Clinical Study Protocol Version 3 J2T-DM-KGAC

A randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of lebrikizumab in patients with moderateto- severe atopic dermatitis

NCT04178967

Approval Date: 20-May-2020

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL TO EVALUATE THE EFFICACY AND SAFETY OF LEBRIKIZUMAB IN PATIENTS WITH MODERATE-TO-SEVERE ATOPIC DERMATITIS

Protocol Number	**DRM06-AD05/J2T-DM-KGAC**
Protocol Final Date	**08 July 2019**
Study Drug	**Lebrikizumab (DRM06/LY3650150)**
IND Number	**119866**
EudraCT Number	**2019-002933-12**
Sponsor	**Dermira, Inc.** **275 Middlefield Road** **Suite 150** **Menlo Park, CA 94025** **USA**
Amendment (1) Date	**16 October 2019**
Amendment (2) Date	**20 May 2020**
Medical Monitor	PPD

[redacted]

PROTOCOL AMENDMENT 2 (SUMMARY OF CHANGES)

The table below summarizes new changes being introduced to Amendment 2. Minor corrections/additions may not be included.

Protocol Section	Description of Change	Rationale
Protocol Title page and Investigator signature page	Added the Eli Lilly trial alias J2T-DM-KGAC. Added the Eli Lilly investigational product alias LY3650150	References Eli Lilly and Company specific Protocol number and Investigational Product alias
Protocol Synopsis	Updated description of study DRM06-AD07 from "open label safety study" to Long Term Extension. This change is made consistently throughout the protocol including in Figure 1, Study Schema Added text "Responders who received placebo during the first 16 weeks of the study and who are re-randomized to lebrikizumab arms will receive a loading dose of lebrikizumab of either 500 mg given at Week 16 or 500 mg given at Weeks 16 and 18, based on the active treatment group assigned in Maintenance."	Design of DRM06-AD-07 protocol has been modified Clarification
Protocol Synopsis and Section 3	Added a clearer definition of the timing of the end of the study per EU Regulation 536-2014: Annex 1 D.17. Added clearer definition of a patient being considered to have completed the study.	Clarification per EU Regulation 536-2014: Annex 1 D.17.
Protocol Synopsis	Added further text to describe dosing of placebo patients after the first 16 weeks of study	Clarification
Protocol Synopsis	Added hormone testing in adolescent patients	Safety monitoring to asses sexual maturation
Section 1.5 Study Conduct Statement	Updated to include language that the clinical trial is to be conducted in compliance with the protocol, with the EU Regulation and with the principles of good clinical practice	EU Regulation 536-2014: Annex 1 D.17.a
Section 2.2	Added Secondary endpoints specific to the maintenance period and to evaluate pharmacokinetics to Table 1	Clarification
Section 2.3	Changed secondary endpoint, "Proportion of patients with EASI-75, EASI-90 and EASI-50 by visit"	Clarification
Section 3	Patients will be offered 'the option to continue' treatment "Patients not achieving an EASI-50 response after 8 weeks of treatment in the Escape Arm will be terminated from the study." Provided definition of responder in footnote for the Schema	Clarification Clarification Clarification

Protocol Section	Description of Change	Rationale
Section 3.1	Updated duration of the study	Clarification
Section 3.2	Defined age of study population as <18 years.	Clarification.
Section 4.1 Inclusion Criterion 1	Changed wording to, "Adults and adolescents (≥12 to <18 years of age and weighing ≥40 kg)"	Clarification
Section 4.1 Inclusion Criterion 7	Added "non-medicated topical" as descriptor for moisturizer.	Clarification
Section 4.1 Inclusion Criterion 10	Text has been modified to use the term highly effective contraceptive measures, as follows: "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, bilateral tubal ligation, 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."	Clarification
Section 4.1 Inclusion Criterion 11	Revised male patient requirement to use contraception for 18 weeks following last dose of study drug.	Consistency with direction for women of child-bearing potential
Section 4.2 Exclusion Criterion 3	Removed brand name Eucrisa and updated text to refer to class of drugs "Phosphodiesterase-4 inhibitors such as crisaborole"	Reflects variance in international registration of crisaborole
Section 4.2 Exclusion Criterion 6.b	Clarified that cell-depleting biologics are B Cell depleting biologics	Clarification
Sections 5.2 and 5.3	Removed reference to kits.	Clarification
Section 5.3 Patient Randomization	Text added "Patients will be assigned a unique identifier by the sponsor. Any patient records, datasets or tissue samples that are transferred to the sponsor will contain the identifier only; patient names or any information	EU Regulation 536-2014: Annex 1 D.17.al

Protocol Section	Description of Change	Rationale
	which would make the patient identifiable will not be transferred."	
Section 5.3.3	Added sentence stating that patients not achieving or maintaining an EASI50 score must be terminated from the trial.	Protocol consistency
Section 5.5.1	Amended details concerning administration at clinic. Added reference to Instructions for Use.	Details provided in Instructions for Use.
Section 6.1 Permitted and Prohibited Treatments and Procedures	Removed brand name Eucrisa and updated text to refer to class of drugs "Phosphodiesterase-4 inhibitors such as crisaborole" Added text detailing to treatment for AD with systemic corticosteroids.	Reflects variance in international registration of crisaborole Clarification
Section 6.2	Removed text referencing sponsor providing moisturizer for use during the study. Removed text that non-medicated moisturizer should be used daily throughout study.	Sponsor not providing. Clarification.
Section 6.3	Revised text to reflect new guidance regarding the use of topical medications to treat symptoms of AD: topical treatments are prohibited from Baseline through Week 16.	US regulatory recommendations regarding the use of topical medication for AD symptoms.
Section 7.1 Screening Visit and Section 8.5.3 Laboratory Evaluations	Added 'review immunization record for adolescent patients' at screening The requirement to perform TB screening serology (QuantiFERON – TB) has been removed from the screening visit	To ensure PI reviews prior to inclusion in trial There is no scientific rational to believe patients exposed to Lebrikizumab are at higher risk to develop or reactivate TB. In countries where tuberculosis is a common disease and where required by regulatory authorities or ethics boards, a specific addendum will allow TB screening and management as per local guidelines
Section 7.4 Week 4 (± 3 Days)	Added blood sample for PK	FDA recommendation to add this timepoint for PK

Protocol Section	Description of Change	Rationale
Section 7.6	Added "except hormones"	Clarification that hormones are not collected at Week 8 per schedule of visits
Section 7.21	Added "Draw blood samples for PK and ADA testing" Changed follow-up visit from phone call to onsite	Added PK and ADA collection requiring onsite visit
Section 8.1.2	Added the requirement to collect immunization record (for adolescent patients) in Medical History	Consistency with Section 7.1
Section 8.2	Added, "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."	Clarification.
Section 8.4	Added "some patients will have" photographs taken.	Clarification.
Section 8.5.3	Added hormones (estradiol and testosterone) to laboratory parameters (for adolescents only)	Asses sexual maturation
Section 8.5.4.3	Added examples of medical events.	Clarification
Section 8.5.4.4 Reporting of SAEs	Text added "Prompt notification by the investigator to the sponsor of a 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 a 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."	EU Regulation 536-2014: Annex 1 D.20.c
Section 8.5.5	New section added to cover the Product Complaint Handling Process	Addition of Product Complaint Handling Process
Section 8.6	Text changed from "Positive ADA results will be further evaluated for neutralizing antibodies" to "Positive ADA results may be further evaluated for neutralizing antibodies".	Allows flexibility in testing process

Protocol Section	Description of Change	Rationale
Section 8.6	Added text "except those receiving systemic rescue medication, as per Section 6.3"	Clarification
Section 9.1	Moved details related to the timing of the primary (Week 16) and Week 52 analyses to a new interim analysis section (Section 9.14.). Added further details regarding primary method of handling missing efficacy data. Included description of the calculation of the pruritus-NRS and sleep loss weekly mean score.	Clarification that an interim analysis will be performed Clarification Clarification on pruritus-NRS and sleep loss score
Section 9.1.1	Updated the definition for ITT population. Clarified the definition for the safety population.	Clarification
Section 9.4	Revised text to include Pruritus-NRS endpoints as part of the sensitivity analyses.	Protocol consistency with US regulatory recommendations.
Section 9.5.1	Revised text for sensitivity analyses with respect to missing data imputation.	Clarification
Section 9.6	Amended multiplicity considerations	Clarification
Section 9.7	Added "It is intended that data from this study will be combined with data from other studies to better characterize the PK of DRM06, as well as to explore the relationship between exposure and efficacy and/or safety outcomes. Further details on PK and PK/PD analyses will be provided in the PK/PD analysis plan. The results of these analyses will be described in a separate PK/PD report."	Clarification
Section 9.9	Added text: Listings and appropriate summary statistics will be provided for immunogenicity data.	Clarification
Section 9.11	Deleted "Data will also be corrected for exposure and reported per 100 patient years"	SAP contains detail of data treatment and presentation
Section 9.12	Deleted "Tables and listings will be in SAS format" Added, "Growth monitoring of adolescents will be summarized."	Clarification
Section 9.14	Added Section 9.14 Interim Analyses. Described plan for interim analysis.	Per ICH E9

Protocol Section	Description of Change	Rationale
Section 10.2 Informed Consent Procedures	Text added to the section on informed consent "the patient's medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities. The ICF will also inform the patient that his/her personal study-related data will be used by the sponsor in accordance with local data protection law; the ICF will describe the level of disclosure of data and seek appropriate consent from the patient for his/her data to be used in the manner described." Provided detail on consent process for minors who reach majority during the study.	EU Regulation 536-2014: Annex 1 D.17.ak Clarification
Section 10.3 Data Protection and Confidentiality	New Section added	EU Regulation 536-2014: Annex 1 D.17.am
Section 10.7 Publication Policy	New section added "In accordance with the sponsor's publication policy the results of this study will be submitted for publication by a peer-reviewed journal"	EU Regulation 536-2014: Annex 1 D.17.ai
Appendix 1 Schedule of Visits and Procedures	Added "review of immunization record (for adolescents) at screening" Added hormone lab collections (estradiol or testosterone) at screening and W16/ET Added blood sample for PK at Week 4 visit. Added blood sample for PK and ADA at safety follow-up visit Removed row for 'phone call' Added associated footnotes for certain assessments	To ensure PI reviews prior to inclusion in trial Assess sexual maturation FDA recommendation to add this timepoint for PK Safety follow-up no longer via phone Clarification
Appendices 3 through 12	These Appendices have been deleted as the instruments are provided in study related training materials.	Sponsor training for efficacy assessments and use of validated instruments is provided and documentation is captured in training materials.

PROTOCOL AMENDMENT 1 (SUMMARY OF CHANGES)

The table below summarizes new changes being introduced to Amendment 1. Minor corrections/additions may not be included.

Protocol Section	Description of Change	Rationale
Protocol Synopsis	Endpoint Section revised to specify a single primary endpoint for FDA and a co-primary endpoint for EMA: 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	Protocol will be conducted in the US and EU countries and endpoints for the EMA must be reflected in protocol
Acronyms	Added: DSMB, RTMS, MAR, MNAR Deleted: IWRS, NRI	Table updated to align with acronyms used in protocol
Section 1.4	Expanded explanation of the contribution of study DRM06-AD03 to dose selection for Phase 3	Clarification
Section 1.5	Updated version of Declaration of Helsinki referenced in protocol	Clarification
Section 2.1	Revised to specify a single primary endpoint for FDA and a co-primary endpoint for EMA: 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.	Protocol will be conducted in the US and EU countries and endpoints for the EMA must be reflected in protocol
Section 2.2	Inserted Table (Table 1) identifying secondary endpoints used for FDA and secondary endpoints for EMA.	Protocol will be conducted in the US and EU countries and endpoints for the EMA must be reflected in protocol

Protocol Section	Description of Change	Rationale
Section 2.3	Changed "Percentage change from Baseline in Sleep-Loss score by visit" to "Change from Baseline in Sleep-Loss score by visit".	Clarification
Section 4.1	Included hyperlink from inclusion criteria (number 4) regarding IGA to protocol section where IGA scale is described.	Clarification
	Revised inclusion criteria (number 10) requirement for contraceptive use from 17 to 18 weeks after the last dose of study drug.	Correction for consistency with Investigator Brochure, dated July 2019
	Added inclusion criteria (number 11) requiring male patients to use an effective barrier method of contraception during the study and for a minimum of three months following the last dose of study drug if sexually active with a female of child bearing potential.	Correction and protocol consistency
Sections 5.2, 5.3 and 5.4.1	Removed protocol reference to IWRS and replaced with electronic data capture (EDC) system.	Protocol update
Table 3	For Patients Entering Escape Arm, changed "next visit" to "next administration"	Clarification
Section 6.1	Prohibit the use of cannabinoid treatments for AD.	Clarification
Section 7.10	Deleted text directing study sites to complete a "Pre-randomization Checklist" at Week 16.	Correction
Section 8.5.3	Added TB serology laboratory testing to screening laboratory procedures	Correction
Section 8.5.5	Improved clarity of text directing site procedures for the occurrence of pregnancies on study.	Clarification
Section 8.8, Protocol Synopsis and Section 3	Protocol now includes an independent data safety monitoring board (DSMB) for the periodic review of safety data collected in this study.	Feedback from the Paediatric Committee (PDCO), for the EMA, recommended the inclusion of a DSMB for any study involving pediatric patients.

