Official Title: A Randomized, Double-blind, Placebo-controlled, Phase 2a Study to Evaluate the Efficacy and Safety of OpSCF in the Treatment of Adult Subjects With Moderate to Severe Atopic Dermatitis

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A Randomized, Double-blind, Placebo-controlled, Phase 2a Study to Evaluate the Efficacy and Safety of OpSCF in the Treatment of Adult Subjects with Moderate to Severe Atopic Dermatitis

PROTOCOL OpSCF201
Investigational New Drug (IND) Number: 161777

FINAL

VERSION 2.1

20-DEC-2023

Sponsor:	Opsidio, LLC. PO Box 802 Bryn Mawr, PA 19010 United States
Sponsor Medical Expert:	[redacted] MD [redacted] [redacted] [redacted]
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PROTOCOL VERSION HISTORY

Version	Rationale for amendment	Main changes to the protocol
1.0 / 28-JUL-2023	Initial version	N/A
2.0 / 29-SEP-2023	To clarify timing for completion of PP-NRS questionnaire.	Sections 1.1, 1.3 (Table 1), 4.1, and 8.1.2.1: Clarified that PP-NRS is to be recorded at approximately the same time of day and is not required to be recorded at the study center on visit days.
	To clarify that tape strips and biopsies are to be collected at the ET visit (if the ET visit occurs prior to Week 16).	Sections 1.1, 1.3, 4.1, and 8.3.4: Clarified that lesional and nonlesional tape strips and biopsies are to be collected at the ET visit, if applicable, and if the ET visit occurs prior to Week 16.
	To combine the safety objectives and endpoints for the placebo-controlled period and the OLE.	Sections 1.1 and 3: Safety objectives and endpoints were combined for the placebo-controlled period and the OLE.
	To give more flexibility regarding the order at which study assessments should be conducted.	Section 1.3: Removed the requirement to perform reported outcomes prior to the other efficacy assessments.
	To clarify consent to tape strip and biopsy collection.	Sections 1.1, 1.3 (Table 1), and 4.1: Clarified that subjects who consent to tape strip collection must also consent to biopsy collection. Removed 'optional' for tape strip and biopsy sample collection, as these procedures may become mandatory during the course of the study in order to have a minimum of 20 subjects consenting to these procedures.
	To clarify timing for completion of POEM, DLQI, and ADCT questionnaires.	Sections 1.3 (Table 1), 8.1.2.2, 8.1.2.3, and 8.1.2.4: Clarified that POEM, DLQI, and ADCT questionnaires may be completed prior to or on visit days.
	To remove the distance requirement of the Week 4 and Week 16 skin biopsies.	Sections 1.3 (Table 1), 4.1 and 8.3.4.2: Removed distance requirement of the Week 4 and Week 16 skin biopsies.
	To clarify that the dose justification is based on preliminary data.	Section 2.1.4: Clarified that dose justification is based on preliminary data.
	To clarify instructions regarding discontinuation of study drug.	Section 6.5.4: Clarified that subjects who permanently discontinue study drug are encouraged to complete the schedule study visits and assessments planned for the treatment period during which discontinuation occurred (placebo-controlled or OLE).

2.1 / 20-DEC-2023	To clarify that tape strips should not be collected from the face, neck, or hands, as requested by the FDA.	Sections 1.3 (Table 1), 4.1, and 8.3.4.1: Clarified that tape strips should not be collected from esthetically or functionally sensitive anatomical locations, such as the face, neck, or hands.
	To clarify that skin biopsies should not be collected from the face, neck, or hands, as requested by the FDA.	Sections 1.3 (Table 1), 4.1, and 8.3.4.2: Clarified that tape strips should not be collected from esthetically or functionally sensitive anatomical locations, such as the face, neck, or hands.
	To clarify that additional safety tests may be performed at unscheduled visits.	Section 1.3: Included details on additional safety tests that may be performed at unscheduled visits during the study.
	To correct the age at which FSH confirmation is not required.	Section 8.2.4 (Table 5): Age at which FSH confirmation is not required was corrected to 55 years.
	To specify that leftover blood samples may be stored and used for future analyses.	Sections 8.2.4, 8.3.1, 8.3.2, and 8.3.3: Specified that leftover blood samples may be stored and used for future analyses.

Abbreviation: ADCT, Atopic Dermatitis Control Tool; DLQI, Dermatology Life Quality Index; ET, early termination; FDA, Food and Drug Administration; FSH, follicle-stimulating hormone; N/A, not applicable; OLE, open-label extension; POEM, Patient-Oriented Eczema Measure; PP-NRS, Peak Pruritus Numeric Rating Scale.

STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with the protocol, International Council for Harmonisation (ICH) Good Clinical Practice (GCP), and applicable local regulations. The principal investigator will assure that no planned deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the institutional review board (IRB)/research ethics board (REB), except where necessary to eliminate an immediate hazard(s) to the trial subjects. All personnel involved in the conduct of this study have completed ICH GCP training.

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the IRB/REB for review and approval. Approval of both the protocol and the consent form must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IRB/REB before the changes are implemented to the study. All changes to the consent form will be IRB/REB approved.

SIGNATURE PAGE

The signatures below constitute the approval of this protocol and provide the necessary assurances that this trial will be conducted according to this protocol, applicable local regulations, and ICH GCP guidelines.

Name	Title	Signature and date (DD-MMM-YYYY)
[redacted] MD DocuSigned by: [redacted] Signer Name: [redacted] Signing Reason: I approve this document Signing Time: 20-Dec-2023 | 06:12:36 PST 6E9A6FD8137D40B4AF7A05C9DE8A884B	[redacted] Opsidio, LLC.	20-Dec-2023 | 06:12:39 PST
[redacted], MSc DocuSigned by: [redacted] Signer Name: [redacted] Signing Reason: I approve this document Signing Time: 20-Dec-2023 | 09:23:16 EST D96D4D3C2ADE46CEA93C89D6469C1E56	[redacted] Innovaderm Research Inc.	20-Dec-2023 | 09:23:18 EST

PRINCIPAL/QUALIFIED INVESTIGATOR SIGNATURE PAGE

Investigator Name: [redacted] MD

Signature: [redacted] MD (Dec 20, 2023 12:40 EST) **Date:** 20-Dec-2023

(DD-MMM-YYYY)

Institution Name: [redacted]

By my signature, I confirm that I have read the protocol and that I agree to personally supervise the conduct of this study at my study site and to ensure its conduct in accordance with the ethical principles that have their origin in the Declaration of Helsinki and in compliance with the protocol, informed consent, institutional review board/independent ethics committee procedures, instructions from sponsor's representatives, ICH GCP guidelines, and applicable local regulations governing the conduct of clinical studies.

LIST OF ABBREVIATIONS

AD	atopic dermatitis
ADA	anti-drug antibody
ADCT	Atopic Dermatitis Control Tool
AE	adverse event
ALT	alanine aminotransferase
anti-HBc	antibody to hepatitis B core antigen
anti-HBs	hepatitis B surface antibody
AST	aspartate aminotransferase
β-hCG	β-human chorionic gonadotropin
BMI	body mass index
BSA	body surface area
BUN	blood urea nitrogen
CL/F	clearance
CMH	Cochran Mantel Hansel test
COVID-19	Coronavirus disease-2019
CPK	creatine phosphokinase
CRF	case report form
CRO	contract research organization
CV%	percent of coefficient of variance
DSMB	Data and Safety Monitoring Board
DLQI	Dermatology Life Quality Index
EASI	Eczema Area and Severity Index
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EOS	end of study
ET	early termination
FDA	Food and Drug Administration
FIH	first in human
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl-transferase
GLP	Good Laboratory Practice
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCT	hematocrit
HCV	hepatitis C virus
Hgb	hemoglobin
HIV	human immunodeficiency virus
HOME	Harmonising Outcome Measures for Eczema
ICH	International Council for Harmonisation
ICF	informed consent form
IgE	Immunoglobuline E
IL	interleukin

ILC	innate lymphoid cells
IRB	institutional review board
IV	intravenous
IVIg	intravenous immunoglobulin
IWRS	Interactive Web Response System
JAK	Janus kinase
LDH	lactate dehydrogenase
LMW	low molecular weight
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MMRM	mixed model for repeated measures analysis
MPV	mean platelet volume
N/A	not applicable
NOAEL	no-observed-adverse-effect level
NRI	Non-Responder Imputation
NSAID	nonsteroidal anti-inflammatory drug
OLE	open-label extension
PD	pharmacodynamic
PK	pharmacokinetic
PLT	platelets
POEM	Patient-Oriented Eczema Measure
PP	per-protocol
PPD	purified protein derivative
PP-NRS	Peak Pruritus Numeric Rating Scale
PT	preferred term
PUVA	psoralen-UV-A
QoL	quality of life
RBC	red blood cell (count)
REB	research ethics board
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SCF	stem cell factor
SD	standard deviation
SOC	System organ class
SoE	schedule of events
TB	tuberculosis
TEAE	treatment-emergent adverse event
TGFβ	transforming growth factor β
ULN	upper limit of normal
UV	ultraviolet
V/F	volume of distribution
vIGA-AD	Validated Investigator Global Assessment for Atopic Dermatitis

WBC	white blood cell (count)
WHO	world health organization
WOCBP	women of childbearing potential

1 PROTOCOL SUMMARY

1.1 Synopsis

Name of Sponsor/Company:	**Name of Investigational Product:**	**Name of Active Ingredient:**
Opsidio, LLC	OpSCF	OpSCF

Title of Study:

A Randomized, Double-blind, Placebo-controlled, Phase 2a Study to Evaluate the Efficacy and Safety of OpSCF in the Treatment of Adult Subjects with Moderate to Severe Atopic Dermatitis

Phase of Development:

Phase 2a

Study Center(s):

Approximately 20 study centers located in the United States and Canada will participate in this study.

Number of Subjects (planned):

Approximately 48 subjects with moderate to severe atopic dermatitis (AD) are planned to be randomized into this study (approximately 24 subjects in each arm).

Duration of Study:

The maximum study duration for each subject is up to 71 weeks, from screening to the end of the study (EOS) visit. This includes a screening period of up to 30 days, a 16-week placebo-controlled period, a 36-week open-label extension (OLE), and a 15-week follow-up period.

Investigational Product, Dosage, and Mode of Administration:

Subjects will be randomized in a 1:1 ratio at baseline (Day 1) to receive OpSCF 600 mg or placebo, administered subcutaneously (SC) every 2 weeks for 14 weeks for a total treatment period of 16 weeks. OpSCF will be available as 1 mL of a 100 mg/mL liquid in glass vials and administered over three subcutaneous injections of 200 mg (2.0 mL) each. Matching placebo composition will be identical to OpSCF but will not contain the active ingredient. Randomization will be stratified by baseline Validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD) score (vIGA-AD = 3 [moderate] vs. vIGA-AD = 4 [severe]). Randomization will also be stratified for the tape strip/skin biopsy consent status (yes/no) (a minimum of approximately 20 subjects total will be enrolled with tape strip/skin biopsy consent).

After the placebo-controlled period, subjects will have the opportunity to continue into the OLE, where all subjects will receive OpSCF 600 mg administered SC every 4 weeks for a treatment period of 36 weeks. The OLE will be followed by a 15-week follow-up period.

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Objectives and Endpoints:

OBJECTIVES	ENDPOINTS
Primary objective	
To evaluate the efficacy of OpSCF in adult subjects with moderate to severe AD	Primary efficacy endpoint: • Percent change from baseline in EASI at Week 16
Secondary objectives	
To evaluate the safety and tolerability of OpSCF in adult subjects with moderate to severe AD during the placebo-controlled period and the OLE	Secondary safety endpoints: • Incidence of AEs and SAEs • Changes in vital signs, clinical laboratory parameters, and ECGs
To evaluate the effect of OpSCF on AD signs and symptoms and quality of life in adult subjects with moderate to severe AD	Secondary efficacy endpoints (at Weeks 2, 4, 6, 8, 10, 12, 14, and 16 or otherwise specified): • Percent change from baseline in EASI at Weeks 2, 4, 6, 8, 10, 12, and 14 • Change from baseline in EASI • Proportion of subjects achieving EASI50 • Proportion of subjects achieving EASI75 • Proportion of subjects achieving EASI90 • Proportion of subjects achieving at least a 2-grade reduction from baseline to clear (0) or almost clear (1) in vIGA-AD • Proportion of subjects achieving at least a 2-grade reduction from baseline in vIGA-AD • Change and percent change from baseline in weekly average of the daily PP-NRS • Proportion of subjects achieving at least a 4-point reduction from baseline in weekly average of the daily PP-NRS • Change and percent change from baseline in BSA involved with AD • Change from baseline in ADCT at Weeks 2, 4, 8, 12, and 16 • Change from baseline in POEM at Weeks 2, 4, 8, 12, and 16 • Change from baseline in DLQI at Weeks 2, 4, 8, 12, and 16
To evaluate the PK profile of OpSCF in adult subjects with moderate to severe AD	Secondary PK endpoint: • Serum concentrations of OpSCF in subjects receiving the active treatment and PK parameters, as data permit.
Exploratory objectives	
To evaluate the PD, immunogenicity, blood and skin biomarkers in adult subjects with moderate to severe AD	Exploratory PD endpoints: • Change from baseline in blood biomarkers and IgE at Weeks 4, 8, 12, and 16 • Change from baseline in skin biomarkers collected using skin biopsies at Weeks 4 and 16 (for consenting subjects)

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	• Change from baseline in skin biomarkers collected using tape strips at Weeks 4 and 16 (for consenting subjects) • Presence of ADA to OpSCF in subjects receiving the active treatment at Day 1 and Weeks 2, 4, 6, 8, 12, and 16
To evaluate the effect of OpSCF on AD signs and symptoms and quality of life in adult subjects with moderate to severe AD during the OLE	Exploratory efficacy endpoints (at Weeks 20, 24, 28, 32, 36, 40, 44, 48, and 52 or otherwise specified): • Percent change from baseline in EASI • Change from baseline in EASI • Proportion of subjects achieving EASI50, EASI75, and EASI90 • Proportion of subjects achieving at least a 2-grade reduction from baseline to clear (0) or almost clear (1) in vIGA-AD • Proportion of subjects achieving at least a 2-grade reduction from baseline in vIGA-AD • Change and percent change from baseline in PP-NRS • Proportion of subjects achieving at least a 4-point reduction from baseline in the PP-NRS • Change and percent change from baseline in BSA involved with AD • Change from baseline in ADCT at Weeks 20, 24, 28, 36, 44, and 52 • Change from baseline in POEM at Weeks 20, 24, 28, 36, 44, and 52 • Change from baseline in DLQI at Weeks 20, 24, 28, 36, 44, and 52
To evaluate immunogenicity and blood biomarkers in adult subjects with moderate to severe AD during the OLE	Exploratory PD endpoints (at Weeks 24, 32, 40, and 48): • Change from baseline in blood biomarkers • Presence of ADA to OpSCF

Abbreviations: AD, atopic dermatitis; ADA, antidrug antibody; ADCT, Atopic Dermatitis Control Tool; AE, adverse event; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; EASI-50, at least 50% improvement from baseline in Eczema Area and Severity Index; EASI-75, at least 75% improvement from baseline in Eczema Area and Severity Index; EASI-90, at least 90% improvement from baseline in Eczema Area and Severity Index; ECG, electrocardiogram; IgE, Immunoglobuline E; OLE, open-label extension; PP-NRS, Peak Pruritus Numeric Rating Scale; PD, pharmacodynamic; PK, pharmacokinetic; POEM, Patient-Oriented Eczema Measure; SAE, serious adverse event; vIGA-AD; Validated Investigator's Global Assessment for Atopic Dermatitis.

Study Design:

This is a Phase 2a, multicenter, randomized, double-blind, placebo-controlled, parallel-group study designated to evaluate the efficacy and safety of OpSCF in adult subjects with moderate to severe AD. This study will also evaluate the serum concentration of OpSCF and explore the immunogenicity and pharmacodynamics (PD) of OpSCF in subjects with moderate to severe AD.

Approximately 48 adult female and male subjects who are ≥ 18 and ≤ 75 years of age with moderate to severe AD will be randomized in this study. To be eligible for the study, subjects will need to have a history of AD for at least 6 months prior to the screening visit. Subjects will also need to have the following characteristics at screening and on Day 1: Eczema Area and Severity index (EASI) score ≥ 16, vIGA-AD score ≥ 3, and AD covering ≥ 10% of the body surface area (BSA). Randomization will be stratified by baseline vIGA-AD score (vIGA-AD = 3 [moderate] vs. vIGA-AD = 4 [severe]).

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Randomization will also be stratified for the tape strip/skin biopsy consent status (yes/no) (a minimum of approximately 20 subjects total will be enrolled with tape strip/skin biopsy consent).

