Weeks 4, 8, 12: 125 mg (one 1-mL injection of 125 mg/mL drug product and one 1-mL injection of placebo)

Weeks 6, 10, 14: Two 1-mL injections of placebo

Treatment Group 2: Lebrikizumab, 250 mg every 4 weeks

Baseline: Loading dose of 500 mg (four 1-mL injections of 125 mg/mL drug product)

Week 2: Four 1-mL injections of placebo

Weeks 4, 8, 12: 250 mg (two 1-mL injections of 125 mg/mL drug product)

Weeks 6, 10, 14: Two 1-mL injections of placebo

Treatment Group 3: Lebrikizumab, 250 mg every 2 weeks

Baseline and Week 2: Loading dose of 500 mg (four 1-mL injections of 125 mg/mL drug product)

Week 4, 6, 8, 10, 12, 14: 250 mg (two 1-mL injections of 125 mg/mL drug product)

Treatment Group 4: Placebo every 2 weeks

Baseline and Week 2: Four 1-mL injections of placebo

Week 4, 6, 8, 10, 12, 14: Two 1-mL injections of placebo

Key Inclusion Criteria:

- Male or female, 18 years or older.
- Chronic AD as defined by Hanifin and Rajka (1980) that has been present for ≥1 year before the screening visit (see Appendix 2)
- Eczema Area and Severity Index (EASI) score ≥16 at the screening and the Baseline visit.
- Investigator Global Assessment (IGA) score ≥3 (scale of 0 to 4) at the screening and the Baseline visit.
- ≥10% body surface area (BSA) of AD involvement at the screening and the Baseline visit.

Key Exclusion Criteria:

- Treatment with any of the following agents within 4 weeks prior to the Baseline visit:
  - Immunosuppressive/immunomodulating drugs (e.g., systemic corticosteroids, cyclosporine, mycophenolate-mofetil, IFN-γ, Janus kinase inhibitors, azathioprine, methotrexate, etc.)
  - Phototherapy and photochemotherapy (PUVA) for AD.
- Treatment with topical corticosteroids (TCS) or topical calcineurin inhibitors (TCI) within 1 week prior to the Baseline visit.
- Treatment with:
  - An investigational drug within 8 weeks or within 5 half-lives (if known), whichever is longer, prior to the Baseline visit.
  - Dupilumab within 3 months prior to Baseline visit.
  - Cell-depleting biologics, including rituximab, within 6 months prior to the Baseline visit.
  - Other biologics within 5 half-lives (if known) or 16 weeks prior to Baseline visit (whichever is longer).

5 SELECTION OF PATIENTS

5.1 Inclusion Criteria

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

1. Male or female, ≥18 years.
2. Chronic AD as defined by Hanifin and Rajka (1980) that has been present for ≥1 year before the screening visit (see Appendix 2).
3. Eczema Area and Severity Index (EASI) score ≥16 at the screening and the Baseline visits.
4. Investigator Global Assessment (IGA) score ≥3 (scale of 0 to 4) at the screening and the Baseline visits.
5. ≥10% body surface area (BSA) of AD involvement at the screening and the Baseline visits.
6. History of inadequate response to treatment with topical medications; or determination that topical treatments are otherwise medically inadvisable (e.g., because of important side effects or safety risks).
7. Applied a stable dose of topical emollient (over-the-counter moisturizer) twice daily for ≥7days prior to the Baseline visit.
8. Willing and able to comply with all clinic visits and study-related procedures and questionnaires.
9. Provide signed informed consent.

5.2 Exclusion Criteria

Patients meeting any of the criteria below are not for this study:

1. History of anaphylaxis.
2. Participation in a prior lebrikizumab clinical study.
3. 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.
4. Treatment with TCS or TCI within 1 week prior to the Baseline visit.
5. Treatment with biologics as follows:
   a. Treatment with an investigational drug within 8 weeks or within 5 half-lives (if known), whichever is longer, prior to the Baseline visit.
   b. Dupilimab within 3 months of Baseline visit.
   c. Cell-depleting biologics, including to rituximab, within 6 months prior to the Baseline visit.
   d. Biologics within 5 half-lives (if known) or 16 weeks prior to Baseline visit, whichever is longer.

- 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.

