A Randomised, Double-blind, Placebo-controlled Study to Assess the Efficacy and Safety of Orally Administered DS107 in Adult Patients with Moderate to Severe Atopic Dermatitis

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Table of Contents

LIST OF FIGURES

LIST OF TABLES

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, applicable country regulations, the International Conference on Harmonization (ICH) Good Clinical Practices Guidelines and the Declaration of Helsinki.

SPONSOR:

Signature: **Date:**

Dr. Markus Weissbach
Chief Medical Officer, DS Biopharma

CLINICAL EXPERT:

Signature: **Date:**

Prof. Emma Guttman-Yassky
Prof of Dermatology at Icahn School of Medicine at Mount Sinai

STATISTICIAN:

Signature: **Date:**

Winfried Koch
Statistical Consultant, BDS Koch

PRINCIPAL SITE 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, Independent Ethics Committee (IEC) procedures, instructions from DS Biopharma representatives, the Declaration of Helsinki, International Conference on Harmonization (ICH) Good Clinical Practices Guidelines, and national/local regulations governing the conduct of clinical studies.

The signature also confirms that the Investigator agrees that the results of this study may be used for submission to national and/or international registration and supervising authorities. The authorities will be notified of the Investigators name, address, qualifications and extent of involvement.

PROTOCOL SYNOPSIS

STUDY TITLE:	A Randomised, Double-blind, Placebo-controlled Study to Assess the Efficacy and Safety of Orally Administered DS107 in Adult Patients with Moderate to Severe Atopic Dermatitis
SHORT TITLE:	Efficacy and Safety of Orally Administered DS107 in Adult Patients with Moderate to Severe Atopic Dermatitis
PHASE:	II
STUDY DURATION:	20 weeks (Treatment Duration: 16 weeks)
INVESTIGATIONAL PRODUCT:	DS107 Capsules Placebo
OBJECTIVE:	*Efficacy Objective:* • To compare the efficacy of orally administered DS107 versus placebo, in the treatment of adult patients with moderate to severe Atopic Dermatitis (AD). *Safety Objective:* • To assess the safety of orally administered DS107 versus placebo, in adult patients with moderate to severe AD.
PRIMARY ENDPOINTS:	• Proportion of patients achieving a vIGA-AD™ score of 0 (clear) or 1 (almost clear) and a decrease of at least 2 points in vIGA-AD™ in treated population compared to placebo population from baseline at Week 16. • Proportion of patients achieving EASI-75 (≥75% improvement from baseline) in treated population compared to placebo population at Week 16. ***Note:*** *Each of the independent primary endpoints will be analysed separately. Success in either of the primary endpoints denotes successful proof of efficacy.*
SECONDARY ENDPOINTS:	• Proportion of patients achieving a vIGA-AD™ score of 0 (clear) or 1 (almost clear) and a decrease of at least 2 points in vIGA-AD™ in treated population compared to placebo population from baseline to Week 4, 8, 12, 18 and 20 and the change in proportion of patients from Week 16 to Week 18 and 20. • Proportion of patients achieving EASI-75 (≥75% improvement from baseline) in treated population compared to placebo population at Week 4, 8, 12, 18 and 20 and the change in proportion of patients from Week 16 to Week 18 and 20.

	• Change from baseline in vIGA-AD™ score in treated population compared to placebo population to Week 4, 8, 12, 16, 18 and 20, and from Week 16 to Week 18 and 20. • Change from baseline in EASI in treated population compared to placebo population to Week 4, 8, 12, 16, 18 and 20, and from Week 16 to Week 18 and 20. • Proportion of patients achieving a decrease of at least 4 points in worst itch NRS in treated population compared to placebo population from baseline to Week 4, 8, 12, 16, 18 and 20 and the change in proportion of patients from Week 16 to Week 18 and 20. • Proportion of patients achieving a decrease of at least 3 points in worst itch NRS in treated population compared to placebo population from baseline to Week 4, 8, 12, 16, 18 and 20 and the change in proportion of patients from Week 16 to Week 18 and 20. • Change from baseline in worst itch NRS in treated population compared to placebo population to Week 4, 8, 12, 16, 18 and 20, and from Week 16 to Week 18 and 20. • Proportion of patients achieving EASI-50 (≥50% improvement from baseline) in treated population compared to placebo population at Week 4, 8, 12, 16, 18 and 20 and the change in proportion of patients from Week 16 to Week 18 and 20. • Change from baseline in the Body Surface Area (BSA) affected by AD in treated population compared to placebo population to Week 4, 8, 12, 16, 18 and 20, and from Week 16 to Week 18 and 20. • Change from baseline in the SCORing Atopic Dermatitis (SCORAD) score in treated population compared to placebo population to Week 4, 8, 12, 16, 18 and 20, and from Week 16 to Week 18 and 20. • Incidence of treatment emergent adverse events (TEAEs) and serious adverse events (SAEs)
EXPLORATORY ENDPOINTS:	• Proportion of patients achieving a decrease of at least 2 points in vIGA-AD™ in treated population compared to placebo population from baseline to Week 4, 8, 12, 16, 18 and 20 and the change in proportion of patients from Week 16 to Week 18 and 20. • Change from baseline in the Dermatology Life Quality Index (DLQI) score in treated population compared to placebo population to Week 4, 8, 12, 16, 18 and 20, and from Week 16 to Week 18 and 20.

	• Change from baseline in the Patient Orientated Eczema Measure (POEM) score in treated population compared to placebo population to Week 4, 8, 12, 16, 18 and 20, and from Week 16 to Week 18 and 20. • Change in sleep quality assessment (Athens Insomnia Scale) in treated population compared to placebo population from baseline to Week 4, 8, 12, 16, 18 and 20, and from Week 16 to Week 18 and 20. • Change from baseline in the Patient-Oriented SCORAD (PO-SCORAD) score in treated population compared to placebo population to Week 4, 8, 12, 16, 18 and 20, and from Week 16 to Week 18 and 20. • Trough plasma levels in treated population compared to placebo population at Baseline/Day 0, Week 4, Week 8 and Week 16. • Determination of AD biomarkers in treated population compared to placebo population at Baseline/Day 0 and Week 16.
SAFETY VARIABLES:	• Adverse event (AE) and serious adverse event (SAE) frequency and severity. • Safety laboratory parameters (haematology, clinical chemistry). • Clinical safety examinations (vital signs, physical examination).
STUDY DESIGN:	This is a multicenter, double-blind, placebo controlled, 2-arm, Phase II study with 16 weeks of active treatment and a 4 week follow up period. Patients will be randomized (1:1) at baseline visit to either receive 2g DS107 once daily or placebo once daily for 16 weeks.
TOTAL NUMBER OF RANDOMISED PATIENTS:	220
STUDY POPULATION:	
INCLUSION CRITERIA:	1. Patients with a clinically confirmed diagnosis of active AD according to the American Academy of Dermatology Consensus Criteria that has been present for at least 6 months before the screening visit. 2. Patients with moderate to severe AD at baseline as defined by a vIGA-AD™ score of 3 or 4 at baseline.

	3. Patients with an EASI score of ≥16 at screening and baseline. 4. Patients with AD covering a minimum 10% of the body surface area (BSA) at baseline. 5. Patients with a worst itch NRS score in a day of ≥4 (on 11 point NRS) at the screening and baseline visits. 6. Patients whose pre-study clinical laboratory findings do not interfere with their participation in the study, in the opinion of the Investigator. 7. Patients who are able and willing to stop all current treatments for AD throughout the study (except for allowed emollients). 8. Patients who are on a stable dose of a bland emollient for at least 7 days prior to baseline. ***Note:*** *Patients who have been on a stable emollient with an active ingredient (for example urea, ceramide and hyaluronic acid) for at least 12 weeks prior to screening and are otherwise eligible may continue using their pre-existing emollients, if deemed appropriate by the investigator and if they are willing and able to continue using the same stable emollient for the duration of the study.* 9. Male or female patients aged 18 years and older on the day of signing the informed consent form (ICF). 10. Female patients and male patients with female partners of child bearing potential must use highly effective birth control methods or have a sterilised partner for the duration of the study. ***Note:*** • *Highly effective birth control methods are defined as methods that can achieve a failure rate of less than 1% per year when used consistently and correctly. Such methods include systemic hormonal contraceptives, intrauterine device or sexual abstinence.* • *Hormonal contraceptives must be on a stable dose for at least one month before baseline.* • *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.*

	11. Recent history (within 6 months before the screening visit) of inadequate response to treatment with topical medications or for whom topical treatments are otherwise medically inadvisable (e.g., because of important side effects or safety risks). ***Note**:* • *Inadequate response is defined as failure to achieve and maintain remission or a low disease activity state (comparable to vIGA-AD™ 0=clear to 2=mild) despite treatment with a daily regimen of topical corticosteroids (TCS) of medium to higher potency (± topical calcineurin inhibitors (TCI) as appropriate), applied for at least 28 days or for the maximum duration recommended by the product prescribing information (e.g., 14 days for super-potent TCS), whichever is shorter.* • *Patients with documented systemic treatment for AD (for example systemic corticosteroids, cyclosporine) in the past 6 months are also considered as inadequate responders to topical treatments and are potentially eligible for treatment with DS107 after appropriate washout.* • *Important side effects or safety risks are those that outweigh the potential treatment benefits and include intolerance to treatment, hypersensitivity reactions, significant skin atrophy, and systemic effects, as assessed by the Investigator or by the patient's treating physician.* 12. Patients who are able to communicate well with the Investigator, to understand and comply with the requirements of the study, and understand and sign the written informed consent prior to initiation of any study specific activities or procedures.
EXCLUSION CRITERIA:	1. Patients with other skin conditions that might interfere with AD diagnosis and/or evaluation (such as psoriasis or current active viral, bacterial and fungal topical skin infections) as assessed by the Investigator. 2. Patients who have used systemic treatments that could affect AD less than 4 weeks prior to Baseline Visit (Day 0), e.g. retinoids, methotrexate, cyclosporine, hydroxycarbamide (hydroxyurea), azathioprine and oral/injectable corticosteroids. Intranasal corticosteroids and inhaled corticosteroids for stable medical conditions are allowed. 3. Patients with previous exposure to DS107. 4. Patients who have used any topical medicated treatment for AD (except for emollients) two weeks prior to start of treatment/Baseline (Day 0) including but not limited to,

	topical corticosteroids, calcineurin inhibitors, tars, bleach, antimicrobials and bleach baths. 5. Patients who use emollients containing urea, ceramides or hyaluronic acid less than 12 weeks prior to Baseline (Day 0). 6. Patients who have had excessive sun exposure, have used tanning booths or other ultraviolet (UV) light sources four weeks prior to Baseline (Day 0) and/or are planning a trip to a sunny climate or to use tanning booths or other UV sources between screening and follow-up visits. 7. Patients who have a history of hypersensitivity to any substance in DS107 or placebo capsules. 8. Patients who have a history of hypersensitivity to soy beans or soy lecithin. 9. Patients who have a white cell count or differential white cell count outside of the normal reference range at screening. ***Note:*** *For patients with a mild leucocytosis or leucopenia and otherwise a normal white cell blood count may be enrolled following consultation with the medical monitor by the investigator.* 10. Patients who have 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. 11. Patients who have a clinically significant impairment of renal or hepatic function. 12. Patients with significant uncontrolled cardiovascular, neurologic, malignant, psychiatric, respiratory or hypertensive disease, as well as uncontrolled diabetes and flouride arthritis or any other illness that, in the opinion of the Investigator, is likely to interfere with completion of the study. 13. Patients with active infectious diseases (e.g., hepatitis B, hepatitis C or advanced disease secondary to infection with human immunodeficiency virus). 14. Patients with a history of clinically significant drug or alcohol abuse in the opinion of the Investigator in the last year prior to Baseline (Day 0). 15. Patients who have participated in any other clinical study with an investigational drug within 3 months before the first day of administration of study treatment. 16. Patients who have had treatment with biologics as follows:

	a. Any cell-depleting agents including but not limited to rituximab: within 6 months before the screening visit, or until lymphocyte count returns to normal, whichever is longer, b. Other biologics influencing cell proliferation: within 6 months before the screening visit. c. Dupilumab or other monoclonal antibodies within 5 half-lives (if known) or 16 weeks prior to baseline visit, whichever is longer 17. Patients who are pregnant, planning pregnancy, breastfeeding and/or are unwilling to use adequate contraception (as specified in Inclusion Criterion 10) during the trial. 18. Patients, in the opinion of the Investigator, not suitable to participate in the study.
TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION:	DS107 capsules will be provided as a capsule containing 500mg DGLA per unit dose. Placebo will be provided as a matching capsule. This study will involve one dose level of DS107 for 16 weeks (2g DS107 OD = 4 capsules) or placebo (OD = 4 matching capsules). Investigational Medicinal Product (IMP) will be administered approximately 2 hours after food consumption at the same time each day. Patients will be instructed to not consume food for approximately 1 hour after IMP administration
EVALUATION CRITERIA: SAFETY	• Physical examination • Vital signs, including blood pressure (BP), pulse and temperature • Clinical laboratory tests (haematology, biochemistry) • Pregnancy test for females of child bearing potential • AEs • Concomitant medications (CMs)
BEHAVIOURAL RESTRICTIONS	• Patients will be asked to refrain from any travel to sunny climates or use of tanning equipment, saunas and swimming throughout the duration of the study. • Extensive UV exposure or UV-B devices within four weeks of the trial and during the trial.
RESCUE TREATMENT	If medically necessary (i.e., to control intolerable AD symptoms), rescue treatment for AD may be provided to study patients at the discretion of the investigator. If possible, investigators should avoid administration of rescue treatments before Week 4 due to the expected time to onset of treatment-response following DS107 treatment.

	For the purpose of efficacy analysis, patients who receive rescue treatment during the study treatment period will be considered treatment failures from the time rescue treatment is used. Topical corticosteroids or calcineurin inhibitors may be used for rescue, but should be reserved for problem areas only, eg, face, neck, intertriginous and genital areas, etc. If a patient receives rescue treatment with systemic corticosteroids or non-steroidal systemic immunosuppressive drugs (cyclosporine, methotrexate, mycophenolate mofetil, azathioprine, etc.) study treatment will be immediately discontinued. Investigators should make every attempt to conduct efficacy and safety assessments (eg, disease severity scores, safety labs) immediately before administering any rescue treatment.
STATISTICAL ANALYSIS	The primary analysis will be conducted in the full analysis set (FAS) population. A longitudinal mixed model for binary outcomes (GENMOD) will be used to separately analyze the binary primary and secondary efficacy endpoints at Week 16. Change from baseline for secondary and exploratory endpoints (vIGA-AD™, EASI, NRS, BSA, SCORAD, DLQI, POEM, AIS and PO-SCORAD) will be analysed using mixed model with repeated measures (MMRM). The models will include Treatment Arm as a factor and respective baseline value as a covariate, with the treatment-by-visit interaction term as a random effect to account for missing data at Week 16. Sensitivity analyses will be performed to assess the robustness of the Missing at Random (MAR) assumptions that support the GENMOD methods above for imputing missing data.
SPONSOR:	DS Biopharma

LIST OF ABBREVIATIONS

15-HETrE	15-hydroxyeicosatrienoic acid
AD	Atopic Dermatitis
AE	Adverse Event
AIS	Athens Insomnia Scale
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
API	Active Pharmaceutical Ingredient
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BD	Bis Die (Twice Daily)
BDRM	Blind Data Review Meeting
BMI	Body Mass Index
BP	Blood Pressure
BPM	Beats Per Minute
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CM	Concomitant Medication
C_{max}	Maximum Concentration
CMH	Cochran-Mantel-Haenszel test
COX	Cyclooxygenase
CPK	Creatinine Phosphokinase
CRA	Clinical Research Associate
CRO	Contract Research Organisation
CRF	Case Report Form
CRL	Charles River Laboratories
CsA	Cyclosporin A
CTA	Clinical Trials Agreement
DGLA	Dihomo-Gamma-Linolenic Acid
DLQI	Dermatology Life Quality Index
DM	Data Manager
EASI	Eczema Area and Severity Index

EC	Ethics Committee
EDC	Electronic Data Capture
ECG	Electrocardiography
eCRF	electronic Case Report Form
ET	Early Termination
EU	European Union
FAS	Full Set Analysis
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GLMM	Generalised Linear Mixed Model
ICF	Informed Consent Form
IEC	Independent Ethics Committee
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IFN-γ	Interferon-Gamma
IGA	Investigator Global Assessment
IgE	Immunoglobulin E
IL	Interleukin
IMP	Investigational Medicinal Product
ISF	Investigator Site File
IWRS	Interactive Web Response System
kg	Kilogram
LDH	Lactate Dehydrogenase
LSLV	Last Subject Last Visit
MAR	Missing at Random
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model with Repeated Measures
NOAEL	No Observed Adverse Event Limit
NRS	Numeric Rating Scale
OD	Once Daily
OTC	Over The Counter

PDE4	Phosphodiesterase 4
PGD_1	Prostaglandin D1
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PI	Principal Investigator
PIS	Patient Information Sheet
PK	Pharmacokinetics
POEM	Patient Orientated Eczema Measure
PO-SCORAD	Patient Oriented Scoring of Atopic Dermatitis
PP	Per Population
PPS	Per Protocol Set
PUVA	Psoralen & Ultraviolet A
PV CRO	Pharmacovigilance Contract Research Organisation
SAE	Serious Adverse Event
SAS	Safety Analysis Set
SAP	Statistical Analysis Plan
SCORAD	Scoring of Atopic Dermatitis
SDV	Source Data Verification
SOP	Standard Operating Procedure
SPC	Summary of Products Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TCI	Topical Calcineurin Inhibitors
TCS	Topical Corticosteroids
TNF-α	Tumor Necrosis Factor-Alpha
UAE	Unexpected Adverse Event
US	United States
UV-A/B	Ultraviolet-A/B
VAS	Visual Analogue Scale
vIGA-AD™	Validated Investigator Global Assessment Scale for Atopic Dermatitis.

