A RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE II STUDY TO ASSESS THE EFFICACY AND SAFETY OF ORALLY ADMINISTERED DS107G TO PATIENTS WITH MODERATE TO SEVERE ATOPIC DERMATITIS

PROTOCOL # DS107G-02

Final

VERSION 2.2
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PROTOCOL SUMMARY OF CHANGES

Amendment	Rational for amendment	Major changes to the protocol
V2.1 / 13 MAR 2015	1) Addition of later testing for interleukins blood levels.	1) Interleukin evaluation was added in the following sections: Endpoints (page 17), study procedures (pages 26-28), safety assessments (page 32) and study flow chart (page 41).
V2.2 / 22 JUL 2015	1) In the case where the subject ends the study before completion and has an early termination visit, the subject will also return for the safety assessments listed at Week 10, two weeks after the early termination visit.	1) The Week 10 safety assessments for the subject who ends the study before completion will include (added in the Discontinuations section/pages 19-20): - Concomitant medications - Safety labs (only if there was a clinically significant change from baseline at the Week 8 / ET visit) - Urine pregnancy test, if female of childbearing potential - Vital signs - Physical exam - Adverse events The Study Flow Chart was updated accordingly (page 41).
	2) Adjustment of the statistical analysis for the primary endpoint to take into account the stratification by site included in the randomization.	2) Cochran-Mantel-Haenszel test with site as a stratification factor will be used for the statistical analysis instead of the chi-square test to compare between groups for the primary endpoint. A supportive analysis will be performed using a Fisher's exact test. (was added in the Efficacy analysis section/page 37).
	3) Change in the evaluation of the impact of missing values on the primary endpoint.	3) Supportive analysis using the last observation carried forward (LOCF) will be performed instead of the tipping point analysis. (was added in the Efficacy analysis section/page 37).

SIGNATURE PAGE

The signatures below constitute the approval of this protocol and the attachments, and provide the necessary assurances that this trial will be conducted according to local legal and regulatory requirements and applicable Canadian regulations, U.S. federal regulations and ICH guidelines.

Sponsor:

Signature: _____ **Date:** 11 Aug 2015

Sponsor Medical Advisor:

Signature: _____ **Date:** 11 AUG - 2015

International Clinical Co-ordinating Investigator:

Signature: _____ **Date:** Jul 29 2015

Study Statistician:

Signature: _____ **Date:** 04/AUG/2015

PRINCIPAL/QUALIFIED INVESTIGATOR SIGNATURE PAGE

Investigator name: _____

Signature: _____ **Date:** _____

Institution Name: _____

By my signature, I agree to personally supervise the conduct of this study at my study site and to ensure its conduct is in compliance with the protocol, informed consent, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) procedures, instructions from Innovaderm Research representatives, the Declaration of Helsinki, International Conference on Harmonization (ICH) Good Clinical Practices Guidelines, applicable Canadian regulations, U.S. federal regulations, and local regulations governing the conduct of clinical studies.

LIST OF ABBREVIATIONS

15 HETrE	15 hydroxyeicosatrienoic acid
AD	Atopic dermatitis
AE	Adverse Event/Adverse Experience
BMI	Body Mass Index
BSA	Body Surface Area
COX	Cyclooxygenase
CRF	Case Report Form
DGLA	Dihomo-gamma-linolenic acid
DLQI	Dermatology Life Quality Index
EASI	Eczema Area and Severity Index
ECRF	Electronic Case Report Form
EDC	Electronic Data Capture
ET	Early Termination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLA	Gamma-linolenic acid
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonization
IGA	Investigator's Global Assessment
IMP	Investigational medicinal product
ITT	Intent-to-treat
IRB	Institutional Review Board
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LOCF	Last observation carried forward
LPO	Lipoxygenase
MedDRA ©	Medical Dictionary for Regulatory Activities
PGE	Prostaglandine E
POEM	Patient Oriented Eczema Measure
PP	Per Protocol
PUVA	Psoralen and Ultra Violet A
REB	Research Ethics Board

SAE	Serious Adverse Event/Serious Adverse Experience
SOC	System Organ Classification
SCORAD	SCORing of Atopic Dermatitis
TEWL	Trans Epithelial Water Loss
UV, UVA, UVB	Ultra Violet (A or B)
VAS	Visual Analog Scale

SUMMARY

Title: **A Randomised, Double-blind, Placebo-Controlled, Phase II Study to Assess the Efficacy and Safety of orally administered DS107G to Patients with Moderate to Severe Atopic Dermatitis**

Phase: IIa

Population: Approximately 100 male or female subjects, aged 18 years or older, moderate to severe atopic dermatitis will be included in this study.

Number of Sites: Approximately 20 centers in Canada and US will participate in this study

Study Duration: 10 to 14 weeks including screening and follow-up

Hypothesis: DS107G is superior to placebo for improvement of IGA score in patients with moderate to severe atopic dermatitis.

Objectives:

Primary objective:
To compare the efficacy of orally administered DS107G capsules versus placebo, in the treatment of adult patients with moderate to severe atopic dermatitis.

Secondary objective:
To assess the safety of orally administered DS107G capsules versus placebo, in adult patients with moderate to severe atopic dermatitis.

Endpoints:

Primary Endpoint

Proportion of patients achieving an IGA (Investigator Global Assessment) of 0 (clear) or 1 (almost clear) and a decrease of at least 2 points in IGA at Week 8.

Secondary Endpoints

- Change from baseline in IGA at week 2, 4 and 8.
- Change from baseline in EASI (Eczema Area and Severity Index) at week 2, 4 and 8.
- Proportion of patients achieving at least a 1-point decrease in IGA at week 8
- Change from baseline in the Patient Orientated Eczema Measure (POEM) at week 2, 4 and 8.
- Change from baseline in the Dermatology Life Quality Index (DLQI) score at week 2, 4 and 8.
- Change from baseline in SCORAD at week 2, 4 and 8.

- Change from baseline in the patient's Visual Analog Scale (VAS) pruritus score at Week 2, 4 and 8.
- Change from baseline in Body Surface Area (BSA) at Week 2, 4 and 8.
- Number of treatment-emergent adverse events (TEAEs) in each treatment group.

Exploratory Endpoints

- Change from baseline in Trans epidermal water loss (TEWL) at week 2, 4 and 8 (selected sites only).
- Plasma total and free DGLA concentrations at Baseline, weeks 4 and 8.
- Plasma total fatty acid profile at Baseline, week 4 and week 8 (sample to be retained and analyzed at a later date).
- Interleukin profile at Baseline, week 4 and week 8 (Sample to be retained and analyzed at a later date).

Overall Study Design

Approximately 100 patients with moderate to severe atopic dermatitis will be included in this multicenter, double-blind, placebo controlled, phase IIa study. All subjects will sign an informed consent and undergo screening for study eligibility. Subjects will be randomized (1:1) at baseline visit to either receive oral DS107G 2 g, or placebo once daily for 8 weeks in a fasting state.

Subjects will come to the clinic on 6 occasions: at screening, baseline, week 2, week 4, week 8 (end of treatment/early termination) and week 10 (follow-up). All subjects will exit the study at the Week 10 visit. The primary efficacy variable will be the proportion of patients achieving an IGA of 0 (clear) or 1 (almost clear) and a decrease of at least 2 points in IGA at week 8. Secondary efficacy variables will include IGA at other visits, pruritus (obtained from the SCORAD visual analog scale), EASI, BSA, POEM, DLQI, SCORAD and TEWL (for selected sites only). Safety will be assessed through adverse events, physical examination, vital signs and safety laboratory tests (including pregnancy tests for women of childbearing potential). Pharmacokinetic samples will be obtained at Baseline (Day 0), week 4 and week 8 visits in order to measure total and free DGLA plasma trough levels. Separate plasma samples will be retained for later analysis of total fatty acid profile and interleukin profile.

Inclusion Criteria

1. Male or female subject aged 18 years and older on the day of signing the informed consent form (ICF).
2. Clinically confirmed diagnosis of active atopic dermatitis according to Hanifin and Rajka criteria (Appendix G).
3. Moderate to severe atopic dermatitis at baseline as defined by an IGA of minimum 3 at baseline visit.
4. Atopic dermatitis covering minimum 10% of the body surface area at baseline.
5. Body mass index (BMI) is between 18 and 35 kg/m^2 inclusively.
6. Female patients of childbearing potential must use adequate contraception or have a sterilized partner for the duration of the study: systemic hormonal contraceptives, intrauterine device or barrier method of contraception in conjunction with spermicide, or agree to sexual abstinence.

Hormonal contraceptives must be on a stable dose for at least one month before baseline. Note: Women of non-child bearing potential are;

- women who have had surgical sterilization (hysterectomy or bilateral oophorectomy or tubal ligation)
- women greater than 60 years of age
- women greater than 40 and less than 60 years of age who have had a cessation of menses for at least 12 months and a follicle-stimulating hormone (FSH) test confirming non-childbearing potential (FSH ≥40 mIU/mL) or cessation of menses for at least 24 months without FSH levels confirmed.

7. Patients who are able and willing to stop treatment for atopic dermatitis throughout the study (except for allowed emollients; see Section 6.3.1).

8. Capable and willing to give signed informed consent and the consent must be obtained prior to any study related procedures.