6.9 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 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, TCS (except when given for rescue therapy), TCI, cyclosporine, azathioprine, methotrexate, phototherapy, or photochemotherapy) are not permitted during the study and during the interval prior to entry into the study as defined in the exclusion criteria. In addition, the use of a tanning booth/parlor is not permitted during the trial.

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

6.10 Rescue Therapy

Patients requiring rescue therapy should consider the addition of TCS prior to considering systemic treatment. Any patient who requires TCS treatment may stay in the study and should continue the TCS for as brief a period as possible. Any patient requiring systemic therapy to treat their AD during the study will be discontinued from the study and the end of study visit assessment should be completed per Schedule of Visits and Procedures. TCS use must be recorded on the concomitant medications eCRF, indicated as “AD therapy”.

7 STUDY PROCEDURES

The required procedures for each study visit are outlined in the study Schedule of Visits and Procedures. 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 prior to performing any study procedures.
- Review Inclusion/Exclusion Criteria.
- Collect demographic information.
- Complete medical history/review of systems.
- Collect concomitant-medication and procedure/therapy information.
- Perform a complete physical examination, including height and weight.
- Measure vital signs.
- Draw blood samples for laboratory tests, including serum pregnancy test (screening visit only).
- Collect urine sample for urinalysis.
- Complete the following assessments:

- Measure vital signs.
- Collect concomitant-medication information.
- Review and record AEs.
- Review compliance report on the electronic tablet for the daily assessments (pruritus NRS, sleep-loss NRS, and ADIQ) and remind patient to continue daily record.
- At **Day 29, 57, and 85**, draw blood samples for laboratory tests, and collect urine for urinalysis and pregnancy test (WOCBP only).
- At **Day 29, 57, and 85**, complete the following assessments:
  - Investigator's Global Assessment (IGA)
  - Eczema Area and Severity Index (EASI)
  - Body Surface Area (BSA)
- At **Day 57** complete the following assessments:
  - Dermatology Life-Quality Index (DLQI)
  - Hospital Anxiety and Depression Scale (HADS).
- At **Day 15, 29, 57, and 85**, collect blood samples for PK (see Section 8.2.2 for instructions).
- At **Day 15 and 29**, collect a pre-dose blood sample for ADA testing (see Section 8.2.2 for instructions).
- Administer study drug.
- Remind the patient to apply an emollient twice daily.
- Remind the patient to use the tablet daily.
- Schedule next visit.

7.4 Visit Day 113 (Week 16) (+/- 3 Day) (End-of-Treatment/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 patient's records and the eCRF.

- Confirm emollient use.
- Perform a complete physical examination, including weight.
- Measure vital signs.
- Collect concomitant medication and procedure/therapy information.
- Review and record AEs.
- Collect a 12-lead ECG.
- Draw blood samples for laboratory tests (hematology and chemistry).
- Draw a blood sample for PK and ADA testing.
- Collect urine for urinalysis and urine pregnancy test (WOCBP only).

A grade of 0 to 4 will be assessed by the Investigator or designee. Assessors must be trained and certified by the Sponsor prior to conducting this assessment. Assessments will be recorded in the eCRF.

8.2.1.2 Eczema Area and Severity Index (EASI)

The EASI (Appendix 4) 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. A grade of 0 to 72 will be assessed by the Investigator or designee.

Assessors must be trained and certified by the Sponsor prior to conducting this assessment. Assessments will be recorded in the eCRF.

8.2.1.3 Body Surface Area (BSA)

The BSA (Appendix 5) 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.

Assessments will be recorded in the eCRF. Assessors must be trained and certified by the Sponsor prior to conducting this assessment.

8.2.1.4 Pruritus

Pruritus will be assessed by the patient using a Pruritus Numeric Rating Scale (NRS) (Appendix 6). The Pruritus NRS is an 11-point scale used by patients to assess their worst itch severity over the past 24 hours with 0 indicating “No itch” and 10 indicating “Worst itch imaginable”. At Week 16, a global impression of change for itching question will be requested.

Assessments will be recorded daily by the patient using an electronic diary and transferred into the clinical database.

8.2.1.5 Sleep-Loss

Quality of sleep will be assessed by the patient using a sleep-loss question (Appendix 7) over the past 24 hours.

Assessments will be recorded daily by the patient using an electronic diary and transferred into the clinical database.

