurred in a more severe form, might have caused death)
- Requires inpatient hospitalization or results in prolongation of an existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event that may not be immediately life-threatening, result in death, or require hospitalization, but based on appropriate medical judgment, it jeopardizes the patient, or may require medical or surgical intervention to prevent one of the outcomes listed. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

The Investigator should institute any clinically necessary supplementary investigation of SAE information. In the case of patient death, any post-mortem findings/reports will be requested.

8.4.4.4. Reporting of Serious Adverse Events

All SAEs, as defined in Section 8.4.4.3, regardless of causal relationship, must be reported to the Sponsor or designee within 24 hours of the Investigator becoming aware of the event. As soon as the Investigator becomes aware of an AE that meets the criteria for an SAE, the SAE should be documented to the extent that information is available.

Serious adverse events will be recorded from the time of informed consent/assent until the end of the study. If, in the opinion of the Investigator, an SAE occurring outside the specified time window (i.e., following patient completion or terminations of the study) is deemed to be drug-related, the event should be reported with 24 hours.

Serious adverse events must be recorded on study-specific SAE forms which will be provided to the site. The minimum information required for SAE reporting includes the identity of the PI, site number, patient number, event description, SAE term(s), reason why the event is considered serious (i.e., the seriousness criteria), and PI's assessment of the relationship of the event to study drug. Additional SAE information including medications or other therapeutic measures used to treat the event, and the outcome/resolution of the event should also be recorded on the SAE form.

In all cases, the Investigator should continue to monitor the clinical situation and report all material facts relating to the progression or outcome of the SAE. The Investigator may be required to provide supplementary information as requested by the Sponsor or its designee.

When reporting SAEs, the following additional points should be considered:

- Although signs, symptoms, and tests that support the diagnosis of an SAE should be provided, the Investigator should report the diagnosis or syndrome as the SAE term.
- Death should not be reported as an SAE, but as an outcome of a specific SAE (unless the event preceding the death is unknown). If an autopsy was performed, the autopsy report should be provided.

Although most hospitalizations necessitate reporting of an SAE, some hospitalizations do not:

- Hospitalization for elective or previously scheduled surgery, or for a procedure for a pre-existing condition that has not worsened after administration of study drug (e.g., a previously scheduled ventral hernia repair). SAEs must, however, be reported for any surgical or procedural complication that lead to prolongation of the hospitalization.
- Events that result in hospital stays for observation of <24 hours and that do not require a therapeutic intervention/treatment (e.g., an emergency room visit for hematuria that results in a diagnosis of cystitis and discharge to home on oral antibiotics).

The Sponsor will process and evaluate all SAEs as soon as the reports are received. For each SAE received, the Sponsor will determine whether the criteria for expedited reporting to relevant regulatory authorities have been met.

The Sponsor will assess the likelihood that each SAE is related to study treatment, with the current Investigator's Brochure used as the reference document to assess expectedness of the event to study drug.

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.5. Product Complaints

A product complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a trial intervention. The sponsor collects product complaints on investigational products and drug delivery systems used in clinical studies in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements. Participants will be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the investigational product or drug delivery system so that the situation can be assessed.

9.11. Other Safety Data

Laboratory data will be presented in a by patient listing. Any clinically significant laboratory abnormalities will be captured as AEs. Changes from Baseline in safety laboratory values will be summarized by treatment group at each follow-up evaluation during the treatment period using descriptive statistics or frequency tables as applicable. Tables and listings will be in SAS format. Additionally, changes from Baseline in safety laboratory values will be summarized using shift tables according to normal ranges.

Vital signs will be presented by treatment group as absolute values and changes from Baseline using descriptive statistics.

Medical histories will be coded using the MedDRA dictionary and presented in a by-patient listing. Concomitant medications will be coded using the WHO-Drug dictionary. Concomitant medications will be summarized by treatment, drug class, and preferred term. Physical examination data will be presented in a by-patient listing. Growth monitoring of adolescents will be summarized.

9.12. Sample-Size Determination

For FDA

Approximately 225 patients will be randomized at a 2:1 ratio to lebrikizumab or placebo (150 patients:75 patients). The assumed IGA score of 0 or 1 at Week 16 response rates are 38% for lebrikizumab 250 mg Q2W and 13% for placebo. The assumption for lebrikizumab is based on the DRM06-AD01 Phase 2b study, the proportion of patients who achieved an IGA score of 0 or 1 at Week 16 using the rescue medication non-response sensitivity analysis, adjusting for the allowed use of TCS/TCI. The placebo response rates are based on the review of historical TCS clinical studies in atopic dermatitis (Simpson et al. 2016). This study has power >95% for testing superiority of lebrikizumab to placebo based on a two-sided Fisher's exact test with alpha of 0.05.

