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

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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 Operating Officer/Medical Director,
DS Biopharma

CLINICAL EXPERT:

Signature: **Date:**

Prof. Mark Lebwohl
Chairman, Department of Dermatology, Mount Sinai School of Medicine

STATISTICIAN:

Signature: **Date:**

Philip Lavin, PhD
Principal, Lavin Consulting LLC.

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, Phase 2b Study to Assess the Efficacy and Safety of Orally Administered DS107 in Patients with Moderate to Severe Atopic Dermatitis
SHORT TITLE:	Efficacy and Safety Study of Orally Administered DS107 in Moderate to Severe Atopic Dermatitis Patients
PHASE:	2b
STUDY DURATION:	10 weeks (Treatment Duration: 8 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 ENDPOINT:	Proportion of patients achieving an Investigator's Global Assessment (IGA) of 0 (clear) or 1 (almost clear) and a decrease of at least 2 points in IGA in treated population compared to placebo population at Week 8.
SECONDARY ENDPOINTS:	• Proportion of patients achieving an IGA score of 0 (clear) or 1 (almost clear) and a decrease of at least 2 points in IGA in treated population compared to placebo population from baseline to Week 2, 4, 6 and 10. • Proportion of patients achieving a decrease of at least 2 points in IGA in treated population compared to placebo population from baseline to Week 2, 4, 6, 8 and 10. • Change from baseline in Eczema Area and Severity Index (EASI) in treated population compared to placebo population at Week 2, 4, 6, 8 and 10. • Change from baseline in Numeric Rating Scale (NRS) for Pruritus in treated population compared to placebo population at Week 2, 4, 6, 8 and 10.
EXPLORATORY ENDPOINTS:	• Change from baseline in the Dermatology Life Quality Index (DLQI) score in treated population compared to placebo population at Week 2, 4, 6, 8 and 10. • Change from baseline in the Patient Orientated Eczema Measure (POEM) score in treated population compared to

	placebo population at Week 2, 4, 6, 8 and 10. • Change from baseline in the Patient Global Impression of Severity (PGI-S) score in treated population compared to placebo population at Week 2, 4, 6, 8 and 10. • Change from baseline in the Patient Global Impression of Change (PGI-C) score in treated population compared to placebo population at Week 2, 4, 6, 8 and 10. • Plasma DGLA concentrations in treated population compared to placebo population at Baseline/Day 0, Week 4, Week 8 and Week 10 (samples to be retained and analysed for the potential analysis at a later date). • Determination of AD biomarkers at Baseline/Day 0, and Week 8 (samples to be retained for the potential analysis at a later date).
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:	A minimum of 300 patients with moderate to severe AD will be included in this multicenter, double-blind, placebo controlled, 3-arm phase 2b study. All patients will sign an informed consent and undergo screening for study eligibility. Patients will be randomized (1:1:1) at baseline visit to either receive 1g DS107 once daily, 2g DS107 once daily or placebo once daily for 8 weeks. Patients will come to the clinic on 7 occasions: at Screening, Baseline, Week 2, Week 4, Week 6, Week 8 (end of treatment/early termination) and Week 10 (follow-up). All patients will exit the study at the Week 10 visit.
TOTAL NUMBER OF RANDOMISED PATIENTS:	300
STUDY POPULATION:	
INCLUSION CRTIERIA:	1. Patients with a clinically confirmed diagnosis of active AD according to Hanifin and Rajka criteria. 2. Patients with moderate to severe AD at baseline as defined by an IGA of minimum 3 at baseline. 3. Patients with an EASI score of ≥12 at screening and baseline.

	4. Patients with AD covering a minimum 10% of the body surface area at baseline. 5. Patients whose pre-study clinical laboratory findings do not interfere with their participation in the study, in the opinion of the Investigator. 6. Patients who are able and willing to stop all current treatments for AD throughout the study (except for allowed emollients). 7. Patients who are on a stable dose of a bland emollient applied BD (twice daily) for at least 7 days prior to baseline. 8. Male or female patients who are aged 18 years and older on the day of signing the informed consent form (ICF). 9. Female patients and male patients with female partners of child bearing potential must use adequate contraception or have a sterilized partner for the duration of the study. Adequate contraception is defined as: systemic hormonal contraceptives, intrauterine device or barrier method of contraception in conjunction with spermicide, or agree to sexual abstinence. Hormonal contraceptives must be on a stable dose for at least one month before baseline. 10. 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.
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 (other than biologics) 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 who have used any topical medicated treatment for AD two weeks prior to start of treatment/ Baseline (Day 0), including but not limited to, topical corticosteroids, tars and bleach. 4. Patients who use topical products containing urea, ceramides or hyaluronic acid two weeks prior to Baseline.

