TITLE PAGE

Clinical Study Protocol

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
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
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Confidentiality Statement

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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
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
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IFN	interferon
IL	interleukin
IRB	Institutional Review Board
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
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. PROTOCOL SUMMARY

1.1. Protocol Synopsis

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 No.	ESK-001-006	
Sponsor:	Alumis Inc.	
Investigational Product:	ESK-001	
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 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

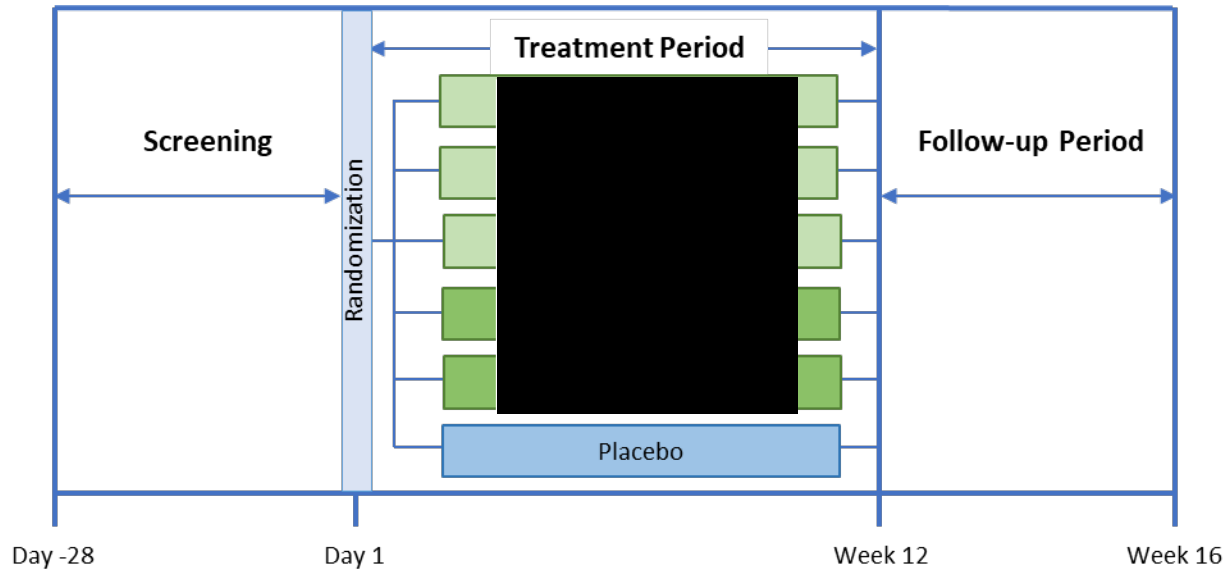
	To assess the change in psoriasis and TYK2-related skin-based biomarkers with ESK-001 treatment	Change from baseline in psoriasis and TYK2-related skin biomarkers in response to ESK-001 treatment
	To assess the change in psoriasis and TYK2-related blood-based biomarkers with ESK-001 treatment	Change from baseline in psoriasis and TYK2-related blood-based biomarkers in response to ESK-001 treatment
	To assess the change 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
Overall Design:	This is a randomized, double-blind, placebo-controlled study in patients with moderate to severe psoriasis.	
Brief Summary:	The purpose of this study is to assess the clinical efficacy, safety, PK, and PD 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. • 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. • Efficacy (including PASI, sPGA, QoL measures), safety, and PK will be assessed. • Exploratory pharmacodynamic (PD) assessments include blood- and skin-based RNA, proteomic, and other molecular markers. • Continued treatment will be offered in a separate open-label extension study.	
Treatment Arms:	Patients fulfilling all eligibility criteria will be randomized in a 1:1:1:1:1:1 manner to receive oral doses of ESK-001 at one of 5 dose levels [redacted] or placebo.	
Number of Patients:	Approximately 210 patients will be randomly assigned to one of the 6 study arms (35 patients per arm).	
Study Duration:	The total duration of study participation for each patient will be approximately 20 weeks. The study includes a screening period of approximately 4 weeks. The treatment period of 12 weeks is followed by a safety follow-up period of 4 weeks. Eligible patients may participate in an open-label extension study following completion of the End-of-Study Visit at Week 16.	
Safety Monitoring Committee:	A safety monitoring committee (SMC) comprising representatives from the Sponsor, clinical research organization (CRO), two independent physicians and a statistician will be utilized in this study.	
Study Population	Inclusion Criteria: 1. Able and willing to provide signed informed consent to participate in this study 2. Males or females, age 18-75 years, inclusive, at the Screening Visit 3. Total body weight >40 kg (88 lb) 4. Diagnosis of plaque psoriasis for ≥6 months 5. Plaques covering ≥10% of body surface area (BSA)	

	6. Psoriasis area severity index (PASI) score ≥12 and static Physician's Global Assessment (sPGA) score ≥3 7. Women of childbearing potential (WOCBP) must agree to adhere to highly effective methods of contraception for the entirety of the study and for 30 days after the last dose of study drug 8. Males who are sexually active with WOCBP must agree to use highly effective methods of contraception for the entirety of the study and for 90 days after the last dose of study drug Exclusion Criteria: 1. Diagnosis of non-plaque psoriasis (guttate, inverse, pustular, erythrodermic, drug induced) 2. Diagnosis of immune-mediated conditions that are commonly associated with psoriasis (e.g., uveitis, inflammatory bowel disease) or other inflammatory skin conditions that may interfere with the study assessment 3. Patients with psoriatic arthritis, who are receiving systemic (oral, SC, IM or IV) immunosuppressant medications (including corticosteroids, immunosuppressants, biologics) or who has or is expected, in the opinion of the investigator, to develop unstable disease. • Patients who are receiving a stable therapeutic regimen for their psoriatic arthritis that does not include immunosuppressants (e.g., NSAIDs) may be included in the study 4. Pregnant, lactating, or planning to get pregnant during the study period 5. Has used topical medications/treatments that could affect psoriasis evaluation within 2 weeks of the first administration of study drug 6. Has received phototherapy or any systemic medications/treatments that could affect psoriasis evaluation within 4 weeks of Study Day 1 7. Has received any therapeutic agent targeted to IL-12 or IL-23 within 6 months, IL-17 within 4 months, or any TNFα inhibitor(s) within 2 months of first administration of study drug 8. Is currently receiving or has received any systemic immunosuppressants or immunomodulatory drugs (e.g., methotrexate, cyclosporine) within 4 weeks of the first administration of study drug or 5 half-lives whichever is longer 9. Has received agents that modulate B cells (e.g., rituximab, ocrelizumab) within 6 months of first administration of study drug 10. Has received agents that modulate T cells (e.g., abatacept, alemtuzumab) within 3 months of first administration of study drug 11. Has received JAK inhibitors (e.g., baricitinib, tofacitinib) or TYK2 inhibitors within 4 weeks of first administration of study drug 12. History of lack of clinical response to any therapeutic agent targeted to IL-12, IL-17 or IL-23 (e.g., ustekinumab, risankizumab, secukinumab, ixekizumab) at approved doses after at least 3 months of treatment 13. History of lack of clinical response, in the Investigator's opinion, to 2 or more biologic therapies at approved doses after at least 3 months of treatment 14. Has received any investigational agent, within 30 days or 5 half-lives (whichever is longer) of any study drug or is currently enrolled in an investigational study 15. Is currently receiving proton pump inhibitors such as omeperazole or esomeprazole. It is acceptable to substitute a histamine 2 receptor blocking drug or oral antacids prior to Study Day 1

16. Patients with QTcF >450 msec (males) or >470 msec (females) at screening
17. Unstable cardiovascular disease, defined as a recent clinical deterioration (e.g., unstable angina, rapid atrial fibrillation) or a cardiac hospitalization within the last 3 months
    - Patients requiring medications to treat underlying stable chronic cardiovascular disease, including but not limited to β-blockers, should be on a stable dose for at least 4 weeks before Study Day 1
18. Active herpes viral infection, including herpes simplex 1 and 2 and herpes zoster identified on examination and/or medical history within 2 months of administration of study drug
19. Patients with hepatitis C virus (HCV), or hepatitis B virus (HBV) or human immunodeficiency virus (HIV) or active or inadequately treated latent tuberculosis (TB) infection at screening
20. Has any of the following lab abnormalities:
    - Absolute neutrophil count <1.5 X 10^9/L
    - Hemoglobin <9 g/dL
    - AST/ALT ≥2 x upper limit of normal (ULN)
    - Albumin <3 g/dL
    - Total bilirubin ≥2 x ULN (patients with a history of Gilbert's syndrome are not eligible)
    - Glomerular filtration rate <50 (Cockcroft and Gault method)
21. History of any immune-mediated or inflammatory medical condition for which patient requires current systemic (oral, SC, IM or IV) corticosteroids
    - Stable doses of inhaled corticosteroids for treatment of asthma are allowed
22. History of serious bacterial, fungal, or viral infections that led to hospitalization and IV antibiotic treatment within 90 days prior to screening, or any recent serious infection requiring antibiotic treatment within 30 days of Study Day 1
23. Known current malignancy or current evaluation for a potential malignancy or history of malignancy within the past 5 years prior to screening, except for adequately treated basal cell skin carcinoma, carcinoma in situ of the cervix and breast ductal carcinoma in situ
24. Live vaccines (e.g., varicella, measles, mumps, rubella, cold-attenuated intranasal influenza vaccine, and bacillus Calmette-Guérin) within 4 weeks of Study Day 1
25. Patient has a known hypersensitivity to any component of the study drug
26. Patient has planned surgery during the study period
27. Any acute or chronic illness/condition or evidence of an unstable clinical condition that in the investigator's judgement will substantially increase the risk to the patient if he or she participates in the study
28. History of mental illness within the last 5 years, unless the patient fulfills one of the following conditions:
    - Receiving a fixed regimen of psychiatric medications for at least 6 months before screening and displays no sign of acute mental illness and, in the opinion of the investigator, the patient is able and safe to participate in the study
    - Has not required or been prescribed any psychiatric medication (including but not limited to antidepressants or anxiolytics) within 12

