Clinical Study Protocol J2T-DM-KGAE Amendment 1

An open-label, single-arm study to assess the safety and efficacy of lebrikizumab in adolescent patients with moderate-to-severe atopic dermatitis

NCT04250350

Approval Date: 12-May-2020

AN OPEN-LABEL, SINGLE-ARM STUDY TO ASSESS THE SAFETY AND EFFICACY OF LEBRIKIZUMAB IN ADOLESCENT PATIENTS WITH MODERATE-TO-SEVERE ATOPIC DERMATITIS

Protocol Number	**DRM06-AD17/J2T-DM-KGAE**
Protocol Final Date	**14 November 2019**
Study Drug	**Lebrikizumab (DRM06/LY3650150)**
IND Number	**119866**
EudraCT Number	**2019-004301-28**
Sponsor	**Dermira, Inc.** **275 Middlefield Road** **Suite 150** **Menlo Park, CA 94025** **USA**
Amendment (1) Date	**12 May 2020**
Medical Monitor	PPD

[redacted]

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 Title page and Protocol Header throughout, Signature Pages	Added Eli Lilly protocol and investigational product unique identifiers.	References Eli Lilly and Company protocol and investigational product identifiers
Title Page, Signature Page	New Medical Monitor identified for study.	Personnel change
Throughout	Changed "open-label extension" to "long-term extension".	To align with the rollover protocol design
Acronyms	Updated	Consistency with protocol changes
Protocol Synopsis	Included "Asia Pacific region" to study site locations	Update to reflect participating study site locations
Protocol Synopsis and Section 3	Patients completing this 52-week study will be offered "active lebrikizumab" treatment in the long-term extension study, DRM06-AD07. Added a clearer definition of the timing of the end of the study per EU Regulation 536-2014: Annex 1 D.17.o. Added clearer definition of a patient being considered to have completed the study.	Clarification Clarification per European (EU) Regulation 536-2014: Annex 1 D.17.o
Protocol Synopsis, Section 2, 3.2 and 4.1	Defined age of study population as <18 years.	Clarification
Section 1.4	Added dose regimen.	Clarification
Section 1.5	Study Conduct Statements expanded to include language on protocol compliance. IRB/IEC review, applicable guidelines, laws and regulations and compensation per the EU regulation 536-2014: Annex 1 D.17.a.	Clarification per EU regulation 536-2014: Annex 1 D.17.a
Synopsis, Section 2.1	Added primary endpoint.	Clarification

Protocol Section	Description of Change	Rationale
Section 2.2	Added details for secondary endpoints.	Clarification
Section 3.2	Removed text concerning prospective approval of protocol deviations.	Statement repeated text in Section 4
Section 4.1	Inclusion criterion #7: Added "non-medicated, non-prescription". Inclusion criteria #9: "acceptable contraception" changed to "highly effective". List of highly effective contraceptive measures revised. Inclusion criteria #10: males must use an effective barrier method of contraception for a minimum of 18 weeks following the last dose (changed from three months.	Clarification Clarification Consistency with female requirements for inclusion
Section 4.2	Exclusion criteria #3: "Eucrisa" replaced with "phosphodiesterase-4 inhibitors". Exclusion criterion #6: add "medicated" Exclusion criteria #9: deleted reference to ACQ-5.	Globally recognized nomenclature Clarification Correction to error in protocol; ACQ-5 not utilized in this study
Section 5.1	Delete reference to placebo solution. Removed details concerning investigational product.	Correction to error in protocol; no placebo used in this study Details provided in other study-related documents
Section 5.2	Added "according to the country's regulatory requirements".	Clarification
Section 5.4.1	Removed details concerning administration at clinic. Added reference to Directions for Use.	Details provided in Directions for Use
Section 6.1	Added instructions on the use of systemic corticosteroids. Removed "severe" from description of infections.	Clarification Systemic antibiotics allowed for all acute infections.
Section 6.3	Clarified how topical and systemic treatments for AD may be used in the trial.	Clarification
Section 6.4	Deleted and moved text to Section 6.3.	Clarification

