Official title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Clinical Study to Assess the Efficacy and Safety of Tildrakizumab in the Treatment of Moderate to Severe Nail Psoriasis.

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TITLE PAGE

Protocol Title:	**A Multicenter, Randomized, Double-Blind, Placebo-Controlled Clinical Study to Assess the Efficacy and Safety of Tildrakizumab in the Treatment of Moderate to Severe Nail Psoriasis**
Protocol Number:	**TILD-18-19**
Amendment Number:	**Amendment 3, 23-Dec-2022**
Product:	**Tildrakizumab**
Short Title:	**Efficacy and Safety Profile of Tildrakizumab in Subjects with Moderate to Severe Nail Psoriasis**
Study Phase:	**3b**
Sponsor Name:	**Sun Pharmaceutical Industries Limited [SPIL]**
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Date of Initial Protocol:	**22 February 2019**
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[redacted]

Sponsor's Signature Page

[redacted]

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ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATWC	Active treatment worst case
BSA	Body surface area
CFR	Code of Federal Regulations
CGIC	Clinician Global Impression of Change
CGIS	Clinician Global Impression of Severity
ClinRO	Clinician-reported outcome measure
CRF	Case report form
CRO	Contract research organization
CSR	Clinical study report
C-SSRS	Columbia-suicide severity rating scale
DBF	Database Freeze
DBL	Database Lock
DLQI	Dermatology life quality index
DMARDs	Disease-modifying antirheumatic agents
DMC	Data Monitoring Committee
ECG	Electrocardiogram
ECI	Event of clinical interest
eCRF	Electronic case report form
EDC	Electronic data capture
ePRO	electronic patient-reported outcome
EoS	End of study
EoT	End of treatment
f-PGA	Fingernail physician global assessment
FSH	Follicle-stimulating hormone
GCP	Good clinical practice
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HRT	Hormone replacement therapy
ICF	Informed consent form
ICH	International council for harmonisation
IEC	Independent ethics committee
IL	Interleukin
IRB	Institutional review board
ITT	Intent-to-Treat

Abbreviation	Definition
IV	Intravenous
IWRS	Interactive web response system
LTBI	Latent tuberculosis infection
MACE	Major adverse cardiovascular events
MMRM	Mixed model repeated measures
mNAPSI	Modified Nail Psoriasis Severity Index
NAPPAQoL	Nail assessment in psoriasis and psoriatic arthritis with three components: a questionnaire assessing quality of life
NAPSI	Nail psoriasis severity index
NRS	Numeric rating scale
PASI	Psoriasis area and severity index
PFS	Prefilled syringe
PGA	Physician global assessment
PGA-F	Physician global assessment fingernail
PGA-S	Physician global assessment skin
PGIC	Patient global impression of change
PGIC-P	Patient global impression of change for pain
PGIS	Patient global impression of severity
PGIS-P	Patient global impression of severity for pain
PPS	Per protocol set
PRO	Patient-reported outcome
QoL	Quality of life
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SoA	Schedule of Activities
SOP	Standard operating procedure
s-PGA	Static Physician's global assessment
SSRE	Sample size re-estimation
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
TH	T-helper cell
TNF	Tumor necrosis factor
TNFI	Tumor necrosis factor inhibitor
ULN	Upper limit of normal
ViSENPsO	Visual medical scale to evaluate nail psoriasis severity
VPV	ViSENPsO Psychometric Validation
WOCBP	Woman of childbearing potential

1.0 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: **A Multicenter, Randomized, Double-blind, Placebo-controlled Clinical Study to Assess the Efficacy and Safety of Tildrakizumab in the Treatment of Moderate to Severe Nail Psoriasis**

Short Title: **Efficacy and Safety Profile of Tildrakizumab in Subjects with Moderate to Severe Nail Psoriasis**

Rationale:

Psoriasis is a chronic inflammatory skin disorder and affects approximately 1% to 2% of people worldwide. Nail psoriasis occurs in approximately 50% of patients with plaque psoriasis and is associated with pain and discomfort, causing a significant burden to quality of life (QoL) and work function. Currently approved biological treatments for moderate to severe plaque psoriasis include tumor necrosis factor (TNF) antagonist agents, a p40 (interleukin [IL] 12 and IL 23) antagonist, p19 (IL 23) antagonists, and IL-17 antagonist agents. Despite the availability of treatment options for plaque psoriasis, nail lesions remain difficult to treat. Thus, there remains an unmet need for effective therapeutic options for nail psoriasis.

Recent studies have demonstrated that IL-23-dependent T-helper (Th)17 cells control much of the inflammatory damage that is observed in psoriasis. Based on this rationale, several therapeutic anti-IL-23 antibodies were developed and entered into clinical studies. Tildrakizumab, an anti-IL 23p19 antibody, demonstrates comparable efficacy in psoriasis to other biological compounds in the IL-23 pathway. It has a favorable safety profile and convenient dosing at Weeks 0, 4, and every 12 weeks after that.

Tildrakizumab was approved as ILUMYA™ in the United States on 20 March 2018 for the treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy and in Australia on 06 September 2018 for the treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy.

This study is planned to be a multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of tildrakizumab in the treatment of moderate to severe nail psoriasis.

One tool appearing in the US product labeling to assess nail involvement in plaque psoriasis is the 5-point Physician's Global Assessment Scale for Fingernails (PGA-F). However, this clinician-reported outcome measure (ClinRO) scale has shown poor inter-rater reliability, relying on physician experience with nail psoriasis with only sparse textual descriptors to help in assessing severity categories (no visual exemplification of the respective severity ratings). In addition, the exact form of PGA-F that has supported product labeling is a proprietary measure

and is unavailable to SPIL. Given these measurement challenges, there is a need to develop new tools that evaluate nail psoriasis severity.

Given that, a new ClinRO, the Visual Medical Scale to Evaluate Nail Psoriasis Severity (ViSENPsO), was developed to assess fingernail pathology severity. A Contract Research Organization, ICON, conducted in-depth, semi-structured qualitative interviews with dermatologists to support the content validity of the new measure. The interviews were complemented by systematic mixed methods, using rating and ranking tasks that have allowed the measure development team to ensure professional consensus informs elements of the new scale. The overall ClinRO development process will also be complemented by patient interviews to aid understanding of how patients experience nail psoriasis severity, contrasting evaluations and understandings with those of expert dermatologists.

