Statistical Analysis Plan

Stride

Protocol Title:	A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of ESK-001 in Patients with Moderate to Severe Plaque Psoriasis
Protocol Number:	ESK-001-006
Protocol Version/Date:	Version 3.0, 09 August 2022 Version 3.1 CZ, 10 January 2023
Investigational Product:	ESK-001
Study Phase:	Phase 2
Sponsor Name:	Alumis Inc.
Legal Registered Address:	611 Gateway Blvd, Suite 820 South San Francisco, CA 94080, United States
SAP Version/Date:	Version 1.0, 20 July 2023
NCT Number:	NCT05600036

SIGNATURE PAGE

Protocol Number: ESK-001-006

Protocol Title: A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of ESK-001 in Patients with Moderate to Severe Plaque Psoriasis

SAP Version: Version 1.0

Date: 20JUL2023

Name, Title, Function	Signature	Date
[redacted]		
[redacted]		
[redacted]		
[redacted]		

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BID	twice per day (bis in die)
BMI	body mass index
BP	blood pressure
bpm	beats per minute
BSA	body surface area
C_{max}	maximum plasma concentration
COVID-19	coronavirus disease 2019
CRO	clinical research organization
CYP	cytochrome P450
DILI	drug-induced liver injury
DLQI	Dermatology Life Quality Index
ECG	electrocardiogram
eCRF	electronic case report form
EOS	end of study
EQ-5D	Standardized measure of health-related quality of life developed by the EuroQol Group
EQ-5D-5L	Standard layout for recording an adult person's current self-reported health state. Consists of a standard format for respondents to record their health state according to the EQ-5D-5L descriptive system and the EQ VAS
ET	early termination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ICH	International Council for Harmonisation
IFN	interferon
IL	interleukin
IxRS	interactive voice/web response system
JAK	Janus kinase

Abbreviation	Definition
MedDRA	Medical Dictionary for Regulatory Activities
NOAEL	no-observed-adverse-effect level
NRS	Pruritus numerical rating scale
PASI	Psoriasis Area and Severity Index
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PRO	patient-reported outcomes
QD	once per day (quaque die)
QOL	quality of life
QTc	QT interval corrected for heart rate
RNA-seq	RNA sequencing
ROW	Rest of world
SAE	serious adverse event
SMC	safety monitoring committee
SOA	Schedule of Assessments
sPGA	static Physician's Global Assessment
STAT	signal transducers and activators of transcription
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
Th	T helper
TYK2	tyrosine kinase 2
ULN	upper level of normal
US	United States
WHO	World Health Organization
WOCBP	women of childbearing potential

1 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the procedures and the statistical methods that will be used to analyze and report results for the clinical study ESK-001-006 Protocol Version 3.0 (Dated 09Aug2022). The SAP will be finalized prior to study unblinding and database lock for the clinical study report (CSR). Biomarker analysis defined in the biomarker-related exploratory objectives in the protocol is not included as part of the scope of the CSR (with the exception of T/B/NK cell counts as described in Section 10) and therefore will not be defined in this SAP. The analysis plan for these exploratory objectives will be detailed in a separate SAP authored by Precision Immunology at Alumis.

2 STUDY OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To compare the Psoriasis Area and Severity Index (PASI-75) between doses of ESK-001 and placebo after 12 weeks of treatment	• Proportion of patients with moderate to severe psoriasis achieving ≥75% reduction in PASI score at 12 weeks between doses of ESK-001 and placebo
Secondary	
• To assess the safety and tolerability of ESK-001 dose in moderate to severe psoriasis patients	• Incidence of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs)
• To characterize the pharmacokinetics (PK) of ESK-001	• Plasma concentrations and PK parameters of ESK-001
• To assess the response rate in static Physician's Global Assessment (sPGA) score after 12 weeks of treatment	• Proportion of patients achieving an sPGA score of "0" ("cleared") or "1" ("minimal") after 12 weeks of ESK-001 treatment compared with placebo
• To assess the response rate in PASI-50, 90, and 100 score after 12 weeks of treatment	• Proportion of patients achieving PASI-50, 90, and 100 after 12 weeks of ESK-001 treatment compared with placebo
• To compare the response rate in PASI-75 among ESK-001 treatments	• Proportion of patients achieving PASI-75 at 12 weeks compared among the ESK-001 treatments
• To assess the effect on body surface area (%BSA) involved with psoriasis after 12 weeks of treatment	• Change from baseline in %BSA after 12 weeks of ESK-001 treatment compared with placebo
• To assess the change in Dermatology Life Quality Index (DLQI)	• Change from baseline in DLQI at Week 12 in ESK-001 compared with placebo
Exploratory	
• To assess the change in pruritus numerical rating scale (NRS) after 12 weeks of treatment	• Change from baseline in NRS score after 12 weeks of ESK-001 treatment compared with placebo
• To assess the change in EQ-5D	• Change from baseline in EQ-5D at Week 12 in ESK-001 compared with placebo
• To assess the change in psoriasis and TYK2-related skin-based biomarkers with ESK-001 treatment	• Change from baseline in psoriasis and TYK2-related skin biomarkers in response to ESK-001 treatment

Objectives	Endpoints
• To assess the change in psoriasis and TYK2-related blood-based biomarkers with ESK-001 treatment	• Change from baseline in psoriasis and TYK2-related blood-based biomarkers in response to ESK-001 treatment
• To assess the change in transcriptomic- and proteomic-based biomarkers in blood and skin with ESK-001 treatment	• Change from baseline in transcriptomic and proteomic expression in response to ESK-001 treatment