Exclusion Criteria

1. Female patients with positive pregnancy test at screening or Day 0 visit (baseline) or lactating women.
2. Any clinically significant controlled or uncontrolled medical condition or laboratory abnormality that would, in the opinion of the investigator, put the patient at undue risk or interfere with interpretation of study results.
3. Clinically significant impairment of renal or hepatic function.
4. Other skin conditions that might interfere with atopic dermatitis diagnosis and/or evaluation (such as psoriasis or current viral, bacterial and fungal skin infections).
5. History of hypersensitivity to any substance in DS107G or placebo capsules.
6. Use of biologics 3 months prior to start of treatment/ Day 0 visit (baseline), or 5 half-lives (whichever is longer).
7. Use of systemic treatments (other than biologics) that could affect atopic dermatitis less than 4 weeks prior to baseline visit (Day 0), e.g. retinoids, calcineurin inhibitors, methotrexate, cyclosporine, hydroxycarbamide (hydroxyurea), azathioprine and oral/injectable corticosteroids; Intranasal corticosteroids and inhaled corticosteroids for stable medical conditions are allowed.
8. Treatment with any experimental drug within 30 days prior to Day 0 visit (baseline), or 5 half-lives (whichever is longer).
9. Excessive sun exposure, use of tanning booths or other ultraviolet (UV) light sources 4 weeks prior to Day 0 visit (baseline) and/or is planning a trip to sunny climate or to use tanning booths or other UV sources between screening and follow-up visits.
10. Use of any topical medicated treatment for atopic dermatitis 2 weeks prior to start of treatment/Day 0 visit (baseline), including but not limited to, topical corticosteroids, calcineurin inhibitors, tars, bleach, antimicrobials and bleach baths.
11. Use of topical products containing urea, ceramides or hyaluronic acid 2 weeks prior to Day 0.
12. Use of anti-histamines for atopic dermatitis within 2 weeks of baseline.
13. Significant uncontrolled cardiovascular (a history of ECG abnormalities that are clinically significant in the opinion of the investigator), neurologic, malignant, psychiatric, respiratory or hypertensive disease, as well as diabetes and arthritis.
14. Medical history of chronic infectious disease (e.g., hepatitis B, hepatitis C or infection with human immunodeficiency virus).

15. History of clinically significant drug or alcohol abuse in the last year prior to Day 0 (baseline).

Statistical Analysis

Continuous variables will be summarized in tables and will include the number of subjects, mean, standard deviation, median, minimum, maximum and inter-quartile range. Categorical variables will be presented in tables as frequencies and percentages.

All statistical tests will be two-sided and will be performed with a significant level of 0.05, unless otherwise specified.

1 BACKGROUND

1.1 Atopic Dermatitis

Atopic dermatitis is a chronic inflammatory skin disorder characterized by the presence of pruritus, papules, lichenification, excoriations, xerosis and oozing (1). The prevalence of AD has increased in the last few decades, affecting up to 20 percent of young children with the majority of cases starting in children younger than 5 years of age. Most cases improve by adulthood. The prevalence of atopic dermatitis in adults has been reported to be 1–3% (2-4) but more recent reports suggest that it may be much higher (5)(Silverberg JI). Atopic dermatitis can have a significant impact on morbidity and quality of life because of loss of sleep caused by pruritus, and the social stigma of a visible skin condition.

AD is a multifactorial disease, with genetics, environment, and impaired immune response being the predominant factors (1, 6). Dendritic cells, T lymphocytes, macrophages, keratinocytes, mast cells, and eosinophils all play a role in AD by releasing proinflammatory cytokines and chemokines which induce the inflammatory response characteristic of atopic dermatitis lesions (7).

Most of currently approved treatments for AD are topical and include corticosteroids, pimecrolimus and tacrolimus (8). Corticosteroids have been the mainstay of treatment for AD and different potencies and formulations are available. Topical corticosteroids are effective for the treatment of AD but their use is limited by the potential for local side effects such as skin atrophy and striae, Systemic absorption of corticosteroids can also induce diabetes, cataracts, osteoporosis and suppression of the hypothalamic pituitary axis. In addition, transient improvement is often followed by a rebound flare-up on discontinuation of treatment. Other treatments available include topical calcineurin inhibitors (eg, pimecrolimus, tacrolimus), and coal tar preparations. Cases of lymphoma have been reported in patients treated with calcineurin inhibitors. Patients with more severe disease are treated with ultraviolet B and A phototherapy or oral agents such as corticosteroids, cyclosporine, mycophenolate mofetil, methotrexate and azathioprine (9). There is a need for the development of novel treatments for atopic dermatitis.

1.2 DS107G

Dihomo-gamma-linolenic acid (DGLA) is an essential fatty acid found naturally in the body as the 2-carbon elongation product of gamma-linolenic acid (GLA). DGLA has a wide range of desirable biological effects. DGLA is metabolized by cyclooxygenase (COX) and lipoxygenase (LPO) enzymes to form eicosanoids, prostaglandins (PG) of the 1 series and also hydroxyl-fatty acid as 15 hydroxyeicosatrienoic acid DGLA (15 HETrE).

DGLA is present in the human diet at levels up to 0.115 g per measure (10, 11). DGLA is also present in breast milk, with recorded levels ranging from 0.44% at Week 6 of lactation to 0.27% at Week 30 of lactation (12). DGLA is a ubiquitous constituent of normal tissues with a very benign safety profile when dosed to high levels. This is supported by the results of toxicity studies on orally administered DGLA published in the scientific literature and by recently completed preclinical and clinical studies which have shown no safety concerns. A number of pre-clinical studies with oral DGLA were described by Kawashima et al(13). These showed that DGLA had very low oral toxicity (LD50 more than 10 000 mg/kg), which is consistent with experience and expectation for other lipids of this class.

Oral DGLA has been successfully dosed in healthy human subjects, at doses of up to 450 mg/day for up to four weeks, without any adverse effects or changes to blood biochemical parameters (14, 15). The content of DGLA in serum phospholipids was dose dependent, returning to baseline after a 4-week washout period. There were also no notable differences in serum lipid concentrations or any adverse signs related to treatment (14).

Based on the wide range of desirable biological effects observed for GLA, DGLA and its metabolites on inflammation and skin function (16-20), there is a clear rationale for development of DGLA as a treatment for inflammatory skin diseases.

Oral DGLA (DS107G) administered to healthy volunteers in a Phase I trial (DS107G-01) as a single 500-, 1000-, 2000-, or 4000-mg dose under fasted conditions; as a single 1000-mg dose under fed conditions; and as multiple 2000- and 4000-mg doses taken once daily for 28 consecutive days was well tolerated. The most common TEAE was diarrhea (reported as 'loose stools') which was mild to moderate in severity and of relatively short duration. The plasma pharmacokinetics of free and total DGLA were linear with single doses, but may be saturable with repeated doses or high concentrations. Plasma concentrations of free and total DGLA achieved steady-state by approximately Day 14. Free DGLA distributes well into skin: skin blister fluid concentrations were similar to plasma concentrations after about Day 8 of repeated dosing. Total DGLA concentrations are higher in plasma than in skin; the distribution to skin may be saturable.

For more information on DS107G, refer to the most recent version of the investigator brochure.

1.3 Rationale for this study

Both DGLA and its metabolites have been shown to have various anti-inflammatory effects in the body (21). With advancement of purification technologies of fatty acids, purified DGLA is now available. The technology involves purifying GLA from plant oils such as borage oil and then converting to DGLA by adding two carbons.

Supplementation of human or guinea pig diets with evening primrose or borage oil (vegetable oils that contain GLA) raises epidermal PGE1 concentrations. Evening primrose oil has been used in the clinical management of inflammatory disorders of the skin, including inflammation due to acne and atopic dermatitis, and its reported beneficial effects may be due, at least in part, to epidermal generation of PGE1 & 15-HETrE from elevated tissue DGLA concentrations (22). This is supported by a recent study showing that clinical efficacy of evening primrose oil in AD is correlated with plasma levels of DGLA. In murine models, administration of DGLA also prevents the development of AD (23).

This study will compare the safety and efficacy of one daily dose of DS107G (2g) to placebo in patients with moderate to severe atopic dermatitis.

2 STUDY HYPOTHESIS AND OBJECTIVES

Hypothesis:

DS107G is superior to placebo for improvement of IGA score in patients with moderate to severe atopic dermatitis.

***Primary objective*:**

To compare the efficacy of orally administered DS107G capsules versus placebo, in the treatment of adult patients with moderate to severe atopic dermatitis.

***Secondary objective*:**

To assess the safety of orally administered DS107G capsules versus placebo, in adult patients with moderate to severe atopic dermatitis.

3 STUDY ENDPOINTS

3.1 Primary Endpoint

- Proportion of patients achieving an IGA (Investigator Global Assessment) of 0 (clear) or 1 (almost clear) and a decrease of at least 2 points in IGA at Week 8.

3.2 Secondary Endpoints

- Change from baseline in IGA at week 2, 4 and 8.
- Change from baseline in EASI (Eczema Area and Severity Index) at week 2, 4 and 8.
- Proportion of patients achieving at least a 1-point decrease in IGA at week 8.
- Change from baseline in the Patient Orientated Eczema Measure (POEM) at week 2, 4 and 8.
- Change from baseline in the Dermatology Life Quality Index (DLQI) score at week 2, 4 and 8.
- Change from baseline in SCORAD at week 2, 4 and 8.
- Change from baseline in the patient's Visual Analog Scale (VAS) pruritus score at Week 2, 4 and 8.
- Change from baseline in Body Surface Area (BSA) at Week 2, 4 and 8.
- Number of treatment-emergent adverse events (TEAEs) in each treatment group.