The next step is to psychometrically validate the ViSENPsO. A Statistical Analysis Plan (SAP) for the ViSENPsO Psychometric Validation (VPV) describing the methodological approaches that will be used to psychometrically validate the ViSENPsO in line with Food and Drug Administration (FDA) guidance (FDA, 2009; Powers et al., 2017) shall be prepared. The SAP for VPV will specifically define the analysis cohort and variables, outline the statistical methods and analyses to be conducted on the data, and shall describe the criteria that will be used to interpret results. The SAP for VPV will include corresponding unique table shells and an index or samples for any other analytic items (e.g., listings, figures, and replicate tables). The psychometric validation of the ViSENPsO will use data from SPIL's TILD-18-19 trial to evaluate the efficacy and safety of tildrakizumab in the treatment of moderate to severe nail psoriasis.

Objectives and Endpoints

EFFICACY OBJECTIVES	EFFICACY ENDPOINTS
Primary Efficacy Objective	**Primary Efficacy Endpoint**
• To assess the efficacy of tildrakizumab in subjects with moderate to severe nail psoriasis, as measured by the proportion of subjects who achieve at least a 75% improvement from baseline in total-modified Nail Psoriasis Severity Index (mNAPSI) at Week 28. .	• The proportion of subjects who achieve at least a 75% improvement from baseline in total-mNAPSI at Week 28.
Secondary Objectives	**Secondary Endpoints**
• To assess the efficacy of tildrakizumab in the treatment of moderate to severe nail psoriasis compared with placebo as measured by the ViSENPsO at Week 28 (Key secondary objective)	• The proportion of subjects with a score of "0 - normal" or "1 – minimal nail psoriasis" and at least a 2-point decrease from baseline at Week 28 as measured by the ViSENPsO. (Key secondary endpoint)

EFFICACY OBJECTIVES	EFFICACY ENDPOINTS
• To assess the effect of tildrakizumab on nail pain compared with placebo as measured by nail pain numeric rating scale (NRS) score at Week 28.	• The proportion of subjects with at least 3 point decrease from baseline in Nail Pain NRS score at Week 28 in subjects with baseline nail pain NRS score of $\geq 3^{*}$
• To assess the effect of tildrakizumab on nail pain compared with placebo as measured by nail pain numeric rating scale (NRS) score at Week 28.	• Change in patient-reported nail pain NRS score from Baseline at Week 28
• To assess the efficacy of tildrakizumab in the treatment of moderate to severe nail psoriasis compared with placebo as measured by mNAPSI, NAPSI, and ViSENPsO at Week 28.	• The proportion of subjects achieving total-fingernail mNAPSI 90, mNAPSI 100, NAPSI 75, NAPSI 90, and NAPSI 100 at Week 28. • Change in total-fingernail mNAPSI score from baseline at Week 28. • Change in total-fingernail NAPSI score from baseline at Week 28. • The proportions of ViSENPsO category results at Week 28 compared between treatment groups.
• To assess the efficacy of tildrakizumab in the treatment of plaque psoriasis compared with placebo, as measured by Psoriasis Area and Severity Index (PASI), Physician's Global Assessment-Skin (PGA-S) score and body surface area (BSA) involvement at Week 28.	• The proportion of subjects achieving PASI 75, PASI 90, and PASI 100 at Week 28. • The proportion of subjects achieving a PGA-S score of "clear" or "almost clear" with at least a 2-point reduction from baseline to Week 28. • Percentage change in total BSA involvement from baseline to Week 28.
• To assess the effect of tildrakizumab on nail pain compared with placebo as measured by nail pain NRS score improvement from baseline at Week 28.	• The proportion of subjects with at least 30% decrease in Nail Pain NRS score from Baseline at Week 28 in subjects with a baseline nail pain NRS score of $\geq 3^{*}$.
Exploratory Objectives	**Exploratory Endpoints**
• To assess the effect of tildrakizumab over time at measured time points through Week 52 as measured by mNAPSI, NAPSI, Nail Pain NRS, BSA, PGA-S, s-PGA, PASI, [redacted]	• Change from baseline in mNAPSI, NAPSI, Nail Pain NRS, BSA, PGA-S, s-PGA, PASI, [redacted]
• To assess the effect of tildrakizumab on QoL as measured by: o Dermatology Life Quality Index (DLQI) o Nail Assessment in Psoriasis and Psoriatic Arthritis QoL (NAPPA- QoL).	• Change from Baseline in DLQI score (total and 6 domain scores) and NAPPA-QoL score at measured time points through Week 52.
• To assess the effect of tildrakizumab measured by using anchor scales: o Clinician Global Impression of Change (CGIC). o Clinician Global Impression of Severity (CGIS) o Patient Global Impression of Change (PGIC).	• Change from baseline in CGIC, CGIS, PGIC, PGIC-P, PGIS, and PGIS-P at measured time points through Week 52.

EFFICACY OBJECTIVES	EFFICACY ENDPOINTS
○ Patient Global Impression of Severity (PGIS). ○ Patient Global Impression of Severity for pain (PGIS-P). ○ Patient Global Impression of Change for pain (PGIC-P).	
[*]NRS of ≥3 will be based on average score from 7-daily records at Baseline.	

SAFETY OBJECTIVE	SAFETY ENDPOINT
• To assess the safety and tolerability of tildrakizumab in subjects with moderate to severe nail psoriasis over 52 weeks.	• The percentage of subjects with incidence, seriousness, and severity of all adverse events. • The percentage of subjects with severe infections defined as any infection meeting the regulatory definition of a serious adverse event (SAE), or any infection requiring intravenous (IV) antibiotics, whether or not reported as a serious event as per the regulatory definition. • The percentage of subjects with malignancies (excluding carcinoma in situ of the cervix). • The percentage of subjects with non-melanoma skin cancer. • The percentage of subjects with melanoma skin cancer. • The percentage of subjects with major adverse cardiovascular events (MACE). • The percentage of subjects with study treatment-related hypersensitivity reactions (e.g., anaphylaxis, urticaria, angioedema, etc.). • The percentage of subjects with injection site reactions (e.g., pain, erythema, edema, etc.)

Overall Design:

This is a multicenter, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of tildrakizumab in the treatment of moderate to severe psoriasis of the nails.