Subjects who have had prior exposure to biologics or Janus Kinase (JAK) inhibitors must 1) have a sufficiently long washout period (per the exclusion criteria), and 2) must have discontinued these therapies for AD for reasons other than lack of efficacy. Prior clinical trial involvement is permissible and the history will be recorded.

All subjects will read and sign an informed consent form (ICF) prior to any screening procedures being performed. Subjects who fulfill all of the inclusion criteria and none of the exclusion criteria will be accepted into the study. After a screening period of no more than 30 days (from Day -30 to Day -1), eligible subjects will be randomized (1:1) on Day 1 to receive OpSCF at 600 mg or placebo administered SC every 2 weeks for 14 weeks, for a total treatment period of 16 weeks. Subjects who complete the placebo-controlled period will have the opportunity to continue into the OLE, where all subjects will receive OpSCF 600 mg administered SC every 4 weeks for 36 weeks. The OLE will be followed by a 15-week follow-up period. Subjects who decide to withdraw or are withdrawn after completing the placebo-controlled period will undergo the 15-week follow-up period. For scheduled study visits, subjects will come to the study centers on up to 22 occasions for the entire study including the OLE, as described in the Schedule of Events (SoE). In addition, a follow-up call will be performed at Week 67.

Efficacy will be assessed using validated instruments including EASI, vIGA-AD, and BSA, in addition to the Peak Pruritus Numeric Rating Scale (PP-NRS) which will be assessed daily in the placebo-controlled period before or on the visit days only during the OLE. Quality of life will be evaluated using Atopic Dermatitis Control Tool (ADCT), Patient-Oriented Eczema Measure (POEM), and Dermatology Life Quality Index (DLQI).

Safety will be assessed by adverse events (AEs), physical examination, vital signs, 12-lead electrocardiogram (ECG), injection site evaluation, and clinical laboratory tests.

Blood samples will be collected from all subjects predose (if applicable) at specified visits to evaluate serum concentrations of OpSCF. In addition, blood samples for pharmacokinetic (PK) analysis will be collected during Week 14 (Day 99, predose) and on Days 102 and 106.

Blood samples will be collected in all subjects at specified visits to assess the PD, immunogenicity, and blood biomarkers.

In a subset of a minimum of approximately 20 subjects who consent to the procedures, the effect of OpSCF on skin biomarkers will also be evaluated by collecting tape strips and skin biopsies at Day 1, Week 4, and Week 16 (or at the ET visit if it occurs prior to Week 16). Subjects consenting to tape strip collection must also consent to biopsy collection.

In a subset of subjects who consent, optional medical photographs will be taken at specified visits to illustrate the outcome of the trial.

Inclusion/Exclusion Criteria:

Inclusion criteria:

In order to be eligible to participate in this study, a subject must meet all of the following criteria, either at the screening and Day 1 visits or only at 1 of the specified visits (screening or Day 1) as noted in the criterion:

1. Male or female subject aged 18 to 75 years (inclusive) at the time of consent.

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2. Subject has clinically confirmed diagnosis of active AD, according to Hanifin and Rajka criteria.
3. Subject has at least a 6-month history of AD before screening (information obtained from medical chart or subject's physician, or directly from the subject).
4. Subject has an EASI score of ≥ 16 at screening and Day 1.
5. Subject has moderate to severe AD as defined by a vIGA-AD score of ≥ 3 at screening and Day 1.
6. Subject has AD covering ≥ 10% of the total BSA at screening and Day 1.
7. Subject has been using an emollient (except those containing urea) daily for at least 1 week prior to Day 1 and agrees to continue using that same emollient daily at the same frequency (ideally once or twice daily) throughout the study. However, on the day of scheduled visits, subjects cannot apply emollient before their scheduled visit time.

   Note: Every effort should be made to keep the same emollient throughout the study for the same body region. However, the chosen emollient may differ depending on the body region (eg, body vs face emollient may be different).
8. Subject is deemed by the investigator to be eligible for systemic therapy.
9. For female subjects of childbearing potential involved in any sexual intercourse that could lead to pregnancy: the subject must agree to use a highly effective contraceptive method from at least 4 weeks prior to Day 1 until at least 105 days after the last dose of study product. Highly effective contraceptive methods include hormonal contraceptives (eg, combined oral contraceptive, patch, vaginal ring, injectable, or implant), intrauterine devices or intrauterine systems, vasectomized partner(s) (provided his vasectomy was performed ≥ 4 months prior to screening, with surgical success confirmed by the subject), tubal ligation, or double barrier methods of contraception (eg, male condom with cervical cap, male condom with diaphragm, and male condom with contraceptive sponge) in conjunction with spermicide.

   Note: Subjects using hormonal contraceptives must have been on a stable dose for at least 4 weeks before Day 1.

   Note: The above list of contraceptive methods does not apply to subjects who are abstinent for at least 4 weeks before Day 1 and will continue to be abstinent from penile-vaginal intercourse throughout the study. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject. Periodic abstinence (calender, symptothermal, post-ovulation methods) is not aceptable.

   Note: Female subjects must agree to not have egg retrieval from Day 1 until at least 105 days after the last dose of study product.

   Note: A female subject of nonchildbearing potential is defined as follows:
   - Female subject who has had surgical sterilization (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy).
   - Female subject who has had a cessation of menses for ≥ 12 months prior to the screening visit without an alternative medical cause, and a follicle-stimulating hormone (FSH) test confirming nonchildbearing potential (refer to laboratory reference ranges for confirmatory levels). No FSH confirmation is required for women older than 55 years who have had a cessation of menses for ≥ 12 months prior to screening.
10. For male subject involved in any sexual intercourse that could lead to pregnancy, subject must agree to use one of the highly effective contraceptive methods listed in Inclusion Criterion 9 from Day 1 until at least 105 days after the last dose of study product. If the female partner of a male subject uses any of the hormonal contraceptive methods listed above, this contraceptive method should be used

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by the female partner from at least 4 weeks before Day 1 until at least 105 days after the last dose of study product.

Note: Male subjects must refrain from donating sperm from Day 1 until at least 105 days after the last dose of product.

11. Female subject of childbearing potential has had a negative serum pregnancy test at screening and negative urine pregnancy test at Day 1.
12. Subject is willing to participate and is capable of giving informed consent.

    Note: Consent must be obtained prior to any study-related procedures.
13. Subject must be willing and able to comply with all study procedures and must be available for the duration of the study.

Exclusion criteria:

A subject who meets any of the following criteria at the screening visit and/or Day 1, as applicable, will be excluded from participation in this study:

1. Subject is a female who is breastfeeding, pregnant, or who is planning to become pregnant during the study.
2. Subject has clinically infected atopic dermatitis**.**
3. Subject has a history of skin disease or presence of skin condition that, in the opinion of the investigator, would interfere with the study assessments.
4. Subject has a history of cancer or lymphoproliferative disease within 5 years prior to Day 1. Subjects with successfully treated nonmetastatic cutaneous squamous cell or basal cell carcinoma and/or localized carcinoma in situ of the cervix are not to be excluded.
5. Subject had a major surgery within 8 weeks prior to Day 1 or has had a major surgery planned during the study.
6. Subject has any clinically significant medical condition or physical/laboratory/ECG/vital signs abnormality that would, in the opinion of the investigator, put the subject at undue risk or interfere with interpretation of study results.
7. Subject has a history of erythrodermic, refractory or unstable skin disease, including AD, that requires frequent hospitalizations and/or frequent intravenous treatment for skin infections over the last year.
8. Subject is known to have immune deficiency or is immunocompromised.
9. Current or past history of certain infectious diseases including:

    - Subject has known active tuberculosis (TB) or positive infection test. Subject will be evaluated for latent TB infection with a purified protein derivative (PPD) test or a QuantiFERON-TB Gold test. Subjects who demonstrate evidence of latent TB infection (either PPD $\geq$ 5 mm of induration or positive QuantiFERON-TB Gold test, irrespective of bacille Calmette-Guérin vaccination status) will not be allowed to participate in the study.

      Note: Subjects with documented completed treatment for latent TB may be allowed to participate in the study without retesting, as per investigator's judgement.

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- Active infection(s) requiring treatment with intravenous anti-infectives within 30 days, or oral/intramuscular anti-infectives within 14 days prior to the screening visit.
- Chronic recurring infection and/or active viral infection that, based on the investigator's clinical assessment, makes the subject an unsuitable candidate for the study.
- Subject has a positive result for hepatitis B virus (HBV; positive for hepatitis B surface antigens [HBsAg] or positive for hepatitis B antibodies to core antigens [anti-HBc]; subjects having a negative HBsAg and a positive anti-HBc may enroll if they have a positive hepatitis B surface antibody [anti-HBs] demonstrating natural immunity).
- Subject has a positive result for hepatitis C virus (HCV; positive for HCV antibodies; however, a subject with documented proof of cure from HCV may be enrolled).
- Subject has a positive result for human immunodeficiency virus (HIV).
- Coronavirus disease-2019 (COVID-19) infection: in asymptomatic subjects who tested positive for COVID-19, at least 5 days must have passed since a COVID-19 positive test result and the screening or Day 1 visit. Subjects with mild/moderate COVID-19 infection can be enrolled if fever is resolved without use of antipyretics for 24 hours and other symptoms improved, or if 5 days have passed since the COVID-19 positive test result (whichever comes last) and the screening or Day 1 visit. Subjects may be rescreened if deemed appropriate by the investigator based upon the subjects's health status.

10. Subject is not able to tolerate SC drug administration.
11. Subject has any of the following laboratory values at the screening visit:
    - Hemoglobin < 10.0 g/dL (< 110.0 g/L)
    - White blood cell count < 3.0 x 10^9/L (< 3000/mm^3);
    - Absolute neutrophil count of < 1.5 x 10^9/L (< 1500/mm^3);
    - Absolute lymphocyte count of < 0.8 x 10^9/L (<800/mm^3);
    - Platelet count < 100 x 10^9/L;
    - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) values > 2 times the upper limit of normal (ULN).
12. Subject used a biologic or JAK inhibitor for the treatment of AD and discontinued for lack of efficacy.
13. Subject has used dupilumab within 26 weeks prior to Day 1.
14. Subject has used tralokinumab within 12 weeks prior to Day 1.
15. Subject has received an intravenous immunoglobulin (IVIg) therapy within 12 weeks prior to Day 1.
16. Subject has used doxepin, hydroxyzine, or diphenhydramine within 1 week prior to Day 1.
17. Subject has used topical products containing urea within 1 week prior to Day 1.
18. Subject has used systemic antibiotics within 2 weeks or topical antibiotics within 1 week prior to Day 1.

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19. Subject has used any topical medicated treatment that could affect AD within 2 weeks prior to Day 1, including, but not limited to, topical corticosteroids, crisaborole, calcineurin inhibitors, ruxolitinib, tars, antimicrobials, medical devices, and bleach baths.
20. Subject has used systemic treatments (other than biologics) that could affect AD less than 4 weeks prior to Day 1, including, but not limited to, retinoids, calcineurin inhibitors, methotrexate, cyclosporine, hydroxycarbamide (hydroxyurea), azathioprine, oral/injectable corticosteroids, baricitinib, upadacitinib, and abrocitinib.

    Note: Intranasal corticosteroids and inhaled corticosteroids are allowed. Eye and ear drops containing corticosteroids are also allowed.
21. Subject has received any marketed or investigational biological agent within 12 weeks or 5 half-lives (whichever is longer) prior to Day 1 (except those listed in Exclusion Criteria 13 and 14 that are to be excluded as specified).
22. Subject has received a live vaccine with replicating potential or attenuated vaccine within 4 weeks prior to Day 1 or plans to receive a live vaccine with replicating potential or attenuated vaccine during the study and up to 4 weeks or 5 half-lives (of the study product), whichever is longer, after the last study product administration.

    Note: Nonlive-attenuated vaccines, (eg, ribonucleic acid [RNA]-based vaccines, inactivated adenovirus-based vaccines, protein-based vaccines), including nonlive-attenuated vaccines or boosters for COVID-19, are allowed during the study. Live vaccines that are incapable of replicating are permitted.
23. Subject is currently receiving a nonbiological investigational product or device or has received one within 4 weeks or five half-lives of the drug (whichever is longer) prior to Day 1.
24. Subject has excessive sun exposure, is planning a trip in a sunny climate, or has used tanning booths within 4 weeks prior to Day 1, or is not willing to minimize natural and artificial sunlight exposure during the study. Use of sunscreen products and protective apparel are recommended when exposure cannot be avoided.
25. Subject has received any ultraviolet (UV)-B phototherapy (including tanning beds) or excimer laser within 4 weeks prior to Day 1.
26. Subject has had psoralen-UV-A (PUVA) treatment within 4 weeks prior to Day 1.
27. Subject has used OpSCF.
28. Subject has a known or suspected allergy to OpSCF or any component of the investigational product.
29. Subject has a known history of clinically significant drug or alcohol abuse in the last year prior to Day 1.
30. Subject is institutionalized because of legal or regulatory order.
31. For subjects consenting to biopsy collection only:
    - Subject has a history of an allergic reaction or significant sensitity to lidocaine or other local anesthetics.
    - Subject has a history of hypertrophic scarring or keloid formation in scars or suture sites.

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- Subject has a bleeding disorder or has taken anticoagulant medication, such as heparin, low molecular weight (LMW) heparin, warfarin, antiplatelet agents (except low-dose aspirin ≤ 81 mg which will be allowed), direct acting oral anticoagulants (dabigatran, rivaroxaban, and apixaban) within 2 weeks prior to Day 1, or has a contraindication to skin biopsies. Nonsteroidal anti-inflammatory drugs (NSAIDs) will not be considered antiplatelets and will be allowed.

Statistical methods:

Continuous variables will be summarized in tables and will include the number of subjects, mean, standard deviation (SD), percent of coefficient of variance (CV%), median, minimum, and maximum. Categorical variables will be presented in tables as frequencies and percentages. All inferential statistical tests will be performed at a nominal 2-sided significance level of 0.1. Randomization will be stratified by baseline vIGA-AD score (vIGA-AD = 3 [moderate] vs. vIGA-AD = 4 [severe]). Randomization will also be stratified for the tape strip/skin biopsy consent status (yes/no) (a minimum of approximately 20 subjects total will be enrolled with tape strip/skin biopsy consent). The stratification for tape strip/skin biopsy consent status will be done for administrative purposes only and is not an important prognostic factor at baseline.

A statistical analysis plan (SAP) will provide additional details on the approach to the analysis and data displays.

Efficacy Analyses:

The primary efficacy endpoint of percent change from baseline in EASI at Week 16 will be analyzed using a mixed model for repeated measures analysis (MMRM) based on observed data where the visit will be the time factor; and the randomization stratification factor (ie, vIGA-AD score only), treatment group, and interaction term for treatment-by-visit will be the fixed effects and the baseline EASI value will be the covariate. An unstructured variance-covariance matrix will be used.

For categorical efficacy endpoints involving proportions of vIGA-AD, EASI, and PP-NRS (eg, the proportion of subjects achieving at least a 2-grade reduction from baseline to clear (0) or almost clear (1) in vIGA-AD at Week 16), a Cochran Mantel Hansel test (CMH) controlling for the randomization stratification factor (ie, vIGA-AD score only) will be performed. Details on handling missing data will be specified in the SAP.

Safety Analyses:

The safety analysis will include reported AEs and other safety information (ie, clinical laboratory evaluations, vital signs, and 12-lead ECG results). A summary of safety results will be presented for each treatment group.

PK Analyses:

OpSCF serum concentration data will be summarized based on nominal timepoints using descriptive statistics, such as mean, SD, CV%, median, minimum and maximum.

Data from this study may be combined with data from other studies for population PK and exposure-response analyses. A non-linear mixed-effects modeling approach may be used to estimate the population central values and the empirical Bayesian estimates of the individual values of OpSCF

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Opsidio, LLC	OpSCF	OpSCF

clearance (CL/F) and volume of distribution (V/F). Additional parameters may be estimated if useful in the interpretation of the data.

PD Analyses:

Skin and blood biomarker levels will be compared to placebo adjusted change from baseline over time for each treatment group, and the parameters will be summarized by treatment group using descriptive statistics.