3.3 Exploratory Endpoints

- Change from baseline in Trans epidermal water loss (TEWL) at week 2, 4 and 8 (selected sites only).

- Plasma total and free DGLA concentrations at Baseline, weeks 4 and 8.

- Plasma total fatty acid profile at Baseline, week 4 and week 8 (sample to be retained and analyzed at a later date).

- Interleukin profile at Baseline, week 4 and week 8 (Sample to be retained and analyzed at a later date)

4 STUDY DESIGN

Approximately 100 patients with moderate to severe atopic dermatitis will be included in this multicenter, double-blind, placebo controlled, phase IIa study. All subjects will sign an informed consent and undergo screening for study eligibility. Subjects will be randomized (1:1) at baseline visit to either receive oral DS107G 2 g, or placebo once daily for 8 weeks in a fasting state.

Subjects will come to the clinic on 6 occasions: at screening, baseline, week 2, week 4, week 8 (end of treatment/early termination) and week 10 (follow-up). All subjects will exit the study at the Week 10 visit. The primary efficacy variable will be the proportion of patients achieving an IGA of 0 (clear) or 1 (almost clear) and a decrease of at least 2 points in IGA at week 8. Secondary efficacy variables will include IGA at other visits, pruritus (obtained from the SCORAD visual analog scale), EASI, BSA, POEM, DLQI, SCORAD and TEWL (for selected sites only). Safety will be assessed through adverse events, physical examination, vital signs and safety laboratory tests (including pregnancy tests for women of childbearing potential). Pharmacokinetic samples will be obtained at Baseline (Day 0), week 4 and week 8 visits in order to measure total and free DGLA plasma trough levels. Separate plasma sample will be retained for later analysis of total fatty acid profile and interleukin profile

5 STUDY POPULATION

Approximately 100 subjects with moderate to severe atopic dermatitis as per IGA score and a BSA of minimum 10% may be included in this study. Subjects will be men or women, 18 years or older.

5.1 Inclusion Criteria

Subjects may be eligible if they meet all the following inclusion criteria at the screening and baseline visits unless specified otherwise:

1. Male or female subject aged 18 years and older on the day of signing the informed consent form (ICF).

2. Clinically confirmed diagnosis of active atopic dermatitis according to Hanifin and Rajka criteria (Appendix G).

3. Moderate to severe atopic dermatitis at baseline as defined by an IGA of minimum 3 at baseline visit.

4. Atopic dermatitis covering minimum 10% of the body surface area at baseline.

5. Body mass index (BMI) is between 18 and 35 kg/m^2 inclusively.

6. Female patients of childbearing potential must use adequate contraception or have a sterilized partner for the duration of the study: systemic hormonal contraceptives, intrauterine device or barrier method of contraception in conjunction with spermicide, or agree to sexual abstinence.

Hormonal contraceptives must be on a stable dose for at least one month before baseline. Note: Women of non-child bearing potential are;

- women who have had surgical sterilization (hysterectomy or bilateral oophorectomy or tubal ligation)
- women greater than 60 years of age
- women greater than 40 and less than 60 years of age who have had a cessation of menses for at least 12 months and a follicle-stimulating hormone (FSH) test confirming non-childbearing potential (FSH ≥40 mIU/mL) or cessation of menses for at least 24 months without FSH levels confirmed.

7. Patients who are able and willing to stop treatment for atopic dermatitis throughout the study (except for allowed emollients; see Section 6.3.1).

8. Capable and willing to give signed informed consent and the consent must be obtained prior to any study related procedures.

5.2 Exclusion Criteria

Subjects will not be eligible if they meet any of the following criteria at the screening and baseline visits unless specified otherwise:

1. Female patients with positive pregnancy test at screening or Day 0 visit (baseline) or lactating women.
2. Any clinically significant controlled or uncontrolled medical condition or laboratory abnormality that would, in the opinion of the investigator, put the patient at undue risk or interfere with interpretation of study results.
3. Clinically significant impairment of renal or hepatic function.
4. Other skin conditions that might interfere with atopic dermatitis diagnosis and/or evaluation (such as psoriasis or current viral, bacterial and fungal skin infections).
5. History of hypersensitivity to any substance in DS107G or placebo capsules.
6. Use of biologics 3 months prior to start of treatment/ Day 0 visit (baseline), or 5 half-lives (whichever is longer).
7. Use of systemic treatments (other than biologics) that could affect atopic dermatitis less than 4 weeks prior to baseline visit (Day 0), e.g. retinoids, calcineurin inhibitors, methotrexate, cyclosporine, hydroxycarbamide (hydroxyurea), azathioprine and oral/injectable corticosteroids; Intranasal corticosteroids and inhaled corticosteroids for stable medical conditions are allowed.
8. Treatment with any experimental drug within 30 days prior to Day 0 visit (baseline), or 5 half-lives (whichever is longer).
9. Excessive sun exposure, use of tanning booths or other ultraviolet (UV) light sources 4 weeks prior to Day 0 visit (baseline) and/or is planning a trip to sunny climate or to use tanning booths or other UV sources between screening and follow-up visits.
10. Use of any topical medicated treatment for atopic dermatitis 2 weeks prior to start of treatment/Day 0 visit (baseline), including but not limited to, topical corticosteroids, calcineurin inhibitors, tars, bleach, antimicrobials and bleach baths.
11. Use of topical products containing urea, ceramides or hyaluronic acid 2 weeks prior to Day 0.
12. Use of anti-histamines for atopic dermatitis within 2 weeks of baseline.

13. Significant uncontrolled cardiovascular (a history of ECG abnormalities that are clinically significant in the opinion of the investigator), neurologic, malignant, psychiatric, respiratory or hypertensive disease, as well as diabetes and arthritis.
14. Medical history of chronic infectious disease (e.g., hepatitis B, hepatitis C or infection with human immunodeficiency virus).
15. History of clinically significant drug or alcohol abuse in the last year prior to Day 0 (baseline).

5.3 Study Restrictions

Each subject will be questioned on the specific points listed below prior to drug administration. If a subject admits a non-compliance with these restrictions, the Principal Investigator (or designee) and/or the sponsor will decide whether or not the subject will be permitted to remain in the study. Non-compliance with these restrictions will be recorded.

- Subjects will be instructed to abstain from planning a trip to sunny climate or use of tanning equipment between screening and follow-up visits.

- Subjects will be instructed to abstain from using any drugs/treatments that may influence atopic dermatitis (refer to exclusion criteria and prohibited therapies or procedures section) throughout the study.

- Subjects will be required to start fasting at least 8 hours before drug administration upon waking. Fasting will continue for at least 60 minutes following drug administration, after which subject can have breakfast. Water will be allowed at all times during the fasting period, but no other fluids will be permitted. Medication(s) for other conditions that are permitted in the study can be taken as usual.

- For Baseline (Day 0), week 4 and week 8 visits, a blood draw will be performed for PK analysis. PK samples must be taken pre-dose; therefore, study drug administration will occur during the visit for Day 0 and week 4 visits. Because dosing will occur at the clinic on Day 0 and week 4, subjects will be required to fast for at least 8 hours prior to study drug administration and will be allowed to have a meal 60 minutes after study drug administration.

5.4 Discontinuations

Subjects have the right to withdraw from the study at any time for any reason without penalty. The investigator also has the right to withdraw subjects from the study if he feels it is in the best interest of the subject or if the subject is uncooperative or non-compliant. It is understood by all concerned that an excessive rate of withdrawal can render the study un-interpretable; therefore, unnecessary withdrawal of subjects should be avoided. Should a subject decide to withdraw, all efforts will be made to complete and report the observations, particularly the follow-up examination, as thoroughly as possible.

The investigator or one of his or her staff members should contact the subject either by telephone or through a personal visit to determine as completely as possible the reason for the withdrawal, and record the reason in subject's source document and CRF. A complete final early termination (week 8) evaluation at the time of the subject's withdrawal should be made with an explanation of why the subject is withdrawing from the study. If the reason for removal of a subject is an adverse event or an abnormal laboratory test result, the principal specific event or test will be recorded. Subjects who discontinue the study before week 8 visit will be asked to come for an early termination visit as soon as possible and have the assessments listed at week 8 performed. They will also be asked to return two weeks later for the safety assessments listed at

week 10.

Reasons for discontinuation include:

- The investigator decides that the subject should be withdrawn. If this decision is made because of a serious or persistent adverse event, laboratory abnormality, or intercurrent illness, the study drug is to be discontinued and appropriate measures are to be taken. The investigator will notify the Sponsor or designee immediately.
- The subject or attending physician requests that the subject be withdrawn from the study.
- The subject for any reason requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication. In this case, discontinuation from the study occurs immediately upon introduction of the new agent.
- The subject is lost to follow-up, in this case, a reasonable attempt to contact the subject and ascertain his/her status must be made and these attempts must be documented.
- Serious protocol violation, including persistent non-compliance.
- The Sponsor or Regulatory Authorities, for any reason, stops the study. All subjects will be discontinued from the study and notified of the reasons for the discontinuation.
- Pregnancy at any time during the study.
- Other: the subject may withdraw from the study for any other reason, including withdrawal of consent.