Subjects with a clinical diagnosis of chronic plaque psoriasis for at least 6 months and moderate to severe psoriasis of the nails at screening and baseline (mNAPSI score of ≥20, ViSENPsO of ≥3, and PASI≥12) as well as moderate to severe plaque psoriasis at screening and baseline (s-PGA score of at least ≥3, and BSA involvement of ≥10%) and who are considered candidates for systemic therapy will be enrolled in the study.

After a screening period of 28 days, all eligible subjects will be randomly allocated (in a 1:1 ratio after stratification according to previous use of TNF-alpha inhibitors [yes/no] and baseline body weight [≤90 kg or >90 kg]) on Day 1 to receive either tildrakizumab 100 mg or placebo by subcutaneous (SC) injection on Week 0 (Day 1), 4, and 16. Subjects should receive the first dose of study treatment within 24 hours of randomization.

At Week 16, subjects who experience significant worsening of plaque psoriasis (defined as an increase in s-PGA by at least 2 from the baseline measurement) will be eligible for an early escape. Subjects selected for early escape by the Principal Investigator at Week 16 will have study medication discontinued and will complete the End of Treatment visit assessment, followed by the observational safety follow-up period. Subjects entering early escape may be replaced to meet the planned evaluable sample size goal for the primary endpoint analysis.

At Week 28, subjects initially randomized to placebo will be switched over to receive tildrakizumab 100 mg at Weeks 28, 32, and 44. Subjects initially randomized to tildrakizumab 100 mg will continue to receive tildrakizumab at Weeks 28, 40, and 52. In order to maintain the blind, subjects in both treatment arms will receive matching placebo injections at specified time points as described in the Schedule of Assessment (SoA).

Subjects who experience significant worsening of plaque psoriasis at Week 28 (defined as an increase in s-PGA by, at least 2 from the baseline measurement) will be discontinued from treatment. Subjects who do not fulfill this criterion at Week 28 will continue to receive tildrakizumab in Part 2, as described above.

After Week 52 (or early termination of study treatment prior to Week 52), the study treatment should be stopped, and the subjects will enter the 20-week observational safety follow-up period following the last dose of study treatment. During the follow-up period, subjects should continue on study-approved concomitant medications only; however, may be placed on other appropriate therapies for safety concerns or significant worsening of psoriasis based on the judgment of the Investigator. The subjects will not receive study treatment during the follow-up period.

The subject's disease activity (response to study treatment) will be evaluated using the ViSENPsO, mNAPSI, NAPSI, NRS, BSA, s-PGA, PGA-S, PASI, CGIC, CGIS, NAPPA-QoL, PGIC, PGIS, PGIS-P, PGIC-P, and DLQI. CGIC, CGIS, PGIC, PGIS, PGIS-P, and PGIC-P are considered anchor scales in this study.

Safety assessments, including adverse event (AE)/serious adverse event (SAE) monitoring, vital signs, physical examinations, electrocardiograms, and laboratory measurements will be performed during the study.

An interim analysis may be performed that could include an unblinded sample size re-estimation (SSRE). Sample size of the study could be increased as a result of this SSRE. In the event of an increase in sample size, the total sample size of the study will not exceed a total of approximately 282 randomized subjects.

Following the last subject's Week 28 visit (or early termination prior to Week 28), Week 28 analysis may be conducted on available data to evaluate safety and efficacy, and a Week-28 clinical study report (CSR) may be developed after database lock (DBL). In this case, when all the randomized patients have either completed the Week 28 evaluations or have stopped study participation prior to the Week 28 visit, the first database freeze (DBF) will occur (referred to as Week 28 DBF hereafter). When all patients randomized in this trial have either completed the Week 72 evaluations or have ceased study participation prior to the Week 72 visit, the second DBL will take place [referred to as the Final (Week 72) DBL henceforth], and subsequent CSR will be generated. The sponsor might opt to have a single DBL and CSR at the last subject's Week 72 visit (or early termination prior to Week 72) without a DBL at Week 28.

A final analysis will be performed when the last subject has completed the study.

Number of Investigators and Study Centers:

Up to approximately 35 Investigators and study centers globally, are expected to participate in this study.

Number of Subjects:

Approximately 96 eligible subjects will be randomly assigned to study treatment for an estimated total of 48 subjects per treatment arm. It is assumed up to 10% of the subjects may drop out, leaving 43 evaluable subjects per arm for the primary endpoint analysis at Week 28.

Treatment Groups and Duration:

The study duration per subject will be approximately 18 to 19 months, and the total duration of the study will be approximately 3 years.

The study consists of a screening period of 28 days, a 52-week treatment period (a 28-week double-blind placebo-controlled treatment period followed by a 24-week double-blind, active treatment period), and a 20-week observational follow-up period.

Part 1: Double-blind, placebo-controlled part, where subjects will receive either tildrakizumab 100 mg (Arm A) or placebo (Arm B) SC at Weeks 0, 4, and 16. At Week 16, subjects who experience significant worsening of plaque psoriasis (defined as an increase in s-PGA by at least 2 from the baseline measurement) will be eligible for an early escape. Subjects selected for early escape by the Principal Investigator at Week 16 will have study medication discontinued and will complete the End of Treatment visit assessment, followed by the observational safety follow-up period.

Part 2: At Week 28, subjects initially randomized to placebo will be switched over to receive tildrakizumab 100 mg at Weeks 28, 32, and 44. Subjects initially randomized to tildrakizumab 100 mg will continue to receive the active drug at Weeks 28, 40, and 52. In order to maintain the blind, subjects in both treatment arms will receive matching placebo injections at specified time

points as described in the SoA. Subjects who experience significant worsening of plaque psoriasis at Week 28 (defined as an increase in s-PGA by, at least 2 from the baseline measurement) will be discontinued from treatment.

Part 3: After Week 52 (or early termination of study treatment prior to Week 52), subjects will enter the 20-week observational safety follow-up period when tildrakizumab treatment will be stopped.

Statistical methods:

The primary efficacy endpoint is the proportion of subjects who achieve at least a 75% improvement from baseline in the total modified Nail Psoriasis Severity Index (mNAPSI). The key secondary efficacy endpoint is the proportion of subjects with a score of "0 - normal" or "1 – minimal nail psoriasis" and at least a 2-point decrease from baseline at Week 28 as measured by the ViSENPsO. For each endpoint, the tildrakizumab 100 mg dose will be compared with the placebo at Week 28. Both the primary and key secondary efficacy endpoints will be analyzed using the Cochran-Mantel-Haenszel (CMH) test, incorporating prior use of TNF-alpha inhibitors and baseline body weight as stratifications factors. In addition, the Miettinen and Nurminen (M&N) common risk (the response rate) difference between tildrakizumab 100 mg and placebo arm, along with the 95% confidence interval (CI) will be estimated. The analyses will be based on the Intent-to-treat (ITT) population. All analyses will also be conducted for the Per Protocol Set (PPS) populations as supportive.