Protocol Section	Description of Change	Rationale
Section 9.1	Specification on the timing of the primary analysis: The primary analysis will be performed when all patients have completed the Induction Period at Week 16. The Induction Period summary tables for primary, secondary and other efficacy endpoints will be presented with the unblinded treatment groups. The analysis will be performed by an unblinded statistician(s) who is independent from the day-to-day study oversight and operation. This is not an interim analysis since patients who responded at Week 16 will be re-randomized into the Maintenance period. Only overall treatment group results will be presented at this time; individual patient treatment assignments will not be released until end of study. The final time-course analysis, including the maintenance period analysis, will be performed when all patients have finished Week 52 and the database has been locked. Study tabulation datasets, analysis datasets and data listings will not be distributed, and the double-blind individual patient treatment assignments for both periods will not be revealed until that time. Sensitivity Analyses: Removed the Non-Response Imputation (NRI) as a sensitivity analysis and will conduct an MCMC multiple imputation for all missing values, Last Observation Carried Forward (LOCF) and Tipping point analysis as sensitivity analyses.	Clarification on timing of the primary analysis and change to the specified sensitivity analyses to be conducted for this study.
Section 9.2	Endpoint Section revised to specify a single primary endpoint for FDA and a co-primary endpoint for EMA: 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	Protocol will be conducted in the US and EU countries and endpoints for the EMA must be reflected in protocol

Protocol Section	Description of Change	Rationale
Section 9.5	Sensitivity Analyses: Removed the Non-Response Imputation (NRI) as a sensitivity analysis and will conduct an MCMC multiple imputation for all missing values, Last Observation Carried Forward (LOCF) and Tipping Point analysis as sensitivity analyses.	Since the primary efficacy analysis assigns baseline values for the use of topical rescue medications, systemic rescue medications and withdrawal due to lack of efficacy, the non-response imputation is redundant and has been replaced with more appropriate sensitivity analyses.
Section 9.6	Secondary endpoints have been separated and specified for the US and EMA. The hierarchical order for the secondary endpoints has also been specified for the US and EMA. For EMA, the protocol now specifies secondary endpoints at Week 52 for the Maintenance Period.	Protocol will be conducted in the US and EU countries and secondary endpoints, adjustments for multiplicity and the hierarchical order of analysis for EMA must be reflected in protocol
Section 9.13	A sample size determination has been described separately, for EMA, based on success rates from the DRM06-AD01 Phase 2b study, for both the IGA and the EASI-75.	Protocol will be conducted in the US and EU countries and the determination of the study sample size must be reflected in the protocol.

SPONSOR SIGNATURE PAGE

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL TO EVALUATE THE EFFICACY AND SAFETY OF LEBRIKIZUMAB IN PATIENTS WITH MODERATE-TO-SEVERE ATOPIC DERMATITIS

Protocol Number:	**DRM06-AD05**
Protocol Final Date:	**08 July 2019**
Amendment (1) Date:	**16 October 2019**
Amendment (2) Date:	**20 May 2020**

The signature below constitutes approval of this protocol. I certify that I have the authority to approve this protocol on behalf of the Sponsor, Dermira, Inc. The study will be conducted in accordance with this protocol and all applicable laws, rules, and regulations and International Conference on Harmonization Good Clinical Practice (ICH GCP), regulations of the United States (US) Food and Drug Administration (FDA), and the ethical principles that have their origin in the Declaration of Helsinki.

Authorized by:

PPD

INVESTIGATOR SIGNATURE PAGE

Protocol Number:	**DRM06-AD05**
Protocol Final Date:	**08 July 2019**
Amendment (1) Date:	**16 October 2019**
Amendment (2) Date:	**20 May 2020**

I have read this protocol, including the appendices, and agree that it contains all necessary details for carrying out the study as described. I will conduct this protocol as outlined herein, according to the ethical principles that have their origin in the Declaration of Helsinki, International Conference on Harmonization (ICH) guidelines for Good Clinical Practice (GCP) and applicable laws, rules and regulatory requirement(s) including those of the United States (US) Food and Drug Administration (FDA).

I agree to obtain the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approval of the protocol and informed consent prior to the start of the study.

I agree to obtain formal written informed consent in accordance with applicable federal and local regulations and international guidelines from all patients prior to their entry into the study.

I have received and reviewed the Investigator's Brochure including the potential risks and side effects of the product and instructions for use.

I agree to report to the Sponsor any adverse events that occur during the study in accordance with the ICH GCP guideline and the protocol.

I agree to ensure that all associates, colleagues, and employees assisting me with the conduct of the study are informed of their responsibilities in meeting the above commitments and the commitments set forth in the Investigator's Agreement.

I agree to maintain adequate and accurate records and to make those records available for inspection in accordance with the ICH GCP guideline, and federal and local requirements.

I understand that the study may be terminated, or enrollment suspended at any time by the Sponsor, with or without cause, or by me if it becomes necessary to protect the best interests of the study patients.

_____ _____

Investigator's Signature Date

_____

Investigator's Name (print)

PROTOCOL SYNOPSIS

Title:	A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL TO EVALUATE THE EFFICACY AND SAFETY OF LEBRIKIZUMAB IN PATIENTS WITH MODERATE-TO-SEVERE ATOPIC DERMATITIS
Protocol Number:	DRM06-AD05
Phase:	3
Number of Sites:	Approximately 100 sites in the United States (US), European Union (EU) and Asia/Pacific region.

Study Population:

Adolescent patients (≥12 to <18 years weighing ≥40 kg) and adults with moderate-to-severe atopic dermatitis (AD) who are candidates for systemic therapy.

Sample Size:

Approximately 400 patients with moderate-to-severe AD, including approximately 50 adolescent patients.

Study Objectives:

To evaluate the safety and efficacy of lebrikizumab compared with placebo in patients with moderate-to-severe AD.

Duration of Patient Participation:

Screening: Maximum duration of 30 days

Induction Period: 16 weeks

Maintenance Period: 36 weeks

Safety Follow Up: 12 weeks

Maximum total participation: 66 weeks

For patients terminating early or not rolling into the long-term extension study (LTE), a safety follow-up visit will occur 12 weeks after last dose of study medication.

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 52 visit and rolling into LTE study

- For subjects not continuing into LTE, when subject had either week 52 or Early Termination Visit (ETV), and safety follow up visit (12 weeks after last IP administration)

Study Treatment:

Lebrikizumab, 250 mg (2 mL injection of 125 mg/mL)

Placebo, 2 mL injection.

Study Design:

This is a randomized, double-blind, placebo-controlled, parallel-group study which is 52 weeks in duration. The study is designed to confirm the safety and efficacy of lebrikizumab as monotherapy for moderate-to-severe atopic dermatitis utilizing a 16-week induction treatment period and a 36-week long-term maintenance treatment period.

Eligible adult and adolescent (≥12 to <18 years weighing ≥40 kg) patients with moderate-to-severe atopic dermatitis 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 Induction Period, approximately 400 patients will be stratified and randomized 2:1 to 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.

After completion of the Week 16 visit, patients who have responded to treatment [defined as having an IGA of 0 or 1 or a 75% reduction in EASI from Baseline to Week 16 (EASI-75)] will enter the Maintenance Period and will be re-randomized 2:2:1 to one of the following treatment groups: lebrikizumab 250 mg Q2W, lebrikizumab 250 mg given every four weeks (Q4W), or placebo Q2W. Patients will be instructed to self-administer study drug at home.

Responders who received placebo during the first 16 weeks of the study and who are re-randomized to lebrikizumab arms will receive a loading dose of lebrikizumab of either 500 mg given at Week 16 or 500 mg given at Weeks 16 and 18, based on the active treatment group assigned in Maintenance.

Patients who do not achieve an IGA of 0 or 1 or an EASI-75 at Week 16, and those patients not maintaining an EASI-50 response following re-randomization at Week 24, 32, 40 or 48, will be assigned to an Escape Arm and receive lebrikizumab 250 mg as long-term treatment Q2W through Week 52. Patients not achieving an EASI-50 response after 8 weeks of treatment in the Escape Arm will be terminated from the study.

Efficacy will be measured through the IGA, EASI, BSA, SCORAD, Pruritus and Sleep-loss scores.

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. Additionally, adolescents will be monitored for hormones.

Serum samples will be collected for pharmacokinetic analysis and immunogenicity.

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.

Photographs of a selected target lesion will be obtained in a subset of patients participating in this study.

Patients completing this 52-week study 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.

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.

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

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ACRONYMS

Acronym	Term
ACQ-5	Asthma Control Questionnaire
AD	atopic dermatitis
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
ALT	alanine amino-transferase
ANCOVA	analysis of covariance
AST	aspartate amino-transferase
AUC	area under the curve
BP	blood pressure
BSA	body surface area
BUN	blood urea nitrogen
C	Celsius
CFR	Code of Federal Regulations
Cmax	maximum (or peak) serum concentration
DLQI/CDLQI	Dermatology Life Quality Index/Children's Dermatology Life Quality Index
DSMB	Data Safety Monitoring Board
EASI	Eczema Area and Severity Index
EASI-50	50% reduction in EASI from Baseline to Week 16
EASI-75	75% reduction in EASI from Baseline to Week 16
eCRF	electronic case report form
EDC	electronic data capture
EMA	European Medicines Agency
EQ-5D	standardized instrument developed by the EuroQol Group
ET	early termination
EU	European Union
F	Fahrenheit
FDA	Food and Drug Administration
FLG	filaggrin
GCP	good clinical practice
GGT	gamma-glutamyl transferase

Acronym	Term
HCT	hematocrit
HGB	hemoglobin
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	independent ethics committee
IFN	interferon
Ig	immunoglobin
IGA	Investigator Global Assessment
IL	interleukin
IRB	institutional review board
ITT	intent-to-treat
IV	intravenous
LDH	Lactic dehydrogenase
LOCF	last observation carried forward
LOR	loricrin
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCMC	Markov chain Monte Carlo
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
NRS	numerical rating scale
PFS-NSD	pre-filled syringe with a pre-assembled needle safety device
PIP	proximal interphalangeal
PK	pharmacokinetics
POEM	Patient Oriented Eczema Measure
PP	per protocol
PROMIS	Patient-Reported Outcomes Measurement Information System
PUVA	psoralen (P) and ultraviolet A (UVA) therapy
Q2W	every 2 weeks
Q4W	every 4 weeks
QoL	quality of life

Acronym	Term
RBC	red blood cells
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SCORAD	SCORing Atopic Dermatitis
SD	standard deviation
SOC	system organ class
TB	tuberculosis
TCI	topical calcineurin inhibitor
TCS	topical corticosteroid
TEAE	treatment-emergent adverse event
TSLP	thymic stromal lymphopoietin
US	United States
USP	United States Pharmacopeia
VAS	visual analog scale
WBC	white blood cells
WHO	World Health Organization
WOCBP	women of childbearing potential

1. BACKGROUND

1.1. Atopic Dermatitis

Atopic dermatitis (AD) is a complex disease that is determined by genetic, environmental and immunologic factors (Werfel, 2016; Simon, 2019).

Genetic studies of AD (Auriemma, 2013; Bieber, 2012; Weidinger, 2018) have shown that genes encoding for cytokines involved in the regulation of the immune system (IL-4, IL-5, and IL-13), are strongly associated with the development of AD (He, 2003; Hummelshoj, 2003; Novak, 2002). In addition, variants of genes that encode for proteins involved in skin barrier function such as filaggrin (FLG) and loricrin (LOR) are also associated with AD (Van Bever, 2011). Since FLG plays a central role in skin barrier integrity, loss of function mutations of the FLG gene is considered a major contributor to the development of early childhood AD (Bieber, 2008; Tanei, 2009; Bieber, 2012; Flohr, 2013).

Reduced epithelial barrier function, which represents the first line of protection against the environment, is thought to lead to sensitization to environmental allergens, associated with elevated immunoglobulin E (IgE) (present in about 50% to 80% of all patients with AD, particularly in children [Werfel, 2016]) and consistent with the presence in the skin of Type 2 cytokines (IL-4, IL-5, IL-9, IL-13, IL-25, IL-31, IL-33, and thymic stromal lymphopoietin [TSLP]) and inflammation. Type 2 cytokines increase epidermal thickening, sensitization, inflammation, pruritus and decrease the expression of antimicrobial peptides and the barrier proteins FLG, LOR, and involucrin. IL-13 in particular can reduce epithelial integrity and barrier function through downregulation of FLG, LOR, and involucrin (Kim, 2008) and can act on keratinocytes in the skin to downregulate their differentiation (Howell, 2008). IL-13 also induces T-cell chemoattractants that mediate T-cell infiltration into AD lesions (Purwar, 2006) and may also induce IL-5 expression and eosinophil infiltration through the induction of eosinophil chemoattractants (Esche, 2004). Increased expression of IL-13 has consistently been reported in AD skin lesions and is associated with disease severity (Choy, 2012; Hamid, 1996; Jeong, 2003; La Grutta, 2005; Neis, 2006; Suarez-Farinas, 2013; Tazawa, 2004). The ubiquitous presence of IL-13 in the skin of patients with AD supports the evaluation of anti-IL-13 therapies in patients with AD.

1.1.1. Epidemiology of Pediatric Atopic Dermatitis

AD is one of the most common chronic medical diseases—15–30% of children and 2–10% of adults are affected, and the prevalence appears to have increased over the past two to three decades (Williams, 2008), with some geographic variability. With respect to disease severity, about 67% of AD pediatric patients have mild disease, 14 to 26% have moderate disease and 2 to 7% have severe disease (Silverberg, 2017). Approximately 85% of all cases of AD begin before age 5, with up to 70% of children having spontaneous remission before adolescence (Bieber, 2008; Hua, 2014; Illi, 2004).

1.1.2. Clinical Manifestations

Clinically, AD is characterized by xerosis, erythematous crusted eruption (dermatosis), lichenification and intense pruritus (Bieber, 2008), which along with the distribution, chronicity and history of skin lesions, form the basis for making the diagnosis AD. Flares are frequently

triggered by exposure to environmental factors, irritants, and allergens (Bieber, 2009). Several clinical patterns, with differing distributions of skin lesions in distinct age groups, have been noted (Weidinger, 2016; Weidinger, 2018).

The infantile stage (up to 2 years of age) is characterized by eczema that is usually localized to the face, scalp, and extensor aspects of the arms and legs. The lesions are characterized by pruritic, red, eczematous plaques, erythema, papules, vesicles, excoriations, oozing, and formation of crusts.

The adult stage (from puberty onwards) is less predictable. Affected patients may have had only a few outbreaks since infancy, or they may have had a chronic, relapsing course. Lesions frequently localize to the face and neck (head-and neck dermatitis), as well in the flexures of the elbows and knees, and a considerable portion of patients (around 30%) develop atopic hand eczema, which may interfere with workplace activities. Like affected children, adolescents and adults commonly have lichenification of the flexures and have facial dermatitis.