1 INTRODUCTION

1.1 Therapeutic Area and Disease Background

AD is a common chronic inflammatory skin disease that affects 15 to 30% of children and 2 to 10% of adults (Williams and Flohr 2006, Silverberg *et al.* 2013).

AD progresses with erratic and often unpredictable flare-ups/exacerbations and is characterized by extremely dry, itchy skin which leads to scratching, resulting in further irritation and inflammation. As the skin loses moisture from the epidermal layer, it becomes increasingly dry and may begin to crack, weep, crust, and scale. This damage to the integrity of the skin renders it less protective and more prone to infection and environment influences (allergens and irritants).

AD demonstrates specific age-dependent manifestations. Adult patients in the chronic phase demonstrate lichenified lesions which are associated with dryness, erythema and pruritus. The lesions most commonly occur on flexural folds; the face, the neck, the upper arms and back, and the dorsa of the hands, feet, fingers and toes. Adult patients may also develop exudation and crusting as a result of bacterial infections (Schultz-Larsen & Hanifin 2002).

In all stages of AD, pruritus that continues throughout the day and worsens at night, causes sleep loss, irritability and generalised stress, which substantially impairs the patient's quality of life (Simpson 2010, Suarez *et al.* 2012).

The mechanisms underlying the pathogenesis of AD remain unclear. Many studies have demonstrated the involvement of genetic predisposition, immune dysfunction, emotional and environmental stimuli and epidermal barrier dysfunction in its development and progression. It is well recognised however that IgE-mediated reactions (Bos *et al.* 1994) and elevated eosinophil levels (Kapp 1993) are involved in causing inflammation associated with AD. Additionally the overactiveation of acute, allergic Th2 response results in the secretion of pro-inflammatory mediators. The chronic phase is characterised by a predominantly Th1 response as the disease progresses. The multifactorial pathology likely accounts for the heterogeneity associated with AD onset and severity and suggests a requirement for a multimodal therapeutic approach (Leung & Guttman-Yassky 2014).

DS107 is being studied in oral (capsule) and topical (cream) formulation.

DS107 capsules, contain >95% pure dihomo-γ-linoleic acid (DGLA) as active pharmaceutical ingredient, has been developed for the treatment of AD due to its potent antibacterial and anti-inflammatory properties. The multimodal mechanism of action of both topical and DS107 capsules has been shown to improve the signs and symptoms of AD including pruritus and patient quality of life in two previous proof-of-concept Phase 2a studies.

1.2 Standard Treatment

Currently, there is no treatment available to cure AD. Generally, symptomatic repeated treatments are necessary to achieve a stable state in which flare-ups are controlled and the number of flares reduced.

First-line therapy includes topical corticosteroids during an exacerbation and long-term emollient use thereafter. Other available treatment for AD includes topical calcineurin inhibitors, phototherapy, and systemic corticosteroid therapy or Cyclosporin A (CsA) in more difficult cases (Eichenfield et al. 2014).

Emollients have long been used to improve epidermal barrier function and alleviate dry skin in patients with AD. However, emollients alone rarely control AD unless it is of mild severity. Topical corticosteroids have been the pillar of medicated therapy for AD since their introduction nearly 50 years ago. However, the common side effects (skin atrophy, striae, burning, pruritus, and folliculitis)

associated with the use of corticosteroids mean that they can only be used as a short-term therapy (Eichenfield et al. 2014).

The introduction of topical calcineurin inhibitors represented the first new class of medication approved for the treatment of AD since topical corticosteroids. Topical calcineurin inhibitors pimecrolimus (Elidel®) and tacrolimus (Protopic®) are immunomodulating agents that act locally on T-cells by suppressing transcription and release of pro-inflammatory cytokines (IL-2, IL-3, IL-4, IL-5, IFN-γ, TNF-α) (Gutfreund et al. 2013). Inhibiting cytokine production leads to decreased inflammation and serves to block T-cell activation which can trigger and maintain skin inflammation (Simpson 2010). These agents have been shown to reduce the extent, severity, and symptoms of AD in adults and children; however, they can cause skin irritation at the site of the application. Common local side effects include burning sensations, itching, erythema, and infection (Ashcroft et al. 2005).

Phototherapy can be a useful adjunct in the treatment of AD (Reynolds et al. 2001). However, it can cause short-term adverse effects including erythema, skin pain, itching, and pigmentation as well as long-term effects including premature skin aging and cutaneous malignant diseases (Leung & Bieber 2003).

The use of systemic treatments to manage the symptoms of AD has been rare. Oral corticosteroids, immunosuppressants, antifolates, and antihistamines have been used in the past with moderate efficacy and poor safety profiles resulting in a short treatment window (Eichenfield et al. 2014).

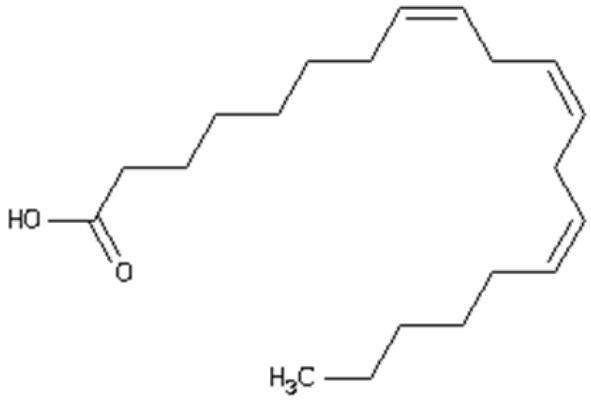
Recent regulatory approvals of the monoclonal antibody dupilumab, an IL-4Rα antagonist that inhibits the signalling of Th2 cytokines IL-4 and IL-13; and crisaborole a topically applied PDE4 inhibitor have introduced two new treatment options for AD.

Despite recent advances, there is still an unmet need for safe and effective oral treatment options for patients with moderate to severe AD.

1.3 Drug Class

DS107 capsules contain the active pharmaceutical ingredient (API) DGLA a long-chain polyunsaturated fatty acid endogenously present in the body.

Figure 1: Structure of DGLA



1.4 Preclinical Pharmacology

Numerous preclinical studies have been performed to determine the mechanisms of action of DS107 in inflammatory skin diseases including AD. The results of the studies have highlighted a multi-modal

mechanism of action in which DS107 exerts its therapeutic effect, including direct anti-bacterial mechanisms as well as direct and indirect anti-inflammatory mechanisms.

The effect of DS107 on the release of proinflammatory cytokines from human monocytes has been studied and shows that DS107 significantly reduces the secretion of IL-1β and IL-8 from triggered monocytes. Both IL-1β and IL-8 play an important role in the pathogenesis of AD. Inhibition of these pro-inflammatory pathways with DS107 capsules may provide significant improvements in the clinical manifestations of AD. It has been shown that metabolism of DGLA via COX-1 and COX-2 pathways results in the production of potent anti-inflammatory eicosanoids such as prostaglandins (specifically PGD_1) and thromboxanes (Kawashima *et al.* 2008; Amagai *et al.* 2015). Additionally, lipoxygenation of DGLA results in the production of monohydroxy fatty acid 15-hydroxyeicosatrienoic acid (15-HETrE) which has shown potent anti-inflammatory properties (Iverson *et al.* 1992).

In addition to anti-inflammatory mechanisms, DS107 significantly inhibits the growth of *Staphylococcus aureus* and *Propionibacterium acnes* and also has direct bactericidal activity against both (Desbois & Lawlor 2013).

DGLA has been reported to supress acute and chronic inflammation in whole preclinical mouse studies. Oral administration of up to 600 mg/kg DGLA has shown dose dependent improvements in severity of skin lesions in animal models of AD. DGLA treatment is correlated with decreased plasma total IgE concentrations which may contribute to resolving the AD lesions (Kawashima *et al.* 2008).

In the same study DGLA also significantly decreases the number of scratch events and duration of scratching in animal models of AD (Kawashima *et al.* 2008; Amagai *et al.* 2015). The improvement in clinical scores and pruritus has been associated with the generation of PGD_1 via DGLA metabolism (Amagai *et al.* 2015).

1.5 Toxicology

Oral Toxicology

A 13-week oral study in rats using DGLA did not show any significant treatment-related adverse events and so the No Observed Adverse Event Limit (NOAEL) was set at 2000 mg/kg per day. Read-across from linoleic acid would suggest that repeated exposure to DS107 capsules at levels found in this product is unlikely to cause adverse effects (Kawashima *et al.* 2009).

DS107 was very well tolerated in rats given up to 2,000 mg/kg/day for up to 26 weeks. Safety margins at the NOAEL in this study (2,000 mg/kg/day) were very large (i.e., 18- to 30-fold and 11- to 24-fold that seen in human subjects given 4g/day DS107 when based on unesterified DGLA for AUC and C_{max}, respectively). In dogs, a pattern of dose-related, intermittent/sporadic, limb withdrawal and/or limited limb usage was seen at repeated doses >150 mg/kg/day in the 39-week study. This effect was completely reversible upon cessation of dosing. There was no correlative finding, including histopathology at the affected joints that could explain this effect. The NOAEL for this effect was 50 mg/kg/day, which corresponded to a safety margin of 1.1- to 1.6-fold and 3.1- to 3.7-fold greater than that seen in human subjects given 4g/day DS107 for AUC and C_{max}, respectively. Lack of similar DS107 related effects on mobility in rats (doses up to 2g/kg/day for 26 weeks) and humans (doses up to 4g/day for 8 weeks) suggests the effect in dogs is species specific.

Topical Toxicology

Local tolerance has been assessed in several non-clinical studies, the most relevant of which is the GLP-compliant toxicity study, conducted by Charles River Laboratories (CRL Study-521831, 2012), in which DS107 cream was applied topically daily for 13 weeks to minipigs. Reaction to treatment was seen at the administration sites as very slight to well-defined erythema with red spots on or outside the edges of sites and dry flaky skin in some cases. Reactions were mild to moderate and 91-day treatments were completed for most animals. All findings were reversible. In this study there were no histopathology findings at main study kill (Day 92) attributed to treatment. Microscopic findings at the

different treatment sites were considered to have arisen spontaneously and/or to have been associated with the administration procedure. Other microscopic findings observed were considered incidental, of the nature commonly observed in this strain and age of minipig. They were of similar incidence and/or severity in control and treated animals and were therefore considered unrelated to administration of DS107 Cream. Toxicokinetic analysis of plasma samples taken from the minipigs over the 13-week treatment period did not show any significant systemic exposure of DS107 following topical administration.

Mutagenicity

Previously, DGLA exhibited no mutagenicity in an Ames test regardless of the presence or absence of S9 mix (Kawashima *et al.* 2009). A recent DS Biopharma sponsored Ames test showed no substantial increases in revertant colony numbers with any of the tester strains following exposure to DS107, at any dose level, in the presence or absence of S9 mix. Therefore, DS107 was considered to be negative for the induction of mutagenicity in this *in vitro* assay when tested in accordance with regulatory guidelines. Furthermore, in a mouse lymphoma assay sponsored by the company, DS107 was not associated with genotoxicity in the presence or absence of metabolic activation.

Conclusion

No undue toxicological hazard or risk for patients treated with DS107 capsules has been identified in a battery of non-clinical toxicology studies. 26-week rat and 39-week dog chronic toxicity studies with greater systemic exposure at the determined NOAEL than human subjects receiving doses of oral DS107 capsules of up to 4g daily are considered adequate to support further clinical trials of greater than 6 months duration (per ICH M3 (R2)) for subjects given daily oral DS107 doses of up to 4g daily.

1.6 Previous Clinical Studies with DS107

DS107 is being studied in oral (capsule) and topical (cream) formulation. Topical DS107 has been administered to 524 subjects during the course of one Phase 1 trial (DS107E-01) and five Phase 2 trials (DS107E-02, DS107E-03, DS107E-04, DS107E-05, DS107E-06). In addition, three well-controlled clinical studies have been conducted to assess the safety and efficacy of DS107 capsules. To date, DS107 capsules has been administered to 304 healthy volunteers/patients during the course of one Phase 1 trial (DS107G-01) and two Phase 2 trials (DS107G-02 & DS107G-03) for AD. Up to 4g DS107 capsules has been clinically tested and is well tolerated in healthy volunteers and patients with moderate to severe AD. Below are a list of the completed studies which utilise DS107 capsules.

Table 1: Summary of DS107 Capsules Use in Human Healthy Volunteers/Patients

DS107G-01 A Randomised, Double-Blind, Placebo-Controlled, Single-Ascending Dose and Multiple Dose Phase 1 Study to Assess the Safety, Pharmacokinetics and Effect of Food on Orally Administered DS107 in Healthy Subjects.					
Phase	**Duration**	**Indication**	**IMP Concentration**	**# Healthy Volunteers**	**Status**
1 (safety)	Single Dose and Multiple Dose (28 days)	Healthy Volunteers	500mg 1g 2g 4g	48	Completed
DS107G-02 A Randomised, Double-blind, Placebo-Controlled, Phase 2 Study to Assess the Efficacy and Safety of Orally Administered DS107 to Patients with Moderate to Severe AD					

Phase	Duration	Indication	IMP Concentration.	# Patients	Status
2a (safety & efficacy)	8 Weeks	Moderate to Severe AD	2g	102	Completed
DS107G-03 A Randomised, Double-blind, Placebo-controlled, Phase 2b Study to Assess the Efficacy and Safety of Orally Administered DS107 in Patients with Moderate to Severe Atopic Dermatitis					
Phase	**Duration**	**Indication**	**IMP Concentration.**	**# Patients**	**Status**
2b (safety & efficacy)	8 Weeks	Moderate to Severe AD	1g 2g	321	Completed

DS107 Capsules Phase 1 Study (DS107G-01)

This study was a randomised, double-blind, placebo-controlled, single-ascending dose and multiple dose Phase 1 study to assess the safety, pharmacokinetics and effect of food on orally administered DS107 in 48 healthy volunteers. In the single dose part of the study healthy volunteers were randomised to 4 cohorts and administered either 500mg, 1g, 2g or 4g DS107 capsules. In the multiple dose of the study healthy volunteers were randomised to 2 cohorts and administered either 2g or 4g DS107 capsules once daily for 28 days.

Under fasted conditions, both free and total DGLA increased in a linear manner following oral administration. Although not evaluated statistically, administration of a single 1g dose of DS107 capsules under fasted conditions resulted in an approximately 50% higher rate.

There were no deaths, Serious Adverse Events (SAEs), discontinuations due to AEs, considered to be not recovered/resolved, or AEs considered to be definitely related to study drug in this study. The most common AEs were gastrointestinal in nature which were of relatively short duration and resolved without intervention.

Overall, DS107 capsules administered to 48 healthy volunteers as a single 500mg, 1g, 2g, or 4g dose under fasted conditions; as a single 1g dose under fed conditions; and as multiple 2g and 4g doses taken once daily for 28 consecutive days was well tolerated.

DS107 Capsules Phase 2a Study (DS107G-02)

This 8 week study was a randomized, placebo-controlled, double-blind, multi-centre Phase 2a trial to investigate the efficacy, safety, tolerability and bioavailability of 2g DS107 administered orally once daily versus 2g placebo administered orally once daily in adult patients with moderate to severe AD. The primary efficacy endpoint was defined as the proportion of patients achieving an Investigator Global Assessment (IGA) of 0 (clear) or 1 (almost clear) and a decrease of at least two points in IGA at Week 8. Secondary efficacy variables included IGA measurements, pruritus (obtained from the SCORAD VAS), EASI, BSA, POEM, DLQI and SCORAD.

There was a trend toward a statistically significant higher number of patients who achieved an IGA score of 0 or 1 and a 2 point drop in the DS107 capsules group at Week 8 in comparison to placebo: 11 (21.6%) responders in the DS107 capsules group, and 6 (11.8%) in the placebo group (p-value: 0.057). A similar trend was also observed in the number of patients achieving a decrease of at least 2 points in the IGA score at Week 8 with 14 (27.5%) in the DS107 capsules group and 8 (15.7%) in the placebo group (p-value: 0.065).

Further analysis was performed on the severity groups (moderate and severe/very severe at baseline) comparing the DS107 capsules group to the placebo group in terms of responders, using the Cochran-Mantel-Haenszel (CMH) test stratified for site. The proportion of responders was always greater in the DS107 capsules group compared to the placebo group in both the moderate and the severe/very severe populations.