Efficacy hypothesis testing will be controlled for multiplicity using a step-down sequential testing approach for the primary and key secondary endpoints. If the test on the primary endpoint is significant at the alpha = 0.05 level, then the test comparing the key secondary endpoint between treatment arms will also be conducted at the 0.05 level. The subsequent test will not be conducted if the null hypothesis of the previous test is not rejected.

Secondary and exploratory efficacy endpoints obtained from Week 28 to Week 52 will be evaluated using summary statistics.

Safety endpoints will be analyzed descriptively based on the safety analysis set (SAF), defined as all subjects who received at least 1 dose of study treatment. Subjects will be summarized based on the actual treatment they received.

Intent-to-Treat (ITT): All randomized subjects who were dispensed study treatment, regardless of whether treatment was taken by the subject or not. The primary efficacy population will be the ITT.

Per Protocol Set (PPS): All subjects in the ITT population who complete the 28-week placebo-controlled treatment without any major protocol deviations.

Safety Analysis Set: All randomized subjects who have taken at least one dose of study treatment, based on the treatment received.

Sample Size Determination:

Conservatively assuming the mNAPSI75 response rates between active drugs and placebo of 35 vs. 10 (Results from a similar therapeutic agent, Adalimumab had shown response rates of 46 vs. 3) and assuming Normal Approximation and a Z-test (pooled) for proportions and a two-sided alpha (α) of 0.05 approximately 43 subjects per treatment arm (for a total 86) will need to be randomized in a 1:1 ratio, stratified for prior use of TNF-alpha inhibitors (yes/no) and baseline body weight (≤90 kg or >90 kg). Under these assumptions, 48 subjects in each arm, after accounting for up to 10% dropout, will yield at least 80% power. Accordingly, approximately 96 subjects [48 per arm] shall be randomized in the study.

Data Monitoring Committee: An independent Data Monitoring Committee (DMC) may be established for periodic review of safety data from the study. The composition and responsibilities of the DMC will be described in the DMC Charter. The DMC will have access to unblinded data.

[redacted]

1.3 Schedule of Activities

Table 1: Schedule of Activities

	Screening	PART 1 Double-blind Placebo-controlled								PART 2 Double-blind Active Treatment					PART 3 OSFU
Week		**0 (Baseline)**	**4**	**8**	**12**	**16[a]**	**20**	**24**	**28[b]**	**32**	**36**	**40**	**44**	**52[c] EoT**	**72 EoS**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
Day	**Within 28 Days**	**1**	**+/- 3 days**	**+/- 3 days**	**+/- 3 days**	**+/- 3 days**	**+/- 3 days**	**+/- 3 days**	**+/- 3 days**	**+/- 3 days**	**+/- 7 days**	**+/- 7 days**	**+/- 7 days**	**+/- 7 days**	**+/- 7 days**
Written informed consent	X														
Inclusion/Exclusion criteria	X	X[d]													
Demographic information	X	X[e]													
Physical examination	X	X												X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE[f] /Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Medical/ Medication history	X														
Chest X-ray[g]	X														
QuantiFERON[h]	X														
HIV, HbsAg, and HCV serology	X														
ECG		X												X	
Randomization[i]		X													
IWRS entry	X	X	X			X			X	X		X	X	X	X
Study treatment administration[j]		X	X			X			X	X		X	X	X	
Hematology/chemistry/Urinalysis[k]	X[l]	X							X					X	X
Lipids[k]		X							X					X	
Serum pregnancy test	X													X	
Urine pregnancy test[m]		X	X	X	X	X	X	X	X	X	X	X	X	X	
C-SSRS[n]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Efficacy assessments (ViSENPsO, NAPSI, mNAPSI, PGA-S, pain NRS, BSA, and PASI)[o, p]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
s-PGA [q]	X	X				X			X						
CGIS	X	X			X				X		X			X	

	Screening	PART 1 Double-blind Placebo-controlled								PART 2 Double-blind Active Treatment					PART 3 OSFU
Week		**0 (Baseline)**	**4**	**8**	**12**	**16[a]**	**20**	**24**	**28[b]**	**32**	**36**	**40**	**44**	**52[c] EoT**	**72 EoS**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
Day	**Within 28 Days**	**1**	**+/- 3 days**	**+/- 3 days**	**+/- 3 days**	**+/- 3 days**	**+/- 3 days**	**+/- 3 days**	**+/- 3 days**	**+/- 3 days**	**+/- 7 days**	**+/- 7 days**	**+/- 7 days**	**+/- 7 days**	**+/- 7 days**
CGIC					X				X		X			X	
DLQI and NAPPA-QoL		X			X				X		X			X	
PGIS	X	X			X				X		X			X	
PGIS-P	X	X			X				X		X			X	
PGIC					X				X		X			X	
PGIC-P					X				X		X			X	

Abbreviations: AE=Adverse event, BSA = body surface area; CGIC = Clinician Global Impression of Change; CGIS = Clinician Global Impression of Severity; C-SSRS = Columbia-Suicide Severity Rating Scale; DLQI = Dermatology Life Quality Index; ECG = electrocardiogram; EoT = End of Treatment; EoS = End of Study; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IWRS = Interactive Web Response System; mNAPSI=modified Nail Psoriasis Severity Index; NAPPA-QoL = Nail Assessment in Psoriasis and Psoriatic Arthritis Quality of Life; NAPSI = Nail Psoriasis Severity Index; NRS = Numeric Rating Scale; OSFU = Observational Safety Follow-up; PASI = Psoriasis Area and Severity Index; PGA-S = Physician Global Assessment-Skin; PGIC = Patient Global Impression of Change; PGIC-P = Patient Global Impression of Change for pain; PGIS = Patient Global Impression of Severity; PGIS-P = Patient Global Impression of Severity for pain; SC = subcutaneous; TB = tuberculosis; SC = subcutaneous; s-PGA = static Physician's Global Assessment; TB = tuberculosis; ViSENPsO= Visual Medical Scale to Evaluate Nail Psoriasis Severity; TEAE = Treatment-emergent Adverse Event