6 TREATMENT

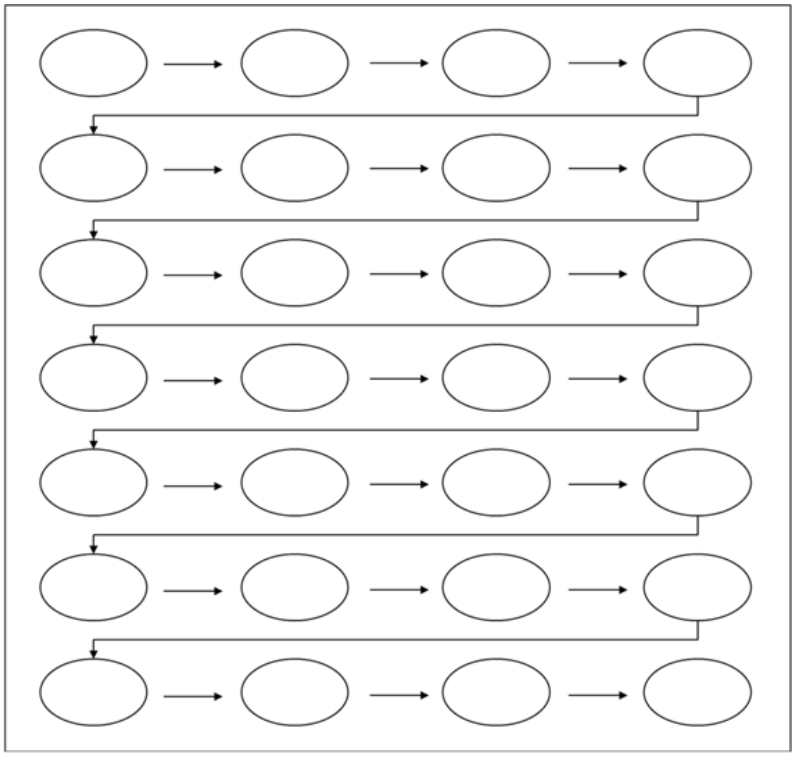
6.1 Treatment Administration

Subjects who fulfill all the inclusion and none of the exclusion criteria may be accepted in the study. Each subject must read and sign an informed consent form prior to any screening procedures being performed. This study involves a comparison of DS107G (2 g) with placebo, administered orally once daily upon waking for a total duration of 8 weeks. The last study drug administration should occur on the day preceding week 8 visit / Early Termination (ET) visit. Subjects will be randomized to one of the two treatment groups in a 1:1 ratio:

- Treatment group A: 2 grams DS107G (4 capsules)
- Treatment group B: 2 grams placebo capsules (4 capsules)

Subjects will be required to start fasting at least 8 hours before drug administration upon waking. Fasting will continue for at least 60 minutes following drug administration, after which subjects can have breakfast. Water will be allowed at all times during the fasting period, but no other fluids will be permitted. Medication(s) for other conditions that are permitted in the study can be taken as usual.

Blister packs will consist of 7 rows of 4 capsules. Each row constitutes one daily dose. Subjects will be instructed to take the 4 capsules **from left to right**, top to bottom, as shown below:



6.2 Study Treatment

6.2.1 *Description*

DS107G capsules will be provided by Dignity Sciences as opaque, oval soft gelatin capsules containing 500mg of DGLA free fatty acid (FFA).

Placebo capsules will be also provided by Dignity Sciences as opaque, oval soft gelatin capsules containing 500mg of liquid paraffin.

DS107G capsules will be supplied in manufactured form (blinded), packaged in aluminum foil blisters of 28 units. Placebo will be presented in identical blisters and packs and stored/packaged the same as DS107G capsules. Study medication will be labelled according to US and Canadian regulations.

6.2.2 *Storage Conditions*

The study medication will be provided by the sponsor to the investigator and will be kept, on site, in a locked room or cabinet with limited access. DS107G and placebo capsules should be stored at a controlled room temperature between 15-30°C and will only be supplied to subjects in the trial under the supervision of the investigator.

6.2.3 *Study Drug Dispensing and Return*

Study drug will be dispensed by the study site to the subject at each study visit. Subjects are to return all study drug blister packs (used and unused) to the study site. The capsules within blister packs will be counted prior to dispensing and upon return and the counts will be recorded in the source documents and eCRF. Each subject is to be instructed on the importance of returning study drug at the next study visit. If a subject does not return study drug, he/she will be instructed to return it as soon as possible.

6.2.4 *Drug Accountability*

The investigator is responsible for maintaining accurate records of the study medication received initially, the study drug dispensed/used, the returned medication by subjects and the medication destroyed or returned to the Sponsor or designee. All study drug accountability forms and treatment logs must be retained in the Investigator's study file. These records must be available for inspection by the Sponsor, its designees or by regulatory agencies at any time.

Used drug boxes/blister packs will be stored safely until destruction and must be accounted for by the investigator. The study monitor will perform drug accountability for all study drug at the site and assist in returning study drug, including used and unused study drug to the Sponsor or designee. After verification of the drug accountability by the sponsor, the investigator will ensure proper destruction or return of the remaining study product.

Any study medication accidentally or deliberately destroyed will be accounted for. Any discrepancies between amounts dispensed and returned will be explained.

Drug inventory and accountability records will be maintained at each site as per GCP/ICH guidelines.

6.2.5 *Method of Assignment to Treatment*

Approximately 100 patients will be randomized into double-blind treatment groups in a 1:1 ratio by an Interactive Web Response System (IWRS) or Interactive Voice Response System (IVRS), as follows:

- Treatment group A: 2 grams DS107G (4 capsules)
- Treatment group B: 2 grams placebo capsules (4 capsules)

A randomization list permuted blocks and stratified by site will be generated by Dignity Sciences or its designee. The randomization schedule with study drug assignments will be generated prior to the start of the study and will be known only to the individuals responsible for labeling the study drug. The IVRS or IWRS will assign a study drug kit number to each subject and the contents will be based on the randomization code.

At the investigational site, each subject will be assigned a patient identifier number during screening that will be used on all patient documentation. The patient identifier number will contain the site number and the patient number assigned in numerical order at the screening visit (e.g.: 02-010 for the tenth patient screened at the site #02). Numbers will be assigned in ascending order starting with 001.

6.2.6 *Rationale for Selection and Timing of Doses in the Study*

Doses up to 4 g have been well tolerated in healthy subjects. The dose of 2 g has been selected as the tested dose in the current study based primarily on the pharmacokinetic results from the Phase I trial which suggested saturable skin levels of total DGLA with repeated oral dosing of greater than 2g per day.

In addition the following factors were considered:

(a) there were less frequent transient gastrointestinal instances recorded at a dose of 2g compared to 4g daily
(b) the number of capsules (4) administered daily. A higher dose would be possible but is deemed less desirable as too many capsules may have a negative impact on patient adherence to treatment.

6.2.7 *Breaking of Study Blinding*

At all times, treatment and randomization information will be kept confidential and will not be released to the investigator, the study staff, the CRO or the sponsor's study team until following the conclusion of the study.

Blinding codes should only be broken in emergency situations for reasons of subject safety. The method will be either a manual or electronic process. When the blind for a subject has been broken, the reason must be fully documented. Whenever possible, the investigator should contact the Sponsor or its designee before breaking the blind. If the blind is broken, the investigator should promptly inform the Medical Monitor. Documentation of breaking the blind should be recorded with the date and time the blind was broken, and the names of the personnel involved.

The subject for whom the blind has been broken will be discontinued from the study and undergo the early termination (ET) procedures listed at the Week 8 visit. They will be also asked to return two weeks after the early termination visit for the safety assessments listed at Week 10. In cases where there are ethical reasons to have the subject remain in the study, the investigator must obtain specific approval from the Sponsor or its designee for the subject to continue in the study.

6.3 Concomitant Therapy

All medications (including over-the-counter drugs, vitamins, and antacids) taken ≤4 weeks prior to screening and throughout the study must be recorded. All medications taken for atopic dermatitis in the 2 months prior to screening must be recorded.

Medication entries should be specific to the generic name. Trade name may be used for combination drugs. Entries will include the dose, unit, and frequency of administration, route of administration, start date, discontinuation date, and indication. If the medication is discontinued, or the dosage changed, these details must be recorded.

The Investigator should assess any concomitant procedures, medications, and dietary supplements for acceptability that are not explicitly prohibited.

6.3.1 *Permitted therapies*

6.3.1.1 Emollients

Subjects can apply a bland emollient of their choice on their skin, including AD lesions, provided that emollient use is **initiated at least 2 weeks prior to Day 0** and continues at the same frequency and on the same skin areas throughout the study. Subjects will be requested to avoid using emollients containing any active ingredient which has or may have an effect on atopic dermatitis including the following ingredients:

- Urea
- Ceramide
- Hyaluronic acid

Every effort should be made to keep the same emollient throughout the study. The commercial name of the selected emollient(s) will be recorded in the source document and the eCRF. No other products may be applied to the lesions during the study.

6.3.1.2 Other permitted therapies

Non-sedative anti-histamines (e.g. loratadine, fexofenadine) are allowed during the study only if used to treat medical conditions other than atopic dermatitis. Such medications are allowed during the study only if the subject has been on a stable dose for at least 2 weeks prior to Day 0 and continues to use the same agent everyday throughout the study

Inhaled and intranasal corticosteroids for stable medical conditions are allowed.

