A Randomised, Double-blind, Vehicle-Controlled, Phase IIb Study to Assess the Efficacy and Safety of Topically Applied DS107 Cream to Adults with Mild to Moderate Atopic Dermatitis

Protocol Number # DS107E-06

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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 Investigator's name, address, qualifications and extent of involvement.

PROTOCOL SYNOPSIS

STUDY TITLE:	A Randomised, Double-blind, Vehicle-Controlled, Phase IIb Study to Assess the Efficacy and Safety of Topically Applied DS107 Cream to Adults with Mild to Moderate Atopic Dermatitis
SHORT TITLE:	Safety and Efficacy Study of Topically Applied DS107 Cream in Mild to Moderate Atopic Dermatitis Patients
PHASE:	IIb
STUDY DURATION:	10 weeks (Treatment Duration: 8 weeks)
INVESTIGATIONAL PRODUCT:	DS107 Cream Vehicle Cream
OBJECTIVE:	*Efficacy Objective:* • To compare the efficacy of topically applied DS107 cream (1% & 5%) versus vehicle, in the treatment of adult patients with mild to moderate Atopic Dermatitis (AD). *Safety Objective:* • To compare the safety of topically applied DS107 cream (1% & 5%) versus vehicle, in the treatment of adult patients with mild to moderate AD.
PRIMARY ENDPOINTS:	*Primary Endpoint* • Change from baseline in Numeric Rating Scale (NRS) for Pruritus in treated population compared to vehicle population at Week 8. *Co-Primary Endpoint* • Change from baseline in Eczema Area and Severity Index (EASI) in treated population compared to vehicle population at Week 8.
SECONDARY ENDPOINTS:	• Change from baseline in NRS for Pruritus in treated population compared to vehicle population at Weeks 2, 4, 6 and 10. • Proportion of patients achieving a decrease of at least 2.7 points in NRS in treated population compared to vehicle population from baseline to Week 2, 4, 6, 8 and 10. • Change from baseline in EASI in treated population compared to vehicle population at Weeks 2, 4, 6 and 10. • 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 vehicle population from baseline to Week 2, 4, 6, 8 and 10. • Proportion of patients achieving a decrease of at least 2 points in IGA in treated population compared to vehicle population from baseline to Week 2, 4, 6, 8 and 10. • Change from baseline in IGA score in treated population compared to vehicle population at Weeks 2, 4, 6, 8 and 10.
EXPLORATORY ENDPOINTS:	• Change from baseline in the Dermatology Life Quality Index (DLQI) score in treated population compared to vehicle 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 vehicle 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 vehicle 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 vehicle population at Week 2, 4, 6, 8 and 10. • Determination of AD biomarkers in treated population compared to vehicle population at Baseline/Day 0 and Week 8/Early Termination (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, urinalysis). • Clinical safety examinations (vital signs, physical examination).
STUDY DESIGN:	Approximately 300 patients with mild to moderate AD will be included in this multicenter, double-blind, vehicle controlled, 3-arm, Phase IIb 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 5% DS107 cream, 1% DS107 cream or vehicle cream twice daily for 8 weeks. During the 8 weeks of treatment patients will have to liberally

	apply their assigned treatment topically to all affected or commonly affected areas twice daily (morning and evening). Patients will come to the clinic on 7 occasions: at Screening, Baseline, Week 2, Week 4, Week 6, Week 8 (end of treatment) 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 CRITERIA:	1. Patients with a clinically confirmed diagnosis of active AD according to Hanifin and Rajka criteria. 2. Patients with mild to moderate AD at baseline as defined by an IGA score of 3 or 2 at baseline visit. Patients who are classified as having moderate AD should also have an EASI score of ≥12 at the baseline visit. 3. Patients with AD covering a minimum 5% of the body surface area at baseline. 4. Patients whose pre-study clinical laboratory findings do not interfere with their participation in the study, in the opinion of the Investigator. 5. Patients who are able and willing to stop current treatments for AD, including the use of emollients on the affected skin, throughout the study. 6. Male or female patients aged 18 years and older on the day of signing the informed consent form (ICF). 7. 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. 8. 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 topical 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, calcineurin inhibitors, tars, bleach, antimicrobials and bleach baths. 4. Patients who use topical products containing urea, ceramides or hyaluronic acid two weeks prior to Day 0. 5. Patients who use anti-histamines for AD within 3 days 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 who have had excessive sun exposure, have used tanning booths or other ultraviolet (UV) light sources four weeks prior to baseline (Day 0) and/or are planning a trip to a sunny climate or to use tanning booths or other UV sources between screening and follow-up visits. 7. Patients who have a history of hypersensitivity to any substance in DS107 or vehicle cream. 8. Patients who have a white cell count outside of the normal reference range at screening, which cannot be justified by the investigator. 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 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 7) 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 cream will be provided as a cream containing either 5% or 1% DS107. Vehicle will be provided as a matching cream. This study will involve two dose levels of DS107 for 8 weeks (5% DS107 cream BD or 1% DS107 cream BD) and a vehicle control BD.
EVALUATION CRITERIA: SAFETY	• Physical examination • Vital signs, including blood pressure (BP), pulse and temperature • Clinical laboratory tests (haematology, biochemistry, and urinalysis) • Pregnancy test for females of child bearing potential • AEs • Concomitant medications (CMs)

BEHAVIOURAL RESTRICTIONS	• Patients will be asked to refrain from any travel to sunny climates or use of tanning equipment, saunas and swimming throughout the duration of the study. • Extensive UV exposure or UV-B devices within four weeks of the trial and during the trial.
OTHER RESTRICTIONS	• Patients will be asked to refrain from the application of all emollients and creams to any area of skin impacted by AD during the course of this study.
STATISTICAL ANALYSIS	The primary analysis will be conducted in the full analysis set (FAS) population. Final analyses will be conducted using exact two-sided 97.4% confidence intervals for each DS107 dose minus vehicle difference; this strategy (Dunnett's procedure) preserves the overall two-sided 5% Type I error. This allows either DS dose (1% and 5%) to be separately tested. A hierarchical testing sequence will be adopted, giving a pre-defined testing order for multiple efficacy endpoints. A generalised linear mixed model (GLMM) will be used to separately analyze the continuous primary and co-primary efficacy endpoints at Week 8. The models will include Treatment Arm as a factor and respective baseline value as a covariate, with the treatment-by-visit interaction term as a random effect to account for missing data at Week 8. In addition, IGA-response will be analysed using a longitudinal mixed model for binary outcomes (GENMOD). Change from baseline for secondary and exploratory endpoints (IGA, DLQI, POEM, PGI-S and PGI-C) will be analysed using mixed model with repeated measures (MMRM) with Treatment Arm as a factor and respective baseline value as a covariate, with the treatment-by-visit interaction term as a random effect to account for missing data at Week 8. Sensitivity analyses will be performed to assess the robustness of the Missing at Random (MAR) assumptions that support 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)
BP	Blood Pressure
BPM	Beats Per Minute
CM	Concomitant Medication
COX	Cyclooxygenase
CRA	Clinical Research Associate
CRO	Contract Research Organisation
CRF	Case Report Form
CsA	Cyclosporin A
CTA	Clinical Trial Agreement
DGLA	Dihomo-Gamma-Linolenic Acid
DLQI	Dermatology Life Quality Index
DM	Data Manager
DS	DS Biopharma
EASI	Eczema Area and Severity Index
EC	Ethics Committee
EDC	Electronic Data Capture
FAS	Full Analysis Set
FSH	Follicule Stimulating Hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GLMM	Generalised Linear Mixed Model
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IGA	Investigator's Global Assessment
IgE	Imunnoglobulin E
IMP	Investigational Medicinal Product