a. Subjects who experience significant worsening of plaque psoriasis at Week 16 (defined as an increase in static Physician's Global Assessment [s-PGA] by at least 2 from the baseline measurement) will be eligible for an early escape.
b. Subjects initially randomized to the placebo arm will begin tildrakizumab subcutaneous (SC) treatment at Week 28 for Part 2 of the study.
c. Subjects who withdraw from the study will undergo the assessment corresponding to the last assessment of the study part from which they are leaving. Week 52 assessments (EoT) should be conducted approximately 4 weeks after administration of the last dose of study treatment.
d. Perform a check that all inclusion/exclusion criteria remain satisfied at Baseline, including those related to results from tests performed at the Screening visit.
e. Height and weight only.
f. Adverse events reported prior to initiation of study treatment (Day 1) are to be recorded as non-TEAE.
g. Chest X-ray is required only if a subject has positive or 2 indefinite QuantiFERON results.
h. Any subject who is started on prophylactic treatment for latent TB during the Screening Period may be randomized 4 weeks after initiation of treatment without the need for rescreening.
i. Following completion of Baseline assessments and confirmation that all inclusion/exclusion criteria have been met.

j. All study procedures of Baseline should be completed prior to study treatment administration. Following randomization, study treatment administration will begin on Day 1 of Week 0, Week 4, Week 16, and Week 28. At Week 28, subjects initially randomized to placebo will be switched over to receive tildrakizumab 100 mg at Weeks 28, 32, and 44. Subjects initially randomized to tildrakizumab 100 mg will continue to receive the active drug at Weeks 28, 40, and 52. In order to maintain blind, subjects who were initially randomized to placebo will receive matching placebo injections at Weeks 40 and 52, while subjects who were initially randomized to tildrakizumab will receive matching placebo injections at Weeks 32 and 44. Study treatment will be administered after performing all study-specific procedures for a particular visit.

k. Blood samples are to be collected (pre-SC dose where applicable), after ECG and vital signs measurements. At visits where lipids are to be assessed, the blood samples are to be collected (pre-SC dose where applicable) after at least 12 hours fasting, following ECG and vital signs measurements. The following parameters will be reported at Screening only: Serum pregnancy, hepatitis B, hepatitis C, and HIV.

l. Subjects with fungal nail infection whose fungal culture will be sent to the laboratory would have a Screening Period of 6 weeks.

m. Urine pregnancy tests will be performed at the study center using materials supplied by the central laboratory.

n. The subjects will be assessed for suicidal ideation and behavior at Screening using Screening C-SSRS, at Baseline, using Baseline C-SSRS, and each subsequent visit using the C-SSRS Since Last Visit version as specified in SoA.

o. The efficacy assessments, ViSENPsO, NAPSI, mNAPSI, PGA-S, BSA, and PASI will be assessed at each visit during the study, starting at the Screening visit. Nail pain NRS will be based on the average score from 7-daily records at Baseline (if average of at least 4 out of the 7 daily recall observations in the week prior to baseline) and single-day recording at Screening.
At all visits where efficacy assessments are made, the PROs (in particular nail pain NRS, PGIS, PGIS-P, PGIC, PGIC-P, C-SSRS, and QoL questionnaires) must be completed by the subject prior to efficacy assessments performed by the Investigator or designee. The order of the efficacy assessments evaluated by the Investigator should be the global assessments (e.g. ViSENPsO, s-PGA, PGA-S, CGIC and CGIS) followed by other efficacy assessments (e.g., mNAPSI, NAPSI, BSA and PASI).

p. For a subset of n=50 subjects, the ViSENPsO will be administered to the same patient by two internal experts to assess inter-rater reliability at the Baseline and at EoT visits. The subset at EoT need not be the same set of subjects who had these assessments at baseline.

q. s-PGA criteria will be applicable for assessing eligibility and early escape at week 16 and week 28.

2.0 INTRODUCTION

2.1 Background

Psoriasis is a chronic inflammatory skin disorder and affects approximately 1% to 2% of people worldwide, with approximately 25% of subjects suffering from moderate to severe chronic plaque psoriasis. Plaque psoriasis, the most common form, affects 80% to 90% of patients. Nail psoriasis occurs in approximately 50% of patients with plaque psoriasis and is associated with pain and discomfort, causing a significant burden to quality of life (QoL) and work function (1). Nail psoriasis affects the nail matrix and the nail bed. The clinical manifestations of psoriasis of the nail matrix include pitting (most common lesion), nail plate crumbling, and leukonychia, while clinical manifestations of psoriasis of the nail bed include the presence of oil-drop or salmon patch dyschromia, onycholysis, subungual hyperkeratosis and splinter hemorrhages (2). Treatment includes topical agents, phototherapy, and/or systemic agents (conventional agents and biological treatments) (3, 4).

2.2 Study Rationale

Biological therapies are indicated for the treatment of subjects with moderate to severe chronic plaque psoriasis who are candidates for phototherapy or systemic therapy. Currently approved biological treatments for moderate to severe plaque psoriasis include tumor necrosis factor (TNF) antagonist agents, i.e., etanercept (Enbrel®), infliximab (Remicade®), and adalimumab (Humira®), and the p40 (IL-12 and IL-23) antagonist ustekinumab (Stelara®). Despite the availability of treatment options for plaque psoriasis, nail lesions remain difficult to treat. The use of topical therapy, typically the first line of treatment for plaque psoriasis, is often challenging because of the poor diffusion into the nail tissue (1, 5). Patient satisfaction and compliance with topical therapy are known to be low (6). Thus, there remains an unmet need for effective therapeutic options for nail psoriasis.