Protocol Section	Description of Change	Rationale
Section 7, 8.4.3 and Schedule of Visit and Procedures	Added hormone testing: estradiol in female patients and testosterone in male patients at screening, weeks 16, 32 and 52.	Safety monitoring to assess sexual maturation
Section 7.1 and 8.1.2	Added "review immunization record".	To ensure PI reviews prior to inclusion in trial
Section 7.4, Section 7.19, Schedule of Visit and Procedures	Added PK sample collection in addition to the ADA sample.	FDA recommendation
Section 7.6	Added collection of urine sample for urinalysis	Correction for protocol consistency: listed in the Schedule of Events and Procedures
Section 7.18	Deleted and combined with Section 7.17.	Same procedures conducted for Week 52 and Early Termination visit
Section 7.19	Changed follow-up visit from phone call to onsite.	Allow collection of PK and ADA samples
Section 8.2.1, Appendices 3, 4, 5 and 6	Deleted efficacy scales and patient reported outcome instruments.	Use of validated scales and instruments are provided in other study related materials and don't need to be duplicated in protocol.

Protocol Section	Description of Change	Rationale
Section 8.4.3, Schedule of Visits and Procedures	Removed requirement to perform TB screening serology	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 8.4.4.3	Added examples of medical events.	Clarification
Section 8.4.4.4	Expanded language notifying investigators of responsibilities of prompt reporting of SAEs, reporting requirements to IRB/IECs and the sponsors obligations to report safety information per EU Regulation 536-2014: Annex 1 D.20.c.	Per EU Regulation 536-2014: Annex 1 D.20.c
Section 8.4.5	Added new section to describe process for product complaints	Addition of Product Complaint Handling process
Section 8.6.2	Removed “systemic” from description of rescue medication outlined in Section 6.3 Changed reference from Section 5.4 to 6.3.	Clarification Clarification
Section 8.6.3 and Section 9.1	Removed text concerning treatment group blind.	Clarification: study is not blinded
Section 9.1.1	Removed “and have at least one post-baseline assessment”.	Clarification: All patients who receive a dose will be included in the Safety Population
Sections 9.2, 9.7 and 9.8	Removed “by treatment group”.	Clarification: study has only 1 treatment group
Section 9.6	Provided additional details on exposure and compliance. Defined ‘compliant’.	Clarification

Protocol Section	Description of Change	Rationale
Section 9.8	Added "Growth monitoring of adolescents will be summarized."	Clarification
Section 9.9	Updated sample size determination section to reflect that safety exposure determined sample size for this study.	Clarification
Section 9.10	Added new section (Section 9.10) to describe plan for interim analyses.	Per ICH E9
Section 10.2	Provided detail on consent process for minors who reach majority during the study.	Clarification
Section 10.3	Added new section (Section 10.3) regarding protection of patient data and maintenance of patient confidentiality.	Per EU Regulation 536-2014: Annex 1 D.17.ak EU Regulation 536-2014: Annex 1 D.17.al, EU Regulation 536-2014: Annex 1 D.17.am
Section 10.7	Added new section (Section 10.7) on publication policy.	Per EU Regulation 536-2014: Annex 1 D.17.ai

SPONSOR SIGNATURE PAGE

AN OPEN-LABEL, SINGLE-ARM STUDY TO ASSESS THE SAFETY AND EFFICACY OF LEBRIKIZUMAB IN ADOLESCENT PATIENTS WITH MODERATE-TO-SEVERE ATOPIC DERMATITIS

Protocol Number	**DRM06-AD17/J2T-DM-KGAE**
Protocol Final Date	**14 November 2019**
Amendment (1) Date	**12 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 Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines for Good Clinical Practice (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

AN OPEN-LABEL, SINGLE-ARM STUDY TO ASSESS THE SAFETY AND EFFICACY OF LEBRIKIZUMAB IN ADOLESCENT PATIENTS WITH MODERATE-TO-SEVERE ATOPIC DERMATITIS

Protocol Number: **DRM06-AD17/J2T-DM-KGAE**

Protocol Final Date: **14 November 2019**

Amendment (1) Date: **12 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 Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (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:	An Open-Label, Single-Arm Study to Assess the Safety and Efficacy of Lebrikizumab in Adolescent Patients with Moderate-to-Severe Atopic Dermatitis
Protocol Number:	DRM06-AD17
Phase:	3
Number of Sites:	Approximately 70 sites in North America, Asia Pacific region and the European Union (EU).

Study Population:

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

Sample Size:

200 patients

Study Objective:

To evaluate the safety and efficacy of lebrikizumab in adolescent patients (≥12 to <18 years weighing ≥40 kg) with moderate-to-severe AD.