	5. Patients who use anti-histamines for AD within 2 weeks of baseline. Non-sedative anti-histamines for other indications may be used throughout the study provided the patient is on a stable dose for 4 weeks prior to Baseline. 6. Patients with the presence of an active or chronic allergic reaction as evidenced by an irregular white cell count determined by eosinophils > 0.3 x 10^9 /L at the screening visit. 7. 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. 8. Patients who have a history of hypersensitivity to any substance in DS107 or placebo capsules. 9. 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. 10. Patients who have a clinically significant impairment of renal or hepatic function. 11. Patients with significant uncontrolled cardiovascular, neurologic, malignant, psychiatric, respiratory or hypertensive disease, as well as uncontrolled diabetes and fluoride arthritis or any other illness that, in the opinion of the investigator, is likely to interfere with completion of the study. 12. Patients with chronic infectious diseases (e.g., hepatitis B, hepatitis C or infection with human immunodeficiency virus). 13. 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). 14. 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. 15. 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. 16. Patients who are pregnant, planning pregnancy, breastfeeding and/or are unwilling to use adequate contraception (as specified in inclusion criterion 9) during the trial. 17. 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 two dose levels of DS107 for 8 weeks (1g DS107 OD or 2g DS107 OD) and a placebo control (OD)
EVALUATION CRITERIA: SAFETY	• Physical examination, including height and weight. • Vital signs, including blood pressure (BP), pulse and temperature. • Clinical laboratory tests (haematology, biochemistry, virology and urinalysis). • Pregnancy test for females of child bearing potential. • Adverse Events. • Concomitant medications.
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 will be prohibited within four weeks of the trial and during the trial.
STATISTICAL ANALYSIS	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. All statistical tests will be two-sided and will be performed with significance of 0.05. No adjustment for multiplicity will be applied. A generalised linear mixed model (GLMM) will be used to model the primary endpoint, IGA-response at Week 8. The model will include Treatment Arm as a factor and baseline IGA score as a covariate, with the treatment-by-visit interaction term as a random effect to account for missing data at Week 8.

	IGA-responders at other time points will also be analysed using GLMM. Change from baseline endpoints (EASI, NRS, DLQI, POEM, PGI-S and PGI-C) will be analysed using mixed model with repeated measures (MMRM) with Treatment Arm as a factor and baseline value as a covariate, with the treatment-by-visit interaction term as the repeated effect to account for missing data. Sensitivity analyses will be performed to assess the robustness of the Missing at Random (MAR) assumptions that underpin the GLMM methods above for imputing missing data.
SPONSOR:	DS Biopharma

LIST OF ABBREVIATIONS

15-HETrE	15-hydroxyeicosatrienoic acid
AD	Atopic Dermatitis
AE	Adverse Event
BD	Bis Die (Twice Daily)
BMI	Body Mass Index
BP	Blood Pressure
BPM	Beats Per Minute
COX	Cyclooxygenase
CRA	Clinical Research Associate
CRO	Contract Research Organisation
CRF	Case Report Form
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
ECG	Electrocardiography
EDC	Electronic Data Capture
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 Conference on Harmonisation
IFN-γ	Interferon-Gamma
IGA	Investigators Global Assessment
IgE	Imunnoglobulin E

IL	Interleukin
IMP	Investigational Medicinal Product
ISF	Investigator Site File
IWRS	Interactive Web Response System
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
PGD_1	Prostaglandin D1
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PIS	Patient Information Sheet
PK	Pharmacokinetics
POEM	Patient Orientated Eczema Measure
PP	Per Population
PPS	Per Protocol Set
PUVA	Psoralen & Ultraviolet A
PV CRO	Pharmacovigilance Contract Research Organisation
SAE	Serious Adverse Event
SAF	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
TNF-α	Tumor Necrosis Factor-Alpha
UV-A/B	Ultraviolet-A/B
VAS	Visual Analogue Scale

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 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 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 where 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 very 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 proinflammatory 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 also serves to block T-cell activation which can trigger and maintain skin inflammation (Simpson, 2010). They 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).

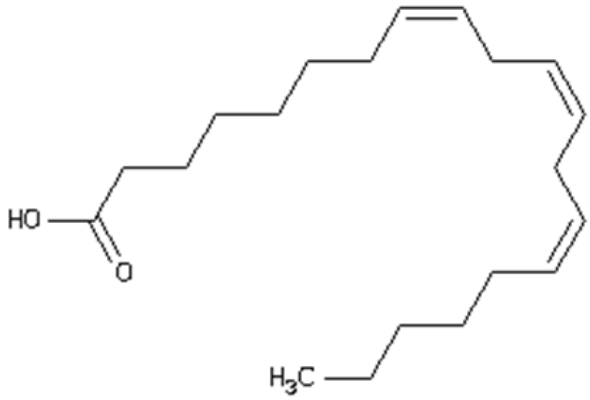
Phototherapy can be a useful adjunct in treatment of AD (Reynolds et al. 2001). However it can cause short term adverse effects including erythema, skin pain, itching and pigmentation as well as long term effects including premature skin aging and cutaneous malignant diseases (Leung and Bieber 2003).

The use of systemic treatments to manage the symptoms of AD has been rare. Oral corticosteroids, immunosuppressants, anti-folates and anti-histamines have been used in the past with moderate efficacy and poor safety profiles resulting in a short treatment window (Eichenfield et al. 2014). There is currently an unmet need for a safety and effect systemic treatment for patients with moderate to severe AD.

1.3 Drug Class

DS107 capsules contain the 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 showing 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 Advese 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).

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

Overall in these non-clinical safety studies it was concluded that DS107 is well tolerated and safe. Therefore it can be concluded that there are no safety concerns to indicate undue toxicological hazard or risk for patients treated with DS107 capsules.

1.6 Previous Clinical Studies with DS107

Two well-controlled clinical studies have been conducted to assess the safety and efficacy of DS107 capsules. To date, DS107 capsules has been administered to 87 healthy volunteers/patients during the course of one Phase 1 trial (DS107G-01) and one Phase 2a trial (DS107G-02) 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	500 mg 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

DS107 Capsules Phase 1 Study

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

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 Scoring of Atopic Dermatitis [SCORAD] visual analog scale [VAS]), Eczema Area and Severity Index [EASI], body surface area (BSA), Patient-Oriented Eczema Measure (POEM), Dermatology Life Quality Index (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 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 AE's 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.