Patients with AD have a high disease burden and their quality of life (QoL) is significantly affected. In one study, AD was shown to have a greater negative effect on patient mental health than diabetes and hypertension (Zuberbier, 2006). Patients with moderate-to-severe AD have a higher prevalence of social dysfunction and sleep impairment, which are directly related to the severity of the disease (Williams, 2008). Depression, anxiety, and social dysfunction not only affect patients with AD, but also affect their caregivers (Zuberbier, 2006). Compared with psoriasis, another common and debilitating skin disease, patients with AD have lower physical vitality, social functioning, role-emotional, and mental health scores (Kiebert, 2002).

1.1.3. Treatment for AD

The therapeutic approach to AD consists primarily of trigger avoidance, skin hydration with bathing, and use of moisturizers and anti-inflammatory therapies consisting predominantly of topical corticosteroids (TCS). In many patients, treatment with TCS provides some measure of symptomatic relief but does not always adequately control the disease. In those patients who have persistent moderate-to-severe disease not responding adequately to TCS, the step-up options include topical calcineurin inhibitors (TCIs), phototherapy, and immunosuppressive agents such as oral corticosteroids, cyclosporine, azathioprine, methotrexate, and mycophenolate mofetil. Among these, only cyclosporine is approved for treatment of moderate-to-severe AD (nationally licensed in many European countries, but not in the US), and its use is limited to patients ≥16 years for a maximum treatment period of 8 weeks. Recently, a clinically efficacious and relatively safe treatment, anti-IL-4R monoclonal antibody, dupilumab, was approved for the treatment of adult and adolescent patients with moderate-to-severe AD. In spite of these treatments, AD remains a major societal burden and a significant unmet medical need.

1.2. Lebrikizumab

Lebrikizumab is a humanized monoclonal immunoglobulin (Ig) G4 antibody (huIgG4) with a mutation in the hinge region that increases stability. Lebrikizumab binds specifically to soluble human interleukin (IL)-13 with high affinity, and potently inhibits IL-13 signaling through the IL-4Rα/IL-13Rα1 complex. Because lebrikizumab binds to IL-13 in a non-receptor binding domain (i.e., a portion of the molecule not involved in binding to its receptor), antibody-bound

IL-13 can still bind its receptor (IL-13Rα1), but the engaged receptor complex cannot be activated.

1.3. Study Rationale and Benefit-Risk Assessment

1.3.1. Scientific Rationale

The use of lebrikizumab for AD is supported by numerous preclinical studies demonstrating that AD is characterized by the increased expression of IL-13 in skin. Moreover, clinical trials (a Phase 2a study GS29250 [Section 1.3.1.1] and a Phase 2b study DRM06-AD01 [Section 1.3.1.3]) with lebrikizumab demonstrated significant clinical benefit in patients with AD. Additional detailed discussion of the lebrikizumab studies is provided in the lebrikizumab Investigator's Brochure.

1.3.1.1. Summary of Study GS29250 (TREBLE)

Study Design

TREBLE was a Phase 2, global, randomized, double-blind, placebo-controlled trial designed to evaluate the safety and efficacy of lebrikizumab in adult patients (18–75 years of age) with persistent moderate to severe AD, inadequately controlled by TCS. The study consisted of 3 study periods: a run-in period (2 weeks), a treatment period (12 weeks), and a safety follow-up period (8 weeks). Patients applied emollient at least once daily and TCS of medium potency to all active skin lesions twice daily through the study. A total of 212 patients were randomized as follows: 53 to the lebrikizumab 250 mg, single dose group; 53 to the lebrikizumab 125 mg, single dose group; 52 to the lebrikizumab 125 mg Q4W group; and 54 to the placebo Q4W group.

Efficacy Results

- EASI-50 at Week 12 (primary endpoint) was achieved by patients treated with lebrikizumab 125 mg Q4W, with a treatment difference between this group and placebo) of 20.1% p = 0.0261).
- Lebrikizumab 125 mg Q4W group demonstrated statistically significant differences from placebo in EASI-75 and SCORAD-50 and adjusted mean change from baseline to Week 12.

Safety Results

- Injection-site reactions occurred infrequently (1.3% all lebrikizumab treated vs. 1.9% placebo); all events were non-serious, lasted a median of 1 to 3 days, and did not lead to treatment discontinuation or interruption.
- Herpes viral infections and zoster occurred infrequently, but only among lebrikizumab-treated patients (6 of 156 [3.8%]); all events were non-serious, and none led to treatment discontinuation or dose interruption of lebrikizumab.

- Eosinophil-associated adverse events (AEs) were reported infrequently, but only occurred among lebrikizumab-treated patients (3.2%); however, all events were non-serious, did not result in interruption of treatment, and there were no other associated clinical symptoms noted.
- Allergic conjunctivitis events were only reported in lebrikizumab-treated patients (8 of 156 patients [5.1%] vs. 0% in placebo treated patients); all events were non-serious, did not lead to treatment discontinuation, all events recovered or resolved, and all patients had a history of asthma. Imbalances in allergic conjunctivitis events were not reported in previous lebrikizumab trials.
- The overall incidence of skin infection (noted in the system organ class [SOC] of infections and infestations) was 9.6% in all lebrikizumab arms combined, compared to 22% in the placebo arm.

Conclusions

The results of this trial suggested that lebrikizumab (on a background of mandatory twice daily TCS treatment) provided some treatment benefit, as measured through EASI and SCORAD, but also suggested that higher lebrikizumab dosing might provide greater clinical benefit. In addition, lebrikizumab was well tolerated with a safety profile generally consistent with that observed in previous trials conducted in other indications.

1.3.1.2. Summary of Study GS29735 (ARBAN)

Study Design

ARBAN was a Phase 2, randomized, open-label study designed to evaluate the safety and efficacy of lebrikizumab monotherapy in adult patients (18–75 years of age) with persistent moderate to severe AD, who were inadequately controlled by TCS. A total of 55 patients were randomized to treatment: 28 to lebrikizumab 125 mg Q4W and 27 to TCS.

Efficacy Results

- EASI-50 was achieved by 53.6% and 51.9% of patients in the lebrikizumab and TCS groups, respectively, with a treatment difference of 1.7%. EASI-75 was achieved by 39.3% and 37.0% of patients in the 2 groups, respectively, with a treatment difference of 2.3%.
- IGA scores of 0 or 1 were observed for 7.1% of patients in the lebrikizumab group and 25.9% of patients in the TCS group, giving a treatment difference of −18.8% (95% CI: −37.9%, 0.3%).
- The percent of patients achieving SCORAD-50 or SCORAD-75 showed treatment differences of −19.3% and −7.5%, respectively.

Safety Results

- AEs were reported for a higher proportion of patients in the lebrikizumab group compared with the TCS group (64.3% vs. 37.0%); a higher proportion of patients in the lebrikizumab group, compared with the TCS group, had an AE in the SOC of infections and infestations (42.9% vs. 25.9%). Upper respiratory tract infections were more common in the lebrikizumab group (14.3% vs. 3.7%).
- The overall incidence of skin infection (in the SOC of infections and infestations) was 17.9% in the lebrikizumab group and 7.4% in the placebo/TCS group.
- No serious AEs (SAEs), deaths, anaphylaxis, malignancy, protocol-defined parasitic or targeted intracellular infections of interest, herpes viral infections or zoster, or eosinophilia-associated AEs were reported.

Conclusions

Lebrikizumab was well tolerated at the dose of 125 mg Q4W; the safety profile was generally consistent with previous experience with lebrikizumab in previous trials.

1.3.1.3. Summary of Dose Ranging Study DRM06-AD01

Study Design

DRM06-AD01 was a Phase 2b, randomized, double-blind, placebo-controlled, dose-ranging study to evaluate the safety and efficacy of lebrikizumab in adult patients with moderate to severe AD. A total of 280 patients were randomized to 1 of 4 treatment groups (in a 3:3:3:2 ratio): 73 to lebrikizumab 125 mg Q4W (with a loading dose of 250 mg); 80 to lebrikizumab 250 mg Q4W (with a loading dose of 500 mg); 75 to lebrikizumab 250 mg Q2W (with a loading dose of 500 mg given at baseline and Week 2); 52 to placebo Q2W.

Efficacy Results

- Statistically significantly greater proportions of patients in each of the lebrikizumab 250 mg Q4W and 250 mg Q2W groups achieved EASI-50, EASI-75, or EASI-90 at Week 16 than the placebo group.
- A statistically significantly greater proportion of patients in each of the lebrikizumab 250 mg Q4W and 250 mg Q2W groups had both an IGA score of 0 or 1 and a $\geq$ 2-point improvement in IGA score at Week 16 than the placebo group.
- The lebrikizumab 250 mg Q2W group had a statistically significantly greater proportion of patients who achieved a $\geq$ 4-point improvement in pruritus NRS compared with the placebo group.
- Positive changes in pruritus correlated with positive changes in sleep; the lebrikizumab 250 mg Q4W and 250 mg Q2W groups had statistically significant percent reductions in sleep loss due to itching compared with placebo (p=0.0459 and p=0.0062, respectively).

Safety Results

- The incidences of conjunctivitis (2.6% all lebrikizumab groups, 0 placebo), herpes infections (2.2% all lebrikizumab groups, 0 placebo), and herpes zoster (0.9% all lebrikizumab groups, 0 placebo) were relatively low.
- Three patients (1.3%) in the lebrikizumab groups and 2 patients (3.8%) in the placebo group had an SAE. Those reported in the lebrikizumab groups were severe chest pain (1 patient in the 250 mg Q2W group), femur fracture of moderate severity (1 patient in the 125 mg Q4W group), and panic attack of moderate severity (1 patient in the 250 mg Q2W group). Those reported in the placebo group were severe chronic obstructive pulmonary disease, severe edema peripheral, and severe pulmonary embolism. All SAEs were considered by the investigator as not related to study drug.
- Most AEs were considered not related to study drug; those considered related were reported for 16.2% of patients in the lebrikizumab groups and 5.8% of patients in the placebo group

Conclusions

This Phase 2b study showed that higher doses of lebrikizumab provided greater clinical benefit. All lebrikizumab doses induced statistically significant reductions in EASI scores compared to placebo, and a good dose response was observed for all primary and key secondary efficacy endpoints. The best response for all endpoints was observed with the highest lebrikizumab dose (250 mg Q2W), although the next highest dose (250 mg Q4W) also induced significant improvement in virtually all endpoints. All doses of lebrikizumab were well tolerated, without a dose response noted; AEs were generally mild or moderate and considered unrelated to study drug. These results provided the basis for dose selection for the pivotal Phase 3 studies.

1.3.1.4. Summary of DRM06-AD03 Phase 1 PK Study

Study Design

DRM06-AD03 was a Phase 1, randomized, parallel-group study to evaluate the pharmacokinetics (PK) and safety of lebrikizumab in healthy adult volunteers (18 to 45 years of age, inclusive). A total of 41 subjects were randomized as follows: 21 subjects received two 1-mL (125 mg) SC injections and 20 subjects received one 2-mL (250 mg) SC injection. The primary objective was to compare the PK (AUC, C_{max}) of the 2 lebrikizumab dosing regimens. Blood samples were collected prior to dosing and on Days 2, 4, 6, 8, 11, 15, 29, 43, 57, 71, 85 and 99 for PK and Day 29, 43, 57, 71, 85 and 99 for anti-drug antibodies (ADA).

Pharmacokinetic Results

For each AUC comparison (i.e., AUC_{last}, AUC_{inf}, and $AUC_{0\text{-}57d}$) geometric mean ratios were close to 1 with 90% CIs within the range of 80% to 125%, except for AUC_{inf}, which was just above the upper bound, with a value of 132%. The C_{max} geometric mean ratio was 0.89 with a 90% CI of 73%–108%.

Conclusions

Both the AUC and C_{max} results indicated similar overall exposure between the 2 lebrikizumab dosing regimens evaluated in this study, i.e., two 1-mL (125 mg) SC injections versus one 2-mL (250 mg) SC injection. Data from this study support the use of the 2-mL (250 mg) pre-filled syringe with a pre-assembled needle safety device (PFS-NSD) in the Phase 3 pivotal trials.

1.4. Rationale for Dose and Treatment Regimen

The dosing regimen of 500 mg loading dose at baseline and Week 2, followed by 250 mg Q2W lebrikizumab was selected for study in the Induction Period (baseline to Week 16) in this trial, based on an evaluation of safety, efficacy and PK data from the DRM06-AD01 and DRM06-AD03 trials (see above). For the Maintenance Period in this trial, both a 250 mg lebrikizumab Q4W dosing regimen and a 250 mg lebrikizumab Q2W dosing regimen were selected for exploration, in order to determine whether both regimens, one which involves less frequent dosing, might be effective in maintaining disease control over an extended period of time.

The DRM06-AD03 PK study conducted in healthy adults demonstrated that a single SC injection of 2-mL (250 mg) of lebrikizumab delivered comparable levels of lebrikizumab as did two 1-mL (125 mg) SC injections. This simulated the conditions under which study drug will be administered in Phase 3, further supporting the dose and treatment regimen for Phase 3 trials, lebrikizumab 250mg Q2W with a loading dose of 500mg given at Baseline and Week 2.

Adolescent Patients

In this Phase 3 study, adolescent patients (≥12 to <18 years weighing ≥40 kg), will be included and will receive the same doses of lebrikizumab described above for adults. The justification for this approach is as follows:

Both adults and adolescent patients have similar disease characteristics, typified by prominent Type 2 skin inflammation and similar clinical manifestations. In addition, both groups tend to have similar efficacy outcomes in response to therapies, including dupilumab (Simpson, 2018; Treister, 2019). Pharmacokinetic modeling and simulations of lebrikizumab dosing (population PK modeling of pooled data from 2259 adult asthma patients and a subsequent external posterior predictive check with lebrikizumab PK data from the DRM06-AD01 trial in adult AD patients) revealed similar kinetics for adults and adolescent patients, 12 to <18 years of age. The maximal exposures are predicted to be slightly (≤ 35%) higher in adolescent patients than in adults for any given dose due to the lower adolescent weight ranges and lebrikizumab exposure dependence on weight; however, the safety profile in adolescent patients, based on the exposure-response relationship analysis and on partial extrapolation, is comparable to that observed in adults.

