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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16.1.9 Documentation of Statistical Methods

OpSCF201 Statistical Analysis Plan V1.0 08-OCT-2024

OpSCF201 PK Statistical Analysis Plan V1.0 07-OCT-2024

Statistical Analysis Plan

Study 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**
Protocol Number and Version:	**OpSCF201 V2.1, dated 20-Dec-2023**
Product:	**OpSCF**
Sponsor:	**Opsidio, LLC.** **PO Box 802** **Bryn Mawr, PA 19010** **United States**
Version:	**Final V1.0**
Date:	**08-Oct-2024**
Prepared by:	**Innovaderm Research Inc.** **3530 Saint-Laurent boulevard, Suite 300** **Montreal, Quebec, H2X 2V1** **Canada**

STATISTICAL ANALYSIS PLAN REVISION SUMMARY			
Version	**Version Date**	**Author**	**Summary of Changes**
Final V1.0	08-Oct-2024	[redacted]	Initial version

SIGNATURE PAGE

AUTHOR

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This statistical analysis plan will be reviewed and revised as needed. The most recent version will replace the previous version in place.

TABLE OF CONTENT

ABBREVIATIONS

AD	Atopic dermatitis
ADA	Anti-drug antibody
ADCT	Atopic Dermatitis Control Tool
AE	adverse events
anti-HBc	antibody to hepatitis B core antigen
Anti-HBs	hepatitis B surface antigen
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical
BMI	body mass index
BOCF	baseline observation carried forward
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
COVID-19	coronavirus disease 2019
CRO	contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
CV%	percent of coefficient of variance
DBP	diastolic blood pressure
DLQI	Dermatology Life Quality Index
EAIR	exposure-adjusted incidence rate
EASI	Eczema Area and Severity Index
ECG	electrocardiogram
eCRF	electronic case report form
EOS	End of study
ET	early termination
HbsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IA	interim analysis
ICF	informed consent form
IgE	Immunoglobuline E
ITT	intent-to-treat
JAK	Janus kinase
LLN	lower limit of normal
LLT	lowest level term
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MH	Mantel-Haenszel
mITT	modified intent-to-treat
MMRM	mixed-model for repeated measurements
msec	millisecond

n	number of subjects with non-missing data
NRI	non-responder imputation
OLE	open-label extension
PD	pharmacodynamic
PDMP	protocol deviation management plan
PK	pharmacokinetic
POEM	Patient-Oriented Eczema Measure
PP	per protocol
PP-NRS	Peak Pruritus Numeric Rating Scale
PT	preferred term
Q2W	once every 2 weeks
Q4W	once every 4 weeks
QT	QT interval
QTcF	Fridericia's correction formula for QT interval
SAE	serious adverse event
SAP	statistical analysis plan
SAS	statistical analysis system®
SBP	systolic blood pressure
SC	subcutaneous
SD	standard deviation
SE	standard error
SOC	system organ class
SoE	Schedule of Events
TEAE	treatment-emergent adverse event
TLF	tables, listings, and figures
ULN	upper limit of normal
vIGA-AD	validated Investigator's Global Assessment for Atopic Dermatitis
WHO	World Health Organization

1 INTRODUCTION

This statistical analysis plan (SAP) describes the planned analysis and reporting for Opsidio clinical protocol OpSCF201. The analyses described in the SAP are based upon the protocol version 2.1, dated 20-DEC-2023.

This SAP has been developed and finalized prior to the database lock for the interim analysis (IA).

Analyses related to pharmacokinetics (PK), pharmacodynamics (PD), and skin biomarkers are not covered in this SAP and will be described in a separate document.

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

OBJECTIVES	ENDPOINTS
	• 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)* • 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

OBJECTIVES	ENDPOINTS
	• 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.

* Endpoints are not covered in this SAP and are described in a separate document.

3 STUDY DESIGN

3.1 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 atopic dermatitis (AD). This study will also evaluate the serum concentration of OpSCF and explore the immunogenicity and PD of OpSCF in subjects with moderate to severe AD.

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 subcutaneous (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 Eczema Area and Severity Index (EASI), validated Investigator's Global Assessment for Atopic dermatitis (vIGA-AD), and body surface area (BSA), in addition to the Peak Pruritus Numeric Rating Scale (PP-NRS) which will be assessed daily in the placebo-controlled period and before or on the visits during the OLE. Quality of life will be evaluated using Atopic Dermatitis Control Tool (ADCT), Patient-Oriented Eczema Measures (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.

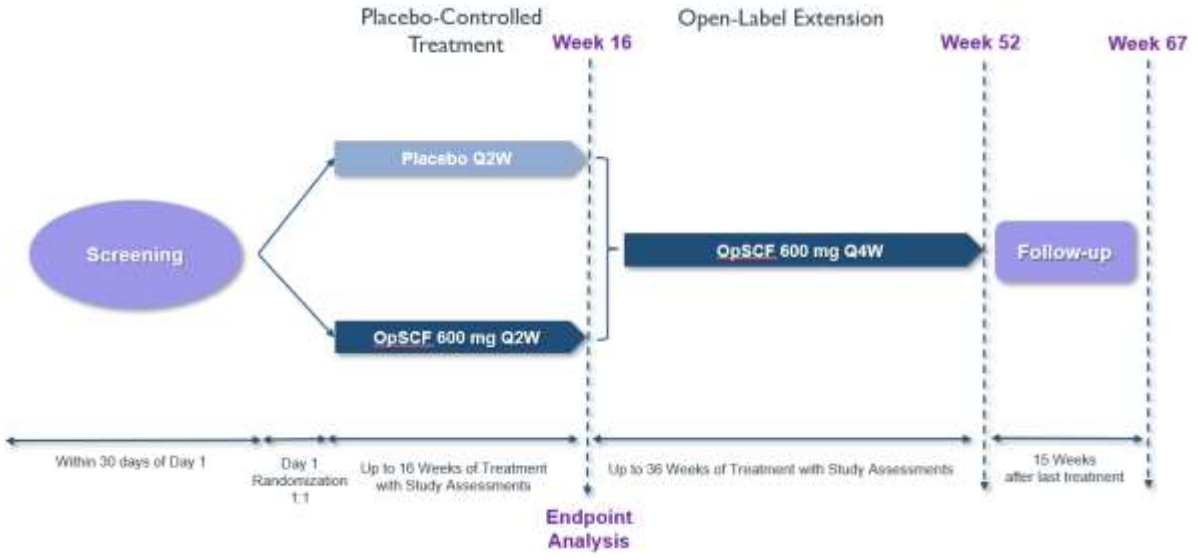
Blood samples will be collected from all subjects predose (if applicable) at specified visits to evaluate serum concentrations of OpSCF. In addition, blood samples for PK analysis will be collected at Week 14 (Day 99, predose) and on Days 102 and 106.

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.

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

The diagram below illustrates the overall study design for this study.



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

3.2 Schedule of Events

Table 1 provides a description of the procedures planned at each visit.

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															

Study visits	**Screening**	**Treatment period**															**ET[b]**
		Placebo-Controlled										**OLE**		**Follow-up[b]**			
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	
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

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	
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				
Tape strip collection (as applicable)[j]		X		X								X					X[m]
Skin biopsies collection (as applicable)[k]		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	
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[1]					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[1]					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[o]		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 at home on a daily basis starting at screening and during the placebo-controlled period (up to the Week 16 visit) using a diary. On visit days, the PP-NRS will be completed by the subject at the study center using the daily diary. During the OLE and the follow-up period, the PP NRS will be completed at the visits only.
h Will be done at Weeks 20, 24, 28, 36, and 44.
i Study drug 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 drug administration. At Weeks 4, 6, 24, and 28 subjects will remain under observation for at least 1 hour after study drug administration. At any other visit, subjects may remain under observation after the study drug administration, based on the investigator's judgement.
j Optional, 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 (even if the lesion has cleared).
k Optional, 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, at least 1 cm away from previous scar, even if the lesions have cleared), and two 4.5-mm punch biopsies at Week 16 (lesional and nonlesional from the same areas; outside the scar of the previous biopsies, at least 1 cm away from the previous scar, even if the lesions have cleared). Tape strips and biopsies should be collected from adjacent sites within the same lesion, whenever possible.
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.

3.3 Treatment Groups, Randomization, and Replacement, Blinding, and Unblinding Procedures

Treatment groups

Placebo-Controlled Period: Up to 16 weeks

- OpSCF 600mg (three 2.0 mL injections) Q2W
- Placebo Q2W

Open Label Extension period: Up to 36 weeks

- OpSCF 600mg (three 2.0 mL injections) Q4W

Randomization and Blinding

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 either OpSCF or placebo. Randomization will occur prior to first dosing, at Day 1 visit. The randomization list will be generated using a validated software (IWRS). 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.

Subjects who discontinue the study will not be replaced.

The placebo-controlled period of this study will be double-blinded while the OLE will be open-label. Two database locks will occur during this study: first, an interim database lock after all subjects have completed or discontinued early from the placebo-controlled period, whichever occurs first, and data from the screening and placebo-controlled period have been cleaned and secondly, the final database lock after all subjects have completed or discontinued early from the study, whichever occurs first, and data from the OLE and Follow-up periods have been cleaned. Treatment and randomization information will be kept confidential and will not be released to the investigator, the study staff, and the subjects until the end of the study after the final database lock. The contract research organization (CRO), and the sponsor's study teams will be unblinded to the

treatment and randomization information after the Primary Analysis of the double-blinded placebo-controlled period.