ISF	Investigator Site File
ITT	Intention-To-Treat
IWRS	Interactive Web Response System
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model with Repeated Measures
NOAEL	No Observed Adverse Event Limit
NRS	Numeric Rating Scale
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
PPS	Per Protocol Set
PUVA	Psoralen & Ultraviolet A
PV CRO	Pharmacovigilance Contract Research Organisation
SAE	Serious Adverse Event
SAS	Safety Analysis Set
SAP	Statistical Analysis Plan
SCORAD	SCORing AD
SDV	Source Data Verification
SOP	Standard Operating Procedure
SPC	Summary of Products Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
Th	T helper cell
TNF-α	Tumor Necrosis Factor-Alpha
UV-A/B	Ultraviolet-A/B
VAS	Visual Analogue Scale

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 & Hanifin, 2013).

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

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

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

The mechanisms underlying the pathogenesis of AD remain unclear. Many studies have demonstrated the involvement of genetic predisposition, immune dysfunction, emotional and environmental stimuli and epidermal barrier dysfunction in its development and progression. It is well recognised however that IgE-mediated reactions (Bos et al. 1994) and elevated eosinophil levels (Kapp 1993) are involved in causing inflammation associated with AD. Additionally the overactivation 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 cream, a bioactive lipid containing >95% pure dihomo-γ-linolenic 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 DS107 cream has been

shown to improve the signs and symptoms of AD including pruritus and patient quality of life in a previous proof-of-concept Phase IIa study.

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 severe 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 they can only be used as a short-term therapy.

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, INF-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).

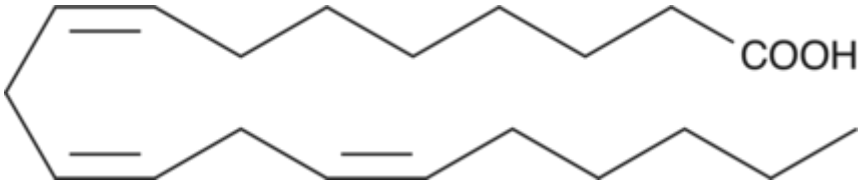
Phototherapy can be a useful adjunct in treatment of AD (Reynolds et al. 2001). However it can cause short term adverse effects including erythema, skin pain, itching and pigmentation as well as long term effects including premature skin aging and cutaneous malignant diseases (Leung and Bieber 2003).

A multi-therapeutic approach that incorporates short-term management of flares and longer-term strategies to prolong the time between flares is needed for the treatment of AD. Therefore there is an unmet medical need for more effective well tolerated AD therapies that can be used safely in the long term.

1.3 Drug Class

DS107 cream contains the active pharmaceutical ingredient DGLA, a long-chain polyunsaturated fatty acid endogenously present in the body.

Figure 1: Structure of DS107 cream



1.4 Preclinical Pharmacology

Numerous preclinical studies have been performed to determine the mechanism of actions of DS107 in inflammatory skin disease 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 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, Amagi 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 animal preclinical studies, when administered in the diet. Oral administration of up to 600 mg/kg DGLA has shown dose dependent improvements in the severity of skin lesions in animal models of AD. DGLA treatment is correlated with decreased plasma IgE concentrations which may contribute to resolving the AD lesions.

In the same study DGLA was shown to also significantly decreases the number of scratch events and duration of scratching in animal models of AD (Kawashima et al. 2008; Amagi 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

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. Reaction was 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. The microscopic findings 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.

Oral Toxicology

A 13-week oral study in rats using Oral DS107 did not show any significant treatment-related effect 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 Oral DS107 at levels found in this product is unlikely to cause adverse effects (Kawashima et al. 2009).

Mutagenicity

Previously, DS107 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.

1.6 Previous Clinical Studies with DS107

DS107 cream has been administered to date in 294 healthy volunteers/patients during the course of one Phase I trial (DS107E-01) and four Phase II trials (DS107E-02, DS107E-03, DS107E-04 and DS107E-05) for Acne Vulgaris (AV) and AD. Up to 5% DS107 cream is well tolerated in healthy volunteers and patients with AD. Below are a list of the completed and on-going trials which utilise DS107 cream.

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

DS107E-01 A Randomised, Double Blind, Vehicle Controlled, Multiple Ascending Dose Phase I Study to Investigate the Local Tolerability of Topical DGLA					
Phase	**Duration**	**Indication**	**IMP Conc.**	**# Healthy Volunteers**	**Status**
I (safety)	2 weeks	Healthy Volunteers	0.1% 0.5% 1% 2.5% 5%	30	Completed
DS107E-02 A Randomised, Double-blind, Vehicle-Controlled, Phase II Study to Assess the Efficacy and Safety of Topically Applied DGLA Cream in Patients with Mild to Moderate AD					
Phase	**Duration**	**Indication**	**IMP Conc.**	**# Patients**	**Status**
IIa (safety & efficacy)	4 weeks	Mild to Moderate AD	0.1% 1% 5%	203	Completed
DS107E-03 A Randomised, Double-blind, Vehicle-Controlled, Phase II Study to Assess the Efficacy and Safety of Topically Applied DGLA Cream in Patients with Mild to Moderate Acne Vulgaris					
Phase	**Duration**	**Indication**	**IMP**	**# Patients**	**Status**

			Conc.		
IIa (safety & efficacy)	12 weeks	AV	1% 5%	154	Completed
DS107E-04 A Prospective, Randomised, Vehicle-controlled, Double-blind, Exploratory Clinical Trial to Assess the Efficacy and Steroid Sparing Potential of DGLA Cream Topically Applied to Patients with Moderate to Severe AD					
Phase	**Duration**	**Indication**	**IMP Conc.**	**# Patients**	**Status**
Exploratory (safety & efficacy)	5 weeks	Moderate to Severe AD	5%	40 (planned)	On-going
DS107E-05 A Prospective, Randomised, Vehicle-controlled, Double-blind, Exploratory Clinical Trial to Assess the Efficacy and Steroid Sparing Potential of DGLA Cream Topically Applied to Childhood Patients with Moderate to Severe AD					
Phase	**Duration**	**Indication**	**IMP Conc.**	**# Patients**	**Status**
Exploratory (safety & efficacy)	9 weeks	Moderate to Severe AD	1%	40 (planned)	On-going

DS107 Cream Phase I Study (DS107E-01)

In this 2 week study, DS107 cream was administered topically to healthy human volunteers twice daily for 14 days. The safety margins concerning systemic safety risks and local tolerability following topical drug application were addressed and the safety margin calculated for the trial highlighted the lack of any systemic safety risks for humans exposed to DS107 cream when applied topically. The healthy volunteers were randomised to 5 cohorts and applied either 0.1%, 0.5%, 1%, 2.5% or 5% DS107 cream to one arm and the vehicle cream to the other arm. No clinically relevant dermal reactions were observed in this study as a result of topical application of DS107 cream.