	months before screening and, in the opinion of the investigator, the patient is able and safe to participate in the study 29. Patient who, for any reason, is deemed by the investigator to be inappropriate for this study or is unable to comply with the study protocol
Statistical Considerations:	Randomization will be stratified by prior use of biologics and geographic region. Efficacy analyses will be based on the intent-to-treat (ITT) approach. All patients randomized will be included in the analysis, and subjects will be analyzed according to their randomized treatment. The primary efficacy analysis will compare the proportion of patients in the active treatment groups with ≥75% improvement in PASI at Week 12 relative to baseline to placebo using the Cochran-Mantel-Haenszel test and will be stratified by prior use of biologics and geographic region. Safety will be assessed through the summary of adverse events, serious adverse events, laboratory test results, ECG parameters, and vital signs. Safety analyses will include all subjects who receive at least one dose of either ESK-001 or placebo. Subjects will be analyzed according to the actual treatment received.

1.2. Study Schema



1.3. 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.

2. INTRODUCTION

2.1. Background

Psoriasis is a chronic inflammatory immune-mediated skin disease, characterized by abnormal epidermal growth, usually presenting as red, scaly patches, papules or plaques (plaque psoriasis). (Rendon and Schäkel, 2019). The prevalence of psoriasis in the US is approximately 2 to 3% (World Health Organization [WHO], 2016).

The pathogenesis of psoriasis is complex involving the interplay of genetic and environmental factors, resulting in a dysregulated immune response involving T helper (Th) type 1 and Th17 cells (Polese et al., 2020). Interleukin (IL)-23 and IL-12 are believed to key cytokines in the immune-pathogenesis of psoriasis. In response to the release of IL-23, activated T cells migrate from the dermis to epidermis and secrete cytokines such as IL-17, which causes proliferation of keratinocytes and the classic inflammatory lesions of psoriasis (Zeng et al., 2017). The clinical relevance of these cytokine pathways for moderate to severe psoriasis has been established by the respective FDA-approved targeted therapies including ustekinumab (anti-IL-12/23) and secukinumab(anti-IL17). The pathogenic effect of the IL-23/IL-17 axis is mediated by the Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathway (Winthrop, 2017).

The search for effective small molecules to block JAK/STAT signaling led to the discovery of tyrosine kinase 2 (TYK2) inhibitors (Nogueira, Puig et al. 2020). TYK2 signaling pathways include the central cytokines IL-12 and IL-23. Importantly, TYK2 has also been validated as a therapeutic target in psoriasis by oral TYK2 inhibitors and particularly from positive Phase 3 studies with deucravacitinib (Bristol Myers Squibb, 2021). Based on available clinical data it appears these inhibitors' specificity for TYK2 avoids the safety liabilities of JAK inhibitors. Although these findings are encouraging, considerable unmet need remains for patients with psoriasis and ESK-001 has the potential for improved efficacy and safety associated with higher target engagement and greater target specificity.

2.5. Risk-Benefit Assessment

ESK-001 is being developed as an oral treatment for moderate to severe psoriasis. Based on the mechanism of action of ESK-001, the likelihood of benefit for patients enrolled in this study is expected to be high since substantial clinical efficacy has already been demonstrated by other molecules with the same mechanism of action, i.e., inhibition of TYK2 (Papacharalambous et al., 2020; Papp et al., 2018). Furthermore, patients will be offered the opportunity to receive ESK-001 after they complete the study by enrolling in a long-term open label extension study.

Initial studies in healthy participants have demonstrated ESK-001 was tolerated well and had no safety findings of clinical concern. The nature and frequency of safety assessments in this study are guided by the safety profile of other TYK2 inhibitors being developed in psoriasis and the potential immunomodulatory effects of TYK2 inhibition. These inhibitors have been generally well tolerated and with an acceptable safety profile. Based on ESK-001's high specificity for TYK2, the safety concerns associated with JAK inhibition are considered to have been reduced. In addition, a safety monitoring committee will be convened, including a cardiologist, to oversee overall patient safety, including the potential for adverse events associated with JAK inhibition.

Taken together the overall benefit-risk assessment is favorable and supports this Phase 2 study in psoriasis patients with moderate to severe disease.

3. 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
• 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

Objectives	Endpoints
• 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

4. STUDY DESIGN

4.1. Overview

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.
- 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).

[redacted]

4.3. Order of Assessments

The following priority order will be in effect, if applicable, when more than one assessment is required at a predose and postdose time point, with PK blood sampling being performed nearest to the specified time:

1. 12-lead ECG
2. Vital signs
3. PROs (DLQI, EQ-5D, NRS)
4. Adverse Event and Concomitant Medication collection
5. Disease activity skin assessments (PASI, BSA, sPGA); physical examination
6. PK and PD/biomarkers blood sampling
7. Blood and urine sampling for safety assessments
8. Skin biopsy and skin tape stripping (if consent obtained)
9. Study drug administration by the site staff

4.4. Study Duration

The estimated study duration for each patient is approximately 20 weeks and includes:

1. The screening period: up to 4 weeks
2. Treatment period: 12 weeks
3. Safety follow-up period: 4 weeks

4.5. Study Completion

For the entire study, study completion is defined as the last visit of the last patient for any protocol related activity (last patient, last visit). For individual patients, study completion is defined as the time of the patient's last data collection.

5. STUDY POPULATION

The study population will consist of male and female adult patients with moderate to severe psoriasis. Patients must meet all the inclusion criteria and none of the exclusion criteria.

5.1. Number of Patients

Approximately 210 patients will be enrolled in the clinical study according to the inclusion/exclusion criteria. Patients who discontinue study drug or the study early for any reason may be replaced by enrollment of another patient. The Sponsor may choose, based on the evolving data (e.g., safety) from ESK-001 studies, to enroll up to 50 additional patients.

5.2. Inclusion Criteria

Patients who meet the following criteria will be considered eligible to participate in the clinical study:

1. Able and willing to provide signed informed consent to participate in this study
2. Males or females, age 18-75 years, inclusive, at the Screening Visit
3. Total body weight >40 kg (88 lb)
4. Diagnosis of plaque psoriasis for ≥6 months
5. Plaques covering ≥10% of body surface area (BSA)
6. Psoriasis area severity index (PASI) score ≥12 and static Physician's Global Assessment (sPGA) score ≥3
7. Women of childbearing potential (WOCBP) must agree to adhere to highly effective methods of contraception for the entirety of the study and for 30 days after the last dose of study drug
8. Males who are sexually active with WOCBP must agree to use highly effective methods of contraception for the entirety of the study and for 90 days after the last dose of study drug

5.3. Exclusion Criteria

Patients who meet one or more of the following criteria will be ineligible to participate in the clinical study:

1. Diagnosis of non-plaque psoriasis (guttate, inverse, pustular, erythrodermic, drug induced)
2. Diagnosis of immune-mediated conditions that are commonly associated with psoriasis (e.g., uveitis, inflammatory bowel disease) or other inflammatory skin conditions that may interfere with the study assessment
3. Patients with psoriatic arthritis who are receiving systemic (oral, SC, IM or IV) immunosuppressant medications (including corticosteroids, immunosuppressant biologics) or who has or is expected, in the opinion of the investigator, to develop unstable disease.
    - Patients who are receiving a stable therapeutic regimen for their psoriatic arthritis that does not include immunosuppressants (e.g. NSAIDs) may be included in the study