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

3.4 Changes from Planned Analyses Described in the Protocol

Description of the change	Rationale for change
Baseline definitions (refer to protocol Section 9.3.2) Following text was added to update baseline definitions (refer to Section 6.1) For the ePRO assessments (ADCT, DLQI and POEM), when the assessment was performed on the same date as the first dose of study drug, but the time is after the dosing, the assessment will be considered baseline.	To account for ePRO assessments (ADCT, DLQI and POEM) performed post dose.
Modified intent-to-treat (mITT) analysis set (refer to protocol Section 9.2) "This analysis set will include all subjects who received at least one dose of the study product." was updated to (refer to Section 5.3) "The modified Intent-to-Treat (mITT) analysis set will include all randomized subjects who received at least one dose of the study drug."	To align with Intent-to-Treat principle which includes all randomized subjects.

Description of the change	Rationale for change
Per-protocol analysis set (PP) analysis set (refer to protocol Section 9.2) 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. was updated to (refer to Section 5.4) The per-protocol (PP) analysis set will include all randomized subjects who received at least one dose of study drug and who provided evaluable data for the primary endpoint with no major protocol deviations (refer to Section 8.2) that may affect the efficacy evaluations, and no use of any rescue medications that may affect the efficacy evaluations.	To account for the effect of any rescue medications during the treatment period.

4 PLANNED ANALYSES

4.1 Data Monitoring Committee

Not applicable.

4.2 Interim 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, the SAP has been signed and 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. Analyses of exploratory efficacy endpoints during the OLE period will not be performed for this IA. Furthermore, at final analysis, 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.

4.3 Final Analysis

Final analysis will be performed after all clinical trial data are entered into the database, any discrepancies in the data are resolved, database is locked, and study is unblinded. At final analysis, only descriptive statistics will be provided for the exploratory efficacy and safety endpoints collected during the OLE period.

5 ANALYSIS SETS

Placebo-controlled Period:

5.1 All Screened Subjects Analysis Set

The 'all screened subjects' analysis set will include all subjects who signed an informed consent.

This analysis set will be used for the summary of the disposition for the overall study.

5.2 Intent-to-Treat Analysis Set

The Intent-to-Treat (ITT) analysis set will include all randomized subjects. Subjects will be analyzed according to their randomized treatment group.

Analysis of disposition and demographic & other baseline characteristics for placebo-controlled period will be performed based on this analysis set.

5.3 Modified Intent-to-Treat Analysis Set

The modified Intent-to-Treat (mITT) analysis set will include all randomized subjects who received at least one dose of the study drug. Subjects will be analyzed according to their randomized treatment group.

Analysis of all the efficacy endpoints for placebo-controlled period will be performed primarily based on this analysis set.

5.4 Per-Protocol Analysis Set

The per-protocol (PP) analysis set will include all randomized subjects who received at least one dose of study drug and who provided evaluable data for the primary endpoint with no major protocol deviations (refer to Section 8.2) that may affect the efficacy evaluations, and no use of any rescue medications that may affect the efficacy evaluations. The exclusion of subjects from the PP analysis set will be finalized before study unblinding and before the primary database lock.

All subjects will be analyzed according to the actual treatment they received during the placebo-controlled period. A supportive analysis to the main analysis of primary efficacy endpoint during placebo-controlled period will be performed based on this analysis set.

5.5 Safety Analysis Set

The safety analysis set will include all subjects who received at least one dose of study drug.

All subjects will be analyzed according to the actual treatment they received during the placebo-controlled period. This analysis set will be used to summarize surgical and medical history, disease history, prior and concomitant medications, exposure to and compliance with study drug, and all safety data during placebo-controlled period.

Other analysis sets, including the PK analysis set, PD analysis set, and skin biomarker analysis set will be defined in separate analysis plans.

Open-Label Extension (OLE) Period:

5.6 All OLE Enrolled Subjects Analysis Set

This analysis set includes all subjects who were enrolled in the OLE period.

This analysis set will be used for the summary of the disposition and analysis set data for the OLE Period.

5.7 OLE Analysis Set

This analysis set will include all subjects who entered the OLE period and received at least one dose of the study drug during the OLE.

This analysis set will be used to summarize both efficacy and safety data collected during the OLE period. For efficacy data, participants will be analyzed according to the treatment they were assigned to while for safety data, participants will be analyzed according to the treatment received.

6 GENERAL CONSIDERATIONS

Table, listing, and figure (TLFs) Shells will be provided in a separate document. Refer to Appendix 1 for a general description of TLF format and layout.

6.1 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 drug (OpSCF or placebo). If the last non-missing assessment was performed on the same date as the first dose of study drug 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. For the ePRO assessments (ADCT, DLQI and POEM), when the assessment was performed on the same date as the first dose of study drug, but the time is after the dosing, the assessment will be considered 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 non-missing assessment (including unscheduled/retest assessments) collected before the first dose of the active study drug (OpSCF) on Day 1 for subjects who received OpSCF in the placebo-controlled period or before the first dose of the active study drug (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 will be defined as the average of all non-missing daily 24-hour PP-NRS scores reported over the last 7 days prior to the first study drug administration. If more than one PP-NRS score is available on the same day, the worst score of the day will be considered for the calculation of average. A minimum of 3 PP-NRS data are needed to calculate a weekly average.

6.2 Change and Percent Change from Baseline

Change from baseline is defined for both the placebo-controlled treatment period and OLE period as the post-baseline value minus the baseline value of the corresponding endpoints in the corresponding period, unless otherwise specified.

Change from baseline at post-baseline visit X will be calculated as:

Assessment value at post-baseline visit X – Baseline value

Percent change from baseline at post-baseline visit X will be calculated as:

[(Assessment value at post-baseline visit X – Baseline value) / Baseline value] * 100

Should the baseline value be 0 (zero), percent change from baseline will be set to missing.

6.3 Study Day

Study Day will be calculated from the first dose of study drug as follows and will be used to show start/end day of assessments or events:

(Date of assessment/event – Date of first dose of study drug) if date of assessment/event is before the date of first dose of study drug.

or

(Date of assessment/event – Date of first dose of study drug) + 1 if date of assessment/event is on or after the date of first dose of study drug.

The placebo-controlled treatment period day will be the same as the study day.

OLE period day will be calculated from the date of first dose of study treatment during the OLE period as given below:

(Date of assessment/event – Date of first dose of OLE study drug) + 1.

In the situation where the assessment/event date is partially or completely missing, the Study Day will be missing.

6.4 Windowing Conventions

For by-visit summary and analysis (when applicable), data will be summarized and analyzed by nominal visit as scheduled and reported in the clinical database (EDC) (refer to Table 1 for planned visit schedule) . Retest, unscheduled, and early termination (ET) visits will only be considered if a scheduled measurement is not available and a retest, unscheduled, and/or ET measurement falls within protocol-adjusted analysis visit window for that scheduled measurement, as described in Table 33a, 3b, 3c, 3d, 4a and 4b.

If more than one assessment falls within the same adjusted analysis visit windows and a scheduled measurement is not available, the measurement collected closest to the scheduled visit target study day will be used for the by-visit summary. Similarly, if more than one assessment is recorded for the same scheduled visit, the measurement collected closest to the scheduled visit target study day will be used for the by-visit summary. If two measurements or more are equidistant from a scheduled visit target study day, the measurement collected after the scheduled visit target study day will be used.

For summary and analysis (when applicable) not presented by visit (e.g., worst post-baseline value), all data (scheduled, retest, unscheduled, and ET) will be considered.

All data collected during scheduled, retest, unscheduled, and ET visits will be listed.

For subjects enrolled in placebo-controlled (PC) period the following windows will be applied to retest, unscheduled, and/or ET measurements if a measurement for the nominal visit is not available:

Table 3a: Adjusted Analysis Visit Windows for Placebo-Controlled Period except ECG, ADCT, POEM, DLQI and PP-NRS:

Analysis Visit	Target Study Day	Lower Limit	Upper Limit
Week 2	15	2	22
Week 4	29	23	36
Week 6	43	37	50
Week 8	57	51	64
Week 10	71	65	78
Week 12	85	79	92
Week 14	99	93	106
Week 16	113	107	116

Table 3b: Adjusted Analysis Visit Windows for Placebo-Controlled Period for ECG

Analysis Visit	Target Study Day	Lower Limit	Upper Limit
Week 16	113	2	116

Table 3c: Adjusted Analysis Visit Windows for Placebo-Controlled Period: ADCT, POEM and DLQI

Analysis Visit	Target Study Day	Lower Limit	Upper Limit
Week 2	15	2	22
Week 4	29	23	36
Week 8	57	37	71
Week 12	85	72	99
Week 16	113	100	116

For calculating weekly mean of the daily PP-NRS assessment during PC period, Days 8 to 14 comprise of Week 2, Days 22 to 28 comprise of Week 4, and so on up to Week 16. If more than one PP-NRS score is available on the same day, the worst score of the day will be considered for the calculation of average. At least 3 daily assessments should be present to calculate the weekly mean.