6.3.2 *Prohibited therapies or procedures*

The following topical therapies or procedures are prohibited during the study for all subjects:

- Topical medicated treatments that could affect atopic dermatitis, including but not limited to:
    - topical corticosteroids
    - calcineurin inhibitors
    - tars
    - bleach
    - antimicrobials
    - bleach baths

- Any topical product containing urea, ceramides or hyaluronic acid
- Systemic therapy that could affect atopic dermatitis, e.g. retinoids, calcineurin inhibitors, methotrexate, cyclosporine, hydroxycarbamide (hydroxyurea), azathioprine and oral/injectable corticosteroids
- Anti-histamines (except non-sedative anti-histamine)
- Any biological agent
- UVA or UVB phototherapy
- Psoralen + Ultraviolet A (PUVA) therapy
- Excessive sun exposure or use of tanning booth
- Any investigational agent

6.3.3 *Assessment of Compliance*

Treatment compliance will be assessed at each visit by direct questioning, review of the subject's compliance log and capsule count, and will be based on the latter. Subjects will be given a paper diary at each visit along with study medication. Subjects will indicate any missed doses on the diary, as well as the timing of the last food ingestion prior to study drug administration and food ingestion following study drug administration. Subjects will be instructed to bring all capsules and blister packs (used and unused) and compliance log to the next study visit. Any deviation from the prescribed dosage regimen will be recorded in the source document and in the eCRF. Subjects who are significantly noncompliant will be counseled.

7 STUDY PROCEDURES

Please refer to Appendix A for a flowchart of procedures to perform at each visit.

7.1 Screening, Visit 1 (Day -30 to -1)

Screening evaluation will only be performed after the subject has agreed to participate and has signed and dated the informed consent form. No treatment or trial related procedures will be initiated before the informed consent is signed. Day 0 visit must be performed, at the latest, 30 days after the screening visit.

Screening evaluation will be performed according to inclusion and exclusion criteria. If the subject fulfils all inclusion criteria and no exclusion criteria, the subject may be included in the study.

The following procedures will be performed at the screening visit:

- Informed consent
- Review of Inclusion-Exclusion criteria, including review of Hanifin and Rajka criteria (Appendix G)
- Assign subject identifier number (Site number – Subject number)
- Demographics
- Concomitant medications
- Medical/ surgical history
- Physical examination
- Vital signs
- BMI
- Safety labs (chemistry, coagulation, hematology and urinalysis)
- Serum pregnancy test (women of childbearing potential only) and FSH level test for women greater than 40 and less than 60 years of age who have had a cessation of menses for at least 12 months but less than 24 months
- BSA evaluation
- IGA

7.2 Baseline, Visit 2 (Day 0)

Subjects are required to fast for at least 8 hours prior to study drug administration. They will be allowed to have a meal 60 minutes after study drug administration.

The following procedures will be performed at this visit:

- Confirm eligibility with inclusion and exclusion criteria
- Update or confirm medical/surgical history
- Concomitant medications
- Vital signs
- BMI
- Safety labs and biomarkers of inflammation (chemistry, coagulation, hematology, urinalysis, and interleukin profile).
- Urine pregnancy test (women of childbearing potential only)
- Pre-dose blood draw pharmacokinetics
- Blood draw total fatty acid profile
- BSA evaluation
- IGA
- EASI assessment
- SCORAD assessment (including VAS pruritus assessment)
- POEM questionnaire

- DLQI questionnaire
- TEWL assessment (for selected sites only)
- Randomize subject in IVRS/IWRS
- Study drug administration
- Dispensing of study drug
- Dispensing of Subject Compliance Log
- Adverse events evaluation (after first study drug administration)

7.3 Week 2, Visit 3 (Day 14 ± 2 days)

The following procedures will be performed at this visit:

- Vital signs
- Urine pregnancy test (women of childbearing potential only)
- BSA evaluation
- IGA
- EASI assessment
- SCORAD assessment (including VAS pruritus assessment)
- POEM questionnaire
- DLQI questionnaire
- TEWL assessment (for selected sites only)
- Collection and dispensing of study drug Review, collection and dispensing of Subject Compliance log
- Capsule count
- Concomitant medications
- Adverse events evaluation

7.4 Week 4, Visit 4 (Day 28 ± 2 days)

Subjects are required to fast for at least 8 hours prior to study drug administration. They will be allowed to have a meal 60 minutes after study drug administration.

The following procedures will be performed at this visit:

- Vital signs
- Urine pregnancy test (women of childbearing potential only)
- Physical examination
- Safety labs and biomarkers of inflammation (chemistry, coagulation, hematology, urinalysis, and interleukin profile).
- Pre-dose blood draw pharmacokinetics (if study medication was taken prior to the visit, subject must come back the next day)
- Blood draw total fatty acid profile
- BSA evaluation
- IGA
- EASI assessment
- SCORAD assessment (including VAS pruritus assessment)
- POEM questionnaire
- DLQI questionnaire
- TEWL assessment (for selected sites only)
- Study drug administration (instruct subject that last dose should occur on the day preceding week 8 visit)
- Collection and dispensing of study drug

- Review, collection and dispensing of Subject Compliance log
- Capsule count
- Concomitant medications
- Adverse events evaluation

7.5 Week 8, Visit 5 (Day 56 ± 2 days) (End of Treatment/Early Termination Visit)

The following procedures will be performed at this visit:

- Ongoing medical history review
- Vital signs
- Physical examination
- BMI
- Safety labs and biomarkers of inflammation (chemistry, coagulation, hematology, urinalysis and interleukin profile).
- Serum pregnancy test (women of childbearing potential only)
- Blood draw pharmacokinetics (if study medication was taken prior to the visit, subject must come back the next day)
- Blood draw total fatty acid profile
- BSA evaluation
- IGA
- EASI assessment
- SCORAD assessment (including VAS pruritus assessment)
- POEM questionnaire
- DLQI questionnaire
- TEWL assessment (for selected sites only)
- Collection of study drug
- Review and collection of Subject Compliance log
- Capsule count
- Concomitant medications
- Adverse events evaluation

7.6 Follow-up/Week 10, Visit 6 (Day 70 ± 3 days)

The following procedures will be performed at this visit:

- Ongoing medical history review
- Vital signs
- Physical examination
- Safety labs (chemistry, coagulation, hematology and urinalysis): **only if clinically significant change from baseline in safety lab results at week 8.** Urine pregnancy test (women of childbearing potential only)
- BSA evaluation
- IGA
- EASI assessment
- SCORAD assessment (including VAS pruritus assessment)
- POEM questionnaire
- DLQI questionnaire
- TEWL assessment (for selected sites only)
- Concomitant medications
- Adverse events evaluation

7.7 Early termination visit

In the case the subject ends the study before completion, the procedures listed at Week 8 visit should be completed (section 7.5). Subject will also return two weeks later for the following Follow-up/Week 10 safety assessments:

- Concomitant medications
- Safety labs (only if there was a clinically significant change from baseline at the ET visit)
- Urine pregnancy test, if female of childbearing potential
- Vital signs
- Physical exam
- Adverse events

8 STUDY ASSESSMENTS

8.1 Efficacy Assessments

Clinical evaluations of atopic dermatitis will be performed by an experienced and qualified dermatologist (board certified or equivalent). To assure consistency and reduce variability, the same assessor should perform all assessments on a given subject whenever possible.

8.1.1 *Investigator's Global Assessment (IGA)*

The Investigator's Global Assessment (IGA) of Disease Severity (Appendix B) (25, 26) will be assessed at each visit. The IGA is a global assessment of the current state of the disease. It is a 6-point morphological assessment of overall disease severity and will be determined according to the following definitions: 0 (clear), 1 (almost clear), 2 (mild), 3 (moderate), 4 (severe) and 5 (very severe). In order to be eligible, subjects must have an IGA score >/= 3 at Baseline visit (Day 0).

8.1.2 *Eczema Area and Severity Index (EASI)*

The Eczema Area and Severity Index (EASI) will be assessed at each visit, except screening visit. It quantifies the severity of a subject's atopic dermatitis based on both lesion severity and the percent of BSA affected (24). The EASI is a composite score ranging from 0-72 that takes into account the degree of erythema, induration/papulation, excoriation, and lichenification (each scored from 0 to 3 separately) for each of four body regions, with adjustment for the percent of BSA involved for each body region and for the proportion of the body region to the whole body. A detailed procedure of EASI score calculation is provided in Appendix C.

8.1.3 *Body Surface Area (BSA)*

The overall BSA affected by AD will be evaluated (from 0 to 100%) at each visit. One patient's palm represents 1% of his/her total BSA. For all study visits except at screening, the BSA of involved skin will be measured with the SCORAD measurement (see below for description) and evaluated as a separate endpoint. In order to be eligible, subjects must have a BSA of at least 10% at Baseline visit (Day 0).

8.1.4 *SCORing Atopic Dermatitis (SCORAD)*

SCORAD will be measured at each visit, except the screening visit. The SCORAD grading system was developed by the European Task Force on Atopic Dermatitis (1993) and has been a standard tool to assess the AD severity in clinical studies in Europe (27, 28). Six items (erythema, edema/papulation, oozing/crusts, excoriation, lichenification, and dryness) will be selected to evaluate the AD severity. The overall BSA affected by AD will be evaluated (from 0 to 100%) and included in the SCORAD scores. Loss of sleep and pruritus will be evaluated by patients on a visual analog scale (0-10). The sum of these measures represents the SCORAD which can vary from 0 to 103. The detailed procedure of SCORAD score calculation is provided in Appendix D.