8.2.1.6 Atopic Dermatitis Impact Questionnaire (ADIQ)

The ADIQ (Appendix 8) is a 17-item questionnaire used to assess the patients’ AD-specific health-related QoL. The questionnaire assesses AD’s impact on emotions, energy, activities of daily living, and social activities. The ADIQ has a recall specification of 7 days.

Assessments will be recorded by the patient using an electronic diary and transferred into the clinical database.

8.2.1.7 Patient Oriented Eczema Measure (POEM)

The POEM (Appendix 9) is a 7-item questionnaire used by the patient to assess the severity of the patient’s eczema over the last week. All seven answers carry equal weight and are scored as: No days=0; 1– 2 days =1; 3–4 days=2; 5–6 days=3; everyday=4.

The POEM is completed by the patient in the clinic. Assessments will be recorded in the eCRF.

8.2.1.8 Dermatology Life Quality Index (DLQI)

The DLQI (Appendix 10) is a 10-question instrument used to measure 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).

The DLQI is completed by the patient in the study clinic. Assessments will be recorded in the eCRF.

8.2.1.9 Hospital Anxiety and Depression Scale (HADS)

The HADS (Appendix 11) assesses anxiety and depression in a non-psychiatric population. The HADS has two subscales (depression and anxiety), both with 7 questions.

Responses are based on the relative frequency of symptoms over the past week, using a four-point scale ranging from 0 (not at all) to 3 (very often indeed).

HADS is completed by the patient in the clinic. Assessments will be recorded in the eCRF.

8.2.1.10 Global Assessment of Change–AD

The Global Assessment of Change for AD (Appendix 12) will be one question asked at Week 16 and the Early-Termination visit. The value of the question is to capture the patient's impression of overall change in their AD.

This will be completed by the patient in the clinic. Assessments will be recorded in the eCRF

8.2.2 PK and ADA Sampling

Serum PK and ADA samples on Day 1, 15, 29, 57 (PK only), 85 (PK only), 113, and 169 will be taken predose. PK and ADA samples will be collected from all patients including those assigned to the placebo group to maintain the blinding of the treatment assignment. Positive ADA results will be further evaluated for antidrug antibodies. The procedural instructions will be provided in a separate PK and Serum Antibody Sampling manual.

9 ASSESSMENT OF SAFETY

9.1 Assessment of Safety

9.1.1 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 be recorded as part of the screening physical exam and only the patient's weight will be recorded with the Baseline and the week 16 physical examination. Findings will be recorded in the eCRF.

At subsequent study visits, a symptom-directed physical examination may be conducted.

9.1.2 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,

Table 2 Laboratory Parameters

Hematology	Chemistry	Urine
• 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)

9.1.5 Adverse Events (AEs)

An AE is defined as any untoward medical occurrence associated with the use of a study drug in humans, whether considered drug related. An AE can, therefore, be any unfavorable and unintended sign (including clinically significant abnormal laboratory finding), symptom or disease temporally associated with the use of the study drug, whether related to the investigational product.

AEs 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 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).

9.1.5.1 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 recorded 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 9.1.6. Unless a diagnosis is available, 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 9.1.6.)

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 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.

9.1.6 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.

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.

9.1.6.1 Reporting of SAEs

All SAEs, as defined in Section 9.1.6, 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 an SAE form. 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.

9.1.7 Adverse Events of Special Interest (AESI)

AESIs in this study include:

- Anaphylactic reactions or acute allergic reactions that require immediate treatment
- Malignancies (excluding non-melanoma skin cancers).

All AESIs must be reported to the sponsor and designee within 24 hours of identification.

9.1.8 Pregnancy

In the instance that a patient becomes pregnant during participation in the study, the patient must be withdrawn from study drug but may continue study participation. The Investigator must perform medical assessments as clinically indicated and continue to follow the patient for ≥4 weeks after delivery, at a minimum. Details for both the mother and baby must be obtained.

Although pregnancy is not itself an AE or SAE, maternal/fetal complications or abnormalities will be recorded as AEs or SAEs, as appropriate.

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

10 STUDY DISCONTINUATIONS

10.1 Study Termination

The Sponsor has the right to terminate or to stop 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. Should this be necessary, patients should be scheduled for an Early-termination visit (Section 7.4).