4. Pregnant, lactating, or planning to get pregnant during the study period
5. Has used topical medications/treatments that could affect psoriasis evaluation within 2 weeks of the first administration of study drug
6. Has received phototherapy or any systemic medications/treatments that could affect psoriasis evaluation within 4 weeks of Study Day 1
7. Has received any therapeutic agent targeted to: IL-12or IL-23 within 6 months, IL-17 within 4 months, or any TNFα inhibitor(s) within 2 months of first administration of study drug
8. Is currently receiving or has received any systemic immunosuppressants or immunomodulatory drugs (e.g., methotrexate, cyclosporine) within 4 weeks of the first administration of study drug or 5 half-lives whichever is longer
9. Has received agents that modulate B cells (e.g., rituximab, ocrelizumab) within 6 months of first administration of study drug
10. Has received agents that modulate T cells (e.g., abatacept, alemtuzumab) within 3 months of first administration of study drug
11. Has received JAK inhibitors (e.g., baricitinib, tofacitinib) or TYK2 inhibitors within 4 weeks of first administration of study drug
12. History of lack of clinical response to any therapeutic agent targeted to IL-12, IL-17 or IL-23 (e.g., ustekinumab, risankizumab, secukinumab, ixekizumab) at approved doses after at least 3 months of treatment
13. History of lack of clinical response, in the Investigator's opinion, to 2 or more biologic therapies at approved doses after at least 3 months of treatment
14. Has received any investigational agent, within 30 days or 5 half-lives (whichever is longer) of any study drug or is currently enrolled in an investigational study
15. Is currently receiving proton pump inhibitors such as omeperazole or esomeprazole. It is acceptable to substitute a histamine 2 receptor blocking drug or oral antacids prior to Study Day 1
16. Patients with QTcF >450 msec (males) or >470 msec (females) at screening
17. Unstable cardiovascular disease, defined as a recent clinical deterioration (e.g., unstable angina, rapid atrial fibrillation) or a cardiac hospitalization within the last 3 months
    - Patients requiring medications to treat underlying stable chronic cardiovascular disease, including but not limited to β-blockers, should be on a stable dose for at least 4 weeks before Study Day 1
18. Active herpes viral infection, including herpes simplex 1 and 2 and herpes zoster identified on examination and/or medical history within 2 months of administration of study drug

19. Patients with hepatitis C virus (HCV), or hepatitis B virus (HBV) or human immunodeficiency virus (HIV) or active or inadequately treated latent tuberculosis (TB) infection at screening
20. Has any of the following lab abnormalities:
    - Absolute neutrophil count <1.5 X 10^9/L
    - Hemoglobin <9 g/dL
    - AST/ALT ≥2 x upper limit of normal (ULN)
    - Albumin <3 g/dL
    - Total bilirubin ≥2 x ULN (patients with a history of Gilbert's syndrome are not eligible)
    - Glomerular filtration rate <50 (Cockcroft and Gault method)
21. History of any immune-mediated or inflammatory medical condition for which patient requires current systemic (oral, SC, IM or IV) corticosteroids
    - Stable doses of inhaled corticosteroids for treatment of asthma are allowed
22. History of serious bacterial, fungal, or viral infections that led to hospitalization and IV antibiotic treatment within 90 days prior to screening, or any recent serious infection requiring antibiotic treatment within 30 days of Study Day 1
23. Known current malignancy or current evaluation for a potential malignancy or history of malignancy within the past 5 years prior to screening, except for adequately treated basal cell skin carcinoma, carcinoma in situ of the cervix and breast ductal carcinoma in situ
24. Live vaccines (e.g., varicella, measles, mumps, rubella, cold-attenuated intranasal influenza vaccine, and bacillus Calmette-Guérin) within 4 weeks of Study Day 1
25. Patient has a known hypersensitivity to any component of the study drug
26. Patient has planned surgery during the study period
27. Any acute or chronic illness/condition or evidence of an unstable clinical condition that in the investigator's judgement will substantially increase the risk to the patient if he or she participates in the study
28. History of mental illness within the last 5 years, unless the patient fulfills one of the following conditions:
    - Receiving a fixed regimen of psychiatric medications for at least 6 months before screening, displays no sign of acute mental illness and, in the opinion of the investigator, the patient is able and safe to participate in the study
    - Has not required or been prescribed any psychiatric medication (including but not limited to antidepressants or anxiolytics) within 12 months before screening and, in the opinion of the investigator, the patient is able and safe to participate in the study
29. Patient who, for any reason, is deemed by the investigator to be inappropriate for this study or is unable to comply with the study protocol

5.4. Lifestyle Restrictions

5.4.1. Dietary Restrictions

Foods such as star fruit juice, Seville orange juice, and grapefruit juice that are strong to moderate inhibitors of P450 (CYP) 3A4 should be avoided.

Study drug can be taken with or without food.

5.4.2. Highly Effective Contraception

Highly effective methods of birth control are defined as those which result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly.

For female patients - WOCBP:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
    - Oral
    - Intravaginal
    - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
    - Oral
    - Injectable
    - Implantable

  Note: Hormonal contraception must be supplemented with another form of contraception that may include but is not limited to another form of highly effective contraception (e.g., IUD) or other barrier methods (such as male condom plus spermicide or female diaphragm).
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal ligation
- Vasectomized partner. Note that a vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the woman of childbearing potential trial patient and that the vasectomized partner has received medical assessment of the surgical success.
- Sexual abstinence. Sexual abstinence is considered a highly effective method only if the subject is refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.
- Same sex partner

Women who have not menstruated for at least 12 months and with follicle-stimulating hormone (FSH) levels ≥30 mIU/mL will be considered postmenopausal and will not be required to use contraception.

For male patients with a partner of childbearing potential:

Men must agree to use two acceptable methods of contraception (e.g., condom plus spermicide), at least one of which must be a barrier method for the entire duration of the study, and for 3 months following last study drug administration.

6. STUDY DRUGS AND CONCOMITANT THERAPY

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

6.4. Study Drug Accountability

The Investigator or his/her designated representatives will dispense study drug per the Schedule of Assessments (see Section 1.3).

The Investigator is responsible for the control of drugs under investigation. Adequate records of the receipt (e.g., Drug Receipt Record) and disposition (e.g., Investigation Drug Dispensing Log) of the study drug must be maintained. The Investigation Drug Dispensing Log must be kept current and should contain the following information:

- The identification (ID) if the patient to whom the study drug was dispensed (that is, patient ID number and year of birth)
- The date(s), quantity, and lot number(s) of the study drug dispensed to the patient
- The ID of the person who dispense the study drug

All used and unused drug supplies must be returned by the patient at every visit.

All records and used and unused drug supplies must be available for inspection by the study monitor at every monitoring visit. Reconciliation of all drug supplies (ESK-001 or placebo) will be performed by the study monitor.

6.5. Destruction of Study Drug

When the study is completed, the Investigator will destroy or return to the Sponsor any used and unused study drug (e.g., empty, partially used, and unused containers), to the Sponsor as requested. Copies of the completed Drug Dispensing Log and Drug Return Record(s) will be returned to the Sponsor. The Investigator's copy of the Drug Return Record(s) must accurately document the return or destruction of all drug supplies to the Sponsor.

Local or institutional regulations may require immediate destruction of used study drug for safety reasons. In these cases, it may be acceptable for investigational study center staff to destroy dispensed study drug before a monitoring inspection, provided that source document verification is performed on the remaining inventory and reconciled against the documentation of quantity shipped, dispensed, returned, and destroyed, and provided that adequate storage and integrity of drug has been confirmed. Written authorization must be obtained from the Sponsor or Sponsor designees after final accountability prior to destruction.

Unused study drug from the site that has not been stored properly should not be destroyed until the monitor and/or Sponsor approve the destruction.

Written documentation of destruction must contain the following:

- Identity of study drug destroyed
- Quantity of study drug destroyed
- Date of destruction
- Method of destruction
- Name and signature of responsible person who destroyed the study drug

6.6. Patient Identification and Randomization Procedure

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

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. Patients will be randomized 1:1:1:1:1:1 one of the 6 treatment arms (5 dose levels of ESK-001, placebo).

Randomization will be stratified by prior use of biologics and geographic region. 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.

6.7. Blinding and Emergency Unblinding

ESK-001 tablets and placebo-to-match ESK-001 tablets will be matched for shape, size and color.

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.

At the study site, only the Principal Investigator should be unblinded. If, in the Investigator's opinion, and for the safety of the patient other study site personnel are required to be aware of the treatment assignment, the Investigator will contact the Sponsor's Medical Monitor prior to further unblinding and ensure that the minimum number of personnel are informed.

The 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.

6.8. Administration of Study Drug

The study site staff will administer a dose of study drug to each patient on Day 1 (first dose), and on the Week 4, 8, and 12 visit days. Patients should be clearly instructed not to take study drug on these study Days, but to bring their study drug with them to the clinic and take [redacted]

Study drug will be dispensed to patients as a 4-week supply at the Day 1, Week 4, and Week 8 visits.

[redacted]

At the Week 4, 8 and 12 study visits patients must return all study drug [redacted]

6.9. Continued Access to Investigational Product

After completion of the Week 16 End-of-Study (EOS) Visit, Patients will be eligible to receive extended open-label treatment with ESK-001 by participating in a separate open-label extension (OLE) study (Protocol No. ESK-001-007). To participate in this OLE study patients must have

completed this study, ESK-001-006, meet all eligibility criteria for the OLE study, and be willing and able to complete all of its required assessments.

6.10. Treatment of Overdose

Standard symptomatic support measures should be used in the case of excessive pharmacological effects or overdose. No antidotes are available.