Table 3d: Analysis Week Windows for PP-NRS

Analysis Visit	Target Study Day	Start Day	End Day
Baseline	1	-7	-1
Week 1*	8	1	7
Week 2	15	8	14
Week 3	22	15	21
Week 4	29	22	28
Week 5	36	29	35
Week 6	43	36	42
Week 7	50	43	49

Analysis Visit	Target Study Day	Start Day	End Day
Week 8	57	50	56
Week 9	64	57	63
Week 10	71	64	70
Week 11	78	71	77
Week 12	85	78	84
Week 13	92	85	91
Week 14	99	92	98
Week 15	106	99	105
Week 16	113	106	112

* For Day 1, only the assessment post study drug administration will be considered for the average calculation.

For subjects enrolled in OLE period the following windows will be applied similarly to retest, unscheduled, and/or ET measurements if a measurement for the nominal visit is not available. If more than one PP-NRS score is available on the same day, the worst score of the day will be considered.

Table 4a: Adjusted Analysis Visit Windows for OLE Period except ECG:

Analysis Visit	Target Study Day	Lower Limit	Upper Limit
Week 20	141	117	155
Week 24	169	156	183
Week 28	197	184	211
Week 32	225	212	239
Week 36	253	240	267
Week 40	281	268	295
Week 44	309	296	323
Week 48	337	324	351

Analysis Visit	Target Study Day	Lower Limit	Upper Limit
Week 52	365	352	N/A

Table 4b: Adjusted Analysis Visit Windows for OLE Period and Follow-up for ECG:

Analysis Visit	Target Study Day	Lower Limit	Upper Limit
Week 52	365	117	N/A

6.5 Software Version

All analyses will be performed using SAS® software Version 9.4 or higher.

7 STATISTICAL CONSIDERATIONS

7.1 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.

7.2 Multicenter Studies

This study will be conducted at multiple sites in United States and Canada. Data from all sites will be pooled together in the summaries and analyses.

7.3 Handling of Dropouts or Missing data

Unless otherwise specified in the sections below, no missing data will be imputed.

7.3.1 Efficacy Data

For the main analysis of primary efficacy and secondary efficacy endpoints that are continuous in nature (refer to Section 13), missing post-baseline data will not be imputed before being analyzed using a mixed-model for repeated measurements (MMRM) model since, under a MMRM model, the missing data are predicted by the observed data via the model of conditional mean.

7.3.1.1 Non-Responder Imputation

Missing data associated with categorical secondary efficacy endpoints will be imputed as per the non-responder imputation (NRI) method. Following this method, if a value is missing for a given post-baseline assessment, this value is imputed to 'No' (i.e., not achieving the endpoint criteria).

7.3.1.2 Baseline Observation Carried Forward and Last Observation Carried Forward

A sensitivity analysis will be carried out with respect to the main analysis of the primary efficacy endpoint, where missing post-baseline data of subjects who discontinued early from the trial due to lack of efficacy or AE(s) will be first imputed using BOCF while missing data for all other subjects will be imputed using last observation carried forward (LOCF) method before performing the MMRM analysis as for the main analysis of the primary efficacy endpoint.

7.3.1.3 Last Observation Carried Forward

A sensitivity analysis will be carried out with respect to the main analysis of binary secondary efficacy endpoints involving EASI, vIGA-AD and PP-NRS where, missing observations will be imputed with the last non-missing, post-baseline observed value.

7.3.2 Safety Data

Partially or completely missing medication and AE start and stop dates will be imputed as described in Appendix 2 and will only be used for the classification of each medication as prior or concomitant (refer to Section 11) and each AE as treatment-emergent (refer to Section 14.1) or not. That is, imputed dates will not be used to compute duration and will not be presented in subject data listings.

7.4 Descriptive Statistics

Continuous endpoints will be summarized using descriptive statistics i.e., number of subjects with non-missing data (n), mean, standard deviation (SD), percent of coefficient of variance (CV%), median, minimum, and maximum.

Categorical endpoints will be summarized using frequencies and percentages.

7.5 Adjustment for Covariates and/or Fixed Effect

For continuous efficacy endpoints, MMRM models will include the baseline observed values as covariate, visit as time factor and the stratification factor (i.e., baseline vIGA-AD score: 3 [Moderate] vs 4 [Severe]), treatment group, and interaction term for treatment-by-visit as fixed effects.

For proportion based secondary endpoints, Cochran-Mantel-Haenszel (CMH) test will adjust for the baseline vIGA-AD score stratification factor: 3 [Moderate] vs 4 [Severe].

No adjustment for the stratification for the biopsy consent will be done in any of the analysis models since it is not an important prognostic factor at baseline (stratification was done for administrative purposes only).

7.6 Coverage of Confidence Intervals and Statistical Tests

Confidence intervals (CIs) will be two-sided with 90% coverage in line with sample size calculation. Two-sided CIs with 95% coverage will also be presented for information purposes in selected endpoints only.

Unless otherwise specified, all statistical tests will be two-sided and will be performed with a significant level of 0.1.

7.7 Multiple Comparisons/Multiplicity

No adjustments for multiple comparisons/multiplicity will be made for this study.

7.8 Examination of Subgroups

Subgroup analysis for the primary efficacy endpoint will be performed by the randomized stratification factor of vIGA-AD score [3(Moderate) vs 4(Severe)]. In addition, analysis will be performed for the primary efficacy endpoint and key secondary efficacy endpoints for the following subgroups:

- Sex at birth (Male vs Female)
- Median age (<X vs ≥X)
- Median weight (<X vs ≥X)

8 STUDY SUBJECTS

8.1 Disposition of Subjects

All subjects who provide informed consent will be accounted for in this study. The number of subjects screened and rescreened will be presented. The number and percentage of subjects with screen failure will be presented for all screened subjects, except for those who were rescreened and did not fail the second screening. Reason for screen failure will be summarized similarly but for subjects with screen failure. The number of subjects randomized will also be presented overall

and by treatment group. The study completion status (across both treatment periods) will be presented overall and by treatment group, along with the reasons for study discontinuation.

For the placebo-controlled period, the number, and percentage of subjects included in each analysis set, who completed or discontinued early from the placebo-controlled treatment period will be presented overall and by treatment group for all randomized subjects. Reason for discontinuation from study treatment during this period will be presented similarly for subjects who discontinued early from study drug during the placebo-controlled period. For subjects who completed this study period, the number and percentage of subjects who enrolled or not into in the OLE period will be provided overall and by randomized treatment group.

For the Open-Label Extension period, the number and percentage of subjects included in the OLE analysis set will be presented overall and by randomized treatment sequence, who completed or discontinued early from the OLE treatment period will be presented overall and by randomized treatment sequence for all OLE enrolled subjects. Reason for discontinuation from study treatment during this period will be presented similarly but for subjects who discontinued early from study drug during the OLE period.

Number of days in each study period and in study (across both study periods) will be calculated as follows and summarized with descriptive statistics overall and by treatment groups in the placebo-controlled period and by randomized treatment sequence in the OLE period:

Number of days in placebo-controlled treatment period =

(Date of completion/discontinuation from the placebo-controlled period

–

Date of first dose of study drug)

+1

Number of days in OLE period =

(Date of completion/discontinuation from the OLE period

–

Date of first dose in the OLE period)

+1

Number of days in the study =

(Date of completion/discontinuation from the study

–

Date of first dose in the study)

+1

A listing of subject's disposition will be provided. Information on first screening for subjects who were rescreened, including the rescreened subject identifier, will be presented under the first screening subject identifier. A listing of subject's randomization information and a listing of subjects included/excluded from each of the analysis sets, with reason for exclusion, will also be provided.

8.2 Protocol Deviations

A blinded data review will be conducted before the primary database lock and study unblinding by the Medical Monitor and Sponsor to classify each protocol deviation as important or non-important (refer to Protocol Deviation Management Plan [PDMP]).

During this blinded data review, important protocol deviations will be further classified as major or minor by the Medical Monitor and Sponsor, where a major protocol deviation is defined as an important protocol deviation potentially having an impact on data sets, study results, efficacy endpoint and populations, so affecting the efficacy evaluations. Major protocol deviations include, but are not limited to:

- Violation of key inclusion/exclusion criteria
- Having a compliance with study drug < 80% or > 120%
- Having received prohibited medications

With the following exception, classification of each protocol deviation as important or non-important and of each important protocol deviation as major or minor will be finalized and approved by Sponsor before the database lock and study unblinding. The exception is that after the database lock and study unblinding, randomized subjects who received more than one treatment group in the same study period will also be considered as having an important major protocol deviation.

The number of events and the number and percentage of subjects with at least one important protocol deviation will be summarized by Sponsor's deviation category and sub-category overall and by randomized treatment group based on the Modified ITT analysis set for the placebo-

controlled period and by randomized treatment sequence for the OLE period. Site-level protocol deviations will be reported once for each subject randomized at that site. Similarly, major protocol deviations will also be summarized in the same table.

A listing of all protocol deviations will be provided and important, major, and deviations associated with COVID-19 will be flagged.

A PD will be assigned to PC period if it occurs before the first OLE dose date. If a subject does not enroll into OLE period, all PDs will be assigned to PC period. A PD will be assigned to both the study periods if it occurs on the day of the first OLE dose date. A PD will be assigned to OLE period if it occurs on or after the first OLE dose date.