Topical DS107

Three 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, 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.

Two Phase 2 proof-of-concept studies were completed with DS107 cream: Study DS107E-02 in patients affected by mild to moderate AD, and Study DS107E-03 in patients with mild to moderate acne vulgaris.

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 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.

2 RISK BENEFIT ASSESSMENT

To date, DS107 capsules has been administered to 87 healthy volunteers/patients during the course of one Phase 1 trial and one Phase 2a trial for moderate to severe AD. Up to 4g DS107 capsules was well tolerated in healthy volunteers up to 4 weeks. 2g DS107 capsules was well tolerated and safe in 51 patients with moderate to severe AD. The effect of DS107 capsules on the signs and symptoms of AD was consistently higher than placebo for all of the efficacy endpoints evaluated in this study, both investigator scores and patient scores. Following a battery of toxicology studies, and considering the endogenous nature of this molecule, it was concluded that DS107 is safe and well tolerated.

Based on both the favourable safety profile and the therapeutic potential of DS107 capsules in a disease that currently lacks effective 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 Phase I safety study.

The proof-of-concept Phase 2a study 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 a similar efficacy observed in severe/very severe AD patients, however, the sample size was deemed too small to determine the statistical significance.
The two previous clinical studies indicate that DS107 capsules is well tolerated and safe in both healthy patients and patients with moderate to severe AD. The Phase 2a study highlights the efficacy of DS107 capsules and indicates that further efficacy could be obtained by optimizing the dosing regime and/or concentration. Therefore, the goal for this dose-finding study is to examine the efficacy of 2g DS107 capsules OD and 1g DS107 capsules OD for a treatment period of 8 weeks in patients with moderate to severe AD.

The design of the current study is a randomised, placebo-controlled, and double-blind parallel group comparison in which the efficacy and safety of an 8 week treatment with DS107 capsules is assessed in 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, the positive signals in the Phase 2a study in patients 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 versus placebo, in the treatment of adult patients with moderate to severe AD.

Safety Objective:

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

5 STUDY ENDPOINTS

5.1 Primary Endpoint

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

5.2 Secondary Endpoints

- Proportion of patients achieving an IGA score of 0 (clear) or 1 (almost clear) and a decrease of at least 2 points in IGA in treated population compared to placebo population from baseline to Week 2, 4, 6 and 10.
- Proportion of patients achieving a decrease of at least 2 points in IGA in treated population compared to placebo population from baseline to Week 2, 4, 6, 8 and 10.
- Change from baseline in Eczema Area and Severity Index (EASI) in treated population compared to placebo population at Week 2, 4, 6, 8 and 10.
- Change from baseline in Numeric Rating Scale (NRS) for Pruritus in treated population compared to placebo population at Week 2, 4, 6, 8 and 10.

5.3 Exploratory Endpoints

- Change from baseline in the Dermatology Life Quality Index (DLQI) score in treated population compared to placebo population at Week 2, 4, 6, 8 and 10.
- Change from baseline in the Patient Orientated Eczema Measure (POEM) score in treated population compared to placebo population at Week 2, 4, 6, 8 and 10.
- Change from baseline in the Patient Global Impression of Severity (PGI-S) score in treated population compared to placebo population at Week 2, 4, 6, 8 and 10.
- Change from baseline in the Patient Global Impression of Change (PGI-C) score in treated population compared to placebo population at Week 2, 4, 6, 8 and 10.
- Plasma DGLA concentrations in treated population compared to placebo population at Baseline/Day 0, Week 4, Week 8 and Week 10 of (samples to be retained and analysed for the potential analysis at a later date).
- Determination of AD biomarkers at Baseline/Day 0, and Week 8 (samples to be retained and analysed at a later date for the potential analysis).

6 STUDY DESIGN

6.1 General

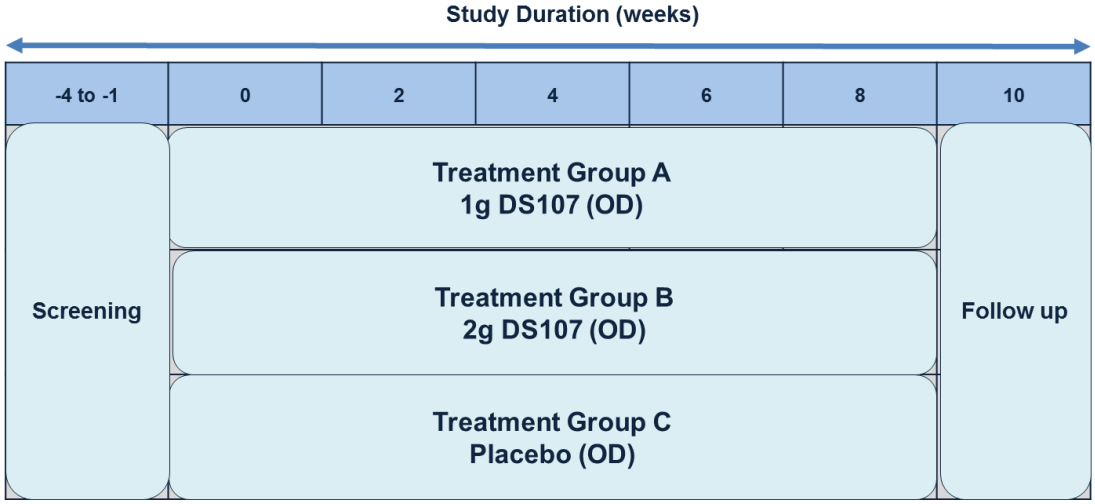
This is a randomised, placebo-controlled, double-blind, parallel group, multi-centre 3-arm Phase 2b study to investigate the efficacy of orally administered DS107 and the dose-response relationship between DS107 capsules and placebo in AD patients 18 years and older.