Duration of Patient Participation:

Screening: Maximum duration of 30 days

Treatment Period: 52 weeks

Safety Followup: 12 weeks after last dose administered at Week 50

Maximum total participation: 66 weeks

Study Treatment:

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

Study Design:

This open-label, single arm study is 52 weeks in duration. The study is designed to assess the safety and efficacy of lebrikizumab in adolescent patients with moderate-to-severe atopic dermatitis.

Eligible patients (≥12 to <18 years weighing ≥40 kg) will have moderate-to-severe atopic dermatitis for at least one year, defined according to the American Academy of Dermatology Consensus Criteria, have 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%.

Approximately 200 patients will receive 250 mg lebrikizumab (loading doses of 500 mg given at Baseline and Week 2) by subcutaneous (SC) injection every 2 weeks (Q2W). Study drug injections will be administered in the clinic through Week 8 and patients or their caregivers will be instructed on self-administration of the study drug for injections following the Week 8 visit.

Efficacy will be measured using the Investigator's Global Assessment (IGA), Eczema Area and Severity Instrument (EASI) and body surface area (BSA).

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

Quality of life and impact of disease will be assessed using the Dermatology Life Quality Index (DLQI)/ Children's Dermatology Life Quality Index (CDLQI) and Patient-Reported Outcomes Measurement Information System (PROMIS)® Anxiety and Depression measures.

Serum samples will be collected for pharmacokinetic analysis and immunogenicity.

Patients completing this 52-week study will be offered active lebrikizumab treatment in a separate long-term extension study (DRM06-AD07).

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

A patient is considered to have completed the study if he/she has completed all required phases of the study including the last visit shown in the Schedule of Visits and Procedures. For patients continuing into the long-term extension study, the last study visit is the Week 52 visit. For patients who do not continue into the long-term extension study, the last study visit is the safety follow-up visit, occurring approximately 12 weeks after the last study drug 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.

Primary Endpoint:

Describe the proportion of patients discontinued from study treatment due to adverse events through the last treatment visit.

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ACRONYMS

Acronym	Term
ACQ-5	Asthma Control Questionnaire
AD	atopic dermatitis
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
AUC	area under the curve
AUC_{0-t}	AUC from 0 to time t
AUC_{inf}	AUC from 0 to infinity
AUC_{last}	AUC from time 0 to the last time with quantifiable concentration
BSA	body surface area
C	Celsius
C_{max}	maximum (or peak) serum concentration
D/d	Day
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
EASI-75	75% reduction in EASI from Baseline
EASI-90	90% reduction in EASI from Baseline
eCRF	electronic case report form
ET	early termination
EU	European Union
FDA	Food and Drug Administration
FLG	filaggrin
GCP	good clinical practice
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	independent ethics committee
IFN	interferon

Acronym	Term
Ig	immunoglobin
IGA	Investigator Global Assessment
IgE	Immunoglobulin E
IL	interleukin
IRB	institutional review board
LOR	loricrin
MCH	mean corpuscular hemoglobin
MedDRA	Medical Dictionary for Regulatory Activities
nAB	neutralizing antibodies
PFS-NSD	pre-filled syringe with a pre-assembled needle safety device
PK	pharmacokinetics
PROMIS	Patient-Reported Outcomes Measurement Information System
Q2W	every 2 weeks
Q4W	every 4 weeks
SAE	serious adverse event
SC	subcutaneous
SCORAD	SCORing Atopic Dermatitis
SCORAD-50	50% reduction in SCORAD
SCORAD-75	75% reduction in SCORAD
SD	standard deviation
SOC	system organ class
TB	tuberculosis
TCI	topical calcineurin inhibitor
TCS	topical corticosteroid
TEAE	treatment-emergent adverse event
US/USA	United States
W	week
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 (human interleukin (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 United States (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. Despite 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 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 administered every 4 weeks (Q4W) group; and 54 to the placebo Q4W group.

Efficacy Results

- Eczema Area and Severity Index (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 SCORing Atopic Dermatitis (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%.
- Investigator Global Assessment (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. 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 administered every 2 weeks (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 ≥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 ≥4-point improvement in pruritus numerical rating scale (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) subcutaneous (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, followed by 250 mg Q2W lebrikizumab was selected for study in this trial, based on an evaluation of safety, efficacy and PK data from the DRM06-AD01 and DRM06-AD03 trials (Section 1.3.1.3 and 1.3.1.4).