DS107 Cream Phase IIa Study in AD (DS107E-02)

The study was a randomized, vehicle-controlled, double-blind, multi-centre Phase IIa trial to investigate the efficacy, safety, tolerability and bioavailability of three topically applied DS107 cream concentrations (0.1%, 1% and 5%) versus a matching vehicle in adult patients with mild to moderate AD. For all efficacy variables (change in mEASI, IGA, VAS, POEM and DLQI), there was a consistent trend of improvement from baseline over the study period (day 0 to day 28) for the 1% and 5% DS107 cream treatment groups. This trend of improvement displayed no evidence of treatment plateau, suggesting that greater and clinically significant improvement from baseline may be expected if treatment was to be continued for a longer time period. No SAEs were observed throughout the course of this study. The DS107 cream treatment groups were similar to the vehicle groups in terms of number of adverse events and event severity. No deaths or other SAEs occurred during the study.

Other than one strongly elevated CPK value in one patient (reported as not drug related AE) at the last visit in the 5% DS107 group, no clinically relevant treatment differences were seen in any of the laboratory parameter. In the vital signs parameters, the mean values were stable across treatment groups. Overall, DS107 cream appears safe and well tolerated, with a profile similar to vehicle.

DS107 Cream Phase IIa Study in Acne Vulgaris (DS107E-03)

This 12 week study was a randomized, vehicle-controlled, double-blind, multi-centre proof of concept Phase IIa trial to investigate the efficacy, and safety of topically applied DS107 cream in patients with mild to moderate AV. This vehicle-controlled trial involved topical application of DS107 cream to all affected areas of the skin at dose strengths of 1% and 5% DS107 cream.

All treatment groups displayed clinical significance in the improvement in the symptoms of AV after 12 weeks of treatment with 1% DS107 cream, 5% DS107 cream or the vehicle cream. DS107 cream did not show statistically significant differences regarding efficacy over vehicle cream. Sixty (39.0%) patients experienced an adverse event (AE) during the study. All AEs were mild in severity and resolved without intervention. The number of patients experiencing an AE was comparable between the treatment groups. The results of the laboratory and vital sign assessments did not reveal any safety concerns during the study for any treatment group.

DS107 Cream Exploratory Phase II Study in Adults with AD (DS107E-04)

The 5 week exploratory Phase II study is designed to evaluate the efficacy and steroid sparing potential of 5% DS107 cream. Adult patients with moderate to severe AD will be treated with a potent glucocorticosteroid (mometasone furoate) for one week. Patients will then apply 5% DS107 cream twice daily as a maintenance therapy to prevent relapse. Efficacy and safety of DS107 following one week treatment with mometasone furoate will be compared to vehicle cream following one week treatment with mometasone furoate. The primary efficacy endpoint is defined as the change in EASI at Week 5 compared to vehicle. This trial is on-going.

DS107 Cream Exploratory Phase II Study in toddlers with AD (DS107E-05)

The 9 week exploratory Phase II study is designed to evaluate the efficacy and steroid sparing potential of 1% DS107 cream in infant patients with moderate to severe AD. Toddlers between the age of 3-12 months with moderate to severe AD will be treated with a 0.1% hydrocortisone butyrate cream once daily (morning) and DS107 cream once daily (evening) for one week. Patients'

parents/guardians will then apply either 1% DS107 cream or vehicle cream twice daily as a maintenance therapy for the following 8 weeks to prevent relapse. Efficacy and safety of DS107 cream will be assessed over time. The primary efficacy endpoints are defined as the change in IGA score from baseline to Week 9 and the SCORAD change from baseline to Week 9. This trial is on-going.

2 RISK BENEFIT ASSESSMENT

To date, DS107 cream has been administered to 294 healthy volunteers/patients during the course of one Phase I trial and four Phase II trials for AD and AV. DS107 cream at a concentration of up to 5% was well tolerated in healthy volunteers and patients with AD and AV with no SAEs reported over a dosing period of up to 12 weeks. Oral DS107 has also been administered orally in two well controlled clinical trials in healthy volunteers (Phase 1) and patients with moderate to severe AD (Phase IIa). There were no drug related SAEs on either study. Furthermore there were no drug related AEs associated with safety lab results, physical exams or vital signs. All AEs were mild to moderate in severity and resolved without interevention. Overall orally administered DS107 was well tolerated at concentrations up to 4 g.

Based on both the favourable safety profile and the therapeutic potential of DS107 cream 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 cream for the treatment of mild to moderate AD**.**

3 RATIONALE FOR THE STUDY

The previous clinical studies indicate that DS107 cream is well tolerated and safe in both healthy volunteers and patients with AD and AV. The proof-of-concept Phase IIa study (DS107E-02) demonstrated that both 1% and 5% DS107 cream has a clinically relevant effect adult patients with mild to moderate AD. These results illustrate a clear rationale for the development of DS107 as a topical agent for the treatment of AD.

No plateau in treatment efficacy was observed during the Phase IIa study within a 4 week treatment period with topical DS107 cream which indicates that the maximum efficacy may not yet have been determined and should be further evaluated by optimizing the dosing duration and/or concentration. Therefore, the goal for this dose-finding study is to examine the efficacy of 5% DS107 cream BD and 1% DS107 cream BD for a treatment period of 8 weeks in patients with mild to moderate AD.

The design of the current study is a randomised, vehicle-controlled, and double-blinded parallel group comparison in which the efficacy and safety of an 8 week treatment with DS107 cream is assessed in patients with mild to moderate AD. The design of the study was selected to minimise potential bias during the safety and efficacy assessments.

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

Based on the afore-mentioned preclinical studies demonstrating the efficacy of DS107 in animal models of AD and the positive signals in the Phase IIa study in patients, there is a clear rationale for the further development of DS107 cream as a treatment for patients with mild to moderate AD.

4 STUDY OBJECTIVES

Efficacy Objective:

- To compare the efficacy of topically applied DS107 cream (1% & 5%) versus vehicle, in the treatment of adult patients with mild to moderate AD.

Safety Objective:

- To compare the safety of topically applied DS107 cream (1% & 5%) versus vehicle, in the treatment of adult patients with mild to moderate AD.