It is planned that at least 300 patients with at least 100 patients per treatment group, 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. Patients will be randomized (1:1:1) at baseline visit to either receive 2g DS107, 1g DS107 or placebo once daily for 8 weeks.

Patients will come to the clinic on 7 occasions: at Screening/Visit 1, Baseline/Visit 2, Week 2/Visit 3, Week 4/Visit 4, Week 6/Visit 5 and /Week 8/Visit 6 (end of treatment) and Week 10/Visit 7 (follow-up). Early termination visits will be recorded for patients who withdraw from the study early. All patients will exit the study at the Week 10 visit. At the screening visit, after giving informed consent to participate, patients will be assessed using the screening examinations. Patients who meet the inclusion criteria and who do not meet the exclusion criteria will be enrolled.

Unlike other oral treatments for AD (e.g. steroids) a treatment effect of DS107 capsules is not immediately expected to occur after start of treatment, but to increase constantly over time reaching its maximum effect within a time period over 4-6 weeks. Therefore, every effort should be undertaken to continue treatment with DS107 at least for 4 weeks to determine the efficacy of DS107. Patients not willing to continue to participate in the study due to the apparent lack of efficacy within the first 4 weeks of treatment therefore should be replaced.
A schematic diagram of the overall timeframe of the study is given in Figure 2.

Figure 2: Study Outline



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 9.2.11. 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 9.2.11).

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 three parallel group treatment regimens in a 1:1:1 randomization:

- Treatment group A: 1g DS107 (2 DS107 capsules and 2 placebo capsules) administered once-daily for 8 weeks

- Treatment group B: 2g DS107 (4 DS107 capsules) administered once-daily for 8 weeks

- Treatment group C: Placebo (4 placebo capsules) orally administered once-daily for 8 weeks

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

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. Patients should only be permitted to screen for this study if they are free of any sub-clinical infection (indicated by the presence of an Eosinophil count below 0.3 x 10^9 /L within 1 month of screening). 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 Hanifin and Rajka criteria.

2. Patients with moderate to severe AD at baseline as defined by an IGA of minimum 3 at baseline.

3. Patients with an EASI score of ≥12 at screening and baseline.

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

5. Patients whose pre-study clinical laboratory findings do not interfere with their participation in the study, in the opinion of the investigator.

6. Patients who are able and willing to stop all current treatments for AD throughout the study (except for allowed emollients).

7. Patients who are on a stable dose of a bland emollient applied BD (twice daily) for at least 7 days prior to baseline.

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

9. Female patients and male patients with female partners of child bearing potential must use adequate contraception or have a sterilized partner for the duration of the study. Adequate contraception is defined as: systemic hormonal contraceptives, intrauterine device or barrier method of contraception in conjunction with spermicide, or agree to sexual abstinence. Hormonal contraceptives must be on a stable dose for at least one month before baseline.

10. 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.

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 (other than biologics) 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 who have used any topical medicated treatment for AD two weeks prior to start of treatment/ Baseline (Day 0), including but not limited to, topical corticosteroids, tars and bleach.

4. Patients who use topical products containing urea, ceramides or hyaluronic acid two weeks prior to Baseline.

5. Patients who use anti-histamines for AD within 2 weeks of baseline. Non-sedative anti-histamines for other indications may be used throughout the study provided the patient is on a stable dose for 4 weeks prior to Baseline.

6. Patients with the presence of an active or chronic allergic reaction as evidenced by an irregular white cell count determined by eosinophils > 0.3 x 10^9 /L at the screening visit.

7. 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.

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

9. 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.

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

11. 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.

12. Patients with chronic infectious disease (e.g., hepatitis B, hepatitis C or infection with human immunodeficiency virus).

13. 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).

14. 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.

15. 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.

16. Patients who are pregnant, planning pregnancy, breastfeeding and/or are unwilling to use adequate contraception (as specified in inclusion criterion 9) during the trial.

17. 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 informed consent form (ICF). The patients will then receive a copy of the signed and dated patient information sheet (PIS)/informed consent form (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 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. 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 8/Visit 6 visit will be asked to come for an early termination visit as soon as possible and have the assessments listed at Week 8/Visit 6 performed. They will also be asked to return two weeks later for the safety assessments listed at Week 10/Visit 7.

There will be two main categories for withdrawals from the study: "complete withdrawal" and "withdrawals from investigational product".

7.5.1 Complete Withdrawal

Discontinuation of investigational product and all efficacy and safety evaluations. Standard reasons for withdrawing from further participation in the study and from the follow-up visits may be:

- Patients decision (withdrawal of consent to participate)
- Patient lost to follow-up (drop-out)

7.5.2 Withdrawals from Investigational Product

Discontinuation of investigational product, but continued follow-up visits, including efficacy and safety evaluations. Standard reasons for withdrawing from taking further investigational product, but continuing follow-up visits and safety evaluations may be:

- Unacceptable adverse events
- Patient request
- Investigator's discretion
- Intercurrent illness
- Lack of efficacy
- Pregnancy

7.6 Patient Replacement

Patients who are withdrawn from the study due to an adverse event 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.