The proportion of moderate patients achieving an IGA of 0 (clear) or 1 (almost clear) and a decrease in 2 point in IGA score was significantly greater in the DS107 capsules group (8/29 patients, 28%) compared to placebo group (6/38 patients, 16%) in patients with moderate AD at baseline ($p = 0.036$). Similar efficacy trends were observed in the severe/very severe population where 3 out of 22 patients (13%) treated with DS107 capsules met the responder criteria compared to 0 out of 13 patients in the placebo group. Statistical significance could not be achieved due to the low number of patients in each group and lack of primary response in placebo.

The effect of DS107 capsules was consistently higher than placebo for all of the efficacy endpoints evaluated in this study, both investigator scores and patient scores. Pruritus is the most important symptom for patients suffering from AD. It has a significant impact on sleep and quality of life (Hong *et al.* 2011). Pruritus sensation was significantly decreased from Baseline at Week 4 in patients receiving DS107 compared to patients receiving placebo. This difference in pruritus was both statistically and clinically significant as shown by a decrease in pruritus of 39.5% for patients randomized to DS107 and of only 10.05% in patients randomized to placebo at Week 4.

No deaths or SAEs were observed throughout the course of this study. There were no drug related AEs associated with safety lab results, physical exams or vital signs. AEs were mild to moderate and transient. The most common AEs observed in the DS107 group were gastrointestinal in nature. Overall the tolerance of DS107 capsules administered over 8 weeks was acceptable in comparison with placebo and DS107 appears safe and well tolerated.

DS107 Capsules Phase 2b Study (DS107G-03)

This was a randomised, double-blind, placebo-controlled, Phase 2b study to assess the efficacy and safety of 1g or 2g DS107 administered orally once daily versus placebo administered orally once daily in adult patients with moderate to severe AD. The primary efficacy endpoint was defined as the proportion of patients achieving an IGA of 0 (clear) or 1 (almost clear) and a decrease of at least two points in IGA at Week 8. Secondary and exploratory efficacy variables included IGA measurements, pruritus (obtained from the NRS), EASI, BSA, POEM, DLQI, Patient Global Impression of Severity (PGI-S) score and Patient Global Impression of Change (PGI-C) score.

When the data was analyzed by baseline AD severity, a clear trend towards a dose-dependent IGA response was observed in the severe sub-group (n=45). At Week 8, there was a dose-dependent IGA response; more patients in the DS107 treatment groups (2g DS107 – 41.7%, 1g DS107 – 37.5%) than the placebo treated group (25.0%) achieved treatment success.

The trend of improvement displayed no evidence of treatment plateau, suggesting that greater clinically meaningful improvements from baseline could be expected with a larger sample size or if treatment were to be continued for a longer time period. 2g DS107 (50.0%) and 1g DS107 (50.0%) demonstrated a trend towards sustained superiority in IGA response over placebo (33.3%) at Week 10 (Follow-up).

Although most scores and indexes achieved clinically meaningful improvements at Week 8, with improvements at each time point during the study, no statistically significant differences among the treatment groups were observed, with notably high placebo responses across multiple endpoints.

Similar to the primary endpoint, a clear trend towards a dose-dependent improvement in pruritus NRS is observed in the severe sub-group. At Week 8, there was a dose-dependent NRS mean change from baseline; patients in the DS107 treatment groups (2g DS107 – 3.9 point reduction, 1g DS107 – 3.4 point reduction) achieved clinically meaningful and greater changes from baseline than placebo treated patients (2.3 point reduction).

Pharmacodynamics findings from the recent Oral Phase 2b study have helped to elucidate the mechanisms by which DS107 exerts its anti-inflammatory effects. Serum biomarker analysis revealed that DS107 reverses the high-grade systemic immune activation of AD by downregulating cytokines associated with inflammation, immune activation and angiogenesis. Biomarker data indicate that DS107 exerts many of its effects by inhibiting T-cell activation and can potentially be an oral disease modifying agent for AD. The expression of CD40 and other promoters of T-cell activation and differentiation was significantly inhibited. Additionally, multiple markers of fibrosis and cellular proliferation were significantly inhibited by DS107 highlighting its previously undescribed potential to treat fibrotic diseases.

DS107 capsules were well tolerated with no significant differences in reported treatment-emergent adverse events, event severity, or seriousness versus placebo.

Overall, the percentage of patients experiencing at least one AE during their participation in the study was similar among treatment groups (33.7%, 38.9%, and 32.7% for 1 g DS107, 2 g DS107, and placebo patients, respectively). More treated with 2g DS107 experienced at least 1 AE assessed to be related to study drug compared to patients treated with placebo most of which were gastrointestinal and mild/moderate in severity. No other significant differences were noted in occurrence of AEs.

Most AEs were mild or moderate in severity. No deaths occurred in this study. Three SAEs were reported during this study. All were assessed by the reporting Investigator to be severe in intensity and unrelated to study drug. Additionally, all resolved without sequelae.

Topical DS107

Six studies have been completed with DS107 Cream.

A Phase 1 clinical study (DS107E-01) was carried out to investigate the safety and tolerability of topically administered DS107 cream in human volunteers at five dose levels (0.1%, 0.5%, 1%, 2.5% and 5%) applied twice daily for 14 days (with a matched placebo cream).

Topical administration of DS107 cream at dose strengths of 0.1%, 0.5%, 1%, 2.5% and 5% (up to 30 mg topical DGLA/day) had no clinically significant effect on any of the following parameters; vital signs, electrocardiogram (ECG) or laboratory safety parameters; haematology, biochemistry, urinalysis. No serious or non-serious expected or unexpected adverse events related to the IMP were observed. There were no clinically significant abnormalities or changes from baseline values in the local tolerability assessments. There were no clinically significant abnormalities or changes from baseline values in the local tolerability assessments. All patients completed study procedures as per protocol and there were no significant protocol deviations affecting the safe conduct of the study.

Study DS107E-02 was a randomized, double-blind, placebo-controlled Phase 2 study to assess the efficacy and safety of topically applied DS107 cream in patients with mild to moderate AD. Four parallel groups of patients with confirmed AD were investigated in this study to compare three different doses of DS107 cream (0.1%, 1%, and 5%) with placebo over a 28-day treatment period. During the 28 days of treatment, patients liberally applied their assigned treatment to all affected or commonly affected areas twice daily (morning and evening).

DS107 Cream treatment groups in Study DS107E-02 were similar to the vehicle group for number of adverse events, event severity and seriousness. No deaths or SAEs occurred during the study. Except for creatinine phosphokinase (CPK), no large treatment differences were seen in any of the laboratory parameter mean values. The mean values of the vital sign parameters were largely stable across treatment groups. Overall, DS107 cream was well tolerated, with a safety profile similar to the vehicle cream.

Study DS107E-03 was a Phase 2 proof-of-concept study in patients with mild to moderate Acne Vulgaris carried out as a double-blind, randomised study with two active treatment groups of 1% and 5% DS107 and a vehicle group. The study consisted of a washout period (maximum 14 days); a 12-

week treatment period and a 4-week follow-up period. During the 12 weeks of treatment, patients applied the assigned treatment to all affected areas of skin twice daily (morning and evening).

The safety profile of 1% and 5% DS107 Cream in Study DS107E-03 did not significantly differ from the vehicle treatment group. A very low incidence of AEs was reported during the trial, with no significant differences between treatment groups; most of the AEs were of mild intensity. Of these, a minority of cases were assessed as treatment-related. The results of the laboratory and vital sign assessments did not reveal any safety concerns during the study for any treatment group.

DS107E-04 was a randomised, vehicle-controlled, double-blind, exploratory clinical trial to assess the efficacy and steroid sparing potential of DGLA cream topically applied to patients with moderate to severe AD. The primary objective was to evaluate the clinical efficacy of alternating treatment with Mometasone Furoate and 5% topical DGLA formulation OD compared to Mometasone Furoate and vehicle OD for 1 week, with a 4 week follow-up with either DGLA formulation alone twice daily (BD) or vehicle alone BD in adult patients with moderate to severe AD. Secondary objectives included the evaluation of DGLA cream in the treatment of itch severity, improvement of clinical signs and symptoms in AD EASI, IGA, SCORAD, target lesion score, improvement of quality of life, investigation of skin barrier function, days to relapse and rescue medication use as well as assessment of skin tolerability. The overall assessment of the Investigator at Visit 7 (Day 42) or at early termination (ET) with respect to the subject's response to the effects of the IMP yielded similar results for both treatment groups. A clinically significant response was assessed for 7 of 16 patients with data (43.75%) of the DGLA group and for 8 of 18 patients with data (44.44%) in the vehicle group.

Overall, analyses of the secondary efficacy variables in the PPS showed similar results for the two treatments.

One SAE occurred during this study. It applied to a patient in the DGLA group who was hospitalised due to the event. The event was of severe intensity and the relationship to the IMP was judged by the Investigator as unrelated. No patient died during the study. Overall, there were only small changes between baseline and the last treatment visit in the means of the evaluated safety parameters. No relevant differences between the treatment groups could be observed.

DS107E-05 was a randomised, vehicle-controlled, double-blind, exploratory clinical trial to assess the efficacy and steroid sparing potential of DGLA cream topically applied to early childhood patients with moderate to severe AD. Due to unsatisfactory recruitment progress, the study was terminated prematurely. The small amount of data collected and the fact that no patients completed the study, data analysis are not robust enough to draw any efficacy conclusions.

There were 19 AEs reported in the five patients enrolled in this study; all AEs were considered by the Investigator to be not related to the administration of study drug. There was also one SAE which was deemed to be not related to the administration of study drug. No other SAEs or deaths were reported. There were no clinically meaningful abnormalities or trends identified in observed values or changes from baseline. Overall, there were no safety signals seen during the study conduct. The study IMP appeared to be well tolerated by patients.

DS107E-06 was a randomised, double-blind, vehicle-controlled, Phase 2b study to assess the efficacy and safety of topically applied DS107 Cream to adults with mild to moderate AD. The primary endpoints were to observe a change from baseline in NRS for pruritus in the treated population compared to vehicle at Week 8 as well as a change in baseline in EASI in treated versus vehicle populations at Week 8. Secondary and exploratory efficacy variables included IGA measurements, BSA, POEM, DLQI, PGI-S score and PGI-C score.

Analysis of EASI scores based on the binary response regulatory endpoint EASI-75 (proportion of patients achieving an improvement from baseline of at least 75% on the Eczema Area and Severity) revealed a dose-response trend of superiority of DS107 versus vehicle cream. An improvement from baseline to Week 8 of at least 75% on the Eczema Area and Severity Index (EASI-75) was reported in more patients who received 5% DS107 (41.0%) than in patients who received vehicle (30.0%). 5% DS107 (48.2%) demonstrated statistically significant superiority in

EASI-75 over vehicle (30.9%) at Week 10 (p=0.0194), with no evidence of a plateau in treatment effect. At Week 8, there was a similar dose-dependent trend in the proportions of subjects achieving an IGA score of 0 or 1 and a decrease of at least 2 points from baseline as more patients in the DS107 treatment groups (5% DS107 – 30.1%, 1% DS107 – 23.5%) achieved treatment success than in the vehicle group (18.8%). At Week 10, 5% DS107 demonstrated sustained and statistically significant superiority in IGA response over both 1% DS107 and vehicle. The trend of improvement for both IGA treatment response and EASI-75 treatment response displayed no evidence of treatment plateau, suggesting that greater clinically meaningful improvements from baseline could be expected if treatment were to be continued for a longer time period.

No deaths occurred in this study. Two SAEs were reported during this study. One subject treated with 1% DS107 and one vehicle-treated subject experienced an SAE during their participation in this trial. Both were by the reporting Investigator to be unrelated to study drug. Additionally, both resolved without sequelae.

2 RISK BENEFIT ASSESSMENT

To date, DS107 capsules has been administered to 304 healthy volunteers/patients during the course of one Phase 1 trial (DS107G-01) and two Phase 2 trials (DS107G-02 & DS107G-03) for AD. Up to 4g DS107 capsules has been clinically tested and is well tolerated in healthy volunteers and patients with moderate to severe AD. 2g DS107 capsules was well tolerated and safe in 164 patients with moderate to severe AD.

The effect of DS107 capsules on the signs and symptoms of AD, efficacy endpoints and pharmacodynamic biomarkers was consistently superior to placebo in Phase 2 clinical studies in patients with moderate to severe AD, with a similar pattern in both Investigator scores and patient scores.

Based on the endogenous nature of the active pharmaceutical ingredient, exposure margins from non-clinical toxicology studies, a favourable clinical safety profile observed in three clinical studies and the observed therapeutic efficacy of DS107 capsules in a disease with a persistent unmet need for additional effective and well tolerated therapies, it can be concluded that there is a positive risk-benefit ratio for the continued investigation of DS107 capsules as a treatment for moderate to severe AD.

3 RATIONALE FOR THE STUDY

DS Biopharma (the Sponsor) showed a good safety profile for DS107 capsules for doses up to 4g, based on results of the Phase I safety study.

The proof-of-concept Phase 2a study then demonstrated a significant improvement in clinical efficacy measures after 8 weeks of treatment with DS107 capsules in patients with AD. Importantly, there was a significant improvement in the number of moderate AD patients who achieved the primary endpoint compared to placebo treated patients. There was also a similar efficacy observed in severe/very severe AD patients, however, the sample size was deemed too small to determine the statistical significance.

When data from the Phase 2b study was analyzed by baseline AD severity, a clear trend towards a dose-dependent IGA response was observed in the severe sub-group (n=45). At Week 8, more patients in the DS107 treatment groups (2g DS107 – 41.7%, 1g DS107 – 37.5%) than the placebo treated group (25.0%) achieved treatment success. However, due to a profound placebo effect statistically significant differences versus placebo could not be detected. This study also displayed no evidence of treatment plateau, suggesting that greater clinically meaningful improvement from baseline could be expected if treatment were to be continued for a longer time period.

The three previous clinical studies indicate that DS107 capsules is well tolerated and safe in both healthy patients and patients with moderate to severe AD. They highlight the efficacy of DS107 capsules and indicate that further efficacy could be obtained by optimizing the dosing regime and/or concentration and treatment duration.

Therefore, the goal for this study is to examine the efficacy of 2g DS107 capsules OD for a treatment period of 16 weeks in patients with moderate to severe AD.

The design of the current study is a randomised, placebo-controlled, double-blind, parallel group comparison in which the efficacy and safety of a 16 week treatment with DS107 capsules is assessed in adult patients with moderate to severe AD. The design of the study minimises bias during the safety and efficacy assessments.

The novel mechanism of action and safety profile of DS107 capsules offer a potential benefit to AD patients and would represent a new class of medicine for this disease.

Based on the afore mentioned preclinical studies demonstrating the efficacy of DS107 in animal models of AD and the positive signals in the Phase 2a and Phase 2b patient studies there is a clear rationale for the further development of DS107 capsules as a treatment for patients with moderate to severe AD.

4 STUDY OBJECTIVES

Efficacy Objective:

- To compare the efficacy of orally administered DS107 (2g) versus placebo, in the treatment of adult patients with moderate to severe AD.

Safety Objective:

- To assess the safety of orally administered DS107 (2g) versus placebo, in adult patients with moderate to severe AD.

5 STUDY ENDPOINTS

5.1 Primary Endpoint

- Proportion of patients achieving a vIGA-AD™ score of 0 (clear) or 1 (almost clear) and a decrease of at least 2 points in vIGA-AD™ in treated population compared to placebo population from baseline at Week 16.

- Proportion of patients achieving EASI-75 (≥75% improvement from baseline) in treated population compared to placebo population at Week 16.

Note: Each of the independent primary endpoints will be assessed separately. Success in either of the primary endpoints denotes treatment success.

5.2 Secondary Endpoints

- Proportion of patients achieving a vIGA-AD™ score of 0 (clear) or 1 (almost clear) and a decrease of at least 2 points in vIGA-AD™ in treated population compared to placebo population from baseline to Week 4, 8, 12, 18 and 20 and the change in proportion of patients from Week 16 to Week 18 and 20.

- Proportion of patients achieving EASI-75 (≥75% improvement from baseline) in treated population compared to placebo population at Weeks 4, 8, 12, 18 and 20 and the change in proportion of patients from Week 16 to Week 18 and 20.

- Change from baseline in vIGA-AD™ score in treated population compared to placebo population to Weeks 4, 8, 12, 16, 18 and 20, and from Week 16 to Week 18 and 20.

- Change from baseline in EASI in treated population compared to placebo population to Weeks 4, 8, 12, 16, 18 and 20, and from Week 16 to Week 18 and 20.

- Proportion of patients achieving a decrease of at least 4 points in worst itch NRS in treated population compared to placebo population from baseline to Week 4, 8, 12, 16, 18 and 20 and the change in proportion of patients from Week 16 to Week 18 and 20.

- Proportion of patients achieving a decrease of at least 3 points in worst itch NRS in treated population compared to placebo population from baseline to Week 4, 8, 12, 16, 18 and 20 and the change in proportion of patients from Week 16 to Week 18 and 20.

- Change from baseline in worst itch NRS in treated population compared to placebo population to Week 4, 8, 12, 16, 18 and 20 and from Week 16 to Week 18 and 20.

- Proportion of patients achieving EASI-50 (≥50% improvement from baseline) in treated population compared to placebo population at Week 4, 8, 12, 16, 18 and 20 and the change in proportion of patients from Week 16 to Week 18 and 20.

- Change from baseline in the Body Surface Area (BSA) affected by AD in treated population compared to placebo population to Weeks 4, 8, 12, 16, 18 and 20, and from Week 16 to Week 18 and 20.