5 STUDY ENDPOINTS

5.1 Primary Endpoints

Primary Endpoint

- Change from baseline in Numeric Rating Scale (NRS) for Pruritus in treated population compared to vehicle population at Week 8.

Co-Primary Endpoint

- Change from baseline in Eczema Area and Severity Index (EASI) in treated population compared to vehicle population at Week 8.

5.2 Secondary Endpoints

- Change from baseline in NRS for Pruritus in treated population compared to vehicle population at Weeks 2, 4, 6 and 10.
- Proportion of patients achieving a decrease of at least 2.7 points in NRS in treated population compared to vehicle population from baseline to Weeks 2, 4, 6, 8 and 10.
- Change from baseline in EASI in treated population compared to vehicle population at Weeks 2, 4, 6 and 10.
- 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 vehicle population from baseline to Weeks 2, 4, 6, 8 and 10.
- Proportion of patients achieving a decrease of at least 2 points in IGA in treated population compared to vehicle population from baseline to Weeks 2, 4, 6, 8 and 10.
- Change from baseline in IGA score in treated population compared to vehicle population at Weeks 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 vehicle population at Weeks 2, 4, 6, 8 and 10.
- Change from baseline in the Patient Orientated Eczema Measure (POEM) score in treated population compared to vehicle population at Weeks 2, 4, 6, 8 and 10.
- Change from baseline in the Patient Global Impression of Severity (PGI-S) score in treated population compared to vehicle population at Weeks 2, 4, 6, 8 and 10.
- Change from baseline in the Patient Global Impression of Change (PGI-C) score in treated population compared to vehicle population at Weeks 2, 4, 6, 8 and 10.
- Determination of AD biomarkers in treated population compared to vehicle population at Baseline/Day 0 and Week 8/Early Termination (samples to be retained for the potential analysis at a later date).

6 STUDY DESIGN

6.1 General

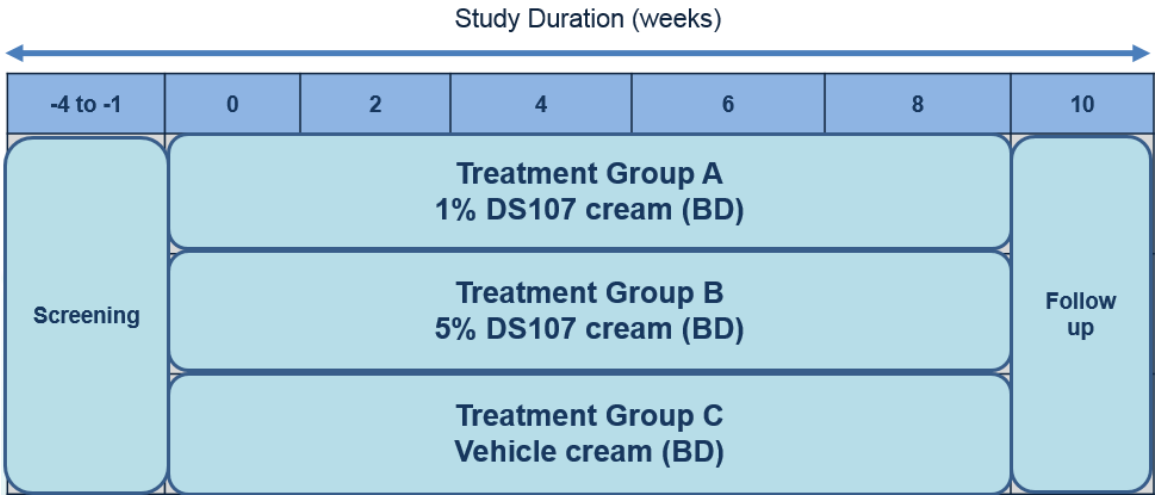
This is a randomised, vehicle-controlled, double-blind, parallel group, multi-centre Phase IIb study to investigate the efficacy of topically administered DS107 cream and the dose-response relationship between DS107 cream and vehicle cream in AD patients 18 years and older.

It is planned that approximately 300 patients, 100 patients per treatment group, with mild to moderate 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 5% DS107 cream, 1% DS107 cream or vehicle cream twice 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, 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.

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. 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 9.2.9).

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: 1% DS107 cream applied topically to all affected or commonly affected areas twice-daily for 8 weeks

- Treatment group B: 5% DS107 cream applied topically to all affected or commonly affected areas twice-daily for 8 weeks

- Treatment group C: Vehicle cream applied topically to all affected or commonly affected areas twice-daily for 8 weeks

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

An area for treatment will be defined at the start of the study and DS107 or vehicle cream will be applied to that area (and any newly affected areas) for the complete 8 week duration. Emollients can be applied to other areas of dry skin not in the defined treatment area. Patients will be instructed to apply the IMP/vehicle cream liberally to the affected area, after breakfast and dinner respectively for 8 weeks (except on the days of clinic visits when patients will be instructed to abstain from applying IMP/vehicle cream for 6 hours prior to the visit and to apply IMP/vehicle cream as soon as possible after the clinic visit).

7 PATIENTS AND SCREENING

In order to participate in this study the patients must meet all of the following inclusion criteria (see section 7.2) and must not meet any of the following exclusion criteria (see section 7.3). Inclusion in the trial starts with the informed consent signature. The inclusion and exclusion criteria are to be verified at the screening visit (Visit 1) and at the start of treatment/baseline visit (Visit 2).

7.1 Source of Patients

The study population will consist of male and female patients with confirmed diagnosis of AD aged between 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 mild to moderate AD at baseline as defined by an IGA score of 3 or 2 at baseline visit. Patients who are classified as having moderate AD should also have an EASI score of ≥12 at the baseline visit.

3. Patients with AD covering a minimum 5% of the body surface area at baseline.

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

5. Patients who are able and willing to stop current treatments for AD, including the use of emollients on the affected skin, throughout the study.

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

7. 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.

8. 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 topical 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, calcineurin inhibitors, tars, bleach, antimicrobials and bleach baths.
4. Patients who use topical products containing urea, ceramides or hyaluronic acid two weeks prior to Day 0.
5. Patients who use anti-histamines for AD within 3 days 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 who have had excessive sun exposure, have used tanning booths or other ultraviolet (UV) light sources four weeks prior to baseline (Day 0) and/or are planning a trip to a sunny climate or to use tanning booths or other UV sources between screening and follow-up visits.
7. Patients who have a history of hypersensitivity to any substance in DS107 or vehicle cream.
8. Patients who have a white cell count outside of the normal reference range at screening, which cannot be justified by the investigator.
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 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 7) 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 of 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 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 Medicinal Product (IMP)".

7.5.1 Complete Withdrawal

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

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

7.5.2 Withdrawals from IMP

Discontinuation of IMP, but continued follow-up visits, including efficacy and safety evaluations. Standard reasons for withdrawing from taking further IMP, 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. Patients who withdraw from the study due to a lack of efficacy after four weeks of treatment will not 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 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, 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.