Immunogenicity:

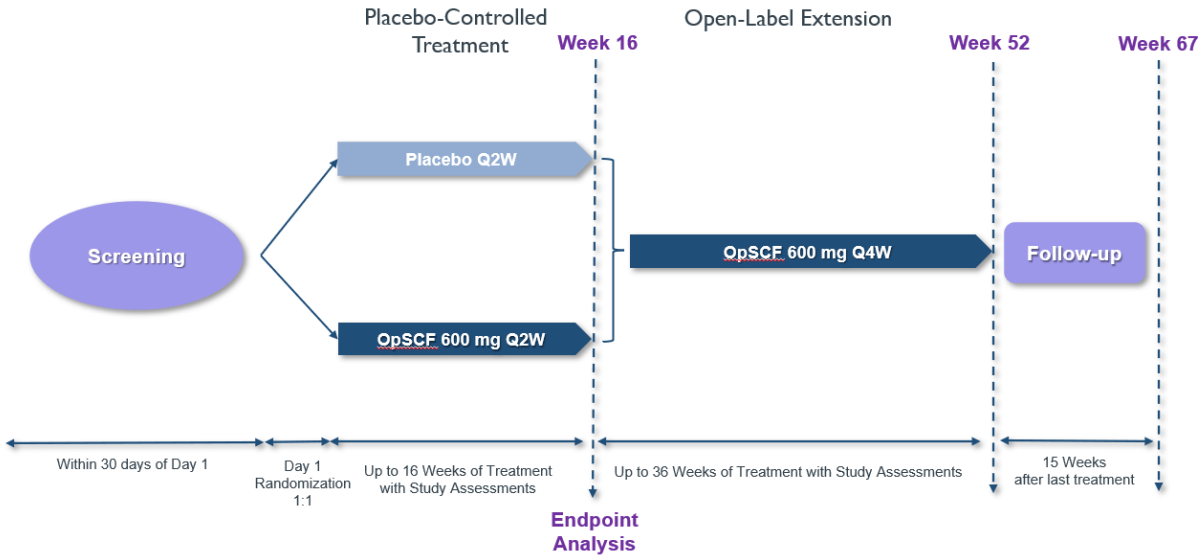
The ADA levels will be compared to placebo adjusted change from baseline over time for each treatment group, and the parameters will be summarized by treatment group using descriptive statistics.

Sample Size Consideration:

For the primary efficacy endpoint of percent change from baseline in EASI at Week 16, a total sample size of 48 subjects (24/arm) will have approximately 80% power to detect an effect size of 0.73 with a 2-sided statistical significance level of 0.1.

1.2 Study Diagram

Figure 1. Study Diagram



Abbreviations: Q2W, once every 2 weeks; Q4W, once every 4 weeks.

1.3 Schedule of Events

The screening evaluation will only be performed after the subject has agreed to participate and has signed and dated the ICF. No treatment or trial-related procedures will be initiated before the informed consent is signed. The Day 1 visit must be performed, at the latest, 30 days after the screening visit.

The screening evaluation will be performed according to the inclusion and exclusion criteria. If the subject fulfills all inclusion criteria and no exclusion criteria, he or she may be included in the study.

Table 1 provides a description of the procedures to be performed at each visit.

Unless specified otherwise, the study assessments scheduled during the study visits should preferably be performed before the study product administration.

Additional safety tests may be performed at unscheduled visits during the course of the study, if deemed necessary by the investigator. Repeat or unscheduled tests or samples may be taken for safety reasons or for technical issues.

Table 1. Schedule of Events

Study visits	**Screening**	**Treatment period**												**Follow-up[b]**		**ET[b]**
		Placebo-Controlled										**OLE**				
Week		**W0**	**W2**	**W4**	**W6**	**W8**	**W10**	**W12**	**W14**		**W16**	**W20, 24, 28, 32, 36, 40, 44, 48**	**W52**	**W56**	**W67 (Phone call)**	
Day	**-30 to -1[a]**	**1**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**102**	**106**	**113**	**141, 169, 197, 225, 253, 281, 309, 337**	**365 (EOT)**	**393**	**470 (EOS)**	
Window (days)	**N/A**	–	±1	±3	±3	±3	±3	±3	±1	±1	±1	±3	±3	±3	±4	±4	
Informed consent	X															
Demographics	X															
Medical and surgical history	X	X														
Inclusion-exclusion criteria	X	X														
Pregnancy test[c]	X	X	X	X	X	X	X	X	X			X	X	X	X	X	X
Physical examination[d]	X	X	X	X	X	X	X	X	X			X	X	X	X		X
Vital signs[e]	X	X	X	X	X	X	X	X	X			X	X	X	X		X
Electrocardiogram	X	X										X		X			X
Clinical laboratory tests (biochemistry, hematology, urinalysis)	X	X	X	X	X	X	X	X	X			X	X	X	X		X

Study visits	**Screening**	**Treatment period**													**Follow-up[b]**		**ET[b]**
		Placebo-Controlled										**OLE**					
Week		**W0**	**W2**	**W4**	**W6**	**W8**	**W10**	**W12**	**W14**		**W16**	**W20, 24, 28, 32, 36, 40, 44, 48**	**W52**	**W56**	**W67 (Phone call)**	
Day	**-30 to -1[a]**	**1**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**102**	**106**	**113**	**141, 169, 197, 225, 253, 281, 309, 337**	**365 (EOT)**	**393**	**470 (EOS)**	
Window (days)	**N/A**	–	±1	±3	±3	±3	±3	±3	±1	±1	±1	±3	±3	±3	±4	±4	
Serology (HBV [HBsAg, anti-HBc, anti-HBs], HCV, HIV)	X																
Tuberculosis evaluation[f]	X																
EASI	X	X	X	X	X	X	X	X	X			X	X	X	X		X
BSA	X	X	X	X	X	X	X	X	X			X	X	X	X		X
vIGA-AD	X	X	X	X	X	X	X	X	X			X	X	X	X		X
ADCT[p]		X	X	X		X		X				X	X[h]	X	X		X
PP-NRS[g]	X———											X	X	X	X		X
POEM[p]		X	X	X		X		X				X	X[h]	X	X		X
DLQI[p]		X	X	X		X		X				X	X[h]	X	X		X
Randomization		X															
Study treatment administration[i]		X	X	X	X	X	X	X	X			X	X				

Study visits	**Screening**	**Treatment period**													**Follow-up[b]**		**ET[b]**
		Placebo-Controlled										**OLE**					
Week		**W0**	**W2**	**W4**	**W6**	**W8**	**W10**	**W12**	**W14**			**W16**	**W20, 24, 28, 32, 36, 40, 44, 48**	**W52**	**W56**	**W67 (Phone call)**	
Day	**-30 to -1[a]**	**1**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**102**	**106**	**113**	**141, 169, 197, 225, 253, 281, 309, 337**	**365 (EOT)**	**393**	**470 (EOS)**	
Window (days)	**N/A**	–	±1	±3	±3	±3	±3	±3	±1	±1	±1	±3	±3	±3	±4	±4	
Tape strip collection (as applicable)[j]		X		X								X					X[m]
Skin biopsies collection (as applicable)[k]		X		X								X					X[m]
Blood sampling for PK (predose, if applicable)		X	X	X	X	X		X	X	X	X	X	X				X
Blood sampling for ADA (predose)		X	X	X	X	X		X				X	X[l]				X
Blood sampling for IgE analyses (predose)		X		X		X		X				X					X[m]
Blood sampling for biomarker analyses (predose)		X		X		X		X				X	X[l]				X[m]
Optional medical photographs[n]		X	X	X		X		X				X					X[m]

Study visits	Screening	Treatment period												Follow-up[b]		ET[b]
		Placebo-Controlled										OLE				
Week		W0	W2	W4	W6	W8	W10	W12	W14		W16	W20, 24, 28, 32, 36, 40, 44, 48	W52	W56	W67 (Phone call)	
Day	-30 to -1[a]	1	15	29	43	57	71	85	99	102	106	113	141, 169, 197, 225, 253, 281, 309, 337	365 (EOT)	393	470 (EOS)	
Window (days)	N/A	–	±1	±3	±3	±3	±3	±3	±1	±1	±1	±3	±3	±3	±4	±4	
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events evaluation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Injection site evaluation[e]		X	X	X	X	X	X	X	X			X	X	X			X

Abbreviations: AD, atopic dermatitis; ADA, anti-drug antibody; ADCT, Atopic Dermatitis Control Tool; anti-HBc, antibody to hepatitis B core antigen; anti-HBs, hepatitis B surface antigen; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; EOS, end of study; EOT, end of treatment; ET, early termination; HbsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IgE, immunoglobulin E; N/A, not applicable; OLE, open-label extension; PP-NRS, Peak Pruritis Numeric Rating Scale; PK, pharmacokinetic; POEM, Patient-Oriented Eczema Measure; SC, subcutaneous; vIGA-AD, Validated Investigator's Global Assessment scale for Atopic Dermatitis.

[a] Screening period must be a minimum of 7 days in order to collect PP-NRS between Day -7 and Day -1 and calculate a weekly average baseline score prior to Day 1.

[b] Subjects who do not participate in the OLE will undergo the 15-week follow-up period after Week 16 is completed. For these subjects, the first follow-up visit will take place at Week 20 and the follow-up phone call will take place at Week 31. For subjects who discontinue the study early, an ET visit will be conducted at the time of early termination and subject will undergo the follow-up period afterwards.

[c] For female subjects of childbearing potential, serum pregnancy test at screening, and urine pregnancy test at the other visits. For the follow-up phone call at Week 67, subjects will be provided with a pregnancy test to be performed at home and the results will be communicated by subjects during the phone call.

[d] Complete physical examination at screening, Week 16, and Week 52 (end of treatment period). Brief physical examinations at all other visits.

[e] Including height and weight. Height will be measured only at screening.

[f] If purified protein derivative is used, a second visit will be necessary for purified protein derivative reading only.

[g] Subjects will complete their PP-NRS on a daily basis at approximately the same time of day starting at screening and during the placebo-controlled period (up to the Week 16 visit) using a diary. During the OLE and the follow-up period, the PP-NRS will be completed at the visit days only.

[h] Will be done at Weeks 20, 24, 28, 36, and 44.

[i] Study product administration will be performed on-site at each specified visit. Subject will receive OpSCF 600 mg or placebo administered SC every 2 weeks during the placebo-controlled period. At Week 16, after all assessments are completed, the administration of the first dose of the OLE will be performed. During the OLE, all subjects will receive OpSCF 600 mg administered SC every 4 weeks. On Day 1 and Week 2 of the placebo-controlled period, and Weeks 16 and 20 at the beginning of the OLE, subjects will remain under observation for at least 2 hours after study product administration. At Weeks 4, 6, 24, and 28 subjects will remain under observation for at least 1 hour after study product administration. At any other visit, subjects may remain under observation after the study product administration, based on the investigator's judgement.

[j] Only for a minimum of approximately 20 subjects who consent to the procedure, skin tape strips will be collected predose on Day 1 (one from lesional skin and one from nonlesional skin in the vicinity of the lesional skin), from the same lesional skin at Week 4 (even if the lesion has cleared), and from the same lesional and nonlesional skin at Week 16 (or at the ET visit if it occurs prior to Week 16; even if the lesion has cleared). These procedures should not be performed on esthetically or functionally sensitive anatomical locations (ie, the face, neck, or hands).

[k] Only for a minimum of approximately 20 subjects who consent to the procedure (the same subjects who consent to tape strips); two 4.5-mm skin biopsies predose on Day 1 (one from lesional skin and one from nonlesional skin in the vicinity of the lesional skin), one 4.5-mm skin biopsy at Week 4 (from the same lesional skin; outside the scar of the previous biopsies, even if the lesions have cleared), and two 4.5-mm punch biopsies at Week 16 (or at the ET visit if it occurs prior to Week 16; lesional and nonlesional from the same areas; outside the scar of the previous biopsies, even if the lesions have cleared). Tape strips and biopsies should be collected from adjacent sites within the same lesion, whenever possible. These procedures should not be performed on esthetically or functionally sensitive anatomical locations (ie, the face, neck, or hands).

[l] Will only be collected at Weeks 24, 32, 40, and 48.

[m] Will be collected at ET visit only if early termination occurred during the placebo-controlled period.

[n] Optional, in a subset of subjects who consent to the procedure, medical photographs of a selected representative AD lesion will be taken.

[o] Sites of injection will be evaluated for possible injection site reaction assessments approximately 30 minutes post-injection, when applicable. Any injection site reactions will be recorded as AE. Additional follow-up after Week 52 can be performed for any ongoing injection site reactions.

[p] The questionnaires will be assessed before or on the visit days.

2 INTRODUCTION

2.1 Background

2.1.1 Atopic Dermatitis

Atopic dermatitis (AD) is a chronic inflammatory skin disease that typically develops during childhood and may persist into adulthood. It is characterized by recurrent, pruritic, localized skin lesions, such as erythematous papules, vesicles, plaques, edema, and crusting.[1,2] The prevalence of AD is estimated at 20-30% in children and 1-3% in adults.[1,3] Although disease onset typically occurs in early infancy, AD may also start in mid- or late life. Patients with AD are at higher risk of other atopic disorders, including food allergies, allergic conjunctivitis/rhinitis, and asthma.[4-6] Various other health problems negatively impact patients quality of life (QoL).[7,8] Chronic pruritis and inflammation/pain can lead to sleep disturbance and mental health symptoms. An individual with AD is at higher risk for multiple neuropsychiatric disorders, including attention deficit (hyperreactivity) disorder, depression, and suicidal ideation, speech disorders in childhood, headaches, and seizures.[8-10] There are also cardio-metabolic and musculoskeletal (osteroporosis, injuries, and fractures) comorbidities.[9,11]

The etiology of AD is not entirely clear, however interactions among genetic and environmental factors, skin barrier dysfunction, microbial dysbiosis, and immune dysregulation, among other external triggers, are known to play a role in the pathogenesis of the disease. Inflammation is thought to be initiated by the disruption of the epidermal barrier, and subsequent activation of epidermal dendritic and innate lymphoid cells (ILC), which stimulate Th2 cells to release cytokines into the skin, namely interleukin-4 (IL-4), IL-13, and IL-31. Release of cytokines leads to barrier dysfunction, inflammation, and pruritus, which characterize the disease state.[12-14]

Emollients and topical corticosteroids (including corticosteroids, calcineurin inhibitors, and crisaborole) are the first-line treatments for AD. Phototherapy and systemic anti-inflammatory agents may also be used to manage skin inflammation in patients with AD. Patients who do not achieve adequate and sustained alleviation of AD symptoms with topical treatments are prescribed systemic steroids or other systemic immunosuppressive agents (including cyclosporine, azathioprine, methotrexate and mycophenolate mofetil).[1,2,15] While these can be effective as temporary treatments of flare-ups, extended use has been associated with many potential side effects. Two recent developments for treatment of AD include: the biologic agents dupilumab and tralokinumab approved for moderate to severe AD, and oral Janus kinase (JAK) inhibitors approved or in late-stage clinical development.[2,16,17] Nevertheless, despite the recent progress in the field, there is a need for novel safe and efficacious agents for the treatment of AD.

2.1.2 Role of SCF in Atopic Dermatitis

Stem cell factor (SCF) is the only known ligand for the Receptor Tyrosine Kinase c-kit, which is operative in many essential physiologic processes in mammals. SCF exists as two splice variants, a shorter isoform of 220 amino acids (SCF220) and a longer isoform of 248 amino acids (SCF248). Preclinical genetic studies have shown that SCF220 which does not include Exon 6 is responsible

for several homeostatic processes, including hematopoiesis, spermatogeneisis and hair color. The longer SCF248 isoform that includes Exon 6 is upregulated at sites of inflammation, and is responsible for the activation and proliferation of inflammatory immune cells. Genetic reconstitution studies were done on SCF-deficient mice that are are runted, anemic, have no coat pigment and the males are sterile. Reconstitution of these mice with only SCF 220 corrects these defects, however the mice are deficient in mast cells. Reconstitution with only SCF248 has no effect on the runting, anemia, coat color or fertility, however they have normal mast cells. SCF220 is constitutively expressed in bone marrow, melanocytes and testis, whereas the longer isoform, SCF248, is inducible in certain stromal cell types, particularly by inflammatory cytokines such as IL-13.[18-20]

SCF248 plays a key role in the positive feed-forward loop of chronic inflammation by activating c-kit-positive immune cells. These include mast cells, ILC2 and ILC3 lymphocytes, and eosinophils which secrete a variety of proinflammatory cytokines including IL-4, IL-9, IL-13, IL-25, and transforming growth factor β (TGFβ), as well as others. These cytokines activate local structural cells that may be fibroblasts, epithelial cells, keratinocytes, or monocytic cells, and they in turn secrete cytokines and, importantly, express SCF248 on their surface. This surface-expressed SCF248 stimulates additional c-kit-positive immune cells, creating a feed-forward loop of more cytokine generation and more SCF248 expression, leading to an amplification and chronicity of the disease process. It has been demonstrated that blocking SCF prevents it from activating the c-kit-positive immune cells and the further generation of cytokines.[14,18,21]

2.1.3 OpSCF

OpSCF (also referred to as VH1/VK3) is a humanized IgG4κ mAb directed against the longer, 248 amino acid splice variant of stem cell factor (SCF248) and does not bind to the shorter SCF220. Because OpSCF is specific for SCF248, its effects are limited to areas of inflammation where SCF248 has been upregulated, and leaves the functions of c-kit mediated by SCF220 intact. This provides the therapeutic efficacy of preventing local c-kit activation, without the off-target pharmacologic effects of a pan-anti-SCF therapy or broad c-kit blockade. It is therefore hypothesized that treatment with OpSCF will suppress the cycle of inflammation characterized in AD by inhibiting the pro-inflammatory activity of SCF248.[14]

Certain immune cells, particularly mast cells, ILC2 and ILC3 lymphocytes, and eosinophils depend on c-kit occupancy by SCF for activation and proliferation. There is evidence that blocking SCF, particularly SCF248, breaks the cycle of chronic inflammation by decreasing the production of inflammatory cytokines and returning an inflammatory environment back towards normal.[14,18,21]

2.1.3.1 Nonclinical Studies

Thirteen (13) and 26-week Good Laboratory Practice (GLP)-compliant toxicology studies were performed in rats (13-week study) and cynomolgus monkeys (13- and 26-week studies) up to doses of 100 mg/kg body weight. After 26 weeks of OpSCF administration, there were no OpSCF-related clinical observations, effects on appetite, body weight or body weight gain, and no OpSCF-related changes in ophthalmology, electrocardiology, blood pressure, respiratory rate, neurological assessments, hematology, coagulation, serum chemistry, and urinalysis parameters. At terminal

necropsy, there were no OpSCF-related organ weight changes, macroscopic, or histopathologic observations. The no-observed-adverse-effect level (NOAEL) was considered to be 100 mg/kg.