1.5. Study Conduct Statement

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH Good Clinical Practice (GCP) Guidelines

- Applicable laws and regulations

The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs [and/or UADEs] or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

Investigator sites are compensated for participation in the study as detailed in the clinical trial agreement.

2. STUDY OBJECTIVES AND ENDPOINTS

To evaluate the safety and efficacy of lebrikizumab compared with placebo in patients with moderate-to-severe AD.

2.1. Primary Endpoint

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

2.2. Secondary Endpoints

Table 1: Secondary Endpoints

FDA	EMA
• Percentage of patients achieving EASI-75 (≥75% reduction from Baseline in EASI score) at Week 16 • Percentage of patients achieving EASI-90 (≥90% reduction from Baseline in EASI score) at Week 16 • Percentage change in Pruritus Numerical Rating Scale (NRS) score 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 Week 16 • Percentage change in EASI score from Baseline to Week 16 • 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	• Percentage of patients achieving EASI-90 (≥90% reduction from Baseline in EASI score) at Week 16 • Percentage change in Pruritus Numerical Rating Scale (NRS) score from Baseline to Week 16 • Percentage of patients with a Pruritus NRS of ≥5-points at Baseline who achieve a ≥4-point reduction 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 Week 16 • Percentage change in EASI score 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 • 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 • 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

Table 1: Secondary Endpoints (Continued)

FDA	EMA
Specific for Maintenance Period: • Percentage of patients from those re-randomized having achieved EASI-75 at Week 16 who continue to exhibit EASI-75 at Week 52 (EASI-75 calculated relative to baseline EASI score) • Percentage of patients from those re-randomized having achieved IGA 0 or 1 and a ≥2-point improvement from Baseline at Week 16 who continue to exhibit an IGA 0 or 1 and a ≥2-point improvement from Baseline at Week 52	Specific for Maintenance Period: • Percentage of patients from those re-randomized having achieved EASI-75 at Week 16 who continue to exhibit EASI-75 at Week 52 (EASI-75 calculated relative to baseline EASI score) • Percentage of patients from those re-randomized having achieved IGA 0 or 1 and a ≥2-point improvement from Baseline at Week 16 who continue to exhibit an IGA 0 or 1 and a ≥2-point improvement from Baseline at Week 52 • Percentage of patients from those with a Pruritus NRS of ≥4-points at baseline re-randomized having achieved ≥4-point reduction from baseline at Week 16 who continue to exhibit ≥4-point reduction from baseline at Week 52 • Percentage of patients from those with a Pruritus NRS of ≥5-points at baseline re-randomized having achieved ≥4-point reduction from baseline at Week 16 who continue to exhibit ≥4-point reduction from baseline at Week 52 • Percentage change in SCORAD (having achieved EASI-75 at Week 16) from baseline at Week 52
Evaluate the pharmacokinetics of lebrikizumab. • Average serum lebrikizumab concentration	Evaluate the pharmacokinetics of lebrikizumab. • Average serum lebrikizumab concentration

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 52 weeks in duration. The study is designed to confirm the safety and efficacy of lebrikizumab as monotherapy for moderate-to-severe atopic dermatitis utilizing a 16-week induction treatment period and a 36-week maintenance treatment period (Figure 1).

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

During the 16-week Induction Period, approximately 400 patients will be stratified and randomized 2:1 to either 250 mg lebrikizumab (loading dose of 500 mg given at Baseline and Week 2) or placebo by SC injection Q2W. All study drug injections will be administered in the clinic.

After completion of the Week 16 visit, patients who have responded to treatment [defined as having an IGA of 0 or 1 or a 75% reduction in EASI from Baseline to Week 16 (EASI-75)] will enter the Maintenance Period and will be re-randomized 2:2:1 to one of the following treatment groups: lebrikizumab 250 mg Q2W, lebrikizumab 250 mg Q4W, or placebo Q2W. Patients will be instructed to self-administer study drug at home.

Patients who do not achieve an IGA of 0 or 1 or an EASI-75 at Week 16 and those patients not maintaining an EASI-50 response following re-randomization at Week 24, 32, 40 or 48 will be assigned to an Escape Arm and receive lebrikizumab 250 mg as open-label treatment Q2W through Week 52. Patients not achieving an EASI-50 response after 8 weeks of treatment in the Escape Arm will be terminated from the study.

Efficacy will be measured through the IGA, EASI, BSA, SCORAD, Pruritus and Sleep-loss scores.

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. Additionally, adolescents will be monitored for hormones.

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.

Photographs of a selected target lesion will be obtained in a subset of patients participating in this study.

Patients completing this 52-week study will be offered the option of continued treatment in a separate long-term extension study (DRM06-AD07).

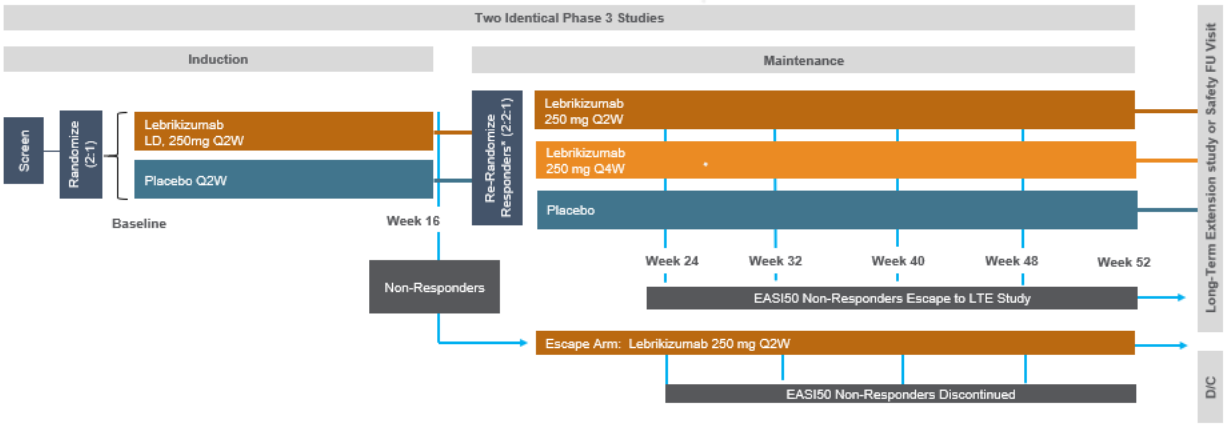
Patients who early terminate or choose not to enter the long-term extension study will undergo a follow-up visit approximately 12 weeks after the last study drug injection for safety follow-up.

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 52 visit and rolling into LTE study
- For subjects not continuing into LTE, when subject had either week 52 or ETV, 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



* Responder is defined as having an IGA of 0 or 1 or a 75% reduction in EASI from Baseline to Week 16 (EASI-75)

3.1. Duration of the Study

The total duration of a patient's participation in this study will be approximately 66 weeks (Screening: maximum duration of 30 days; Induction Period: 16 weeks; Maintenance Period: 36 weeks; Follow Up: 12 weeks from last dose at Week 50).

3.2. Study Population and Number of Patients

Approximately 400 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.
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.
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 child bearing potential
12. Provide signed informed consent/assent as described in Section 10.2.

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. 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.

5. STUDY DRUG

5.1. Investigational Medicinal Product

Lebrikizumab is a sterile liquid solution containing 125 mg/mL lebrikizumab, histidine acetate, sucrose, polysorbate 20, and sterile water for injection, USP, pH 5.4–6.0. Placebo solution is identical in appearance and content to the active solution except for lebrikizumab. All study drug (lebrikizumab and placebo) will be supplied as a sterile pre-filled syringe with a pre-assembled needle safety device (PFS-NSD). Each pre-filled syringe is intended for a single 2 mL dose (250 mg) administered subcutaneously (SC).

5.2. Storage and Labeling

Study drug is to be stored under refrigerated conditions (2–8°C) and protected from excessive light and heat. Study drug should not be frozen, shaken or stored at room temperature. Temperature excursions outside of 2–8°C must be reported to the Sponsor or the designee. Clinical trial material will be labeled according to country's regulatory requirements.

5.3. Patient Randomization

Patients will be assigned a unique identifier by the sponsor. Any patient records, datasets or tissue samples that are transferred to the sponsor will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred. All patients

will be randomly allocated to receive the study treatment using an electronic data capture system at the Baseline visit. The allocation to treatment will be prospectively stratified by geographic region (US versus EU versus rest of world), age (adolescent patients 12 to <18 years versus adults ≥18 years) and disease severity (IGA 3 versus 4). At the Baseline visit (Day 1), once a patient is considered eligible to participate in the study, demographic and stratification information will be entered into the EDC system to receive a medication number assigning a kit to a patient.

During the Maintenance Period, the EDC will be used to re-randomize a patient to a maintenance treatment based on the IGA or EASI score at Week 16.

5.3.1. Induction Period (Day 1 to Week 16)

Patients will be randomized 2:1 to one of the following treatment groups:

- Lebrikizumab 250 mg Q2W: 500 mg lebrikizumab administered at Baseline and Week 2 (loading dose; two PFS-NSD) and 250 mg Q2W through Week 14
- Placebo: 4 mL (two PFS-NSD) administered at Baseline and Week 2 and 2 mL Q2W through Week 14

5.3.2. Maintenance Period (Week 16 to Week 52)

After completion of the Week 16 visit, patients who have responded to treatment [defined as having an IGA score of 0 or 1 or, at least a 75% reduction in EASI from Baseline to Week 16 (EASI-75)] will be re-randomized 2:2:1 to one of the following treatment groups:

- Lebrikizumab 250 mg Q2W: 250 mg lebrikizumab given every 2 weeks through Week 50
- Lebrikizumab 250 mg Q4W: 250 mg lebrikizumab given every 4 weeks through Week 50
- Placebo: placebo given every 2 weeks

Responders who received placebo during the first 16 weeks of the study and who are re-randomized to lebrikizumab arms will receive a loading dose of lebrikizumab of either 500 mg given at Week 16 or 500 mg given at Weeks 16 and 18, based on the active treatment group assigned in Maintenance. To maintain study blinding, all patients re-randomized in the Maintenance period will receive the same number of injections at all visits throughout the Maintenance Period using an appropriate combination of active and placebo injections (Table 2).

Table 2: Maintenance Period Dosing Schedule by Treatment Group

Induction Treatment Assignment	Maintenance Treatment Assignment	Maintenance Loading Dose	Week 20, 24, 28, 32, 36, 40, 44, 48	Week 22, 26, 30, 34, 38, 42, 46, 50
Active	Lebrikizumab 250 mg Q2W	Week 16: one active and one placebo injection Week 18: one active and one placebo injection	One active injection	One active injection
	Lebrikizumab 250 mg Q4W	Week 16: one active and one placebo injection Week 18: two placebo injections	One active injection	One placebo injection
	Placebo	Week 16: two placebo injections Week 18: two placebo injections	One placebo injection	One placebo injection
Placebo	Lebrikizumab 250 mg Q2W	Week 16: two active injections Week 18: two active injections	One active injection	One active injection
	Lebrikizumab 250 mg Q4W	Week 16: two active injections Week 18 two placebo injections	One active injection	One placebo injection
	Placebo	Week 16: two placebo injections Week 18: two placebo injections	One placebo injection	One placebo injection

5.3.3. Escape Arm

Patients who require topical or systemic rescue treatment (Section 6.3) for atopic dermatitis during the Induction Period, or, are non-responders at Week 16, will be eligible for treatment in an Escape Arm where patients will receive lebrikizumab Q2W from Week 16 through Week 52. In addition, patients who do not maintain an acceptable response during the Maintenance Period (have an EASI score <50% of baseline), will be eligible for the Escape Arm.

To enter the Escape Arm, patients must have been compliant with study visits during the Induction Period or the Maintenance Period, respectively. Patients receiving systemic rescue medication (Section 6.3) will be required to washout for 5 half-lives prior to initiating treatment in the Escape Arm. All patients eligible for the Escape Arm will receive blinded loading doses, based on their prior treatment assignment (see Table 3 below), followed by 250 mg lebrikizumab Q2W through Week 52 on study in an open-label fashion. Patients in the Escape Arm must

comply with study visits every 4 weeks. Patients in the Escape Arm, not achieving or maintaining an EASI50 score after 8 weeks of treatment will be terminated from the trial.

Table 3: Escape Arm Dosing Schedule by Treatment Group

Induction Group Assignment	Maintenance Treatment Assignment	Maintenance Loading Dose (Blinded)	Week 20 to 50 (Unblinded: 250mg Q2W)
Patients entering Escape Arm at Week 16			
Active	Escape arm	Week 16: one active and one placebo injection Week 18: one active and one placebo injection	One active injection
Placebo	Escape arm	Week 16: two active injections Week 18: two active injections	One active injection
Patients entering Escape Arm at Week 24, 32, 40 and 48			
	Lebrikizumab 250 mg Q2W	At entry: one active and one placebo injection At next administration: one active and one placebo injection	One active injection
	Lebrikizumab 250 mg Q4W	At entry: one active and one placebo injection At next administration: one active and one placebo injection	One active injection
	Placebo	At entry: two active injections At next administration: two active injections	One active injection

5.4. Study Blinding

The Sponsor or designee, the Investigator, study-site personnel, and the patient will be blinded to treatment assignment. The integrity of the clinical study will be maintained by observing the treatment blind. If knowledge of a patient's treatment assignment is required for the patient's clinical care and/or safety, the Investigator should consult with the Sponsor's medical monitor prior to breaking the blind.

5.4.1. Unblinding Treatment Assignment

Unblinding the treatment assignment of a patient may only be performed in emergencies where knowledge of the patient's treatment assignment is essential for management of the patient's medical care. Unblinding the treatment assignment by the investigator under any other circumstances will be considered a protocol violation. The investigator should make every effort to contact the Sponsor or designee prior to unblinding a patient's treatment assignment. In the event of any unblinding, emergency or accidental, the sponsor must be notified within 1 business day.