9 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic and other baseline characteristics will be summarized overall and by treatment group using descriptive statistics based on the ITT analysis set for the PC period. The list of demographic and baseline characteristics to be summarized includes:

- Age (years) as collected on electronic Case Report Form (eCRF)
- Age groups: <40 years, 40-65 years and >65 years
- Sex at birth
- Ethnicity
- Race
- Baseline height (cm)
- Baseline weight (kg)
- Baseline body mass index (BMI) (kg/m^2), derived as the baseline weight (kg) divided by the square of the baseline height (m^2) i.e., baseline height (m) x baseline height (m)
- Number of AD episodes/ flareups in the last 12 months
- Baseline BSA (%)
- Baseline total EASI score
- Baseline EASI score by head

- Baseline EASI score upper extremities
- Baseline EASI score trunk
- Baseline EASI score lower extremities
- Baseline vIGA-AD score
- Actual Baseline vIGA-AD category: 3[Moderate] and 4[Severe]
- Actual Tape Strip/ Skin Biopsy Consent: Yes and No
- Baseline PP-NRS score
- Baseline POEM score
- Baseline DLQI score
- Baseline ADCT score

Subjects who reported more than one race will be summarized as Multiple in the table and all races selected will be displayed in the listing.

A listing of all demographics and other baseline characteristics will be provided.

10 SURGICAL AND MEDICAL HISTORY

Surgical and medical history will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA), version 26.1.

Incidence of surgical and medical history will be summarized by system organ class (SOC) and preferred term (PT) overall and by treatment group based on the safety analysis set. Subjects who experienced the same surgical and medical history multiple times within the same SOC will be counted only once for the corresponding SOC. Similarly, subjects who experienced the same surgical and medical history multiple times within the same PT will be counted only once for the corresponding PT. Surgical and medical history will be sorted alphabetically by SOC and within each SOC, PTs will be presented by decreasing order of overall frequency.

A listing of all surgical and medical history will be provided followed by AD disease history at screening.

11 PRIOR AND CONCOMITANT MEDICATIONS

Medications will be coded according to the World Health Organization (WHO) Drug [B3 September, 2023].

Prior medications are defined as any medication started and discontinued prior to the first dose of study drug. Concomitant medications for PC period are defined as any medication taken on or after the first dose of study drug, including those who started prior to the date of the first dose of study drug and continued past that date until the PC period completion/discontinuation date. Concomitant medications for the OLE period are defined as any medication taken on or after the first dose of OLE study drug.

See Appendix 2 for handling of partially or completely missing medication start and stop dates.

Incidence of prior medications will be summarized by anatomical therapeutic chemical (ATC) class level 3 and preferred drug name overall and by treatment group based on the safety analysis set for the overall study. Concomitant medications will be summarized similarly for PC period based on safety analysis set and OLE period separately based on the OLE analysis set.

Subjects with multiple medications within the same ATC class level 3 will be counted only once for that ATC class level 3. Similarly, subjects with multiple medications within the same preferred drug name will be counted only once for that preferred drug name. Prior medications will be sorted alphabetically by ATC class level 3 and within each ATC class level 3, the preferred drug name will be presented by decreasing order of overall frequency.

A listing of all medications (prior and concomitant including AD medications) will be provided. A separate listing of prior AD therapy will be provided.

12 EXPOSURE TO AND COMPLIANCE WITH STUDY DRUG

Duration of exposure to study drug, in days, will be computed overall and for each study period as

follows:

Overall duration of exposure (days) =

(Date of last dose of study drug, regardless of the study period + 13 if the subject is/was on PC period + 14 if subject is on OLE period

–

Date of first dose of study drug during the placebo-controlled period)

+ 1

Duration of exposure for placebo-controlled period (days) =

(Date of last dose of study drug during the placebo-controlled period + 13

–

Date of first dose of study drug during the placebo-controlled period)

+ 1

Duration of exposure for OLE period (days) =

(Date of last dose of study drug during the OLE period + 27

–

Date of first dose of study drug during the OLE period)

+ 1

Compliance with study drug (%) during placebo-controlled period will be calculated as follows:

$$\frac{\textbf{Total number of doses administered during the placebo} - \textbf{controlled period}}{\textbf{Total Number of expected doses during the placebo} - \textbf{controlled period}} \textbf{ x 100}$$

Where the total number of expected doses during the placebo-controlled period =

[(Date of last dose during PC period – Date of first dose during the PC period in days + 3) / 14 days], rounded to the ceiling.

Compliance with study drug (%) during OLE period will be calculated as follows:

$$\frac{\textbf{Total number of doses administered during the OLE period}}{\textbf{Total Number of expected doses during the OLE period}} \textbf{ x 100}$$

Where, Total number of expected doses during the OLE period =

[(Date of last dose during OLE period – Date of first dose during OLE period in days + 3) / 28 days], rounded to ceiling.

Overall compliance with study drug (%) will be calculated as follows:

$$\frac{\textbf{Total number of doses administered overall}}{\textbf{Total Number of expected doses overall}} \textbf{ x 100}$$

where, the total number of expected doses overall will be the sum of number expected number of doses during the placebo-controlled period and OLE period.

Compliance with study drug (%) will also be categorized as follows:

- <80%
- 80%-120%
- >120%

Duration of exposure to study drug (days), and compliance with study drug (%) will be summarized using descriptive statistics by treatment group based on the safety analysis set for the placebo-controlled period and by actual treatment sequence based on the OLE analysis set for the OLE period. Number and percentage of subjects in each category of compliance with study drug (%) will also be presented. Overall duration of exposure and compliance for each subject will only be presented in the listing.

Study drug exposure and compliance will be listed.

13 EFFICACY ANALYSES

Unless otherwise specified, all efficacy endpoints will be summarized by treatment group and visit, when applicable, based on the modified ITT analysis set for placebo-controlled period and by randomized treatment sequence and visit based on the OLE analysis set for the OLE period.

13.1 Primary Efficacy Endpoint

13.1.1 Definition of Primary Efficacy Endpoint

The primary efficacy endpoint for this study is:

- Percent change from baseline in EASI at Week 16.

The EASI quantifies the severity of a subject's AD based on both lesion severity and the percentage of BSA affected. 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.

The EASI score is obtained by using the formula below:

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

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

When the index value for an anatomical site is missing, the total EASI score will also be set to missing.

13.1.2 Hypothesis Testing

The null hypothesis is that the mean percent change from baseline in EASI at Week 16 does not differ between OpSCF201 and placebo. The alternative hypothesis is that the mean percent change from baseline in EASI at Week 16 does differ between OpSCF201 and placebo.

$H0: \mu 1 = \mu 2$ versus $H1: \mu 1 \neq \mu 2$

Where, μ_1 = Mean percent change from baseline in EASI at Week 16 for a OpSCF201 treatment group

μ_2 = Mean percent change from baseline in EASI at Week 16 for the Placebo treatment group

The primary efficacy estimand is described as below:

Population: Adult Subjects with Moderate to Severe Atopic Dermatitis

Endpoint: Mean Percent Change from Baseline in EASI at Week 16

Intercurrent Events: Subjects may be exposed to possible intercurrent events during the 16 Weeks PC treatment period that could potentially impact the estimates of estimand, such as study discontinuation due to lack of efficacy or adverse events. A sensitivity analysis will be performed, where post-baseline value for subjects who discontinue study due to lack of efficacy or adverse events will be imputed using BOCF method and for the subjects who discontinue study for other reasons will be imputed using LOCF method as described in 7.3.1.2.

Population-level summary: Difference in percent change from baseline in EASI at Week 16 between the OpSCF201 and Placebo.

13.1.3 Main Analysis

The observed and percent change from baseline values in EASI will be summarized by visit and treatment group, when applicable using descriptive statistics, with their corresponding two-sided 90% CIs based on the mITT analysis set.

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 as time factor; stratification factor (ie, actual vIGA-AD strata 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. If convergence issues arise, the autoregressive (order 1) [AR (1)] structure will be used. If the AR (1) structure also does not converge, other covariance structures (e.g., Toeplitz, ANTE (1), etc) deemed appropriate to fit the data will be used and the structure with the smallest Akaike Information Criteria corrected (AICc) value will be selected.

The least square mean (LS mean) estimates and associated standard errors (SE) will be provided by treatment group and visit. Difference in LS mean estimates between the two treatment groups

and associated SE at each visit will also be provided, along with its two-sided 90% CI, two-sided 95% CI and p-value. The main contrast of interest will be at Week 16.

Additionally, LS mean estimates of the percent change from baseline (and associated CIs) over time will be displayed graphically by treatment group.

13.1.4 Sensitivity Analyses

The following sensitivity analysis will be performed on the primary efficacy endpoint:

- Post-baseline missing values will be imputed using the BOCF method for subjects who discontinued due to an adverse event associated with AD or lack of efficacy and using LOCF for other subjects as described in 7.3.1.2.

13.1.5 Supportive Analyses

As a supportive analysis, the main analysis of the primary efficacy endpoint (refer to Section 13.1.3) will be repeated but based on the PP analysis set.