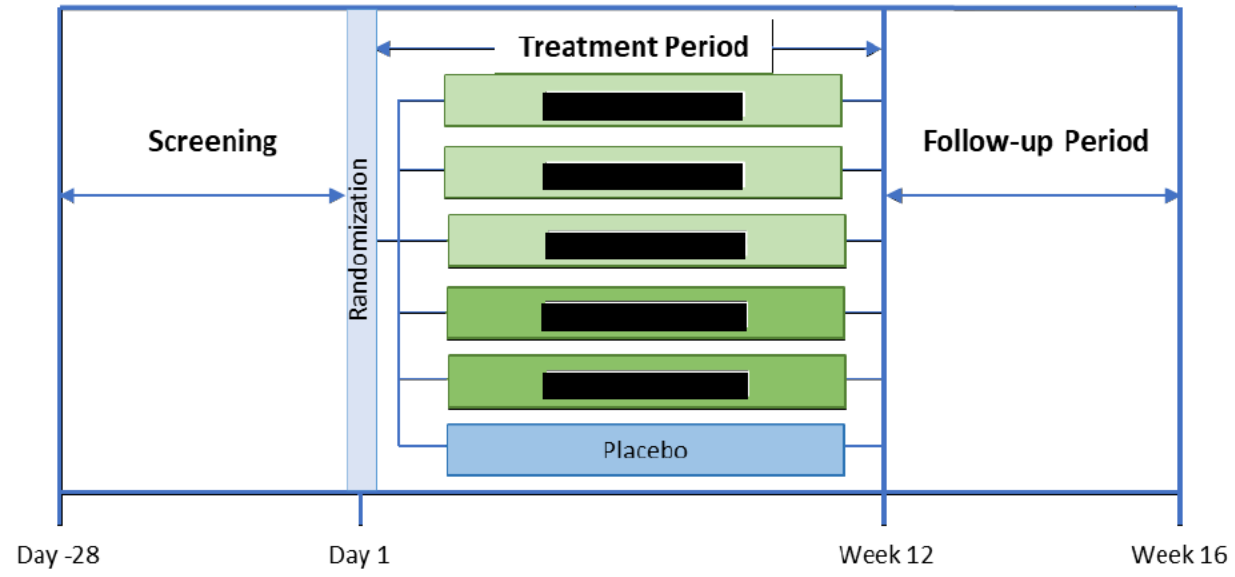
3 STUDY DESIGN

This is a randomized, double-blind, placebo-controlled study in patients with moderate to severe psoriasis. The purpose of this study is to assess the clinical efficacy, safety, and PK of ESK-001 compared to placebo in patients with moderate to severe psoriasis.

Study details include:

- Overall study duration will be approximately 20 weeks.
- The treatment period will be 12 weeks with a 4-week safety follow-up period.
- Study will be conducted at approximately 65 sites in North America and Europe.
- Study size is planned for a total of approximately 210 patients randomized across 6 study arms (5 assigned to ESK-001 and 1 assigned to placebo).
- Efficacy (including PASI, sPGA, QoL measures), safety, and PK will be assessed.
- Exploratory PD assessments include blood- and skin-based RNA, proteomic, and other molecular markers
- Patients completing the study will be eligible to enter an open-label extension study to receive ESK-001 long term (if all extension study entry criteria are met).

Figure 1 Study Schema

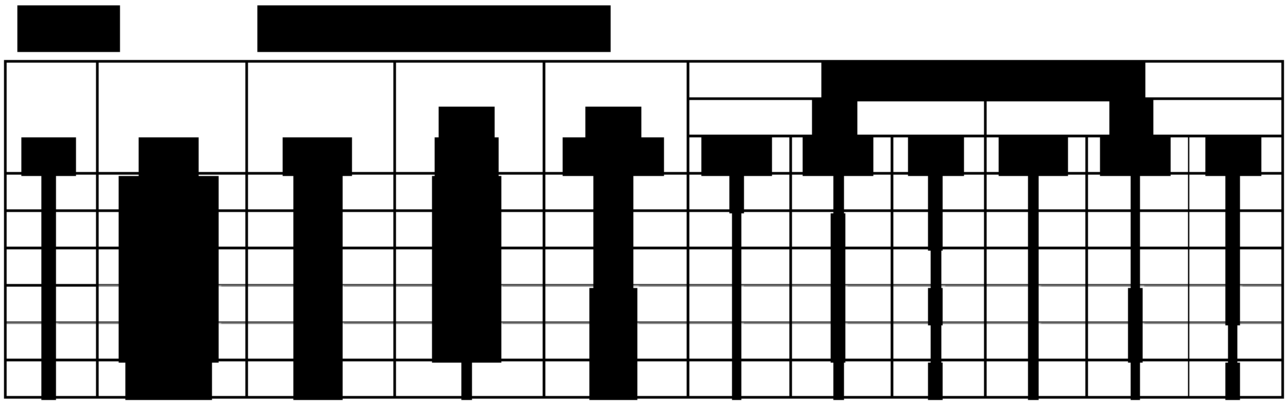


All screened patients are assigned unique identification numbers. Screened patients who drop out of the clinical study before randomization will retain their unique identification number.

Patients who meet the inclusion/exclusion criteria will be randomized in a 1:1:1:1:1:1 ratio to one of the 6 treatment arms (5 dose levels of ESK-001, placebo). Blister card wallets will provide blinded serial numbers for allocation using randomization through an interactive voice/web response system (IxRS) or equivalent process of distribution of the study drug throughout the duration of the study.

Randomization will be stratified by prior use of biologics (yes/no) and geographic region (North America/ROW). A permuted block randomization scheme will be used to obtain approximately a 1:1:1:1:1:1 ratio among the treatment arms within each stratum.

The ESK-001 dose levels that will be administered in each arm of the study are outlined in Table 1. Patients will take assigned blinded study drug, ESK-001 or placebo. [redacted]



Study drug assignment for each patient will not be disclosed to the Investigator, study center personnel, patients, or the Sponsor or representatives on the clinical study team. Study site personnel will remain blinded throughout the entirety of the study.

If at any time during the study a decision about a patient's medical condition requires knowledge of the treatment assignment, the study blind may be broken by the Principal Investigator, (through the IxRS), for that specific patient only. If in the opinion of the Investigator, there is no impact on patient safety, the Investigator is strongly encouraged to contact the Sponsor's Medical Monitor prior to unblinding. The reason for unblinding must be documented in the IxRS or appropriate study documentation.

The independent Safety Monitoring Committee (SMC) must be informed by the Sponsor's Medical Monitor of any case of unblinding. Additionally, the SMC may unblind individual treatment assignment for further safety evaluation at their discretion. Responsibilities of the SMC are described in Section 11.