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

If the study is terminated by the Sponsor, all data available for the patient at the time of discontinuation must be recorded in the patient's records and the eCRF.

10.2 Early Termination of Study Patients

The Investigator will make every reasonable effort 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 study will have an Early-Termination visit scheduled (Section 7.4) as soon as possible. All information, including the reason for early discontinuation will be recorded in the patient's study records and in the eCRF.

Before a patient can be terminated early due to loss of follow-up, the Investigator must show documented attempts to contact the patient regarding study participation on two separate occasions (telephone contact) followed by a certified letter of contact.

Three sets of AE tabulations are anticipated, one for the treatment period, one for the post-treatment (follow-up) period, and one for the combined treatment and post treatment period. The denominator used for the treatment period will correspond to the number of patients in the safety population. Data will also be corrected for exposure and reported per 100 patient-years.

11.8 Other Safety Data

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

ECGs and 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.

11.9 Sample-Size Determination

The sample size for this study was based mainly on clinical considerations.

12 ADMINISTRATION

12.1 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.

12.2 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.

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 by the

Schedule of Visits and Procedures (cont'd)

Study Procedure	Treatment Period		Follow-up/EOS			Unscheduled Visit[b]	Early Termination[b]
Visit (V)	**V9**	**V10**	**V11**	**V12**	**V13 Phone Call**		
Week (W)	**W14**	**W16**	**W20**	**W24**	**W32**		
Day (D)	**D99**	**D113**	**D141**	**D169**	**D225**		
Visit Window (d)	**±3d**	**±3d**	**±7d**	**±7d**	**±7d**		
Safety:							
Weight		X					X
Vital Signs	X	X	X	X		X	X
Physical Examination		X					X
Adverse Events	X	X	X	X	X	X	X
Concomitant Medication	X	X	X	X		X	X
Procedure/Therapy	X	X	X	X		X	X
12-Lead ECG		X					X
Laboratory Testing:							
Hematology, Chemistry		X		X			X
Urinalysis		X		X			X
Pregnancy Test (WOCBP only)		Urine		Urine			Urine
Efficacy:							
IGA		X	X	X			X
EASI		X	X	X			X
BSA		X	X	X			X
Pruritus (daily)[a]	X	X					X
Sleep-loss (daily)[a]	X	X					X
ADIQ[a]	X	X					X
POEM		X					X
DLQI		X					X
HADS		X					X
Global Assessment of Change–AD		X					X
PK/Drug Concentration and Anti-Drug Antibody (ADA) Samples[c]:							
PK Sample		X		X			
ADA Sample		X		X			
Treatment:							
Administer Study Drug	X						
Reminders:							
Apply emollient twice daily	X	X	X	X			
Use electronic tablet daily	X						

[a] Pruritus NRS, sleep-loss NRS, and ADIQ are completed on an electronic tablet issued to the patient at the Baseline visit.

[b] If applicable.

[c] PK and ADA samples taken pre-dose on dosing days (There is no dosing at the Week 16 and Week 24 visits).

5. CCI [redacted]

- ☐ [redacted]
- ☐ [redacted]
- ☐ [redacted]
- ☐ [redacted]
- ☐ [redacted]

6. CCI [redacted]

- ☐ [redacted]
- ☐ [redacted]
- ☐ [redacted]
- ☐ [redacted]
- ☐ [redacted]

7. CCI [redacted]

- ☐ [redacted]
- ☐ [redacted]
- ☐ [redacted]
- ☐ [redacted]
- ☐ [redacted]

8. CCI [redacted]

- ☐ [redacted]
- ☐ [redacted]
- ☐ [redacted]
- ☐ [redacted]
- ☐ [redacted]

Appendix 10. Dermatology Life Quality Index (DLQI)

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick (X) one box for each question.

1.	Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	 Not relevant ☐
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	 Not relevant ☐
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	 Not relevant ☐
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	 Not relevant ☐
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	 Not relevant ☐
7.	Over the last week, has your skin prevented you from **working** or **studying**?	Yes No	☐ ☐	
	If "No", over the last week how much has your skin been a problem at **work** or **studying**?	A lot A little Not at all	☐ ☐ ☐	
8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	 Not relevant ☐
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	 Not relevant ☐
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	 Not relevant ☐

❒ **Please check you have answered EVERY question. Thank you.**

- Use of prescription moisturizers within 7 days of the Baseline visit.