- Change from baseline in the SCORing Atopic Dermatitis (SCORAD) score in treated population compared to placebo population to Weeks 4, 8, 12, 16, 18 and 20, and from Week 16 to Week 18 and 20.

- Incidence of treatment emergent adverse events (TEAEs) and serious adverse events (SAEs)

5.3 Exploratory Endpoints

- Proportion of patients achieving a decrease of at least 2 points in vIGA-AD™ in treated population compared to placebo population from baseline to Week 4, 8, 12, 16, 18 and 20 and the change in proportion of patients from Week 16 to Week 18 and 20.

- Change from baseline in the Dermatology Life Quality Index (DLQI) score in treated population compared to placebo population to Weeks 4, 8, 12, 16, 18 and 20, and from Week 16 to Week 18 and 20.

- Change from baseline in the Patient Orientated Eczema Measure (POEM) score in treated population compared to placebo population to Weeks 4, 8, 12, 16, 18 and 20, and from Week 16 to Week 18 and 20.

- Change in sleep quality assessment (Athens Insomnia Scale) in treated population compared to placebo population from baseline to Week 4, 8, 12, 16, 18 and 20 and from Week 16 to Week 18 and 20.

- Change from baseline in the Patient-Oriented SCORAD (PO-SCORAD) score in treated population compared to placebo population to Weeks 4, 8, 12, 16, 18 and 20, and from Week 16 to Week 18 and 20.

- Trough plasma levels in treated population compared to placebo population at Baseline/Day 0, Week 4, Week 8 and Week 16.

- Determination of AD biomarkers in treated population compared to placebo population at Baseline/Day 0 and Week 16.

6 STUDY DESIGN

This is a randomised, placebo-controlled, double-blind, parallel group, multi-centre 2-arm Phase 2 study to investigate the efficacy of orally administered DS107 in AD patients.

It is planned that at least 220 patients suffering from moderate to severe AD will be included in this study. All patients will sign an informed consent and undergo screening for study eligibility.

Before the comparative treatment period can commence, patients will return to the site for a baseline assessment of their disease and eligible patients will be randomly allocated to one of the treatment regimens in a 1:1 randomization:

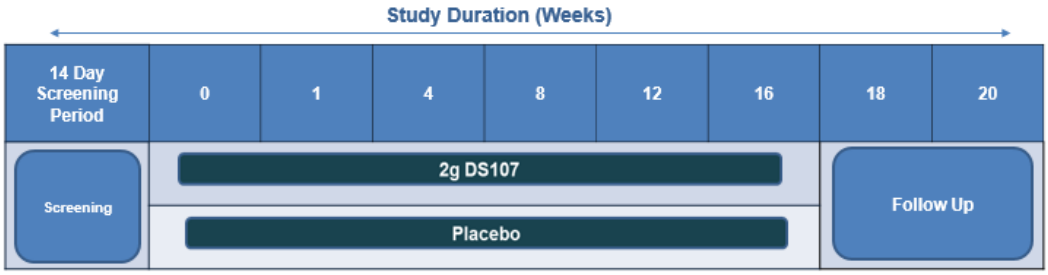
- 2g DS107 (4 DS107 capsules) orally administered once daily for 16 weeks
- Placebo (4 placebo capsules) orally administered once daily for 16 weeks

There is a 4 week follow-up period.

To maintain the double-blind conditions, DS107 capsules and placebo will be identical in appearance.

A schematic diagram of the overall timeframe of the study is given in Figure 2.

Figure 2: Study Outline



7 PATIENTS AND SCREENING

In order to participate in this study the patients must meet all of the following inclusion criteria and must not meet any of the following exclusion criteria. Inclusion in the trial starts with the informed consent signature. The inclusion and exclusion criteria are to be verified at the screening visit (Visit 1) and at the start of treatment/baseline visit (Visit 2).

7.1 Source of Patients

The study population will consist of male and female patients with confirmed diagnosis of AD aged 18 years or older. Patients will be identified and recruited by the investigational sites.

7.2 Inclusion Criteria

1. Patients with a clinically confirmed diagnosis of active AD according to the American Academy of Dermatology Consensus Criteria that has been present for at least 6 months before the screening visit.

2. Patients with moderate to severe AD at baseline as defined by a vIGA-AD™ score of 3 or 4 at baseline.

3. Patients with an EASI score of ≥16 at screening and baseline.

4. Patients with AD covering a minimum 10% of the body surface area (BSA) at baseline.

5. Patients with a worst itch NRS score in a day of ≥4 (on 11 point NRS) at the screening and baseline visits.
6. Patients whose pre-study clinical laboratory findings do not interfere with their participation in the study, in the opinion of the Investigator.

7. Patients who are able and willing to stop all current treatments for AD throughout the study (except for allowed emollients).
8. Patients who are on a stable dose of a bland emollient for at least 7 days prior to baseline.

   Note:

   Patients who have been on a stable emollient with an active ingredient (for example urea, ceramide and hyaluronic acid) for at least 12 weeks prior to screening and are otherwise eligible may continue using their pre-existing emollients, if deemed appropriate by the investigator and if they are willing and able to continue using the same stable emollient for the duration of the study

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

10. Female patients and male patients with female partners of child bearing potential must use highly effective birth control methods or have a sterilised partner for the duration of the study.

    Note:

- *Highly effective birth control methods are defined as methods that can achieve a failure rate of less than 1% per year when used consistently and correctly. Such methods include systemic hormonal contraceptives, intrauterine device or sexual abstinence.*

- *Hormonal contraceptives must be on a stable dose for at least one month before baseline.*

- *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.*

11. Recent history (within 6 months before the screening visit) of inadequate response to treatment with topical medications or for whom topical treatments are otherwise medically inadvisable (e.g., because of important side effects or safety risks).

***Note**:*

- *Inadequate response is defined as failure to achieve and maintain remission or a low disease activity state (comparable to vIGA-AD™ 0=clear to 2=mild) despite treatment with a daily regimen of Topical corticosteroids (TCS) of medium to higher potency (± Topical calcineurin inhibitors (TCI) as appropriate), applied for at least 28 days or for the maximum duration recommended by the product prescribing information (e.g., 14 days for super-potent TCS), whichever is shorter.*

- *Patients with documented systemic treatment for AD (for example systemic corticosteroids, cyclosporin) in the past 6 months are also considered as inadequate responders to topical treatments and are potentially eligible for treatment with DS107 after appropriate washout.*

- *Important side effects or safety risks are those that outweigh the potential treatment benefits and include intolerance to treatment, hypersensitivity reactions, significant skin atrophy, and systemic effects, as assessed by the Investigator or by the patient's treating physician.*

12. Patients who are able to communicate well with the Investigator, to understand and comply with the requirements of the study, and understand and sign the written informed consent prior to initiation of any study specific activities or procedures.

7.3 Exclusion Criteria

1. Patients with other skin conditions that might interfere with AD diagnosis and/or evaluation (such as psoriasis or current active viral, bacterial and fungal skin infections) as assessed by the Investigator.

2. Patients who have used systemic treatments that could affect AD less than 4 weeks prior to baseline visit (Day 0), e.g. retinoids, methotrexate, cyclosporine, hydroxycarbamide (hydroxyurea), azathioprine and oral/injectable corticosteroids. Intranasal corticosteroids and inhaled corticosteroids for stable medical conditions are allowed.

3. Patient with previous exposure to DS107.

4. Patients who have used any topical medicated treatment for AD (except for emollients) two weeks prior to start of treatment/ Baseline (Day 0), including but not limited to, topical corticosteroids, calcineurin inhibitors, tars, bleach, antimicrobials and bleach baths.

5. Patients who use emollients containing urea, ceramides or hyaluronic acid less than twelve weeks prior to Baseline.

6. Patients who have had excessive sun exposure, have used tanning booths or other ultraviolet (UV) light sources four weeks prior to Baseline (Day 0) and/or are planning a trip to a sunny climate or to use tanning booths or other UV sources between screening and follow-up visits.

7. Patients who have a history of hypersensitivity to any substance in DS107 capsules or placebo capsules.

8. Patients who have a history of hypersensitivity to soy beans or soy lecithin.

9. Patients who have a white cell count or differential white cell count outside of the normal reference range at screening.

   Note:
   For patients with a mild leucocytosis or leucopenia and otherwise a normal white cell blood count may be enrolled following consultation with the medical monitor by the investigator.

10. Patients who have 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.

11. Patients who have a clinically significant impairment of renal or hepatic function.

12. Patients with significant uncontrolled cardiovascular, neurologic, malignant, psychiatric, respiratory or hypertensive disease, as well as uncontrolled diabetes and floride arthritis or any other illness that, in the opinion of the Investigator, is likely to interfere with completion of the study.

13. Patients with active infectious disease (e.g., hepatitis B, hepatitis C or advanced disease secondary to infection with human immunodeficiency virus).

14. Patients with a history of clinically significant drug or alcohol abuse in the opinion of the Investigator in the last year prior to Baseline (Day 0).

15. Patients who have participated in any other clinical study with an investigational drug within 3 months before the first day of administration of study treatment.

16. Patients who have had treatment with biologics as follows:
    a. Any cell-depleting agents including but not limited to rituximab: within 6 months before the screening visit, or until lymphocyte count returns to normal, whichever is longer,
    b. Other biologics influencing cell proliferation: within 6 months before the screening visit.
    c. Dupilumab or other monoclonal antibodies within 5 half-lives (if known) or 16 weeks prior to baseline visit, whichever is longer

17. Patients who are pregnant, planning pregnancy, breastfeeding and/or are unwilling to use adequate contraception (as specified in Inclusion Criterion 10) during the trial.

18. Patients, in the opinion of the Investigator, not suitable to participate in the study.

7.4 Screening and Consent

It is the responsibility of the Investigator, or a person designated by the Investigator (if acceptable to local regulation), to obtain written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives and potential risks/benefits of the study. Patients will be given the opportunity to ask questions to the investigational team. It must also be explained to the patients that they are completely free to refuse to enter the study or to withdraw from it at any time for any reason. The patient will be given sufficient time to consider participation in the study. If, after this, the patient agrees to participate, they will be asked to sign and date one original copy of the written ICF. The patients will then receive a copy of the signed and dated patient information sheet (PIS)/ICF. The original signed ICF will be filed in the Investigator Site File (ISF). The PIS will contain site contact information in case of any questions or medical emergency.

If new safety information results in significant changes in the risk/benefit assessment or any new information presents that may affect willingness to continue to participate, the consent form should be updated and approved if necessary by the Research Ethics Board/Institutional Review Board. All patients (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. Any written information given to potential patients will be submitted to, and approved by, the respective Ethics Committee(s) (EC) prior to implementation.

The Investigator will maintain a Patient Screening Log to collect information on all patients who sign an ICF regardless of whether or not they meet the study eligibility criteria following completion of the screening evaluations. After completion of screening, all patients deemed eligible to take part in this study will be entered onto an Enrolment Log.

7.5 Withdrawal of Patients

Patients have the right to withdraw from the study at any time for any reason without penalty. The Investigator must explain this to the patient and that this will in no way prejudice their future treatment. The Investigator also has the right to withdraw patients from the study if he feels it is in the best interest of the patient or if the patient 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 patients should be avoided. Should a patient 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 patient either by telephone or through a personal visit to determine as completely as possible the reason for the withdrawal, and record the reason in patient's source document and case report form (CRF). A complete final early termination evaluation at the time of the patient's withdrawal should be made with an explanation of why the patient is withdrawing from the study when ever possible. If the reason for removal of a patient is an adverse event or an abnormal laboratory test result, the principal specific event or test will be recorded. Patients who discontinue the study before Week 16/Visit 7 visit will be asked to come for an early termination visit as soon as possible and have the assessments listed at Week 16/Visit 7 performed. They will also be asked to return two weeks later for the safety assessments listed at Week 18/Visit 8.

Patients who develop Grade 3 or higher National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), that is determined to be possibly or probably attributable to the study drug will be discontinued.

7.6 Patient Replacement

Patients who are withdrawn from the study due to an adverse event or lack of effect will not be replaced. Patients who are withdrawn for other reasons (such as lost to follow up, personal reasons) may be replaced.

7.7 Protocol Violations

All protocol violations will be reviewed by the Medical Monitor as and when each violation is detected. Based on this review a decision on the patient's continuation in the trial will be reached and this decision will be documented as appropriate. Notification will be made to the relevant authorities as required.

7.8 Stopping Criteria

Trial will be stopped if more than one patient has a Grade 3 or higher AE on the CTCAE scale in any one category that is determined to be possibly or probably attributable to study drug.

8 STUDY CONDUCT

8.1 Study Schedule

Patients will come to the clinic on 8 occasions: at Screening/Visit 1, Baseline/Visit 2, Week 4/Visit 4, Week 8/Visit 5, Week 12/Visit 6, Week 16/Visit 7 (end of treatment), Week 18/ Visit 8 (follow up) and Week 20/Visit 9 (follow-up). A telephone visit will also be performed at Week 1/Visit 3.

Patients who discontinue the study early will be asked to attend the investigative site as soon as possible so that assessments scheduled for Visit 7 can be conducted at an Early Termination visit.

In the event that treatment is occurring, a wash out period of up to 4 weeks may be necessary. At the Screening Visit, after giving informed consent to participate, patients will be assessed using the screening examinations. Eligible patients with confirmed AD using the American Academy of Dermatology Consensus Criteria and who meet all the inclusion criteria and do not meet the exclusion criteria at the baseline visit will be enrolled.

During the treatment period and follow-up period patients will be restricted from using any other treatment for AD, with the exception of the same emollients they have been consistently using since the screening visit. A tabulated flow chart of the study is presented in Appendix 1 (Section 15.1).

8.2 Screening

8.2.1 Screening Visit (Visit 1)

The patient must sign and date the ICF before any study-specific procedures are conducted.

Once informed consent has been obtained, the Investigator will assign a Patient Number (as per Section 10.5) and the following screening procedures/assessments will occur:

- Demographic data
- Medical / surgical history (as detailed in Section 9.2.1)
- Assessment of inclusion/exclusion criteria (Sections 7.2 & 7.3)
- Samples for clinical laboratory safety tests (haematology, serum biochemistry and FSH levels (when applicable) as detailed in Section 9.2.4)
- Sample for pregnancy test (only female patients of child-bearing potential, as detailed in Section 9.2.5)
- Virology (as detailed in Section 9.2.6)
- Vital signs (blood pressures, heart rate and body temperature), as detailed in Section 9.2.3)
- Physical examination (as detailed in Section 9.2.2)
- Body Mass Index (as detailed in Section 9.2.8)
- Body Surface Area (as detailed in Section 9.1.4)
- Validated Investigator's Global Assessment (as detailed in Section 9.1.1)
- Eczema Area and Severity Index (EASI) (as detailed in Section 9.1.2)
- NRS Pruritus Assessment (as detailed in Section 9.1.3)
- Concomitant medication assessment (as detailed in Section 9.2.13)
- Emollient use capture (as detailed in Section 9.2.13.1)

8.3 Treatment Period

Following completion of a successful screening visit, patients will begin the comparative treatment period (16 weeks).

At the start of the comparative treatment period, after confirmation of continued eligibility, patients will be randomly assigned at the baseline visit (Visit 2) to one of the two treatment regimens.

Patients will be instructed to take 4 capsules of IMP which will contain either 2g DS107 or placebo. Every effort should be made to ensure IMP administration is at the same time each day. Each self-administration of IMP will be recorded in a patient compliance log.

Unscheduled visits may occur when a patient needs to make a visit in between the scheduled visit dates due to an adverse event (AE), difficulty complying with the study protocol requirements, or a significant change in their disease state. All procedures that are medically necessary should be followed.

Once patients are enrolled on the study they will be restricted from using any other treatment for AD, with the exception of emollients, as defined in Section 9.2.13.1. Any medication (prescription as well as over the counter (OTC) drugs) or therapeutic intervention deemed necessary for the patient, and which in the opinion of the Investigator do not interfere with the safety and efficacy evaluations, may be continued unless they are included in the list of 'Concomitant Medications' (Section 9.2.13).

Patients who discontinue the study early will have all study procedures scheduled for Visit 7 (see Section 8.3.6) performed as soon as possible after patient withdrawal so that all study-related information can be recorded.

8.3.1 Baseline (Visit 2)

Note: it must be ensured that inclusion criteria regarding the severity of the disease remain relatively unchanged since screening in order to exclude patients responding to the emollient use since screening visit i.e. IGA score must be unchanged and EASI score should not change by more than 10%. Patients will attend the investigational site at Visit 2 when the following procedures/assessments will occur.