13.1.6 Subgroup Analysis

Subgroup analysis of the primary efficacy endpoint will be performed by the randomized stratification factor by vIGA-AD score [3(Moderate) vs 4(Severe)] based on the mITT analysis set. Baseline vIGA-AD strata variable will be excluded in the analysis model. Also, subgroup analysis will be performed for the primary efficacy analysis for each additional subgroups mentioned in section 7.8.

13.2 Secondary Efficacy Endpoints

13.2.1 Definition of Secondary Efficacy Endpoints

Secondary efficacy endpoints are:

<u>Endpoints involving EASI</u>

- Percent change from baseline in EASI at Weeks 2, 4, 6, 8, 10, 12, and 14. *
- Change from baseline in EASI at Weeks 2, 4, 6, 8, 10, 12, 14 and 16. *
- Proportion of subjects achieving EASI50 at Weeks 2, 4, 6, 8, 10, 12, 14 and 16. *
- Proportion of subjects achieving EASI75 at Weeks 2, 4, 6, 8, 10, 12, 14 and 16. *
- Proportion of subjects achieving EASI90 at Weeks 2, 4, 6, 8, 10, 12, 14 and 16. *

EASI score is calculated as described in primary efficacy endpoint section. The change and percent change from baseline in EASI will be calculated as described in Section 6.2. The proportion of subjects achieving EASI50, EASI75 and EASI90 will be determined as having at least 50%, 75% and 90% improvement in EASI score from baseline respectively.

Endpoints involving vIGA-AD

- Proportion of subjects achieving at least a 2-grade reduction from baseline to clear (0) or almost clear (1) in vIGA-AD at Weeks 2, 4, 6, 8, 10, 12, 14 and 16. *
- Proportion of subjects achieving at least a 2-grade reduction from baseline in vIGA-AD at Weeks 2, 4, 6, 8, 10, 12, 14 and 16. *

* Subgroup analysis will be performed for these secondary endpoints.

The validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD) will be assessed by the principal investigator or sub-investigator at each study visit using the descriptors that best describe the overall appearance of the lesions at the visit. The score ranges from 0-4 based on the following morphological descriptions:

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 or 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.

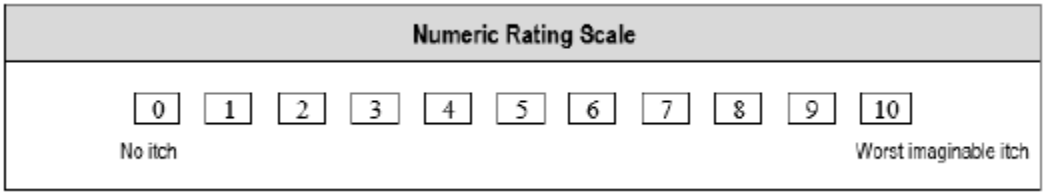
The proportion of subjects with vIGA-AD score of clear (0) or almost clear (1) at each post-baseline visit and having ≥2 grade reduction in vIGA-AD from baseline will be the proportion of subjects achieving at least a 2-grade reduction from baseline to clear (0) or almost clear (1) in vIGA-AD at each concerned visit.

The proportion of subjects with reduction from baseline of ≥2 grade in vIGA-AD score at each post-baseline visit will be the proportion of subjects achieving at least a 2-grade reduction from baseline at the concerned visit.

Endpoints involving PP-NRS

- Change and percent change from baseline in weekly average of the daily PP-NRS at Weeks 2, 4, 6, 8, 10, 12, 14 and 16.
- Proportion of subjects achieving at least a 4-point reduction from baseline in weekly average of the daily PP-NRS at Weeks 2, 4, 6, 8, 10, 12, 14 and 16. *

PP-NRS is based on the Numeric Rating Scale which is used to assess the level of itch the subject is experiencing. The following question will be asked to subject: "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?" Based on the score provided by subject, the PP-NRS score is assigned.



Proportion of subjects achieving at least a 4-point reduction from baseline will be calculated using the weekly average of daily PP-NRS score and is the proportion of subjects who have ≥4 points reduction in the NRS score at respective post-baseline visits comparing with the baseline. This endpoint will be considered only for subjects with baseline PP-NRS of ≥4.

Change and percent change from baseline in BSA involved with AD at Weeks 2, 4, 6, 8, 10, 12, 14 and 16.

The overall BSA affected by AD will be evaluated (from 0% to 100%) at the specific visits. It will be calculated using the palm surface area method. This method states that palmar surface of 1 hand (using the patient's hand and including the fingers) represents 1% of his or her total BSA.

Change from baseline in ADCT at Weeks 2, 4, 8, 12, and 16.

ADCT 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. Each question carries equal weight and is scored from 0 to 4, for a total score ranging between 0 and 24.

Change from baseline in POEM at Weeks 2, 4, 8, 12, and 16.

POEM is a self-assessment of disease severity using 7 questions asked to subject. A maximum value of 28 can be assigned based on the subject's response to 7 questions scored from 0 to 4.

Change from baseline in DLQI at Weeks 2, 4, 8, 12, and 16.

DLQI is a 10 questions questionnaire to measure how much skin problems have affected a subject's life over the last week. The DLQI is calculated by summing the score of each question resulting in a maximum of 30 and a minimum of 0. The higher the score, the more quality of life is impaired.

13.2.2 Main Analysis

The secondary endpoint involving proportions will be translated as a responder analysis, where a subject will be classified as responder if he or she achieves the endpoint criteria at the specific visit, otherwise the subject will be classified as a non-responder. Missing data will be imputed as per the NRI method (refer to Section 7.3.1.1).

At each visit, the number and proportion of subjects achieving the endpoint will be presented by treatment group, along with their two-sided 90% exact Clopper-Pearson CI.

The Cochran Mantel-Haenszel (CMH) test will be used, stratified by actual vIGA-AD score stratum. The proportion differences (with two-sided 90% CI and two-sided 95% CI), odds ratios (with two-sided 90% CI and two-sided 95% CI), and p-values from the CMH test will be reported.

The continuous secondary efficacy endpoints involving change and percent change from baseline will be analyzed using the same approach (i.e., MMRM) as described for the primary efficacy analysis (Section 13.1.3).

In addition, graphical representation will be provided for LS mean estimates of the change from baseline (and associated CIs), proportion of subjects achieving EASI 50, EASI 75 and EASI 90; proportion of subjects achieving at least 2 grade reduction from baseline in vIGA-AD of clear or

almost clear and proportion of subjects achieving at least a 4-point reduction from baseline in weekly average of daily PP-NRS.

13.2.3 Sensitivity Analyses

Sensitivity analyses for the main analysis of secondary efficacy endpoints involving binary endpoints for EASI, vIGA-AD and PP-NRS will be performed using observed data and LOCF method (7.3.1.3).

13.2.4 Supportive Analyses

No supportive analyses will be performed for the main analysis of secondary efficacy endpoints.

13.2.5 Subgroup Analysis

Subgroup analysis will be performed for the key secondary efficacy endpoints (marked * in section 13.2.1) for the additional subgroups described in section 7.8 except for the randomized stratification factor of vIGA-AD score.

13.3 Exploratory Efficacy Endpoints

13.3.1 Definition of Exploratory Efficacy Endpoints

The exploratory efficacy endpoints are analyzed as described in the secondary efficacy endpoints section.

However, unlike the daily PP-NRS assessment for PC period, PP-NRS assessment will be conducted only at the specified visits in OLE period. So, the change and percent change from baseline will be based on the PP-NRS value of that specified visit alone rather than weekly average as mentioned in the placebo-controlled period. However, the baseline will still be derived using the weekly average of the daily PP-NRS values.

The exploratory endpoint in the PC period include:

- Change from baseline in blood biomarkers and IgE at Weeks 4, 8, 12, and 16

The exploratory endpoints in the OLE period include:

- Percent change from baseline in EASI at Weeks 20, 24, 28, 32, 36, 40, 44, 48, and 52
- Change from baseline in EASI at Weeks 20, 24, 28, 32, 36, 40, 44, 48, and 52
- Proportion of subjects achieving EASI50, EASI75, and EASI90 at Weeks 20, 24, 28, 32, 36, 40, 44, 48, and 52

- Proportion of subjects achieving at least a 2-grade reduction from baseline to clear (0) or almost clear (1) in vIGA-AD at Weeks 20, 24, 28, 32, 36, 40, 44, 48, and 52
- Proportion of subjects achieving at least a 2-grade reduction from baseline in vIGA-AD at Weeks 20, 24, 28, 32, 36, 40, 44, 48, and 52
- Change and percent change from baseline in the PP-NRS at Weeks 20, 24, 28, 32, 36, 40, 44, 48, and 52
- Proportion of subjects achieving at least a 4-point reduction from baseline in the PP-NRS at Weeks 20, 24, 28, 32, 36, 40, 44, 48, and 52
- Change and percent change from baseline in BSA involved with AD at Weeks 20, 24, 28, 32, 36, 40, 44, 48, and 52
- 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
- Change from baseline in blood biomarkers at Weeks 24, 32, 40, and 48

13.3.2 Main Analysis

For the main analysis of the exploratory efficacy endpoints, descriptive statistics (Section 7.4) by randomized treatment sequence and by visit, will be provided based on the mITT analysis set for placebo-controlled period and OLE analysis set for OLE period. No inferential statistical testing will be done on the efficacy endpoints. Imputation will not be done on the missing data associated with the exploratory efficacy endpoints. Along with the endpoints presented above, summary table will be similarly provided for each study period for proportion of subjects achieving PP-NRS score ≤ 1.