4 DETERMINATION OF SAMPLE SIZE

The sample size is determined based on the primary efficacy endpoint. Calculations are based on a 1:1:1:1:1:1 randomization ratio (ESK-001 doses 1-5 vs. placebo) and will provide at least 99% power to detect 50% increase in the PASI-75 response rate in an active arm (i.e., 60% response rate) compared to the placebo assuming the response rate is 10% in the placebo arm. With a two-sided, two-sample test at a significance level of 0.05, a sample size of 35 patients per arm for a total of 210 patients is planned.

5 GENERAL STATISTICAL CONSIDERATIONS

The primary analysis for the efficacy endpoints will be conducted using data collected through the 12-week treatment period. Data will be cleaned and locked prior to conducting the primary analysis.

The final analysis will be conducted after all subjects have completed their Week 16 or end of study (EOS) visit and after all study data is cleaned and locked.

SAS® version 9.4 or higher will be used for statistical analyses, tabulations, and graphical presentations.

In general, descriptive summaries will be presented by treatment groups (placebo and ESK-001 dose levels) and overall, for values at each visit. The descriptive summary for continuous variables will also be provided for the change from baseline and, if appropriate, for the change from week 12 to week 16. Summaries of continuous variables will include the number of subjects (N), mean, standard deviation (SD), median, Q1, Q3, minimum, and maximum. If there are variables with highly skewed distribution (e.g. log-normal distribution), then the geometric mean and %CV will also be reported in descriptive summaries. Inferential analysis for those variables may be performed after log-transformation as deemed appropriate. Descriptive summaries for categorical variables will include the number and percentage of subjects. Unless otherwise stated, denominators for percentages will be the number of subjects in the analysis population.

Between-group comparisons will focus on the comparative performance of a single ESK-001 dose versus placebo. All statistical tests will be conducted at a 2-sided significance level of 0.05. The corresponding p-values and two-sided 95% confidence intervals will be reported.

In general, baseline is defined as the last non-missing value prior to the first dose date and time. For subjects randomized but not dosed, the last non-missing value prior to the randomization date will be used as baseline. For any additional considerations, refer to each specific data section for details.

In general, efficacy data and other non-safety data will be presented by analysis visits as defined by the analysis visit window. Data collected at unscheduled or early termination (ET) visits will also be mapped to analysis visits as defined in Appendix B. If a value does not fall within an analysis window, it will not be included in the summary analysis or comparative analysis.

However, these values will be included in data listings and SAS data sets. When more than 1 value is available within the same analysis visit, the value collected closest to the target visit day will be used for analysis. If 2 values are equidistant to a target visit day (for example, 1 value is before and the other value is after the target day), then the value from the later date will be used for analysis.

Safety lab, ECG and PK data will be summarized by the nominal visit (per protocol). Unscheduled visits will be presented in listings only.

5.1 Analysis Populations

The following analysis populations are defined in this study:

- Modified Intent-to-Treat (mITT) Population: All randomized subjects who received at least one dose of study drug, with analyses conducted according to the assigned treatment. This will be the analysis population used for the primary efficacy analysis at Week 12.
- Intent-to-treat (ITT) Population: All randomized subjects, regardless of whether they receive study drug, with analyses conducted according to the assigned treatment.
- Per-protocol (PP) Population: All subjects in the ITT population who have received at least one dose of study drug as assigned, have both baseline and at least one post-baseline PASI score, and have no important protocol deviations (IPD) which may affect key primary and secondary efficacy endpoints in the treatment period.
- Safety Analysis Population: All randomized subjects who receive at least one dose ofstudy drug with analyses conducted by actual treatment received.
- PK Analysis Population: All randomized subjects who receive at least 1 dose of ESK-001 and have at least one non-missing PK concentration with analysis conducted by actual treatment received.

5.2 Stratification Factors and Subgroups

The baseline values for the following stratification factors will be summarized using descriptive statistics:

- Prior use of biologics or JAK inhibitors (yes/no)
- Geographic region (North America /rest of world (ROW))

The assigned (IXRS) and actual stratification factors will be summarized and listed for the mis-stratified subjects. In the event which any errors are made in specifying the stratification factors for randomization, all efficacy analyses will be based on the actual classification according to the clinical database.

The following subgroups may be included in the analysis of safety and/or efficacy data.

- BSA involvement (10–20 %, > 20 %)
- PASI (≤ 20, > 20)
- Baseline modified sPGA score (3, 4, 5)
- Sex (Male, Female)
- Race (White, Non-white)
- Age category (< 40 years, 40–65 years, ≥ 65 years)
- Geographical region (North America, ROW)
- Baseline weight category (<90 kg, ≥ 90 kg)
- Baseline BMI category (<30 kg/m^2, ≥30 kg/ m^2)
- Prior use of psoriasis medication (yes, no)
- Prior use of systemic therapies (yes, no)
- Prior use of phototherapies (yes, no) (as collected in MH where MHTERM='Phototherapy' or 'UV light therapy')
- Prior use of biologics (yes, no)
- Prior use of JAK inhibitors (yes, no)
- Prior use of TYK 2 molecules (yes, no)
- Presence of co-morbidities (yes, no; co-morbidities considered include a history of diabetes, cardiovascular diseases, obesity, depression, hypertension, psoriatic arthritis)

5.3 Missing Data

In general, missing data will not be imputed unless specifically stated in this SAP. Refer to Section 7 on handling of missing data for responder analyses.

Handling of Missing Data:

For data collected with start and end dates such as medical history and concomitant medications, the following may be applied to missing or partial dates:

- Start Dates:

- If day is missing, then impute it to be the start of the month (eg, 01MMMYYYY); except if the month and year is equal to the first dose date month and year then impute the day to be the same day as the first dose date.
- If month is missing, then impute it to be the start of the year (eg, 01JANYYYY), except if the year is equal to the first dose date year then impute the day and month to be the same as the first dose date.
- If year is missing, then do not impute.