- Verification of inclusion/exclusion criteria (Sections 7.2 & 7.3)
- Patient Randomisation (as detailed in Section 10.5)
- Samples for clinical laboratory safety tests (haematology and serum biochemistry as detailed in Section 9.2.4)
- Pharmacokinetic Sampling (as detailed in Section 9.2.9)
- Biomarker Sampling (as detailed in Section 9.2.10)
- Vital signs (blood pressures, heart rate and body temperature), as detailed in Section 9.2.3);
- Physical examination (as detailed in Section 9.2.2)
- Electrocardiogram (ECG) (as detailed in Section 9.2.7)
- Dispense Study Drug
- Dispense Patient Compliance Log
- Body Surface Area (as detailed in Section 9.1.4)
- Validated Investigator's Global Assessment (as detailed in Section 9.1.1)
- Eczema Area and Severity Index (EASI) (as detailed in Section 9.1.2)
- NRS Pruritus assessment (as detailed in Section 9.1.3)
- Dermatology Life Quality Index (DLQI) Questionnaire (as detailed in Section 9.1.5)

- Patient Orientated Eczema Measure (POEM) questionnaire (as detailed in Section 9.1.6)
- SCORing AD (SCORAD) questionnaire (as detailed in Section 9.1.7)
- Athens Insomnia Scale (AIS) (as detailed in Section 9.1.8)
- Patient- Orientated SCORAD questionnaire (as detailed in Section 9.1.9)
- Concomitant medication assessment (as detailed in Section 9.2.13)
- Review emollient usage and capture
- AE assessment (as detailed in Section 11)

If all study entry criteria are satisfied the Investigator will randomize the patient and provide the patient with the DS107 capsules or placebo capsules from one of the patient treatment packs available at the site (allocated via the central randomization).

The first administration of DS107 or placebo will be carried out after the Baseline visit. Following this DS107 capsules or placebo medication will be administered once daily. IMP will be administered approximately 2 hours after food consumption at the same time each day. Patients will be instructed to not consume food for approximately 1 hour after IMP administration.

Patients will be given a compliance log to document administration of DS107 capsules or placebo. Clinical staff will explain to the patient how to use the compliance log to document IMP administration compliance.

An NRS for the assessment of pruritus will be captured on a daily basis from screening through to the follow up visit.

Similarly, emollient use will also be captured on a daily basis from screening through to the follow-up visit.

Collection of AEs will begin after the first administration of IMP has occurred.

On completion of this visit, patients will be advised that they will be contacted by telephone one week later to discuss their progress on the trial. They will then be required to return to the investigational site at Week 4/Visit 4 and to bring with them the unused DS107 capsules/placebo patient packs, the used DS107 capsules/placebo patient packs, and the patient compliance log.

8.3.2 Week 1 (Visit 3)

Patients will receive a telephone call from site staff at Week 1.

IMP compliance and administration will be discussed to ensure correct dosing. Patients will also be asked to discuss the patient logs for confirmation of compliance.

The following procedures/assessments will also occur:

- Concomitant medication assessment (as detailed in Section 9.2.13)
- AE assessment (as detailed in Section 11)

The patient will be reminded that IMP will continue to be administered approximately 2 hours after food consumption at the same time each day. Patients will be reminded to not consume food for approximately 1 hour after IMP administration.

An NRS for the assessment of pruritus will continue to be captured on a daily basis from screening to the follow-up visit. Emollient use will also continue to be captured on a daily basis for the same period.

On completion of this visit, patients will be advised that they will be required to return to the investigational site at Visit 4 and to bring with them the unused DS107/placebo patient packs, the used DS107/placebo patient packs, and the patient compliance log.

8.3.3 Week 4 (Visit 4)

Patients will return to the investigational site at Week 4/Visit 4.

For accountability purposes, patients will be required to bring both the used DS107/placebo patient packs and unused DS107/placebo patient packs supplied at Visit 2. Patients will be required to provide the patient compliance log for confirmation of compliance.

The following procedures/assessments will occur:

- Samples for clinical laboratory safety tests (haematology and serum biochemistry as detailed in Section 9.2.4)
- Pharmacokinetic Sampling (as detailed in Section 9.2.9)
- Vital signs (blood pressures, heart rate and body temperature), as detailed in Section 9.2.3);
- Physical examination (as detailed in Section 9.2.2)
- Dispense Study Drug
- Collect Study Drug
- Dispense Patient Compliance Log
- Collect and Review Patient Compliance Log
- IMP Accountability (as detailed in Section 10.6)
- Body Surface Area (as detailed in Section 9.1.4)
- Validated Investigator's Global Assessment (as detailed in Section 9.1.1)
- Eczema Area and Severity Index (EASI) (as detailed in Section 9.1.2)
- NRS Pruritus assessment (as detailed in Section 9.1.3)
- Dermatology Life Quality Index (DLQI) Questionnaire (as detailed in Section 9.1.5)
- Patient Orientated Eczema Measure (POEM) questionnaire (as detailed in Section 9.1.6)
- SCORing AD (SCORAD) questionnaire (detailed in Section 9.1.7)
- Athens Insomnia Scale (AIS) (as detailed in Section 9.1.8)
- Patient- Orientated SCORAD questionnaire (as detailed in Section 9.1.9)
- Concomitant medication assessment (as detailed in Section 9.2.13)
- Review emollient usage and capture
- AE assessment (as detailed in Section 11)

DS107 or placebo patient packs will be returned and additional patient treatment packs of DS107 or placebo will be supplied to the patient.

IMP will continue to be administered approximately 2 hours after food consumption at the same time each day. Patients will be reminded to not consume food for approximately 1 hour after IMP administration. The patient compliance log will be provided to the patient who will be instructed to complete this as before.

An NRS for the assessment of pruritus will continue to be captured on a daily basis from screening to the follow-up visit. Emollient use will also continue to be captured on a daily basis for the same period.

On completion of this visit, patients will be advised that they will be required to return to the investigational site at Visit 5 and to bring with them the unused DS107/placebo patient packs, the used DS107/placebo patient packs, and the patient compliance log.

8.3.4 Week 8 (Visit 5)

Patients will return to the investigational site at Week 8/Visit 5.

For accountability purposes, patients will be required to bring both the used DS107 /Placebo patient packs and unused DS107/Placebo patient packs supplied at Visit 4. Patients will be required to provide the patient compliance log for confirmation of compliance.

The following procedures/assessments will occur:

- Samples for clinical laboratory safety tests (haematology and serum biochemistry as detailed in Section 9.2.4)
- Pharmacokinetic Sampling (as detailed in Section 9.2.9)
- Vital signs (blood pressures, heart rate and body temperature), as detailed in Section 9.2.3);
- Physical examination (as detailed in Section 9.2.2)
- Dispense Study Drug
- Collect Study Drug
- Dispense Patient Compliance Log
- Collect and Review Patient Compliance Log
- IMP Accountability (as detailed in Section 10.6)
- Body Surface Area (as detailed in Section 9.1.4)
- Validated Investigator's Global Assessment (as detailed in Section 9.1.1)
- Eczema Area and Severity Index (EASI) (as detailed in Section 9.1.2)
- NRS Pruritus assessment (as detailed in Section 9.1.3)
- Dermatology Life Quality Index (DLQI) Questionnaire (as detailed in Section 9.1.5)
- Patient Orientated Eczema Measure (POEM) questionnaire (as detailed in Section 9.1.6)
- SCORing AD (SCORAD) questionnaire (detailed in Section 9.1.7)
- Athens Insomnia Scale (AIS) (as detailed in Section 9.1.8)
- Patient- Orientated SCORAD questionnaire (as detailed in Section 9.1.9)
- Concomitant medication assessment (as detailed in Section 9.2.13)
- Review emollient usage and capture
- AE assessment (as detailed in Section 11)

DS107 or placebo patient packs will be returned and additional patient treatment packs of DS107 or placebo will be supplied to the patient.

IMP will continue to be administered approximately 2 hours after food consumption at the same time each day. Patients will be reminded to not consume food for approximately 1 hour after IMP administration. The patient compliance log will be provided to the patient who will be instructed to complete this as before.

An NRS for the assessment of pruritus will continue to be captured on a daily basis from screening to the follow up visit. Emollient use will also continue to be captured on a daily basis for the same period.

On completion of this visit, patients will be advised that they will be required to return to the investigational site at Visit 6 and to bring with them the unused DS107/placebo patient packs, the used DS107/placebo patient packs, and the patient compliance log.

8.3.5 Week 12 (Visit 6)

Patients will return to the investigational site at Week 12/Visit 6.

For accountability purposes, patients will be required to bring both the used DS107/placebo patient packs and unused DS107/placebo patient packs supplied at Visit 5. Patients will be required to provide the patient compliance log for confirmation of compliance.

The following procedures/assessments will occur:

- Vital signs (blood pressures, heart rate and body temperature), as detailed in Section 9.2.3);
- Physical examination (as detailed in Section 9.2.2)
- Dispense Study Drug
- Collect Study Drug
- Dispense Patient Compliance Log
- Collect and Review Patient Compliance Log
- IMP Accountability (as detailed in Section 10.6)
- Body Surface Area (as detailed in Section 9.1.4)
- Validated Investigator's Global Assessment (as detailed in Section 9.1.1)
- Eczema Area and Severity Index (EASI) (as detailed in Section 9.1.2)
- NRS Pruritus assessment (as detailed in Section 9.1.3)
- Dermatology Life Quality Index (DLQI) Questionnaire (as detailed in Section 9.1.5)
- Patient Orientated Eczema Measure (POEM) questionnaire (as detailed in Section 9.1.6)
- SCORing AD (SCORAD) questionnaire (detailed in Section 9.1.7)
- Athens Insomnia Scale (AIS) (as detailed in Section 9.1.8)
- Patient- Orientated SCORAD questionnaire (as detailed in Section 9.1.9)
- Concomitant medication assessment (as detailed in Section 9.2.13)
- Review emollient usage and capture
- AE assessment (as detailed in Section 11)

DS107 or placebo patient packs will be returned and additional patient treatment packs of DS107 or placebo will be supplied to the patient.

IMP will continue to be administered approximately 2 hours after food consumption at the same time each day. Patients will be reminded to not consume food for approximately 1 hour after IMP administration. The patient compliance log will be provided to the patient who will be instructed to complete this as before.

An NRS for the assessment of pruritus will continue to be captured on a daily basis from screening to the follow-up visit. Emollient use will also continue to be captured on a daily basis for the same period.

On completion of this visit, patients will be advised that they will be required to return to the investigational site at Visit 7 and to bring with them the unused DS107/placebo patient packs, the used DS107/placebo patient packs, and the patient compliance log.

8.3.6 Week 16 (Visit 7) / End of Treatment or Early Termination

Patients will return to the investigational site at Visit 7. **The last dose of DS107/placebo should be taken the day before Visit 7.**
For accountability purposes, patients will be required to bring both the used DS107/Placebo patient packs and unused DS107/Placebo supplied at Visit 6. Patients will be required to provide the patient compliance log for confirmation of compliance.

The following procedures/assessments will occur:

- Samples for clinical laboratory safety tests (haematology and serum biochemistry as detailed in Section 9.2.4)
- Pharmacokinetic Sampling (as detailed in Section 9.2.9)
- Biomarker Sampling (as detailed in Section 9.2.10)
- Sample for pregnancy test (only female patients of child-bearing potential, as detailed in Section 9.2.5)
- Vital signs (blood pressures, heart rate and body temperature), as detailed in Section 9.2.3);
- Physical examination (as detailed in Section 9.2.2)
- Electrocardiogram (ECG) (as detailed in Section 9.2.7)
- Body Mass Index (as detailed in Section 9.2.8)
- Collect Study Drug
- Collect and Review Patient Compliance Log
- IMP Accountability (as detailed in Section 10.6)
- Body Surface Area (as detailed in Section 9.1.4)
- Validated Investigator's Global Assessment (as detailed in Section 9.1.1)
- Eczema Area and Severity Index (EASI) (as detailed in Section 9.1.2)
- NRS Pruritus assessment (as detailed in Section 9.1.3)
- Dermatology Life Quality Index (DLQI) Questionnaire (as detailed in Section 9.1.5)
- Patient Orientated Eczema Measure (POEM) questionnaire (as detailed in Section 9.1.6)
- SCORing AD (SCORAD) questionnaire (detailed in Section 9.1.7)
- Athens Insomnia Scale (AIS) (as detailed in Section 9.1.8)
- Patient- Orientated SCORAD questionnaire (as detailed in Section 9.1.9)
- Concomitant medication assessment (as detailed in Section 9.2.13)
- Review emollient usage and capture
- AE assessment (as detailed in Section 11)

The DS107 or placebo patient packs will be returned. No further DS107 or placebo patient packs or patient compliance logs will be issued. Following completion of the study assessments at this visit, there will be continued study restrictions in line with those described in Sections 9.2.12.

An NRS for the assessment of pruritus will continue to be captured on a daily basis from screening to the follow up visits. Emollient use will also continue to be captured on a daily basis for the same period.

On completion of this visit, patients will be advised that they will be required to return to the investigational site at Visit 8 to assess any AEs since this visit, and conduct safety and efficacy assessments.

8.3.7 Week 18 (Visit 8) / Follow-up 1

Two weeks after Visit 7 (or early withdrawal visit), patients will return to the investigational site and the follow up procedures/assessments will occur:

- Samples for clinical laboratory safety tests (haematology and serum biochemistry as detailed in Section 9.2.4) – for abnormal values developed during treatment only.
- Vital signs (blood pressures, heart rate and body temperature), as detailed in Section 9.2.3);
- Physical examination (as detailed in Section 9.2.2)

- Body Surface Area (as detailed in Section 9.1.4)
- Validated Investigator's Global Assessment (as detailed in Section 9.1.1)
- Eczema Area and Severity Index (EASI) (as detailed in Section 9.1.2)
- NRS Pruritus assessment (as detailed in Section 9.1.3)
- Dermatology Life Quality Index (DLQI) Questionnaire (as detailed in Section 9.1.5)
- Patient Orientated Eczema Measure (POEM) questionnaire (as detailed in Section 9.1.6)
- SCORing AD (SCORAD) questionnaire (detailed in Section 9.1.7)
- Athens Insomnia Scale (AIS) (as detailed in Section 9.1.8)
- Patient- Orientated SCORAD questionnaire (as detailed in Section 9.1.9)
- Concomitant medication assessment (as detailed in Section 9.2.13)
- Review emollient usage and capture
- AE assessment (as detailed in Section 11)

8.3.8 Week 20 (Visit 9) / Follow up 2

Two weeks after Visit 8, patients will return to the investigational site and the final procedures/assessments will occur:

- Vital signs (blood pressures, heart rate and body temperature), as detailed in Section 9.2.3);
- Physical examination (as detailed in Section 9.2.2)
- Body Surface Area (as detailed in Section 9.1.4)
- Validated Investigator's Global Assessment (as detailed in Section 9.1.1)
- Eczema Area and Severity Index (EASI) (as detailed in Section 9.1.2)
- NRS Pruritus assessment (as detailed in Section 9.1.3)
- Dermatology Life Quality Index (DLQI) Questionnaire (as detailed in Section 9.1.5)
- Patient Orientated Eczema Measure (POEM) questionnaire (as detailed in Section 9.1.6)
- SCORing AD (SCORAD) questionnaire (detailed in Section 9.1.7)
- Athens Insomnia Scale (AIS) (as detailed in Section 9.1.8)
- Patient- Orientated SCORAD questionnaire (as detailed in Section 9.1.9)
- Concomitant medication assessment (as detailed in Section 9.2.13)
- Review emollient usage and capture
- AE assessment (as detailed in Section 11)

9 ASSESSMENTS

9.1 Efficacy Assessments

9.1.1 Validated Investigator Global Assessment (vIGA-AD™)

The clinical severity of AD will be evaluated by the Investigator at each visit using the vIGA-AD™ scale (Appendix 3).

The vIGA-AD™ scale awards a score of 0-4 based on a 5-point severity scale from clear to severe disease (0 = clear, 1 = almost clear, 2 = mild disease, 3 = moderate disease, 4 = severe disease). The scale uses clinical characteristics of erythema, infiltration, papulation and oozing/crusting as scoring guidelines for the overall severity assessment. vIGA-AD™ will be assessed at every clinic visit.

9.1.2 Eczema Area Severity Index (EASI)

EASI (Appendix 4) quantifies the severity of a patient's AD based on both lesion severity and the percent of BSA affected (Hanifin *et al.* 2001). 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, half points are permitted) 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.

9.1.3 Pruritus NRS

Severity of pruritus related to AD will be self-assessed by patients daily using the NRS (Appendix 5). Patients will be asked to estimate the intensity of pruritus at its worst over the previous 24 hours. The Pruritus NRS is a single-question assessment tool that will be used to assess the patient's worst itch as a result of AD in the previous 24 hours. Patients will score their pruritus due to AD on a scale of 0 – 10, with 0 (no itch) and 10 (worst itch imaginable) (Phan *et al.* 2012). Patients will complete the rating scale daily starting at screening through to the last study visit.

9.1.4 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. BSA will be evaluated at every clinic visit.

9.1.5 Dermatology Life Quality Index (DLQI) Questionnaire

The effect of AD on patient quality of life will be self-assessed by the patient at every clinic visit starting from baseline, using the DLQI (Appendix 6) developed by Finlay and Khan (1994).

DLQI has a maximum value of thirty based on the patients response to ten questions scored according to the following scale:

- Very Much = 3
- A lot = 2
- A little = 1
- Not at all = 0
- Not relevant = 0
- Question unanswered = 0

- Question 7: "prevented work or studying" = 3

9.1.6 Patient Orientated Eczema Measure (POEM)

The POEM will be assessed at each clinic visit, except the screening visit. The POEM developed by Charman *et.al.* 2004 (Appendix 7) 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

9.1.7 SCORing Atopic Dermatitis (SCORAD)

SCORAD will be measured at each clinic 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. 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 8.