In recent years, accumulating data have implicated the IL-23/Th17 pathway in psoriasis pathogenesis. Recent genome-wide association studies have identified psoriasis risk alleles around gene regions that encode IL-23 (IL23A, IL12B) and the IL-23 receptor (IL-23R) (7, 8). Both p19 and p40 sub-units of IL-23 are over-expressed in psoriatic skin lesions, while the unique p35 sub-unit of IL-12 is not (9). Th17 cells, and the cytokines they elaborate, are abundant in psoriasis lesions, where they exert pro-inflammatory and pro-acanthotic effects (10, 11). Compelling evidence for the functional role of IL-23p19 in psoriasis is demonstrated by a xenotransplant mouse model of psoriasis using AGR-129 mice wherein the administration of anti-human IL-23p19 inhibited the development of psoriatic lesions comparable to anti-TNF-α blockers, the current benchmark in psoriasis treatment (12). It has been shown that disease improvement with anti-TNF-α therapy correlated with the rapid down-modulation of IL-23 and Th17 cell products, and successful response to treatment was dependent on the inactivation of the IL-23/Th17 pathway (13, 14). Thus, while the use of IL-12/IL-23 p40 antagonists (e.g., ustekinumab and briakinumab) have been clinically validated in psoriasis (15-18), recent data suggest that the efficacy of these antagonists likely depends primarily, if not exclusively, on their

ability to neutralize IL-23 rather than IL-12 (8, 19, 20). This provides the rationale for selectively targeting IL-23p19 in subjects with nail psoriasis.

Tildrakizumab is a high affinity (297 pM), humanized IgG1/K antibody that specifically binds to IL-23p19 (SN 08197) but does not bind human IL-12 (IL-12p40 and p35 heterodimer) or human p40. Tildrakizumab 100 mg by subcutaneous (SC) injection has recently been approved by the Food and Drug Administration for the treatment of moderate to severe chronic plaque psoriasis. Detailed information regarding the safety/tolerability of tildrakizumab can be found in the Investigator's Brochure (IB) (21).

Some special populations of patients will not be included in this study, such as those with hepatic, renal, and blood abnormalities, as well as infections, malignancy, myocardiopathy, and psychiatric disorders. Once we are evaluating a biological product to treat a nail condition, and based on the intrinsic characteristic of side effects that are generally observed in the class of biological products, we believe that these clinical conditions do not warrant the risk of generating or aggravating any of these clinical conditions, based on the following data:

- Liver function test elevations have been reported with the use of tumor necrosis factor inhibitors (TNF-I) in patients with rheumatoid arthritis receiving adalimumab, etanercept, or infliximab (22). The overall incidence of liver function test elevations >1x ULN with TNF-I use was uncommon, and abnormalities >2x ULN were rarely observed. Significant differences were most consistently observed with infliximab, less commonly with adalimumab, and were not observed with etanercept compared with comparator disease-modifying antirheumatic agents (DMARDs) (23).
- It is already described in the literature cases of vasculitis developed in association with the use of tumor necrosis factor-α (TNF-α) inhibitors. Although cutaneous small-vessel vasculitis was the most common finding, but systemic vasculitis, including peripheral nerve and renal vasculitis, was also frequently observed. (23, 24)
- Cases of drug-induced hemolytic anemia after treatment with infliximab and adalimumab for treating ulcerative colitis and psoriasis, respectively, were described. (25, 26)
- An observational cohort study was conducted using medical and outpatient pharmacy claims from 2 large US health insurance claims databases from January 1, 2003, through September 30, 2015. The databases included 31,595 patients in the Optum Clinformatics Data Mart and 76,112 patients in Truven MarketScan who were new users of acitretin, adalimumab, apremilast, etanercept, infliximab, methotrexate, and ustekinumab. The pooled PS-matched analysis yielded a decreased rate of overall serious infection in users of apremilast (hazard ratio [HR], 0.50; 95% CI, 0.26-0.94), etanercept (HR, 0.75; 95% CI, 0.61-0.93), and ustekinumab (HR, 0.65; 95% CI, 0.47-0.89) compared with methotrexate. We did not find a different rate of overall serious infection among users of acitretin, adalimumab, and infliximab compared with methotrexate. (27)

- There is little research on the use of biologic treatment in psoriasis patients with a history of established malignancy (28). The existing evidence is not in all cases sufficient in order to provide adequate insight into the management of these complex situations (29); however, positive associations between cutaneous squamous cell carcinomas and certain therapies have been found, and there is conflicting evidence regarding the risk of lymphoma and melanoma. Further studies are needed to determine the long-term safety of newer psoriasis treatments (interleukin [IL]-12/23, IL-17, Janus kinase 1/3, and phosphodiesterase-4 inhibitors), specifically their safety in patients with a history of cancer (30).
- In a Korean, nationwide population-based prospective cohort study with a 15-year observational period. During the baseline period (1997-2000), total 1,773,786 Korean subjects who received health insurance from the National Health Insurance System were enrolled, and 5,788 subjects were defined as a psoriasis group. The number of new-onset malignancies was collected during the observational period (2001-2015). Patients with psoriasis had a higher adjusted hazard ratio (aHR) for the development of overall malignancy (aHR 1.08, 95% confidence interval [CI] 1.00-1.18) and gastric cancer (aHR 1.31, 95% CI 1.08-1.58) compared to controls. The risks of non-Hodgkin lymphoma and non-melanoma skin cancer were significantly increased only in patients with psoriasis who received systemic treatments (aHR 2.86, 95% CI 1.07-7.61 and aHR 3.93, 95% CI 1.47-10.47, respectively) (31).
- Severe dilated cardiomyopathy induced by adalimumab and ustekinumab (32). Cardiac tamponade related to infliximab induction therapy was described, likely due to a type 3 hypersensitivity immune-complex reaction resulting in a reactive pericardial effusion (33). However, major cardiovascular events with tildrakizumab is considered low (34).
- Patients with psoriasis have an increased risk of psychiatric comorbidities, suicidal ideation, and long-term course of the disease compared with patients who have other dermatological conditions (35, 36). However, concerns have been raised regarding the potential link between interleukin-17R blockade in the treatment of psoriasis and suicide, even if the current literature provides no evidence to support this association (36).

This study is planned to be a multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of the approved dose of tildrakizumab (100 mg by SC injection) in the treatment of moderate to severe nail psoriasis.

2.3 Benefit/Risk Assessment

Details about specific benefits and risks for subjects in this clinical study can be found in the Investigator Brochure (IB) and the informed consent form (ICF).

Given that efficacy benefits were reported in the completed Phase 2b study (Protocol P05495) and Phase 3 studies (P010 and P011) in plaque psoriasis, there is an expectation that subjects

treated with tildrakizumab will demonstrate improvement in nail psoriasis disease activity and Quality of life at Week 28. The study design allows early identification of subjects who have worsening of psoriasis at Week 16 and Week 28 and will be discontinued from treatment.