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, or from taking new or not previously prescribed anti-histamines or any antimicrobial medication. 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. Emollients can be applied to other areas of dry skin not in the defined treatment area. A list of 'medications and therapeutic regimens excluded from the study' is defined below (Section 9.2.9).

8.2 Clinic Visits

A tabulated flow chart of the study is presented in Appendix 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/events will occur:

- Demographic data
- Medical 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 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)
- Investigator's Global Assessment (IGA) (as detailed in Section 9.1.1)
- Eczema Area and Severity Index (EASI) (as detailed in Section 9.1.2)
- Body Surface Area (BSA) (as detailed in Section 9.1.4)
- NRS pruritus assessment (as detailed in Section 9.1.3)
- Concomitant medication assessment (as detailed in Section 9.2.9)

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.

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 apply DS107 cream or vehicle cream in the morning and in the evening (except on the mornings of clinic visits when patients will be instructed to abstain from applying DS107/vehicle cream prior to the visit. They will apply DS107/vehicle cream as soon as all of the efficacy assessments are complete during the clinic visit). 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)

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 Section Appendix 2 (15.2))
- Patient randomisation (as detailed in Section 10.5)
- Samples for clinical laboratory safety tests (haematology, urinalysis and serum biochemistry as detailed in Section 9.2.4)
- Biomarker sampling (as detailed in Section 9.2.6)
- Vital signs (blood pressures, heart rate and body temperature), as detailed in Section 9.2.3)
- Physical examination (as detailed in Section 9.2.2)
- Dispense study drug
- Dispense patient compliance log
- Study drug administration (on site) (as detailed in Section 10.3)
- Investigator's Global Assessment (IGA) (as detailed in Section 9.1.1)
- Body Surface Area (BSA) (as detailed in Section 9.1.4)
- Eczema Area and Severity Index (EASI) (as detailed in Section 9.1.2)
- NRS pruritus assessment (as detailed in Section 9.1.3)
- Dermatology Life Quality Index (DLQI) Questionnaire (as detailed in Section 9.1.5)
- Patient Orientated Eczema Measure (POEM) (as detailed in Section 9.1.6)
- Patient Global Impression of Severity Questionnaire (PGI-S) (as detailed in Section 9.1.7)
- Patient Global Impression of Change Questionnaire (PGI-C) (as detailed in Section 9.1.8)
- Concomitant medication assessment (as detailed in Section 9.2.9)

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

The first application of DS107 or vehicle cream will be carried out at site once all baseline assessments have been completed. The patient will carry out their second application of DS107 or vehicle cream in the evening of Day 0.

Patients will be given a compliance log to document application of the DS107 or vehicle cream. Clinical staff will explain to the patient how to use the compliance log to document IMP application compliance.

All dispensed DS107 cream and vehicle cream should be weighed (tube only, without the outer carton but including the tube lid) upon dispensing.

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

Collection of AEs will begin after the first application 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 bring with them the unused DS107/vehicle cream, the used DS107/vehicle cream, and the patient compliance log. Patients should not apply DS107 or vehicle cream on the morning of their return site visit (Visit 3).

8.2.4 Week 2 (Visit 3)

Patients will return to the investigational site at Week 2/Visit 3. Patients should not apply DS107 or vehicle cream on the morning of Visit 3.

For accountability purposes, patients will be required to bring both the used and unused DS107/vehicle cream 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)
- Study drug administration (on site) (as detailed in Section 10.3)
- Investigator's Global Assessment (IGA) (as detailed in Section 9.1.1)
- Body Surface Area (BSA) (as detailed in Section 9.1.4)
- Eczema Area and Severity Index (EASI) (as detailed in Section9.1.2)
- NRS pruritus assessment (as detailed in Section 9.1.3)
- Dermatology Life Quality Index (DLQI) Questionnaire (as detailed in Section9.1.5)
- Patient Orientated Eczema Measure (POEM) (as detailed in Section 9.1.6)
- Patient Global Impression of Severity Questionnaire (PGI-S) (as detailed in Section 9.1.7)
- Patient Global Impression of Change Questionnaire (PGI-C) (as detailed in Section 9.1.8)
- Concomitant medication assessment (as detailed in Section 9.2.9)
- AE assessment (as detailed in Section 11)

The DS107 or vehicle cream will be returned and six tubes of DS107 or vehicle cream will be supplied to the patient. The cream will continue to be applied twice-daily. The patient compliance log will be provided to the patient who will be instructed to complete this as before.

All dispensed DS107 cream and vehicle cream should be weighed (tube only, without the outer carton but including the tub lid) upon dispensing and again upon return of product.

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

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/vehicle cream, the used DS107/vehicle cream, and the patient compliance log. Patients should not apply DS107 or vehicle cream on the morning of their return site visit (Visit 4).

8.2.5 Week 4 (Visit 4)

Patients will return to the investigational site at Week 4/Visit 4. Patients should not apply DS107 or vehicle cream on the morning of Visit 4.

For accountability purposes, patients will be required to bring both the used and unused DS107/vehicle cream supplied at Visit 3. 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)
- Study drug administration (on site) (as detailed in Section 10.3)
- Investigator's Global Assessment (IGA) (as detailed in Section 9.1.1)
- Body Surface Area (BSA) (as detailed in Section 9.1.4)
- 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 Section9.1.5)
- Patient Orientated Eczema Measure (POEM) (as detailed in Section 9.1.6)
- Patient Global Impression of Severity Questionnaire (PGI-S) (as detailed in Section 9.1.7)
- Patient Global Impression of Change Questionnaire (PGI-C) (as detailed in Section 9.1.8)
- Concomitant medication assessment (as detailed in Section 9.2.9)
- AE assessment (as detailed in Section 11)

The DS107 or vehicle cream will be returned and six tubes of DS107 or vehicle cream will be supplied to the patient. The cream will continue to be applied twice-daily. The patient compliance log will be provided to the patient who will be instructed to complete this as before.

All dispensed DS107 cream and vehicle cream should be weighed (tube only, without the outer carton but including the tube lid) upon dispensing and again upon return of product.

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

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/vehicle cream, the used DS107/vehicle cream, and the patient compliance log. Patient should not apply DS107 or vehicle cream on the morning of their return site visit (Visit 5).

8.2.6 Week 6 (Visit 5)

Patients will return to the investigational site at Week 6/Visit 5. Patients should not apply DS107 or vehicle cream on the morning of Visit 5.