8.1.5 *Visual Analog Scale of Pruritus*

For all study visits except screening, the pruritus severity score will be recorded with the SCORAD measurement and this will be evaluated as a separate endpoint. This will be evaluated by asking subjects to indicate on the 10-cm scale (0-10) of the assessment form the point corresponding to the average value for the last three days/nights.

8.1.6 *Patient-Oriented Eczema Measure (POEM)*

The Patient-Oriented Eczema Measure (POEM) will be assessed at each visit, except screening visit. The POEM developed by Charman et.al. (29, 30) is a self-assessment of disease severity by the patient. POEM has a maximum value of twenty eight based on the patient's response to seven questions scored according to the following scale:

- No Days = 0
- 1-2 Days = 1
- 3-4 Days = 2
- 5-6 Days = 3
- Everyday = 4

A detailed description of the POEM assessment is provided in Appendix E.

8.1.7 *Dermatology Quality of Life (DLQI) Questionnaire*

The DLQI is a simple 10-question validated questionnaire which will be completed at each visit, except screening. The questionnaire is provided in Appendix F.

8.1.8 *Transepidermal Water Loss (TEWL) (at selected sites only)*

The clinical severity of AD and associated effect on skin barrier function will be evaluated at each visit, except the screening visit. This evaluation will be performed at selected sites that have demonstrated previous experience with this device.

At Baseline (Day 0), the investigator will select three representative areas of active AD for each subject; the location of these sites will be recorded. At subsequent visits, TEWL readings for each area of AD will be taken in standard room ambient conditions (22-25˚C, 40-60% relative humidity); the mean of the TEWL measurements will be used for the analyses.

8.2 Safety Assessments

8.2.1 *Vital Signs*

The following vital signs will be recorded at every visit in a seated position, after having sat calmly for at least 5 minutes: systolic and diastolic blood pressure (mmHg), pulse (bpm), body temperature (°C) and respiratory rate (breath/min).

Weight (kg) and Height (cm) will be collected to calculate the BMI, and will be recorded at the Screening, Baseline and week 8 visits. The height will only be recorded once at the screening visit and the same value will be used for BMI calculation at baseline and Week 8 visits.

Any abnormal finding related to vital signs that the investigator considers to be clinically significant, must be recorded as an AE.

8.2.2 *Physical Examination*

The following sites/systems will be included in the physical examination. Each system will be scored as normal/abnormal (non-clinically significant or clinically significant). Pertinent details must be recorded for any clinically significant findings.

- General appearance
- Dermatological (except Atopic dermatitis)
- Head, Eyes, Ears, Nose, Throat (HEENT)
- Respiratory
- Cardiovascular
- Abdominal
- Neurological
- Musculoskeletal
- Lymphatic

8.2.3 *Clinical Laboratory Tests*

Laboratory tests will be performed at screening, Day 0, Week 4 and Week 8. If Week 8 results indicate a clinically significant change from baseline, laboratory tests will also be performed at Week 10. The tests will include urinalysis, hematology with differential and coagulation testing, a standard chemistry panel (chemistry includes liver function tests and cholesterol), coagulation, serum pregnancy test (screening and week 8 / Early termination visits) for women of childbearing potential (WOCBP). At baseline (Day 0), week 2, week 4 and week 10 visits, a urine pregnancy test will be performed for women of childbearing potential (conducted at the investigator site). At screening visit, FSH levels will be tested for women greater than 40 and less than 60 years of age who have had a cessation of menses for at least 12 months but less than 24 months. The specific tests in these panels are listed below:

Table 1 Clinical Laboratory Testing

Laboratory testing	Tests included
Hematology	Basophils, Eosinophils, HCT, HGB, Lymphocytes, MCH, MCV, Monocytes, Neutrophils, platelets, RBC, WBC
Coagulation panel (frozen)	APTT, INR, PT
Serum Chemistry	Albumin, Alkaline Phosphatase, ALT, AST, Chloride, Cholesterol (non-fasting), CK, Creatinine (Enzymatic), GGT, Glucose Random, LDH, Potassium, Sodium, Total Bilirubin, Triglycerides, Urea (BUN), Uric Acid β-hCG for females of childbearing potential (Screening and week 8 / Early termination)
Urinalysis	Blood, Glucose, pH, Protein
Laboratory Tests Required at Screening only	FSH levels for women greater than 40 and less than 60 years of age who have had a cessation of menses for at least 12 months but less than 24 months.

8.2.4 *Total and Free DGLA plasma levels, Total Fatty Acid Profile and Interleukins levels*

At Baseline, week 4 and week 8 visits, blood draws will be performed **prior to study drug administration** (no study drug administration at week 8 visit). If a subject comes to the clinic after taking their daily dose of study medication, this subject will be required to come back the following day for PK blood draws. Total DGLA and free DGLA trough plasma levels will be measured. A second blood draw will be performed for later evaluation of total fatty acid profile in plasma. The blood draw for serum chemistry analysis will be split in two aliquots for chemistry analysis and later evaluation of interleukins.

The date and time of the subject's last dose at home before the visit will be recorded accurately. The study site will instruct subjects not to take their daily study drug dose at home for week 4 visit. Dosing will occur in the clinic during the study visit. The exact time of the sample collection must be recorded.

Blood samples will be processed as soon as possible, no later than 1 hour after blood collection. The plasma obtained will be transferred in polypropylene tubes. Each tube will be labeled in order to identify the analyte to be assayed. All samples will be frozen in an upright position. The detailed instruction for PK, Total Fatty Acid and interleukin sample collection, processing, storage and shipment will be provided in the central laboratory manual. The labels on each tube will include at least the following information:

- Study protocol
- Site number
- Subject identification number
- Visit name
- Analyte name
- Primary (A) or Duplicate (B)

Shipment of the experimental samples will be shipped to ICON Central Laboratories.

Detailed instructions for shipment will be provided in the central laboratory manual. Samples will then be shipped to the analytical facility and will be analyzed using a validated analytical method in compliance with their standard operating procedures.

Blood specimens for PK analysis will be maintained in a blinded fashion.

9 ADVERSE EVENTS

An adverse event is any untoward medical occurrence in a patient administered a pharmaceutical product, without regard to the possibility of a causal relationship with this treatment.

Investigators are responsible for monitoring the safety of subjects who are participating in this study and for alerting the Sponsor of any event that seems unusual, even if this event may be considered an unanticipated benefit to the subject. The investigator is responsible for appropriate medical care of subjects during the study.

The investigator remains responsible for following through an appropriate health care option, adverse events that are serious or that caused the subject to discontinue before completing the study. The subject should be followed until the event is resolved or stable. Follow-up frequency is left to the discretion of the investigator.

Safety will be evaluated by collecting adverse events, vital signs, performing physical examinations and evaluating laboratory results. The reported adverse events will be coded according to MedDRA terminology.

Prior to enrollment, study site personnel will note the occurrence and nature of each subject's medical condition(s) in the appropriate section of the source document and CRF. During the study, site personnel will again note any change in the condition(s) and the occurrence and nature of any adverse events.

If a subject experiences an adverse event after the first dose of the study drug, the event will be recorded as an adverse event in the source document and CRF. All AEs will be described in the source documents and in the CRF.

9.1.1 *Adverse Events Causality*

The investigator will establish causality of the AE to experimental treatment. The investigator should take into account the subject's history, most recent physical examination findings, and concomitant medications.

The following definitions will be used to determine causality of an AE:

- Not related: temporal relationship of the onset of the AE, relative to the experimental treatment is not reasonable or another cause can explain the occurrence of the AE.

- Related: temporal relationship of the onset of the AE, relative to the experimental treatment is reasonable, follows a known response pattern to the treatment, and an alternative cause is unlikely.

9.1.2 *Adverse Events Severity*

The intensity of an AE is an estimate of the relative severity of the event made by the investigator based on his or her clinical experience and familiarity with the literature. The following definitions are to be used to rate the severity of an AE:

- Mild: The symptom is barely noticeable to the subject and does not influence performance of daily activities. Treatment is not ordinarily indicated.

- Moderate: The symptom is sufficiently severe to make the subject uncomfortable, and performance of daily activities is influenced. Treatment may be necessary.

- Severe: The symptom causes severe discomfort, and daily activities are significantly impaired or prevented. Treatment may be necessary.

9.1.3 *Serious Adverse Events*

If a patient experiences a serious adverse event after the first dose of the study drug, the event will be recorded as a serious adverse event. All AEs will be described in the source documents and in the CRF.

A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening,
- requires in-subject hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect.