The study has also been designed to minimize potential risks to subjects; all subjects will undergo screening procedures aimed at reducing the likelihood and impact of any such risks. In addition, regular safety monitoring during the treatment period for all subjects will ensure that any unanticipated effects of study participation are identified promptly and managed appropriately. Given the long half-life ($T_{1/2}$) of tildrakizumab at doses previously studied, subjects will continue to be monitored throughout a 20-week wash-out period following the EoT visit, during which no active study treatment will be administered.

This study will be performed in compliance with the protocol, the International Council for Harmonisation (ICH), Good Clinical Practice (GCP), and applicable regulatory requirements.

3.0 OBJECTIVES AND ENDPOINTS

Table 2: Study Objectives and Endpoints

OBJECTIVES	ENDPOINTS
PRIMARY EFFICACY OBJECTIVE	**PRIMARY EFFICACY ENDPOINT**
To assess the efficacy of tildrakizumab in subjects with moderate to severe nail psoriasis, as measured by the proportion of subjects who achieve at least a 75% improvement from baseline in total-modified Nail Psoriasis Severity Index (mNAPSI) at Week 28.	The proportion of subjects who achieve at least a 75% improvement from baseline in total-mNAPSI at Week 28.
SECONDARY OBJECTIVES	**SECONDARY ENDPOINTS**
• To assess the efficacy of tildrakizumab in the treatment of moderate to severe nail psoriasis compared with placebo as measured by ViSENPsO at Week 28. (Key secondary objective)	• The proportion of subjects with a score of "0 - normal" or "1 – minimal nail psoriasis" and at least a 2-point decrease from baseline at Week 28 as measured by the ViSENPsO. (Key secondary endpoint)
• To assess the effect of tildrakizumab on nail pain compared with placebo as measured by nail pain numeric rating scale (NRS) score at Week 28.	• The proportion of subjects with at least 3 point decrease from baseline in Nail Pain NRS score at Week 28 in subjects with baseline nail pain NRS score of $\geq 3^{*}$
• To assess the effect of tildrakizumab on nail pain compared with placebo as measured by nail pain numeric rating scale (NRS) score at Week 28.	• Change in patient-reported nail pain NRS score from Baseline at Week 28.
• To assess the efficacy of tildrakizumab in the treatment of moderate to severe nail psoriasis compared with placebo as measured by mNAPSI, NAPSI, and ViSENPsO at Week 28.	• The proportion of subjects achieving total-fingernail mNAPSI 90, mNAPSI 100, NAPSI 75, NAPSI 90, and NAPSI 100 at Week 28. • Change in total-fingernail mNAPSI score from baseline at Week 28. • Change in total-fingernail NAPSI score from baseline at Week 28. [redacted]
• To assess the efficacy of tildrakizumab in the treatment of plaque psoriasis compared with placebo, as measured by Psoriasis Area and Severity Index (PASI), Physician's Global Assessment-Skin (PGA-S) score and body surface area (BSA) involvement at Week 28.	• The proportion of subjects achieving PASI 75, PASI 90, and PASI 100 at Week 28. • The proportion of subjects achieving a PGA-S score of "clear" or "almost clear" with at least 2-point reduction from baseline to Week 28. • Percentage change in total BSA involvement from baseline to Week 28.

OBJECTIVES	ENDPOINTS
• To assess the effect of tildrakizumab on nail pain compared with placebo as measured by nail pain NRS score improvement at Week 28.	• The proportion of subjects with at least a 30% decrease in Nail Pain NRS score from Baseline at Week 28 in subjects with a baseline nail pain NRS score of > 3*.

EXPLORATORY OBJECTIVES	EXPLORATORY ENDPOINTS
• To assess the effect of tildrakizumab over time at measured time points through Week 52 as measured by mNAPSI, NAPSI, Nail Pain NRS, BSA, PGA-S, static Physician's Global Assessment (s-PGA), PASI, [redacted]	• Change from Baseline in mNAPSI, NAPSI, Nail Pain NRS, BSA, PGA-S, s--PGA, PASI, [redacted]
• To assess the effect of tildrakizumab on Quality of Life (QoL) as measured by: o Dermatology Life Quality Index (DLQI) and o Nail Assessment in Psoriasis and Psoriatic Arthritis QoL (NAPPA- QoL).	• Change from Baseline in DLQI score (total and 6 domain scores) and NAPPA-QoL score at measured time points through Week 52.
• To assess the effect of tildrakizumab measured by using anchor scales: o Clinician Global Impression of Change (CGIC) o Clinician Global Impression of Severity (CGIS) o Patient Global Impression of Change (PGIC). o Patient Global Impression of Severity (PGIS). o Patient Global Impression of Severity for pain (PGIS-P). o Patient Global Impression of Change for pain (PGIC-P).	• Change from Baseline in CGIC, CGIS, PGIC, PGIC-P, PGIS, and PGIS-P at measured time points through Week 52.
SAFETY OBJECTIVE	**SAFETY ENDPOINT**
To assess the safety and tolerability of tildrakizumab in subjects with moderate to severe nail psoriasis over 52 weeks.	• The percentage of subjects with incidence, seriousness, and severity of all adverse events. • The percentage of subjects with severe infections defined as any infection meeting the regulatory definition of a serious adverse event (SAE), or any infection requiring intravenous (IV) antibiotics, whether or not reported as a serious event as per the regulatory definition. • The percentage of subjects with malignancies (excluding carcinoma in situ of the cervix). • The percentage of subjects with non-melanoma skin cancer.

	• The percentage of subjects with melanoma skin cancer. • The percentage of subjects with MACE. • The percentage of subjects with study treatment-related hypersensitivity reactions (e.g., anaphylaxis, urticaria, angioedema, etc.). The percentage of subjects with injection site reactions (e.g. pain, erythema, edema etc.).
[*] *NRS of ≥3 will be based on the average score from 7-daily records at Baseline.*	

4.0 STUDY DESIGN

4.1 Overall Design

This is a multicenter, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of tildrakizumab in the treatment of moderate to severe psoriasis of the nails. The study will be conducted in up to approximately 35 study centers globally. The study duration per subject will be approximately 18 to 19 months, including a treatment duration of 52 weeks, and the total study duration will be approximately 3 years. The study design is presented in Figure 1.