Unblinding will occur using the EDC system. The Investigator must record the date and time the blind was broken, the names of the personnel involved, and the reason that treatment assignment information was required. The date and time that the Sponsor or designee was notified will also be recorded.

5.5. Study Drug Administration

Study drug will be administered to all patients in the clinic by designated and trained site staff from Baseline to Week 14 (last injection prior to Maintenance Period).

5.5.1. Instructions for Administration in the Clinic

Syringes should be at room temperature prior to injection (refer to the applicable Instructions for Use provided by the sponsor).

5.5.2. Instructions for Administration at Home

During the Maintenance Period, patients or caregivers will be instructed to self-administer study drug during the Maintenance Period.

Study site staff will instruct the patient or their caregiver on the proper injection technique and the patient or their caregiver will demonstrate for site staff proper injection technique prior to beginning at-home administration. An instruction card with details of the injection procedures will be provided to the patient/caregiver to take home, and dosing compliance will be captured via an electronic diary.

Patients or caregivers who are not capable of administering study drug at home may continue to receive study drug injections in the clinic.

5.6. Study Drug Accountability

The Investigator must keep an accurate record of the number of cartons received, the study drug dispensed/used, and those returned to the Sponsor or designee. The Sponsor or designee will provide forms to facilitate inventory control. All study-drug accountability forms and treatment logs must be retained in the Investigator's permanent study file, and these records must be available for inspection at any time by the Sponsor, its designees, or by regulatory agencies.

The study monitor will perform drug accountability for all study drug at the site, and will assist in returning all used, unused, and expired study drug, to the Sponsor/designees, or destroy it according to the study site's standard operating procedure, if accepted by the Sponsor.

6. CONCOMITANT MEDICATIONS AND PROCEDURES

All medications (including over-the-counter drugs, vitamins, and antacids) and over-the-counter emollient(s) taken/used at screening and throughout the study must be recorded. Patients should be instructed to consult with the Investigator prior to initiating any new medication (either self-administered non-prescription drugs or prescription therapy prescribed by another physician) while participating in the study. The Investigator is expected to examine the acceptability of all

concomitant medications, topical preparations, and dietary supplements taken by patients participating in the trial.

- Medication entries should be specific to product name (if a combination drug product) and spelled correctly.
- The brand and specific product name for any over-the-counter emollient(s) should be noted and spelled correctly.
- Information on the dose, unit, frequency, route of administration, start date, discontinuation date, indication, and reason for use will be recorded.
- The use of any concomitant medication must relate to an AE listed on the AE eCRF or the patient's medical history unless it is a supplement or used as preventative care.

6.1. Permitted and Prohibited Treatments and Procedures

The use of concomitant medications for other medical conditions (e.g., hypertension, diabetes, acute infections) is permitted during this study. Inhaled corticosteroids and bronchodilators to control asthma are permitted.

The introduction of medications or therapies for other medical conditions known to affect AD (e.g., systemic corticosteroids, mycophenolate-mofetil, IFN-y, Janus kinase inhibitors, TCI, cyclosporine, azathioprine, methotrexate, phototherapy, or photochemotherapy, phosphodiesterase-4 inhibitors such as crisaborole) are not permitted during the study. The use of systemic corticosteroids for the treatment of AD is prohibited and requires permanent discontinuation of Investigational Product. If used for treatment of AE (e.g. worsening of existing condition such as asthma exacerbation), it will still be treated as rescue medication as per Section 6.3.

Acute infections can be treated with systemic antibiotics, use of which must be recorded in the eCRF. However, chronic treatment with systemic antibiotics is not permitted.

The use of a tanning booth/parlor is not permitted during the trial.

Cannabinoid treatments for AD are prohibited.

Planned or anticipated major medical procedures or surgeries should be avoided during the trial.

See Section 6.3 for details on approved rescue medications and timing of use.

6.2. Moisturizers

Non-medicated moisturizers are to be used during the study. The patient may continue her/his current over-the-counter moisturizer regimen, if approved by the Investigator.

6.3. Rescue Treatment for Atopic Dermatitis

Induction Period

The use of topical or systemic treatments for atopic dermatitis is prohibited from Baseline through Week 16 in this study. Patients who experience intolerable AD symptoms and require treatment should, preferably, be started on topical treatments (e.g., mid-potency TCS) prior to instituting systemic treatments for AD symptoms, in accordance with best practice.

If systemic rescue treatments (e.g., oral corticosteroids, phototherapy, cyclosporin, etc.) are required, study drug must be discontinued. The patient should continue to attend all study visits through Week 16 and be assessed for safety and efficacy according to the schedule of events.

Patients requiring topical or systemic rescue medication who complete the study through Week 16 will be eligible to continue to the Escape Arm after the Week 16 visit has been completed. Patients who required systemic rescue medication must wait for rescue medication washout (≥5 half-lives of the medication) prior to entering the Escape Arm.

Maintenance Period

Intermittent use of topical rescue medications for AD is permitted during the Maintenance Period. Patients who may require short-term systemic treatment for symptoms of AD during the Maintenance Period will be assessed on a case by case basis and must be discussed with the Medical Monitor prior to initiating treatment.

Escape Arm

Intermittent use of topical rescue medications for AD is permitted for patients who are in the Escape Arm. Patients who may require short-term systemic treatment for symptoms of AD during the Escape Arm will be assessed on a case by case basis and must be discussed with the Medical Monitor prior to initiating treatment. Patients requiring long-term systemic treatment for symptoms of AD in the Escape Arm (e.g., non-responders) must be discontinued from the study.

The Sponsor may supply the study sites with a mid-potency and a low-potency TCS that can be provided to patients for use, if needed (e.g., triamcinolone acetonide 0.1% cream and hydrocortisone 1%cream).

All topical and systemic treatments for AD must be captured in the eCRF.

7. STUDY PROCEDURES

The required procedures for each study visit are outlined in Appendix 1. The timing of each study day is relative to the day of initial dosing (Day 1, Baseline).

7.1. Screening Visit

The purpose of the screening visit/period is to ensure that appropriate patients are entered into the study and that they remain stable during the pre-treatment period.

- Obtain written informed consent/assent prior to performing any study procedures
- Review Inclusion/Exclusion Criteria
- Complete medical history/review of systems
- Review immunization record for adolescent patients
- Collect demographic information
- Measure vital signs
- Perform a complete physical examination, including height and weight

- Collect concomitant medication and procedure/therapy information
- Complete the following assessments: Investigator's Global Assessment (IGA), Body Surface Area (BSA), and Eczema Area and Severity Index (EASI)
- Draw blood samples for laboratory tests, including serum pregnancy
- Collect urine sample for urinalysis
- Assign eDiary and instruct the patient on the completion of the following assessments: Pruritus and Sleep-Loss (daily), and POEM (weekly)
- Instruct the patient to apply a moisturizer at least twice daily

7.2. Baseline Visit (Day 1) Induction Period

- Administer the DLQI/CDLQI and EQ-5D
- Administer the PROMIS (Patient-Reported Outcomes Measurement Information System): Anxiety and Depression measures
- Collect the ACQ-5 assessment for patients with comorbid asthma
- Update medical history/review of systems and concomitant medication and procedure/therapy information
- Complete the following assessments: IGA, BSA, EASI and SCORAD
- Review compliance report on the eDiary and confirm moisturizer use
- Measure vital signs
- Draw a pre-dose blood sample for PK and anti-drug antibody (ADA) testing
- Conduct urine pregnancy test (WOCBP only)
- Re-assess and confirm patient eligibility (Inclusion/Exclusion criteria)
- Randomize the patient, receive kit assignment, and administer study drug
- Remind patient to record the following: Pruritus and Sleep-Loss (daily), and POEM (weekly)

Sites collecting photos will also:

- Obtain written informed consent for collecting photos
- Select a target lesion and obtain a photograph

7.3. Week 2 (± 3 Days)

- Complete the following assessments: IGA, BSA and EASI
- Review and record AEs and update concomitant medication and procedure/therapy information
- Review compliance report on the eDiary, confirm moisturizer use and remind patient to record the following: Pruritus and Sleep-Loss (daily), and POEM (weekly)

- Measure vital signs
- Administer study drug

Sites collecting photos will also:

- Obtain photographs of the target lesion

7.4. Week 4 (± 3 Days)

- Administer the DLQI/CDLQI
- Complete the following assessments: IGA, BSA and EASI
- Review and record AEs and update concomitant medication and procedure/therapy information
- Measure vital signs
- Draw a pre-dose blood sample for PK and ADA testing
- Conduct urine pregnancy test (WOCBP only)
- Administer study drug
- Review compliance report on the eDiary, confirm moisturizer use and remind patient to record the following: Pruritus and Sleep-Loss (daily), and POEM (weekly)

7.5. Week 6 (± 3 Days)

- Complete the following assessments: IGA, BSA, and EASI
- Review and record AEs and update concomitant medication and procedure/therapy information
- Review compliance report on the eDiary, confirm moisturizer use and remind patient to record the following: Pruritus and Sleep-Loss (daily), and POEM (weekly)
- Measure vital signs
- Administer study drug

7.6. Week 8 (± 3 Days)

- Administer the DLQI/CDLQI
- Complete the following assessments: IGA, BSA and EASI
- Review and record AEs and update concomitant medication and procedure/therapy information
- Review compliance report on the eDiary, confirm moisturizer use and remind patient to record the following: Pruritus and Sleep-Loss (daily), and POEM (weekly)
- Measure vital signs
- Draw blood samples for laboratory tests, except hormones

- Collect a urine sample for urinalysis
- Conduct urine pregnancy test (WOCBP only)
- Administer study drug

Sites collecting photos will also:

- Obtain photographs of the target lesion

7.7. Week 10 (± 3 Days)

- Complete the following assessments: IGA, BSA, EASI
- Review and record AEs and update concomitant medication and procedure/therapy information
- Review compliance report on the eDiary, confirm moisturizer use and remind patient to record the following: Pruritus and Sleep-Loss (daily), and POEM (weekly)
- Measure vital signs
- Administer study drug

7.8. Week 12 (± 3 Days)

- Administer the DLQI/CDLQI
- Complete the following assessments: IGA, BSA and EASI
- Review and record AEs and update concomitant medication and procedure/therapy information
- Review compliance report on the eDiary, confirm moisturizer use and remind patient to record the following: Pruritus and Sleep-Loss (daily), and POEM (weekly)
- Measure vital signs
- Conduct urine pregnancy test (WOCBP only)
- Administer study drug

7.9. Week 14 (± 3 Days)

- Complete the following assessments: IGA, BSA and EASI
- Review and record AEs and update concomitant medication and procedure/therapy information
- Review compliance report on the eDiary, confirm moisturizer use and remind patient to record the following: Pruritus and Sleep-Loss (daily), and POEM (weekly)
- Measure vital signs
- Administer study drug

7.10. Week 16 (± 3 Days) Transition to Maintenance Period

- Administer the DLQI/CDLQI, and EQ-5D
- Administer the PROMIS measures
- Collect ACQ-5 for patients with comorbid asthma
- Complete the following assessments: IGA, BSA, EASI and SCORAD
- Perform a complete physical examination, including height and weight
- Review and record AEs and update concomitant medication and procedure/therapy information
- Review compliance report on the eDiary, confirm moisturizer use and remind patient to record the following: Pruritus and Sleep-Loss (daily), and POEM (weekly)
- Measure vital signs
- Draw pre-dose blood samples for laboratory tests, PK and ADA testing
- Collect a urine sample for urinalysis
- Conduct urine pregnancy test (WOCBP only)
- Re-randomize the patient to the Maintenance Period
- Train the patient to self-administer study drug
- Administer one injection and observe the patient self-injecting
- Dispense study drug for Week 18 injections

Sites collecting photos will also:

- Obtain a photograph of the target lesion

7.11. Week 20 (± 5 Days)

- Complete the following assessments: IGA, BSA and EASI
- Review and record AEs and update concomitant medication and procedure/therapy information
- Review compliance report on the eDiary, confirm moisturizer use and remind patient to record the following: Pruritus and Sleep-Loss (daily), and POEM (weekly)
- Measure vital signs
- Conduct urine pregnancy test (WOCBP only)
- Administer or observe the patient self-injecting study drug
- Dispense study drug for Week 22 injection
- Remind the patient to apply moisturizer and to complete the eDiary as instructed

7.12. Week 24 (± 5 Days)

- Complete the following assessments: IGA, BSA and EASI
- Review and record AEs and update concomitant medication and procedure/therapy information
- Review compliance report on the eDiary, confirm moisturizer use and remind patient to record the following: Pruritus and Sleep-Loss (daily), and POEM (weekly)
- Measure vital signs
- Conduct urine pregnancy test (WOCBP only)
- Administer or observe the patient self-injecting study drug
- Dispense study drug for Week 26 injection
- Remind the patient to apply moisturizer and to complete the eDiary as instructed

7.13. Week 28 (± 5 Days)

- Complete the following assessments: IGA, BSA and EASI
- Review and record AEs and update concomitant medication and procedure/therapy information
- Review compliance report on the eDiary, confirm moisturizer use and remind patient to record the following: Pruritus and Sleep-Loss (daily), and POEM (weekly)
- Measure vital signs
- Conduct urine pregnancy test (WOCBP only)
- Administer or observe the patient self-injecting study drug
- Dispense study drug for Week 30 injection
- Remind the patient to apply moisturizer and to complete the eDiary as instructed

7.14. Week 32 (± 5 Days)

- Administer the DLQI/CDLQI
- Complete the following assessments: IGA, BSA and EASI
- Perform a complete physical examination, including height and weight
- Review and record AEs and update concomitant medication and procedure/therapy information
- Review compliance report on the eDiary, confirm moisturizer use and remind patient to record the following: Pruritus and Sleep-Loss (daily), and POEM (weekly)
- Measure vital signs
- Draw blood samples for laboratory tests, PK and ADA testing