6.11. Treatment Compliance

Accountability and patient compliance will be assessed by maintaining adequate study drug dispensing records and tablet counts. The Investigator is responsible for ensuring that dosing is administered in compliance with the protocol. See Section 6.4 for instructions on drug accountability procedures.

6.12. Prior and Concomitant Medication

Prior and concomitant medication as well as vaccination use after screening will be recorded on the prior and concomitant eCRF. Prior medications should be collected from the past 10 years.

Antiviral Medications

Based on in vitro assessments, ESK-001 has the potential for drug-drug interaction with antiviral medications metabolized through CYP3A4, CYP2D6 and P-gp pathways (eg, Paxlovid [nirmatrelvir + ritonavir]). Co-administration with ESK-001 may affect the systemic exposure levels of antiviral medications or ESK-001. The benefit:risk assessment for administration of anti-viral medications with a narrow therapeutic index should be discussed with the medical monitor whenever possible.

Acid Reducing Agents

The use of Proton Pump Inhibitors (PPIs) are not permitted on study due to the potential to decrease ESK-001 exposure. However, the use of H2 blockers (e.g., famotidine or ranitidine) and calcium carbonate-containing antacids (eg, Tums® or Rolaids®) are allowed during the study but should be taken at least 2 hours after a dose of study drug.

6.12.1. Allowed Vaccinations

Inactivated vaccines (including but not limited to COVID-19 vaccines and boosters) will be allowed while on study. The study site should follow local guidelines related to COVID-19.

6.12.2. Prohibited Medications

Medication and treatment restrictions applicable before the dosing period are listed as exclusion criteria in Section 5.3. These restrictions are applicable for the duration of the study and are summarized in Table 2. Prior and concomitant medication will be recorded.

Table 2 Prohibited Treatments

Treatment Category	Examples [A]	Washout Period [B]
Topical medications or treatments that could affect psoriasis evaluation	corticosteroids, anthralin, calcipotriene, vitamin D derivatives, retinoids	2 weeks
Phototherapy or systemic medications or treatments that could affect psoriasis evaluation	oral or injectable corticosteroids, retinoids, 1,25-dihydroxy vitamin D3	4 weeks
Therapeutic agents targeted to IL-12 or IL-23	ustekinumab, guselkumab, tildrakizumab, risankizumab	6 months
Therapeutic agents targeted to IL-17	secukinumab, ixekizumab, brodalumab	4 months
TNFα inhibitors	etanercept, infliximab, adalimumab	2 months
Systemic immunosuppressants or immunomodulatory drugs	corticosteroids (oral/IV/IM/SC), methotrexate, azathioprine, cyclosporine, mycophenolate mofetil	4 weeks or 5 half-lives [C]
Agents that modulate B cells	rituximab, ocrelizumab	6 months
Agents that modulate T cells	abatacept, alemtuzumab	3 months
JAK inhibitors or TYK2 inhibitors	baricitinib, tofacitinib, upadacitinib, ruxolitinib, fedratinib, deucravacitinib	4 weeks
Investigational agents		30 days or 5 half-lives [C]
Proton pump inhibitors	omeperazole, esomeprazole, pantoprazole	Prior to Study Day 1

A. Including but not limited to
B. Prior to randomization on Study Day 1
C. Whichever is longer

7. DISCONTINUATION

7.1. Discontinuation of the Study or Site

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to:

- Incidence or severity of adverse events in this or other studies indicating a potential safety risk to patients.
- Unsatisfactory patient recruitment e.g., excessively slow
- Poor protocol adherence
- Incomplete or inaccurate data recording
- Poor compliance with the International Conference on Harmonisation (ICH) guidelines for Good Clinical Practice (GCP)

In any instance of early discontinuation of the study, the Sponsor will notify, in writing, the investigators, regulatory authorities and ethics committees, and will specify the reason(s) for termination.

7.2. Study Drug Discontinuation

Patients should discontinue study drug for any of the following reasons:

- Malignancy, not including local and non-serious basal, squamous cell skin cancer or ductal carcinoma in situ
- Pregnancy
- Anaphylaxis, anaphylactoid or serious hypersensitivity reaction
- Use of any medication, intended to chronically treat psoriasis (refer to Section 6.12.2), other than those documented at screening
- Adverse event which in the opinion of the investigator or SMC precludes the patient from safely continuing in the study
- Patient is noncompliant with study requirements

The date and reason for discontinuation should be documented in the eCRF.

Patients who discontinue study drug should continue in the study to complete all scheduled assessments.

Those patients who are unwilling or unable to complete all remaining study assessments should return to the study site 2 weeks (± 7 days) after the date study drug was discontinued, to complete the early study termination assessments (ET Visit).

7.3. Discontinuation of Individual Patients

Reasons for patient discontinuation from the study may include but are not limited to any of the following reasons:

- Patient withdrawal of consent
- Discretion of the Investigator, if it is deemed not safe, or in the patient's best interest, to continue
- SMC recommendation
- Patient is lost to follow-up

The date and reason for discontinuation should be documented in the eCRF.

Patients who discontinue the study should return to the site to complete the early study termination assessments (ET Visit) within 2 weeks (± 7 days) from the date of discontinuation.

If a patient discontinues the study without notifying the Investigator, every effort should be made to contact the patient to identify the reason for discontinuation and to encourage the patient to complete the applicable ET visit assessments. If documented attempts to contact the patient fail, and a reason for the patient's discontinuation is undiscoverable, a patient can be declared as "lost to follow up" at the end of the study. All efforts to contact the patient should be documented in the source documents.

8. STUDY ASSESSMENTS AND PROCEDURES

For timing of assessments, refer to the Schedule of Assessments (SOA) in Section 1.3.

8.1. Eligibility Screening

Informed consent will be obtained at Screening before performing any study procedures.

Patients will undergo Screening assessments, including, but not limited to blood sampling, ECG, clinical assessment and various QoL assessments. Patients may be rescreened once no sooner than 2 weeks after an initial screen failure after discussion with the medical monitor.

Medical and medication history as well as demographic data, including biological sex, age, race, body weight (kg) and height (cm) will be recorded.

8.2. Efficacy Assessments

8.2.1. Psoriasis Area and Severity Index

Disease activity will be assessed by the Psoriasis Area and Severity Index (PASI) at the timepoints indicated in the Schedule of Assessments (see Section 1.3). The PASI system 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 A. The primary and secondary endpoints are based on the PASI response at the end of treatment (12-week timepoint).

8.2.2. Psoriasis Body Surface Area

Measurement of psoriasis body surface area (BSA) involvement is estimated using the handprint method with the size of a patient's handprint representing ~1% of body surface area involved. The total BSA = 100% with breakdown by body region as follows: head and neck = 10% (10 handprints), upper extremities = 20% (20 handprints), trunk including axillae and groin = 30% (30 handprints), lower extremities including buttocks = 40% (40 handprints). BSA assessments should be performed by a dermatologist or appropriately trained investigator who is experienced in the assessment of psoriasis patients.

8.2.3. Physician's Global Assessment

Patients will be assessed by the static Physician's Global Assessment (sPGA) at the timepoints indicated in the Schedule of Assessments (see Section 1.3). Appendix B presents the scoring system used for the sPGA.

8.2.4. Patient-Reported Outcomes

Quality of life (QoL) will be assessed by patient-reported outcomes: the Dermatology Life Quality Index (DLQI), the EQ-5D, and the pruritus numerical rating scale (NRS) at the timepoints indicated in the Schedule of Assessments (see Section 1.3). The 10-question DLQI is presented in Appendix C, the 5-question EQ-5D-5L is shown in Appendix D, and the pruritus NRS is presented in Appendix E.

8.3. Safety Assessments

ESK-001 is not an approved drug and as a result the entire safety profile is not known at this time. This Phase 2 study will contribute to the understanding of the safety profile for ESK-001 and for its use in patients with moderate to severe psoriasis.

Safety assessments will consist of recording all AEs and SAEs, protocol-specified laboratory variables, vital signs, and the results from other protocol-specified tests that are deemed critical to the safety evaluation of ESK-001. Dedicated eCRFs will be used to collect information on specific AEs, including SAEs, and pregnancies.

8.3.1. Adverse Events

An AE is defined as any untoward medical occurrence in any study participant enrolled in a clinical investigation administered a pharmaceutical product regardless of causal attribution.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not it is thought to be related to the investigational product.

In addition to new events, any increase in the severity or frequency of a pre-existing condition that occurs is considered an AE.

Only clinically significant laboratory test abnormalities (in the medical opinion of the Investigator) that require active management (e.g., abnormalities that require study drug discontinuation, more frequent follow-up assessments, further diagnostic investigation, etc.) should be listed as AEs. See Section 8.3.1.3 for more details.

If the AE constitutes a disease or syndrome (e.g., upper respiratory tract infection), only the diagnosis (e.g., upper respiratory tract infection) should be recorded as an AE and not the individual symptoms (fever, headaches, body aches, runny nose, sore throat, etc.). If an AE is due to an inactivated vaccine, the AE together with the etiology should clearly be recorded.