9.1.8 Athens Insomnia Scale (AIS)

The severity of sleep disturbance will be self-assessed daily starting from baseline using the Athens Insomnia Scale (AIS).

The AIS is a self-administered psychometric instrument consisting of eight items (Appendix 11). The first five items of the AIS (assessing difficulty with sleep induction, awakenings during the night, early morning awakening, total sleep time, and overall quality of sleep) correspond to Criterion A for the diagnosis of insomnia according to ICD-10 (International Statistical Classification of Diseases and Related Health Problems 10th Revision), while the requirements of a minimum frequency (at least three times a week) and duration (1 month) of any complaint correspond to Criterion B of the ICD-10. The ICD-10 requirements of marked distress caused by the sleep problem and/or interference with ordinary activities of daily living (Criterion C) are covered through the strictly subjective nature of the response options for every item of the scale as well as through the content of the last three items pertaining to the next day consequences of insomnia (problems with sense of well-being, functioning, and sleepiness during the day).

Each item of the AIS can be rated 0-3 as detailed in Appendix 9.

The responders are requested to rate positively if they had experienced the sleep difficulty described in each item at least three times a week between the study visits (Soldatos et al. 2000).

9.1.9 Patient Oriented SCORAD (PO-SCORAD)

The PO-SCORAD will be measured at each clinic visit, except the screening visit. The PO-SCORAD is the SCORAD completed by the patients themselves. It is a self-evaluation tool developed by the European Task Force on Atopic Dermatitis (2011). Six items (erythema, edema/papulation, oozing/crusts, excoriation, lichenification, and dryness) will be selected to evaluate the AD severity. The overall surface affected, loss of sleep and pruritus will also be evaluated by patients on a visual analog scale. The detailed procedure of PO-SCORAD is provided in Appendix 10.

9.2 Safety Assessments

9.2.1 Medical / Surgical History

A complete review of the patient's medical history will be undertaken by the Investigator or designee at the Screening Visit (Visit 1) to ensure that no exclusion criteria have been met. Any concomitant disease, whether considered relevant for the study or not by the Investigator, must be reported in the CRF. The date of diagnosis or duration of the condition should be noted where possible.

9.2.2 Physical Examination

A physical examination will be performed by the Investigator as per the Study Flow Chart (Appendix 1) in accordance with local practices. This examination will be symptom-directed, i.e., a standard panel of body systems will not be assessed unless indicated by patient. For example should the patient report to the Investigator the presence of 'rash' then the skin would be evaluated. It is not required that additional body systems are assessed unless clinically warranted. Any clinically significant abnormal results should be recorded in the CRF. Changes in findings of the physical examination compared with the baseline examination should be recorded as an AE.

9.2.3 Vital Signs

Vital sign measurements will be performed as per the Study Flow Chart (Appendix 1). Measurements to be taken include:

- Blood pressure: will be performed as supine (after at least 5 minutes of rest) systolic and diastolic blood pressure (in mmHg)
- Heart rate: taken at rest (in bpm)
- Temperature: will be taken as per clinic practice. Temperature and route will be recorded in the CRF.

Vital signs measurements will be performed before any blood samples are taken. All new findings or changes to previous findings considered clinically significant will be recorded in the CRF as an AE if the finding is made after the patient has signed the ICF.

9.2.4 Clinical Laboratory Safety Tests: Haematology and Serum Biochemistry

Blood samples will be taken as per the Study Flow Chart (Appendix 1) for routine haematology and serum biochemistry tests. All samples will be analysed in the central laboratory.

Table 2: Clinical Laboratory Safety Tests

Haematology:	Full blood count to include red cell count, haemoglobin, haematocrit, white cell count, differential white cell count, platelet count and reticulocyte count.
Serum biochemistry:	Urea (blood urea nitrogen; BUN), creatinine, uric acid, total bilirubin, potassium, , alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), creatine phosphokinase (CPK), albumin, total protein, cholesterol, triglycerides, glucose.

If required a Follicle-Stimulating Hormone (FSH) test to confirm non-child bearing potential will be carried out at screening only.

Details of the volume of blood to be taken, sample preparation and handling are contained in a separate Laboratory Procedures Manual. Laboratory results will be reviewed for clinically significant values by each Investigator following sample analysis and verification. The report must be signed and dated by the Investigator before insertion in the CRF.

Additional blood may be required for repeats of safety laboratory test.

9.2.5 Pregnancy Test

For female patients of childbearing potential, a pregnancy test will be carried out at screening and Week 16/Visit 7/ET Visit, as per the Study Flow Chart (Appendix 1).

9.2.6 Virology

A blood sample will be taken to perform virology tests including human immunodeficiency virus (HIV), Hepatitis C and Hepatitis B at screening as detailed in Study Flow Chart (Appendix 1).

9.2.7 Electrocardiogram (ECG)

A 12-lead ECG 10 mm/1 mv, 25 mm/s with a 10 second lead II rhythm strip will be recorded on the days indicated in Study Flow Chart (Appendix 1). Patients will be rested quietly in a fully supine position for 5 minutes before the ECG is taken.
Use of a 6-lead ECG is acceptable if no 12-lead ECG is available.

9.2.8 Body Mass Index (BMI)

Weight (kg) and height (cm) will be collected to calculate the BMI (kg/m²), and will be recorded at Screening/Visit 1and Week 16/Visit 7/Early Termination (ET). The height will only be recorded once at the screening visit and the same value will be used for BMI calculation at Week 16/Visit 7/ET visits.

9.2.9 DGLA Plasma Concentration Sampling

Blood samples for trough total DGLA plasma concentration analysis will be collected via direct venepuncture as per the Study Flow Chart (Appendix 1).

The detailed instruction for DGLA plasma sample collection, processing, storage and shipment will be provided in a separate procedure.

9.2.10 Biomarker Sampling

Blood samples will be collected via direct venepuncture as per the Study Flow Chart (Appendix 1). The samples will be stored for the potential analysis of AD biomarkers at a later date.

The detailed instruction for biomarker sample collection, processing, storage and shipment will be provided in a separate procedure.

9.2.11 Sample Storage, Handling and Shipping

Sample storage, handling and shipping will be done as per standard operating procedures and as specified in the Laboratory Procedures Manual.

9.2.12 Adverse Event Assessment

See Section 11.

9.2.13 Concomitant Medication

Any medication (prescription as well as over the counter (OTC) drugs, vitamins and antacids) or therapeutic intervention deemed necessary for the patient, and which, in the opinion of the Investigator, do not interfere with the safety and efficacy evaluations, may be continued unless they are included in the list of 'medications and therapeutic regimens excluded from the study' outlined below. However, the Investigator should be cautious in evaluating the need for change in dosage and should carefully assess if any concomitant medication is necessary.

Any medications, herbal medicines, natural health remedies and nutritional supplements used within 30 days prior to Screening (Visit 1) until completion (Visit 8) are to be recorded in the concomitant medication module in the CRF system. The generic name of the medication (i.e., not local trade names), along with start date, stop date, dose, route, regimen and indication shall be recorded as applicable in the CRF system.

Any new medications or changes to the dose or regimen of pre-existing medications will be updated on a routine basis during the study.

Investigational new drugs (i.e. drugs that are not marketed in the local market) should not be co-administered with the IMPs during the entire period of the study.

9.2.13.1 Permitted Therapies

9.2.13.1.1 Emollients

All patients should be applying bland emollient, **initiated at least 7 days prior to Baseline/Day 0,** usually twice a day on their skin including AD lesions. Emollient use must continue at the same frequency and on the same skin areas throughout the study. Any change in the frequency, application of the skin area or the emollient by the patient must be documented in the patient's compliance log. Patients will be asked to avoid using emollients containing any active ingredient which has or may have an effect on AD including the following ingredients:

- Urea
- Ceramide
- Hyaluronic acid

Note:

Patients who have been on a stable emollient with an active ingredient (for example urea, ceramide and hyaluronic acid) for at least 12 weeks prior to screening and are otherwise

eligible may continue using their pre-existing emollients, if deemed appropriate by the investigator and if they are willing and able to continue using the same stable emollient for the duration of the study

Every effort should be made to use the same emollient throughout the study. The commercial name of the selected emollient(s) will be recorded in the source document and the eCRF, along with the frequency and quantity. Patients will also record on a daily basis their emollient use as instructed by the clinic staff. No other products may be applied to the lesions during the study. On the day of the visit, patients should apply emollient after all assessments have taken place.

9.2.13.1.2 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 AD. Such medications are allowed during the study only if the patient has been on a stable dose for at least 4 weeks prior to Baseline/Day 0 and continues to use the same agent everyday throughout the study.

Inhaled and intranasal corticosteroids for stable medical conditions are allowed.

9.2.13.2 Medications and therapeutic regimens excluded from use in the study

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

- Topical medicated treatments that could affect AD, including but not limited to:
  - topical corticosteroids
  - tars
- Any topical product containing urea, ceramides or hyaluronic acid
- Systemic therapy that could affect AD, e.g. retinoids, methotrexate, cyclosporine, hydroxycarbamide (hydroxyurea), azathioprine and oral/injectable corticosteroids
- Any biological agent
- UV-A or UV-B phototherapy
- Psoralen + Ultraviolet A (PUVA) therapy
- Use of tanning booth
- Any other investigational medicinal product
- Traditional medicine, herbal extracts and supplements used to treat AD

9.2.14 Restrictions

Behavioural

Patients will be asked to refrain from any travel to sunny climates or use of tanning equipment, saunas and swimming throughout the duration of the study.

Extensive UV exposure or UV-B devices will be prohibited within 4 weeks of the start of the trial and during the trial.

Other

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

Patients will be required to administer the drug 2 hours after the consumption of food. Medication(s) for other conditions that are permitted in the study can be taken as usual. Patients will also be instructed to not consume food for approximately 1 hour after IMP administration.

9.2.15 Rescue Treatment

If medically necessary (ie, to control intolerable AD symptoms), rescue treatment for AD may be provided to study patients at the discretion of the investigator. If possible, investigators should avoid administration of rescue treatments before Week 4 due to the expected time to onset of treatment-response following DS107 treatment.

For the purpose of efficacy analysis, patients who receive rescue treatment during the study treatment period will be considered treatment failures from the time rescue treatment is used.

Topical corticosteroids or calcineurin inhibitors may be used for rescue, but should be reserved for problem areas only, eg, face, neck, intertriginous and genital areas, etc. If a patient receives rescue treatment with systemic corticosteroids or non-steroidal systemic immunosuppressive drugs (cyclosporine, methotrexate, mycophenolate mofetil, azathioprine, etc.) study treatment will be immediately discontinued.

Investigators should make every attempt to conduct efficacy and safety assessments (eg, disease severity scores, safety labs) immediately before administering any rescue treatment.

10 INVESTIGATIONAL MEDICINAL PRODUCT / INVESTIGATIONAL DRUG

10.1 Investigational Medicinal Product (IMP)

The following medication supplies will be used in the study:

DS107 capsules:

Each DS107 capsule contains 500mg DGLA as an active ingredient in an opaque, oval soft gelatin capsule.

Placebo capsule:

Each matching placebo capsule contains 500mg of liquid paraffin in an opaque oval soft gelatin capsule.

10.2 Supply, Packaging, Labelling, Handling and Storage

DS107 capsules will be provided by the Sponsor as opaque, oval soft gelatin capsules containing 500mg of DGLA.

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

DS107 capsules will be supplied in manufactured form (blinded), packaged in cold formed aluminium foil blisters of 28 units. Placebo will be presented in identical blisters and packs and stored/packaged the same as DS107 capsules. Study medication will be labelled according to EU and US regulations.

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. DS107 and placebo capsules should be stored at a controlled room temperature between 15-25°C and will only be supplied to patients in the trial under the supervision of the Investigator.

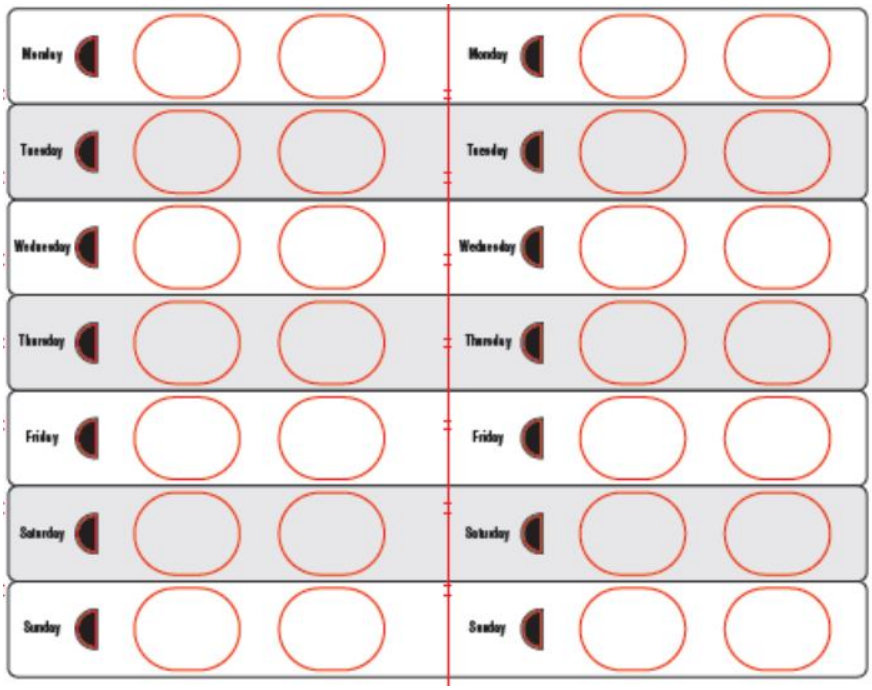
10.3 Dosage and Administration

This study involves a comparison of DS107 (2g) with placebo, administered orally once daily for a total duration of 16 weeks. **The last study drug administration should occur on the day preceding Week 16 (Visit 6) / Early Termination (ET) visit**. Patients will be randomized to one of the two treatment groups in a 1:1 ratio:

- 2g DS107 (4 DS107 capsules) administered once-daily for 16 weeks
- Placebo (4 placebo capsules) orally administered once-daily for 16 weeks

Patients will be required to administer the drug 2 hours after the consumption of food. Medication(s) for other conditions that are permitted in the study can be taken as usual. Patients will be also be instructed to not consume food for approximately 1 hour after IMP administration. On the day of the visit, patients should take dose after all assessments have taken place.

Blister packs will consist of 7 rows of 4 capsules with each weekday detailed. Each row constitutes one dose. Patients will be instructed to take the 4 capsules **from left to right**, on the relevant day, as shown below:



To maintain the blind throughout the study, the DS107 capsules and placebo capsules will be identical in appearance.

10.4 Duration of Treatment

Patients will be orally administered DS107 or placebo once daily for 16 consecutive weeks.

10.5 Methods for Assigning Patients to Treatments

Approximately 220 patients will be randomized into double-blind treatment groups in a 1:1 ratio by an Interactive Web Response System (IWRS) as follows:

- 2g DS107 (4 DS107 capsules) administered once daily for 16 weeks
- Placebo (4 placebo capsules) orally administered once daily for 16 weeks

A randomization list permuted by blocks and stratified by site will be generated by the Sponsor 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 labelling the study drug, the statisticians generating the schedule and the IWRS team responsible for implementing the schedule. The IWRS will assign a medication kit number to each patient and the contents will be based on the randomization code.

At the investigational site, each patient 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.: 102-10 for the tenth patient screened at the site number 02). Patient numbers will be assigned in ascending order starting with 01.

10.6 Drug Accountability

All IMP supplies for this study must be retained in a safe place at all times of the study. Only personnel authorised by the principal Investigator at each site should dispense the IMP and the

accountability is the responsibility of the Investigator. The Investigator or pharmacist must complete the IMP supply form, verifying the receipt of IMP. The patients should return all used and unused packs of IMP to the study site at every visit. Following compliance assessment the packs of IMP will be retained in a secure location at the site until the end of the study. After the Clinical Research Associate (CRA) has completed a final drug accountability review, the IMP may be returned or destroyed only when instructed by the CRA.

11 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

11.1 Definitions of Adverse Events

11.1.1 Seriousness

Adverse Events (AE):

Any undesirable experience occurring to a patient that has signed the ICF and who has taken their first dose of the study drug, whether or not considered related to the investigational IMP(s). All AEs must be recorded in the case report form, defining relationship to IMP and severity. AEs should also be recorded by the Investigator in the patient file/notes.

Serious Adverse Events (SAE):

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.

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

- results in death
- is life-threatening
- requires in-patient 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 patient 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 patient 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.

Unexpected Adverse Event (UAE):

An experience not previously reported in the Investigator's Brochure or similar product information sheet such as the Summary of Products Characteristics (SPC).

11.1.2 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. The following definitions are to be used to rate the severity of an AE:

- Mild: The adverse event is transient and easily tolerated.
- Moderate: The adverse event causes the patient discomfort and interrupts the patient's usual activities.

- Severe: The adverse event causes considerable interference with the patient's usual activities, and may be incapacitating or life-threatening.

11.1.3 Relationship to IMP

The Investigator will establish causality of the AE to experimental treatment. The Investigator should take into account the patient'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.