A GLP-compliant tissue cross reactivity study was performed and demonstrated no off-target binding to a panel of 33 human tissues.

2.1.3.2 Clinical Studies

Study OpSCF-101 was a phase 1 first-in-human (FIH) double blind, randomized, placebo-controlled study that aimed to evaluate the safety, tolerability, pharmacokinetic (PK), and immunogenicity of single (Part A) and multiple (Part B) doses of OpSCF administered via subcutaneous (SC) and intravenous (IV) routes in healthy volunteers.

Results to date demonstrate that OpSCF is well tolerated in single and multiple doses. Possibly or probably drug-related adverse events were uncommon, and to date have all been of Grade 1. Preliminary PK data indicate the half-life of OpSCF in healthy subjects is 16.6 to 19 days. No significant ADA have been detected. Please refer to the Investigator's Brochure for more detail.

2.1.4 Study Rationale

It has been demonstrated that SCF, and specifically SCF248, is increased locally in tissues in a variety of chronic inflammatory diseases, in addition to increased serum levels of the cleaved SCF-Extra Cellular Domain. By using a specific anti-SCF248 antibody in immunohistochemistry and by quantitative polymerase chain reaction assays, it has been shown that the SCF in inflamed tissues is the SCF248 isoform. Additionally, it has been shown that only the SCF248 isoform is upregulated by inflammation in animal models and human disease tissues of AD, severe steroid-resistant asthma, eosinophilic esophagitis, renal fibrosis, idiopathic pulmonary fibrosis, and others. There is evidence that blocking SCF, particularly SCF248, breaks the cycle of chronic inflammation and returns an inflammatory environment back towards normal.

The efficacy of OpSCF has been demonstrated in vitro and in vivo in animal models, including AD and severe allergic asthma models. The non-clinical toxicology program demonstrated a lack of toxicity in 13- and 26-week GLP-compliant toxicology studies in rats and cynomolgus monkeys. While there are approved drugs that inhibit c-kit tyrosine kinase activity (such as imatinib and dasatinib) and an antibody against c-kit in clinical development (barzolvolimab; Celldex Therapeutics), these agents do not distinguish between homeostatic and inflammatory roles of c-kit. However, specifically targeting of the inflammatory SCF248 isoform of SCF has the potential advantage of inhibiting the SCF248-mediated activation of c-kit on immune cells in areas of inflammation, while sparing the essential homeostatic functions of c-kit mediated by SCF220 in other organs.[14]

The primary objective of this study is to assess the efficacy of OpSCF in subjects with moderate to severe AD. The safety, tolerability, and PK profile of OpSCF will also be evaluated as secondary endpoints. Further exploratory objectives will aim to evaluate the PD, immunogenicity, and blood and skin biomarkers of subjects with moderate to severe AD. The dose selected in this study was found to be well tolerated and safe in the previous Phase 1 study (OpSCF-101).

The OpSCF dose planned to be evaluated in this proof-of-concept study is 600 mg SC every 2 weeks (Q2W). This dose is estimated to provide an exposure that is within the range of exposures that were demonstrated to be safe and well-tolerated in healthy subjects in single and multiple ascending dose study, and approximately 19-fold below the NOAEL exposure of rats and 65-fold below the NOAEL exposure in GLP toxicology studies. A dosing frequency of Q2W is selected for the placebo-controlled period based on preliminary PK results demonstrating that OpSCF half-life in serum range from 16.6 to 19 days. The Q4W dosing regimen was selected for the OLE period to decrease the injection burden on subjects while evaluating the efficacy of a Q4W maintenance therapy. The OLE will be used to collect long term safety, efficacy, and PK data.

2.2 Risk/Benefit Assessment

2.2.1 Known Potential Risks

The data from both nonclinical and clinical studies with OpSCF suggest that it is safe and well-tolerated at the doses to be administered in the present study.

2.2.2 Known Potential Benefits

In this Phase 2a study, it is anticipated that subjects will see an improvement in their AD condition as a result of participating in the study, if they are randomized to active study product and/or are continuing into the open-label extension (OLE). Participation in this study may help generate future benefit for larger groups of patients with AD if OpSCF proves to be successful in treating this disease.

2.2.3 Assessment of Risks and Benefits

All quality, pharmacology and toxicology data, and satisfactory safety and tolerability data demonstrated in nonclinical studies are considered sufficient to expect a positive benefit/risk ratio for the treatment of atopic dermatitis with OpSCF, and therefore to initiate this study.

The risk to subjects in this trial will be minimized by compliance with the eligibility criteria, proper study design, and close monitoring.

3 OBJECTIVES AND ENDPOINTS

Table 2. Study Objectives and Endpoints

OBJECTIVES	ENDPOINTS
Primary objective	
To evaluate the efficacy of OpSCF in adult subjects with moderate to severe AD	Primary efficacy endpoint: • Percent change from baseline in EASI at Week 16
Secondary objectives	
To evaluate the safety and tolerability of OpSCF in adult subjects with moderate to severe AD during the placebo-controlled period and OLE	Secondary safety endpoints: • Incidence of AEs and SAEs • Changes in vital signs, clinical laboratory parameters, and ECGs
To evaluate the effect of OpSCF on AD signs and symptoms and quality of life in adult subjects with moderate to severe AD	Secondary efficacy endpoints (at Weeks 2, 4, 6, 8, 10, 12, 14, and 16 or otherwise specified): • Percent change from baseline in EASI at Weeks 2, 4, 6, 8, 10, 12, and 14 • Change from baseline in EASI • Proportion of subjects achieving EASI50 • Proportion of subjects achieving EASI75 • Proportion of subjects achieving EASI90 • Proportion of subjects achieving at least a 2-grade reduction from baseline to clear (0) or almost clear (1) in vIGA-AD • Proportion of subjects achieving at least a 2-grade reduction from baseline in vIGA-AD • Change and percent change from baseline in weekly average of the daily PP-NRS • Proportion of subjects achieving at least a 4-point reduction from baseline in weekly average of the daily PP-NRS • Change and percent change from baseline in BSA involved with AD • Change from baseline in ADCT at Weeks 2, 4, 8, 12, and 16 • Change from baseline in POEM at Weeks 2, 4, 8, 12, and 16 • Change from baseline in DLQI at Weeks 2, 4, 8, 12, and 16
To evaluate the PK profile of OpSCF in adult subjects with moderate to severe AD	Secondary PK endpoint: • Serum concentrations of OpSCF in subjects receiving the active treatment and PK parameters, as data permit.
Exploratory objectives	
	Exploratory PD endpoints:

OBJECTIVES	ENDPOINTS
To evaluate the PD, immunogenicity, blood and skin biomarkers in adult subjects with moderate to severe AD	• Change from baseline in blood biomarkers and IgE at Weeks 4, 8, 12, and 16 • Change from baseline in skin biomarkers collected using skin biopsies at Weeks 4 and 16 (for consenting subjects) • Change from baseline in skin biomarkers collected using tape strips at Weeks 4 and 16 (for consenting subjects) • Presence of ADA to OpSCF in subjects receiving the active treatment at Day 1 and Weeks 2, 4, 6, 8, 12, and 16
To evaluate the effect of OpSCF on AD signs and symptoms and quality of life in adult subjects with moderate to severe AD during the OLE	Exploratory efficacy endpoints (at Weeks 20, 24, 28, 32, 36, 40, 44, 48, and 52 or otherwise specified): • Percent change from baseline in EASI • Change from baseline in EASI • Proportion of subjects achieving EASI50, EASI75, and EASI90 • Proportion of subjects achieving at least a 2-grade reduction from baseline to clear (0) or almost clear (1) in vIGA-AD • Proportion of subjects achieving at least a 2-grade reduction from baseline in vIGA-AD • Change and percent change from baseline in the PP-NRS • Proportion of subjects achieving at least a 4-point reduction from baseline in the PP-NRS • Change and percent change from baseline in BSA involved with AD • Change from baseline in ADCT at Weeks 20, 24, 28, 36, 44, and 52 • Change from baseline in POEM at Weeks 20, 24, 28, 36, 44, and 52 • Change from baseline in DLQI at Weeks 20, 24, 28, 36, 44, and 52
To evaluate immunogenicity and blood biomarkers in adult subjects with moderate to severe AD during the OLE	Exploratory PD endpoints (at Weeks 24, 32, 40, and 48): • Change from baseline in blood biomarkers • Presence of ADA to OpSCF

Abbreviations: AD, atopic dermatitis; ADA, antidrug antibody; ADCT, Atopic Dermatitis Control Tool; AE, adverse event; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; EASI-50, at least 50% improvement from baseline in Eczema Area and Severity Index; EASI-75, at least 75% improvement from baseline in Eczema Area and Severity Index; EASI-90, at least 90% improvement from baseline in Eczema Area and Severity Index; ECG, electrocardiogram; IgE, Immunoglobuline E; OLE, open-label extension; PP-NRS, Peak Pruritus Numeric Rating Scale; PD, pharmacodynamic; PK, pharmacokinetic; POEM, Patient-Oriented Eczema Measure; SAE, serious adverse event; vIGA-AD; Validated Investigator's Global Assessment for Atopic Dermatitis.

4 STUDY DESIGN

4.1 Overall Design

This is a Phase 2a, multicenter, randomized, double-blind, placebo-controlled, parallel-group study designated to evaluate the efficacy and safety of OpSCF in adult subjects with moderate to severe AD. This study will also evaluate the serum concentration of OpSCF and explore the immunogenicity and pharmacodynamics (PD) of OpSCF in subjects with moderate to severe AD.

Approximately 48 adult female and male subjects who are ≥ 18 and ≤ 75 years of age with moderate to severe AD will be randomized in this study. To be eligible for the study, subjects will need to have a history of AD for at least 6 months prior to the screening visit. Subjects will also need to have the following characteristics at screening and on Day 1: Eczema Area and Severity Index (EASI) score ≥ 16, Validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD) score ≥ 3, and AD covering ≥ 10% of the body surface area (BSA). Randomization will be stratified by baseline vIGA-AD score (vIGA-AD = 3 [moderate] vs. vIGA-AD = 4 [severe]). Randomization will also be stratified for the tape strip/skin biopsy consent status (yes/no) (a minimum of approximately 20 subjects total will be enrolled with tape strip/skin biopsy consent).

Subjects who have had prior exposure to biologics or JAK inhibitors must 1) have a sufficiently long washout period (per exclusion criteria [Section 5.2]), and 2) must have discontinued these therapies for AD for reasons other than lack of efficacy. Prior clinical trial involvement is permissible and the history will be recorded.

All subjects will read and sign an informed consent form (ICF) prior to any screening procedures being performed. Subjects who fulfill all of the inclusion criteria and none of the exclusion criteria will be accepted into the study. After a screening period of no more than 30 days (from Day -30 to Day -1), eligible subjects will be randomized (1:1) on Day 1 to receive OpSCF at 600 mg or placebo administered SC every 2 weeks for 14 weeks, for a total treatment period of 16 weeks. Subjects who complete the placebo-controlled period will have the opportunity to continue into the OLE, where all subjects will receive OpSCF 600 mg administered SC every 4 weeks for 36 weeks. The OLE will be followed by a 15-week follow-up period. Subjects who decide to withdraw or are withdrawn after completing the placebo-controlled period will undergo the 15-week follow-up period. For scheduled study visits, subjects will come to the study centers on up to 22 occasions for the entire study including the OLE, as described in the Schedule of Events (SoE). In addition, a follow-up call will be performed at Week 67.

Efficacy will be assessed using validated instruments including EASI, vIGA-AD, and BSA, in addition to the Peak Pruritis Numeric Rating Scale (PP-NRS) which will be assessed daily in the placebo-controlled period and before or on the visit days during the OLE. Quality of life will be evaluated using Atopic Dermatitis Control Tool (ADCT), Patient-Oriented Eczema Measure (POEM), and Dermatology Life Quality Index (DLQI).

Safety will be assessed by adverse events (AEs), physical examination, vital signs, 12-lead electrocardiogram (ECG), injection site evaluation, and clinical laboratory tests.

Blood samples will be collected from all subjects predose (if applicable) at specified visits to evaluate serum concentrations of OpSCF. In addition, blood samples for PK analysis will be collected at Week 14 (Day 99, predose) and on Days 102 and 106.

Blood samples will be collected in all subjects at specified visits to assess the PD, immunogenicity, and blood biomarkers.

In a subset of a minimum of approximately 20 subjects who consent to the procedures, the effect of OpSCF on skin biomarkers will also be evaluated by collecting tape strips and skin biopsies as follows. Subjects consenting to tape strip collection must also consent to biopsy collection.

- On Day 1, skin tape strips will be collected prior to study product administration (one from lesional skin and one from nonlesional skin in the vicinity of the lesional skin). At Week 4 skin tape strips will be collected from the same area of lesional skin, even if the lesion has cleared. At Week 16 (or at the ET visit if it occurs prior to Week 16), skin tape strips will be collected from the same lesional and nonlesional skin in the vicinity of the lesional skin (even if the lesion has cleared).
- On Day 1, two 4.5-mm skin biopsies will be collected prior to the study product administration (one from lesional skin and one from nonlesional skin in the vicinity of the lesional skin). At Week 4, one 4.5-mm skin biopsy will be collected (from the same lesional skin; outside the scar of the previous biopsies, even if the lesion has cleared). At Week 16 (or at the ET visit if it occurs prior to Week 16), two 4.5-mm punch biopsies will be collected (one from the same lesional skin [even if the lesion has cleared] and one from the same nonlesional skin; outside the scar of the previous biopsies,).
- Tape strips and biopsies should be collected from adjacent sites within the same lesion, whenever possible. These procedures should not be performed on esthetically or functionally sensitive anatomical locations (ie, the face, neck, or hands).

In a subset of subjects who consent, optional medical photographs will be taken at specified visits to illustrate the outcome of the trial.

4.2 Scientific Rationale for Study Design

The proposed design is considered appropriate for assessing the preliminary efficacy, safety, tolerability, PK, PD, and immunogenicity of OpSCF compared to a placebo in subjects with moderate to severe AD.

This Phase 2a study will be randomized to ensure random allocation of subjects to treatment arms and reduce bias. Because efficacy assessments of AD have a high degree of subjectivity, the placebo-controlled period of this study will be double-blinded. The highest degree of patient and assessor blinding should be sought to achieve credible inferences. It is also important to have a placebo control in a Phase 2 study to control for confounding factors, such as potential investigator bias, and to ensure that the statistical procedures can be appropriately applied. After completion of the placebo-controlled treatment period, all subjects will have the opportunity to continue into the OLE and to receive the active drug for a treatment period of 36 weeks. During this OLE the randomization status of subjects in the placebo-controlled period will remain blinded to the investigators, site study personnel, and subjects.

4.3 Justification for Dose

The OpSCF dose planned to be evaluated in this proof-of-concept study is 600 mg SC Q2W. This dose provides an exposure that is within the range of exposures that were demonstrated to be safe

and well-tolerated in healthy subjects in a single and multiple ascending dose study, and approximately 10-fold below the exposure of the NOAEL in GLP toxicology studies. A dosing frequency of Q2W is selected for the placebo-controlled period based on preliminary PK results demonstrating that OpSCF half-life in serum range from 16.6 to 19 days. The Q4W dosing regimen was selected for the OLE period to decrease the injection burden on subjects while evaluating the efficacy of a Q4W maintenance therapy. The OLE will be used to collect long term safety, efficacy, and PK data.

4.4 Start of Study Definition

The start of the study is the first act of recruitment of a potential subject (ie, signing the ICF).