- End Dates:
  - If day is missing, then impute it to be the end of the month (eg, 31MMMYYYY), except if the month and year is equal to the last assessment date month and year then the day should be imputed to the last participation date day.
  - If month is missing, then impute it to be the end of the year (eg, 31DECYYYY), except if the year is equal to the last participant date year then the day and month should be imputed to the last participant date dayand month.
  - If year is missing, then do not impute.
- For all other type of dates:
  - If only day is missing, then impute it to be the start of the month (eg,01MMMYYYY).
  - If month and day are missing, then impute it to be the start of the year (eg,01JANYYYY).
  - If year is missing, then do not impute.

5.4 Multiplicity Control

No adjustments for multiplicity control will be performed in this study.

5.5 Data Handling Conventions

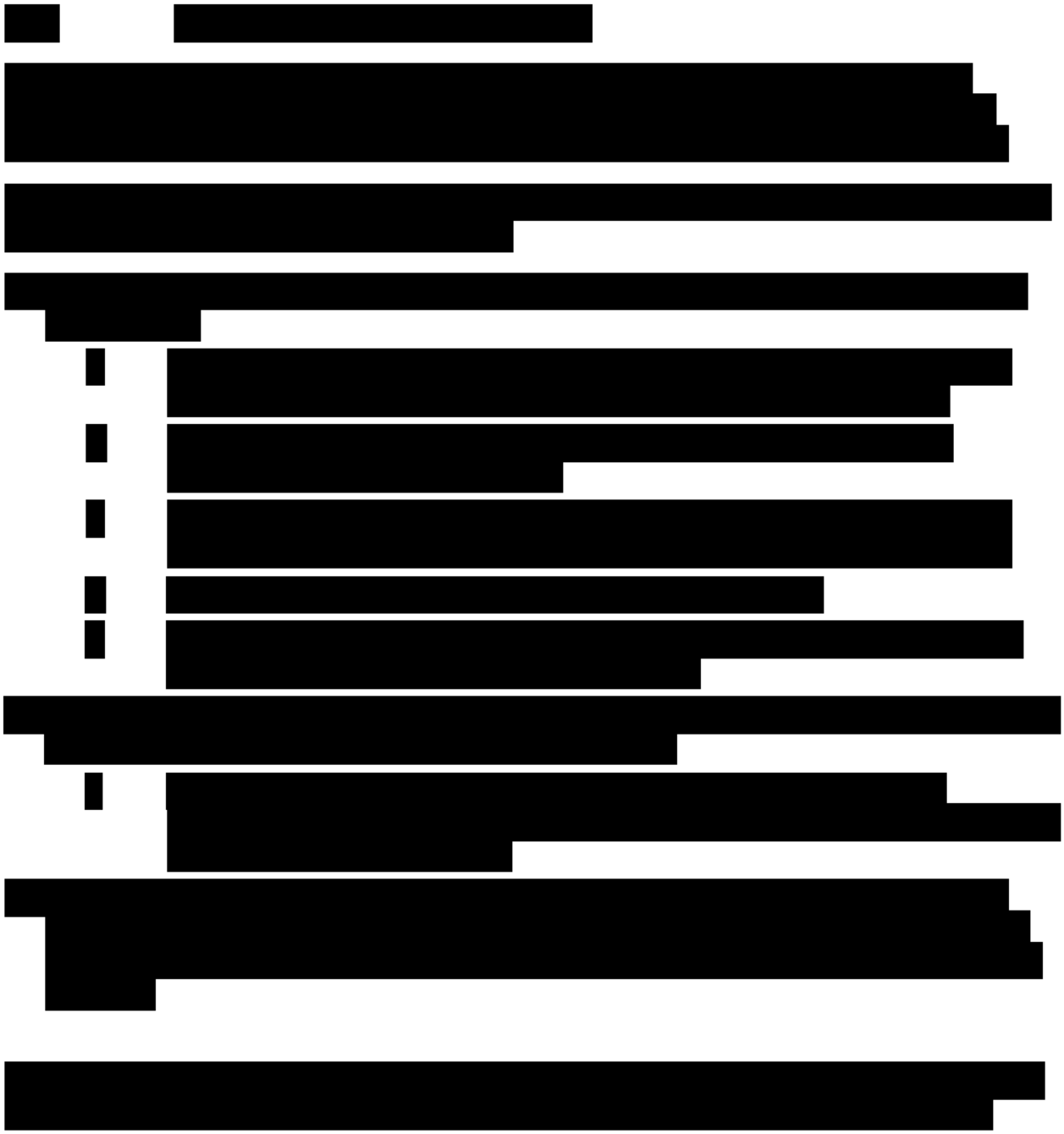
For safety laboratory data that are continuous in nature the following rules will be applied:

- If a result is less than the lower limit of quantitation (LLOQ), it will be imputed to the value of the lower limit minus 1 significant figure (e.g., if the result of the laboratory test is < 30, a value of 29 will be assigned; if the result of the laboratory test is < 30.0, then a value of 29.9 will be assigned; if the result of the laboratory test is < 1, a value of 0.9 will be assigned; if the results of the lab test is < 0.1, a value of 0.09 will be assigned).
- If a result is above the upper limit of quantitation (ULOQ), it will be imputed to the value of the upper limit plus 1 significant figure.

For PK concentration data, the following rules will be applied:

- For values below the LLOQ, 1/2 LLOQ will be imputed unless otherwise specified.

For values above the ULOQ, ULOQ + 1 unit of significant digit will be imputed unless otherwise specified.The actual reported values will be provided in by-subject listings.



6 SUBJECT DISPOSITION

The number and percentage of subjects who complete and who prematurely discontinue study drug or study, with the reasons for early discontinuation, and the stratification factors as entered in IRT will be summarized by randomized treatment assignment for the ITT Population. The number of subjects who screen-failed with reasons for screen failure will be summarized for all screened subjects. The number of randomized subjects by country and site will be summarized.

6.1 Demographics and Baseline Characteristics

Demographic and baseline characteristics including those defined in Section 5.2 will be summarized descriptively by randomized treatment assignment for the ITT Population.

Body surface area (BSA) will be derived using the Du Bois method.

6.2 Study Drug Exposure and Compliance

The extent of study drug exposure and compliance will be assessed and summarized by actual treatment received for the Safety Analysis Population.