- Collect a urine sample for urinalysis
- Conduct urine pregnancy test (WOCBP only)
- Administer or observe the patient self-injecting study drug
- Dispense study drug for Week 34 injection
- Remind the patient to apply moisturizer and to complete the eDiary as instructed

7.15. Week 36 (± 5 Days)

- Complete the following assessments: IGA, EASI, and BSA
- Review and record AEs and update concomitant medication and procedure/therapy information
- Review compliance report on the eDiary, confirm moisturizer use and remind patient to record the following: Pruritus and Sleep-Loss (daily), and POEM (weekly)
- Measure vital signs
- Conduct urine pregnancy test (WOCBP only)
- Administer or observe the patient self-injecting study drug
- Dispense study drug for Week 38 injection
- Remind the patient to apply moisturizer and to complete the eDiary as instructed

7.16. Week 40 (± 5 Days)

- Complete the following assessments: IGA, BSA and EASI
- Review and record AEs and update concomitant medication and procedure/therapy information
- Review compliance report on the eDiary, confirm moisturizer use and remind patient to record the following: Pruritus and Sleep-Loss (daily), and POEM (weekly)
- Measure vital signs
- Conduct urine pregnancy test (WOCBP only)
- Administer or observe the patient self-injecting study drug
- Dispense study drug for Week 42 injection
- Remind the patient to apply moisturizer and to complete the eDiary as instructed

7.17. Week 44 (± 5 Days)

- Complete the following assessments: IGA, EASI, and BSA
- Review and record AEs and update concomitant medication and procedure/therapy information

- Review compliance report on the eDiary, confirm moisturizer use and remind patient to record the following: Pruritus and Sleep-Loss (daily), and POEM (weekly)
- Measure vital signs
- Conduct urine pregnancy test (WOCBP only)
- Administer or observe the patient self-injecting study drug
- Dispense study drug for Week 46 injection
- Remind the patient to apply moisturizer and to complete the eDiary as instructed

7.18. Week 48 (± 5 Days)

- Complete the following assessments: IGA, BSA and EASI
- Review and record AEs and update concomitant medication and procedure/therapy information
- Review compliance report on the eDiary, confirm moisturizer use and remind patient to record the following: Pruritus and Sleep-Loss (daily), and POEM (weekly)
- Measure vital signs
- Conduct urine pregnancy test (WOCBP only)
- Administer or observe the patient self-injecting study drug
- Dispense study drug for Week 50 injection
- Remind the patient to apply moisturizer and to complete the eDiary as instructed

7.19. Week 52 (± 5 Days) End of Study

- Administer the DLQI/CDLQI, and EQ-5D
- Administer the PROMIS measures
- If the patient has reported a history of asthma, collect the ACQ-5 assessment
- Complete the following assessments: IGA, BSA, EASI and SCORAD
- Perform a complete physical examination, including height and weight
- Review and record AEs and update concomitant medication and procedure/therapy information
- Review compliance report on the eDiary and collect eDiary
- Measure vital signs
- Draw blood samples for laboratory tests, PK and ADA testing
- Collect a urine sample for urinalysis
- Conduct urine pregnancy test (WOCBP only)

7.20. Early-Termination Visit

Patients who discontinue the study early for any reason should have these assessments performed at their early-termination visit. The reason for early termination must be recorded in the eCRF (see Section 8.7.1).

- Administer the DLQI/CDLQI, and EQ5D
- Administer the PROMIS measures
- Collect the ACQ-5 assessment for patients with comorbid asthma
- Complete the following assessments: IGA, BSA, EASI and SCORAD
- Perform a complete physical examination, including height and weight.
- Review and record AEs and update concomitant medication and procedure/therapy information
- Review compliance report on the eDiary and collect eDiary
- Measure vital signs
- Draw blood samples for laboratory tests, PK and ADA testing
- Collect a urine sample for urinalysis
- Conduct urine pregnancy test (WOCBP only)

If the Early Termination Visit is during the Induction Period, sites collecting photos will also:

- Obtain a photograph of the target lesion

7.21. Safety Follow-up Visit

Patients who terminate early from the study or do not enroll in the long-term extension study, DRM06-AD07, will undergo a follow up visit approximately 12 weeks after the last study drug injection.

- Update AEs and concomitant mediations and procedures that were ongoing at study termination
- Draw blood samples for PK and ADA testing.

7.22. Unscheduled Visits

If an unscheduled visit is necessary, the following assessments should be included in the visit along with any assessments that are the reason for the visit (e.g., blood draw for a repeat of abnormal lab values):

- Review and record AEs and update concomitant medication and procedure/therapy information
- If the reason for the unscheduled visit is an exacerbation of atopic dermatitis, complete the following assessments: IGA, BSA and EASI

8. DETAILS OF ASSESSMENTS

8.1. Screening Assessments

8.1.1. Demographic Information

Patient age, gender at birth, ethnicity and race will be collected. Race and ethnicity information will only be used to support sub-group analyses assessing phenotype with treatment response. The collection of a patient's race and ethnicity is particularly important, given recent descriptions of disease heterogeneity in AD, with diverse phenotypes and endotypes described based on age, disease chronicity, ethnicity, genetics, IgE status, and underlying molecular mechanisms (Czarnowicki, 2019).

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 (IGA)

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 (Table 4). 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 4: Investigator Global Assessment (IGA)

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 (EASI)

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.

8.2.3. Body Surface Area (BSA)

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. BSA 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 (SCORAD)

SCORAD 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.

8.3.1. Patient Oriented Eczema Measure (POEM)

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 (DLQI)

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. PROMIS® (Patient-Reported Outcomes Measurement Information System): Anxiety and Depression

PROMIS® (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 (ACQ-5)

Patients who report comorbid asthma prior to enrollment will complete the Asthma Control Questionnaire (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. Photography

At a subset of study sites, some patients will have photographs taken of a representative area of AD involvement. Equipment and procedures will be outlined in a separate Photography Manual.

8.5. Assessment of Safety

8.5.1. 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.

8.5.2. 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.

8.5.3. 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 5: 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)

8.5.4. 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).

8.5.4.1. 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 8.5.4.3. 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 8.5.4.3.)

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.

8.5.4.2. Adverse Events of Special Interest (AESIs)

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

AESIs 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.

8.5.4.3. Serious Adverse Events (SAEs)

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.

8.5.4.4. Reporting of SAEs

All SAEs, as defined in Section 8.5.4.3, 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.

SAEs 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.

SAEs 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 a 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 a 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.

8.5.5. 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.

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.

8.5.6. Pregnancy

The investigator should 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.

8.5.7. 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

hypersensitivity reaction might be attributed to the study drug, and particularly if the reaction is severe, for discussions about discontinuing the study medication.

8.6. PK and ADA Sampling

Serum PK and ADA samples will be collected in all patients. Positive ADA results may be further evaluated for neutralizing antibodies. The procedural instructions will be provided in a separate PK and Serum Antibody Sampling manual.

8.7. Study Termination

The Sponsor has the right to terminate the study at any time. Should the study be terminated, the decision and reason will be communicated in writing by the Sponsor to the Investigator and request that all patients be discontinued. Patients should be scheduled for an Early Termination visit. The entire study will be stopped if:

- Evidence has emerged that, in the collective opinion of the Investigators at each site with the concurrence of the Sponsor, or the sole opinion of the Sponsor, continuation of the study is unnecessary or unethical
- The stated objectives of the study are achieved
- The Sponsor discontinues the development of the study drug

All data available for the patient at the time of study discontinuation must be recorded in the patient's records and the eCRF.

8.7.1. Early Termination of Study Patients

The Investigator will make reasonable efforts to keep each patient in the study. However, patients may terminate or be terminated early from the study for the following reasons:

- Voluntarily withdrawal of consent to participate in the study participation, at any time
- Adverse event, laboratory abnormality or inter-current illness which, in the opinion of the Investigator, indicates that continued treatment and/or participation in the study is not in the best interest of the patient
- Serious protocol violation, persistent non-compliance or requirement for medication or procedure prohibited by the protocol
- Lost to follow-up

Patients who are terminated early from the study will have an Early Termination visit scheduled as soon as possible (see Section 7.20). All information, including the reason for early termination will be recorded in the patient's study records and in the eCRF.

Two attempts of contact (e.g., telephone contact) followed by a certified letter of contact to the patient must be documented in a patient's study records for all patients who are believed to be lost to follow-up.

8.7.2. Study Drug Discontinuation

Study drug must be discontinued for patients who experience the following:

- Inter-current illness that would, in the judgment of the Investigator, affect assessments of clinical status to a significant degree
- Treatment-related AEs that are clinically significant, deemed persistent, in the judgment of the Investigator
- Unacceptable toxicity
- Pregnancy
- Use of systemic rescue medication as outlined in Section 6.3

Patients who discontinue study drug permanently during study participation must be scheduled for an Early Termination visit except those receiving systemic rescue medication, as per Section 6.3.

8.8. Data Safety Monitoring Board

An independent data safety monitoring board (DSMB) comprised of members who are independent of the study sponsor and study investigators will monitor patient safety by conducting formal reviews of accumulated safety data that is blinded by treatment group; if requested, the DSMB may have access to the treatment allocation code or any other requested data for the purposes of a risk-benefit assessment.

The DSMB will provide the sponsor with appropriate recommendations on the conduct of the clinical study to ensure the protection and safety of the patients enrolled in the study. The DSMB will also institute any measures that may be required for ensuring the integrity of the study results during the study execution.

All activities and responsibilities of the DSMB are described in the DRM06 DSMB charter.

9. STATISTICAL CONSIDERATIONS

9.1. General Statistical Methodology

All statistical processing will be performed using SAS® unless otherwise stated. Except where noted, all statistical tests will be two-sided and will be performed at the 0.05 level of significance.

Descriptive statistics will be used to provide an overview of the efficacy and safety results. For categorical parameters, the number and percentage of patients in each category will be presented. For continuous parameters, descriptive statistics will include number of subjects (n), mean, standard deviation (SD), median, minimum and maximum. Appropriate inferential statistics will be used for the primary and secondary efficacy variables.

The Pruritus-NRS weekly mean will be calculated as follows: The mean of each patient's baseline and post-baseline Pruritus-NRS scores will be computed for each week based on the previous 7 days. The weekly mean will be calculated if a patient has responses for Pruritus-NRS

on at least 4 of the 7 days of the week. If the patient has 3 or fewer Pruritus-NRS responses, the mean value for that item will be considered missing. All Pruritus-NRS efficacy endpoint analyses will be conducted on the weekly mean. The Sleep-Loss weekly mean will be calculated similar to the Pruritus-NRS weekly mean. All Sleep-Loss efficacy endpoint analyses will be conducted on the weekly mean.

The primary method of handling missing efficacy data will be as follows for both binary and continuous endpoints: for patients who receive topical rescue medication (per section 6.3), any systemic medication for AD or withdraw from the study due to lack of efficacy, set to the patient's baseline value subsequent to this time through Week 16. Markov chain Monte Carlo (MCMC) multiple imputation will be used to handle the remaining missing data. MCMC multiple imputation for all missing values, Non-Response Imputation (NRI), Last Observation Carried Forward (LOCF) and Tipping point analysis will be used for sensitivity analyses. Details about missing data imputation during the maintenance will be described in the SAP.

Demographic data will be summarized by treatment group using descriptive statistics. Patients' baseline characteristics related to efficacy analyses will be compared with descriptive statistics among treatment groups to ensure comparable results.

The number of patients in each analysis set will be summarized. Reasons for study withdrawal during the blinded study will be summarized using frequencies and percentages by treatment group.

A statistical analysis plan (SAP), describing all statistical analyses (induction and maintenance) will be provided as a separate document. The SAP will be finalized prior to unblinding of the study treatments.

9.1.1. Populations Analyzed

Approximately 400 patients (including approximately 50 adolescent patients [≥12 to <18 years of age weighing ≥40 kg]) will be randomized to lebrikizumab 250 mg Q2W or placebo treatment groups in a 2:1 ratio. Efficacy analyses will be performed using the intent-to-treat (ITT) population and the per-protocol (PP) population. Safety analyses will be performed using the safety population.

All patients who are randomized will be included in the ITT population.

All patients who are randomized and receive at least one confirmed dose of study drug will be included in the safety population.

The PP population will include all patients in the ITT population who complete the Week 16 evaluation without any significant protocol violations (i.e., any patient or Investigator activity that could have possibly interfered with the therapeutic administration of the treatment or the precise evaluation of treatment efficacy). The PP population will include patients in the safety population who do not meet any of the following criteria:

- Violated the inclusion/exclusion criteria;
- Used an interfering concomitant medication (see Section 6.3 for definitions of interfering concomitant medications) or underwent a prohibited procedure;
- Did not attend the Week 16 visit;

- Missed more than one post-baseline study visit prior to Week 16;
- Have not been compliant with the dosing regimen (i.e., patients must receive at least 75% of the expected injections of study medication during participation in the study);
- Out of visit window at the Week 16 visit by more than ±4 day.

Patients that discontinue from the study due to an adverse event related to study treatment or documented lack of treatment effect will be included in the PP population. Prior to breaking the blind, other additional criteria may be added to the list to accommodate for unforeseen events that occurred during the conduct of the trial that result in noteworthy study protocol violations.

9.2. Primary Efficacy Analysis

For FDA:

The primary endpoint is the percentage of patients with an IGA 0 or 1 and a ≥2-point improvement from Baseline at Week 16 and will be analyzed using the Cochran-Mantel-Haenszel test adjusted by randomization strata (region, disease severity, age).

For EMA:

Both co-primary endpoints:

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

will be analyzed using the Cochran-Mantel-Haenszel test adjusted by randomization strata (region, disease severity, age).

9.3. Secondary Efficacy Analysis

For dichotomous secondary endpoints, the Cochran-Mantel-Haenszel analysis will be used.

For continuous secondary endpoint, an analysis of covariance (ANCOVA) will be used with factors of treatment and randomization strata (region, disease severity, age) and relevant baseline value.

