Study Title	A MULTI-CENTER, DOUBLE-BLIND, RANDOMIZED, PLACEBO CONTROLLED, PARALLEL-GROUP STUDY, COMPARING TEST TOPICAL PRODUCT TO BRAND TOPICAL PRODUCT AND BOTH ACTIVE TREATMENTS TO A PLACEBO CONTROL IN THE TREATMENT OF MILD TO MODERATE ATOPIC DERMATITIS
Study Design	Randomized, prospective, multicenter, double blind, parallel assignment, placebo controlled therapeutic equivalence study
Study Type	Bioequivalence study with clinical endpoints
Investigational Products	Test Topical Product Reference Topical Product Vehicle of the Test Topical Product
Dosage of Investigational Product	A thin layer is to be applied to all affected skin areas for 2 weeks (14 days)
Objectives	**Primary Objective:** • To establish the bioequivalence between test and reference listed drugs using the primary endpoint in the Per Protocol population **Additional:** • To establish superiority of the each treatment over the placebo using the primary endpoint in the modified intent to treat (mITT) population and Last Observation Carried Forward (LOCF) • To assess individual signs and symptoms of Atopic Dermatitis (i.e., erythema, induration/papulation, lichenification and pruritus) in each treatment group • To compare the safety and tolerability between the test and reference drugs
Study Population	Non-immunocompromised males and females with mild to moderate atopic dermatitis who have failed to respond adequately to other topical prescription treatments, or when those treatments are not advisable. **Age:** 8 years and above

Patient Selection

Screening Criteria:

- Non-immunocompromised male or female aged 8 years and older
- Clinical diagnosis of mild to moderate atopic dermatitis (AD), as defined by the criteria of Hanifin and Rajka
- Failed to respond adequately to other topical prescription treatments for AD, or for whom those treatments are not advisable (The subject/guardian's verbal report of failure to other topical prescription treatments for AD will be adequate.)
- An Investigator's Global Assessment (IGA) of disease severity of mild or moderate at baseline (score of 2 or 3)
- Affected area of AD involvement at least 5% body surface area (BSA) at baseline
- Expected to be able to meet inclusion and exclusion criteria after 7 days treatment with a bland emollient (i.e. Cetaphil® Cream)

Inclusion Criteria:

- Non-immunocompromised male or female aged 8 years and older
- Clinical diagnosis of mild to moderate AD, as defined by the criteria of Hanifin and Rajka (Appendix I)
- Failed to respond adequately to other topical prescription treatments for AD, or for whom those treatments are not advisable (The subject/guardian's verbal report of failure to other topical prescription treatments for AD will be adequate.)
- A diagnosis of AD for at least 3 months (Subject/guardian may verbally report signs and symptoms of atopic dermatitis with an onset at least 3 months prior.)
- An Investigator's Global Assessment (IGA) of disease severity of mild or moderate at baseline (score of 2 or 3)
- Affected area of AD involvement at least 5% body surface area (BSA) at baseline
- Treated with a bland emollient (i.e. Cetaphil® Cream) for at least 7 days
- Willing and able to give written informed consent (and assent as applicable) and willing to comply with the trial protocol
- If female of childbearing age, willing to use an acceptable form of contraceptive measure, should be stable since last 3 months prior to baseline and throughout the study

Exclusion Criteria:

a) Females who are pregnant, breast feeding, or who wish to become pregnant during the study period
b) Active cutaneous bacterial or viral infection in any treatment area at baseline (e.g., clinically infected atopic dermatitis, impetigo)

c) Sunburn, extensive scarring or pigmented lesion(s) in any treatment area at baseline, which would interfere with evaluations
d) History of confounding skin conditions, e.g., psoriasis, rosacea, erythroderma, ichthyosis.
e) History or presence of Netherton's Syndrome, immunological deficiencies or diseases, HIV, diabetes, malignancy, serious active or recurrent infection, clinically significant severe renal insufficiency or severe hepatic disorders
f) Use within one month prior to baseline of
    - Oral or intravenous corticosteroids (Subjects on a stable and continued dose of nasal, or inhaled corticosteroids for asthmatic symptoms may be enrolled at the investigator's discretion when the investigator considers that such will not affect the efficacy or safety evaluations of the study. Ophthalmic corticosteroids are not excluded.)
    - UVA/UVB therapy
    - PUVA (psoralen plus ultraviolet A) therapy
    - Tanning booths
    - Nonprescription UV light sources
    - Immunomodulators or immunosuppressive therapies
    - Interferon
    - Cytotoxic drugs
    - Tacrolimus
    - Pimecrolimus
g) Use within 14 days of baseline of
    - Systemic antibiotics
    - Calcipotriene or other vitamin D preparations
    - Retinoids
h) Use within 7 days prior to baseline of
    - Systemic antihistamines (Subjects on a stable and continued dose of systemic antihistamines may be enrolled at the investigator's discretion when the investigator considers that such will not affect the efficacy or safety evaluations of the study.)
    - Topical antibiotics
    - Topical corticosteroids
    - Other topical drug products
    - Probiotics

i) Use within 24 hours prior to baseline of any topical product (e.g., sunscreens, lotions, creams) in the areas to be treated, except for bland emollient (i.e. Cetaphil® Cream)

j) Known allergy or hypersensitivity any other component of the test product or RLD

k) Not willing to minimize or avoid natural and artificial sunlight exposure during treatment
l) Currently enrolled in an investigational drug or device study or used an investigational drug or investigational device treatment within 30 days prior to first application of the test article

Study Treatment

- **Screening period:**

7 days before visit 2

- **Treatment period:**

The blinded treatment will be administered for two weeks for each subject. Apply a thin layer of cream to all affected skin areas.