Primary Endpoint:

- Percent change in Eczema Area and Severity Index (EASI) from Baseline to Week 16.

Secondary Endpoints:

- Proportion of patients with a 75% improvement from Baseline in EASI (EASI75) at Week 16.
- Proportion of patient with an IGA score of 0 (clear) or 1 (almost clear) and a reduction ≥2 points from Baseline to Week 16 (5-point scale).
- Proportion of patients with EASI <7 at Week 16.
- Proportion of patients achieving EASI50 and EASI90 at Week 16.
- Percent change in the sleep-loss numerical rating scale (NRS) score from Baseline to Week 16.
- Percent change in pruritus NRS score from Baseline to Week 16.
- Proportion of patients with pruritus NRS change of ≥3 from Baseline to Week 16.
- Proportion of patients with pruritus NRS change of ≥4 from Baseline to Week 16.
- Change in Body Surface Area (BSA) involved with AD from Baseline to Week 16.
- Change from Baseline in Atopic Dermatitis Impact Questionnaire (ADIQ) score.

6. Use of prescription moisturizers within 7 days of the Baseline visit.
7. Regular use (more than 2 visits per week) of a tanning booth/parlor within 4 weeks of the screening visit.
8. Treatment with a live (attenuated) vaccine within 12 weeks before the Baseline visit.
9. 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.
10. 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.
11. History of human immunodeficiency virus (HIV) infection or positive HIV serology at screening.
12. Positive with hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), or hepatitis C antibody at the screening visit.
13. In the Investigator's opinion, any clinically significant laboratory results from the chemistry, hematology or urinalysis tests obtained at the screening visit.
14. Presence of skin comorbidities that may interfere with study assessments.
15. History of malignancy 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.
16. 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 (including relevant laboratory abnormalities at screening) 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. Pregnant or breastfeeding women, or women planning to become pregnant or breastfeed during the study.
17. Women of reproductive potential* who are sexually active and unwilling to use adequate birth control. Adequate birth control is defined as agreement to consistently practice an effective and accepted method of contraception† throughout the duration of the study and for 120 days after last dose of study drug.

*The following are considered women who are NOT of reproductive potential: Menopausal women, defined as ≥12 consecutive months without menses (if in question, a follicle stimulating hormone level of ≥25 mU/mL); Women surgically sterilized (history of hysterectomy, bilateral oophorectomy, or bilateral tubal ligation).

†Includes abstinence, oral/implant/injectable/transdermal hormonal contraceptives, intrauterine device, double-barrier contraception (i.e., condom+diaphragm), same sex partner, or a male partner with vasectomy.

  - Investigator's Global Assessment (IGA)
  - Eczema Area and Severity Index (EASI)
  - Body Surface Area (BSA)
- Instruct the patient to apply an emollient twice daily.
- Schedule next visit.

7.2 Baseline Visit (Day 1)

- Confirm emollient use.
- Re-assess and confirm patient eligibility (Inclusion/Exclusion criteria).
- Measure weight and vital signs.
- Collect concomitant medication and procedure/therapy information.
- Query for adverse events (AEs) since the last visit.
- Collect a 12-lead ECG.
- Draw blood samples for laboratory tests (hematology and chemistry)
- Draw a pre-dose blood sample for PK and anti-drug antibody (ADA) testing.
- Conduct urine for urinalysis and urine pregnancy test (WOCBP only).
- Dispense electronic tablet that will be used for home recording of pruritus NRS and sleep-loss NRS (daily), and ADIQ (weekly).
- Train patient on the use of the electronic tablet.
- Review compliance report on the electronic tablet for the assessments (pruritus NRS, sleep-loss NRS, and ADIQ) and remind patient to record daily.
- Complete the following assessments:
  - Investigator's Global Assessment (IGA)
  - Eczema Area and Severity Index (EASI)
  - Body Surface Area (BSA)
  - Patient Oriented Eczema Measure (POEM)
  - Dermatology Life Quality Index (DLQI)
  - Hospital Anxiety and Depression Scale (HADS).
- Randomize the patient.
- Administer study drug.
- Instruct the patient to apply an emollient twice daily.
- Schedule next visit.