Other untoward events occurring in the framework of a clinical study will be recorded as AEs, e.g., those occurring during treatment-free periods (including Screening or post-treatment follow-up periods) in association with study-related procedures and assessments, or under placebo. For study drugs, lack of efficacy may be an expected potential outcome and should not be reported as an AE unless the event is unusual in some way, e.g., greater in severity.

Concomitant illnesses: Medical conditions which existed prior to entry into the clinical study will not be considered AEs unless they worsen (frequency or severity) during the treatment period. Pre-existing conditions will be recorded as part of the participant's medical history. Day to day fluctuations of pre-existing disease should not be recorded as an AE on the AE eCRF.

Disease under study (psoriasis): Disease related progression and worsening signs or symptoms of the disease under study are not AEs and are not to be recorded on the AE page of the eCRF unless the event meets the definition of an SAE or is not consistent with the typical clinical course of the patient's disease as established by the patient's medical history.

Surgical or diagnostic procedures: For medical or surgical procedures (e.g., colonoscopy, biopsy), the medical condition that led to the procedure is an AE. Elective procedures (e.g.,

vasectomy), planned hospitalization, and procedures for treatment of conditions noted in the patient's medical history that have not worsened (e.g., hernia repair) are not considered AEs.

All reported AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

8.3.1.1. Recording of Adverse Events

Adverse events should be collected and recorded for each patient from the date of the first screening/eligibility assessment until the end of their participation in the study, i.e., the patient has discontinued or completed the study.

Reporting of AEs prior to first dose should only include SAEs or AEs resulting from any protocol-related interventions.

Adverse events are to be recorded on the AE page of the eCRF. The following information will be recorded at the time the AE is reported and during follow up during the course of the AE:

- Whether or not the AE is an SAE (see Section 8.3.1.2.1)
- AE severity using CTCAE criteria (see Section 8.3.1.2.2)
- AE relationship to study drug (see Section 8.3.1.2.3)
- Action taken; including but not limited to, none, study drug dose modification or discontinuation, required concomitant medication, required procedure, or other
- Outcome: recorded as event resolved, resolved with sequelae, ongoing, or death

If an adverse event is persistent i.e. continues between various study assessment timepoints without resolution it should be recorded only once (see Section 8.3.1.3).

8.3.1.2. Assessment of Adverse Events

Each AE will be assessed by the Principal Investigator per the categories discussed in the following sections.

8.3.1.2.1. Serious Adverse Events (SAEs)

The Investigator is responsible for determining whether an AE meets the definition of an SAE. An SAE is any AE that results in any of the following outcomes:

- Death
- Life-threatening, i.e., an AE that, in the investigator's opinion, places the subject at immediate risk of death
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability or incapacity, i.e., a substantial disruption in the subject's ability to conduct normal life functions
- A congenital anomaly or birth defect in a neonate or infant born to a mother exposed to study drug

- Significant medical events that, in the opinion of the Investigator, may jeopardize the subject or may require medical or surgical intervention to prevent any of the outcomes listed in this definition.

8.3.1.2.2. Severity

The severity of an event describes the degree of impact upon the subject and/or the need for medical care necessary to treat the event. All clinical AEs encountered during the clinical study will be reported on the AE page of the eCRF. Severity of AEs will be graded based on a modified CTCAE, Version 5.0 and reported in detail as indicated on the eCRF. For any AEs not found in the CTCAE, a description of intensity grading can be found below:

Grade 1 - Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2 - Moderate	Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.
Grade 3 - Severe	Medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.
Grade 4 - Life-threatening	Life threatening consequences; urgent intervention indicated
Grade 5 – Death	Death related to AE

Any change in severity of a persistent AE will be captured by recording a new AE with the current severity and a start date of when the severity changed. The prior event will be updated with a stop date of when the severity changed. When changes in the severity of an AE occur more frequently than once a day, the maximum intensity for the event should be noted for that day.

8.3.1.2.3. Relationship to Study Drug

The Principal Investigator will assess the causality/relationship between the study drug and the AE. One of the categories described in Table 3 should be selected based on medical judgment, considering the definitions below and all contributing factors.

Table 3 Assessment of Relationship of Adverse Events to Study Drug

The Investigator should assess causality by answering either “related” or “unrelated” to the question, “Is there a reasonable possibility that the event may have been caused by the study treatment?”.

Related	A clinical event, including laboratory test abnormality, occuring in a plausible time relationship to treatment administration, and which concurrent disease or other drugs or chemicals cannot explain.
Unrelated	A clinical event, including laboratory test abnormality, with little or no temporal relationship with treatment administration.

The following factors may be used in consideration of causality assessment:

- Temporal relationship of the event onset to initiation of study drug
- Amount and duration of study treatment exposure
- Course of the event, including consideration for challenge/rechallenge:
  - Did the event abate after study treatment was reduced or interrupted? Did the event reappear after study treatment was reintroduced?
- Confounding risk factors in the patient that may explain or are associated with the event
- Concomitant medications known to cause or are associated with the event
- Known association of the event with the disease under study
- Known association of the event with similar study treatments

8.3.1.2.4. Suspected Unexpected Adverse Reactions (SUSARs)

Suspected unexpected adverse reactions (SUSARs) are SAEs that are unexpected per the Reference Safety Information section of the IB and judged by the Investigator and/or Sponsor to be related to ESK-001.

An adverse reaction is ‘unexpected’ if its nature and severity are not consistent with the information about the study drug:

- In the case of a product with a marketing authorization, in the summary of product characteristics for that product.
- In the case of any other investigational product, in the Investigator’s Brochure relating to the trial in question

The Sponsor or designee will report SUSARs to the appropriate regulatory authorities and Investigator’s as required, according to the local law.

8.3.1.3. Reporting Adverse Events

Diagnosis versus Signs and Symptoms

If known, a diagnosis should be recorded on the eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event

should be recorded as an AE or SAE on the eCRF. If a diagnosis is subsequently established, it should be reported as follow-up information and the diagnosis entered in the eCRF.

AEs Occurring Secondary to Other Events

In general, AEs occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause. For example, if severe diarrhea is known to have resulted in dehydration, it is sufficient to record only diarrhea as an AE or SAE on the eCRF.

However, medically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the eCRF. For example, if a severe gastrointestinal hemorrhage leads to renal failure, both events should be recorded separately on the eCRF.

Persistent or Recurrent AEs

A persistent AE is one that extends continuously, without resolution between subject evaluation time points. Such events should only be recorded once in the eCRF unless their severity changes. If a persistent AE changes in severity, it should be recorded as a separate AE on the Adverse Event eCRF.

A recurrent AE is one that occurs and resolves between subject evaluation time points and subsequently recurs. All recurrent AEs should be recorded on an Adverse Event eCRF.

Abnormal Lab Values

Only clinically significant laboratory abnormalities that require active management will be recorded as AEs or SAEs on the eCRF including but not limited to association with clinical findings, change to study drug (e.g. study drug discontinuation), more frequent follow-up assessments, further diagnostic investigation.

If the clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., increased alkaline phosphatase associated with cholecystitis), only the diagnosis (e.g., cholecystitis) should be recorded on the eCRF.

If the clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded as an AE or SAE on the eCRF. If the laboratory abnormality can be characterized by a precise clinical term, the clinical term should be recorded as the AE or SAE. For example, an elevated serum potassium level should be recorded as “hyperkalemia”.

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded as AEs or SAEs on the Adverse Event eCRF, unless their severity, seriousness, or etiology changes.

Follow up of abnormal lab values*:* Repeat testing of the abnormal labs should be performed as clinically indicated, in the opinion of the Investigator, until they have returned to the normal range and/or an adequate explanation of the abnormality is found and the lab value stabilizes.

8.3.1.4. Reporting of SAEs

Any AE that is serious and that occurs during the course of the study from the signing of the informed consent to end of study for each patient must be reported by the Investigator to the following:

- The Sponsor (or designee) and study monitor within 24 hours of the Investigator becoming aware of the event (expedited reporting).
- The investigation site's IRB/IEC by the Investigator in accordance with their regulations.

Initial Notification of a Serious Adverse Event (SAE)

Pharmacovigilance must be informed in writing 24 hours from the time the site investigational team first becomes aware of the event using the EDC system, as well as completing a paper SAE report forms.

A paper SAE form including a written, narrative description of any SAE must be sent via email (preferred) or fax within 24 hours after awareness of the event to:

Email: [redacted]

Phone: [redacted]

Fax: [redacted]

Paper SAE forms must be retained in the Investigator Site File.

In addition to reporting the SAE in the EDC and emailing the paper form, the local CRA and the Medical Monitor must be alerted via phone.

As further information regarding the SAE becomes available, follow-up information should be documented as an update using the paper SAE form. Follow-up information should be reported with 24 hours of awareness.

Related SAEs must be collected and reported regardless of the time elapsed from the last administration of study drug, even if the study has been closed.

Unrelated SAEs must be collected and reported during the study and for up to 30 days after the last dose of study medication.