11.1.4 Reporting of AEs and SAEs

All AEs must be recorded in the case report form, defining relationship to IMP and severity. *The frequency of each AE should always be recorded to indicate if the event is intermittent, continuous, one-time event etc. If the same AE occurs repeatedly at approximately the same strength in the same patient, this AE should be counted only once. If any aspect of the AE changes (including but not limited to severity, frequency, causality), a new AE should be recorded.* AE start and end dates should be clearly defined in the CRF.

As soon as the Investigator is aware of a potential SAE, he/she should report the SAE to the Pharmacovigilance (PV) CRO by fax or e-mail, and in any case no later than 24 hours after the knowledge of such a case. In case of questions regarding an SAE, the investigator or authorized study personnel can contact the PV CRO monitor by phone. The contact information, is provided in the Investigator Site File.

At the time of the call, the Investigator must provide as a minimum requirement, the Patient number, birth date, nature of the SAE, and a preliminary assessment of causality. The Investigator should follow-up the initial notification of the potential SAE by faxing/e-mailing a copy of the form to PV CRO at the number/address provided in the Investigator Site File. The SAE reporting form should be received to the PV CRO within 24 hours after knowledge of such a case.

Follow-up information on an existing SAE that is fatal or life-threatening should be reported by the Investigator to PV CRO within 5 days after the initial report. Where appropriate, hospitalisation or autopsy reports should be made available. All SAEs will be followed up until resolution (i.e., asymptomatic, stabilisation or death).

AE's should be reported for the entire study duration up to and including the follow up period. Following completion of the study, if the Investigator becomes aware of any AE that is potentially related to the IMP, the Sponsor should be notified.

11.2 Serious Adverse Reactions and Unexpected Adverse Reactions

11.2.1 Definitions

Adverse Reaction:

All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions.

The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility i.e. the relationship cannot be ruled out.

For marketed medicinal products, an adverse reaction is a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for modification of physiological function.

Unexpected Adverse Reaction:

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator's Brochure for an unauthorised investigational product or similar product information sheet such as the Summary of Products Characteristics (SPC)).

Suspected Unexpected Serious Adverse Reaction (SUSAR):

Any serious adverse reaction that might be related to the IMP and are unexpected according to the definition above.

11.2.2 Reporting of suspected unexpected serious adverse reactions

Suspected unexpected serious adverse reactions (SUSARs) will be reported by PV CRO according to appropriate Competent Authority and Ethics Committee requirements. SUSARs will be reported to Investigators according to ICH Good Clinical Practice and to local regulations. SUSAR reporting to the Competent Authorities and Ethics Committees will be performed according to local regulations in an unblinded manner. The Competent Authorities will be notified of all SUSARs through the Eudravigilance database.

Fatal and life-threatening SUSARs should be reported by PV CRO as soon as possible to the Competent Authorities and Ethics Committees according to local regulations, and in any case no later than seven calendar days, after knowledge by PV CRO of such a case. Relevant follow-up information on the case will be subsequently communicated within an additional eight days. All other SUSARs shall be reported to the Competent Authorities concerned and to the Ethics Committee concerned according to local regulations as soon as possible but within a maximum of fifteen days of first knowledge by PV CRO.

11.3 Differentiation of Treatment Failure and AE

Please note, that the lack of improvement of the symptoms of AD is not an AE and should be reported as treatment failure.

11.4 Pregnancy Reporting

If a patient or a patient’s partner becomes pregnant during the study, the patient should inform the study site as soon as possible. Upon confirmation of the pregnancy, the patient 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 the Sponsor within 24 hours of confirmation of the pregnancy.

Post-treatment follow-up should be done to ensure patient safety. Pregnancy is not itself an AE or SAE, however maternal/foetal 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 the Sponsor of the outcome as a follow up to the initial Pregnancy Form.

12 STATISTICAL METHODOLOGY AND DATA MANAGEMENT

12.1 Study Design

This clinical trial employs a randomized, double-blind, placebo-controlled parallel group design. Randomisation is used to minimise assignment bias and to increase the likelihood that known and unknown patient attributes (e.g. demographic characteristics) are evenly balanced across the treatment groups. Blinding is used to reduce potential bias during data collection and evaluation of safety and efficacy. The use of placebo as comparator is justified as a reasonable design to assess safety and efficacy in patients based on the brevity of the study duration and the absence of any possible long-term irreversible damage that may be the result of placebo treatment. A full description of the study design is presented in Section 6 above.

12.2 Randomisation

Approximately 220 patients will be randomized into double-blind treatment groups in a 1:1 ratio by an IWRS.

- 2g DS107 (4 DS107 capsules) administered once-daily for 16 weeks
- Placebo (4 placebo capsules) orally administered once-daily for 16 weeks

A randomization list permuted by blocks and stratified by site will be generated by the Sponsor 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 labelling the study drug, the statisticians generating the schedule and the IWRS team responsible for implementing the schedule. The IWRS will assign a medication kit number to each patient and the contents will be based on the randomization code.

At the investigational site, each patient 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.: 102-10 for the tenth patient screened at the site number 02). Patient numbers will be assigned in ascending order starting with 01.

The treatment assignment procedure will use blocks of sufficient size to maintain a blind and balance across treatment arms. Following successful completion of the screening/baseline evaluations and confirmation that the patient is eligible for participation, the patient will be randomised to treatment. This will be performed by the Investigator using the IWRS which will assign a medication number to the patient.

12.3 Estimation of Sample Size

In the Phase 2a trial, IGA response rates of 21.6% and 11.8% were observed for DS107 and placebo respectively resulting in a difference in response rates of 9.8%. Due to the prolonged treatment period of 16 weeks, a clinically relevant difference in IGA response rates of 15% was expected for the current study.
Assuming a placebo response rate of 12% and a true response rate difference of 15% at Week 16 and using a two-sided Chi-Square test on a significance of 5%, then 220 evaluable patients (110 patients per treatment arm) will be needed for 80% power to detect this difference as statistically significant. As the following table shows, the number of patients needed for the

discovery of a 15% response rate difference depends also on the placebo response rate shown in the left column of the table as decimal numbers:

Number of patients per study group required under the assumptions as follows
Chi-square test, 2 x 2 table, Two Proportions, two-sided.
Sample Size 1 as a function of H1: Proportion 1 and Power.
H1: Proportion 2 - Proportion 1=0,15 Significance Level=0,05 Sample Size 2 / Sample Size 1=1

H1: Proportion 1 = Response Rate Placebo	Power 0,7	0,8	0,9
0,06	63,4	80,3	107,0
0,08	71,2	90,2	120,3
0,10	78,6	99,6	132,8
0,12	85,5	108,4	144,6
0,14	92,0	116,6	155,6
0,16	98,0	124,3	165,9
0,18	103,6	131,4	175,4
0,20	108,8	138,0	184,2

It was assumed that similar estimations apply to the primary endpoint EASI-75.

12.4 Blinding and Code Breaking Instructions

All study site personnel, as well as the personnel involved in the monitoring or conduct of the study, will be blinded to the individual patient treatment assignments. Randomisation details will be kept strictly confidential, accessible only in an emergency to authorized persons, until the time of formal unblinding. The blinded code for the trial will be broken only after all patient data has been recorded and verified and the database locked.

Emergency unblinding will be carried out through the IWRS system with relevant site personnel and pharmacovigilance monitors provided with the required system access to carry out un-blinding.

12.5 Data Analysis

Data analysis will be performed at a contract research organisation (CRO). All computations will be conducted using SAS® Version 9.2 or later. Graphical summaries will be produced using SAS®. A detailed description of the analyses to be performed will be provided in the statistical analysis plan (SAP).

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

12.6 Analysis Sets

Enrolled Set
The Enrolled Set consists of all patients who sign informed consent.

Screen Failures
Screen Failures are patients from the Enrolled Set who do not meet the eligibility requirements and are withdrawn from the study prior to randomisation.

Randomised Set
The Randomised Set consists of all patients who are randomised to the study.

Safety Analysis Set (SAS)
The Safety Analysis Set (SAS) consists of all patients who received at least one dose of the medication. SAS is the analysis population for all safety endpoints. Analysis will be done according to the actual treatment patients received.

Full Analysis Set (FAS)
The Full Analysis Set (FAS) consists of all patients who were randomised to the study and received at least one dose of study medication. FAS is the primary analysis population for efficacy endpoints. Analysis will be done according to the treatment patients were randomised to.

Per Protocol Set (PPS)
The Per Protocol Set (PPS) is the subset of FAS who completed the study without any major violations. Protocol violations will be assessed for each patient in a blinded fashion prior to database lock at a Blind Data Review Meeting (BDRM), and the PPS will also be finalised during this meeting. PPS is a supportive analysis population for efficacy endpoints. Analysis will be done according to the treatment patients were randomised to.

12.7 Safety Analysis

Demographic, medical history and physical examination data will be listed for each patient and summarised descriptively.

All AEs recorded during the study will be coded to system organ class and preferred terms using the current version of the Medical Dictionary for Regulatory Activities (MedDRA). AEs will be tabulated and summarised by treatment, relationship to treatment, seriousness and severity.

Clinical laboratory values (haematology and biochemistry) will be listed for each patient by treatment and day. Values outside the laboratory normal ranges will be listed separately with associated comments as to their clinical significance, with potentially clinically significant abnormalities highlighted and summarised by treatment. Most recent clinical laboratory values obtained prior to dosing will be defined as baseline values.

Individual values of vital signs will be listed and summarised descriptively for each treatment and visit.

Concomitant medications (if any), categorised by medication group and subgroup according to the latest version of the World Health Organisation drug dictionary, will be listed and summarised by treatment.

12.8 Statistical Analysis Plan

In addition to the summarised analysis plan outlined below, a separate document, Statistical Analysis Plan (SAP) for DS107G-05 AD3 will detail all analyses to be performed.

12.8.1 Pharmacokinetic Analysis

Plasma concentrations of DGLA will be tabulated and summarised descriptively. Individual and mean plasma concentration-time profiles of DGLA will be presented graphically.

12.8.2 Primary variables

The primary variables will be:

- the proportion of patients achieving an vIGA-AD™ score of 0 (clear) or 1 (almost clear) and a decrease of at least 2 points in vIGA-AD™ from baseline to Week 16.

- the proportion of patients achieving EASI-75 (≥75% improvement from baseline) at Week 16.

Both primary endpoints will be analysed using a Generalised Linear Mixed Model (GLMM) with treatment arm, visit, their interaction treatment-by-visit, and baseline vIGA-AD™ value as factors, and with patient as random effect; this model will especially be used to estimate missing data and the treatment effects at Week 16 taking missing data into account. The primary analysis will be based on the FAS, and repeated for the PPS as a supportive sensitivity analysis. Success in either of the primary endpoints denotes successful proof of efficacy.

If rescue medication is used, the patient will be specified as a non-responder from the time the rescue is used.

The primary statistical analysis assumes "Missing At Random (MAR)" when handling missing data. The treatment effect obtained under the MAR assumption is essentially that which could have been reached if all patients had fully adhered to treatment or, in other words, the effect a patient may expect if they take the medication as directed. This is sometimes known as the 'de jure' or 'efficacy' estimand. Due to the lack of perfect adherence in practice, the 'de facto' or effectiveness treatment effect will also be estimated. This estimand includes assumptions regarding the treatment effects that could be expected to occur when patients discontinue treatment. The *jump to reference* method described by Carpenter *et al*. (2013) will be used to estimate the de facto estimand, using the placebo arm as the reference. This is based on the assumption that patients who discontinue from study drug have no alternative oral treatment option suitable for longer-term use and so their responses are likely to revert to those of the placebo group. An additional sensitivity analysis will evaluate patients who received rescue medication as treatment failures from the visit onwards where rescue treatment startedThe sensitivity analyses for missing data will be performed on the FAS only.

12.8.3 Secondary variables

IGA and EASI-75 responders at other time points will also be analysed using a GLMM model similar to that described in Section 12.8.2.

The efficacy variables and their changes from baseline will be summarized with descriptive statistics per treatment group and visit. This applies to the vIGA-AD™, EASI, NRS scores for pruritus, DLQI, POEM, SCORAD, AIS and PO-SCORAD. Change from baseline endpoints will be analysed using Mixed Model with Repeated Measures (MMRM) with Treatment Arm, Visit and Treatment x Visit Interaction as a factors and baseline value as a covariate, to account for missing data. The secondary efficacy analyses will be based on the FAS only. For vIGA-AD™ as a 5-level ordinal variable, mixed ordinal logistic regression will be used with factors defined as above and IGA at baseline as a factor too.

If rescue medication is used, the patient will be specified as a non-responder from the time the rescue is used

12.8.4 Safety variables

The type and frequency of adverse events will be summarised by MedDRA system organ class and preferred term per treatment group. In addition, the number and proportion of patients with at least one adverse event will be summarised per treatment group.

The number and proportion of patients experiencing serious adverse events, adverse events leading to withdrawal and adverse events possibly or probably related to treatment will be summarized per treatment group. The secondary safety analysis will be based on the Safety Analysis Set only.

12.9 Interim Analysis

An interim analysis may be conducted after at least 50% of planned enrolled patients have completed their Week 16 assessments or an early termination visit. The interim analysis will be conducted in accordance with sponsor standard operating procedure (SOP) "Interim Analysis of Clinical Studies".

An unblinded interim analysis will be performed by an unblinded independent statistician. Interim data and the results of interim analyses will not be accessible by anyone other than the unblinded statistician. The sponsor will remain blinded with procedures in place to ensure the confidentiality of the interim data, as per the sponsor SOP "Interim Analysis of Clinical Studies".

The unblinded statistician will make one of the following recommendations to the sponsor based solely upon the primary efficacy endpoints:

- Modify the sample size
- Continue the study as originally planned

Further details will be described in an interim statistical analysis plan.

12.10 Data Collection / Case Report Forms

Data will be collected using a validated electronic data capture (EDC) solution. Electronic Case report forms (eCRFs) will be utilised for recording data from each patient meeting the eligibility criteria and being randomised in the study; and a limited amount of data will be completed for patients who fail to meet eligibility criteria (i.e. screen failures). Electronic access to the CRF will be available to all investigator sites. All study staff responsible for entering data into the eCRF system will be trained prior to the start-up of the study. A personal log-in will be provided for all responsible personnel to allow for an audit trail relating to the study data to be maintained.

All evaluations performed shall be entered in a timely manner into the eCRF by a member of the site staff delegated responsibility for this specific task by the Principal Investigator of the clinical site. It is the responsibility of the Investigator to ensure that the eCRFs are properly completed. The data in the eCRFs should be consistent with the relevant source documents. The Investigator will sign the designated signature fields of the eCRF to confirm that the information on each screen is accurate and complete. All data must be stored in an unidentifiable form treated with strict confidentiality in accordance with applicable data-protection regulations.

Captured data will be monitored electronically and Source Data Verification (SDV) will take place at the site where all information will be verified against the individual patient records. Any inconsistencies will be presented as queries; either as automatically generated queries if raised by the logical data checks of the eCRF system, or by manually generated queries if raised by the data validation checks or the SDV performed by the Data Manager (DM) or the CRA respectively. Queries shall be resolved in a timely manner by a trained member of the site staff.

12.11 Data Management

Data will be transmitted electronically into the web based EDC system. Data will be coded according to pre-specified dictionaries and in accordance with the CRO Standard Operating

Procedures (SOP). The handling of data, including data quality control, will comply with all applicable regulatory guidelines.

12.12 Protocol Deviations

Protocol deviations will be captured through site self-reporting, CRA source data verification and data management edit checks and will be recorded by the CRA throughout the study in both the monitoring visit reports and in a centralised log.

13 REGULATORY AND ADMINISTRATIVE PROCEDURES

13.1 Institutional Review

Investigators will agree that the study will be conducted according to the principles of the ICH E6 Guideline on (Good Clinical Practice) GCP and the ethical principles that have their origins in the World Medical Association Declaration of Helsinki. The Investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations.

This trial was designed and organised taking all ethical considerations into account. The Protocol and the Patient Information Sheet / Informed Consent Form will be approved by the relevant Competent Authorities and Ethics Committees, and possibly other public bodies according to local requirements before commencement. If a protocol amendment is necessary, this will be prepared with the agreement of the National Co-ordinating Investigator, and signed by the relevant parties. If the amendment is considered to be substantial, it will be submitted to the Competent Authorities and Ethics Committees and possibly other public bodies according to local requirements for review and approval. The protocol amendment will not be implemented before approvals are obtained, if required. Minor amendments which do not affect the safety or physical or mental integrity of the clinical trial participants or the scientific value of the trial (i.e. non-substantial amendments) do not need to be submitted to Competent Authorities until the next substantial amendment.

SUSAR reports and Periodic Safety Reports will be sent to Competent Authorities and Ethics Committees according to local regulations.

13.2 GCP

The study will be managed and conducted according to the latest International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines for Good Clinical Practice (GCP) and applicable regulatory requirement(s) (specifically the principles of GCP in ICH topic E6, as laid down by the Commission Directive 2005/28/EC and in accordance with applicable local laws and guidelines). A copy of the ICH guidelines can be found in the Investigator Site File (ISF).

13.3 Essential Documents

The ICH guideline for GCP lists a number of essential GCP documents required prior to, during, and after the conduct of the study. It is the responsibility of the monitor to ensure that the Investigator is always provided with a copy of such documents prepared by the study management, and it is likewise the responsibility of the Investigator to provide the monitor with essential documents prepared by the Investigator or the local Ethics Committee. A complete list of essential GCP documents can be found in the Investigator Site File.