8 STUDY CONDUCT

8.1 Study Schedule

During the study, six visits to the clinic are scheduled at least one week after the screening visit: one at the start of the comparative treatment period/baseline (Day 0/Visit 2) and five in the comparative treatment period (Week 2/Visit 3, Week 4/Visit 4, Week 6/Visit 5 and Week 8/Visit 6). A final safety follow-up visit (Visit 7) will be conducted two weeks after Visit 6 or two weeks after the final visit attended if the patient does not complete the study. The baseline visit must be performed, at the latest 30 days after the screening visit.

Patients who discontinue the study early will be asked to attend the investigative site as soon as possible so that assessments scheduled for Visit 6 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 Hanifin and Rajka 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 at the baseline visit. Any medication (prescription as well as 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. A list of 'medications and therapeutic regimens excluded from the study' is defined below (Section 9.2.11.2).

8.2 Clinic Visits

A tabulated flow chart of the study is presented in Appendix 1 (Section 15.1).

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)
- Hanifin and Rajka criteria review (as detailed in Appendix 2 [15.2])
- Samples for clinical laboratory safety tests (haematology, serum biochemistry, urinalysis 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)
- 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 9.2.6)
- Body Surface Area (as detailed in Section 9.1.4)
- 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 9.2.11)

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.

8.2.2 Treatment Period

Following completion of a successful screening visit, patients will begin the comparative treatment period (8 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 three treatment regimens.

Patients will be instructed to take 4 capsules of IMP which will contain either 1g DS107 or 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 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.

Patients who discontinue the study early will have all study procedures scheduled for Visit 6 (see Section 8.2.7) performed as soon as possible after patient withdrawal so that all study-related information can be recorded.

8.2.3 Baseline (Visit 2)

Note: it must be ensured that all inclusion regarding the severity of the disease remain unchanged since the screening in order to exclude patients reacting to the emollient use since screening visit. 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)
- Hanifin and Rajka criteria review (as detailed in Appendix 2 (15.2))
- Patient Randomisation (as detailed in Section 10.5)
- Samples for clinical laboratory safety tests (haematology, serum biochemistry, urinalysis as detailed in Section 9.2.4)
- Pharmacokinetic Sampling (as detailed in Section 9.2.7)
- Biomarker Sampling (as detailed in Section 9.2.8)
- 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 9.2.6)
- Dispense Study Drug
- Dispense Patient Compliance Log
- Body Surface Area (as detailed in Section 9.1.4)
- 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 (as detailed in Section 9.1.6)
- Patient Global Impression of Severity Questionnaire as detailed in Section 9.1.7)
- Patient Global Impression of Change Questionnaire as detailed in Section 9.1.8)
- Concomitant medication assessment (as detailed in Section 9.2.11)

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 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 baseline through to the follow up visit. Emollient use will also be captured on a daily basis for the same period.

Collection of AE's will begin after the first administration of IMP has occurred.

On completion of this visit, patients will be advised that they will be required to return to the investigational site at Visit 3 and to bring with them the unused DS107 capsules/Placebo patient packs, the used DS107 capsules/Placebo patient packs, and the patient compliance log.

8.2.4 Week 2 (Visit 3)

Patients will return to the investigational site at Week 2/Visit 3.

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:

- 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)
- 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 (as detailed in Section 9.1.6)
- Patient Global Impression of Severity Questionnaire as detailed in Section 9.1.7)
- Patient Global Impression of Change Questionnaire as detailed in Section 9.1.8)
- Concomitant medication assessment (as detailed in Section 9.2.11)
- AE assessment (as detailed in Section 11)

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

IMP will continue to be administered approximately 2 hours after food consumption at the same time each day. 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 baseline 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.

8.2.5 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 3. Patients will be required to provide the patient compliance log for confirmation of compliance.

The following procedures/assessments will occur:

- Pharmacokinetic Sampling (as detailed in Section 9.2.7)
- 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)
- 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 (as detailed in Section 9.1.6)
- Patient Global Impression of Severity Questionnaire as detailed in Section 9.1.7)
- Patient Global Impression of Change Questionnaire as detailed in Section 9.1.8)
- Concomitant medication assessment (as detailed in Section 9.2.11)
- 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. 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 baseline 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.

8.2.6 Week 6 (Visit 5)

Patients will return to the investigational site at Week 6/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:

- 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)
- 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 (as detailed in Section 9.1.6)
- Patient Global Impression of Severity Questionnaire as detailed in Section 9.1.7)
- Patient Global Impression of Change Questionnaire as detailed in Section 9.1.8)
- Concomitant medication assessment (as detailed in Section 9.2.11)
- 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. 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 baseline 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.

8.2.7 Week 8 (Visit 6) / End of Treatment or Early Termination

Patients will return to the investigational site at Visit 6. **The last dose of DS107/Placebo should be taken the day before Visit 6.**
For accountability purposes, patients will be required to bring both the used DS107/Placebo patient packs and unused DS107/Placebo supplied at Visit 5. 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, serum biochemistry, urinalysis as detailed in Section 9.2.4)
- Pharmacokinetic Sampling (as detailed in Section 9.2.7)
- Biomarker Sampling (as detailed in Section 9.2.8)
- 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)
- Body Mass Index (as detailed in Section 9.2.6)
- 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)
- 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 (as detailed in Section 9.1.6)
- Patient Global Impression of Severity Questionnaire as detailed in Section 9.1.7)
- Patient Global Impression of Change Questionnaire as detailed in Section 9.1.8)
- Concomitant medication assessment (as detailed in Section 9.2.11)
- AE assessment (as detailed in Section 11)

The DS107or Placebo patient packs will be returned. No further DS107or 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 9.2.11 and 9.2.12.