SUSARs are reported to Investigators at each site and associated IRB/IEC when the following conditions occur:

- The event is an SAE
- There is reasonable possibility that the event is an adverse reaction caused by the administered drug
- The adverse reaction is unexpected, that is to say, not foreseen in the IB

Individual SUSARs considered to be a significant safety issues and/or which result in a change to the informed consent form will be reported in an expedited manner to all Investigators and IRB/IECs.

Reporting of any SAEs to applicable regulatory authorities will be the responsibility of the Local Sponsor in compliance with local regulations.

8.3.1.5. Follow-up of Adverse Events

AEs, especially those for which the relationship to study drug is "related", should continue to be followed during the patient's participation in the study until they have returned to baseline status or stabilized at a level acceptable to the Principal Investigator and Medical Monitor.

If after patient study completion, return to baseline status or stabilization cannot be established, an explanation should be recorded in the source documents.

8.3.1.6. Pregnancy

Pregnancies occurring in a female patient or in a male patient's partner while enrolled in this clinical study through 1 month after the last dose of study drug administration, must be reported on a Pregnancy Reporting Form within 24 hours of the investigator, designee, or site personnel learning of the pregnancy.

Pregnancy Reporting Forms should be sent via email (preferred) or fax to:

Email: [redacted]

Phone: [redacted]

Fax: [redacted]

If a patient becomes pregnant while taking study drug, the study drug will be immediately discontinued and the pregnancy must be reported within 24 hours of learning of the event. The investigator will discuss the risks and concerns of investigational drug exposure to a developing fetus and counsel the subject and/or pregnant partner (or ensure such counselling is provided).

An uncomplicated pregnancy will not be considered an AE or SAE. Elective abortions without complications should not be regarded as AEs, unless they were therapeutic abortions . Hospitalization for normal delivery of a healthy newborn should not be considered an SAE.

All pregnancies will be followed through birth. In the event there is a congenital anomaly or birth defect in a neonate or infant born to a mother exposed to study drug both the offspring and mother will be followed for 3 months post-delivery. Any congenital anomaly or birth defect in the offspring of a subject who received investigational product will be reported as an SAE. The outcome of any pregnancy and the presence or absence of any congenital anomaly or birth defect will be recorded in the source documentation and reported to the Sponsor and/or its designee.

The investigator will complete the Pregnancy Reporting Form or paper SAE form, as applicable, and report the information regarding the pregnancy, outcome, and status of the newborn, as appropriate.

8.3.2. Clinical Laboratory Assessments

Samples for clinical laboratory assessments will be collected at the time points detailed in the Schedule of Assessments (see Section 1.3).

Laboratory safety tests may be performed at unscheduled time points, if deemed necessary by the Investigator. Screening laboratory safety tests may be repeated upon discussion with the Sponsor/Medical Monitor.

The Laboratory Manual will supply complete written instructions for collection, handling, processing, storage, and shipping of samples.

8.3.3. Vital Signs

Vital signs will be assessed at the time points detailed in the Schedule of Assessments (see Section 1.3). The following vital signs will be measured:

- Blood pressure (systolic and diastolic [mmHg])
- Heart rate (bpm)
- Body temperature (°C)

BP and heart rate recordings will be made after the patient has been resting supine or semi-recumbent for ≥5 minutes.

8.3.4. Electrocardiograms

12-lead ECGs will be performed at time points detailed in the Schedule of Assessments (see Section 1.3).

The12-lead ECGs will be performed after the patient has been resting supine or semi-reclined for ≥ 5 minutes. The ECG paper tracing will be assessed by the study investigator for any abnormality and for clinical significance. The ECG parameters that will be measured include but are not limited to: PR interval, QRS interval, RR interval, QT interval, and QTc.

The ECGs will be sent electronically to a central location to be analyzed and over-read. The study site should review the centrally read report as soon as possible once available. The central report findings should be compared to the local paper ECG findings reported by the site. Any difference in reported ECG findings should be reconciled by the Investigator. The study team does not require a report back from this central location to act on any findings identified on the paper ECG tracing that, in the opinion of the study investigator, are clinically significant.

8.3.5. Physical Examinations

Physical examinations will be performed at the time points detailed in the Schedule of Assessments (see Section 1.3).

Complete Physical Examination

An assessment of general appearance and a review of systems (dermatologic, head, eyes, ears, nose, mouth/throat/neck, thyroid, lymph nodes, respiratory, cardiovascular, gastrointestinal, extremities, musculoskeletal, neurologic and psychiatric systems). A gynecological or genital examination is not required unless it is deemed necessary in the opinion of the Principal Investigator.

Abbreviated Physical Examination

An assessment of the general appearance, skin, cardiovascular system, respiratory system and abdomen and any symptom-driven assessment as appropriate.

The abbreviated physical examination should be extended to a full physical examination based on the clinical condition of the patient and if considered necessary by the Principal Investigator.

8.4. Pharmacokinetic Assessments

Blood samples for the analysis of plasma concentration levels of ESK-001 (PK) and ESK-001 metabolites will be collected at the time points detailed in the Schedule of Assessments (see Section 1.3).

Samples will be used to evaluate the PK of ESK-001 and its metabolites. Samples collected for analyses of ESK-001 and ESK-001 metabolite plasma concentrations may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study. After the blood samples are analyzed for plasma ESK-001 and ESK-001 metabolite concentrations, any residual samples may be used for exploratory analysis such as additional metabolite profiling and identification, interacting drug concentration measurements, ex vivo protein binding, or development of PK or PD assays.

Details regarding the collection, handling, processing, storage and shipping of samples will be provided in the Laboratory Manual.

8.5. Pharmacodynamic Assessments

Samples for the exploratory analysis of ESK-001 PD effects will be collected at the time points detailed in the Schedule of Assessments (see Section 1.3).

Details regarding the collection, handling, processing, storage and shipping of samples will be provided in the Laboratory Manual.

8.5.1. Skin Biopsy and Tape Stripping (Skin Biomarker Profile)

Skin samples will be collected via skin biopsy and/or tape-stripping at time points specified in the Schedule of Assessments for patients who provide specific consent. The samples will be used to assess skin biomarker response for a number of exploratory purposes that may include but are not limited to studying the ESK-001 mechanism, patient treatment response, and disease progression.

8.5.2. Plasma Biomarker Profile

Plasma-based samples will be collected at time points specified in the Schedule of Assessments to assess blood-based biomarker response for a number of exploratory purposes that may include but are not limited to studying biomarkers of ESK-001 mechanism, treatment response, and disease progression.

8.5.3. Blood RNA-seq Profile (Exploratory Transcriptomics)

RNA-based samples will be collected at time points specified in the Schedule of Assessments to assess transcriptomic biomarker response for a number of exploratory purposes that may include but are not limited to studying the mechanism of ESK-001, patient treatment response, and disease progression.

8.5.4. Blood Cell-Based Biomarkers

Whole blood will be collected at timepoints specified in the Schedule of Assessments to assess the response of immune-stimulated biomarkers for a number of exploratory purposes that may include but are not limited to studying biomarkers of ESK-001 mechanism, treatment response, and disease progression.

8.6. Genetics

Unless prohibited by local ethics committees, a DNA sample will be collected from patients who provide specific consent. The sample will be used for genetic analyses that may include but are not limited to patient-specific ESK-001 metabolism, drug-transport, and ESK-001 response.

9. SAFETY MONITORING COMMITTEE

A Safety Monitoring Committee (SMC) will be convened to review the safety data throughout this study. The SMC will consist of the Sponsor's Medical Director; the study Medical Monitor (from the CRO); two independent physicians with clinical trial experience, one with dermatology expertise and the other a cardiologist; and an independent statistician.

The SMC may meet at any time during the study to review blinded (or unblinded, if required) data when deemed necessary by the SMC.

The SMC will initially convene to review all available safety data after approximately 50 patients have been randomized and completed their Week 4 visit. The SMC will also meet regularly thereafter, based upon accumulating safety data and patient enrollment. The final prescheduled meeting of the SMC will be after study completion; to evaluate all safety data from all patients enrolled in the study. The SMC may also review safety data from eligible patients who complete this study and who enter an ESK-001 open label extension study.

The roles and responsibilities of SMC members and the SMC procedures and communication pathways are detailed in the SMC Charter.

10. STATISTICAL CONSIDERATIONS

Before database lock, a statistical analysis plan will be issued as a separate document, providing detailed methods for the analyses outlined below. Any deviations from the planned analyses will be described and justified in the clinical study report.

The baseline value of any variable will be defined as the last available value prior to the first administration of study drug (ESK-001 or placebo). A patient is considered randomized into the study following treatment assignment by IxRS.

All statistical tests will be two-sided. Except where noted, evaluation of continuous variables will be performed using ANOVA; ANOVA will be replaced by the nonparametric counterpart if normality assumptions are severely violated. Between-group comparisons involving discrete data will be performed using contingency table methodology. Descriptive summaries of continuous data will present the group mean, SD, median, range, and sample size. Descriptive summaries of discrete data will report the number of patients and incidence as a frequency and as a percentage. Statistical comparisons will be performed at the 0.05 level of significance.