The duration of study drug exposure will be presented in weeks and is defined as last dose date – first dose date + 1 day, regardless of intermittent interruptions. The total dose per subject will be calculated as the sum of all doses for a subject and will be presented for active study drug cohorts only.

Study drug compliance will be based on pill count and is defined as the total number of pills taken divided by the expected number of pills based on the duration of exposure.

Study drug exposure, dosage and compliance will be summarized using descriptive statistics. The frequency and percentage of participants with compliance < 80% and those with compliance > 100% will be summarized by treatment group and overall.

Drug interruptions will be summarized as collected in the Study Drug Administration CRF where any reason for study drug administration stopped other than ‘completed’ will be considered as an interruption. The duration of interruption will be calculated using the start and stop dates entered in this CRF. The number of subjects with drug interruptions and the summary

statistics for the duration of interruption (based on the maximum duration of interruption if more than one interruption per subject) will be presented.

6.3 Protocol Deviations

Prior to database lock, all protocol deviations will be reviewed and confirmed by the Sponsor. Important protocol deviations (IPD) will be identified and summarized by category and listed for the Safety Analysis Population.

International Council for Harmonisation (ICH) E3 guidance defines IPD as a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a participant's rights, safety, or well-being.

Any IPDs which impact the interpretation of key primary and secondary efficacy analyses and considered for the Per Protocol Population will be identified through the study protocol deviation review process.

The number of subjects that met IPD category of drug compliance below 80% will be programmatically derived based on calculated subject drug compliance as described in Section 6.2.

6.4 Medical History and Concomitant Procedures

Medical history terms and concomitant procedures will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 25.0. Frequency of medical history and concomitant procedures will be summarized by treatment group, SOC and PT for the Safety Analysis Population. A by subject listing will also be provided.

6.5 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the Anatomical Therapeutic Chemical (ATC) coding scheme of the World Health Organization Drug Dictionary (WHO DD Global B3 March 2022). All concomitant, prior and prior Psoriasis medications will be summarized by treatment group, ATC2 level and standardized medication name for the Safety Analysis Population. A by-subject listing will also be provided.

Prior medication is defined as medication with an end date prior to the first dose in the study and medication taken at any time during the study (ie, first dose through EOS) is considered concomitant.

Prior psoriasis medications collected on a dedicated CRF will be presented separately and will be classified as phototherapies, biologic therapies, or systemic therapies through manual review by the medical monitor.

7 EFFICACY ANALYSES

All efficacy analyses will be conducted using the mITT Analysis Population. A sensitivity analysis using the ITT or PP analysis set may be performed as appropriate.

The primary and secondary endpoints are based on the efficacy response at the end of treatment (ie. Week 12).

In general, for responder type analyses, the difference in the proportion of subjects between two treatment arms at Week 12 or other timepoints (eg. Week 4, 8, if applicable) and the corresponding two-sided 95% CI will be calculated using the Fisher's exact test or the Chi-squared test depending on the number of observations (if cell counts are less than 5 then use Fisher's). A test of significance for the difference in proportion between two treatment groups will be performed using the Cochran Mantel-Haenszel (CMH) test adjusting for randomization stratification factors and the corresponding two-sided p-value will be presented.

A non-responder imputation will be applied to responder analyses in which subjects who drop out of the study before Week 12 will be considered as a non-responder at the week 12 visit. No imputation will be applied at any other post-baseline visits. [redacted]

For continuous efficacy measurements or scores, the treatment difference in the change from baseline between each active treatment and placebo will be compared using an ANCOVA model, with treatment group, visit and randomization stratification factors as fixed effects and baseline measure as a covariate. An unstructured covariance matrix will be used to model the correlation among repeated measurements (if convergence issues are encountered then compound symmetry covariance matrix will be used instead). Within-group least-squares (LS) means, standard errors (SEs), 2-sided 95% CIs, and p-values will be presented for Week 12 and other timepoints, if applicable.

Some efficacy analyses may also be presented by select subgroups of interest such as baseline PASI, age, BMI, race, gender and prior biologic use categories (refer to Section 5.2). However, given the small sample size, test for statistical significance will not be conducted for subgroup analyses.

[redacted]

7.1 Primary Efficacy Analyses

7.1.1 Psoriasis Area and Severity Index

Disease activity will be assessed by the Psoriasis Area and Severity Index (PASI) which derives a score for the severity of psoriatic lesions by evaluating erythema, induration, and scaling in each of 4 body regions, as detailed in Appendix C.

The primary endpoint is the proportion of subjects achieving >=75% reduction in PASI score (PASI-75) at Week 12.

The proportion of subjects achieving PASI-75 will be summarized for each post-dose timepoint by treatment group. The primary efficacy analysis will compare the proportion of subjects achieving PASI-75 at Week 12 between each active treatment and placebo using the CMH method as described in Section 7. This analysis will be repeated at Weeks 4 and 8.

The absolute value, change and percent change from baseline in PASI score will be summarized using descriptive statistics by timepoint and treatment group. Additionally, the difference in the change from baseline between each active treatment and placebo will be assessed using ANCOVA model as described in Section 7. The analysis will be repeated with percent change from baseline as the dependent variable. Estimates of least-squares (LS) means, SEs, 2-sided 95% CIs and p-values will be presented by treatment group for Weeks 4, 8 and 12.

Absolute PASI scores and the proportion of subjects achieving PASI-75, PASI-90, PASI-100, PASI-50 will also be plotted over time by treatment. The proportion of subjects achieving PASI-50, PASI-75, PASI-90 and PASI-100 at Week 12 by treatment will be presented using a bar chart. The percent reduction in PASI at Week 12 for each individual subject will be presented by waterfall plot. Each treatment group will be presented on a separate plot.

7.2 Secondary Efficacy Analyses

7.2.1 Psoriasis Area and Severity Index

To compare the proportion of subjects achieving PASI-75 at 12 weeks among the active treatment groups, the adjusted treatment difference, its associated 95% CI, and two-sided p-value will be presented for all 1:1 treatment comparison using the CMH method.

Time to achievement of each PASI endpoint will also be summarized using descriptive statistics and Kaplan-Meier curves .