An NRS for the assessment of pruritus will continue to be captured on a daily basis from baseline 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 to assess any AEs since this visit, and conduct safety and efficacy assessments.

8.2.8 Week 10 (Visit 7) / Follow up

Two weeks after Visit 6 (or early withdrawal visit), patients will return to the investigational site and the final procedures/assessments will occur:

- Samples for clinical laboratory safety tests (haematology, serum biochemistry, urinalysis as detailed in Section 9.2.4) - Only if clinically significant change from baseline in safety lab results at Week 8 / Visit 6
- Pharmacokinetic Sampling (as detailed in Section 9.2.7)
- 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)
- 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 (as detailed in Section 9.1.6)
- Patient Global Impression of Severity Questionnaire as detailed in Section 9.1.7)
- Patient Global Impression of Change Questionnaire as detailed in Section 9.1.8)
- Concomitant medication assessment (as detailed in Section 9.2.11)
- AE assessment (as detailed in Section 11)

9 ASSESSMENTS

9.1 Efficacy Assessments

9.1.1 Investigator Global Assessment (IGA)

The clinical severity of AD will be evaluated by the investigator at each visit using the IGA scale (Appendix 3) (Futamura et al. 2016).

The IGA 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). IGA uses clinical characteristics of erythema, infiltration, papulation and oozing/crusting as scoring guidelines for the overall severity assessment. IGA will be assessed at every visit.

9.1.2 Eczema Area Severity Index (EASI)

EASI (Appendix 4) will be assessed at Screening, Baseline/Visit 2, Week 2/Visit 3, Week 4/Visit 4, Week 6/Visit 5, Week 8/Visit 6/ET and Follow up Week 10/Visit 7. It 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 at screening and then daily starting at baseline 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 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 Baseline/Visit 2, Week 2/Visit 3, Week 4/Visit 4, Week 6/Visit 5, Week 8/Visit 6/ET and Follow up Week 10/Visit 7 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 visit, except the screening visit. The POEM developed by Charman et.al. 2005 (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 Patient Global Impression of Severity (PGI-S)

The self-report PGI-S is a global index that may be used to rate the severity of a specific condition (a single-state scale) (Appendix 8) (Viktrup et al. 2012). It is a simple, direct, easy to use scale that is intuitively understandable to clinicians. The PGI-S is a single question asking the patient to rate how their AD is now on a scale of 1 (Normal Skin) to 4 (Severe). This will be assessed by the patient at Baseline/Visit 2, Week 2/Visit 3, Week 4/Visit 4, Week 6/Visit 5, Week 8/Visit 6/ET and Follow up Week 10/Visit 7.

9.1.8 Patient Global Impression of Change (PGI-C)

The self-report measure PGI-C reflects a patient's belief about the efficacy of treatment. PGI-C is a 7 point scale depicting a patient's rating of overall improvement (Appendix 9) (Rampakakis et al. 2015). Patients rate their change as "very much improved," "much improved," "minimally improved," "no change," "minimally worse," "much worse," or "very much worse." This will be assessed by the patient at Baseline/Visit 2, Week 2/Visit 3, Week 4/Visit 4, Week 6/Visit 5, Week 8/Visit 6/ET and Follow up Week 10/Visit 7.

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) at every visit 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 signs measurements will be performed as per the Study Flow Chart (Appendix 1) at every visit. 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, Serum Biochemistry, and Urinalysis

Blood and urine samples will be taken as per the Study Flow Chart (Appendix 1) for routine haematology, serum biochemistry and urinalysis 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.
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.
Urinalysis:	pH, protein, glucose, blood.

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

Details of the volume of blood or urine 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 8 /Visit 6/ET visit, as per the Study Flow Chart (Appendix 1).

9.2.6 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 1, Baseline/Visit 2 and Week 8/Visit 6/ET. The height will only be recorded once at the screening visit and the same value will be used for BMI calculation at Baseline/Visit 2 and Week 8/Visit 6 visits.

9.2.7 Pharmacokinetic Sampling

Blood samples for PK analysis will be collected via direct venepuncture as per the Study Flow Chart (Appendix 1) at Baseline/Visit 2, Week 4/Visit 4, Week 8/Visit 6/ET and Week 10/Visit 7/Follow up.

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

9.2.8 Biomarker Sampling

Blood samples will be collected via direct venepuncture as per the Study Flow Chart (Appendix 1) at Baseline/Visit 2, and Week 8/Visit 6/ET and 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.

9.2.9 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.

9.2.10 Adverse Event Assessment

See section 11.

9.2.11 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 7) 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.

9.2.11.1 Permitted Therapies

9.2.11.1.1 Emollients

All patients should be applying a bland emollient of their choice, **initiated at least 7 days prior to Baseline/Day 0,** 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. Patients will be requested 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

Every effort should be made to keep the same emollient throughout the study. The commercial name of the selected emollient(s) will be recorded in the source document and the eCRF, 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.

9.2.11.1.2 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.

9.2.11.2 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
  - bleach
- 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
- Anti-histamines used for AD
- 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

9.2.12 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.

10 INVESTIGATIONAL MEDICINAL PRODUCT / INVESTIGATIONAL DRUG

10.1 Ivestigational 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 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.