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 500 mg given at Baseline and Week 2.

Adolescent Patients

In this Phase 3 study, adolescent patients (≥12 to <18 years weighing ≥40 kg), will receive 250 mg lebrikizumab (loading dose of 500 mg given at Baseline and Week 2) by subcutaneous injection every 2 weeks (Q2W) which is the same dose of lebrikizumab administered in the adolescent/adult Phase 3 studies. . 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, informed consent form (ICF), Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an independent review committee (IRB)/independent ethics committee (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 Code of Federal Regulations (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 in adolescent patients (≥12 to <18 years weighing ≥40 kg) with moderate-to-severe AD.

2.1. Primary Endpoint

Describe the proportion of patients discontinued from study treatment due to adverse events through the last treatment visit.

2.2. Secondary Endpoints

Over the duration of the study:

- Percentage of patients with an IGA score of 0 or 1 and a reduction ≥2-points from Baseline
- Percentage of patients achieving response of EASI-75 (≥75% reduction from Baseline in EASI score)
- Percentage change from baseline in EASI score and percentage of patients achieving EASI-50 and EASI-90 (≥50 and ≥90% reduction from Baseline in EASI score, respectively)
- Change from baseline in body surface area (BSA)
- Change from baseline in Patient-Reported Outcomes Information System (PROMIS)® Anxiety and Depression measures
- Change from baseline and improvement in Dermatology Life Quality Index (DLQI)/Children's Dermatology Life Quality Index (CDLQI)
- Pharmacokinetics (PK)

3. STUDY DESIGN

This open-label, single arm study is 52 weeks in duration. The study is designed to assess the safety and efficacy of lebrikizumab in adolescent patients with moderate-to-severe atopic dermatitis (Figure 1).

Eligible patients (≥12 to <18 years weighing ≥40 kg) will have moderate-to-severe atopic dermatitis for at least one year, defined according to the American Academy of Dermatology Consensus Criteria, have 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%.

Approximately 200 patients will receive 250 mg lebrikizumab (loading doses of 500 mg given at Baseline and Week 2) by subcutaneous (SC) injection every 2 weeks (Q2W). Study drug injections will be administered in the clinic through Week 8 and patients or their caregivers will be instructed on self-administration of the study drug for injections following the Week 8 visit.

Efficacy will be measured using the Investigator's Global Assessment (IGA), Eczema Area and Severity Instrument (EASI) and body surface area (BSA).

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

Quality of life and impact of disease will be assessed using the Dermatology Life Quality Index (DLQI)/ Children's Dermatology Life Quality Index (CDLQI) and Patient-Reported Outcomes Measurement Information System (PROMIS)® Anxiety and Depression measures.

Serum samples will be collected for pharmacokinetic analysis and immunogenicity.

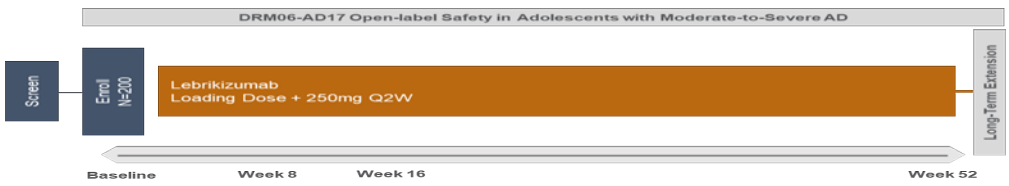
Patients completing this 52-week study will be offered active lebrikizumab treatment in a separate long-term extension study (DRM06-AD07).

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

A patient is considered to have completed the study if he/she has completed all required phases of the study including the last visit shown in the Schedule of Visits and Procedures. For patients continuing into the long-term extension study, the last study visit is the Week 52 visit. For patients who do not continue into the long-term extension study, the last study visit is the safety follow-up visit, occurring approximately 12 weeks after the last study drug administration.