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. *These should also usually be considered serious*.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

9.1.4 *SAE Reporting:*

Any Serious Adverse Event, related or not, occurring during the study must be reported on a SAE Form within **24 hours** of awareness to the CRO:

Innovaderm Research
Fax (514) 221-4199
If a fax is not available within 24 hours of awareness:
Email: efaxcro@innovaderm.ca

The SAE will be reported by the CRO to the following Sponsor's Representative Product Life Limited:

Name: James Wilson
Title: Pharmacovigilance Associate
Company name: Product Life Limited
Tel. (+44 1223) 402660 (Working hours)
Tel. (+44 1223) 402660 (nights, weekends, and holidays) JAM answering service is in operation for all calls outside working hours.
Fax. (+44 1223 413689)
Email: safety@productlife-group.com

Product Life will process and evaluate all SAEs as soon as the reports are received and will assess the expectedness of each SAE to the study treatment. For each SAE received, Product Life will make a determination as to whether the criteria for expedited reporting to relevant regulatory authorities have been met. Product Life will manage the expedited reporting of relevant safety information to concerned regulatory agencies in accordance with local laws and regulations.

9.2 Pregnancy Reporting

If a subject becomes pregnant during the study, the subject should inform the study site as soon as possible. Upon confirmation of the pregnancy, the subject must be withdrawn from study drug but may continue study participation. The Investigator must complete a study-specific Pregnancy Form upon confirmation of a pregnancy and send it to Innovaderm Research within 24 hours of confirmation of the pregnancy. Innovaderm Research will report all cases of pregnancy to the Sponsor in a timely manner (contact information to be used are the same as for SAE reporting). Post-treatment follow-up should be done to ensure subject safety. Pregnancy is not itself an AE or SAE; however, maternal/fetal complications or abnormalities will be recorded as AEs or SAEs, as appropriate. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Innovaderm Research of the outcome as a follow up to the initial Pregnancy Form.

10 DATA QUALITY ASSURANCE/SITE MONITORNG

During the study, monitoring visits will be conducted at regular intervals. The monitoring visits will be conducted to ensure protocol adherence, quality of data, accuracy of entries in the eCRF, drug accountability, compliance with regulatory requirements and continued adequacy of the investigational site and its facilities.

The site may be audited and/or monitored by a quality assurance officer named by the Sponsor and/or regulatory authorities may wish to perform on-site audits. The investigator will be given notice before an audit occurs and will be expected to cooperate with any audit, provide assistance and documentation (including source data) as requested.

11 DATA COLLECTION AND RETENTION

Subject data will be entered by site personnel using Medrio eClinical Overnight, a web based electronic data capture (EDC) and reporting system. This application will be set up for remote entry. Medrio Inc. are the developers and owners of Medrio eClinical Overnight. The EDC software has been fully validated and conforms to 21 CFR Part 11 requirements. Investigator site staff will not be given access to the EDC system until they have been fully trained by the Sponsor or delegate. Designated investigator staff will enter the data required by the protocol into the eCRFs using this web based application. Automatic validation programs check for data discrepancies in the eCRFs and, by generating appropriate error messages, allow

modification or verification of the entered data by the investigator staff before confirming the data. The investigator must certify that the data are complete and accurate by applying an electronic signature to the eCRFs.

The investigator must maintain source documents for each subject in the study, consisting of case and visit notes (clinical medical records) containing demographic and medical information and the results for any tests or assessments. All information on the eCRFs must be traceable to these source documents in the subject's file. Data not requiring a written or electronic record will be defined before study start and will be recorded directly on the eCRFs, which will be documented as being the source data.

The data collected will be encoded and stored electronically in a database system. Validated data may subsequently be transferred to the sponsor.

12 CONFIDENTIALITY OF TRIAL DOCUMENTS AND SUBJECT RECORDS

The investigator must assure that the subjects' anonymity will be maintained and that their identities are protected from unauthorized parties. On CRFs or other document submitted to the Sponsor, subjects should not be identified by their names, but by an identification code. The Investigator should keep a subject enrolment log relating codes with the names of subjects. The Investigator should maintain documents not for submission to the sponsor e.g., subjects' written consent forms, in the strictest confidence.

13 INVESTIGATOR'S FILES/RETENTION OF DOCUMENTS

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These records include, but are not limited to, the identity of all participating subjects, all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence. These documents should be classified into two different separate categories: Investigator Study File and Subject Clinical Source Documents.

The records should be retained by the investigator according to International Conference on Harmonisation (ICH), local regulations, or as specified in the Clinical Trial Agreement (CTA), whichever is longer.

14 SAMPLE SIZE AND STATISTICAL METHODS

14.1 Determination of Sample Size

The primary endpoint can be translated as a responder analysis where a subject will be classified as Responder if he/she achieves an IGA score of 0 (clear) or 1 (almost clear) at Week 8, considering a 2-point decrease from baseline. A sample size of 45 subjects will have a power of 80% to detect a statistically significant difference of 25% between responders from treated group and from the placebo group, based on a chi-square test and an alpha of 0.05. Based on the literature review, it is expected that the placebo could reach up to 7%, so the minimal proportion expected in the treated group should be at least 32%. Allowing for 10% drop-out, a total of 100 subjects should be enrolled in the study.

14.2 Statistical and Analytical Plans

Continuous variables will be summarized in tables and will include the number of subjects, mean, standard deviation, median, minimum, maximum and inter-quartile range. Categorical variables will be presented in tables as frequencies and percentages.

All statistical tests will be two-sided and will be performed with a significant level of 0.05, unless otherwise specified.

14.2.1 *Subject Disposition*

Efficacy will be evaluated on the basis of the ITT population and analyses will be performed based on the randomized treatment and not on the treatment received.

The per-protocol (PP) population will include all subjects who were randomized with no significant protocol deviations. The specific criteria for the PP population and the ITT population will be detailed in a separate statistical analysis plan.

The safety population will be defined as all subjects who received at least one dose of the medication. Analysis will be done according to the actual treatment they received.

14.2.2 *Efficacy analysis*

The primary endpoint can be translated as a responder analysis where a subject will be classified as Responder if he/she achieves an IGA score of 0 (clear) or 1 (almost clear) at Week 8, considering a 2-point decrease from baseline. The comparison between groups for the primary endpoint will be done using a Cochran-Mantel–Haenszel test with site included as a stratification factor. A supportive analysis will be performed using a Fisher's exact test. The primary efficacy analysis will be done using observed values and a supportive analysis will be conducted using the last observation carried forward (LOCF) approach. The analyses will be done using the ITT population and will serve as the primary analysis while the analysis of the primary endpoint using the PP population will be used a sensitivity analysis.

The secondary endpoints involving change from baseline will be analyzed using an analysis-of-covariance (ANCOVA) including the change from baseline as the dependent, the site and treatment group and site as fixed effects, and the baseline value as covariate. Ls-means and 95% CI will be presented along with corresponding p-value from the comparison of treatment. The secondary endpoints involving proportion will be analyzed using a Cochran-Mantel-Haenszel test stratified by site and p-value will be presented.

Analyses for the secondary endpoints will be done using observed data and no imputation will be used for missing observation.

All details regarding the statistical analyses will be included in a separate statistical analysis plan.

14.2.3 *Safety Analysis*

All adverse events (AEs) that occur after the first study drug administration during the study will be classified on the basis of Medical Dictionary for Regulatory Activities (MedDRA) terminology. Descriptions of AEs will include the date of onset, the date the AE ended (if it resolved), the severity and seriousness of the AE, the relationship of the AE to study medication, and the outcome. The focus in this protocol will be limited to treatment emergent adverse events.

Reported AEs will be summarized by the number of subjects reporting the events, as well as by System Organ Class, Preferred Term, severity, seriousness, and relationship to study medication. For the summary of AEs by severity, each patient will be counted only once within a System Organ Class or a Preferred Term by using the AEs with the highest intensity within each category for each analysis. For the summary of AEs by relationship to study medication, each patient will be counted only once within a System Organ Class or a Preferred Term by using the AEs with the greatest reported relationship within each category. For the summary of AEs by relationship to study medication and severity, each patient will be counted only once within a System Organ Class or a Preferred Term by using (1) the greatest reported relationship followed by (2) the highest reported intensity.

All information pertaining to AEs noted during the study will be listed by patient, detailing verbatim, System Organ Class, Preferred Term, start date, stop date, intensity, outcome and relationship to study drug. The AE onset will also be shown relative (in number of days) to the day of test article administration. Serious adverse events (SAEs) will be tabulated by treatment group, relationship to the test article, and a reference to the occurrence of the SAEs to the relative day of dosing.

Concomitant medications will be coded with the WHO-Drug Dictionary and listed by subject.

In addition, a list of subjects who discontinued from the study and a list of subjects who experienced SAEs will also be provided.

Results from laboratory analyses and vital signs will be tabulated using descriptive statistics. The value at visit as well as the change from baseline will be presented descriptively.

No inferential statistics will be done on safety variables (TEAEs, concomitant medication, laboratory and vital signs).

15 ETHICS

15.1 Local Regulations/Declaration of Helsinki

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki (2008) and that are consistent with “Good Clinical Practice” ICH Tripartite Guideline (July 2002) and the applicable laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual.

15.2 Ethical Review

It is the understanding of the Sponsor that this protocol (and any amendment) as well as appropriate consent procedures, will be reviewed and approved by a research ethics board/institutional review board (REB/IRB). This Board must operate in accordance with the current Federal regulations. A letter or certification of approval will be sent by the Investigator to the Sponsor prior to initiation of the study, and also whenever subsequent modifications to the protocol are made.

15.3 Informed Consent

It is the responsibility of the Investigator, or a person designated by the Investigator (if acceptable by local regulation), to obtain written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives and potential hazards of the study. It must also be explained to the subjects that they are completely free to refuse to enter the study or to withdraw from it at any time for any reason.