7.3 Psoriasis Body Surface Area

Measurement of psoriasis body surface area (BSA) involvement is a continuous variable and estimated using the handprint method with the size of a patient's handprint representing ~1% of body surface area involved.

The absolute value and change from baseline in %BSA will be summarized using descriptive statistics by timepoint and treatment group. The absolute value and change from baseline in %BSA will be summarized using descriptive statistics by timepoint and treatment group. Additionally, the difference in the change from baseline between each active treatment and placebo will be assessed using ANCOVA model as described in Section 7. Estimates of least-squares (LS) means, SEs, 2-sided 95% CIs and p-values will be presented by treatment group for Weeks 4, 8 and 12. The absolute value and change from baseline in %BSA over time will be plotted by treatment.

7.4 Physician's Global Assessment

Efficacy will also be assessed by the static Physician's Global Assessment (sPGA) and the scoring system is presented in Appendix D. The frequency and percentage of subjects for each discrete sPGA score (0 through 5) will be summarized by timepoint and treatment group. The proportion of subjects who achieve a sPGA response (defined as sPGA score of "0" ("cleared") or "1" ("minimal")) will be summarized for each post-dose timepoint by treatment group. The adjusted treatment difference in proportion of subjects with a sPGA response of 0 or 1 for each active treatment compared to placebo, its associated 95% CI, and two-sided p-value will be presented for Week 4, 8 and 12 using the CMH method.

Bar charts of the proportion of subjects with the following sPGA scores will be plotted by treatment for each visit: 0, 0/1, 1, 2, 3, 4, 5.

7.5 Patient-Reported Outcomes

Quality of life (QoL) will be assessed by the following patient-reported outcomes (PRO): the Dermatology Life Quality Index (DLQI), the EQ-5D-5L, and the pruritus numerical rating scale (NRS). The two questions collected in NRS questionnaire will be assessed separated as the average itch within the past 24 hours and the worst itch within the past 24 hours. Since the EQ-5D-5L value sets used to calculate the index score are country-specific and there currently are none available for Czech Republic where some subjects are enrolled in this study, the value set for Poland will be used instead as the closest Eastern European country with available scoring instrument.

DLQI score, NRS average and worst itch scores, and the EQ-5D-5L index score are continuous variables, and the absolute value, change and percent change from baseline in each PRO assessment will be summarized using descriptive statistics by timepoint and treatment group. The absolute value, change and percent from baseline for each PRO measure will be summarized using descriptive statistics by timepoint and treatment group. Additionally, the difference in the change from baseline between each active treatment and placebo will be assessed using ANCOVA model as described in Section 7. The analysis will be repeated with percent change from baseline as the dependent variable. Estimates of least-squares (LS) means, SEs, 2-sided 95% CIs and p-values will be presented by treatment group for Weeks 4, 8 and 12. The absolute value over time will be plotted by treatment for the EQ-5D-5L index score, the DLQI score, the NRS average itch and worst itch scores.

Additionally, a responder analysis will be conducted for DLQI where a responder is defined as the subject who achieved a post-baseline score of 0 or 1.

A responder analysis will also be conducted for NRS questionnaire where a responder is defined as a subject who has achieved a post-baseline itch score of < 4.

8 SAFETY ANALYSES

All safety analyses will be performed on the Safety Analysis Population and will be presented by each treatment group and the combined active treatment. In general safety data will be presented by descriptive statistics only and by nominal visit (if applicable). Safety data collected on unscheduled visits will be presented in listings only.

The treatment emergent period is defined as first dose through the end of study for subjects who complete the full treatment period of 12 weeks. If a subject discontinues study drug early, then the treatment emergent period will be first dose through four weeks after last dose.

8.1 Adverse Events

AEs will be coded to MedDRA version 25.0. AEs will be presented by SOC and PT, unless otherwise noted, in order of descending frequency on the overall total, and multiple occurrences of the same event in the same participant will be counted only once in the tables.

The following summaries of AEs will be provided:

- Overall summary of TEAEs
- All TEAEs
- Study drug related TEAE
- TEAEs by severity
- Grade 3 or higher TEAE
- Serious TEAEs (SAEs)
- Study drug-related SAEs
- TEAE leading to treatment discontinuation
- TEAE leading to death

By-subject listings of all AEs, SAEs, TEAEs leading to treatment discontinuation, TEAE leading to death will also be provided.

8.2 12-lead Electrocardiogram

12-lead electrocardiogram (ECG) data will be measured and read by local and central laboratory, and will be summarized for all subjects in the Safety Analysis Population.

8.2.1 ECG Numeric Variables

HR, PR, QRS, and Fridericia-corrected QT (QTcF) interval based on central ECG read and changes from baseline will be summarized by treatment group using descriptive statistics. The change from baseline of these ECG parameters at each time point will be listed for each subject.

8.2.2 Categorical Analysis

The number and percentage of subjects with maximum treatment-emergent post-dose QTcF values based on central ECG read in the following mutually exclusive categories will be summarized by treatment group: > 450 msec, > 480 msec, >500 msec, > 520 msec, and >550 msec. The number and percentage of subjects with maximum post-dose QTcF increase from baseline of > 30 msec and > 60 msec (mutually exclusive) will be summarized by treatment group.

Clinical significance will be summarized by treatment group and overall for the local and central ECG reads separately.

8.3 Safety Laboratory Data

Safety laboratory data and change from baseline will be summarized by treatment group and visit using descriptive statistics.

Laboratory parameters that are graded in CTCAE Version 4.03 will be summarized by CTCAE grade. In the summary of laboratory parameters by CTCAE grade, for parameters with CTCAE grading in both high and low direction (e.g., calcium, glucose, magnesium, potassium, sodium), CTCAE in high and low directions will be summarized separately. Subjects with treatment-emergent laboratory abnormalities of Grade 3 or higher will also be summarized. Shift from baseline to the worst post-baseline CTC grade of Grade 3 or higher will also be presented for select laboratory tests of interest including neutrophils, platelets, hemoglobin, creatine kinase, AST, ALT, total bilirubin, triglycerides, and cholesterol.