7.3 Visits on Day 15, Day 29, Day 43, Day 57, Day 71, Day 85 and Day 99 (+/- 3 Day)

- Confirm emollient use.

- Review compliance report on the electronic tablet for the daily assessments (pruritus NRS, including a global impression of change for itching; sleep-loss NRS; and ADIQ).
- Collect electronic tablets and download any remaining data on device.
- Complete the following assessments:
  - Investigator's Global Assessment (IGA)
  - Eczema Area and Severity Index (EASI)
  - Body Surface Area (BSA)
  - Patient-Oriented Eczema Measure (POEM)
  - Dermatology Life Quality Index (DLQI)
  - Hospital Anxiety and Depression Scale (HADS)
  - Global Assessment of Change for AD.
- Remind the patient to apply an emollient twice daily.
- Schedule next visit.

7.5 Follow-Up Visit Day 141 (Week 20) (+/- 7 Days)

- Measure vital signs.
- Collect concomitant medication and procedure/therapy information.
- Review and record AEs.
- Complete the following assessments:
  - Investigator's Global Assessment (IGA)
  - Eczema Area and Severity Index (EASI)
- Remind the patient to apply an emollient twice daily
- Schedule next visit.

7.6 Follow-Up Visit Day 169 (Week 24) (+/- 7 Days)

- Measure vital signs.
- Collect concomitant medication and procedure/therapy information.
- Review and record AEs.
- Draw blood samples for laboratory tests (hematology and chemistry)
- Draw blood sample for PK and ADA testing.
- Collect urine for urinalysis and urine pregnancy test (WOCBP only).
- Complete the following assessments:
  - Investigator's Global Assessment (IGA)
  - Body Surface Area (BSA).
  - Eczema Area and Severity Index (EASI)

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.

9.1.3 ECGs

12-lead ECG measurements will be obtained in all patients. The patient should rest quietly for at least 5 minutes in a supine position prior to ECG collection. The ECG should be obtained either prior to the time of blood collection, or at least 15 minutes afterwards. The medical monitor may be consulted if needed for interpretation of ECGs.

All study sites will be supplied with standardized, validated, digital, 12-lead ECG machine (12-lead at 25 mm/sec reporting rhythm, ventricular rate, the RR interval, the PR interval, QRS duration, QT and QTcF intervals) capable of recording, storing, printing, and producing high resolution 12-lead ECG data. Study sites will be trained on the use of the equipment prior to study start.

Machine-read ECG recordings will be collected and analyzed centrally. Data will be transferred electronically to the database.

9.1.4 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 of child-bearing potential (WOCBP). Blood and urine will be collected from each patient as specified in the Schedule of Visits and Procedures or as clinically indicated. Laboratory samples are to be shipped on the same day as collected. Laboratory test results will be provided to the sites through a web-based reporting system. Alert values will be emailed to the site. Laboratory data will be transferred to the clinical database from the central laboratory database.

Screening laboratory test results must be reviewed by the Investigator prior to patient enrollment. Patients will fail screening for clinically significant laboratory values. However, at the discretion of the Investigator, screening laboratory tests may be repeated one time to confirm out-of-range results or clinical significance. Specific laboratory tests are listed in Table 2.

The central laboratory should be used for all laboratory testing required for a patient during study participation, including laboratory testing needed for unscheduled visits. Clinically significant laboratory results must be entered as a diagnosis on the AE eCRF rather than as an individual test result. Patients with clinically significant laboratory test results will be evaluated, treated and followed at the discretion of the Investigator until the value returns to clinically acceptable levels.

Throughout the study, all laboratory results should be reviewed and signed by the Investigator within 48 hours of receipt of the report (whenever possible).

Prior to discontinuing a patient from study participation, the Investigator will discuss his/her intentions with the Sponsor Medical Monitor or designee.

10.3 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

Patients who discontinue study drug permanently during study participation must be scheduled for an Early-termination visit (Section 7.4).

11 STATISTICAL CONSIDERATIONS

11.1 General Statistical Methodology

All statistical processing will be performed using SAS® unless otherwise stated. No interim analyses are planned.

Except where noted, all statistical tests will be two-sided and will be performed at the 0.05 level of significance. The inclusion of p-values in the efficacy analyses is to assist in characterizing the therapeutic efficacy of the active medication. No adjustments will be made for multiple comparisons for the efficacy analyses. The primary analysis will be performed when all patients have completed the treatment phase at Week 16. The final time-course data analysis will be performed when all patients have finished Week 32.