For accountability purposes, patients will be required to bring both the used and unused DS107/vehicle cream 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)
- Study drug administration (on site) (as detailed in Section 10.3)
- Investigator's Global Assessment (IGA) (as detailed in Section 9.1.1)
- Body Surface Area (BSA) (as detailed in Section 9.1.4)
- Eczema Area and Severity Index (EASI) (as detailed in Section9.1.2)
- NRS pruritus assessment (as detailed in Section 9.1.3)

- Dermatology Life Quality Index (DLQI) Questionnaire (as detailed in Section 9.1.5)
- Patient Orientated Eczema Measure (POEM) (as detailed in Section 9.1.6)
- Patient Global Impression of Severity Questionnaire (PGI-S) (as detailed in Section 9.1.7)
- Patient Global Impression of Change Questionnaire (PGI-C) (as detailed in Section 9.1.8)
- Concomitant medication assessment (as detailed in Section 9.2.9)
- AE assessment (as detailed in Section 11)

The DS107 or vehicle cream will be returned and six tubes of DS107 or vehicle cream will be supplied to the patient. The cream will continue to be applied twice-daily. The patient compliance log will be provided to the patient who will be instructed to complete this as before.

All dispensed DS107 cream and vehicle cream should be weighed (tube only, without the outer carton but including the tube lid) upon dispensing and again upon return of product.

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

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/vehicle cream, the used DS107/vehicle cream, and the patient compliance log. Patients should not apply DS107 or vehicle cream on the morning of their return site visit (Visit 6).

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

Patients will return to the investigational site at Visit 8. **The last administration of DS107/vehicle cream should be made the evening before Visit 6.**

For accountability purposes, patients will be required to bring both the used and unused DS107/vehicle cream 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, urinalysis and serum biochemistry as detailed in Section 9.2.4)
- Biomarker sampling (as detailed in Section 9.2.6)
- Vital signs (blood pressures, heart rate and body temperature), as detailed in Section 9.2.3)
- Physical examination (as detailed in Section 9.2.2)
- Collect study drug
- Collect and review patient compliance log
- IMP accountability (as detailed in Section 10.6)
- Investigator's Global Assessment (IGA) (as detailed in Section 9.1.1)
- Body Surface Area (BSA) (as detailed in Section 9.1.4),
- Eczema Area and Severity Index (EASI) (as detailed in Section 9.1.2)
- NRS pruritus assessment (as detailed in Section 9.1.3)
- Dermatology Life Quality Index (DLQI) Questionnaire (as detailed in Section 9.1.5)
- Patient Orientated Eczema Measure (POEM) (as detailed in Section 9.1.6)
- Patient Global Impression of Severity Questionnaire (PGI-S) (as detailed in Section 9.1.7)
- Patient Global Impression of Change Questionnaire (PGI-C) (as detailed in Section 9.1.8)
- Concomitant medication assessment (as detailed in Section 9.2.9)
- AE assessment (as detailed in Section 11)

The DS107 or vehicle cream will be returned. No further DS107 or vehicle cream or patient compliance log will be issued. Following completion of the study assessments at this visit, there will be continued study restrictions in line with those described in section 9.2.9 and 9.2.10.

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

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, urinalysis and serum biochemistry as detailed in Section 9.2.4) - Only if clinically significant change from baseline in safety lab results at Week 8 / Visit 6
- Vital signs (blood pressures, heart rate and body temperature), as detailed in Section 9.2.3)
- Physical examination (as detailed in Section 9.2.2)
- Investigator's Global Assessment (IGA) (as detailed in Section 9.1.1)
- Body Surface Area (BSA) (as detailed in Section 9.1.4)
- Eczema Area and Severity Index (EASI) (as detailed in Section 9.1.2)
- NRS pruritus assessment (as detailed in Section 9.1.3)
- Dermatology Life Quality Index (DLQI) Questionnaire (as detailed in Section 9.1.5)
- Patient Orientated Eczema Measure (POEM) (as detailed in Section 9.1.6)
- Patient Global Impression of Severity Questionnaire (PGI-S) (as detailed in Section 9.1.7)
- Patient Global Impression of Change Questionnaire (PGI-C) (as detailed in Section 9.1.8)
- Concomitant medication assessment (as detailed in Section 9.2.9)
- 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 and Severity Index (EASI)

The 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 Numerical Rating Scale (NRS) for Pruritus

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 experienced at its worst over the previous 24 hours. The NRS for pruritus 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 once 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.

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. 2004 (Appendix 7) is a self-assessment of disease severity by the patient. POEM has a maximum value of twenty eight based on the patient's response to seven questions scored according to the following scale:

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

9.1.7 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 patients 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 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 all visits 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.
Serum biochemistry:	Creatinine, uric acid , alkaline phosphatase (ALP), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), creatine phosphokinase (CPK), albumin, cholesterol, triglycerides, glucose.
Urinalysis:	pH, protein, glucose, blood.

Table 3: Total Blood Volume drawn

Test	**Number of Samples**	**Volume per sample (ml)**	**Total (ml)**
Haematology/Biochemistry	4*	9	36
Biomarkers	2	3	6
Total volume			42

*Sample at Visit 7/Follow up will only be taken if a laboratory AE was recorded at Week 8
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 initialled and signed 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, as per the study flow chart (Appendix 1).

9.2.6 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.

9.2.7 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.

9.2.8 Adverse Event Assessment

See Section 11.

9.2.9 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, does 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 IMP during the entire period of the study.

9.2.9.1 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 basline/ Day 0 and continues to use the same agent everyday throughout the study

Inhaled and intranasal corticosteroids for stable medical conditions are allowed.

9.2.9.2 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
  - calcineurin inhibitors
  - tars
  - bleach
  - antimicrobials
  - bleach baths
- Any topical product containing urea, ceramides or hyaluronic acid
- Emollients within the test area (may be applied to areas of dry skin outside of the test area and must be in use for 4 weeks prior to initiation of trial)
- 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
- UVA or UVB 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

9.2.10 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 within 4 weeks of the trial and during the trial.

Other

Patients will be asked to refrain from the application of all emollients and creams to any area of skin impacted by AD during the course of this study.

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.

10 INVESTIGATIONAL MEDICINAL PRODUCT / INVESTIGATIONAL DRUG

10.1 IMP

The following medication supplies will be used in the study:

DS107 cream:

DS107 cream contains DS107 as an active ingredient.

DS107 cream will be supplied in two concentrations: 5% and 1%.

DS107 cream is formulated as a white to off white-cream for topical application.