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

Figure 1: Study Schema



3.1. Duration of the Study

The total duration of a patient's participation in this study will be approximately 66 weeks (Screening: maximum duration of 30 days; Treatment Period: 52 weeks; Safety Follow Up: 12 weeks from last dose at Week 50)

3.2. Study Population and Number of Patients

Approximately 200 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. Male or female adolescent (≥12 years to <18 years and weighing ≥40 kg).
2. Chronic AD (according to American Academy of Dermatology Consensus Criteria) that has been present for ≥1 year before the screening visit (see Appendix 2).
3. Eczema Area and Severity Index (EASI) score ≥16 at the baseline visit.
4. Investigator Global Assessment (IGA) score ≥3 (scale of 0 to 4) at the baseline visit.
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, non-prescription moisturizer at least twice daily for ≥7 days prior to the baseline visit.
8. Willing and able to comply with all clinic visits and study-related procedures and questionnaires.
9. 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.

   NOTE: A woman of childbearing potential 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,

intrauterine hormone-releasing system, 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.

10. 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
11. 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 (e.g., crisaborole) within 1 week prior to the baseline visit.
4. Treatment with any of the following agents within 4 weeks prior to the baseline visit:
   a. Immunosuppressive/immunomodulating drugs (e.g., systemic corticosteroids, cyclosporine, mycophenolate-mofetil, IFN-γ, Janus kinase inhibitors, azathioprine, methotrexate, etc.)
   b. Phototherapy and photochemotherapy (PUVA) for AD.
5. Treatment with the following prior to the baseline visit:
   a. An investigational drug within 8 weeks or within 5 half-lives (if known), whichever is longer.
   b. Dupilumab within 8 weeks.
   c. B cell-depleting biologics, including to rituximab, within 6 months.
   d. Other biologics within 5 half-lives (if known) or 16 weeks, whichever is longer.
6. Use of medicated prescription moisturizers within 7 days of the baseline visit.
7. Regular use (more than 2 visits per week) of a tanning booth/parlor within 4 weeks of the screening visit.
8. Treatment with a live (attenuated) vaccine within 12 weeks of the baseline visit or planned during the study.
9. Uncontrolled chronic disease that might require bursts of oral corticosteroids, e.g., co-morbid severe uncontrolled asthma (history of ≥2 asthma exacerbations within the last 12 months requiring systemic [oral and/or parenteral] corticosteroid treatment or hospitalization for > 24 hours).
10. Active chronic or acute infection requiring treatment with systemic antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals within 2 weeks before the baseline visit, or

superficial skin infections within 1 week before the baseline visit.
NOTE: patients may be rescreened after infection resolves.

11. Evidence of active acute or chronic hepatitis (as defined by the Department of Health & Human Services Centers for Disease Control and Prevention) or known liver cirrhosis.
12. Diagnosed active endoparasitic infections or at high risk of these infections.
13. Known or suspected history of immunosuppression, including history of invasive opportunistic infections (e.g., tuberculosis [TB], histoplasmosis, listeriosis, coccidioidomycosis, pneumocystosis, and aspergillosis) despite infection resolution: or unusually frequent, recurrent, or prolonged infections, per the Investigator's judgment.
14. History of human immunodeficiency virus (HIV) infection or positive HIV serology at screening.
15. In the Investigator's opinion, any clinically significant laboratory results from the chemistry, hematology or urinalysis tests obtained at the screening visit.
16. Presence of skin comorbidities that may interfere with study assessments.
17. History of malignancy, including mycosis fungoides, within 5 years before the screening visit, except completely treated in situ carcinoma of the cervix, completely treated and resolved non-metastatic squamous or basal cell carcinoma of the skin.
18. Severe concomitant illness(es) that in the Investigator's judgment would adversely affect the patient's participation in the study. Any other medical or psychological condition that in the opinion of the Investigator may suggest a new and/or insufficiently understood disease, may present an unreasonable risk to the study patient because of his/her participation in this clinical trial, may make patient's participation unreliable, or may interfere with study assessments.
19. Pregnant or breastfeeding women, or women planning to become pregnant or breastfeed during the study.

5. STUDY DRUG

5.1. Investigational Medicinal Product

Lebrikizumab will be provided to the investigator by the sponsor. Investigational product will be supplied as a solution for subcutaneous injection in a single-use, sterile pre-filled syringe with a pre-assembled needle safety device (PFS-NSD). Each pre-filled syringe is manufactured to contain 250 mg lebrikizumab (2mL injection of 125 mg/mL).

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.

Each PFS-NSD will be packaged in a carton and labeled according to the country's regulatory requirements.