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. The denominator for percentage will be based on the number of patients appropriate for the analysis. For continuous parameters, descriptive statistics will include the number of patients (n), mean, standard deviation (SD), median, and range. Appropriate inferential statistics will be used for the primary and secondary efficacy variables.

For the primary efficacy variable, the primary method of handling missing efficacy data will be the method of MCMC multiple imputation. This method does not rely on the assumption of data missing at random. Additionally, imputation will be conducted within each treatment group independently so the pattern of missing observations in one treatment group cannot influence missing value estimations in another.

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 a 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.

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.

12.3 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 12.5 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.

12.4 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

Appendix 2. Hanifin/Rajka Diagnostic Criteria for Atopic Dermatitis

From: Hanifin JM and Rajka G. Diagnostic features of atopic dermatitis. Acta Derm Venereol (Stockholm) 1980; Suppl 92:44–7.

To establish a diagnosis of atopic dermatitis the patient requires the presence of at least 3 “basic features” and 3 or more minor features listed below.

Basic Features

Must have three or more basic features:

- Pruritus
- Typical morphology and distribution
- Flexural lichenification or linearity in adults
- Chronic or chronically-relapsing dermatitis
- Personal or family history of atopy (asthma, allergic rhinitis, atopic dermatitis)

Minor Features

Plus, three or more minor features:

- Xerosis
- Ichthyosis, palmar hyperlinearity, or keratosis pilaris
- Immediate (type 1) skin-test reactivity
- Elevated serum IgE
- Early age of onset
- Tendency toward cutaneous infections (especially Staph. aureus and Herpes simplex)/impaired cell-mediated immunity
- Tendency toward non-specific hand or foot dermatitis
- Nipple eczema
- Cheilitis
- Recurrent conjunctivitis
- Dennie-Morgan infraorbital fold
- Keratoconus
- Anterior subcapsular cataracts
- Orbital darkening
- Facial pallor/facial erythema
- Pityriasis alba
- Anterior neck folds
- Itch when sweating
- Intolerance to wool and lipid solvents
- Perifollicular accentuation
- Food intolerance
- Course influenced by environmental or emotional factors
- White dermographism/delayed blanch

9. CCI [redacted]

- ☐ [redacted]
- ☐ [redacted]
- ☐ [redacted]
- ☐ [redacted]
- ☐ [redacted]

10. CCI [redacted]

- ☐ [redacted]
- ☐ [redacted]
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11. CCI [redacted]

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12. CCI [redacted]

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DERMATOLOGY LIFE QUALITY INDEX (DLQI) – INSTRUCTIONS FOR USE

The Dermatology Life Quality Index questionnaire is designed for use in adults, i.e. patients over the age of 16. It is self-explanatory and can be simply handed to the patient who is asked to fill it in without the need for detailed explanation. It is usually completed in one or two minutes.

SCORING

The scoring of each question is as follows:

Very much	Scored 3
A lot	Scored 2
A little	Scored 1
Not at all	Scored 0
Not relevant	Scored 0
Question 7, 'prevented work or studying'	Scored 3

The DLQI is calculated by summing the score of each question resulting in a maximum of 30 and a minimum of 0. The higher the score, the more quality of life is impaired.

HOW TO INTERPRET MEANING OF DLQI SCORES

0–1	No effect at all on patient's life
2–5	Small effect on patient's life
6–10	Moderate effect on patient's life
11–20	Very large effect on patient's life
21–30	Extremely large effect on patient's life

REFERENCES

Finlay AY and Khan GK. Dermatology Life Quality Index (DLQI): a simple practical measure for routine clinical use. *Clin Exp Dermatol* 1994; **19:**210-216.

Basra MK, Fenech R, Gatt RM, Salek MS, Finlay AY. The Dermatology Life Quality Index 1994-2007: a comprehensive review of validation data and clinical results. *Br J Dermatol* 2008; **159:**997-1035.

Hongbo Y, Thomas CL, Harrison MA, Salek MS, Finlay AY. Translating the science of quality of life into practice: What do dermatology life quality index scores mean? *J Invest Dermatol* 2005; **125:**659-64.