DS107 Cream Medicinal Ingredients:

DGLA (Di-hommo-gamma-linolenic acid)

DS107 Cream Non-Medicinal Ingredients:

Table 4: DS107 Cream Non-Medicinal Ingredients

Excipient	Function	Status
Steareth-2	Primary Emulsifier	Ph.Eur
Steareth-21	Primary Emulsifier	Manufacturer's In-house Specification
Cetyl Alcohol	Co-emulsifier	Ph.Eur
L(+)Ascorbyl Palmitate	Anti-oxidant	Ph.Eur
all-rac-α-Tocopherol	Anti-oxidant	Ph.Eur
Medium Chain Triglycerides	Emollient	Ph.Eur
Myristyl Myristate	Co-emulsifier, Emollient	Manufacturer's In-House Specification
Isopropyl Palmitate	Emollient	Ph.Eur
Glycerol, Anhydrous	Humectant	Ph.Eur
Methyl 4-Hydroxybenoate	Preservative	Ph.Eur
Ethyl 4-Hydroxybenzoate	Preservative	Ph.Eur
Propyl 4-Hydroxybenzoate	Preservative	Ph.Eur
Bronopol	Preservative	Manufacturer's In-House Specification
Ascorbic Acid	Antioxidant	Ph.Eur
Carbomer	Viscosity Modifier	NF
Xanthan Gum	Thickener	Ph.Eur
Soy Lecithin	Stabilizing Agent	Manufacturer's In-house Specification
Potassium Hydroxide	pH adjustment	Ph.Eur
Mild Care 345	Fragrance	Manufacturer's In-house Specification

Water For Irrigation	Solvent	Ph.Eur

Vehicle cream:

A matching vehicle cream is also supplied. This is identical in composition to the DS107 cream formulation minus active drug substance. The vehicle formulation is based on the formulation of the investigational medicinal product with additional water for irrigation being used to compensate for the absence of active pharmaceutical ingredient in the formulation.

Vehicle Cream Medicinal Ingredients:

None

Vehicle Cream Non-Medicinal Ingredients:

Table 5: Vehicle Non-Medicianl Ingredients

Excipient	Function	Status
Steareth-2	Primary Emulsifier	Ph.Eur
Steareth-21	Primary Emulsifier	Manufacturer's In-house Specification
Cetyl Alcohol	Co-emulsifier	Ph.Eur
L(+)Ascorbyl Palmitate	Anti-oxidant	Ph.Eur
all-rac-α-Tocopherol	Anti-oxidant	Ph.Eur
Medium Chain Triglycerides	Emollient	Ph.Eur
Myristyl Myristate	Co-emulsifier, Emollient	Manufacturer's In-House Specification
Isopropyl Palmitate	Emollient	Ph.Eur
Glycerol, Anhydrous	Humectant	Ph.Eur
Methyl 4-Hydroxybenoate	Preservative	Ph.Eur
Ethyl 4-Hydroxybenzoate	Preservative	Ph.Eur
Propyl 4-Hydroxybenzoate	Preservative	Ph.Eur
Bronopol	Preservative	Manufacturer's In-House Specification
Ascorbic Acid	Antioxidant	Ph.Eur
Carbomer	Viscosity Modifier	NF
Xanthan Gum	Thickener	Ph.Eur
Soy Lecithin	Stabilizing Agent	Manufacturer's In-house Specification
Potassium Hydroxide	pH adjustment	Ph.Eur
Mild Care 345	Fragrance	Manufacturer's In-house Specification
Water For Irrigation	Solvent	Ph.Eur

Drug bulk product and vehicle are manufactured by C.P.M. ContractPharma GmbH & Co., Germany and packaged by Anderson Brecon Limited, UK. Labelled DS107 cream and

matching vehicle cream will be supplied by Anderson Brecon Limited to a central distribution facility as a cream formulation in aluminium tubes packed in cartons with tamper evident seals.

IMPs will be stored at ambient condition (i.e. up to 25°C) and should be used within the assigned expiry date.

10.2 Supply, Packaging, Labelling, Handling and Storage

DS107 cream and vehicle cream will be provided by the Sponsor.

The DS107 cream and vehicle cream will be a white to off white-cream formulation supplied from the manufacturer to the central distribution facility. The central distribution facility will supply the IMP and vehicle to site where it will be handled by the site pharmacy or responsible personnel according to local Regulations. Patients who qualify for randomisation at Baseline/Visit 2 will be given IMP for 2 weeks/14 days at Baseline/Visit 2, Week 2/Visit 3, Week 4/Visit 4, and Week 6/Visit 5.

The DS107 cream and vehicle cream will be labelled with information according to local regulation.

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. The DS107 cream and vehicle cream will be stored at a controlled room temperature of ambient condition (ie. Up to 25°C) in a secure area protected from unintended use and will only be supplied to patients in the trial under the supervision of the Investigator.

10.3 Dosage and Administration

IMP at dose strengths of 5% and 1% DS107 cream or vehicle cream will be topically applied liberally to all affected or commonly affected areas twice daily (morning and evening) by the patients. **The last study drug application 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: 1% DS107 cream applied topically to all affected or commonly affected areas twice-daily for 8 weeks

- Treatment group B: 5% DS107 cream applied topically to all affected or commonly affected areas twice-daily for 8 weeks
- Treatment group C: Vehicle cream applied topically to all affected or commonly affected areas twice-daily for 8 weeks

An area for treatment will be defined at study start and DS107 or vehicle cream will be applied to all that area (and any newly affected areas) for the complete 8 week duration. Emollients can be applied to other areas of dry skin not in the defined treatment area.

DS107 or vehicle cream will not be applied on the morning of clinic visits 3, 4, 5, and 6 (will be applied as soon as all of the efficacy assessments are complete during the clinic visit). To maintain the blind throughout the study, the DS107 cream and vehicle cream will be identical in appearance.

If a patient misses one application of the study product they should apply the study product as usual at the time of the next scheduled application. Patients should remember to note the missed application in the Patient Compliance Log.

10.4 Duration of Treatment

Patients will topically apply either DS107 cream or vehicle cream liberally to all affected or commonly affected areas twice 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: 1% DS107 cream applied topically to all affected or commonly affected areas twice-daily for 8 weeks
- Treatment group B: 5% DS107 cream applied topically to all affected or commonly affected areas twice-daily for 8 weeks
- Treatment group C: Vehicle cream applied topically to all affected or commonly affected areas twice-daily for 8 weeks

A randomization list, permuted blocks and stratified by site will be generated by DS Biopharma or its designee. The randomization schedule with study drug assignments will be generated prior to the start of the study and will be known only to the individuals responsible for labelling the study drug, the statisticians generating the schedule and the IWRS team responsible for implementing the schedule. The IWRS will assign a medication kit number to each patient and the contents will be based on the randomization code.

At the investigational site, each patient will be assigned a patient identifier number during screening that will be used on all patient documentation. The patient identifier number will contain the site number and the patient number assigned in numerical order at the screening visit (e.g.: 102-10 for the tenth patient screened at the site number 02). Patient numbers will be assigned in ascending order starting with 01.

10.6 Drug Accountability

All IMP supplied 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 tubes of IMP to the study site at every visit. Following compliance assessment the tubes 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 will 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 who has signed the ICF and 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 patients 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 SAE.

A SAE (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, a 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 the 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 the 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).

AEs 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 AE 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 is 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 the 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 the 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 the 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 the 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, vehicle-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 vehicle 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 vehicle treatment. A full description of the study design is presented in Section 6 (above).