For EMA:

Approximately 225 patients will be randomized at a 2:1 ratio to lebrikizumab or placebo (150 patients:75 patients). The assumed IGA score of 0 or 1 at Week 16 response rates are 38% for lebrikizumab 250 mg Q2W and 13% for placebo. The assumed EASI75 response rate at Week 16 response rates are 58% for lebrikizumab 250 mg Q2W and 20% for placebo. The assumptions for lebrikizumab are based on the DRM06-AD01 Phase 2b study, the proportion of patients who achieved an IGA score of 0 or 1 and proportion of patients who achieved EASI75 response at Week 16 using the rescue medication non-response sensitivity analysis, adjusting for the allowed use of TCS/TCI. The placebo response rates are based on the review of historical TCS clinical studies in atopic dermatitis (Simpson et al. 2016). This study has power >95% for testing superiority of lebrikizumab to placebo based on a two-sided Fisher's exact test with alpha of 0.05.

9.13. Interim Analyses

A database lock and unblinding will occur, and the analysis will be performed at the time (that is, a cut-off date) the last patient completes Week 16 or the early termination visit from the study. This database lock will include all data collected by the cut-off date. This analysis will be

Study Procedure	Screening	Baseline	Treatment Period								Safety F/U[1]
Pre-dose ADA[3]		X		X						X	X

Table 4: Treatment Period Screening through Week 16 and Safety Follow-Up (Continued)

Study Procedure	Screening	Baseline	Treatment Period								Safety F/U[1]
Day (D); Week (W)	**D-30 to -7**	**D1**	**W2**	**W4**	**W6**	**W8**	**W10**	**W12**	**W14**	**W16 / ET**	**W26**
Visit Window			±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d
Efficacy											
IGA; EASI; BSA	X	X	X	X	X	X	X	X	X	X	
SCORAD		X								X	
E-Diary: Pruritus, Sleep- loss, (daily)	X	X	X	X	X	X	X	X	X	X	
E-Diary: POEM (weekly)	X	X	X	X	X	X	X	X	X	X	
Patient Reported Outcomes / Quality of Life											
DLQI/CDLQI*		X		X		X		X		X	
EQ-5D*		X								X	
ACQ-5*		X								X	
PROMIS Anxiety and Depression Measures*		X								X	
Treatment											
Administer study drug		Loading dose	Loading dose	X	X	X	X	X	X		

[1] For patients terminating early or not rolling into the long term extension study, a safety follow-up will occur 12 weeks after last dose of study medication.
[2] Collect estradiol in adolescent female participants only. Collect testosterone in adolescent male participants only.
[3] nAB testing conducted for positive treatment-emergent ADA responses. Additional immunogenicity sample collected for any patient experiencing a hypersensitivity reaction during study.
*Patient reported outcomes and quality of life measures should all be completed prior to other study assessments.

Primary Endpoint(s):

For FDA:

The primary efficacy endpoint is the percentage of patients with an IGA score of 0 or 1 and a reduction ≥2-points from Baseline to Week 16.

For EMA:

Co-primary endpoints will be used as follows:

- Percentage of patients with an IGA score of 0 or 1 and a reduction ≥2-points from Baseline to Week 16.
- Percentage of patients achieving EASI-75 (≥75% reduction from Baseline in EASI score) at Week 16

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 child bearing potential.
12. Provided signed informed consent/assent as described in Section 10.15.

4.2. 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.

8.2.3. Body Surface Area

The BSA assessment estimates the extent of disease or skin involvement with respect to AD and is expressed as a percentage of total body surface. Body surface area will be determined by the Investigator or designee using the patient palm = 1% rule. Assessors must be trained and certified by the Sponsor prior to conducting this assessment.

8.2.4. SCORing Atopic Dermatitis

SCORing Atopic Dermatitis is a validated clinical tool for assessing the extent and intensity of atopic dermatitis. There are 3 components to the assessment:

- The extent of AD is assessed as a percentage of each defined body area and reported as the sum of all areas, with a maximum score of 100% (assigned as "A" in the overall SCORAD calculation).
- The severity of 6 specific symptoms of AD (redness, swelling, oozing/crusting, excoriation, skin thickening/lichenification, dryness) is assessed using the following scale: none (0), mild (1), moderate (2), or severe (3) (for a maximum of 18 total points, assigned as "B" in the overall SCORAD calculation).
- Subjective assessment of itch and of sleeplessness is recorded for each symptom by the patient or relative on a VAS, where 0 is no itch (or sleeplessness) and 10 is the worst imaginable itch (or sleeplessness), with a maximum possible score of 20 (assigned as "C" in the overall SCORAD calculation).