10.1. Analysis of the Conduct of the Study

The disposition of patients will be summarized by treatment group with respect to the number of patients randomized, treated, and completing the study. For patients who discontinue treatment early, reasons for discontinuation will be summarized by treatment group.

Important Protocol Deviations (IPD) will be summarized. ICH E3 defines important protocol deviations 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 subject's rights, safety, or well-being.

10.2. Analysis of Treatment Group Comparability

Demographics (age, sex, race/ethnicity) and baseline characteristics (e.g., duration of psoriasis, psoriasis severity at baseline, baseline PASI) will be summarized by treatment group.

10.3. Efficacy Analyses

Efficacy analyses will be based on the intent-to-treat (ITT) approach. All patients randomized (ITT population) will be included in the analysis, and subjects will be analyzed according to their randomized treatment. Unless otherwise noted, analyses of efficacy outcome measures will be stratified by prior use of biologics and geographic region.

10.3.1. Primary Efficacy Endpoint

The proportion of patients in the active treatment groups with ≥75% improvement in PASI at Week 12 relative to baseline will be compared between each treatment group and placebo using the Cochran-Mantel-Haenszel test adjusting for stratification factors.

10.3.2. Secondary Efficacy Endpoints

Similar analyses as in the primary efficacy analyses will be performed to compare any two active arms.

The proportion of patients in each treatment group and placebo with sPGA categories 0 or 1 (cleared or minimal) at Week 12 will be compared using the Cochran-Mantel-Haenszel test adjusting for stratification factors.

The proportion of patients in each treatment group and placebo with response rate in PASI-50, 90, and 100 at Week 12 relative to baseline will be compared using methods similar to those used for PASI-75.

Change in percent BSA at Week 12 relative to baseline will be performed using ANOVA or analogous nonparametric methods.

Change from baseline in DLQI at Week 12 relative to baseline will be performed using ANOVA or analogous nonparametric methods.

The proportion of patients in each treatment group and placebo with ≥75% improvement in PASI Week 12 relative to baseline will be compared using the Cochran-Mantel-Haenszel test adjusting for stratification factors.

No adjustments for multiplicity will be performed.

Graphical methods may be used to display efficacy data.

10.3.3. Exploratory Endpoints

- Change from baseline in pruritus NRS score at Week 12 will be performed using ANOVA or analogous nonparametric methods.
- Change from baseline in EQ-5D at Week 12 will be performed using ANOVA or analogous nonparametric methods.
- Change from baseline in psoriasis and TYK2-related skin biomarkers in response to ESK-001 treatment.
- Change from baseline in psoriasis and TYK2-related blood-based biomarkers in response to ESK-001 treatment.
- Change from baseline in transcriptomic and proteomic expression in response to ESK-001 treatment.

Exploratory PD endpoint analyses may not be included in the CSR.

10.4. Safety Analyses

Safety will be assessed through the summary of adverse events, serious adverse events, laboratory test results, ECG parameters, and vital signs. Safety analyses will include all subjects who receive at least one dose of either ESK-001 or placebo. Subjects will be analyzed according to the actual treatment received.

Patient deaths (if any) will be listed.

10.4.1. Adverse Events

Verbatim descriptions of treatment-emergent adverse events will be mapped to thesaurus terms using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be tabulated by body system and preferred term. Summaries of adverse events by severity will be provided. Adverse events judged by the investigator to be related to treatment (ESK-001 or placebo) will be prepared. Serious adverse events will be summarized similarly. Adverse events leading to discontinuation from the study or treatment will be listed and tabulated.

10.4.2. Laboratory Tests

Descriptive summaries of laboratory values, including changes from baseline and treatment-emergent abnormalities, will be generated. Shift tables reflecting changes from baseline (e.g., normal to low, high) will be presented for a subset of laboratory parameters.

The liver function tests, namely ALT, AST, ALP, and TBL, are used to assess possible drug-induced liver toxicity (DILI). A listing of liver function test results that meet DILI criteria will be generated.

10.4.3. 12-Lead Electrocardiogram

The RR, PR, QRS, and QT intervals will be measured and read by a central laboratory. HR will be calculated as 60/ (RR × 1000) (with RR expressed in msec) and rounded to the nearest integer.

Correction for Heart Rate

Corrected QT interval (QTc) will be calculated using the manually over-read QT values. Each individual ECG QT value will be corrected for HR. The measured QT data will be corrected for HR using QTcF as per the following formulae/method (with QT, RR and QTc expressed in msec):

Fridericia's Correction:

$$QTcF = \frac{QT}{(RR/1000)^{(1/3)}}$$

ECG Numeric Variables

HR, PR, QRS, and QTcF will be summarized using descriptive statistics. For each time point of measurement, the changes from baseline will be summarized using descriptive statistics.

Categorical Analysis

The incidence count and percentage of patients with any postdose QTcF values of >450 msec, >480 msec, and >500 msec will be tabulated. Patients with QTcF values >520 msec will be listed with corresponding baseline values, ΔQTcF, and baseline and treatment HR. The incidence count and percentage of patients with ΔQTcF increase from baseline of >30 msec and >60 msec will be tabulated.

10.4.4. Vital Signs

Descriptive summaries of vital signs measurements and changes from baseline will be generated.

10.5. Pharmacokinetic Analysis

Plasma concentrations of ESK-001 will be summarized descriptively by treatment group and time point.

10.6. Missing Data

Detailed missing data methodology will be described in the Statistical Analysis Plan.

10.7. 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.

10.8. Interim Analyses

An independent SMC will be established to monitor safety data during the study. See Section 9 for details.

11. ETHICAL, LEGAL, AND ADMINISTRATIVE ASPECTS

11.1. Data Quality Assurance

The overall procedure for quality assurance of clinical study data, including data collection and management, will be described in the Data Management Plan.

Accurate and reliable data collection will be assured by verification and cross-check of the eCRF against the Investigator's records by the study monitor (source document verification), and the maintenance of Drug Accountability by the Investigator. Monitoring details describing strategy, methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques are provided in the Monitoring Plan and contracts.

Electronic data capture (EDC) will be utilized. All patient data relating to the study will be entered by the study center from the source documents into the electronic case report forms (eCRFs) unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). In no case is the eCRF to be considered as source data for the study.

Validation checks will be programmed within the EDC system to identify potential data discrepancies. Additionally, Sponsor personnel or designee will review the data entered by investigational staff for completeness and accuracy. If potential discrepancies are discovered, electronic data queries stating the nature of the potential discrepancy and requesting clarification will be sent to the site via the EDC system. Designated investigator site staff are required to respond promptly to queries and make necessary changes to the data. The sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations)

For classification purposes, preferred terms will be assigned to the original terms recorded on the eCRF, using MedDRA for AEs, diseases and surgical and medical procedures, and the WHODrug dictionary for drug and herbal treatments.

11.2. Protocol Amendments and Study Completion

Protocol amendments must be made only with the prior approval of the Sponsor or its designees. The Institutional Review Board (IRB)/Independent Ethics Committee (IEC) must be informed of all amendments and give approval for all amendments. For studies conducted out of the US, approval of all substantial amendments must be obtained from the relevant Competent Regulatory Authority before implementation. The Investigator must send a copy of the approval letter from the IRB/IEC to the Sponsor and/or its designees.

Approval must be obtained before any changes can be implemented, except for Changes necessary to eliminate an immediate hazard to study patients, or when the change(s) involves only logistical or administrative aspects of the study (e.g., change in monitor, change of telephone number).

The Sponsor reserves the right to terminate the study, according to the Clinical Study Agreement.

Study completion is defined as the date when all patients have completed the final study visit, and the study database has been locked.

11.3. Informed Consent

The Investigator and Sponsor must agree upon the format and content of the informed consent for (ICF) before it is submitted to the IRB/IEC for approval. A copy of the IRB/IEC approved ICF will be forwarded to the Sponsor. Written IRB/IEC approved informed consent and Health Insurance Portability and Accountability Act (HIPAA) release (or other privacy protection release, as governed by local regulations) must be obtained from each patient before any study-related activities are conducted. The Investigator must retain all original signed and dated ICFs in the patient's file. A copy of the signed and dated ICF must be given to the patient.

The ICF documents the study-specific information the Investigator provides to the patient for the patient's agreement to participate. Among other things, the Investigator or his/her designee will fully explain in layman's terms the nature of the study, along with the aims, methods, anticipated benefits, potential risks, and any discomfort participation may entail. The ICF must be appropriately signed and dated before the patient enters the study.

Patients will be informed of findings from the earlier or concurrent clinical studies (including AEs), if it is considered that such information could potentially affect patients' willingness to participate or continue in the study. Depending on the nature, severity, and seriousness of these AEs, the ICF may be amended as deemed appropriate. All amended signed and dated ICF(s) must be retained in the patients' files at the study sites; and a copy must be given to the patient.