5.3. Study Drug Assignment

Patients will be considered enrolled into this study once all Baseline procedures have been completed and the patient has met the inclusion and exclusion criteria. Open-label study drug will be assigned to each patient using an electronic data capture system (an electronic trial supply management system for drug accountability purposes) at each in clinic visit. All patients will receive open label treatment as follows:

- Lebrikizumab 250 mg Q2W: 500mg lebrikizumab administered at Baseline and Week 2 (loading dose) and 250 mg given every two weeks (Q2W) through Week 52.

5.4. Study Drug Administration

Study drug will be administered subcutaneously to all patients in the clinic by designated and trained site staff from Baseline through the Week 8 visit and at all other scheduled clinic visits. Following the Week 8 visit, patients will be allowed to administer study drug at home. Sufficient study drug should be dispensed to cover at home administrations through next study visit.

5.4.1. 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).

5.4.2. Instructions for Administration at Home

Patients or caregivers will be instructed to self-administer study drug at the Week 8 visit.

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.

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

5.5. 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 electronic case report form (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, crisaborole) are not permitted during the study. If systemic corticosteroids are required for treatment of AE or other medical conditions (e.g. worsening of existing condition such as asthma exacerbation), it can be used for short periods of time as per medical judgement. Patients requiring long-term systemic corticosteroids for treatment of AE or other medical conditions must be discontinued from the study.

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

Additional drugs are to be avoided during the study unless required to treat an AE or for the treatment of an ongoing medical problem. If the need for concomitant medication arises, the investigator should base decisions on the patient and clinical factors. Any additional medication (including the limited use of therapeutic agents which, if used under treatment regimens other than for treatment an AE or for appropriate medical management, might be considered therapies) whether prescription or over-the-counter, used at baseline and/or during the course of the study, must be documented with the start and stop dates.

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

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

All concomitant medications and procedures must be recorded in the eCRF.

6.2. Moisturizers

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

6.3. Treatments for AD

TCS, TCIs and PDE4 inhibitors may be used as needed to treat disease flares during the trial. Patients who may require short-term systemic treatment for symptoms of AD will be assessed on a case-by-case basis and must be discussed with the Medical Monitor prior to initiating treatment.

Cannabinoid treatments for AD are prohibited.

Patients requiring long-term systemic treatment for symptoms of AD (e.g., non-responders) must be discontinued from the study.

Medications used for AD must be recorded 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 (Day -30 to -7)

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
- Collect demographic information
- Measure vital signs
- Review immunization record
- 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
- Draw blood sample for hormone testing

- Collect urine sample for urinalysis
- Instruct the patient to apply a moisturizer at least twice daily

7.2. Baseline Visit (Day 1) Period

- Administer the DLQI/CDLQI and PROMIS anxiety and depression measures
- Update medical history/review of systems and concomitant medication and procedure/therapy information
- Complete the following assessments: IGA, BSA, and EASI
- 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)
- Enroll the patient and administer study drug

7.3. Week 2 (± 3 Days)

- Review and record AEs and update concomitant medication and procedure/therapy information
- Measure vital signs
- Administer study drug
- Confirm moisturizer use

7.4. Week 4 (± 3 Days)

- 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
- Confirm moisturizer use

7.5. Week 6 (± 3 Days)

- Review and record AEs and update concomitant medication and procedure/therapy information
- Measure vital signs

- Administer study drug

7.6. Week 8 (± 3 Days)

- Complete the following assessments: IGA, BSA and EASI
- Review and record AEs and update concomitant medication and procedure/therapy information
- Confirm moisturizer use
- Measure vital signs
- Draw blood samples for laboratory tests
- Collect a urine sample for urinalysis
- Conduct urine pregnancy test (WOCBP only)
- Train the patient to self-administer study drug
- Administer study drug and dispense study drug for next injection

7.7. Week 12 (± 3 Days)

- Review and record AEs and update concomitant medication and procedure/therapy information
- Measure vital signs
- Conduct urine pregnancy test (WOCBP only)
- Administer study drug and dispense study drug for next injection

7.8. Week 16 (± 3 Days)

- Administer the DLQI/CDLQI and PROMIS anxiety and depression measures
- 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
- Measure vital signs
- Draw pre-dose blood samples for laboratory tests, PK and ADA testing
- Draw blood sample for hormone testing
- Collect a urine sample for urinalysis
- Conduct urine pregnancy test (WOCBP only)
- Administer study drug and dispense study drug for next injection