The SCORAD is calculated as: A/5 + 7B/2 + C where the maximum is 103.

8.2.5. Pruritus

Pruritus will be assessed by the patient using a Pruritus Numerical Rating Scale (NRS). The Pruritus NRS is an 11-point scale used by patients to rate their worst itch severity over the past 24 hours with 0 indicating "No itch" and 10 indicating "Worst itch imaginable." Assessments will be recorded daily by the patient using an electronic diary. Data will be transferred to the clinical database.

8.2.6. Sleep-Loss

Sleep-loss due to pruritus will be assessed by the patient. Patients rate their sleep based on a 5-point Likert scale [0 (not at all) to 4 (unable to sleep at all)]. Assessments will be recorded daily by the patient using an electronic diary. Data will be transferred to the clinical database.

8.3. Patient Reported Outcomes and Health-Related Quality of Life

Patient reported outcome and quality of life measures should all be completed prior to other study assessments.

Time Period for Detecting Product Complaints

- Product complaints that result in an adverse event will be detected, documented, and reported to the sponsor during all periods of the study in which the drug is used.
- If the investigator learns of any product complaint at any time after a participant has been discharged from the study, and such incident is considered reasonably related to a drug provided for the study, the investigator will promptly notify the sponsor.

Prompt Reporting of Product Complaints to Sponsor

- Product complaints will be reported to the sponsor within 24 hours after the investigator becomes aware of the complaint.
- The Product Complaint Form will be sent to the sponsor.

Follow-up of Product Complaints

- Follow-up applies to all participants, including those who discontinue study intervention.
- The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the product complaint.
- New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator and submitted to the sponsor

8.4.6. Pregnancy

The Investigator must notify the Sponsor immediately regarding a pregnancy in a (1) female clinical trial patient or (2) female partner of a male clinical trial patient.

Pregnant female patients must be withdrawn from study drug.

If a female partner of a male patient becomes pregnant or suspects she is pregnant by the male patient, the male patient will be advised by the study Investigator to have his female pregnant partner inform her treating physician immediately.

The Investigator must perform medical assessments as clinically indicated and continue to follow the patient for ≥4 weeks after delivery. Medical details for both the mother and baby must be obtained.

The Investigator must complete a study-specific Pregnancy Form upon confirmation of a pregnancy. Pregnancy reporting forms will be provided to the site.

8.4.7. Hypersensitivity Reactions

Patients experiencing any hypersensitivity reaction should receive appropriate symptomatic medical care, as needed. Patients should be instructed to inform the site if a hypersensitivity reaction occurs. At the next study visit, a blood sample must be collected for immunogenicity analysis. The Sponsor or designee should be immediately consulted, particularly if the

treated as the primary analysis because all primary and major secondary study objectives will be assessed at this time. A final database lock will then be conducted after all patients have completed the follow-up period of Study AD06.

APPENDIX 2. AMERICAN ACADEMY OF DERMATOLOGY CONSENSUS CRITERIA FOR CHRONIC ATOPIC DERMATITIS

Atopic dermatitis: Diagnosis recommendations

Patients with presumed atopic dermatitis should have their diagnosis based on the criteria summarized below. On occasion, skin biopsy specimens or other tests (such as serum immunoglobulin E, potassium hydroxide preparation, patch testing, and/or genetic testing) may be helpful to rule out other or associated skin conditions.

Level of Evidence: III Strength of Recommendation: C

Essential features — must be present:

- Pruritus
- Eczema (acute, subacute, chronic)
- Typical morphology and age specific patterns*
- Chronic or relapsing history

*Patterns include:

1. Facial, neck, and extensor involvement in infants and children
2. Current or previous flexural lesions in any age group
3. Sparing of the groin and axillary regions

Important features — seen in most cases, adding support to the diagnosis:

- Early age of onset
- Atopy
- Personal and/or family history
- Immunoglobulin E reactivity
- Xerosis

Associated features — These clinical associations help to suggest the diagnosis of atopic dermatitis but are too nonspecific to be used for defining or detecting atopic dermatitis for research and epidemiologic studies:

- Atypical vascular responses (eg facial pallor, white dermographism, delayed blanch response)
- Keratosis pilaris/ pityriasis alba/ hyperlinear palms/ icthyosis
- Ocular/periorbital changes