9.4. Missing Data

The primary method of handling missing efficacy data will be as follows for both binary and continuous endpoints: for patients who receive topical rescue medication (per Section 6.3), receive systemic rescue medication or withdraw from the study due to lack of efficacy, set to the patient's baseline value subsequent to this time through Week 16. MCMC multiple imputation will be used to handle the remaining missing data. Imputation will be conducted within each treatment group independently so the pattern of missing observations in one treatment group cannot influence missing value imputation in another treatment group. For each imputation process, 25 datasets with imputations will be calculated. Each complete data set will be analyzed with the specified analysis. The results from these analyses will be combined into a single inference using SAS PROC MIANALYZE.

For binary responses related to EASI and IGA, the binary response variables will be calculated based on the multiply imputed datasets that have been created. Because the MCMC algorithm is based on the multivariate normal model, imputed values for IGA will not generally be one of the discrete values used in IGA scoring (0, 1, 2, 3, or 4). Therefore, to derive the binary IGA response variable, standard rounding rules will be applied to the imputed values. For example, if a patient has an IGA score imputed as 1.4 (and assuming a Baseline IGA score of 3), the imputed value would be rounded down to 1, and the minimum change from Baseline of 2 would have been met. This patient would be considered a responder.

For derivation of an EASI-75 response, no rounding will be performed. The imputed Week 16 EASI value will be compared directly to the observed Baseline EASI value to determine whether a reduction of at least 75% was achieved.

For derivation of the following Pruritus-NRS responses, no rounding will be performed. The imputed Pruritus-NRS value will be compared directly to the observed mean baseline Pruritus-NRS value to determine whether the response was achieved:

- Percentage of patients with a Pruritus NRS of ≥4-points at Baseline who achieve a ≥4-point reduction 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 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

Imputation of continuous data will parallel that of binary variables. The imputed values will be used for the following secondary endpoints:

- Percentage change in Pruritus Numerical Rating Scale (NRS) score from Baseline to Week 16
- Percentage change in EASI score from Baseline to Week 16

A total of 2 random seeds will be needed to impute IGA for the two treatment groups. The two seeds have been pre-specified by a random-number generator:

- IGA: Lebrikizumab 250 mg Q2W: Seed = 671970387
- IGA: Placebo Q2W: Seed = 1339715635

A total of 2 random seeds will be needed to impute Pruritus NRS for the two treatment groups. The two seeds have been pre-specified by a random-number generator:

- NRS: Lebrikizumab 250 mg Q2W: Seed = 1461173528
- NRS: Placebo Q2W: Seed = 1492214362

A total of 2 random seeds will be needed to impute EASI for the two treatment groups. Those 2 random seeds have been pre-specified by using a random number generator:

- EASI: Lebrikizumab 250 mg Q2W: Seed=1015171075

- EASI: Placebo Q2W: Seed=1806114500

9.5. Sensitivity Analyses

9.5.1. All Missing Values MCMC Multiple Imputation

In this set of sensitivity analysis, the non-missing assessed values as collected for visits subsequent to rescue medication use will be used. Otherwise, missing values will be imputed using MCMC multiple imputation for the primary endpoint of an IGA 0 or 1 and a ≥2-point improvement from Baseline at Week 16 and the following secondary endpoints: EASI-75 (EMA co-primary endpoint), EASI-90 at Week 16 and Pruritus-NRS Improvement ≥4 points, at Weeks 1, 2, 4 and 16.

9.5.2. Last Observation Carried Forward (LOCF)

In this set of sensitivity analysis, the non-missing assessed values as collected for visits subsequent to rescue medication use will be used. Otherwise, missing values will be imputed using LOCF for the primary endpoint of an IGA 0 or 1 and a ≥2-point improvement from Baseline at Week 16 and the following secondary endpoints: EASI-75 (EMA co-primary endpoint), EASI-90 at Week 16 and Pruritus-NRS Improvement ≥4 points, at Weeks 1, 2, 4 and 16.

9.5.3. Non-Response Imputation

In this set of sensitivity analysis, for patients who receive topical rescue medication (per Section 6.3), receive systemic rescue medication, withdraw from the study due to lack of efficacy and any other missing values, set to non-response subsequent to this time through Week 16 for the primary endpoint of an IGA 0 or 1 and a ≥2-point reduction from Baseline to Week 16 and the following secondary endpoints: EASI-75, EASI-90 and Pruritus-NRS Improvement ≥4 points, all at Week16.

9.5.4. Tipping Point Analysis

Assuming the primary analyses results of endpoints are statistically significant, in this set of sensitivity analysis, assumptions on missing data due to rescue medication and study discontinuation will be varied to investigate if there will be any tipping points. To assess the impact of rescue medication and missing data due to dropout, the rates of response and non-response (including rescue medication use and dropout) will be varied to assess the response rates that tip significant differences to non-significance. The primary endpoint of an IGA 0 or 1 and a ≥2-point improvement from Baseline at Week 16 and the following secondary endpoints: EASI-75 (EMA co-primary endpoint), EASI-90 at Week 16 and Pruritus-NRS improvement ≥4-points, at Weeks 1, 2, 4 and 16 will be assessed using the tipping point analysis.

More details about missing value imputation analysis will be described in the SAP.

9.5.5. Subgroup Analyses

Subgroup analyses will be conducted for the ITT populations for the following subgroups: Adolescents (Age 12 to <18 years) vs. Adults (Age ≥18 years), sex, race, baseline IGA score (3 or 4), region (US, Europe, Rest of the World). Subgroup analysis will be conducted on the

primary endpoint of IGA (0,1), EASI-75, EASI-90 and percent of patients with pruritus improvement ≥4 points, all at Week 16.

Sensitivity analyses will be addressed in a full statistical analysis plan.

9.6. Multiplicity Considerations

The prespecified graphical multiple testing approach (Bretz 2011) will be implemented to control the overall Type I error rate at 2-sided alpha of 0.05 for superiority tests for the hypotheses for the primary and major secondary endpoints. The graphical approach is a closed testing procedure; hence it strongly controls the family-wise error rate across all endpoints (Alosh 2014). The major secondary endpoints will be pre-specified in the SAP prior to first unblinded efficacy analysis.

FDA objectives:

The graphical testing scheme will test IGA (0,1) first before proceeding to test the major secondary endpoints. Details of the specific graphical testing scheme (including testing order, interrelationships, Type I error allocation for the major secondary endpoints, and the associated propagation) will be pre-specified in the SAPs prior to first unblinded efficacy analysis.

EMA objectives:

The Week 16 endpoints of IGA (0,1) and EASI-75 represent a primary endpoint family. The graphical testing scheme will sequentially test IGA (0,1) first, followed by EASI-75 before proceeding to test the major secondary endpoints during induction period. Details of the specific graphical testing scheme (including testing order, interrelationships, Type I error allocation for the major secondary endpoints, and the associated propagation) will be pre-specified in the SAPs prior to first unblinded efficacy analysis. A separate graphical approach may be employed for testing the maintenance period endpoints.

9.7. PK Analysis

Plasma concentration data will be tabulated and summarized (geometric mean, arithmetic mean, minimum, maximum, SD, and % coefficient of variation) by treatment group for each visit at which samples were taken.

It is intended that data from this study will be combined with data from other studies to better characterize the PK of DRM06, as well as to explore the relationship between exposure and efficacy and/or safety outcomes. Further details on PK and PK/PD analyses will be provided in the PK/PD analysis plan. The results of these analyses will be described in a separate PK/PD report.

9.8. Anti-Drug Antibody Data Analysis

The ADA variables will be analyzed using descriptive statistics. Drug concentration data will be examined and the influence of ADAs on individual concentration-time profiles will be evaluated. Assessment of impact of ADA on safety and efficacy may be provided.

9.9. Immunogenicity Data Analysis

Listings and appropriate summary statistics will be provided for immunogenicity data.

9.10. Exposure and Compliance

The extent of exposure to study drug in each treatment group will be summarized by total number of days of exposure, total number of injections, number of missed injections, and number and percentage of patients who are compliant. An injection is considered the full set of injections specified by the protocol for a given treatment.

A patient will be considered compliant with the dosing regimen if the patient received ≥75% of the expected number of injections while enrolled in the study.

9.11. Adverse Events

All AEs occurring during the study will be recorded and coded using the MedDRA dictionary. Treatment-emergent AEs (TEAEs) are defined as AEs with an onset date on or after the date of the first injection of study drug. TEAEs will be summarized by treatment group, including the number of patients reporting an event, system organ class, preferred term, severity, relationship to study drug, and seriousness for the safety population. All serious AEs as well as AEs that led to study discontinuation will be listed by patient.

Three sets of AE tabulations are anticipated, one for the initial period, one for the maintenance period, and one for the combined initial and maintenance period. The denominator used for the treatment period will correspond to the number of patients in the safety population.

9.12. 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. 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.

9.13. Sample-Size Determination

For FDA:

In 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 was approximately 34.7% for lebrikizumab 250 mg Q2W versus 7.7% for placebo. A sample size of 96 for lebrikizumab 250 mg Q2W versus 48 for placebo will have more than 95% power to detect a statistically significant difference with a significance level of .05. However, to ensure sufficient safety information is collected and to ensure sufficient responders for the Maintenance

Period, the sample size will be increased to approximately 400 in total with a randomization ratio of 2:1 lebrikizumab:placebo.

For EMA:

In 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 was approximately 34.7% for lebrikizumab 250 mg Q2W versus 7.7% for placebo, and the proportion of patients who achieved an EASI75 at Week 16 using the rescue medication non-response sensitivity analysis was approximately 48.0% for lebrikizumab 250 mg Q2W versus 11.5% for placebo.

A sample size of 96 for lebrikizumab 250 mg Q2W versus 48 for placebo will have more than 95% power to detect a statistically significant difference with a significance level of .05 for each of the co-primary endpoints, which imply and overall power of at least 90%.

However, to ensure sufficient safety information is collected and to ensure sufficient responders for the Maintenance Period, the sample size will be increased to approximately 400 in total with a randomization ratio of 2:1 lebrikizumab:placebo.

9.14. Interim Analyses

The first database lock and unblinding will occur, and the interim 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 Study DRM06-AD05. This database lock will include all data collected by the cut-off date. Only the induction treatment assignment will be unblinded at the time of this interim lock. Maintenance treatment assignment will remain blinded.

The second database lock and unblinding will occur, and the interim analysis including the maintenance period will be performed at the time (that is, a cut-off date) the last patient completes Week 52 or the early termination visit from Study DRM06-AD05. This database lock will include all data collected by the cut-off date.

The study will not be terminated early on the basis of efficacy following these interim analyses.

A final database lock will then be conducted after all patients have completed the follow-up period of Study DRM06-AD05.

Depending on the regulatory submission timeline, the second database lock and the final database lock maybe combined, that is, one final database lock will occur after all patients have either completed the follow-up period of Study DRM06-AD05, or discontinued the Study early, or entered the long-term extension Study DRM06-AD07.

10. ADMINISTRATION

10.1. Compliance with the Protocol

The study shall be conducted as described in this protocol. All revisions to the protocol must be prepared by the Sponsor. The Investigator will not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study patients. Any significant deviation must be documented and submitted to the IRB/IEC, the Sponsor or designee, and, if required, Regulatory Authority(ies). Documentation of approval signed by the chairperson or designee of the IRB(s)/EC(s) must be sent to the Sponsor and/or designee.

10.2. Informed Consent Procedures

The Informed Consent Form (ICF) will include all elements required by ICH/GCP and applicable regulatory requirements and will adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. The consent form will also include a statement that the Sponsor and regulatory authorities have direct access to patient records and that the patient's medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities. The ICF will also inform the patient that his/her personal study-related data will be used by the sponsor in accordance with local data protection law; the ICF will describe the level of disclosure of data and seek appropriate consent from the patient for his/her data to be used in the manner described.

Prior to the beginning of the study, the Investigator will have the IRB/IEC's written opinion (approval/favorable) of the written informed consent form and any other information to be provided to the patients.

The Investigator must provide the patient or legally acceptable representative with a copy of the consent form and written information about the study in the language in which the patient is most proficient. The language must be non-technical and easily understood. The Investigator should allow time necessary for patient or patient's legally acceptable representative to inquire about the details of the study, then informed consent must be signed and personally dated by the patient or the patient's legally acceptable representative, by the Investigator and/or by the person who conducted the informed consent discussion. The patient or legally acceptable representative should receive a copy of the signed informed consent and any other written information provided to study patients prior to patient's participation in the study.

The informed consent and any other information provided to patients or the patient's legally acceptable representative, should be revised whenever important new information becomes available that is relevant to the patient's consent, and should receive IRB/IEC approval/ favorable opinion prior to use. The Investigator, or a person designated by the Investigator should fully inform the patient or the patient's legally acceptable representative of all pertinent aspects of the study and of any new information relevant to the patient's willingness to continue participation in the study. This communication to the patient should be documented in the source note.

During a patient's participation in the study, any updates to the consent form or to the written information will be provided to the patient in writing.

For patients considered to be minors according to the national legislation in each country, the written consent of the parent or legal guardian must be obtained, as well as the assent of the minor according to his or her capacity to understand the information provided. Patients enrolled as minors who attain legal adulthood during the course of the study must consent in their own right at that time in order to continue participating.

10.3. Data Protection and Confidentiality

Study patients must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient who will be required to give consent for their data to be used as described in the informed consent.

Patients must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Participants will be assigned a unique identifier by the sponsor. Any participant records, datasets or tissue samples that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The Sponsor has processes in place to ensure data protection, information security and data integrity. These processes include appropriate contingency plan(s) for appropriate and timely response in the event of a data security breach.

10.4. Study Documentation and the eCRF

This protocol is to be signed by the investigator responsible for the conduct of this study at the study site. A copy of the signed protocol signature page is to be provided to the Sponsor and retained in the study site's Regulatory Binder.

The Investigator is responsible for ensuring that all study data is accurately recorded on the eCRFs or other study data collection tools. All eCRF entries must be supported by the patient's medical records or source notes. The Investigator must ensure that study observations and findings are legible and recorded accurately and completely.

Original reports, traces and films must be reviewed, signed and dated, and retained by the Investigator for future reference.