Absolute values over time will also be plotted for select laboratory tests of interest including neutrophils, platelets, hemoglobin, creatine kinase, AST, ALT, total bilirubin, triglycerides, and cholesterol. Listings of laboratory values will be generated and the results that are out of the reference range will be flagged.

8.3.1 Potential Drug-induced Liver Injury

The liver function tests, namely alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and total bilirubin (TBL) are used to assess possible drug - induced liver injury (DILI).

A graph of distribution of peak values of ALT versus peak values of TBL will be presented. ALT and TBL values will be presented on a logarithmic scale. The graph will be divided into

4 quadrants with a vertical line corresponding to 3 × the upper limit of normal (ULN) for ALT and a horizontal line corresponding to 2 × ULN for TBL.

The number and percentage of subjects with elevated liver function tests (based on safety laboratory data) during the TEAE period will be summarized by categories of elevation (>3 × ULN, > 5 × ULN, > 10 × ULN, > 20 × ULN for ALT and AST, > 1.5 × ULN for ALP, and > 1.5 × ULN and > 2 × ULN for TBL), along with the following categories of normalization (i.e. return to ≤ 1 × ULN, or return to baseline if baseline > ULN): never normalized, normalized after permanent discontinuation of study drug, normalized during treatment period and elevated after permanent discontinuation of study drug. Potential Hy's law cases will be investigated by summarizing the number of subjects with elevated ALT or AST (> 3 x ULN), elevated ALP (> 2 x ULN) and elevated total bilirubin (> 2 x ULN) where transaminase elevation coincides with or precedes BILI elevation.

8.4 Vital Signs

Vital signs, including heart rate (HR), systolic blood pressure, and diastolic blood pressure, values and changes from baseline will be summarized by treatment group and visit using descriptive statistics, and listed by subject.

8.5 Other Safety Data

Abnormal physical examination results will be listed by subject and clinical significance.

9 PHARMACOKINETIC ANALYSES

9.1 PK Concentration

ESK-001 and two metabolites' concentration values will be summarized with descriptive statistics by timepoint and treatment group, where available, using the PK analysis population. ESK-001 and metabolite concentration-time plots will also be presented.

Boxplots of PK concentration by treatment and timepoint will also be presented for each analyte.

Population PK analyses will be conducted and summarized in a separate report.

10 PHARMACODYNAMIC ANALYSES

T/B/NK cell counts will be summarized descriptively by treatment group and visit, and subject level data will be presented in a listing.

All other pharmacodynamic PD/biomarker endpoints are outside the scope of this SAP and will not be described and reported in a separate analysis plan and report.

11 INTERIM ANALYSIS

No formal interim analysis is planned for this study. Week 12 analysis is the primary analysis to evaluate the efficacy, and week 16 analysis is the safety follow up analysis. Prior to study database lock, the unblinded Week 12 data and analyses will only be reviewed by a select group of individuals who are not directly involved in the study as documented in the study unblinding list governed by SOP-053 Unblinding Events and Procedures.

Per protocol, routine interim safety monitoring during the trial will be conducted by an independent Safety Monitoring Committee (SMC). Based on review of the safety data, the SMC will make recommendation to continue the trial as is or to make modifications to the trial or stop the trial. Details regarding the membership of the SMC, its conduct, frequency of the review of safety data and the scope of the data review are described in the SMC Charter.

12 SUMMARY OF CHANGES FROM PROTOCOL-DEFINED ANALYSES

[redacted]

APPENDIX A SCHEDULE OF ASSESSMENTS

Procedure	Screening	Treatment Period (Weeks)							ET	Safety Follow-up (Weeks)	
			1	2	4	8	12	US		14	16/EOS
Timing of Visit (Days)	-28 to -1	1	8	15	29	57	84	-	-	98	115
Visit Window (Days)	28 to -1		±1	±1	±3	±3	±3	-	-	±3	±3
Informed consent	X										
Inclusion and exclusion criteria	X	X									
Vital signs	X	X	X	X	X	X	X	X	X	X	X
Physical examination [A]	X	X	X	X	X	X	X	X	X	X	X
Medical history	X	X							X		
Pregnancy test (WOCBP only) [B]	X	X			X	X	X	X	X		X
FSH (postmenopausal women only) [C]	X										
HIV, HBV, HCV screening	X										
QuantiFERON TB test [D]	X										
Coagulation	X										
Complete blood count	X	X		X	X	X	X	X	X		X
Serum chemistry	X	X		X	X	X	X	X	X		X
Fasting lipid panel		X				X					X
Immunoglobulin levels (total)		X [E]			X	X	X				X
12-lead ECG	X	X [E]		X	X	X	X	X	X		X
Urinalysis	X	X			X		X		X		X
DNA sample [F]		X									

Procedure	Screening	Treatment Period (Weeks)							ET	Safety Follow-up (Weeks)	
			1	2	4	8	12	US		14	16/EOS
Timing of Visit (Days)	-28 to -1	1	8	15	29	57	84	-	-	98	115
Visit Window (Days)	28 to -1		±1	±1	±3	±3	±3	-	-	±3	±3
Study drug administration at site [G]		X			X	X	X				
Study drug dispensing [H]		X			X	X					
AE/con-med review	X	X	X	X	X	X	X	X	X	X	X
Disease activity skin assessments [I]	X	X	X	X	X	X	X	X	X	X	X
PRO [J]		X		X	X	X	X		X		X
PD/biomarkers Skin biopsy and tape stripping [F,K]		X					X				
Plasma biomarker profile [L]		X [E]		X	X	X	X		X		X
Blood RNA-seq profile [M]		X [E]		X	X	X	X		X		X
Blood cell-based PD biomarkers [N,O]		X			X	X	X			X	
T/B/NK counts		X [E]			X	X	X				X
PK blood sampling [P]		X			X	X	X		X [Q]	X	

Footnotes

EOS = end of study; ET = early termination; US = unscheduled visit

A. Full physical examination at Screening and Day 1; abbreviated physical examination symptom driven at all other visits.
B. Serum pregnancy test at Screening; urine pregnancy test at other indicated visits.
C. Menopause is defined as absence of menses for 12 consecutive months.
D. QuantiFERON TB tests should not be performed within 4 weeks of COVID-19 mRNA vaccinations or boosters. If a patients test result is indeterminate it may be retested one time. If both tests are indeterminate the patient will be considered a screen fail.
E. Predose
F. Optional, collected only if patient provides specific consent.