12.2 Randomisation

Approximately 300 patients will be randomized into double-blind treatment groups in a 1:1:1 ratio as follows:

- Treatment group A: 1% DS107 cream applied topically to all affected or commonly affected areas twice-daily for 8 weeks
- Treatment group B: 5% DS107 cream applied topically to all affected or commonly affected areas twice-daily for 8 weeks
- Treatment group C: Vehicle cream applied topically to all affected or commonly affected areas twice-daily for 8 weeks.

A randomization list, permuted blocks and stratified by site will be generated by DS Biopharma 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

The sample size for the topical DS107 Phase IIb study was informed from the post-hoc analysis of the Phase IIa study. NRS and EASI will be the primary and co-primary efficacy endpoints. The positive efficacy data over 4 weeks showed no sign of a plateau and suggests further improvements may be observed at week 8. Dunnettt's procedure will be used to allow simultaneous comparisons of each DS107 dose vs. vehicle control.

The sample size was estimated from the Phase IIa results at week 4/exit; the mean improvement and corresponding standard deviation for vehicle subjects were used to perform the following calculations. As shown below, 100 patients per treatment arm (300 patients in total) will be required to detect mean advantages of 3.03 units for NRS (10 point scale) and 6.6 units for EASI favoring DS107 vs. vehicle. This assumes a two-sided test with 80% power conducted at the 5% overall significance level with a Dunnettt's adjustment for multiple doses.

Table 6. Sample size calculation

Two group Satterthwaite t-test: No Difference (unequal variances) (equal n's)		
	NRS	**EASI**
Overall Dunnett's Type I Error	0.026	0.026
1 or 2 sided test?	2	2
Target DS107 Mean Reduction, μ1	3.030	6.600
Expected Vehicle Mean Reduction, μ2	1.810	4.000
Mean Difference Goal, μ1 - μ2	1.220	2.600
Phase IIa DS107 Standard Deviation, σ1	2.490	4.450
Phase IIa Vehicle Standard Deviation, σ2	3.040	7.110
Power (%)	80	80
n per group	100	100

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 a pre-specified Interim Statistical Analysis Plan.

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. Changes from baseline and percent changes from baseline will be evaluated for continuous endpoints. 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 SAF 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 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 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 DS107E-06 will detail all analysis to be performed.

12.9.1 Primary Variables

The primary variable will be:

- The change from baseline in NRS for Pruritus in treated population compared to vehicle population at Week 8.

The co-primary variable will be:

- The change from baseline in EASI in treated population compared to vehicle population at Week 8.

The continuous primary and co-primary efficacy endpoints will be separately analyzed using a Generalized Linear Mixed Model (GLMM). The models will include Treatment Arm as a factor and respective baseline value as a covariate, with the treatment-by-visit interaction term as a random effect to account for missing data. The primary analysis will be based on the FAS, and repeated for the PPS as a supportive sensitivity analysis. The models will also allow the estimation of the mean changes from baseline at each on-study visit in addition to Week 8. The change from Week 8 to Week 10 will also be of interest to assess relapse once off study drug.

Sensitivity analyses will be performed to assess the robustness of the Missing at Random (MAR) assumptions that support the GLMM methods above for imputing missing data. 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 vehicle 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 vehicle group. The sensitivity analyses for missing data will be performed on the FAS only.

12.9.2 Secondary variables

IGA-response will be analyzed using a longitudinal mixed model for binary outcomes (GENMOD). The model will include Treatment Arm as a factor and respective baseline value as a covariate, with the treatment-by-visit interaction term as a random effect to account for missing data. The primary analysis will be based on the FAS, and repeated for the PPS as a supportive sensitivity analysis. The models will also allow the estimation of the response percents at each on-study visit in addition to Week 8. The shift from Week 8 to Week 10 will also be of interest to assess relapse once off study drug.

Change from baseline endpoints (IGA, DLQI, POEM, PGI-S and PGI-C) will be analyzed using mixed model with repeated measures (MMRM) with Treatment Arm as a factor and respective baseline value as a covariate, with the treatment-by-visit interaction term as the random effect to account for missing data. The secondary efficacy analyses will be based on the FAS only.

In addition, a hierarchical testing sequence will be adopted, giving a pre-defined testing order for multiple efficacy endpoints as follows: NRS, EASI, IGA, IGA response, PGI-S, PGI-C, DLQI and POEM.

12.9.3 Safety variables

The type and frequency of AEs 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 SAEs, AEs leading to withdrawal and AEs possibly or probably related to treatment will be summarized per treatment group.

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 patients meeting the eligibility criteria and being randomised in the study; 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 PIS/ICF will be approved by the relevant competent authorities (CA) and ethics committees (EC), 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 CA and EC 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 CA.

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

13.2 Good Clinical Practice (GCP)

The study will be managed and conducted according to the latest ICH guidelines for GCP and applicable regulatory requirement(s) (specifically the principles of GCP in ICH topic E6, as laid down by the Commission Directive 2005/28/EC and in accordance with applicable local laws and guidelines). A copy of the ICH guidelines can be found in the investigator site file (ISF).

13.3 Essential Documents

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

13.4 Record Retention

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These records include, but are not limited to, the identity of all participating patients, all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence.

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

13.5 Monitoring / Quality Control

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

Incorrect or missing entries in the CRFs will be queried and will be corrected appropriately.

All clinical data will undergo quality control checks prior to clinical database lock. Edit checks will then be performed for appropriate databases as a validation routine using SAS ® to check for missing data, data inconsistencies, data ranges, etc. Each eCRF is reviewed and signed by the principal ivestigator (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.

The data derived from this trial will be kept for 25 years as per the guidelines of the NNHPD (Natural and Non-prescription Health Products Directorate).

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]**
Biomarker Sampling		**X**				**X**	
Pregnancy Test (β-hCG if female of childbearing potential)	**X**						
Vital Signs	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Physical Examination	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Dispense Study Drug		**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**	
Study Drug Administration (on site)[3]		**X**	**X**	**X**	**X**		
IGA	**X**	**X**	**X**	**X**	**X**	**X**	**X**
BSA	**X**	**X**	**X**	**X**	**X**	**X**	**X**
EASI Assessment	**X**	**X**	**X**	**X**	**X**	**X**	**X**
NRS Pruritus Assessment	**X**	**X**----------					
DLQI Questionnaire		**X**	**X**	**X**	**X**	**X**	**X**
POEM Questionnaire		**X**	**X**	**X**	**X**	**X**	**X**
PGI-C Questionnaire		**X**	**X**	**X**	**X**	**X**	**X**
PGI-S Questionnaire		**X**	**X**	**X**	**X**	**X**	**X**
Concomitant Medications	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Adverse Events[4]			**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. Patients will be instructed to take their last study drug dose the day preceding Week 8 visit.
4. Collection of AE will start after the first study drug administration

15.2 Appendix 2: Diagnostic Features of AD (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 ☐

Please check you have answered EVERY question. Thank you.

15.7 Appendix 7: Patient Orientated Eczema Measure

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

15.8 Appendix 8: 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 AD 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