7.9. Week 20 (± 5 Days)

- Review and record AEs and update concomitant medication and procedure/therapy information
- Measure vital signs
- Conduct urine pregnancy test (WOCBP only)
- Administer study drug and dispense study drug for next injection

7.10. Week 24 (± 5 Days)

- Review and record AEs and update concomitant medication and procedure/therapy information
- Measure vital signs
- Conduct urine pregnancy test (WOCBP only)
- Administer study drug and dispense study drug for next injection

7.11. Week 28 (± 5 Days)

- Review and record AEs and update concomitant medication and procedure/therapy information
- Measure vital signs
- Conduct urine pregnancy test (WOCBP only)
- Administer study drug and dispense study drug for next injection

7.12. Week 32 (± 5 Days)

- Administer the DLQI/CDLQI and PROMIS anxiety and depression measures
- Complete the following assessments: IGA, BSA and EASI
- Review and record AEs and update concomitant medication and procedure/therapy information
- Perform a complete physical examination, including height and weight
- Measure vital signs
- Draw pre-dose blood samples for laboratory tests, PK and ADA testing
- Draw blood sample for hormone testing
- Collect urine sample for urinalysis
- Conduct urine pregnancy test (WOCBP only)
- Administer study drug and dispense study drug for next injection

7.13. Week 36 (± 5 Days)

- Review and record AEs and update concomitant medication and procedure/therapy information
- Measure vital signs
- Conduct urine pregnancy test (WOCBP only)
- Administer study drug and dispense study drug for next injection

7.14. Week 40 (± 5 Days)

- Review and record AEs and update concomitant medication and procedure/therapy information
- Measure vital signs
- Conduct urine pregnancy test (WOCBP only)
- Administer study drug and dispense study drug for next injection

7.15. Week 44 (± 5 Days)

- Review and record AEs and update concomitant medication and procedure/therapy information
- Measure vital signs
- Conduct urine pregnancy test (WOCBP only)
- Administer study drug and dispense study drug for next injection

7.16. Week 48 (± 5 Days)

- Review and record AEs and update concomitant medication and procedure/therapy information
- Measure vital signs
- Conduct urine pregnancy test (WOCBP only)
- Administer study drug and dispense study drug for next injection

7.17. Week 52/Early Termination (± 5 Days)

- Administer the DLQI/CDLQI and PROMIS anxiety and depression measures
- 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
- Measure vital signs

- Draw pre-dose blood samples for laboratory tests, PK and ADA testing
- Draw blood sample for hormone testing
- Collect a urine sample for urinalysis
- Conduct urine pregnancy test (WOCBP only)

7.18. 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 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

7.19. 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, 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.

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. 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.

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. 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.

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.

8.3. 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. 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.

8.3.2. 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.

8.4. Assessment of Safety

8.4.1. Physical Examination

A complete physical examination will be conducted at screening and Week 52 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 per the Schedule of Event and Procedures. At subsequent study visits, a symptom-directed physical examination may be conducted at the discretion of the Investigator. Findings will be recorded as medical history or AE in the eCRF.

8.4.2. Vital Signs

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

8.4.3. Laboratory Evaluations

Laboratory tests will be analyzed using a central laboratory and include hematology with differential, serology, a standard chemistry panel (including liver-function tests), total cholesterol, hormones, 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 1: Laboratory Parameters

Hematology	Chemistry	Urine	Hormones
CBC with differential: Hematocrit Hemoglobin Red blood cells White blood cells Mean corpuscular hemoglobin (MCH) MCH concentration Mean corpuscular volume 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 Creatinine Total Protein Albumin Aspartate aminotransferase Alanine aminotransferase Lactic dehydrogenase Gamma-glutamyl transpeptidase Alkaline phosphatase Bilirubin (total and direct) Total cholesterol Non-fasting glucose For All Female Patients (WOCBP) At Screening: Serum beta human chorionic gonadotropin	pH Specific gravity Protein Glucose Ketones Bilirubin Blood Nitrite Urobilinogen Leukocyte esterase At All Visits Except Screening (WOCBP only): Urine beta human chorionic gonadotropin	Estradiol (for females only) Testosterone (for males only)

8.4.4. Adverse Events

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

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

8.4.4.1. Reporting

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

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

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

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

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

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

8.4.4.2. Adverse Events of Special Interest (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.

8.4.4.3. 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.