4.5 End of Study Definition

A subject is considered to have completed the placebo-controlled phase of the study if he or she has completed all placebo-controlled visits of the study, including the last visit or the last scheduled procedure shown in the Schedule of Events, Table 1. A subject is considered to have completed the OLE phase of the study if he or she has completed the placebo-controlled visits and the OLE visits of the study, including the last visit or the last scheduled procedure shown in the Schedule of Events, Table 1.

The end of the study is defined as completion of the last visit or procedure shown in the schedule of event for the last subject in the trial globally for all sites.

5 STUDY POPULATION

5.1 Inclusion Criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria, either at the screening and Day 1 visits or only at 1 of the specified visits (screening or Day 1) as noted in the criterion:

1. Male or female subject aged 18 to 75 years (inclusive) at the time of consent.
2. Subject has clinically confirmed diagnosis of active AD, according to Hanifin and Rajka criteria (APPENDIX A).
3. Subject has at least a 6-month history of AD before screening (information obtained from medical chart or subject's physician, or directly from the subject).
4. Subject has an EASI score of ≥ 16 at screening and Day 1.
5. Subject has moderate to severe AD as defined by a vIGA-AD score of ≥ 3 at screening and Day 1.
6. Subject has AD covering ≥ 10% of the total BSA at screening and Day 1.
7. Subject has been using an emollient (except those containing urea) daily for at least 1 week prior to Day 1 and agrees to continue using that same emollient daily at the same frequency (ideally once or twice daily) throughout the study. However, on the day of scheduled visits, subjects cannot apply emollient before their scheduled visit time.

   Note: Every effort should be made to keep the same emollient throughout the study for the same body region. However, the chosen emollient may differ depending on the body region (eg, body vs face emollient may be different).
8. Subject is deemed by the investigator to be eligible for systemic therapy.
9. For female subjects of childbearing potential involved in any sexual intercourse that could lead to pregnancy: the subject must agree to use a highly effective contraceptive method from at least 4 weeks prior to Day 1 until at least 105 days after the last dose of study product. Highly effective contraceptive methods include hormonal contraceptives (eg, combined oral contraceptive, patch, vaginal ring, injectable, or implant), intrauterine devices or intrauterine systems, vasectomized partner(s) (provided his vasectomy was performed ≥ 4 months prior to screening, with surgical success confirmed by the subject), tubal ligation, or double barrier methods of contraception (eg, male condom with cervical cap, male condom with diaphragm, and male condom with contraceptive sponge) in conjunction with spermicide.

   Note: Subjects using hormonal contraceptives must have been on a stable dose for at least 4 weeks before Day 1.

   Note: The above list of contraceptive methods does not apply to subjects who are abstinent for at least 4 weeks before Day 1 and will continue to be abstinent from penile-vaginal intercourse throughout the study. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject. Periodic abstinence (calender, symptothermal, post-ovulation methods) is not aceptable.

   Note: Female subjects must agree to not have egg retrieval from Day 1 until at least 105 days after the last dose of study product.

   Note: A female subject of nonchildbearing potential is defined as follows:

- Female subject who has had surgical sterilization (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy).
- Female subject who has had a cessation of menses for ≥ 12 months prior to the screening visit without an alternative medical cause, and a follicle-stimulating hormone (FSH) test confirming nonchildbearing potential (refer to laboratory reference ranges for confirmatory levels). No FSH confirmation is required for women older than 55 years who have had a cessation of menses for ≥ 12 months prior to screening.

10. For male subject involved in any sexual intercourse that could lead to pregnancy, subject must agree to use one of the highly effective contraceptive methods listed in Inclusion Criterion 9 from Day 1 until at least 105 days after the last dose of study product. If the female partner of a male subject uses any of the hormonal contraceptive methods listed above, this contraceptive method should be used by the female partner from at least 4 weeks before Day 1 until at least 105 days after the last dose of study product.

    Note: Male subjects must refrain from donating sperm from Day 1 until at least 105 days after the last dose of product.
11. Female subject of childbearing potential has had a negative serum pregnancy test at screening and negative urine pregnancy test at Day 1.
12. Subject is willing to participate and is capable of giving informed consent.

    Note: Consent must be obtained prior to any study-related procedures.
13. Subject must be willing and able to comply with all study procedures and must be available for the duration of the study.

5.2 Exclusion Criteria

A subject who meets any of the following criteria at the screening and/or Day 1 visits, as applicable, will be excluded from participation in this study:

1. Subject is a female who is breastfeeding, pregnant, or who is planning to become pregnant during the study.
2. Subject has clinically infected atopic dermatitis**.**
3. Subject has a history of skin disease or presence of skin condition that, in the opinion of the investigator, would interfere with the study assessments.
4. Subject has a history of cancer or lymphoproliferative disease within 5 years prior to Day 1. Subjects with successfully treated nonmetastatic cutaneous squamous cell or basal cell carcinoma and/or localized carcinoma in situ of the cervix are not to be excluded.
5. Subject had a major surgery within 8 weeks prior to Day 1 or has had a major surgery planned during the study.
6. Subject has any clinically significant medical condition or physical/laboratory/ECG/vital signs abnormality that would, in the opinion of the investigator, put the subject at undue risk or interfere with interpretation of study results.
7. Subject has a history of erythrodermic, refractory or unstable skin disease, including AD, that requires frequent hospitalizations and/or frequent intravenous treatment for skin infections over the last year.

8. Subject is known to have immune deficiency or is immunocompromised.
9. Current or past history of certain infectious diseases including
    - Subject has known active tuberculosis (TB) or positive infection test. Subject will be evaluated for latent TB infection with a purified protein derivative (PPD) test or a QuantiFERON-TB Gold test. Subjects who demonstrate evidence of latent TB infection (either PPD ≥ 5 mm of induration or positive QuantiFERON-TB Gold test, irrespective of bacille Calmette-Guérin vaccination status) will not be allowed to participate in the study

      Note: Subjects with documented completed treatment for latent TB may be allowed to participate in the study without retesting, as per investigator's judgement.
    - Active infection(s) requiring treatment with intravenous anti-infectives within 30 days, or oral/intramuscular anti-infectives within 14 days prior to the screening visit.
    - Chronic recurring infection and/or active viral infection that, based on the investigator's clinical assessment, makes the subject an unsuitable candidate for the study.
    - Subject has a positive result for hepatitis B virus (HBV; positive for hepatitis B surface antigens [HBsAg] or positive for hepatitis B antibodies to core antigens [anti-HBc]; subjects having a negative HBsAg and a positive anti-HBc may enroll if they have a positive hepatitis B surface antibody [anti-HBs] demonstrating natural immunity).
    - Subject has a positive result for hepatitis C virus (HCV; positive for HCV antibodies; however, a subject with documented proof of cure from HCV may be enrolled).
    - Subject has a positive result for human immunodeficiency virus (HIV).
    - Coronavirus disease-2019 COVID-19 infection: in asymptomatic subjects who tested positive for COVID-19, at least 5 days must have passed since a COVID-19 positive test result and the screening or Day 1 visit. Subjects with mild/moderate COVID-19 infection can be enrolled if fever is resolved without use of antipyretics for 24 hours and other symptoms improved, or if 5 days have passed since the COVID-19 positive test result (whichever comes last) and the screening or Day 1 visit. Subjects may be rescreened if deemed appropriate by the investigator based upon the subjects's health status.
10. Subject is not able to tolerate SC drug administration.
11. Subject has any of the following laboratory values at the screening visit:
    - Hemoglobin < 10.0 g/dL (< 110.0 g/L)
    - White blood cell count < 3.0 x 10^9/L (< 3000/mm3);
    - Absolute neutrophil count of < 1.5 x 10^9/L (< 1500/mm3);
    - Absolute lymphocyte count of < 0.8 x 10^9/L (<800/mm3);
    - Platelet count < 100 x 10^9/L;
    - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) values > 2 times the upper limit of normal (ULN).
12. Subject used a biologic or JAK inhibitor for the treatment of AD and discontinued for lack of efficacy.

13. Subject has used dupilumab within 26 weeks prior to Day 1.
14. Subject has used tralokinumab within 12 weeks prior to Day 1.
15. Subject has received an intravenous immunoglobulin (IVIg) therapy within 12 weeks prior to Day 1.
16. Subject has used doxepin, hydroxyzine or diphenhydramine within 1 week prior to Day 1.
17. Subject has used topical products containing urea within 1 week prior to Day 1.
18. Subject has used systemic antibiotics within 2 weeks or topical antibiotics within 1 week prior to Day 1.
19. Subject has used any topical medicated treatment that could affect AD within 2 weeks prior to Day 1, including, but not limited to, topical corticosteroids, crisaborole, calcineurin inhibitors, ruxolitinib, tars, antimicrobials, medical devices, and bleach baths.
20. Subject has used systemic treatments (other than biologics) that could affect AD less than 4 weeks prior to Day 1, including, but not limited to, retinoids, calcineurin inhibitors, methotrexate, cyclosporine, hydroxycarbamide (hydroxyurea), azathioprine, oral/injectable corticosteroids, baricitinib, upadacitinib, and abrocitinib.

    Note: Intranasal corticosteroids and inhaled corticosteroids are allowed. Eye and ear drops containing corticosteroids are also allowed.
21. Subject has received any marketed or investigational biological agent within 12 weeks or 5 half-lives (whichever is longer) prior to Day 1 (except those listed in Exclusion Criteria 13 and 14 that are to be excluded as specified).
22. Subject has received a live vaccine with replicating potential or attenuated vaccine within 4 weeks prior to Day 1 or plans to receive a live vaccine with replicating potential or attenuated vaccine during the study and up to 4 weeks or 5 half-lives (of the study product), whichever is longer, after the last study product administration.

    Note: Nonlive-attenuated vaccines, (eg, ribonucleic acid [RNA]-based vaccines, inactivated adenovirus-based vaccines, protein-based vaccines), including nonlive-attenuated vaccines or boosters for COVID-19, are allowed during the study. Live vaccines that are incapable of replicating are permitted.
23. Subject is currently receiving a nonbiological investigational product or device or has received one within 4 weeks or five half-lives of the drug (whichever is longer) prior to Day 1.
24. Subject has excessive sun exposure, is planning a trip in a sunny climate, or has used tanning booths within 4 weeks prior to Day 1, or is not willing to minimize natural and artificial sunlight exposure during the study. Use of sunscreen products and protective apparel are recommended when exposure cannot be avoided.
25. Subject has received any ultraviolet (UV)-B phototherapy (including tanning beds) or excimer laser within 4 weeks prior to Day 1.
26. Subject has had psoralen-UV-A (PUVA) treatment within 4 weeks prior to Day 1.
27. Subject has used OpSCF.

28. Subject has a known or suspected allergy to OpSCF or any component of the investigational product.
29. Subject has a known history of clinically significant drug or alcohol abuse in the last year prior to Day 1.
30. Subject is institutionalized because of legal or regulatory order.
31. For subjects consenting to biopsy collection only:
    - Subject has a history of an allergic reaction or significant sensitity to lidocaine or other local anesthetics.
    - Subject has a history of hypertrophic scarring or keloid formation in scars or suture sites.
    - Subject has a bleeding disorder or has taken anticoagulant medication, such as heparin, low molecular weight (LMW) heparin, warfarin, antiplatelets agents (except low-dose aspirin ≤ 81 mg which will be allowed), direct acting oral anticoagulants (dabigatran, rivaroxaban, and apixaban) within 2 weeks prior to Day 1, or has a contraindication to skin biopsies. Nonsteroidal anti-inflammatory drugs (NSAIDs) will not be considered antiplatelets and will be allowed.

5.3 Screen Failures

Screen failures are defined as individuals who consent to participate in the clinical trial but are not subsequently randomly assigned to the study treatment. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse events (SAEs).

Individuals who do not meet the criteria for participation in this trial (screen failure) may be rescreened if deemed acceptable by the investigator, and may enter the study if they meet all study criteria and are expected to remain eligible. Rescreened subjects should be assigned a different subject number than the initial screening. All procedures planned at the screening visit, including signature of a new consent form, will be performed.

6 TREATMENT

6.1 Study Treatment Administered

This study involves SC administration of OpSCF 600 mg (three 2.0 mL injections) Q2W for a treatment period of 16 weeks during the placebo-controlled period, followed by administration of OpSCF 600 mg (three 2.0 mL injections) Q4W for a treatment period of 36 weeks during the OLE. The study product will be administered by trial site staff in the clinic. The date and time of study product administration, and site of injection will be documented. On Day 1 and Week 2 of the placebo-controlled period, and Weeks 16 and 20 at the beginning of the OLE, subjects will remain under observation for at least 2 hours after study product administration. At Weeks 4, 6, 24, and 28, subjects will remain under observation for at least 1 hour after study product administration. At any other visit, subjects may remain under observation after the study product administration, basd on the investigator's judgement. The study products will be provided by the sponsor. Refer to Table 3 for further details regarding the study products.

Table 3. Study Products

	Study products	
Product name	OpSCF	Placebo
Dosage form	1 mL vials of 100 mg/mL solution	1 mL vials without active ingredient
Unit dose strength/dosing level	600 mg, administered as 3 x 2 mL SC injections	N/A, administered as 3 x 2 mL SC injections
Route of administration (placebo-controlled period)	SC, Q2W (total of 8 doses)	SC, Q2W (total of 8 doses)
Route of administration (OLE period)	SC, Q4W (total of 9 doses)	N/A
Dosing instructions	OpSCF should be administered by clinic staff trained in best practice for SC administration of treatments. Refer to the corresponding study manual for more details on the administration method.	The placebo should be administered by clinic staff trained in best practice for SC administration of treatments. Refer to the corresponding study manual for more details on the administration method.
Physical description	The drug product is a clear, colorless liquid, free of visible particles, which may exhibit opalescence.	Placebo is identical to the active solution in color.
Source of procurement	Opsidio LLC	Opsidio LLC

Abbreviations: N/A, not applicable; OLE, open-label extension; Q2W, once every two weeks; Q4W, once every four weeks; SC, subcutaneous.

The contents of the label will be in accordance with all applicable regulatory requirements.

6.2 Dosage Adjustment and Toxicity Management

As there have been no drug-related toxicities identified to date in animal toxicology studies nor in human Phase 1 safety study, there are no anticipated dosage adjustments for this Phase 2a study. In the case of an adverse event the investigator may consult the medical monitor to determine the appropriate course of action regarding the continued administration of study drug.

6.3 Preparation/Handling/Storage/Accountability

6.3.1 Preparation/Storage/Handling

All study products must be stored in a secure environmentally controlled and monitored area in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff. The study product may only be supplied by authorized site staff and may only be given to subjects enrolled into the study.

The study products vials must be refrigerated at 2-8 °C (36- 46°F) until the day of use, and brought to room temperature before use. The study product should be administered within 4 hours of coming to room temperature. Detailed handling instructions will be provided in a study manual.

The study products will be dispensed by the study site only for administration to trial subjects.

6.3.2 Accountability

The investigator is responsible for maintaining accurate records of the study product received initially and of the study product dispensed/used. Any study product accidentally or deliberately destroyed, or returned to the sponsor or designee will be accounted for. Any discrepancies between amounts dispensed and returned will be explained. At the conclusion of the study, all used and unused study products and all medication containers will be returned or destroyed as per approved arrangements by the sponsor.

All study product accountability forms and treatment logs must be retained in the investigator's study files. Product inventory and accountability records will be maintained, as per ICH GCP. These records must be available for inspection at any time by the sponsor, its designees, or by regulatory agencies.

Further guidance and information for final disposition of study products are provided in the study manual.

6.4 Randomization

At the study site, each screened subject will be assigned a subject identifier number during screening that will be used on all subject documentation. The subject identifier number will contain the site number and the subject number and will be assigned in numerical order at the screening visit based on chronological order of screening dates.

Approximately 48 subjects will be randomized 1:1 to OpSCF or placebo.

Randomization will occur prior to first dosing, at Day 1 visit. The randomization list will be generated using a validated software. Randomization will be stratified by baseline disease severity at Day 1 ([vIGA-AD = 3] vs. [vIGA-AD = 4]). Randomization will also be stratified for the tape strip/skin biopsy consent status (yes/no) (a minimum of approximately 20 subjects total will be enrolled with tape strip/skin biopsy consent). The stratification for tape strip/skin biopsy consent status will be done for administrative purposes only and is not an important prognostic factor at baseline.

The master randomization list will be kept secured until the study blind is broken at the end of study. This list will be uploaded into an Interactive Web Response System (IWRS)/Electronic Data Capture (EDC). The investigator or designee will be able to acquire a randomization number for eligible subjects by connecting to the IWRS/EDC.

In addition, a cap will be added in IWRS, to limit the number of subjects declining biopsy and tape strip samples collection to a maximum of approximately 28 subjects.

Further guidance and information can be obtained in the corresponding study manual.