If new safety information results in significant changes in the risk/benefit assessment or any new information that may affect willingness to continue to participate, the consent form should if necessary be reviewed and updated by the Research Ethics Board/Institutional Review Board. All subjects (including those already being treated) should be informed of the new information, given a copy of the revised form and asked to give their consent to continue in the study.

16 PUBLICATION POLICY

Sponsor permission is required for publication but is reflective of applicable laws and regulation. The Publication Policy will be addressed in the Research and Financial agreement, and all details outlined in the agreement will apply to this protocol.

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18 APPENDIX A Study Flow Chart

Visit	Screening	Baseline	Week 2	Week 4	Week 8 / ET visit	Follow up visit / Week 10
Day	**-30 to -1**	**0**	**14 (± 2)**	**28 (± 2)**	**56 (± 2)**	**70 (±3)**
Informed Consent	X					
Demographics	X					
Medical / Surgical History	X	X				
Ongoing medical history[¥]					X	X
Review Inclusion/Exclusion Criteria	X	X				
Hanifin and Rajka criteria	X					
Assign subject identifier number	X					
Randomization		X				
Concomitant Medications	X	X	X	X	X	X[δ]
Safety labs and inflammation biomarkers: Serum Chemistry (including FSH levels at screening when applicable[¥] and interleukin profile), Coagulation, Hematology, urinalysis	X[Φ]	X		X	X	(X**)[Φ, δ]
Pharmacokinetics (pre-dose blood draw)[††]		X		X	X	
Blood draw for fatty acid profile sample[††,]		X		X	X	
Pregnancy Test (β-hCG if female of childbearing potential)*	X	X	X	X	X	X[δ]
Vital Signs	X	X	X	X	X	X[δ]
Physical Examination	X			X	X	X[δ]
BMI	X	X			X	
Study Drug Administration (on site)[€]		X		X	[§]	
Dispense Study Drug		X	X	X		
Collect Study Drug			X	X	X	
Dispense Subject Compliance Log		X	X	X		
Collect and Review Subject Compliance Log			X	X	X	
Capsule count			X	X	X	
BSA	X	X	X	X	X	X
IGA	X	X	X	X	X	X
EASI assessment		X	X	X	X	X
SCORAD assessment / VAS pruritus assessment		X	X	X	X	X
POEM questionnaire		X	X	X	X	X
DLQI questionnaire		X	X	X	X	X
TEWL (selected sites only)		X	X	X	X	X
Adverse Events[†]		X[†]	X	X	X	X[δ]

[¥]: For women greater than 40 and less than 60 years of age who have had a cessation of menses for at least 12 months but less than 24 months

**: Only if clinically significant change from baseline in safety lab results at week 8
*: Serum pregnancy test at screening and week 8 / ET visits, urine test pregnancy for all other visits
††: If a subject took study medication prior to the visit, he/she will be required to come back the following day for PK blood draws.
€: Subjects must be fasting for at least 8 hours before and 60 minutes after drug administration
§: Subjects will be instructed to take their last study drug dose the day preceding week 8 visit.
†: Collection of AE will start after the first study drug administration
¥: Assessment if any ongoing condition has improved since baseline.
Φ: Interleukin profile will not be evaluated at screening and week 10.
δ: In the case the subject ends the study before completion, the subject will also return 2 weeks after the ET visit for safety assessments listed at Week 10.

19 APPENDIX B – INVESTIGATOR'S GLOBAL ASSESSMENT

Score	Grade	Definition
0	Clear	No evidence of disease with the exception of residual pigment changes and/or xerosis
1	Almost clear	Perceptible erythema, papulation/infiltration
2	Mild	Mild erythema, papulation/infiltration
3	Moderate	Moderate erythema, papulation/infiltration
4	Severe	Severe erythema, papulation/infiltration
5	Very Severe	Severe erythema, papulation/infiltration with oozing/crusting

20 APPENDIX C - Eczema Area and Severity Index (EASI)

Four anatomic sites – head, upper extremities, trunk and lower extremities – are assessed for erythema, induration (papules), excoriation and lichenification as seen on the day of the examination. The severity of each sign is assessed using a 4-point scale:

- 0 = No symptoms
- 1 = Slight
- 2 = Moderate
- 3 = Marked

The area affected by atopic dermatitis within a given anatomic site is estimated as a percentage of the total area of that anatomic site and assigned a numerical value according to the degree of atopic dermatitis involvement as follows:

- 0 = no involvement
- 1 = < 10 %
- 2 = 10 to < 30%
- 3 = 30 to < 50%
- 4 = 50 to < 70%
- 5 = 70 to < 90%
- 6 = 90 to 100 %

The EASI score is obtained by using the formula

$$EASI = 0.1 (E_h + I_h + Ex_h + L_h) A_h + 0.2 (E_u + I_u + Ex_u + Ex_u) A_u + 0.3 (E_t + I_t + Ex_t + Ex_t) At + 0.4 (E_l + I_l + Ex_l + Ex_l) A_l$$

Where E, I, Ex, L and A denote erythema, induration, excoriation, lichenification and area, respectively, and h, u, t, and l denote head, upper extremities, trunk, and lower extremities, respectively.

21 APPENDIX D - SCORing Atopic Dermatitis (SCORAD)

Six items (erythema, edema/papulation, oozing/crusts, excoriation, lichenification, and dryness) are selected to evaluate the AD severity. The intensity of each item is graded using a 4-point scale:

- 0 = No symptoms
- 1 = Mild
- 2 = Moderate
- 3 = Severe

The area chosen for grading must be representative (average intensity) for each item. The individual intensity ratings for each item will then be added (ranging from 0-18) and multiplied by 3.5, giving a maximal score of 63.

The overall BSA affected by AD is evaluated (from 0 to 100%) and divided by 5. One patient's palm represents 1% of his/her total BSA. The maximum is 20.

Subjective items include loss of sleep and the occurrence of pruritus. These are evaluated by asking patients to indicate on the 10-cm scale (0-10) of the assessment form the point corresponding to the average value for the last three days/nights. The combined maximum score of these two is 20.

The sum of the above measures represents the SCORAD which can vary from 0 to 103. If the subjective scores of pruritus and loss of sleep are excluded, the SCORAD becomes objective SCORAD (score range 0-83)

22 APPENDIX E - Patient-Oriented Eczema Measure (POEM)

Patient ID #: ___ ___ - ___ ___ ___ Patient Initials: ___ ___ ___

Visit Day: _____ Visit Date (dd-mmm-yyyy):_____

Please circle one response for each of the seven questions below about your eczema. Please leave blank any questions you feel unable to answer.

1. Over the last week, on how many days has your skin been itchy because of your eczema?

No days 1-2 days 3-4 days 5-6 days Every day

2. Over the last week, on how many nights has your sleep been disturbed because of your eczema?

No days 1-2 days 3-4 days 5-6 days Every day

3. Over the last week, on how many days has your skin been bleeding because of your eczema?

No days 1-2 days 3-4 days 5-6 days Every day

4. Over the last week, on how many days has your skin been weeping or oozing clear fluid because of your eczema?

No days 1-2 days 3-4 days 5-6 days Every day

5. Over the last week, on how many days has your skin been cracked because of your eczema?

No days 1-2 days 3-4 days 5-6 days Every day

6. Over the last week, on how many days has your skin been flaking off because of your eczema?

No days 1-2 days 3-4 days 5-6 days Every day

7. Over the last week, on how many days has your skin felt dry or rough because of your eczema?

No days 1-2 days 3-4 days 5-6 days Every day

23 APPENDIX F – Dermatology Life Quality Index (DLQI)

Patient ID #: ___ ___ - ___ ___ ___ Patient Initials: ___ ___ ___

Visit Day: _____ Visit Date (dd-mmm-yyyy):_____

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

1.	Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **yard?**	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐

7.	Over the last week, has your skin prevented you from **working** or **studying**?	yes no	☐ ☐	Not relevant ☐
	If "No", over the last week how much has your skin been a problem at **work** or **studying**?	A lot A little Not at all	☐ ☐ ☐	
8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
10	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐

Please check you have answered EVERY question. Thank you.

24 APPENDIX G - Diagnostic Criteria for Atopic Dermatitis

Per Inclusion Criterion 2, a subject is to have a clinical diagnosis of atopic dermatitis according to the criteria of Hanifin and Rajka (31). The criteria go as follows:

Major Criteria (must have at least three)
Pruritus
Typical morphology and distribution:
Adults: flexural lichenification or linearity
Children and infants: involvement of facial and extensor surfaces
Chronic or relapsing dermatitis
Personal or family history of atopy

Minor Criteria (must have at least three)
Xerosis
Icthyosis/keratosis pilaris/palmer hyperlinearity
Immediate (type 1) skin test reactivity
Elevated serum IgE
Early age at onset
Tendency to skin infections (Staphylococcus aureus, herpes simplex)/impaired cellular immunity
Hand/foot dermatitis
Nipple eczema
Conjunctivitis
Dennie-Morgan fold
Keratoconus
Anterior subcapsular cataracts
Orbital darkening
Facial pallor/erythema
Pityriasis alba
Anterior neck folds
Itch when sweating
Intolerance to wool and lipid solvents
Perifollicular accentuation
Food intolerance
Course influenced by environmental/emotional factors
White demographic/delayed blanch