8.4.4.4. Reporting of SAEs

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

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 principal investigator (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.

8.4.5. Product Complaints

A product complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a trial intervention. The sponsor collects product complaints on investigational products and drug delivery systems used in clinical studies in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements. Participants will be

instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the investigational product or drug delivery system so that the situation can be assessed.

Time Period for Detecting Product Complaints

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

Prompt Reporting of Product Complaints to Sponsor

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

Follow-up of Product Complaints

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

8.4.6. Pregnancy

The investigator 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.

8.4.7. Hypersensitivity Reactions

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

8.5. 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 (nAB). The procedural instructions will be provided in a separate PK and Serum Antibody Sampling manual.

8.6. 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.

8.6.1. 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 7.18). 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.

8.6.2. 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 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 (Section 7.18).

8.6.3. 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.

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

9.1.1. Populations Analyzed

All non-PK analyses will be performed using the Safety Population. All patients who receive at least one confirmed dose of lebrikizumab 250 mg will be included in the Safety Population.

The number of patients included in the Safety population will be summarized.

All PK analyses will be performed using the PK population. All patients who are enrolled and have a pre-dose sample and at least one post-dose analyzable sample will be included in the PK population.

9.2. Efficacy Analysis

Efficacy endpoints IGA, BSA, EASI Percent Change from Baseline, EASI-50, EASI-75, and EASI-90 will be summarized by visit.

9.3. 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.

9.4. Anti-Drug Antibody Data Analysis

The ADA variables will be analyzed using descriptive statistics. Positive ADA results may be further evaluated for neutralizing antibodies.

9.5. Immunogenicity Data Analysis

Listings will be provided for immunogenicity data.

9.6. Exposure and Compliance

The extent of exposure to study drug 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.

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.

9.7. Adverse Events

All AEs occurring during the study will be recorded and coded using the Medical Dictionary for Regulatory Activities (MedDRA). 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, 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.

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.

9.8. 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.

Vital signs will be presented 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 World Health Organization 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.

9.9. Sample-Size Determination

CCI

9.10. Interim Analyses

Interim analyses may be performed for regulatory interactions, safety updates, and disclosures. A final database lock will be conducted after all patients have either completed the 12 Week follow-up visit for this study, discontinued 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.

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.

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 are 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 these 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. Data Publication

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

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12. APPENDICES

APPENDIX 1. SCHEDULE OF VISITS AND PROCEDURES

Study Procedure	Screening	Baseline	Treatment															Safety
Day (D); Week (W)	D-30 to -7	D1	W2	W4	W6	W8	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48	W52/ET	12W Post
Visit Window			±3d	±3d	±3d	±3d	±3d	±3d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Informed Consent/Assent	X																	
Inclusion/Exclusion, Med Hx, Demographics	X	X																
Review Immunization Record	X																	
Safety																		
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical Exam, Weight/Height	X							X				X					X	
HIV, Hepatitis	X																	
Hematology, Chemistry, Urinalysis	X					X		X				X					X	
Pregnancy Test	Serum	urine		urine		urine	urine	urine	urine	urine	urine	urine	urine	urine	urine	urine	urine	
Hormone Testing[1]	X							X				X					X	
Adverse Events			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Meds & Procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy and Patient Reported Outcomes																		
IGA, BSA, EASI	X	X		X		X		X				X					X	
DLQI/CDLQI2[2]		X						X				X					X	
PROMIS Anxiety & Depression[2]		X						X				X					X	
Pharmacokinetics (PK) and Immunogenicity (ADA)																		
Pre-dose PK		X		X				X				X					X	X
Pre-dose ADA[3]		X		X				X				X					X	X
Study Drug																		
Administer Study Drug		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Instruction on Self-Administration						X												
Dispense Drug for At-Home Injection						X	X	X	X	X	X	X	X	X	X	X		

[1] Collect estradiol for females only. Collect testosterone for males only [2] Patient reported outcome and quality of life measures should all be completed prior to other study assessments; [3] nAB testing conducted for positive treatment-emergent ADA responses. Additional immunogenicity sample collected for any patient experiencing a hypersensitivity reaction during study.

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

Atopic dermatitis: Diagnosis recommendations

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

Level of Evidence: III Strength of Recommendation: C

Essential features — must be present:

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

*Patterns include:

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

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

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

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

- Atypical vascular responses (e.g., 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.