6.4.1 Blinding

The placebo-controlled period of this study will be double-blinded. Treatment and randomization information will be kept confidential and will not be released to the investigator, the study staff, the contract research organization (CRO), or the sponsor's study team until the data are locked at the end of the placebo-controlled period. After the data are locked following the placebo-controlled period, data will be unblinded to identified personnel including the sponsor to perform the planned interim analysis to evaluate the primary and secondary efficacy endpoints. However the personnel at the study sites, the subjects and those with direct study responsibilities will remain blinded for the duration of the whole study (see Section 9.3.9 for more details). The final database lock will occur at the end of the study in order to produce the exploratory endpoint descriptive results for the OLE period as well as the secondary safety endpoints of the study.

Details regarding the unblinding procedures for this study will be detailed in the Unblinding Plan.

Breaking the blind should be considered only when knowledge of the treatment assignment is deemed essential for the subject's care. In such case of a medical emergency, the investigator has the sole responsibility for determining if unblinding of a subject's treatment assignment is warranted. Subject safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the medical monitor prior to unblinding a subject's treatment assignment unless this could delay further management of the subject. If a subject's treatment assignment is unblinded, the medical monitor and the sponsor must be notified within 24 hours after breaking the blind. The date and reason for breaking the blind must be documented in the source document and the eCRF.

Any request to unblind a subject for nonemergency purposes must be discussed with the medical monitor prior to unblinding.

In cases of accidental unblinding, the investigator should contact the medical monitor and ensure every attempt is made to preserve the blind to the greatest extent possible.

In the event of an accidental unblinding, the medical monitor, the sponsor and the investigator will convene to determine the best course of action for the subject. The subject may: be allowed to continue in the study, be excluded from the per-protocol (PP) analysis set, move to the OLE phase, or be discontinued, or whatever is deemed to be in the best interests of the subject and consistent with Good Clinical Practices. A plan for Corrective and Preventative Action may be instituted if the unblinding was the result of a failure to follow proper procedures. The decision and the rationale of the committee will be recorded.

6.4.2 Study Treatment Compliance

Study treatment compliance in this study will be based on records under the direct control of the investigator; the study product will always be administered on site. The date and time of each dose administered in the clinic will be recorded.

6.5 Concomitant Therapy

6.5.1 Disease Characteristics and Treatment History

All medications (including over-the-counter drugs, vitamins, herbal/natural products, and antacids) taken within 4 weeks prior to screening and throughout the study must be recorded. In addition, the use of any prohibited medications must be recorded within the timeframe described in the exclusion criteria.

All biologics and JAK inhibitors taken by a subject, including in prior clinical trials, will be documented as medication history. The duration of the treatment and the reason for discontinuation will be documented. Subjects who have used a biologic or JAK inhibitor for the treatment of AD and discontinued for lack of efficacy will be excluded from the study.

Medication entries may be captured as generic or trade names. Trade names should be used for combination drugs. Entries should include as much as possible of the following information: the dose, unit, frequency of administration, route of administration, start date, end date, and indication. If the medication is stopped or the dosage is changed, these details must be recorded.

Details regarding the subject's history of AD, including date of diagnosis, relevant disease characteristics, and other prior treatments, including systemic treatments, radiation, and surgical procedures, will be recorded. A medical history of other conditions related to AD will also be collected at this time.

6.5.2 Permitted Therapies

6.5.2.1 Emollients

Subjects must apply an emollient of their choice (except those containing urea) on their skin, **including on AD lesions**. The emollient use must be **initiated at least 1 week prior to Day 1** and subjects must continue using it at the same frequency (once or twice daily) throughout the study. However, on the day of scheduled visits, subjects cannot apply emollient before their scheduled visit time.

Every effort should be made to keep the same emollient throughout the study for the same body region. However, the chosen emollient may differ depending on the body region (eg, body vs face emollient may be different). The commercial name of the selected emollient(s) will be recorded in the source document and electronic case report form (eCRF). No other products may be applied to the lesions during the study, except as detailed in Section 6.5.4.

6.5.2.2 Other Permitted Therapies

The following therapies are permitted:

- The use of prior or concomitant medications to treat other medical conditions (eg, hypertension, diabetes, acute infections, etc.) is permitted during this study (except as detailed in Section 6.5.3) and will be recorded, as detailed in Section 6.5.1. These should be kept constant as much as possible.
- Intranasal corticosteroids and inhaled corticosteroids are allowed. Eye and ear drops containing corticosteroids are also allowed.
- Use of sunscreen products and protective apparel are permitted when sun exposure cannot be avoided.
- Nonlive-attenuated vaccines, (eg, ribonucleic acid [RNA]-based vaccines, inactivated adenovirus-based vaccines, protein-based vaccines), including nonlive-attenuated vaccines or boosters for coronavirus disease-2019 (COVID-19), are allowed during the study. Live vaccines that are incapable of replicating are permitted.

6.5.3 Prohibited Treatments and Procedures

The introduction of medications or therapies for other medical conditions known to affect AD (except when given for rescue therapy, Section 6.5.4), are prohibited during the study and during the interval prior to entry into the study as defined in the exclusion criteria. Table 4 lists such prohibited medications.

Major elective surgery will not be allowed during the study. If the subject must undergo emergency surgery, the study drug should be interrupted at the time of the surgery.

If in any doubt, investigators are advised to discuss medications with the medical monitor.

The continuation in the study of subjects who start any other prohibited medications or therapies for other reasons will be determined by the investigator, the medical monitor and the sponsor in consultation.

Table 4. Prohibited Therapies or Procedures

Prohibited medications, products, and procedures	Washout period prior to first dose (Day 1)
Dupilumab	26 weeks
Any marketed or investigational biological agent	12 weeks or 5 half-lives (whichever is longer)
Tralokinumab	12 weeks
IVIg therapy	12 weeks
Nonbiological investigational product or device	4 weeks
Live vaccines with replicating potential and live-attenuated vaccines	4 weeks or 5 half-lives (whichever is longer)
Systemic treatments (other than biologics) that could affect AD including, but not limited to, retinoids, calcineurin inhibitors, methotrexate, cyclosporine, hydroxycarbamide [hydroxyurea], azathioprine, oral/injectable corticosteroids, baricitinib, upadacitinib, and abrocitinib.	4 weeks
PUVA treatment, UV-B phototherapy (including tanning beds) or excimer laser, excessive sun exposure or has used tanning booths	4 weeks
Topical medicated treatment that could affect AD including, but not limited to, topical corticosteroids, crisaborole, calcineurin inhibitors, ruxolitinib, tars, antimicrobials, medical devices, and bleach baths	2 weeks
For subjects consenting to biopsies only: Anticoagulant medication, such as heparin, LMW-heparin, warfarin, antiplatelets agents (except low-dose aspirin ≤ 81 mg which will be allowed), direct acting oral anticoagulants (dabigatran, rivaroxaban, and apixaban). NSAIDs will not be considered antiplatelets and will be allowed.	2 weeks
Systemic antibiotics	2 weeks
Topical antibiotics	1 week
Topical products containing urea	1 week
Hydroxyzine and diphenhydramine	1 week
Doxepin	1 week

Abbreviations: AD, atopic dermatitis; IVIg, intravenous immunoglobulin; LMW, low molecular weight; NSAIDs, nonsteroidal anti-inflammatory drug; PUVA, psoralen-UV-A; UV-B, ultraviolet-B.

6.5.4 Rescue Therapy

Rescue treatment for AD may be provided at the Week 6 visit or later, if medically necessary and at the investigator's discretion.

Investigators should attempt to limit the first step of rescue therapy to topical medications, and escalate to systemic medications only for those subjects who do not respond adequately after at least 7 days of topical treatment. Subjects requiring rescue therapy should consider the addition of TCS prior to considering systemic treatment. Any subject who requires TCS treatment may stay in the study and should continue the TCS for as brief a period as possible. Topical calcineurin inhibitors may be used for rescue, but should be reserved for problem areas only, eg, face, neck, intertriginous and genital areas, etc.

Systemic corticosteroids (including oral, intravenous, and intramuscular) are not allowed for routine treatment of AD. Any subject requiring systemic therapy to treat their AD during the study will be discontinued from the study and the end of study visit assessment should be completed per Schedule of Visits and Procedures. If a subject needs rescue treatment with a non-corticosteroid systemic agent (including but not limited to cyclosporine, methotrexate, mycophenolate mofetil, azathioprine, dupilumab) or with an oral, injectable or parenteral corticosteroid, study drug should be permanently discontinued prior to the initiation of rescue systemic agent.

If rescue treatment is medically necessary outside of the parameters described above (ie, to control intolerable AD symptoms), study drug should be permanently discontinued.

Subjects who permanently discontinue study drug should conduct an ET visit and undergo the follow-up period afterwards. Subjects may be asked to come for additional follow-up visits, at the investigator's discretion, after the ET visit to ensure appropriate medical care and AEs follow-up. Rescue medication use must be recorded on the concomitant medications eCRF, indicated as "Rescue AD therapy".

7 DISCONTINUATION AND LOST TO FOLLOW-UP

Subjects have the right to withdraw from the study at any time for any reason without penalty. The investigator also has the right to withdraw subjects from the study if he or she feels it is in the best interest of the subject or if the subject is uncooperative or noncompliant.

Should a subject decide to withdraw, all efforts will be made to complete and report the observations as thoroughly as possible, particularly the examinations outlined in the ET visit.

The investigator or one of his or her staff members should contact the subject to determine as accurately as possible the primary reason for the withdrawal.

A complete final evaluation at the time of the subject's withdrawal should be made with an explanation of why the subject is withdrawing from the study. If the reason for removal of a subject is an AE or an abnormal laboratory test result, the principal specific event or test will be recorded.

If a subject withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.1 Discontinuation

Subjects who discontinue the study after the first dose will be asked to come for the ET visit. After the ET visit, subject will undergo the 15-week follow-up period afterward. Subjects who are discontinued for safety reasons may be asked to come for additional follow-up visits, at the investigator's discretion, after the follow-up period to ensure appropriate medical care and AEs follow-up.

Subjects who discontinue will not be replaced.

Reasons for discontinuation include the following:

- The investigator decides that the subject should be withdrawn. If this decision is made because of a SAE, the study product is to be discontinued in that subject immediately and appropriate measures are to be taken. The investigator will notify the sponsor immediately.
- The investigator requests that the subject be withdrawn from the study.
- The subject, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication may be discontinued as detailed in Section 6.5.3 or rescue medication is administered outside of the parameters described in Section 6.5.4.
- The subject is lost to follow-up. In this case, a reasonable attempt to contact the subject and ascertain his or her status must be made, and these attempts must be documented.
- The subject becomes pregnant at any time during the study.

- The subject may withdraw from the study for any other reason, including withdrawal of consent.
- The sponsor or regulatory authorities, for any reason, stop the study. In this case, all subjects will be discontinued from the study. The investigator will immediately, on discontinuance of the study by the sponsor, in its entirety or at a clinical trial site, inform both the subjects and the IRB/REB of the discontinuance, provide them with the reasons for the discontinuance and advise them in writing of any potential risks to the health of subjects or other persons.

7.2 Lost to Follow-Up

A subject will be considered lost to follow-up if he or she fails to return for scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site will attempt to contact the subject and reschedule the missed visit. The site will then counsel the subject on the importance of maintaining the assigned visit schedule and ascertain if the subject wishes to or should continue in the study.
- Before a subject is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record or study file.
- If all attempts to contact the subject fail, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 Efficacy Assessments

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

8.1.1 Investigator Assessments

8.1.1.1 Eczema Area and Severity Index

The EASI will be assessed at the visits specified in Table 1. The EASI quantifies the severity of a subject's AD based on both lesion severity and the percentage of BSA affected.[22] The EASI is a composite score ranging from 0 to 72 that takes into account the degree of erythema, induration/infiltration (papules), excoriation, and lichenification (each scored from 0 to 3 separately) for each of 4 body regions, with adjustment for the percentage of BSA involved for each body region and for the proportion of the body region to the whole body. A detailed procedure of EASI score calculation is provided in APPENDIX B. To be eligible for this study, subjects must have an EASI score of ≥ 16 at the screening and Day 1 visits.

8.1.1.2 Validated Investigator Global Assessment for Atopic Dermatitis

The vIGA-AD™[23,24] of disease severity will be assessed at the visits specified in Table 1. The vIGA-AD is a global assessment of the current state of the disease. It is a 5-point morphological assessment of overall disease severity. A detailed description of the vIGA-AD score is provided in APPENDIX C. To be eligible for this study, subjects must have a vIGA-AD score of ≥ 3 at the screening and Day 1 visits.

8.1.1.3 Body Surface Area

The overall BSA affected by AD will be evaluated (from 0% to 100%) at the visits specified in Table 1. The palmar surface of 1 hand (using the patient's hand and including the fingers) represents 1% of his or her total BSA.[25] To be eligible for this study, subjects must have a BSA of ≥ 10% at the screening and Day 1 visits.

8.1.2 Subject Assessments

8.1.2.1 Pruritus Numeric Rating Scale

The intensity of pruritus will be recorded daily at approximately the same time of day (from the screening until the Week 16 visit) by the subject in a diary using the PP-NRS[26,27]. During the OLE and the follow-up period, the PP-NRS will be completed before or on the visit days only (refer to Table 1). This will be evaluated by asking subjects to assign a numerical score representing their itch at the worst moment during the previous 24 hours: "On a scale of 0 to 10, with 0 being "no itch" and 10 being "worst itch imaginable", how would you rate your itch at the worst moment during the previous 24 hours?". The PP-NRS is provided in APPENDIX D. The daily (24-hour)

PP-NRS will be recorded from screening to the Week 16 visit, and the weekly mean of the daily PP-NRS will be calculated up to Week 16; at least 3 PP-NRS data are needed to calculate a weekly mean. Therefore, a minimum of 7 days of screening is needed to collect PP-NRS scores between Day -7 and Day -1 and calculate a weekly average baseline score prior to Day 1. After the Week 16 visit, PP-NRS will be collected before or on the visit days only, and no weekly mean PP-NRS will be calculated.

8.1.2.2 Patient-Oriented Eczema Measure

The POEM will be assessed before or on the visit days, as specified in Table 1. The POEM, developed by Charman et al., is a self-assessment of disease severity by the subject.[28] The POEM has a maximum value of 28 based on the subject's response to 7 questions scored from 0 to 4. A detailed description of the POEM assessment is provided in APPENDIX E.

8.1.2.3 Dermatology Life Quality Index Questionnaire

The DLQI will be assessed before or on the visit days, as specified in Table 1. It is a simple 10-question validated questionnaire that has been used in more than 40 different skin conditions.[29] Its use has been described in more than 1000 publications, including many multinational studies. The DLQI is the most frequently used instrument in studies of randomized controlled trials in dermatology. The questionnaire is provided in APPENDIX F.

8.1.2.4 Atopic Dermatitis Control Test

The ADCT will be assessed before or on the visit days, as specified in Table 1. This questionnaire is a self-assessment comprised of 6 concise questions to evaluate subjects' perceptions of AD symptoms and impacts on their life and function over the last week.[30] Each question carries equal weight and is scored from 0 to 4, for a total score ranging between 0 and 24.[30] The ADCT has been recommended by the Harmonizing Outcome Measures in Eczema (HOME) initiative as a core outcome instrument for long-term control of AD in trials over 3 months' duration.[31,32] The questionnaire is provided in APPENDIX G.

8.2 Safety Assessments

8.2.1 Vital Signs

The following vital signs will be recorded at the visits specified in Table 1 with the subject in a seated position, after having sat calmly for at least 5 minutes: systolic and diastolic blood pressure (mm Hg), pulse (bpm), body temperature (°C), and respiratory rate (breath/min).

Weight (kg) and height (cm) will be collected to calculate the body mass index (BMI) and will be recorded at the visits specified in Table 1. The height will only be recorded once at the screening visit and the same value will be used for BMI calculation at other visits.

If deemed appropriate by the investigator, clinically significant findings in the vital signs will exclude a subject from study participation. Any abnormal finding related to vital signs that the investigator considers to be clinically significant must be recorded as an AE.

8.2.2 Physical Examination

The following sites/systems will at least be included in the physical examination, which will be performed at the visits specified in Table 1:

- General appearance
- Dermatological (except AD)
- Head, eyes, ears, nose, throat (HEENT)
- Respiratory
- Cardiovascular
- Abdominal
- Neurological
- Musculoskeletal
- Lymphatic

Information for all physical examinations must be included in the source document. If deemed appropriate by the investigator, clinically significant findings in the physical examination will exclude a subject from study participation. Any significant change will be reported as an AE in the source document and eCRF

8.2.3 Brief Physical Examination

The following sites/systems will at least be included in the brief physical examination that will be performed at the visits specified in Table 1:

- General appearance
- Dermatological (except AD)
- Respiratory
- Cardiovascular
- Abdominal

If deemed appropriate by the investigator based on the subject's condition, a complete physical examination as described in Section 8.2.2 can be performed instead of a brief examination.