13.3.3 Sensitivity Analyses

No sensitivity analyses will be performed for exploratory efficacy endpoints.

13.3.4 Supportive Analyses

No supportive analyses will be performed for exploratory efficacy endpoints.

14 SAFETY ANALYSES

All safety endpoints will be summarized by treatment group and visit for the placebo-controlled period based on the safety analysis set, and for the OLE period by actual treatment sequence and visit based on OLE analysis set.

14.1 Adverse Events

AEs will be coded according to the MedDRA, version 26.1. Adverse events will be reported in the placebo-controlled period or OLE period depending on the onset as described below.

A treatment-emergent adverse event (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). Any AE starting on or after the first dose date will be considered TEAE.

For this study, TEAEs will also be attributed to a study period as follows:

- Placebo-Controlled Treatment Period:

A TEAE will be attributed to this study period if it occurred on or after the first dose of study treatment during the placebo-controlled treatment period but before the first dose of study treatment during the OLE. Should a subject not enter the OLE (either due to discontinuation of study during the placebo-controlled treatment period or because he/she declined participation to the OLE), all subject TEAEs will be attributed to this study period.

- OLE Period:

A TEAE will be attributed to this study period if it occurred on or after the first dose of study treatment during the OLE period.

See Appendix 2 for handling of partially or completely missing AE start and stop dates. In the case where it is not possible to define an AE as treatment emergent or not, the AE will be classified as treatment emergent.

All AE summaries will be presented for each study period separately.

An overall summary table of AEs will be provided. The number of events and the number and percentage of subjects who experienced at least one AE, TEAE, TEAE by greatest reported

relationship (no reasonable possibility or reasonable possibility), TEAE by worst severity (mild, moderate, severe, life-threatening or death), injection site TEAE, serious TEAE, TEAE leading to study treatment discontinuation, TEAE leading to study discontinuation, and TEAE with an outcome of death will be presented.

Incidence of TEAEs will be summarized by SOC and PT. Subjects experiencing multiple TEAEs within a SOC will be counted only once for that SOC. Similarly, subjects experiencing multiple TEAEs within a PT will be counted only once for that PT. TEAEs will be sorted alphabetically by SOC and within each SOC, PTs will be presented by decreasing order of total frequency. Similarly, TEAEs will be summarized by PT alone.

Incidence of TEAEs will be further broken down by greatest reported relationship with study drug, i.e., "no reasonable possibility" or "reasonable possibility". Investigator will decide if there is a reasonable possibility or not for a causal relationship to study treatment after considering the evidence to be sufficient or insufficient based on subject's history, most recent physical examination findings, and concomitant medications. 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.

Incidence of TEAEs will also be further broken down by severity (mild, moderate, severe, life-threatening and death). 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 severity within each category for each analysis.

Incidence of injection site TEAEs will be summarized by PT and lowest level term (LLT). Subjects experiencing multiple injection site TEAEs within a PT will be counted only once for that PT. Similarly, subjects experiencing multiple TEAEs within a LLT will be counted only once for that LLT. TEAEs will be sorted alphabetically by PT and within each PT, LLTs will be presented by decreasing order of total frequency.

Incidence of serious TEAEs, TEAEs leading to discontinuation from study treatment and TEAEs leading to discontinuation from study will be summarized separately by SOC and PT. Subjects experiencing multiple TEAEs within a SOC will be counted only once for that SOC. Similarly, subjects experiencing multiple TEAEs within a PT will be counted only once for that PT.

For all summaries by SOC and PT, TEAEs will be sorted alphabetically by SOC and within each SOC, the PT will be presented by decreasing order of total frequency.

Exposure-adjusted incidence rate (EAIR) will also be reported in addition to the n (%) for the TEAE summary tables by SOC/PT, PT and LLT/PT, which is derived as below.

For each study period, EAIR (100-pt year) is defined as follows within each arm separately:

{(number of subjects with at least one event during a study period / [total time at risk (days) during the study period]} * (365.25 days/years) * 100

where each subject time at risk (days) during a study period is the defined as (date of 1st event during the study period - date of first dose during the study period) + 1 for subjects who had at least one event during the study period and (date of completion/discontinuation from study period - date of first dose during the study period) + 1 for subjects who did not have the event during the study period. For each arm, the total time at risk (days) is then calculated by summing the time at risk (days) across all subjects within the arm.

Listings of all AEs with an outcome death, all serious AEs, TEAEs leading to discontinuation from study treatment and all TEAEs leading to discontinuation from study will be provided separately.

A listing of all AEs will be provided detailing verbatim, SOC, PT, LLT (only for injection site reaction listing), 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 in the respective study period. Injection site AEs and AEs related to overdose will be flagged.

14.2 Clinical Laboratory

Laboratory data will be presented in international system of units (SI) units.

Observed values, changes from baseline and shift to abnormality in chemistry, hematology, and urinalysis tests will be summarized using descriptive statistics. Frequencies and percentages will be presented for each category of qualitative urinalysis tests and a shift to abnormality will also be provided.

Clinical laboratory results were graded with CTCAE grading report flag in laboratory service agreement with Medpace and will be used as is (i.e., not to be re-derived). For clinical laboratory tests with available pre-defined Common Terminology Criteria for Adverse Events (CTCAE) grades, shift tables from baseline to maximum post-baseline grade will be provided for chemistry and hematology. Only subjects with a baseline result and a result at the least one post-baseline visit will be considered.

Shift from Baseline to Overall Maximum Post-Baseline CTCAE Grade for chemistry and hematology will be provided for following CTCAE terms:

1. Anemia
2. Alanine aminotransferase increased,
3. Alkaline phosphatase increased,
4. Aspartate aminotransferase increased,
5. Hypernatremia,
6. Hypertriglyceridemia,
7. Hyperuricemia,
8. Hypoalbuminemia,
9. Hypoglycemia,
10. Hypokalemia,
11. Hyponatremia,
12. INR increased,
13. Lymphocyte count decreased,
14. Neutrophil count decreased,
15. White blood cell decreased.

Separate listings of data for chemistry, hematology, and urinalysis will be provided for each test where a subject had at least one abnormal result i.e., below the lower limit of normal (LLN) or above the upper limit of normal (ULN).

In addition, separate listings of all data for chemistry, hematology, and urinalysis tests will be provided along with a listing for other laboratory assessments.

14.3 Vital Signs

Observed values and changes from baseline in vital signs (systolic blood pressure [SBP], diastolic blood pressure [DBP], pulse rate, respiratory rate, body temperature, weight, and BMI) will be summarized using descriptive statistics. BMI will be calculated for each corresponding weight measurement based on baseline height.

Shift table from baseline to each post-baseline visit describing shifts to potentially clinically significant abnormality from normal and not clinically significant abnormality results will be provided. Only subjects with a baseline result and a result at the specified visit will be considered.

Following vital signs will be flagged as potentially clinically significant if it meets the following pre-defined markedly abnormal criteria:

Vital Sign (unit)	Markedly Abnormal Low	Markedly Abnormal High
SBP (mmHg)	≤ 90	≥ 160
DBP (mmHg)	≤ 60	≥ 100
Pulse rate (bpm)	≤ 55	≥ 100

A listing of all vital sign assessments will be provided.

14.4 Electrocardiogram

Observed values and changes from baseline in ECG tests/intervals i.e., heart rate (beats/min), RR interval (msec), PR interval (msec), QRS duration (msec), QT interval (msec), QTcB interval (msec) and QTcF interval (msec) will be summarized using descriptive statistics by treatment group and visit.

Shift table from baseline to each post-baseline visit describing shifts to abnormality from normal results will be provided for ECG overall interpretation. Only subjects with a baseline result and a result at the specified visit will be considered.

ECG measurements meeting the pre-defined markedly abnormal criteria specified in ICH E14 will be flagged as clinically significant i.e.,

1. QTcB interval (msec) and QTcF interval (msec) observed values:
    - >450 with no pre-existing condition (i.e., baseline value ≤ 450)
    - >480 with no pre-existing condition (i.e., baseline value ≤ 450)
    - >500 with no pre-existing condition (i.e., baseline value ≤ 450)
2. QTcB interval (msec) and QTcF interval (msec) increases from baseline:
    - >30
    - >60

A listing of all ECG tests, intervals, and overall interpretation will be provided. Clinically significant abnormal interpretation will be flagged.

14.5 Physical Examination

Information for all physical examinations will be included in the source documents. Any significant change will be reported as an AE in the source document and eCRF.

14.6 Injection Site Evaluation

Information for Injection Site Evaluation will be included in the source documents. Any significant change will be reported as an AE in the source document and eCRF. Further details are included in section 14.1.

APPENDICES

Appendix 1

Output Conventions

TLF will be generated using SAS® and will be displayed on letter size paper with landscape orientation, 1 inch margin, and 9 pt Courier New font.

The header section will comprise the sponsor's name, protocol number, delivery description, data cut-off date or date of database lock, as applicable, and page number (Page X of Y).

TLF title section will include TLF number, TLF title, and analysis set.