Randomization 1:1:1 (Test: RLD: Placebo)

Study Duration The study duration for each subject would be up to 21 days. There is a screening period of 7 days and a treatment period of 14 days.

Study Visits

4 Visits:
V1-Screening Visit (up to -7 days)
V2-Baseline and Randomization Visit (Day 1)
V3-Interim Visit (Day 8 ± 3 days)
V4- End of Therapy Visit (Day 15 ± 3 days)

Study Measurements

Efficacy:
Signs and Symptoms of Atopic Dermatitis will be scored per body region (Head and Neck; Trunk; Upper Limbs; Lower Limbs). Signs and Symptoms will be scored by the principal investigator or a qualified person delegated by the investigator. It is strongly preferred to have one evaluator for each of the visits per subject. A back up evaluator may be present at baseline in case the primary evaluator is unavailable at follow up.
Pruritus will be assessed by questioning the subject or the subject's guardian regarding the intensity in the 24 hours prior to the visit for the overall condition.

Sign and Symptom	Score	Category	Definition
Erythema	0	None	No erythema present
	1	Mild	Slight erythema: very light-pink
	2	Moderate	Dull red, clearly distinguishable
	3	Severe	Deep/dark red
Induration/ Papulation	0	None	None
	1	Mild	Slightly perceptible elevation
	2	Moderate	Clearly perceptible elevation but not extensive

	3	Severe	Marked and extensive elevation
Lichenification	0	None	None
	1	Mild	Slight thickening of the skin discernible only by touch and with skin markings minimally exaggerated
	2	Moderate	Definite thickening of the skin with skin marking exaggerated so that they form a visible criss-cross pattern
	3	Severe	Thickened indurated skin with skin markings visibly portraying an exaggerated criss-cross pattern
Pruritus	0	None	None
	1	Mild	Occasional, slight itching/scratching
	2	Moderate	Constant or intermittent itching/scratching/discomfort which is not disturbing sleep
	3	Severe	Bothersome itching/scratching/discomfort which is disturbing sleep

Overall Body Surface Area (BSA) Involvement with AD will be assessed and recorded by the investigator or delegate.

Investigator's Global Assessment of Disease Severity Scoring will be scored for the investigator's (or delegate's) assessment of the subject's overall condition as seen at the time of evaluation (static) as explained below:

Score	Category	Definition
0	Clear	Minor residual discoloration, no erythema or induration/papulation, no oozing/crusting
1	Almost Clear	Trace faint pink erythema with almost no induration/papulation and no oozing/crusting
2	Mild disease	Faint pink erythema with mild induration/papulation and no oozing/crusting
3	Moderate disease	Pink-red erythema with moderate induration/papulation and there may be some oozing/crusting
4	Severe disease	Deep/bright red erythema with severe induration/papulation with oozing/crusting

Safety:

Physical Examination: Must include a detailed skin examination. Additionally, examination of head, ears, nose and throat, eyes, central nervous system, respiratory system, cardiovascular system, gastrointestinal system, musculoskeletal system should be assessed.

Vital Signs: Pulse rate, blood pressure and body temperature

Urine Pregnancy Test
Adverse Event Assessments
Application site reactions such as dryness, burning/stinging, erosion, edema, and pain will be assessed scored (as per Appendix IV) and recorded.

Study Endpoints

Primary endpoint:

- The proportion of subjects in each treatment group with treatment success (i.e., a grade of clear or almost clear; a score of 0 or 1, within the treatment area) based on the Investigator's Global Assessment of Disease Severity at the end of treatment (Study Day 15)

Additional endpoints:

- Change in severity from baseline to week 2 (study Day 15) of four individual signs and symptoms of AD (i.e., erythema, induration/papulation, lichenification and pruritus) are considered supportive information
- Application site reactions will be compared between treatment groups.

Safety Endpoints:

Safety assessment through the incidences and severity of all adverse events (AEs) reported during the study and summarized by treatment group

Statistical Analysis:

- Therapeutic equivalence of the test product to the reference product will be evaluated in the PP population. To establish bioequivalence, if the 90% confidence interval (calculated using Yates' continuity correction) of the test - reference difference between products for the primary endpoint (success proportion) is contained within [-0.20, +0.20], then bioequivalence of the test product to the reference product will be considered to have been demonstrated.
- As a parameter for determining adequate study sensitivity, the test product and RLD will be compared to placebo with regard to the primary endpoint from baseline to week 2 (Day 15). Superiority of the test and reference products against the placebo will be tested at the 5% significance level ($p < 0.05$; using Fisher's exact test) in the mITT population using last observation carried forward.
- Supportive information will be presented describing the change in severity from baseline to week 2 (study Day 15) of four individual signs and symptoms of AD (i.e., erythema, induration/papulation, lichenification and pruritus).
- Adverse events that occurred subsequent to the first dose of study drug will be summarized. The number and the proportion of subjects

who experienced AEs will be computed by treatment group. AEs will also be summarized by each severity grade (mild, moderate, severe) and by each relationship grade (none, possibly, probably) in a similar way.

- Application site reactions will be compared via a descriptive analysis between treatment groups.