Information for all physical examinations must be included in the source document. If deemed appropriate by the investigator, clinically significant findings in the physical examination will exclude a subject from study participation. Any significant change will be reported as an AE in the source document and eCRF.

8.2.4 Clinical Laboratory Tests

Laboratory tests will be performed at the visits specified in Table 1. The tests will include urinalysis, hematology with differential, a standard chemistry panel (chemistry includes liver function tests), and serum pregnancy test (screening) for women of childbearing potential

(WOCBP). At the visits specified in Table 1, a urine pregnancy test will be performed for WOCBP (conducted at the investigator site). The specific tests in these panels are listed in Table 5.

Table 5. Clinical Laboratory Testing

Laboratory testing	Tests included
Hematology	HCT, Hgb, MCH, MCHC, MCV, MPV, reticulocytes, PLT, RBC, WBC, and differentials (neutrophils, lymphocytes, monocytes, eosinophils, and basophils relative and absolute)
Biochemistry	Albumin, alkaline phosphatase, ALT, AST, chloride, CPK, creatinine (enzymatic), GGT, glucose random, LDH, potassium, sodium, total bilirubin, triglycerides, urea (BUN), uric acid
Urinalysis	Dipstick and microscopic analysis (as required)
Urine pregnancy test	For female subjects of childbearing potential (as specified in Table 1)
Laboratory tests required at screening only	INR, PT and aPTT FSH levels for female subjects who have had a cessation of menses for ≥ 12 months prior to the screening visit without an alternative medical cause. No FSH confirmation is required for women older than 55 years. β-hCG for female subjects of childbearing potential (screening) Tuberculosis test (PPD or QuantiFERON-TB Gold) Serology (HBV [HBsAg, anti-HBc, anti-HBs], HCV, HIV)

Abbreviations: ALT, alanine aminotransferase; anti-HBc, antibody to hepatitis B core antigen; anti-HBs, hepatitis B surface antibody; AST, aspartate aminotransferase; β-hCG, β-human chorionic gonadotropin; BUN, blood urea nitrogen; CPK, creatine phosphokinase; FSH, follicle-stimulating hormone; GGT, gamma-glutamyl-transferase; HBsAg, hepatitis B surface antigens; HBV, hepatitis B virus; HCT, hematocrit; HCV, hepatitis C virus; Hgb, hemoglobin; HIV, human immunodeficiency virus; LDH, lactate dehydrogenase; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; MPV, mean platelet volume; PLT, platelets; PPD, purified protein derivative; RBC, red blood cell (count); WBC, white blood cell (count).

In case of a screening laboratory value abnormality, the test can be repeated within the original screening time window, if the investigator believes there is a reasonable possibility that the subject would be eligible if retested. Laboratory safety tests may also be performed at unscheduled visits during the course of the study, if deemed necessary by the investigator.

If deemed appropriate by the investigator, clinically significant findings in clinical laboratory testing will exclude a subject from study participation. Any clinically significant value will be reported as an AE.

Leftover blood samples may be stored and used for future analyses.

8.2.5 Electrocardiogram

Twelve-lead ECGs will be performed as a safety assessment at the visits specified in Table 1. Clinically significant findings in the ECG should exclude a subject from study participation (as

deemed appropriate by the investigator). Any clinically significant value will be reported as an AE.

8.2.6 Injection Site Evaluation

Injection site evaluation will be performed at the visits specified in Table 1, approximately 30 minutes post-injection (when applicable). The investigator, or designee, will evaluate the injection site(s) at these visits, and will document the presence or absence of injection site reaction and will open an AE in case of local injection site reactions. Additional follow-up after Week 52 can be performed for any ongoing injection site reactions.

8.3 Other Assessments

8.3.1 Pharmacokinetics

Blood samples will be collected for all subjects to measure serum concentrations of OpSCF at the visits specified in Table 1 (predose, if applicable).

The actual date and time of each blood sample collection will be recorded. Details about the collection, processing, handling, storage, and shipping of samples will be provided in the laboratory manual.

Leftover samples may be stored and used for future analyses.

8.3.2 Biomarkers Assessed in Blood

Blood samples to assess IgE and other biomarker levels will be collected for all subjects at the visits specified in Table 1.

The actual date and time of each blood sample collection will be recorded. Details about the collection, processing, handling, storage, and shipping of samples will be provided in the laboratory manual.

Leftover samples may be stored and used for future analyses.

8.3.3 Immunogenicity

Blood samples to assess ADA will be collected for all subjects at the visits specified in Table 1 (predose).

The actual date and time of each blood sample collection will be recorded. Details about the collection, processing, handling, storage, and shipping of serum samples will be provided in the laboratory manual.

Leftover samples may be stored and used for future analyses.

8.3.4 Biomarkers assessed in Skin

Tape stripping and skin biopsies will be collected in a minimum of approximately 20 subjets who consent to both procedures.

Tape strips and biopsies should be collected from adjacent sites within the same lesion, whenever possible.

8.3.4.1 Tape stripping

Tape stripping is a non-invasive procedure where superficial skin cells is collected using tape strips. For each sampled site, approximately 20 tape strips units will be placed and removed from the exact same site one after the other.

Skin tape strips will be collected on Day 1 prior to the study drug administration (from lesional skin and from nonlesional skin in the vicinity of the lesional skin), and from the same lesional skin at Weeks 4 (even if the lesion has cleared), and from the same lesional and non-lesional skin at Week 16 (or at the ET visit if it occurs prior to Week 16; even if the lesion has cleared). These procedures should not be performed on esthetically or functionally sensitive anatomical locations (ie, the face, neck, or hands).

Details about the collection, processing, handling, storage, and shipping of tape strip samples will be provided in the laboratory manual.

8.3.4.2 Skin Biopsies

A total of five skin biopsies will be collected in this study at the visits specified in Table 1: two 4.5-mm punch biopsies will be collected on Day 1 prior to the study drug administration (one from lesional skin and one from nonlesional skin in the vicinity of the lesional skin), one 4.5-mm punch biopsy will be collected at Week 4 from the same lesional skin (outside the scar of the previous biopsies, even if the lesions have cleared), and two 4.5-mm punch biopsies will be collected at Week 16 (or at the ET visit if it occurs prior to Week 16; one from the same lesional skin and one from the same nonlesional skin, outside the scar of the previous biopsies, even if the lesions have cleared). These procedures should not be performed on esthetically or functionally sensitive anatomical locations (ie, the face, neck, or hands).

The skin will be cleaned, disinfected, and anesthetized before skin biopsies are performed. Sterile gauze will be used to absorb any bleeding. The biopsy sites will be sutured if necessary.

Details about the collection, processing, handling, storage, and shipping of biopsy samples will be provided in the laboratory manual.

8.3.5 Medical Photography

Medical photographs will be performed for subjects who consented to the procedure, at the visits specified in Table 1. A representative AD lesion for each subject will be identified at Day 1, and the same lesion will be photographed at the other visits, even if the lesion has cleared. For subjects consenting to medical photographs, biopsies and tape strips, the representative AD lesion will be

the same lesion where skin samples will be collected. Care will be taken to use the same camera and the same settings for each photograph and at each visit in order to obtain comparable pictures. Medical photographs will be taken using a blue background.

Photographs will be identified as follows: study number, subject number, visit name, and date. Photographs will be kept as electronic files on site and will be transmitted to the sponsor for review.

The photographs taken will not be used for formal data analysis and are for qualitative purposes only.

8.4 Adverse Events and Serious Adverse Events

8.4.1 Definition of Adverse Event

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a study product, whether or not considered related to the study product.

8.4.2 Definition of Treatment-Emergent Adverse Event

A TEAE is any condition that was not present prior to treatment with the study product but appeared following treatment, was present at treatment initiation but worsened during treatment, or was present at treatment initiation but resolved and then reappeared while the individual was on treatment (regardless of the intensity of the AE when the treatment was initiated).

8.4.3 Definition of Serious Adverse Event

An SAE or reaction is any untoward medical occurrence that, at any dose, has any of the following consequences:

- Results in death
- Is life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

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

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

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

8.4.4 Classification of an Adverse Event

8.4.4.1 Relationship to Study Treatment

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

Table 6. Definition of Adverse Event Causality

Causality	Definition
No Reasonable Possibility	After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is insufficient evidence (information) to suggest a causal relationship.
Reasonable Possibility	After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is sufficient evidence (information) to suggest a causal relationship.

Abbreviation: AE, adverse event.

8.4.4.2 Adverse Event Severity

The severity of an AE is an estimate of the relative severity of the event made by the investigator based on his or her clinical experience and familiarity with the literature. The following definitions from the National Cancer Institute (NCI) CTCAE, Version 5.0, published 27-Nov-2017 are to be used to rate the severity of an AE:

Table 7. Definition of Adverse Event Severity

Severity	Definition
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or non-invasive intervention indicated; limiting age appropriate instrumental activities of daily living (ADL)*.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting selfcare ADL**.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

Note: A Semi-colon indicates 'or' within the description of the grade.

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

8.4.4.3 Expectedness

Innovaderm Research Inc. will assess the expectedness of each SAE in relation to the study product.

8.4.5 Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study subject presenting for medical care, or upon review by a study monitor.

All AEs, including local and systemic reactions, will be captured on the appropriate eCRF. Information to be collected includes event description, date of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), date of resolution/stabilization of the event, and the AE outcome (not recovered/not resolved, recovering/resolving, recovered/resolved, recovered/resolved with sequelae, fatal, and unknown). All AEs occurring while on study must be documented appropriately regardless of relationship.

Study site personnel will note the occurrence and nature of each subject's medical condition(s) present prior to the informed consent signature in the appropriate section of the source document and eCRF. During the study, site personnel will note any change in the condition(s) and the occurrence and nature of any AE.

Any medical condition that is present prior to informed consent signature will be considered as part of medical history and not reported as an AE. However, if the study subject's condition deteriorates after the consent signature, it will be recorded as an AE.

Should a subject experience an AE at any time after the informed consent signature until the end of participation in the study, the event will be recorded as an AE in the source document and eCRF. Any SAE related to the study participation (eg, screening procedure) will be recorded in the source document and eCRF from the time consent is given to participate in the study until the end of participation in the study.

The investigator is responsible for appropriate medical care of subjects during the study. The investigator also remains responsible for following through with an appropriate health care option for all AEs that are ongoing at the end of the study. The subject should be followed until the event is resolved or stable. If an AE is ongoing at the end of study, the follow-up duration is left to the discretion of the investigator. Follow-up frequency will be performed at the discretion of the investigator.

Whenever possible, clinically significant abnormal laboratory results are to be reported using the diagnostic that resulted in the clinically significant abnormal laboratory results and not the actual abnormal test.

8.4.6 Adverse Event Reporting

Investigators are responsible for monitoring the safety of subjects who are participating in this study and for alerting the sponsor to any event that seems unusual, even if this event may be considered an unanticipated benefit to the subject.

8.4.7 Serious Adverse Event Reporting

Innovaderm Research Inc. will be the pharmacovigilance unit responsible for the overall pharmacovigilance process for this study. All SAEs, related to the experimental treatment or not, occurring during the course of the study must be reported on an SAE form to the pharmacovigilance unit (see below contact information) within 24 hours of the knowledge of the occurrence (this refers to any AE that meets one or more of the aforementioned serious criteria). The SAE reporting period ends at the end of the follow-up period or if the subject begins an alternative therapy (except for allowed rescue medications per Section 6.5.4).

Reporting should be done by sending the completed SAE form to the following email address (faxing can also be done as a second option in case emailing is not possible).

Safety Contact Information: Innovaderm Drug Safety unit
Email: OpSCF201_drugsafety@innovaderm.com
Fax: (514) 221-4199

The pharmacovigilance unit will inform the medical monitor, the sponsor, and Innovaderm within 1 business day of awareness of a new SAE. The pharmacovigilance unit will process and evaluate all SAEs as soon as the reports are received. For each SAE received, the pharmacovigilance unit, in consultation with the sponsor if needed, will determine as to whether the criteria for expedited reporting to relevant regulatory authorities have been met.

The pharmacovigilance unit will manage the expedited reporting of relevant safety information to concerned regulatory agencies in accordance with local laws and regulations.

The expedited reporting of relevant safety information to concerned regulatory agencies and ethic committee will be performed in accordance with local laws and regulations and will be defined in the Safety Management Plan.

8.4.8 Pregnancy Reporting

If a female subject or a female partner of a male subject becomes pregnant during the study and up to 105 days after the last dose of study product, the subject should inform the study site as soon as possible. Upon confirmation of the pregnancy, the female subject will be discontinued from the study. The investigator must complete a study-specific pregnancy form upon confirmation of a pregnancy and send it to the pharmacovigilance unit within 24 hours of confirmation of the pregnancy (contact information to be used is the same as for SAE reporting). The pharmacovigilance unit will report all cases of pregnancy to the medical monitor, the sponsor, and Innovaderm in a timely manner. Pregnancy is not itself an AE or SAE; however, maternal/fetal complications or abnormalities will be recorded as AEs or SAEs, as appropriate. The investigator

will follow the pregnancy until completion or until pregnancy termination and, in the case of a live-born offspring, to 1 month of age in that infant. The investigator will notify the pharmacovigilance unit and Innovaderm of the outcome as a follow-up to the initial pregnancy form. All pregnancies should be reported to the sponsor and, when applicable, to the ethics committee.

8.4.9 Overdose

Study product overdose is any accidental or intentional use of study product in an amount higher than the dose indicated per protocol for a given subject. Study product compliance (see Section 6.4.2) should be reviewed to detect potential instances of overdose (intentional or accidental).

Any study product overdose during the study should be recorded on the source document and eCRF. In the event of overdose, the subject should be closely monitored for any potential AEs. All AEs associated with an overdose should be entered on the Adverse Event eCRF and reported using the procedures detailed in Section 8.4.7, Serious Adverse Events Reporting, even if the events do not meet seriousness criteria. If the AE associated with an overdose does not meet seriousness criteria, it must still be reported using the SAEs reporting procedures and in an expedited manner but should be noted as non-serious on the form and the Adverse Event eCRF. The excess quantity and duration of the overdose should be recorded.

9 STATISTICAL CONSIDERATIONS

9.1 Sample Size Determination

For the primary efficacy endpoint of percent change from baseline in EASI at Week 16, a total sample size of 48 subjects (24/arm) will have approximately 80% power to detect an effect size of 0.73 with a 2-sided statistical significance level of 0.1.

9.2 Populations for Analyses

For the placebo-controlled period, efficacy will be evaluated on the basis of the modified intent-to-treat (mITT) analysis set. A supportive analysis will also be conducted on the per-protocol (PP) analysis set.

Modified intent-to-treat (mITT) analysis set: This analysis set will include all subjects who received at least one dose of the study product. All subjects will be analyzed according to the treatment group to which they were randomized. The mITT analysis set will be used as the primary analysis population for efficacy.

Per-protocol (PP) analysis set: This analysis set will include all subjects who were randomized, who received at least 1 dose of study product and who provided evaluable data for the primary endpoint with no major protocol deviations affecting the efficacy evaluations. All subjects will be analyzed according to the treatment group that they actually received during the placebo-controlled period.

Safety analysis set: This analysis set will include all subjects who received at least one dose of the study product. All subjects will be analyzed according to the treatment group that they actually received during the placebo controlled-period.

Other analysis sets, including the PK analysis set, PD analysis set, and immunogenicity analysis set may be defined in a separate analysis plans.

For the OLE period, the following analysis set will be used for all efficacy and safety analyses:

OLE analysis set: This analysis set will include all subjects who entered the OLE received at least one dose of the study product during the OLE. The OLE analysis set will be used for summarizing both efficacy and safety data for those subjects who entered the OLE period.

9.3 Statistical Analyses

9.3.1 General Approach

Continuous variables will be summarized in tables and will include the number of subjects, mean, standard deviation (SD), percent of coefficient of variance (CV%), median, minimum, and maximum. Categorical variables will be presented in tables as frequencies and percentages.

All details regarding the efficacy and safety variable definitions, analyses strategy, statistical justification, and techniques for handling missing values will be detailed in a separate statistical analysis plan (SAP) that will be prepared before the first database lock and any analyses are undertaken. Any deviation(s) from the SAP will be described and justified in the final report, as appropriate.

All statistical tests will be two-sided and will be performed with a significant level of 0.1, unless otherwise specified in the SAP. Randomization will be stratified by baseline vIGA-AD score (vIGA-AD = 3 [moderate] vs. vIGA-AD = 4 [severe]). Randomization will also be stratified for the tape strip/skin biopsy consent status (yes/no) (a minimum of approximately 20 subjects total will be enrolled with tape strip/skin biopsy consent). The stratification for tape strip/skin biopsy consent status will be done for administrative purpose only and is not an important prognostic factor at baseline.