The Investigator is expected to promptly review all study data recorded in the patient's source records. Completed eCRFs must be promptly reviewed, signed, and dated by the Investigator or Sub-Investigator at the end of the study. Corrections to data entered into the eCRF will be handled through an electronic query. Corrections to patients' medical or source records should be legible, initialed and dated. At the end of the study, an electronic copy of the investigator's eCRFs will be provided to the Investigator. The Investigator is to retain this data. The Investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on eCRFs. Refer to Section 10.6 regarding retention requirements.

An Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation for each patient treated with the study drug or entered as a control in the investigation. Data reported on the eCRFs that are derived from source documents must be consistent with the source documents or the discrepancies must be explained.

10.5. Study Monitoring

The Sponsor or designee will be responsible for the monitoring of the study. Study monitors will contact and visit the Investigators at regular intervals throughout the study to verify adherence to the protocol, and assess the completeness, consistency, and accuracy of the data by comparing patients' medical records with entries in the eCRF.

The study monitor must be allowed access to laboratory test reports and other patient records needed to verify the entries on the eCRF, provided patient confidentiality is maintained in accordance with local requirements. These records, and other relevant data, may also be reviewed by appropriate qualified personnel independent from the Sponsor or designee, who is appointed to audit the study. Patient confidentiality will be maintained at all times.

By agreeing to participate in this research study, the Investigators agree to co-operate with the study monitor to ensure that any problems detected during the monitoring visits are promptly resolved.

10.6. Retention of Study Documentation

The Investigator must retain study drug disposition records, copies of CRFs and all study-related source documents for the maximum period required by applicable regulations and guidelines, or Institution procedures, or for the period specified by the Sponsor, whichever is longer. The Investigator must contact the Sponsor prior to destroying any records associated with the study.

If the Investigator withdraws from the study (e.g., relocation, retirement), the records shall be transferred to a mutually agreed upon designee (e.g., another Investigator, IRB). Notice of such transfer will be given in writing to the Sponsor or designee.

If the Investigator cannot guarantee this archiving requirement for any or all the documents at the investigational site, arrangements must be made between the Investigator and the Sponsor to store these in a secure archive facility outside the site so they can be returned to the Investigator in case of a regulatory audit. When source documents are required for the continued care of the patient, appropriate copies should be made for storage outside of the site.

10.7. Publication Policy

In accordance with the sponsor's publication policy the results of this study will be submitted for publication by a peer-reviewed journal.

11. REFERENCES

Alosh M, Bretz F, Huque M. Advanced multiplicity adjustment methods in clinical trials. *Stat Med*. 2014;33(4):693-713

Auriemma M, Vianale G, Amerio P, Reale M. Cytokines and T cells in atopic dermatitis. *Eur Cytokine Netw.* 2013;24(1):37-44.

Bieber T, Novak N. Pathogenesis of atopic dermatitis: new developments. *Curr Allergy Asthma Rep* 2009;9(4):291-294.

Bieber T. Atopic dermatitis 2.0: from the clinical phenotype to the molecular taxonomy and stratified medicine. *Allergy.* 2012;67(12):1475-1482.

Bieber T. Atopic dermatitis. *N Engl J Med.* 2008;358(14):1483-1494.

Bretz F, Posch M, Glimm E, Klinglmueller F, Maurer W, Rohmeyer K. Graphical approaches for multiple comparison procedures using weighted Bonferroni, Simes, or parametric tests. *Biom J*. 2011;53(6):894-913.

Choy DF, Hsu DK, Seshasayee D, et al. Comparative transcriptomic analyses of atopic dermatitis and psoriasis reveal shared neutrophilic inflammation. *J Allergy Clin Immunol*. 2012;130(6):1335-1343.

Czarnowicki T, He H, Krueger JG, Guttman-Yassky E. Atopic dermatitis endotypes and implications for targeted therapeutics. *J Allergy Clin Immunol*. 2019;143(1):1-11.

Eichenfield LF, Tom WL, Chamlin SL, et al. Guidelines of care for the management of atopic dermatitis: section 1. Diagnosis and assessment of atopic dermatitis. *J Am Acad Dermatol*. 2014;70(2):338-351.

Esche C, de Benedetto A, Beck LA. Keratinocytes in atopic dermatitis: inflammatory signals. *Curr Allergy Asthma Rep.* 2004;4(4):276-284.

Flohr C, Irvine AD. Systemic therapies for severe atopic dermatitis in children and adults. *J Allergy Clin Immunol*. 2013;132(3):774-774.e6.

Hamid Q, Naseer T, Minshall EM, Song YL, Boguniewicz M, Leung DY. In vivo expression of IL-12 and IL-13 in atopic dermatitis. *J Allergy Clin Immunol.* 1996;98(1):225-231.

He JQ, Chan-Yeung M, Becker AB, et al. Genetic variants of the IL13 and IL4 genes and atopic diseases in at-risk children. *Genes Immun*. 2003;4(5):385-389.

Howell MD, Fairchild HR, Kim BE, et al. Th2 cytokines act on S100/A11 to downregulate keratinocyte differentiation. *J Invest Dermatol.* 2008;128(9):2248-2258.

Hua TC, Hwang CY, Chen YJ et al. The natural course of early-onset atopic dermatitis in Taiwan: a population-based cohort study. *Br J Dermatol*. 2014;170(1):130-135.

Hummelshoj T, Bodtger U, Datta P, et al. Association between an interleukin-13 promoter polymorphism and atopy. *Eur J Immunogenet.* 2003;30(5):355-359.

Illi S, von Mutius E, Lau S, et al. The natural course of atopic dermatitis from birth to age 7 years and the association with asthma. *J Allergy Clin Immunol.* 2004;113(5):925-931.

Jeong CW, Ahn KS, Rho NK, et al. Differential in vivo cytokine mRNA expression in lesional skin of intrinsic vs. extrinsic atopic dermatitis patients using semiquantitative RT-PCR. *Clin Exp Allergy.* 2003;33(12):1717-1724.

Kiebert, G, Sorensen SV, Revicki D, et al. Atopic dermatitis is associated with a decrement in health-related quality of life. *Int J Dermatol*. 2002;41(3):151-158.

Kim BE, Leung DY, Boguniewicz M, Howell MD. Loricrin and involucrin expression is down-regulated by Th2 cytokines through STAT-6. *Clin Immunol*. 2008;126(3):332-337.

La Grutta S, Richiusa P, Pizzolanti G, et al. CD4(+)IL-13(+) cells in peripheral blood well correlates with the severity of atopic dermatitis in children. *Allergy.* 2005;60(3):391-395.

Neis MM, Peters B, Dreuw A, et al. Enhanced expression levels of IL-31 correlate with IL-4 and IL-13 in atopic and allergic contact dermatitis. *J Allergy Clin Immunol.* 2006;118(4):930-937.

Novak N, Kruse S, Kraft S, et al. Dichotomic nature of atopic dermatitis reflected by combined analysis of monocyte immunophenotyping and single nucleotide polymorphisms of the interleukin-4/interleukin-13 receptor gene: the dichotomy of extrinsic and intrinsic atopic dermatitis. *J Invest Dermatol.* 2002;119(4):870-875.

Purwar R, Werfel T, Wittmann M. IL-13-stimulated human keratinocytes preferentially attract CD4+CCR4+ T cells: possible role in atopic dermatitis. *J Invest Dermatol*. 2006;126(5):1043-1051.

Sampson HA, Munoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report. Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol*. 2006;117(2):391-397.

Silverberg JI. Public Health Burden and Epidemiology of Atopic Dermatitis. *Dermatol Clin.* 2017;35(3):283-289.

Simon D, Wollenberg A, Renz H, Simon HU. Atopic Dermatitis: Collegium Internationale Allergologicum (CIA) Update 2019. *Int Arch Allergy Immunol*. 2019;178(3):207-218.

Simpson E, Paller A, Siegfried E, et al. Dupilumab efficacy and safety in adolescents with moderate-to-severe atopic dermatitis: Results from a multicenter, randomized, placebo-controlled, double-blind parallel-group, phase 3 study. Presented at the EADV Congress, September 12-16th, 2018, Paris, France.

Suarez-Farinas M, Dhingra N, Gittler J, et al. Intrinsic atopic dermatitis shows similar TH2 and higher TH17 immune activation compared with extrinsic atopic dermatitis. *J Allergy Clin Immunol*. 2013;132(2):361-370.

Tanei R. Atopic dermatitis in the elderly. *Inflamm Allergy Drug Targets.* 2009;8(5):398-404.

Tazawa T, Sugiura H, Sugiura Y, Uehara M. Relative importance of IL-4 and IL-13 in lesional skin of atopic dermatitis. *Arch Dermatol Res.* 2004;295(11):459-464.

Treister AD, Lio PA. Long-term off-label dupilumab in pediatric atopic dermatitis: A case series. *Pediatr Dermatol*. 2019;36(1):85-88.

Van Bever HP, Llanora G. Features of childhood atopic dermatitis. *Asian Pac J Allergy Immunol*. 2011;29(1):15-24.

Weidinger S, Beck LA, Bieber T, Kabashima K, Irvine AD. Atopic dermatitis. *Nat Rev Dis Primers.* 2018;4(1):1.

Weidinger S, Novak N. Atopic dermatitis. *Lancet.* 2016;387(10023):1109-1122.

Werfel T, Allam JP, Biedermann T, et al. Cellular and molecular immunologic mechanisms in patients with atopic dermatitis. *J Allergy Clin Immunol.* 2016;138(2):336-349.

Williams H, Stewart A, von Mutius E, et al. Is eczema really on the increase worldwide? *J Allergy Clin Immunol.* 2008;121(4):947-954.e15.

Zuberbier, T, Orlow SJ, Paller AS, et al. Patient perspectives on the management of atopic dermatitis. *J Allergy Clin Immunol*. 2006;118(1):226-232.

12. APPENDICES

APPENDIX 1. SCHEDULE OF VISITS AND PROCEDURES

Table 6: Induction Period: Screening Through Week 16

Study Procedure	**Screening**	**Baseline**	**Induction Period**							
Day (D); Week (W)	**D-30 to -7**	**D1**	**W2**±3d	**W4**±3d	**W6** ±3d	**W8**±3d	**W10**±3d	**W12**±3d	**W14**±3d	**W16**±3d/ **ET**
Informed Consent/Assent	X									
Inclusion/Exclusion, Med History/Demographics	X	X								
Review of immunization record (for adolescents)	X									
Randomization		X								X
Safety										
Vital Signs	X	X	X	X	X	X	X	X	X	X
Physical Exam, Weight/Height	X									X
Adverse Events			X	X	X	X	X	X	X	X
Concomitant Medications/Procedures	X	X	X	X	X	X	X	X	X	X
Efficacy										
IGA, BSA, EASI	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
PROMIS Anxiety and Depression Measures		X								X
ACQ-5*		X								X

Study Procedure	**Screening**	**Baseline**	**Induction Period**							
Day (D); Week (W)	**D-30 to -7**	**D1**	**W2**±3d	**W4**±3d	**W6** ±3d	**W8**±3d	**W10**±3d	**W12**±3d	**W14**±3d	**W16**±3d/ **ET**
Photography		X	X			X				X
Laboratory Testing										
HIV, Hepatitis	X									
Hematology, Chemistry, Urinalysis	X					X				X
Estradiol or Testosterone[2]	X									X
Pregnancy Test	Serum	Urine		Urine		Urine		Urine		Urine
Pre-dose PK		X		X						X
Pre-dose ADA[3]		X		X						X
Treatment										
Administer study drug		Loading dose	Loading dose	X	X	X	X	X	X	Loading dose

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

Table 7: Maintenance Period: Week 18 to Week 52/Escape Arm

Study Procedure	Maintenance Period								End of Study	Safety F/U[1]
Week (W)	W20±5d	W24±5d	W28±5d	W32±5d	W36±5d	W40±5d	W44±5d	W48±5d	W52±5d /ET	12 wks after last dose
Safety										
Vital Signs	X	X	X	X	X	X	X	X	X	
Physical Exam, Weight/Height				X					X	
Adverse Events	X	X	X	X	X	X	X	X	X	X
Con Meds/Procedures	X	X	X	X	X	X	X	X	X	X
Efficacy										
IGA, BSA, EASI	X	X	X	X	X	X	X	X	X	
SCORAD									X	
E-Diary: Pruritus, Sleep- loss (daily)	X	X	X	X	X	X	X	X	X	
E-Diary: POEM (weekly)	X	X	X	X	X	X	X	X	X	
Patient Reported Outcomes / Quality of Life										
DLQI/CDLQI*				X					X	
EQ-5D*									X	
PROMIS Anxiety and Depression Measures*									X	
ACQ-5*									X	
Laboratory Testing										
Hematology, Chemistry				X					X	
Estradiol or Testosterone[2]				X					X	
Urinalysis				X					X	
Pregnancy Test	Urine	Urine	Urine	Urine	Urine	Urine	Urine	Urine	Urine	

Study Procedure	**Maintenance Period**								**End of Study**	**Safety F/U[1]**
Week (W)	**W20**±5d	**W24**±5d	**W28**±5d	**W32**±5d	**W36**±5d	**W40**±5d	**W44**±5d	**W48**±5d	**W52**±5d **/ET**	**12 wks after last dose**
Pre-dose PK, ADA[3] Sample				X					X	X
Treatment										
Administer study drug in clinic	X	X	X	X	X	X	X	X		
Dispense syringe for home treatment	X	X	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 outcome and quality of life measures should all be completed prior to other study assessments.

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:

- Facial, neck, and extensor involvement in infants and children
- Current or previous flexural lesions in any age group
- 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
- Perifollicular accentuation/ lichenification/prurigo lesions

Exclusionary conditions — It should be noted that a diagnosis of atopic dermatitis depends on excluding conditions, such as:

- Scabies
- Seborrheic dermatitis
- Contact dermatitis (irritant or allergic)
- Icthyoses
- Cutaneous T-cell lymphoma
- Psoriasis
- Photosensitivity dermatoses
- Immune deficiency diseases
- Erythroderma of other causes

adapted from Eichenfield, 2014.