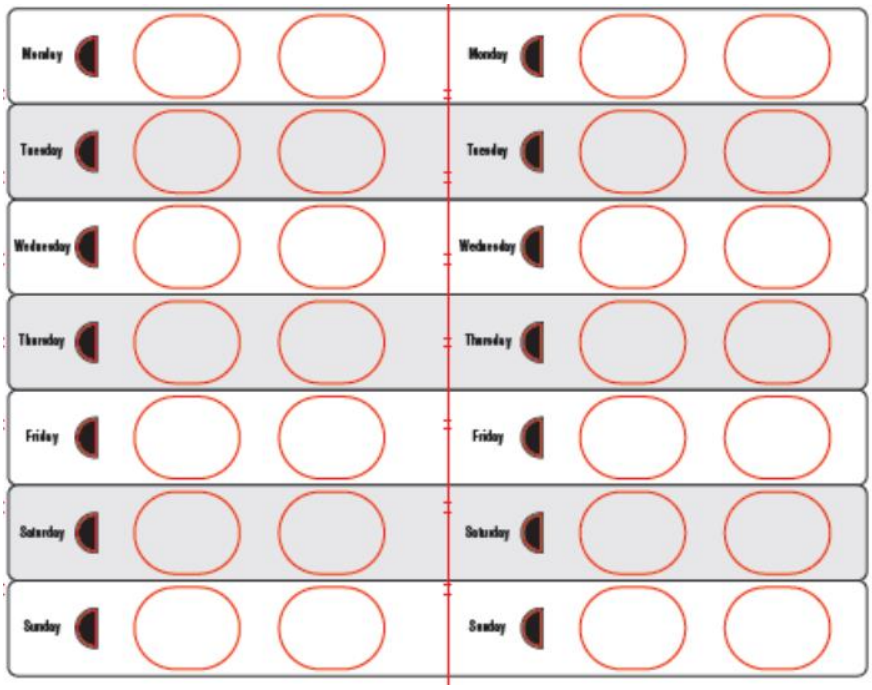
10.3 Dosage and Administration

This study involves a comparison of DS107 (2g and 1g) with placebo, administered orally once daily for a total duration of 8 weeks. **The last study drug administration should occur on the day preceding Week 8 (Visit 6) / Early Termination (ET) visit**. Patients will be randomized to one of the three treatment groups in a 1:1:1 ratio:

- Treatment group A: 1g DS107 (2 DS107 capsules and 2 placebo capsules) administered once-daily for 8 weeks
- Treatment group B: 2g DS107 (4 DS107 capsules) administered once-daily for 8 weeks
- Treatment group C: Placebo (4 placebo capsules) orally administered once-daily for 8 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.

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 8 consecutive weeks.

10.5 Methods for Assigning Patients to Treatments

Approximately 300 patients will be randomized into double-blind treatment groups in a 1:1:1 ratio by an Interactive Web Response System (IWRS) as follows:

- Treatment group A: 1g DS107 (2 DS107 capsules and 2 placebo capsules) administered once-daily for 8 weeks
- Treatment group B: 2g DS107 (4 DS107 capsules) administered once-daily for 8 weeks
- Treatment group C: Placebo (4 placebo capsules) orally administered once-daily for 8 weeks

A randomization list permuted 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 IMPs 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 contact the Pharmacovigilance (PV) CRO monitor by phone, fax or e-mail, and in any case no later than 24 hours after the knowledge of such a case. 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 a copy of the SAE reporting form to PV CRO at the number provided in the Investigator Site File. The faxed 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

At least 300 patients will be randomized into double-blind treatment groups in a 1:1:1 ratio by an IWRS.

- Treatment group A: 1g DS107 (2 DS107 capsules and 2 placebo capsules) administered once-daily for 8 weeks
- Treatment group B: 2g DS107 (4 DS107 capsules) administered once-daily for 8 weeks
- Treatment group C: Placebo (4 placebo capsules) orally administered once-daily for 8 weeks

A randomization list permuted 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. Assuming these rates and a significance of 5%, 300 evaluable patients (100 patients per treatment arm) will yield 45% power for comparisons between the active doses and placebo in this study.

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 Interim Analysis

An interim analysis will be conducted once 50% of planned patients have completed their Week 8 assessments. This will be conducted in accordance with sponsor SOP "Interim Analysis of Clinical Studies".

12.6 Data Analysis

Data analysis will be performed at the CRO. All computations will be completed using SAS® version 9.1.3 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.

12.7 Analysis Populations

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

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

Randomised Population
The Randomised Population 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. SAF 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 are 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.

12.8 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 and severity.

Clinical laboratory values (haematology, biochemistry, and urinalysis) 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. 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 day.

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.

12.9 Statistical Analysis Plan

In addition to the summarised analysis plan outlined below, a separate document, Statistical Analysis Plan (SAP) for DS107G-03 will detail all analyses to be performed.

12.9.1 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.

12.9.2 Primary variables

The primary variable will be the proportion of patients achieving an IGA score of 0 (clear) or 1 (almost clear) and a decrease of at least 2 points in IGA from baseline at Week 8.

The primary endpoint will be analysed using a Generalised Linear Mixed Model (GLMM) with treatment arm and baseline IGA value as factors, with the treatment-by-visit interaction term as the random effect to account for missing data. The primary analysis will be based on the FAS, and repeated for the PPS as a supportive sensitivity analysis.

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. Because of 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. (J Biopharm Stat, 2013; 23(6):1352-71) 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. The sensitivity analyses for missing data will be performed on the FAS only.