G. Administration of the visit day dose of study drug by the site staff. Patients should be reminded to bring their study drug with them to the clinic and take their dose when instructed by the site staff. Randomization occurs prior to first administration of study drug on Day 1.
H. Dispense sufficient study drug to last until the next study visit
I. Includes PASI, BSA and sPGA
J. Patient reported outcomes (DLQI, EQ-5D and NRS)
K. Lesional and nonlesional samples; predose on Day 1
L. Biomarker panel, exploratory proteomics
M. Exploratory transcriptomics
N. To be conducted at selected study sites. Fresh blood needs to be collected and cell assays conducted on the day of collection.
O. PD Samples for patients will be collected on Day 1 and Week 8 predose and 2 hours (±15 min) and 4 hours (±15 min) postdose. At Week 4 and 12 patients will take their dose in the clinic and a PD sample will be collected predose. A random sample will be taken at Week 14.
P. PK Samples for patients will be collected on Day 1 and Week 8 predose and 30 minutes (±5 min), 1 hour (±5 min), 2 hours (±15 min) and 4 hours (±15 min) postdose in a fasted condition. Patients may have a snack between the 2- and 4-hour draw. At Week 4 and 12 patients will take their dose in the clinic and a PK sample will be collected predose. A random sample will be taken at Week 14.
Q. Collected if the ET visit is within 14 weeks of the initiation of study drug treatment.

APPENDIX B ANALYSIS VISITS

The following analysis windows will be used to define the analysis visits for each study assessment type.

Table 2 Analysis Visits for Disease Activity Skin Assessments

Analysis Visit	Target Day	Visit Window (Days)
Baseline	1	Screening – Day 1
Week 1	8	2 – 11
Week 2	15	12 – 21
Week 4	29	22 – 42
Week 8	57	43 – 70
Week 12	85	71 – 91
Week 14	99	92 – 105
Week 16	113	105 – 126

Table 3 Analysis Visits for Patient Reported Outcomes

Analysis Visit	Target Day	Visit Window (Days)
Baseline	1	Screening – Day 1
Week 2	15	2 – 21
Week 4	29	22 – 42
Week 8	57	43 – 70
Week 12	85	71 – 98
Week 16	113	99 – 126

APPENDIX C PSORIASIS AREA AND SEVERITY INDEX (PASI)

The PASI is a grading system used for the evaluation of the severity of psoriatic lesions and their response to treatment. The PASI produces a numeric score that can range from 0 to 72. The severity of a subject's disease is calculated as described below:

The body is divided into 4 regions for determining total body surface area (BSA):

- the head (h), trunk (t), upper extremities (ux) and lower extremities (lx),
- which account for 10% (0.1), 30% (0.3), 20% (0.2), and 40% (0.4) respectively of BSA

Each of these areas are evaluated for erythema (E), induration (I) and scaling (S), which are rated on a scale from 0 to 4.

The scoring system for the signs of disease (erythema, induration and scaling) is below:

0 = none
1 = slight
2 = moderate
3 = severe
4 = very severe

The scoring system for estimating the area (A) of involvement for psoriatic lesions is outlined below:

0 = no involvement
1 = 1% to 9% involvement
2 = 10% to 29% involvement
3 = 30% to 49% involvement
4 = 50% to 69% involvement
5 = 70% to 89% involvement
6 = 90% to 100% involvement

To aid in the area assessments, the following conventions are followed:

a. the neck is considered part of the head

b. the axilla and groin are considered part of the trunk
c. the buttocks are considered part of the lower extremities

The PASI formula is:

$$PASI = 0.1(E_h + S_h + I_h)A_h + 0.3(E_t + S_t + I_t)At + 0.2(E_{ux} + S_{ux} + I_{ux})A_{ux} + 0.4(E_{lx} + S_{lx} + I_{lx})A_{lx}$$

Clinical assessments of response should be performed by the same assessor(s).

APPENDIX D STATIC PHYSICIAN'S GLOBAL ASSESSMENT (SPGA)

The Physician Global Assessment (PGA) is used to determine the subject's psoriasis lesions overall at a given time point. Overall lesions will be graded for induration, erythema, and scaling based on the scales below. The sum of the 3 scales will be divided by 3 to obtain a final PGA score.

Induration (I) (averaged over all lesions; use the National Psoriasis Foundation Reference card for measurement)

0 = no evidence of plaque elevation

1 = minimal plaque elevation, = 0.25 mm

2 = mild plaque elevation, = 0.5 mm

3 = moderate plaque elevation, = 0.75 mm

4 = marked plaque elevation, = 1 mm

5 = severe plaque elevation, = 1.25 mm or more

Erythema (E) (averaged over all lesions)

0 = no evidence of erythema, hyperpigmentation may be present

1 = faint erythema

2 = light red coloration

3 = moderate red coloration 4 = bright red coloration

5 = dusky to deep red coloration

Scaling (S) (averaged over all lesions)

0 = no evidence of scaling

1 = minimal; occasional fine scale over less than 5% of the lesion

2 = mild; fine scale dominates

3 = moderate; coarse scale predominates

4 = marked; thick, nontenacious scale dominates

5 = severe; very thick tenacious scale predominates

Add I + E + S / 3 = (Total Average)

Physician's Static Global Assessment based upon above Total Average

0 = Cleared, except for residual discoloration

1 = Minimal - majority of lesions have individual scores for I + E + S / 3 that averages 1

2 = Mild - majority of lesions have individual scores for I + E + S / 3 that averages 2

3 = Moderate - majority of lesions have individual scores for I + E + S / 3 that averages 3

4 = Marked - majority of lesions have individual scores for I + E + S / 3 that averages 4

5 = Severe - majority of lesions have individual scores for I + E + S / 3 that averages 5

Note: Scores should be rounded to the nearest whole number. If total ≤ 1.49, score = 1; if total ≥ 1.50, score = 2.