9.3.2 Baseline Definitions

Placebo-Controlled Period:

Unless specified otherwise, baseline is defined as the last non-missing assessment (including unscheduled/retest assessments) collected before the first dose of study product (OpSCF or placebo). If the last non-missing assessment was performed on the same date as the first dose of study product and time is not available, the assessment will be considered as baseline, except for AEs and medications starting on the same day as the first dose of study treatment, which will be considered as post-baseline.

Open-Label Extension Period:

For efficacy endpoints, baseline is defined as for the placebo-controlled period. For non-efficacy assessments and unless specified otherwise, baseline is defined as the last nonmissing assessment (including unscheduled/retest assessments) collected before the first dose of the active study product (OpSCF) on Day 1 for subjects who received OpSCF in the placebo-controlled period or before the first dose of the active study product (OpSCF) at Week 16 (for subjects who received the placebo). If the last non-missing assessment was performed on the same date as the first dose of OpSCF and time is not available, the assessment will be considered as baseline, except for AEs and medications starting on the first dose date which will be considered post-baseline.

For the PP-NRS, the baseline scores will be defined as the average of all non-missing daily 24-hour PP-NRS scores reported over the last 7 days prior to randomization (prior to the first study drug administration). A minimum of 3 PP-NRS data are needed to calculate a weekly average.

9.3.3 Efficacy Analyses

Placebo-controlled period:

The comparison between the treatment groups for the primary endpoint, percent change from baseline in EASI at Week 16, will be analyzed using a mixed model for repeated measures analysis (MMRM) where the visit will be the time factor; and the stratification factor (ie, vIGA-AD score only), treatment group, and interaction term for treatment-by-visit will be the fixed effects and the

baseline EASI value will be the covariate. An unstructured variance-covariance matrix will be used.

The primary efficacy analysis will be done using the mITT analysis set and the PP analysis set will be used as supportive analysis.

The secondary efficacy endpoints involving absolute and/or percent change from baseline will be analyzed at each time point using the same approach (ie, MMRM) as described for the primary efficacy analysis.

For categorical efficacy endpoints involving proportions of vIGA-AD, EASI, and PP-NRS (eg, the proportion of subjects achieving at least a 2-grade reduction from baseline to clear (0) or almost clear (1) in vIGA-AD at Week 16), a Cochran Mantel Hansel test (CMH) controlling for the stratification variable (ie, vIGA-AD score only) will be performed. Details on handling missing data will be specified in the SAP.

OLE Period:

For the efficacy variables collected during the OLE period, descriptive summaries by treatment group and by visit, when applicable, will be provided based on the OLE analysis set. No inferential statistical testing will be done on the efficacy variables for the OLE period. More details on this will be provided in the SAP.

Additional exploratory endpoints on response maintenance may be added and would be detailed in the SAP.

9.3.4 Safety Analyses

Safety analyses will be performed by study period using the study population related to the analysis time period (safety analysis set for the placebo-controlled period and OLE analysis set for the OLE period).

All safety data, including AEs and SAEs will be presented and tabulated according to Medical Dictionary for Regulatory Activities (MedDRA) classification. Descriptions of AEs will include the start date, the stop date (if it resolved), the severity and seriousness of the AE, the causality of the AE to study product, and the outcome. The focus in this protocol will be the prevalence of treatment-emergent adverse events (TEAEs).

Adverse events will be reported in the placebo-controlled period or OLE period depending on the onset. If the AE onset was before Week 16 dosing, the AE will be considered in the placebo-controlled period. If the AE had an onset on or after Week 16 dosing, the AE will be considered in the OLE period.

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

within a SOC or a PT by using the AEs with the greatest reported relationship within each category. For the summary of AEs by relationship to study product and severity, each subject will be counted only once within a SOC or a PT by using (1) the greatest reported relationship followed by (2) the highest reported intensity.

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

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

Clinically significant changes in laboratory analyses, vital signs, ECGs, and new findings on physical examination will be recorded as AEs.

Shift tables describing shifts to out-of-normal range will be provided for clinical laboratory results, and normal-abnormal shift tables will be provided for vital signs and ECG overall interpretation.

Concomitant medications will be coded with the World Health Organization (WHO)-Drug Dictionary and listed by subject. Summary of medication classes will also be tabulated.

No inferential statistics will be done on safety variables.

9.3.5 Pharmacokinetic Analyses

OpSCF serum concentration data will be summarized based on nominal timepoints using descriptive statistics, such as mean, SD, CV%, median, minimum and maximum.

Data from this study may be combined with data from other studies for population PK and exposure-response analyses. A non-linear mixed-effects modeling approach may be used to estimate the population central values and the empirical Bayesian estimates of the individual values of OpSCF clearance (CL/F) and volume of distribution (V/F). Additional parameters may be estimated if useful in the interpretation of the data. Results would be reported separately..

9.3.6 Pharmacodynamic Analyses

Skin and blood biomarker levels will be compared to placebo adjusted change from baseline over time for each treatment group, and the parameters will be summarized by treatment group using descriptive statistics.

9.3.7 Immunogenicity

The ADA levels will be compared to placebo adjusted change from baseline over time for each treatment group, and the parameters will be summarized by treatment group using descriptive statistics.

9.3.8 Other Analyses

Descriptive summaries of baseline characteristics, including demographic data and prior concomitant therapy, and of subject disposition will be presented for each study period. In addition, a list of subjects who discontinued from the study will be provided.

Protocol deviations will be summarized by treatment, category, and study period.

9.3.9 Planned Analyses

An unblinded interim analysis (IA), which is the primary endpoint analysis, will be performed for this study after all subjects complete the Week 16 visit or discontinue from the study, whichever occurs first, once data up to Week 16 inclusively have been cleaned and locked. The study will then be unblinded to identified personnel, including the sponsor, for the purpose of an interim analysis as outlined in study unblinding plan. To minimize potential bias introduced in the OLE, no individual subject level assignments will be unblinded to the investigators, site study personnel, and subjects. Since the only efficacy endpoint to be inferentially tested with a controlled alpha is the primary efficacy endpoint of the percent change from baseline in EASI at Week 16, and all secondary and exploratory efficacy endpoints for which nominal statistical inferences will be performed are before or at Week 16, this primary endpoint IA will be the final analysis for the placebo-controlled period of the study. All efficacy analyses performed for this IA will not be re-issued at the time of the final analysis of this study after completion of the OLE period. Furthermore, only descriptive statistics will be provided for the exploratory efficacy and safety endpoints collected during the OLE period. Therefore, no adjustment to the overall alpha level of the study is needed for this IA.

10 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1 Local Regulations/Declaration of Helsinki

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with ICH Tripartite Guideline for GCP and the applicable laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual.

10.2 Ethical Review

It is the understanding of the sponsor that this protocol (and any amendments) as well as appropriate consent procedures, will be reviewed and approved by an REB/IRB. This board must operate in accordance with the current federal regulations. For sites with a local ethics committee, a letter or certification of approval will be sent by the investigator to the sponsor (or CRO) before initiation of the study and also whenever subsequent modifications to the protocol are made.

10.3 Informed Consent Process

An ICF describing in detail the study treatment, study procedures, and risks will be given to the subject, along with an assent form when required.

It is the responsibility of the investigator, or a person designated by the investigator (if acceptable by local regulation), to obtain written informed consent from each individual participating in this study, after adequate explanation of the aims, methods, objectives, and potential hazards of the study.

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be IRB/REB approved, and the subject will be asked to read and review the document. The investigator will explain the research study to the subject and answer any questions that may arise. A verbal explanation will be provided in terms suited to the subject's comprehension of the purposes, procedures, and potential risks of the study and of his or her rights as a research subject. Subjects will have the opportunity to carefully review the written consent form and ask questions prior to signing. The subjects should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate.

The subject will sign the informed consent document prior to any procedures being done specifically for the study. Subjects must be informed that participation is voluntary and that they may withdraw from the study at any time for any reason, without prejudice. A copy of the signed informed consent document will be given to the subjects for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the subject undergoes any study-specific procedures.

The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

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

10.4 Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study subjects, investigators, the sponsor, and regulatory authorities. If the study is prematurely terminated or suspended, the principal investigators will promptly inform study subjects and the IRB/REB, and will provide the reason(s) for the termination or suspension. Study subjects will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension of the study include, but are not limited to the following:

- Determination of unexpected, significant, or unacceptable risk to subjects
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete or evaluable
- Scientific or corporate reasons

The study may resume once concerns about safety, protocol compliance, and data quality are addressed and satisfy the sponsor, IRB/REB, Health Canada, and/or FDA.

10.5 Confidentiality and Privacy

Subject confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor and their interventions. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to subjects. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence.

The investigator must assure that the subjects' anonymity will be maintained and that subjects' identities are protected from unauthorized parties. On CRF or other documents submitted to the sponsor, subjects should not be identified by their names, but by an identification code. The investigator should keep a subject log relating codes with the names of subjects. The investigator should maintain in strict confidence documents not for submission to Opsidio LLC (eg, subjects' written consent forms).

All research activities will be conducted in a setting as private as possible.

The study monitor, other authorized representatives of the sponsor, and representatives of the IRB, regulatory agencies, or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to,

medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

The study subject's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the applicable legal or regulatory requirements, the reviewing IRB, institutional policies, or sponsor requirements.

10.6 Clinical Monitoring

Clinical site monitoring will be conducted to ensure that the rights and well-being of trial subjects are protected; that the reported trial data are accurate, complete, and verifiable; and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), ICH GCP guidelines, and with applicable regulatory requirement(s). Details of clinical site monitoring will be documented in a Monitoring Plan. Centralized monitoring, which consists of remote review of accumulating data from all sites, will be performed as detailed in the Centralized Monitoring Plan.

10.7 Quality Assurance and Quality Control

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation, and completion.

The web-based electronic data capture (EDC), reporting system, and data QC checks will be used to implement quality control (QC) procedures. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

During the study, the sponsor or its representative will conduct monitoring visits at regular intervals. The monitoring visits will be conducted to ensure protocol adherence, quality of data, accuracy of entries on the eCRFs, study product accountability, compliance with regulatory requirements, and continued adequacy of the study site and its facilities.

The site may be audited, monitored, or inspected by a quality assurance officer named by the sponsor, by the REB or IRB, and/or by the regulatory authorities. The investigator will be given notice before an audit occurs and will be expected to cooperate with any audit and provide assistance and documentation (including source data) as requested. The study site will provide direct access to all trial-related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor and inspection by local and regulatory authorities.

10.8 Data Handling and Record Keeping

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

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 documents should be

classified into two separate categories: investigator's study files and subject clinical source documents.

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

The records should be retained by the investigator according to ICH guidelines, local regulations, or as specified in the Clinical Trial Agreement, whichever retention period is longer.

Subject data will be entered by site personnel using Medrio, a web-based EDC and reporting system. This application will be set up for remote entry. Medrio Inc. is the developer and owner of Medrio. The EDC software has been fully validated and conforms to Title 21 of the Code of Federal Regulations, Part 11 requirements. Investigator site staff will not be given access to the EDC system until they have been fully trained. Designated investigator staff will enter the data required by the protocol into the eCRFs using this web-based application. Automatic validation programs check for data discrepancies in the eCRFs and, by generating appropriate error messages, allow modification or verification of the entered data by the investigator staff before confirming the data. The investigator must certify that the data are complete and accurate by applying an electronic signature to the eCRFs.

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

10.9 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol requirements. The noncompliance may be either on the part of the subject, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly. The clinical research associate must ensure that a prompt action is taken to secure compliance. If a noncompliance that significantly affects or has the potential to significantly affect human subject protection or reliability of trial results is discovered, the CRO and the sponsor should perform a root cause analysis and implement appropriate corrective and preventive actions.

Protocol deviations must be sent to the reviewing IRB per their policies. The investigator is responsible for knowing and adhering to the reviewing IRB requirements.

10.10 Publication Policy

The publication policy will be addressed in the Research and Financial Agreement, and all details outlined in the agreement will apply to this protocol. The trial will be registered on ClinicalTrials.gov prior to the first subject being dosed.

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APPENDIX A. Diagnostic Criteria for Atopic Dermatitis

Per Inclusion Criterion 2, a subject is to have a clinical diagnosis of atopic dermatitis according to the criteria of Hanifin and Rajka.[33] The criteria are as follows:

Major Criteria (must have ≥ 3)

- Pruritus
- Typical morphology and distribution:
  - Adults: flexural lichenification or linearity
  - Children and infants: involvement of facial and extensor surfaces
- Chronic or chronically relapsing dermatitis
- Personal or family history of atopy (asthma, allergic rhinitis, atopic dermatitis)

Minor Criteria (must have ≥ 3)

- Xerosis
- Ichthyosis/keratosis pilaris/palmar hyperlinearity
- Immediate (Type 1) skin test reactivity
- Elevated serum IgE
- Early age at onset
- Tendency to skin infections (*Staphylococcus aureus*, herpes simplex)/impaired cellular immunity
- Tendency to nonspecific hand/foot dermatitis
- Nipple eczema
- Cheilitis
- Recurrent conjunctivitis
- Dennie-Morgan infraorbital fold
- Keratoconus
- Anterior subcapsular cataracts
- Orbital darkening
- Facial pallor/erythema
- Pityriasis alba
- Anterior neck folds
- Itch when sweating
- Intolerance to wool and lipid solvents
- Perifollicular accentuation
- Food intolerance
- Course influenced by environmental/emotional factors
- White dermographism/delayed blanch

APPENDIX B. Eczema Area and Severity Index

Four anatomic sites—head, upper extremities, trunk, and lower extremities—are assessed for erythema, induration/infiltration (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 steps **are** allowed; eg, 0.5, 1.5, and 2.5):

0 = none

1 = mild

2 = moderate

3 = severe

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

0 = no involvement

1 = < 10%

2 = 10% to < 30%

3 = 30% to < 50%

4 = 50% to < 70%

5 = 70% to < 90%

6 = 90% to 100%

The EASI score is obtained by using the formula below:

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

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

APPENDIX C. vIGA-AD™

Validated Investigator Global Assessment scale for Atopic Dermatitis

vIGA-AD™

Instructions:

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

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

Notes:

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

For example:

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

2. Excoriations should not be considered when assessing disease severity.

APPENDIX D. Pruritus Numeric Rating Scale

On a scale of 0 to 10, with 0 being "no itch" and 10 being "worst itch imaginable", how would you rate your itch at the worst moment during the previous 24 hours?

Numeric Rating Scale

0	1	2	3	4	5	6	7	8	9	10

No itch — Worst itch imaginable

APPENDIX E. Patient-Oriented Eczema Measure

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

APPENDIX F. Dermatology Life Quality Index

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

1.	Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?	Very much A lot A little Not at all	□ □ □ □	
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much A lot A little Not at all	□ □ □ □	
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **yard?**	Very much A lot A little Not at all	□ □ □ □	Not relevant □
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all	□ □ □ □	Not relevant □
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much A lot A little Not at all	□ □ □ □	Not relevant □
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much A lot A little Not at all	□ □ □ □	Not relevant □
7.	Over the last week, has your skin prevented you from **working** or **studying**?	Yes No	□ □	Not relevant □
	If "No," over the last week how much has your skin been a problem at **work** or **studying**?	A lot A little Not at all	□ □ □	
8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much A lot A little	□ □ □	

		Not at all	□	Not relevant □
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much A lot A little Not at all	□ □ □ □	 Not relevant □
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all	□ □ □ □	 Not relevant □

Please check you have answered EVERY question. Thank you.

If two or more questions are left unanswered the questionnaire is not scored. If two or more response options are ticked, the response option with the highest score should be recorded. If there is a response between two tick boxes, the lower of the two score options should be recorded.

APPENDIX G. Atopic Dermatitis Control Tool

Atopic Dermatitis Control Tool

Please answer the following questions thinking about your experiences with eczema, sometimes called "atopic dermatitis."

1. Over the last week, how would you rate your eczema-related symptoms (for example, itching, dry skin, skin rash)?
   0☐ None 1☐ Mild 2☐ Moderate 3☐ Severe 4☐ Very Severe

2. Over the last week, how many days did you have **intense episodes of itching** because of your eczema?
   0☐ Not at all 1☐ 1-2 days 2☐ 3-4 days 3☐ 5-6 days 4☐ Every day

3. Over the last week, how **bothered** have you been by your eczema?
   0☐ Not at all 1☐ A little 2☐ Moderately 3☐ Very 4☐ Extremely

4. Over the last week, how many nights did you have **trouble falling or staying asleep** because of your eczema?
   0☐ No nights 1☐ 1-2 nights 2☐ 3-4 nights 3☐ 5-6 nights 4☐ Every night

5. Over the last week, how much did your eczema **affect your daily activities**?
   0☐ Not at all 1☐ A little 2☐ Moderately 3☐ A lot 4☐ Extremely

6. Over the last week, how much did your eczema **affect your mood or emotions**?
   0☐ Not at all 1☐ A little 2☐ Moderately 3☐ A lot 4☐ Extremely

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