12.9.3 Secondary variables

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

The continuous efficacy variables and their changes from baseline will be summarized with descriptive statistics per treatment group and visit. This applies to the IGA, EASI, NRS scores for pruritus, DLQI, POEM, PGI-S and PGI-C. Change from baseline endpoints will be analysed using Mixed Model with Repeated Measures (MMRM) with Treatment Arm as a factor and baseline value as a covariate, and with the treatment-by-visit interaction term as the repeated effect to account for missing data. The secondary efficacy analyses will be based on the FAS only.

12.9.4 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.

12.10 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 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.

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 Conference on Harmonisation (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 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 Report and Publication

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

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15 APPENDICES

15.1 Appendix 1: Study Flow-Chart

Visit	Screening/ Visit 1	Baseline / Visit 2	Week 2 / Visit 3	Week 4 / Visit 4	Week 6 / Visit 5	Week 8 / Visit 6 / Early Termination	Week 10 / Visit 7 / Follow up
Day	**-30 to -1**	**0**	**14**	**28**	**42**	**56**	**70**
Visit Window			+/-2 days	+/-2 days	+/-2 days	+/-2 days	+/-3 days
Informed Consent	**X**						
Assign Patient identifier number	**X**						
Demographics	**X**						
Medical / Surgical History	**X**						
Review Inclusion/Exclusion Criteria	**X**	**X**					
Hanifin and Rajka criteria	**X**	**X**					
Randomization		**X**					
Safety labs: Serum Biochemistry (including FSH levels at screening when applicable[1]), Hematology, Urinalysis	**X**	**X**				**X**	**X**[2]
Pharmacokinetic Sampling		**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**
Physical Examination [3]	**X**	**X**	**X**	**X**	**X**	**X**	**X**
BMI	**X**	**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**	
IMP Accountability			**X**	**X**	**X**	**X**	
BSA	**X**	**X**	**X**	**X**	**X**	**X**	**X**
IGA	**X**	**X**	**X**	**X**	**X**	**X**	**X**
EASI assessment	**X**	**X**	**X**	**X**	**X**	**X**	**X**
NRS Pruritus assessment [5]	**X**	**X----------X**					
DLQI questionnaire		**X**	**X**	**X**	**X**	**X**	**X**
POEM questionnaire		**X**	**X**	**X**	**X**	**X**	**X**
PGI-S questionnaire		**X**	**X**	**X**	**X**	**X**	**X**
PGI-C questionnaire		**X**	**X**	**X**	**X**	**X**	**X**
Concomitant Medications	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Emollient use capture [5]		**X----------X**					
Adverse Events [6]		**X**	**X**	**X**	**X**	**X**	**X**

1. FSH requirement to confirm female 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 a laboratory AE recorded at Week 8. In that case only the sample which is the cause of the AE should be re-tested.
3. Physical Examination will be symptom-directed as per section 9.2.2.
4. Patients will be instructed to take their last study drug dose the day preceding Week 8 visit.
5. NRS/Emollient use will be captured electronically through the IWRS by the patient. Patients may use paper to document these assessments also.

6. Collection of AE will start after the first study drug administration.

15.2 Appendix 2: Diagnostic Features of Atopic Dermatitis (Hanifin and Rajka Criteria)

Patients must have confirmed diagnosis of AD based on the Hanifin and Rajka diagnostic criteria. Firm diagnosis of AD requires the presence of at least three of the major criteria described below. In addition to having three of the major criteria, a patient should manifest three minor criteria which are either less specific or relatively rare.

Major criteria:

- Pruritus
- Dermatitis affecting flexural surfaces in adults and the face and extensors in infants and children
- Chronic or relapsing dermatitis
- Personal or family history of cutaneous or respiratory atopy (asthma, allergic rhinitis, AD).

Minor criteria can be divided into 4 categories:

- Facial features: facial pallor, facial erythema, hypopigmented patches, infraorbital darkening, infraorbital folds (Dennie-Morgan folds), cheilitis, recurrent conjunctivitis, anterior neck folds.
- Triggers: foods, emotional factors, environmental factors, skin irritants.
- Complications: susceptibility to cutaneous infections, impaired cell-mediated immunity, immediate skin-test reactivity, elevated IgE, keratoconus, anterior subcapsular cataracts.
- Other: early age of onset, dry skin, ichthyosis, hyperlinear palms, keratosis pilaris, hand and foot dermatitis, nipple eczema, white dermatographism, perifollicular accentuation.

Hanifin & Rajka, 1980.

15.3 Appendix 3: Investigator's Global Assessment (IGA)

IGA Severity	Morphological Description
4 – Severe	Deep/dark red erythema; marked and extensive elevation (papules/infiltration).
3 – Moderate	Dull, red, clearly distinguishable erythema; clearly perceptible lesion elevation (papules/infiltration) but not extensive.
2 – Mild	Visibly detectable, light pink erythema and very slight elevation (papules/infiltration).
1 – Almost Clear	Barely perceptible erythema and/or minimal lesion elevation (papules/infiltration).
0 – Clear	No signs of erythema, lesions, papulation or infiltration

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 ☐

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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

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15.8 Appendix 8: Patient Global Impression of Severity (PGI-S)

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

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

Describe, to the best of your abilities, how your Atopic Dermatitis symptoms are now:

(1) Normal Skin ☐
(2) Mild ☐
(3) Moderate ☐
(4) Severe ☐

15.9 Appendix 9: Patient Global Impression of Change (PGI-C)

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

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

Since the start of the study, my overall status is:

(1)	Very Much Improved	☐
(2)	Much Improved	☐
(3)	Minimally Improved	☐
(4)	No Change	☐
(5)	Minimally Worse	☐
(6)	Much Worse	☐
(7)	Very Much Worse	☐