The footer section will include the source listing(s) (if applicable), list of abbreviations, TLF footnotes, name of the SAS program name, and date and time of the execution of the program.

For categorical summary tables, percentages will be reported to one decimal place. Percentages between 0 and 0.1 (both exclusive) will be displayed as "<0.1" and percentages between 99.9 and 100.0 (both exclusive) will be displayed as ">99.9". Percentages will be based on total number of subjects in the analysis set within each treatment group for efficacy data and based on number of subjects in the analysis set with available data within each treatment group and visit, if applicable for any other type of data.

For descriptive statistics, the minimum and maximum values will keep the same number of decimal places as the original value; the mean and median will be displayed with one additional decimal place than the original value; and the SD, standard error (SE), and CI will be displayed with two additional decimal places than the original value. If derived endpoints are to be summarized, the number of decimals of the derived values is to be chosen on a case-by-case basis, but the rule above applies.

P-values between 0.001 and 0.999, both inclusive, will be reported to 3 decimal places, p-values less than 0.001 will be reported as "<0.001", and p-values greater than 0.999 will be reported as ">0.999".

Listings will be ordered by treatment group, subjects with data available for both PC and OLE period, subject number, endpoint/test, date of assessment/ collection/measurement, and time of assessment/collection/measurement, if applicable. Imputed dates and imputed missing data will not be presented in the listings. For visit names, nominal visit names will be presented followed

by the analysis visit name when both are different (e.g., 'Unscheduled/Week X', etc.) Otherwise, only the nominal visit names will be presented.

Dates & Times Format

Date and time (if available) will be presented in the format yyyy-mm-dd/hh:mm.

Presentation of Treatment Groups

When applicable, treatment groups for placebo-controlled period and full study will be represented as follows:

Treatment Group Full Name in IWRS	Treatment Group Short Name for TLFs
OpSCF	OpSCF 600 mg
Placebo	Placebo

When applicable, treatment sequence groups for OLE Period will be represented as follows:

Treatment Sequence Full Name in IWRS	Treatment Sequence Short Name for TLFs
OpSCF / OpSCF	OpSCF 600 mg/ OpSCF 600 mg
Placebo/ OpSCF	Placebo/ OpSCF 600 mg

Appendix 2

Algorithm for Imputation of Start/Stop Date of Adverse Events and Prior/Concomitant Medications

Event Start Date Imputation

- Imputation of event end date should be done before imputation of event start date.
- *Completely missing*: Impute to the first study treatment date.
- *Missing day and month*: Impute to January 1st, unless year is the same as year of first study treatment dose then impute to the first study treatment date.
- *Missing day*: Impute to the 1st of the month, unless month and year are the same as month and year of first study treatment dose then impute to the first study treatment date.
- If imputed event start date is after event end date (imputed or not), set the event start date to the imputed event end date.

Event Stop Date Imputation

- *Completely missing (and not flagged as "ongoing")*: Impute to the last contact date.
- *Missing day and month*: Impute to December 31st, unless year is the same as last contact date then impute to the last contact date.
- *Missing day*: Impute to the last day of the month, unless year and month are the same as year and month of last contact date then impute to the last contact date.

DocuSign

Certificate Of Completion

Envelope Id: 9B07425E403943B38BF77A24F28D8948
Status: Completed
Subject: Complete with Docusign: OpSCF201_SAP_Final v1.0_08-Oct-2024.pdf
Source Envelope:
Document Pages: 57
Signatures: 3
Envelope Originator:
Certificate Pages: 5
Initials: 0
[redacted]
AutoNav: Enabled
EnvelopeId Stamping: Disabled
Time Zone: (UTC-05:00) Eastern Time (US & Canada)
IP Address: [redacted]

Record Tracking

Status: Original
10/8/2024 5:41:15 PM
Holder: [redacted]
Location: DocuSign

Signer Events	Signature	Timestamp
[redacted] Security Level: Email, Account Authentication (Required)	[redacted] Signature Adoption: Pre-selected Style Signature ID: [redacted] Using IP Address: [redacted] With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 10/8/2024 5:43:35 PM Viewed: 10/8/2024 8:13:49 PM Signed: 10/8/2024 8:14:38 PM
Electronic Record and Signature Disclosure: Not Offered via DocuSign		
[redacted] Opsidio LLC Security Level: Email, Account Authentication (Required)	Signed by: [redacted] Signer Name: [redacted] Signing Reason: I approve this document Signing Time: 08-Oct-2024 | 15:23:30 PDT 6E9A6FD8137D40B4AF7A05C9DE8A884B Signature Adoption: Pre-selected Style Signature ID: [redacted] Using IP Address [redacted] With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 10/8/2024 5:43:36 PM Resent: 10/8/2024 6:21:50 PM Viewed: 10/8/2024 6:23:09 PM Signed: 10/8/2024 6:23:36 PM
Electronic Record and Signature Disclosure: Accepted: 10/8/2024 6:23:09 PM ID: [redacted]		

Signer Events	Signature	Timestamp
[redacted] [redacted] Security Level: Email, Account Authentication (Required), Login with SSO	[redacted] Signature Adoption: Pre-selected Style Signature ID: [redacted] Using IP Address [redacted] With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I am the author of this document	Sent: 10/8/2024 5:43:35 PM Viewed: 10/8/2024 6:27:38 PM Signed: 10/8/2024 6:28:01 PM
Electronic Record and Signature Disclosure: Not Offered via DocuSign		
In Person Signer Events	**Signature**	**Timestamp**
Editor Delivery Events	**Status**	**Timestamp**
Agent Delivery Events	**Status**	**Timestamp**
Intermediary Delivery Events	**Status**	**Timestamp**
Certified Delivery Events	**Status**	**Timestamp**
Carbon Copy Events	**Status**	**Timestamp**
Witness Events	**Signature**	**Timestamp**
Notary Events	**Signature**	**Timestamp**
Envelope Summary Events	**Status**	**Timestamps**
Envelope Sent	Hashed/Encrypted	10/8/2024 5:43:36 PM
Envelope Updated	Security Checked	10/8/2024 6:21:49 PM
Envelope Updated	Security Checked	10/8/2024 6:21:49 PM
Envelope Updated	Security Checked	10/8/2024 6:21:49 PM
Envelope Updated	Security Checked	10/8/2024 6:21:49 PM
Envelope Updated	Security Checked	10/8/2024 6:21:49 PM
Envelope Updated	Security Checked	10/8/2024 6:21:49 PM
Certified Delivered	Security Checked	10/8/2024 6:27:38 PM
Signing Complete	Security Checked	10/8/2024 6:28:01 PM
Completed	Security Checked	10/8/2024 8:14:38 PM
Payment Events	**Status**	**Timestamps**
Electronic Record and Signature Disclosure		

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STATISTICAL ANALYSIS PLAN

For:
Opsidio, LLC.

PROTOCOL No. OpSCF201

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

[redacted]

Prepared by:
Altasciences Company Inc.
575 Armand-Frappier Boulevard
Laval, Quebec
Canada, H7V 4B3

Version: 1.0
Date: 2024/10/07

STATISTICAL ANALYSIS PLAN AND SHELLS APPROVAL

We have carefully read this statistical analysis plan and corresponding shells and agree it contains the necessary information required to handle the statistical analysis of study data.

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Version	Date	Author	Description of Changes
1.0	2024/10/07	[redacted]	Not applicable

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ABBREVIATIONS

AD	atopic dermatitis
ADA	Anti-drug antibody
CV%	coefficient of variation
EDC	Electronic Data Capture
EOS	End of Study
ET	Early Termination
ICH	International Conference on Harmonisation
IP	investigational product
IWRS	Interactive Web Response System
LLOQ	lower limit of quantitation
Min	minimum
Max	maximum
NCA	non-compartmental analysis
OLE	open label extension
PD	pharmacodynamics
PK	pharmacokinetic(s)
Q2W	once every 2 weeks
Q4W	once every 4 weeks
SAP	Statistical Analysis Plan
SD	standard deviation
TFLs	Tables, Figures, and Listings
vIGA-AD	Validated Investigator's Global Assessment for Atopic

1 INTRODUCTION

This Statistical Analysis Plan (SAP) provides a detailed description of the statistical methods and procedures to be implemented for the analyses of data from the Clinical Study Protocol OpSCF201. The analyses described in the SAP are based upon the final version of the Clinical Study Protocol 2.1, dated 20-DEC-2023. The scope of this SAP includes Pharmacokinetics (PK) and antidrug antibody (ADA) analysis.

2 STUDY OBJECTIVES

The objectives of the study and corresponding study endpoints are detailed in Table 2-1.

Table 2-1 Objectives and Related Endpoints

Objective	Endpoint
Primary	
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	
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	<u>Secondary efficacy endpoint: (at Weeks 2, 4, 6, 8, 10, 12, 14, and 16 or otherwise specified):</u> • 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	<u>Secondary PK endpoint:</u> Serum concentrations of OpSCF in subjects receiving the active treatment and PK parameters, as data permit.

Exploratory	
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) • 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.