13.4 Record Retention

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 patients, 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.

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 longest.

13.5 Monitoring / Quality Control

Monitoring visits will be conducted during the study 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.
Incorrect or missing entries in the CRFs will be queried and will be corrected appropriately.
All clinical data will undergo quality control checks prior to clinical database lock. Edit checks will then be performed for appropriate databases as a validation routine using SAS ® to check for missing data, data inconsistencies, data ranges etc. Each eCRF is reviewed and signed by the Principal Investigator (PI).

13.6 Quality Assurance

The site may be audited during or after the study is completed by the Sponsor representatives or regulatory authorities may conduct an inspection. The Investigator(s) will be expected to cooperate with such a visit and to provide assistance and documentation (including all study documentation, and patient source data) as requested.

13.7 Insurance and Liability

Insurance and liability for the study is the responsibility of the Sponsor, DS Biopharma.

13.8 End of Trial

End of Trial is defined as Last Subject Last Visit (LSLV). LSLV is defined as the date the Investigator reviews the last subject's safety data and determines that no further evaluation is required for the subject to complete the trial.

13.9 Confidentiality

All information obtained during the conduct of the study with respect to the patients' state of health will be regarded as confidential. This is detailed in the written information provided to the patient. An agreement for disclosure of any such information will be obtained in writing and is included in the ICF signed by the patient. The study data shall not be disclosed to a third party without the written consent of the Sponsor.

13.10 Data Protection

All information collected for this study will be kept strictly confidential. The Sponsor undertakes to comply with applicable data protection regulations, which are further detailed in the written information provided to the patient. In case of data security breach, this will be reported to the relevant supervisory authority where the breach presents a risk to the affected individuals. This will be reported within 72 hours of becoming aware of the breach. Where a breach is likely to result in a high risk to the affected individuals, the Sponsor will also inform those individuals without undue delay.
In compliance with governmental regulations/ICH GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the regulatory agency(ies), and the IRB/IEC direct access to review the subject's original medical records for verification of study-related procedures and data. For further information, the Sponsor data protection officer can be contacted at dataprotection@dsbiopharma.com.

13.11 Report and Publication

Production of a clinical study report in accordance with the ICH guidelines will be prepared. No information from the study will be published without the prior written consent of the Sponsor.

13.12 COVID-19 Contingency

Due to the unprecedented worldwide COVID-19 pandemic, the Sponsor is implementing measures to assure the safety of trial participants, to maintain compliance with GCP and to minimize risk to trial integrity.

Among these measures are modifications to the protocol to ensure that if difficulties in adhering to protocol-speciifc procedures or protocol-mandated visits are encountered by patients, investigators or study sites, adequate and appropriate contingencies are in place.

COVID-19 contingency measures do not replace the existing protocol procedures and visit schedule.

The following contingencies and actions will be implemented in response to the evolving COVID-19 pandemic:

1. An interim analysis will be conducted after at least 50% of patients have completed their week 16 or end-of-treatment visits as described in Section 12.9 Interim Analysis. Due to the rapidly evolving COVID-19 situation at both a global and country level, a modification to the prospectively planned sample size may be necessary if patient recruitment is not feasible and must be stopped. The interim analysis will safeguard the integrity of the trial and inform whether further patient recruitment is required when conditions at participating sites are amenable to re-initiation of patient recruitment.

2. In a worst-case scenario where a patient is unable to attend the study site for protocol-mandated visits, due to patient considerations (such as COVID-19 infection or quarantine) or study site restrictions;

   A. The investigator will complete all possible assessments via phone for all impacted study visits as described in Appendix 11. COVID-19 Contingency Investigator Assessment Phone Visits.

   - Phone visit assessments must include assessment of adverse events, patient-reported efficacy endpoints and compliance.
   - The patient will be reminded that IMP will continue to be administered approximately 2 hours after food consumption at the same time each day. Patients will be reminded to not consume food for approximately 1 hour after IMP administration.
   - The patient will be reminded that NRS for the assessment of pruritus will continue to be captured on a daily basis from screening to the follow-up visit. Emollient use will also continue to be captured on a daily basis for the same period.
   - On completion of this visit, patients will be advised that they will be required to return to the investigational site at the next scheduled visit and to bring with them the unused DS107/placebo patient packs, the used DS107/placebo patient packs, and the patient compliance log.

   B. IMP will be couriered directly to the patient.

Investigators must make every effort possible to ensure that patients adhere to the protocol procedures and attend all scheduled visits. COVID-19 contingency measures regarding IMP delivery and phone visits must only be used if absolutely necessary and after every effort to follow the protocol visit schedule has been exhausted. Investigator responsibilities as prescribed by ICH GCP, including oversight of patient safety must continue to be observed in all cases whether or not contingency actions relating to COVID-19 are required.

This contingency will facilitate the conduct of appropriate safety monitoring and will preserve the investigational product supply chain.

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15 APPENDICES

15.1 Appendix 1: Study Flow-Chart

Visit	Screening/ Visit 1	Baseline / Visit 2	Week 1/Visit 3	Week 4/ Visit 4	Week 8 / Visit 5	Week 12/ Visit 6	Week 16/ Visit 7 (EOT)	Week 18/ Visit 8 (Follow up 1)	Week 20/ Visit 9 (Follow up 2)
Day	**-14 to -1**	**0**	**7**	**28**	**56**	**84**	**112**	**126**	**140**
Visit Window			+/-2 days	+/-2 days	+/-2 days	+/-2 days	+/-2 days	+/-2 days	+/-2 days
Type of Visit	Onsite	Onsite	Telephone	Onsite	Onsite	Onsite	Onsite	Onsite	Onsite
Informed Consent	X								
Assign Patient Identifier Number	X								
Demographics	X								
Medical/Surgical History	X								
Review Inclusion/Exclusion Criteria	X	X							
Randomization		X							
Safety Labs: Serum Biochemistry (including FSH levels at screening when applicable[1]), Hematology.	X	X		X	X		X	X[2]	
Virology	X								
Trough Plasma Levels		X		X	X		X		
Biomarker Sampling		X					X		
Pregnancy Test (β-hCG if female of childbearing potential)	X						X		
Vital Signs	X	X		X	X	X	X	X	X
Physical Examination[3]	X	X		X	X	X	X	X	X
ECG		X					X		
BMI	X						X		
Dispense Study Drug[4]		X		X	X	X			
Collect Study Drug				X	X	X	X		
Dispense Patient Compliance Log		X		X	X	X			
Collect and Review Patient Compliance Log				X	X	X	X		
Discuss Patient Compliance Log			X						
IMP Accountability				X	X	X	X		
Discuss IMP Compliance			X						
BSA	X	X		X	X	X	X	X	X
vIGA-AD™	X	X		X	X	X	X	X	X
EASI Assessment	X	X		X	X	X	X	X	X
NRS Pruritus Assessment	X----------								----------X
DLQI Questionnaire		X		X	X	X	X	X	X
POEM Questionnaire		X		X	X	X	X	X	X
SCORAD Questionnaire		X		X	X	X	X	X	X
Athens Insomnia Scale		X----------							----------X

PO-SCORAD Questionnaire		X		X	X	X	X	X	X
Concomitant Medications	X	X	X[6]	X	X	X	X	X	X
Emollient Use Capture	X----------								----X
Adverse Events [5]		X	X[6]	X	X	X	X	X	X

1. FSH requirement to confirm female of non-child-bearing potential for women greater than 40 years of age who have had a cessation of menses for at least 12 months. Non-child bearing potential may also be confirmed via cessation of menses for at least 24 months without FSH levels confirmed.
2. Only if clinically significant change from baseline in safety laboratory results at Week 16.
3. Physical Examination will be symptom-directed.
4. Patients will be instructed to take their last study drug dose the day preceding Week 16 visit.
5. Collection of AEs will start after the first study drug administration.
6. Adverse Events and Concomitant Medication will be collected over the phone at this visit.

15.2 Appendix 2: Diagnostic Features of Atopic Dermatitis (American Academy of Dermatology Consensus Criteria)

Essential features — must be present:
• Pruritus
• Eczema (acute, subacute, chronic)
• Typical morphology and age specific patterns*
• Chronic or relapsing history

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

Important features — seen in most cases, adding support to the diagnosis:
• Early age of onset
• Atopy
• Personal and/or family history
• Immunoglobulin E reactivity
• Xerosis

Associated features — These clinical associations help to suggest the diagnosis of atopic dermatitis but are too nonspecific to be used for defining or detecting atopic dermatitis for research and epidemiologic studies:
• Atypical vascular responses (e.g. facial pallor, white dermographism, delayed blanch response)
• Keratosis pilaris/ pityriasis alba/ hyperlinear palms/ icthyosis
• Ocular/periorbital changes
• Perifollicular accentuation/ lichenification/ prurigo lesions

Exclusionary conditions — It should be noted that a diagnosis of atopic dermatitis depends on excluding conditions, such as:
• Scabies
• Seborrheic dermatitis
• Contact dermatitis (irritant or allergic)
• Icthyoses
• Cutaneous T-cell lymphoma
• Psoriasis
• Photosensitivity dermatoses
• Immune deficiency diseases
• Erythroderma of other causes

15.3 Appendix 3: Validated Investigator's Global Assessment for Atopic Dermatitis (vIGA-AD™)

Instructions:

The IGA score is selected using the descriptors below that best describe the overall appearance of the lesions at a given time point. It is not necessary that all characteristics under Morphological Description be present.

Score	Morphological Description
0 – Clear	No inflammatory signs of atopic dermatitis (no erythema, no induration/papulation, no lichenification, no oozing/crusting). Post-inflammatory hyperpigmentation and/or hypopigmentation may be present.
1 – Almost Clear	Barely perceptible erythema, barely perceptible induration/papulation, and/or minimal lichenification. No oozing or crusting.
2- Mild	Slight but definite erythema (pink), slight but definite induration/papulation, and/or slight but definite lichenification. No oozing or crusting.
3- Moderate	Clearly perceptible erythema (dull red), clearly perceptible induration/papulation, and/or clearly perceptible lichenification. Oozing and crusting may be present.
4- Severe	Marked erythema (deep or bright red), marked induration/papulation, and/or marked lichenification. Disease is widespread in extent. Oozing or crusting may be present.

Notes:

1. In indeterminate cases, please use extent to differentiate between scores.

For example:

- Patient with marked erythema (deep or bright red), marked papulation and/or marked lichenification that is limited in extent, will be considered "3 – Moderate".

2. Excoriations should not be considered when assessing disease severity

15.4 Appendix 4: Eczema Area and Severity Index (EASI)

Four anatomic sites – head/neck, 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 (half points are permitted):

- 0 = none
- 1 = mild
- 2 = moderate
- 3 = severe

The area affected by AD 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 AD involvement as follows:

- 0 = no involvement
- 1 = < 10 %
- 2 = 10 to 29%
- 3 = 30 to 49%
- 4 = 50 to 69%
- 5 = 70 to 89%
- 6 = 90 to 100 %

The EASI score is obtained by using the formula:

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

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

15.5 Appendix 5: Numerical Rating Scale for assessment of Pruritus

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

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

Pruritus assessment (itching) (during the past 24 hours)

To help you assess itching, we have drawn a scale from 0 to 10 where 0 represents no itching and 10 represents the worst itching that you can imagine. We would like you indicate on this scale how was your itching at its worst during the past 24 hours. Once determined, circle one number on this scale.

0	1	2	3	4	5	6	7	8	9	10

No itch **Worst imaginable itch**

15.6 Appendix 6: Dermatology Life Quality Index (DLQI)

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

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

DLQI

Score: ☐

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick ☑ 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 **garden?**	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
6	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
7	Over the last week, has your skin prevented you from **working** or **studying**?	yes no	☐ ☐	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.

15.7 Appendix 7: Patient Orientated Eczema Measure

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

15.8 Appendix 8: 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).

15.9 Appendix 9: Athens Insomnia Scale

1. SLEEP INDUCTION *(time it takes you to fall asleep after turning-off the lights)*

0	**1**	**2**	**3**
No problem	Slightly delayed	Markedly delayed	Very delayed or did not sleep at all

2. AWAKENINGS DURING THE NIGHT

0	**1**	**2**	**3**
No problem	Minor problem	Considerable problem	Serious problem or did not sleep at all

3. FINAL AWAKENING EARLIER THAN DESIRED

0	**1**	**2**	**3**
Not earlier	A little earlier	Markedly earlier	Much earlier or did not sleep at all

4. TOTAL SLEEP DURATION

0	**1**	**2**	**3**
Sufficient	Slightly insufficient	Markedly insufficient	Very insufficient or did not sleep at all

5. OVERALL QUALITY OF SLEEP *(no matter how long you slept)*

0	**1**	**2**	**3**
Satisfactory	Slightly unsatisfactory	Markedly unsatisfactory	Very unsatisfactory or did not sleep at all

6. SENSE OF WELL-BEING DURING THE DAY

0	**1**	**2**	**3**
Normal	Slightly decreased	Markedly decreased	Very decreased

7. FUNCTIONING (PHYSICAL AND MENTAL) DURING THE DAY

0	**1**	**2**	**3**
Normal	Slightly decreased	Markedly decreased	Very decreased

8. SLEEPINESS DURING THE DAY

0	**1**	**2**	**3**
None	Mild	Considerable	Intense

15.10 Appendix 10: Patient-Oriented SCORAD

PO-SCORAD on Day .....

Last name: ..... First name: .....

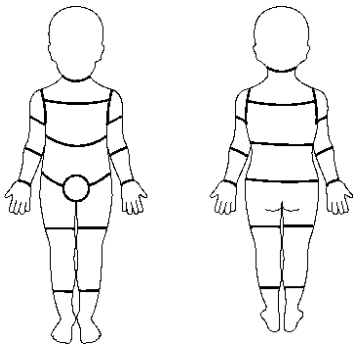
Date of birth: ..... Today's date: .....

Who is filling out this questionnaire?

O The patient
O The patient, assisted by a parent
O The patient's mother
O The patient's father
O The patient's brother / sister
O Other (please specify) .....

- **Surface affected**

O patient under 2 years old O patient over 2 years old



Using the drawing provided, shade the areas affected by eczema.

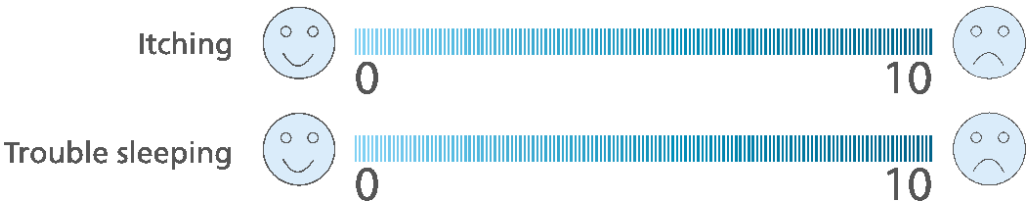
- **Intensity of symptoms**

Criteria	Intensity (from 0 to 3)
Dryness*	
Redness	
Swelling	
Oozing/scabs	
Scratch marks	
Thickening of skin	

* Dryness is evaluated on the skin not affected by eczema.

- **Subjective symptoms:** itching + trouble sleeping

visual analogue scale
(average for last 48 hrs) (from 0 to 10)



You can download a free application that will help you calculate the PO SCORAD automatically. Your computer will create a curve as your eczema evolves and you can print it and give it to your doctor.

Today's PO SCORAD:

Please visit: PoScorad sur Google play et Apple store
www.opened-dermatology.com
ou www.fondation-dermatite-atopique.org

15.11 Appendix 11: COVID-19 Contingency Investigator Assessment Phone Visits

Only to be used if a patient is unable to attend the Investigational Site due to COVID-19. Every effort should be made to complete the Study Visit at the Investigational Site.

Please conduct all of the following:

- Phone call to be completed by PI/Sub-Investigator
- Please complete all Patient Reported Assessments as listed in the flowchart below
- Please provide/email copies of Patient Scales to Patients prior to Phone call
- Please document Phone Visit in Source Notes
- Data to be entered into eCRF

Visit	**Week 4/ Visit 4**	**Week 8 / Visit 5**	**Week 12/ Visit 6**	**Week 18/ Visit 8 (Follow up 1)**	**Week 20/ Visit 9 (Follow up 2)**
Day	**28**	**56**	**84**	**126**	**140**
Visit Window	+/-2 days	+/-2 days	+/-2 days	+/-2 days	+/-2 days
Concomitant Medications	**X**	**X**	**X**	**X**	**X**
Adverse Events	**X**	**X**	**X**	**X**	**X**
DLQI Questionnaire	**X**	**X**	**X**	**X**	**X**
POEM Questionnaire	**X**	**X**	**X**	**X**	**X**
PO-SCORAD Questionnaire	**X**	**X**	**X**	**X**	**X**
Discuss NRS Pruritus Assessment	**X**	**X**	**X**	**X**	**X**
Discuss Athens Insomnia Scale	**X**	**X**	**X**	**X**	**X**
Discuss Emollient Use Capture	**X**	**X**	**X**	**X**	**X**
Discuss Patient Compliance Log	**X**	**X**	**X**		
Discuss IMP Compliance	**X**	**X**	**X**		
Courier Study Drug	**X**	**X**	**X**		