11.4. Data Handling and Record Keeping

11.4.1. Patient Confidentiality and Disclosure of Data

The Investigator must ensure that each patient's anonymity is maintained as described below. On the eCRFs or other documents submitted to the Sponsor and/or its designees, patients must only be identified by study, Patient Identification Number, and demographics, and pertinent restrictions of local regulations. No other personal identifies will be used, and data will be de-identified in a manner compliant with Privacy Laws and, for US patients, the HIPAA regulations. Documents that are not for submission to the Sponsor and/or its designee (e.g., signed ICFs and Patient Information Sheets) should be kept in strict confidence by the Investigator in compliance with Federal regulations or other applicable laws or ICF and GCP guidelines. The Investigation and institution must permit authorized representatives of the Sponsor and/or its designee, representatives of the FDA, national and local health authorities, and the IRB/IEC direct access to review the patients' original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying and reproducing any records and reports that are needed for the evaluation of the study. The Investigation is obligated to inform the patient in the ICF that his/her study-related records will be reviewed, by the above-named representatives.

Patients will be informed that data will be held on file, by the Sponsor, and that these data may be viewed by staff including the study monitor and by external auditors on behalf of the Sponsor and appropriate regulatory authorities. Patients will also be informed that a study report will be prepared and may be submitted to regulatory authorities and for publication. However, patients will be identified in such reports only by Patient Identification Number and demographics,

pertinent to restrictions of local regulations. All patient data will be held in strict confidence, as allowed by law.

Upon the patient's permission, medical information may be given to the patient's personal physician or other appropriate medical personnel responsible for the patient's welfare.

11.4.2. Electronic Case Report Forms (eCRFs)

The data collected in the source documents for this study will be entered by designated study staff into the eCRF which uses fully validated software that conforms to 21 CFR Part 11 requirements. An audit trail will maintain a record of initial entries and changes made, time and date of entry, and name of person making the entry or change. Site staff will not be given access to the EDC system until they have been trained.

Guidance on completion of eCRFs will be provided in CRF completion guidelines.

The Investigator must ensure that complete data for the clinical study are collected, accurately documented in the appropriate sections of the eCRF, and adequately supported by appropriate source documentation. For each patient enrolled, the Investigator is responsible for verifying the accuracy, completeness, and timeliness of the data entries by electronically signing the eCRF.

A site-specific eCRF archive and audit trail will be provided at the close of the study to each Investigator. The Sponsor or designee will retain the eCRF archive and audit trail for all investigative sites.

11.4.3. Retention and Availability of Records

The Investigator is required to retain the study records and reports until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing application in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. If no marketing application is to be filed, or an application is not approved for the drug, the Investigator will retain the study records for 2 years after shipment and delivery of the drug for investigational use is discontinued and the Sponsor has so notified the FDA, per 21 CFR 312.27. Study records should, however, be retained longer if required by the applicable national and/or local regulatory requirements or by agreement with the Sponsor.

The Investigator must make study data accessible to the monitor, other authorized representative of the Sponsor, and regulatory agency inspectors upon request. A file for each patient must be maintained that includes the signed ICF and the Investigators copies of all source documentation related to that patient. The Investigator must ensure the reliability and availability of source documents from which the information on the eCRF was transcribed.

11.4.4. Audits and Inspections

In accordance with ICH, GCP and the Sponsor and/or its designee audit plans, this study may be selected for audit. Inspection of site facilities (e.g., pharmacy, drug storage areas, laboratories) and review of study-related records will occur to evaluate the study conduct and compliance with the protocol, ICH, GCP, and applicable regulatory requirements. The Investigator/institution should make available for direct access all requested study-related records (ICH GCP 4.9.7) to

appropriately qualified personnel from the Sponsor or its designees, or to health authority inspectors after appropriate notification. The verification of the eCRF data must be by direct inspection of source documents. The Investigation/institution should take measures to prevent accidental or premature destruction of these documents.

If for any reason the study records are moved to another location, the Investigator should notify the Sponsor of the new location.

11.5. Publication Policy

Alumis assumes full responsibility relating to this function and retains exclusive property rights over the results of the study, which Alumis may use as it deems fit.

If the study has multiple centers, the first publication must include complete results from data analyzed by Alumis from multiple centers. The Investigator commits himself not to publish or communicate data collected in only one center or part of a center before the publication of the complete results of the study unless prior written agreement from the other Investigators and Alumis has been obtained.

A copy of any intended publication or communication related to the study or related to the results obtained during or after the study shall be submitted to Alumis at least 90 days before the forecasted date of distribution or submission for publication. The authoring Investigator shall take Alumis's comments into due consideration and hereby agrees to incorporate any changes in any such publication or communication that Alumis may reasonably require to protect Alumis's proprietary rights and interests. Should the authoring Investigator decide to not incorporate changes reasonably required by Alumis, the authoring Investigator shall provide the reasons in writing to Alumis.

In the case where Alumis is in the process of filing a patent application on the results of the study, Alumis may delay its authorization for publication or communication of the results of the study until the date of international registration of the patent.

12. REFERENCE LIST

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13. APPENDICES

Appendix A 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 B 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

Appendix B, continued

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.

Appendix C Dermatology Life Quality Index (DLQI)

Hospital No: …… **Date:** ……

Name: …… **Score:** ……

Address: …… **Diagnosis:** ……

……

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

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

Appendix D EQ-5D-5L

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

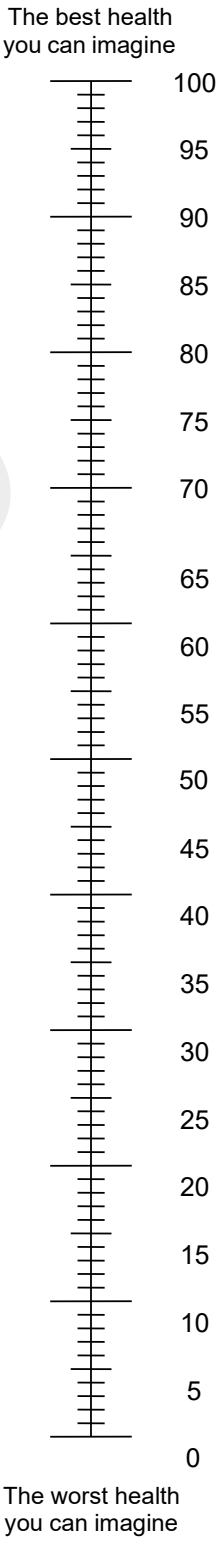
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = [ ]



Appendix E Pruritus Numerical Rating Scale (NRS)

1. Numerical Rating Scale. On a scale from 0 (no itch) to 10 (worst imaginable itch)…
…how was your itch, on average, within the past 24 hours? Please select one number.
0 1 2 3 4 5 6 7 8 9 10
…how was your worst itch in the past 24 hours? Please select one number.
0 1 2 3 4 5 6 7 8 9 10

Phan NQ et al. Acta Derm Venereol. 2012;92:502-7

Verweyen E at al. Acta Derm Venereol. 2019;99:657-66

Appendix F Signature Page: Declaration of Sponsor or Responsible Medical Expert

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

This clinical study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational product, as well as with the moral, ethical and scientific principles governing clinical research as set out in the guidelines on Good Clinical Practice (GCP) applicable to this clinical study.

Sponsor Signatory/Responsible Medical Expert

[redacted]

[redacted]

Date

Appendix G Signature Page: Investigator Study Acknowledgement/Disclosure

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

Version 3.0, 09 August 2022

By my signature, I confirm that my staff and I understand that the protocol and the Investigators Brochure are the confidential and proprietary property of the Sponsor. Further, I/we have carefully read and understand the protocol and agree to comply with the conduct and terms of the study specified therein. In particular, I/we have agreed to:

1. Comply with the E6 International Conference on Harmonisation (ICH) Tripartite Guideline on Good Clinical Practice (GCP) applicable Food and Drug Administration (FDA) Code of Federal Regulations (CRFs) and all applicable country regulations.
2. Have read and understood the Investigators Brochure, including potential risks and side effects of the drug.
3. Personally conduct or oversee the study according to the protocol, its amendments, study manuals, and study guides.
4. Ensure that written and dated approval/favorable opinion from the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) for the protocol, any amendments to the protocol, written informed consent form, any consent form updates, and Investigators Brochure (IB) are available before initiation of any study-related procedure and assure periodic review by the IRB/IEC as required per local and country regulations.
5. Obtain written informed consent from each study patient or his/her legally acceptable representative (if applicable).
6. Report all serious adverse events (SAEs) to Alumis or its agents and the IRB/IEC, as required by the protocol and country and IRB/IEC requirements.
7. Assure access by study monitors to original source documents.
8. Cooperate fully with any study-related Good Clinical Practice (GCP) audit as performed by Alumis, its agents, the US Food and Drug Administration (FDA), and/or the Regulatory Health Authorities of the participating country(ies).
9. Maintain confidentiality and assure security of confidential documents such as the protocol, informed consent, case report forms, IB, final study reports, study data, study reference manuals, study guides, manuscript and/or unpublished data and correspondence.

Principal Investigator Name	Site Number
Principal Investigator Signature	Date