3 STUDY DESIGN

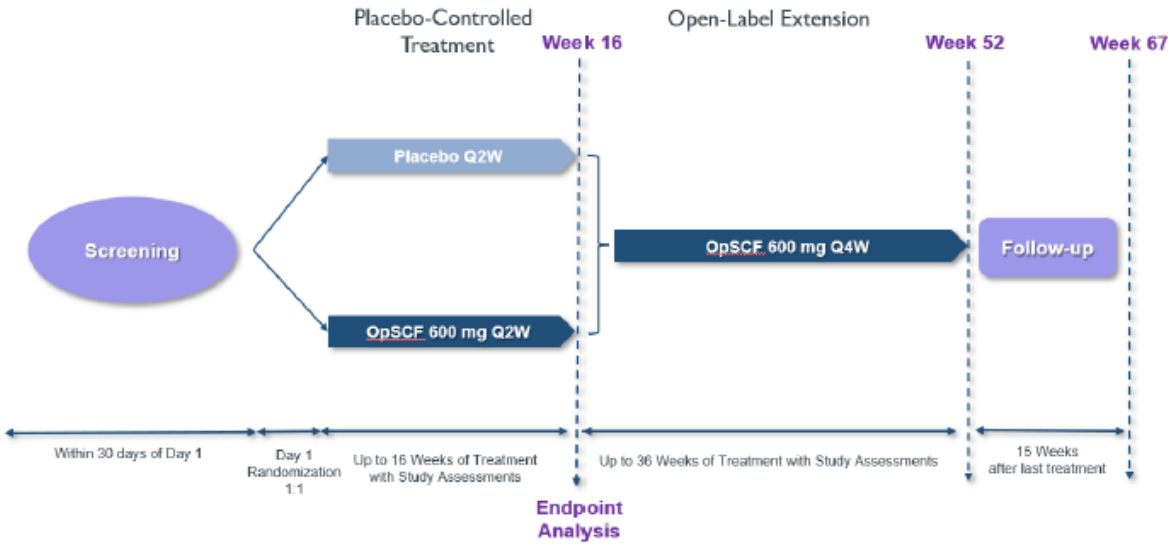
3.1 General Description

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 atopic dermatitis (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]).

The following figure(s) summarize the study schematic and design:

Figure 3-1 Study Diagram



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

3.2 Treatments

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 Open Label Extension (OLE) (refer to Table 3 Study Products in Study Protocol).

Study treatments in this study include:

- OpSCF

  Dosage formulation: oral 1 mL vials of 100 mg/mL solution

- Placebo

  Dosage formulation: 1 mL vials without active ingredient

3.3 Study Procedures

For complete details on the study assessments to be performed for each study period [Placebo-Controlled and OLE periods (refer to Table 1 Schedule of Events in Study Protocol].

3.4 Randomization and Unblinding Procedures

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 (refer to section 6.4 of Study Protocol).

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.

3.5 Determination of Sample Size

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.

4 ANALYSIS POPULATIONS

The following populations will be used for respective analysis:

PK analysis set: All subjects who have received at least 1 investigational product (IP) with sufficient PK data to derive at least 1 OpSCF PK parameter and without having any major protocol deviations that could interfere with planned PK analyses. Subjects who do not complete the sampling schedule may be included in the PK analysis for only the PK parameters that are judged not to be affected by the missing sample(s). Participant who received only placebo will not be included in the PK analysis set.

Immunogenicity analysis set: All subjects who have received at least 1 dose of the study drug (placebo and active drug) with at least 1 post dose ADA assessment and without having any major protocol deviations that could interfere with the planned ADA analyses. Subjects who do not complete the sampling schedule may be included in the immunogencity analysis for only the ADA parameter that are judged not to be affected by the missing sample(s).

5 DATA HANDLING AND PRESENTATION

All PK and immunogenocity and statistical outputs will be generated using SAS software, version 9.4 or higher.

All programs used to generate PK and immunogenocity statistical analyses will be validated according to Altasciences' Standard Operating Procedures (SOPs).

The analyses described in this plan are considered a priori, in that they have been defined prior to database lock. Any analyses performed subsequent to database lock will be considered post hoc and exploratory, and will be identified in the Clinical Study Report (CSR).

5.1 Pharmacokinetic Analysis

In general, all PK summary tables will be presented for the PK analysis set.

Individual raw PK concentrations will be displayed with 3 significant figures.

Summary statistics for concentrationswill be displayed with the same precision as the individual values, with the exception of number of observations (n) and CV% which will be presented with 0 and 1 decimal place, respectively.

5.2 Baseline

Unless otherwise specified, the baseline value will be defined as the last non-missing evaluation prior to the first dose of study drug, including unscheduled assessment(s), if applicable.

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.

Open-Label Extension 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 study drug (placebo or active drug) on Day 1. If the last non-missing assessment was

performed on the same date as the first dose of OpSCF (or placebo) and time is not available, the assessment will be considered as baseline.

6 PHARMACOKINETIC ANALYSIS

The PK analysis will be carried out according to Altasciences SOPs.

6.1 Missing Values

The lack of concentration values due to failure to collect the sample, a lost or compromised sample or due to the subject's early termination from the study will be termed "missing" in the dataset, and no imputation will be done. If duplicate samples are collected, the predose sample closest to the dosing time will be used for analysis, and the other sample will be excluded from analysis and presented in a separate listing. Unscheduled samples will be excluded from the analysis and presented in a separate listing.

If the actual collection day of a predose or postdose PK sample is unknown, but a valid concentration value has been measured, the sample will be set to missing in the PK analysis and will be presented in a listing excluded from descriptive statistics. Unknown baseline collection times will be handled on a case-by-case basis.

6.2 Measurements Below the Lower Limit of Quantitation

Concentration values below the LLOQ will be replaced with zero for mean PK profile representations as well as for descriptive statistic calculations.

6.3 Actual Time

The individual concentration/time profiles and the mean concentration/time profiles and tables presenting summary statistics of concentration-time series will be presented using nominal sampling times.

6.4 Non-Compartmental Analysis

As only trough samples are collected for this study, no non-compartmental analysis (NCA) will be performed.

The PK parameters for OpSCF are presented in Table 6-1.

Table 6-1 Pharmacokinetic Parameter of OpSCF in Serum

Parameter	Definition
Placebo-Controlled Period and Open-Label Extension Period	
C_{trough}	Observed concentration at the end of the dosing interval.

6.5 Pharmacokinetic Statistical Methodology

All tables, figures, and listings (TFLs), when appropriate, will be stratified by treatment period, by day, and by ADA status.

6.5.1 Summary Statistics

Summary statistics of the individual concentration data will be calculated with SAS for the PK analysis set. Summary statistics will be calculated for concentration at each individual time point and for the PK parameter.

Concentration data will be summarized by group using the following statistics: number of observations (n), number of missing subjects (NMiss), number of subjects below the LLOQ (LLOQ [N]), arithmetic mean (mean), SD, minimum (min), median, maximum (max), 5^{th} and 95^{th} percentiles (5% and 95%). Pharmacokinetic parameter will be summarized using these same statistics, as well as geometric mean and geometric CV%.

C_{trough} will be displayed graphically and summarized descriptively by week to assess for steady state.

OpSCF serum concentration at planned visit will be summarized for ADA evaluable subjects, ADA positive subjects, and ADA negative subjects.

7 EXPLORATORY ANALYSIS

7.1 Immunogenicity Analysis

7.1.1 ADA Definitions

The following definitions will be used in the immunogenicity analyses.

For any ADA sample, if ADA is confirmed positive, it is is considered as ADA positive; ADA negative otherwise. ADA evaluable subject: A subject with at least one sample taken after drug administration during the treatment period that is appropriate for ADA testing (with reportable result).

For any given subject, incidence of anti-drug antibody (treatment emergent) to OPSCFis defined when a subject was 1) anti-drug antibody negative or missing assessment at baseline (prior to the first OPSCFdose) and became anti-drug antibody positive at one or more time points post baseline; or 2) anti-drug antibody positive at baseline and showed a 4-fold or greater increase in titer values relative to baseline.

7.1.2 ADA Analysis

Presence of ADA to OpSCF in subjects receiving the active treatment during Placebo-Controlled Period (Day 1 and Weeks 2, 4, 6, 8, 12, and 16) and the OLE Period (at Weeks 24, 32, 40, and 48) will be summarized for the immunogenicity analysis set.

Time since last OpSCF Dose (in weeks) at planned visits will be summarized by treatment.

Immunogenicity assessments against OpSCF over study duration 0-16 weeks and 0-48 Weeks will be summarized by treatment. The summary tables will include ADA evaluable subjects.

Immunogenicity assessments against OPSCF at planned visits will be summarized by immunogenicity status. The summary tables will include ADA evaluable subjects.

The time course of ADA titer development in ADA incidence (treatment-emergent) subjects will be summarized.

Listing of overview of the subject level drug serum concentration and ADA information and listing of any positive ADA in placebo-treated subjects will be provided.

8 INTERIM ANALYSES AND DATA SAFETY MONITORING

PK and ADA analyses specified in this SAP will be performed as part of the planned defined interim analysis outlined in the protocol for the primary efficacy analysis and at the time of unblinding.

9 GENERAL INFORMATION RELATED TO DATA PRESENTATIONS

The formats and layouts of TFLs are provided in a separate document as common displays. Their numbering and general content follow the International Conference on Harmonisation (ICH) E3 guidelines. Actual formats and layouts may be altered slightly from those presented as necessary to accommodate actual data or statistics.

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