Approximately 96 eligible subjects (approximately 48 per arm) with moderate to severe plaque psoriasis and concomitant moderate to severe nail psoriasis will be randomized into the study. Eligible subjects will be randomized to one of the 2 arms in a 1:1 ratio: Arm A: Tildrakizumab 100 mg, SC (n = 48) and Arm B: Placebo, SC (n = 48). The number of subjects with prior use of TNF-alpha inhibitors will be capped at 40%, and the analysis will be stratified based on prior use of these biologics. The randomization (1:1) to tildrakizumab and placebo will be stratified by 2 factors: prior use of TNF-alpha inhibitors (Yes/No) and Baseline body weight (≤90 kg or >90 kg).

In a clinical trial with moderate-to-severe-plaque-psoriasis subjects, guselkumab was compared to adalimumab (VOYAGE 1, NCT02207231). One of the endpoints was nail disease. In that American population, about 20.9% of the subjects had experienced the use of biologic agents before joining the trial (37). In another trial, a 32-week study of secukinumab in subjects with nail psoriasis, performed in Germany, Australia, the Czech Republic, the USA, China, and Switzerland, 23.3% of the subjects had had previous exposure to a biological systemic psoriasis therapy (38). Based on these two recent manuscripts, the experience of the prior use of biological products in psoriasis ranges between 20% through 23.3%. To avoid excessive variability among the clinical sites, which could represent an issue and generate data not compatible with the population at large, it was decided to assume a conservative cap at 40% for this study.

The study will comprise 3 parts:

4.1.1 PART 1: Double-blind Placebo-controlled (Day 1 to Week 28)

After a Screening Period of up to 28 days and on Day 1, all eligible subjects will be randomized

1:1 to receive either tildrakizumab 100 mg or placebo administered by SC injection on Week 0 (Day 1), Week 4, and Week 16. Subjects should receive the first dose of study treatment within 24 hours of randomization. The treatment period for the double-blind, placebo-controlled part of the study is 28 weeks.

Early Escape: At Week 16, subjects who experience significant worsening of plaque psoriasis (defined as an increase in s-PGA by at least 2 from the baseline measurement) will be eligible for an early escape. (Appendix 20) Subjects selected for early escape by the Principal Investigator at Week 16 will have study medication discontinued and will complete the End of Treatment visit

assessment, followed by the observational safety follow-up period. Subjects entering early escape may be replaced so as to meet the planned evaluable sample size goal for the primary endpoint analysis.

An interim analysis may be performed that could include an unblinded sample size re-estimation (SSRE). The sample size of the study could be increased as a result of this SSRE. In the event of an increase in sample size, the total sample size of the study will not exceed a total of approximately 282 randomized subjects.

4.1.2 PART 2: Double-blind Active Treatment Extension (Week 28 to Week 52)

At Week 28, subjects initially randomized to placebo will be switched over to receive tildrakizumab 100 mg at Weeks 28, 32, and 44. Subjects initially randomized to tildrakizumab 100 mg will continue to receive tildrakizumab at Weeks 28, 40, and 52. In order to maintain the blind, subjects in both treatment arms will receive matching placebo injections at specified time points as described in the SoA.

Subjects who experience significant worsening of plaque psoriasis at Week 28 (defined as an increase in s-PGA by, at least 2 from the baseline measurement) will be discontinued from treatment. Subjects who do not fulfill this criterion at Week 28 will continue to receive tildrakizumab in Part 2, as described above.

4.1.3 PART 3: Observational Safety Follow-up (Week 52 to Week 72)

After Week 52 (or early termination of study treatment prior to Week 52), the study treatment should be stopped and all subjects, including those who terminated early from Part 1 and, 2 will enter the 20-week Observational Safety Follow-up period to monitor safety and tolerability for 20 weeks following the last dose of study treatment. During the follow-up period, subjects should continue on study-approved concomitant medications only, however, may be placed on appropriate therapies for safety concerns or significant worsening of psoriasis based on the judgment of the Investigator. The subjects will not receive study treatment during the follow-up period.

The study may have a primary analysis, which will be performed when the last subject has completed the Week 28 visit, and a final analysis to be performed when the last subject has completed the study.

Subjects who withdraw from the study will undergo the assessment that corresponds to the last assessment of the study part from which they are leaving. Subjects discontinued from study treatment at any time (apart from the withdrawal of informed consent) will complete the EoT (Week 52) assessment approximately 4 weeks after the last dose of study treatment and enter the 20-week observational safety follow-up. Subjects who withdraw from the study during Part 3 will undergo the Week 72 (End of Study [EoS]) assessments approximately 4 weeks after their last visit.

4.2 Scientific Rationale for Study Design

This is a randomized, double-blind, placebo-controlled, Phase 3 study to evaluate the efficacy and safety of tildrakizumab administered by SC injection in subjects with moderate to severe nail psoriasis. The study has been developed based on design features used in the completed Phase 2b protocol for subjects with psoriasis as well as ongoing Phase 3 studies for subjects with plaque psoriasis. In this study, tildrakizumab will be compared with a placebo. Placebo-controlled studies are the best way to ensure the accurate assessment (in absolute terms) of the safety and tolerability of a new molecular entity.

The study has been designed with 4 distinct phases (Screening, Double-blind Placebo-controlled period, Double-blind active treatment period, and an Observational safety follow-up period).

This enables scientific evaluation of efficacy at Week 28. The 52-week treatment duration is expected to provide adequate time to assess the safety and efficacy of tildrakizumab in subjects with nail psoriasis.

4.3 Justification for Dose

The dose of tildrakizumab was selected based on the results of Phase 2 dose-ranging study, P05495, and two Phase 3 studies (P010 and P011), in addition to an exposure-response model that was developed using these results.

In P05495, 4 treatment regimens of tildrakizumab were compared with a placebo (5, 25, 100, and 200 mg SC, administered at Weeks 0 and 4 and then every 12 weeks until Week 52). Unbalanced randomization was used to define dose-response relationships and to support the re-randomization of subjects in 2 treatment arms during the maintenance phase of the study (Part 2). At Week 16, Psoriasis Area and Severity Index (PASI) 75 response rates (primary endpoint) were 33% in the 5 mg arm, 64% in the 25 mg arm, 66% in the 100 mg arm, 74% in the 200 mg arm, and 4% in the placebo arm. The difference between each active dose versus placebo in terms of PASI 75 was statistically significant ($p \leq 0.001$). The proportion of subjects with PGA "clear" or "minimal" at Week 16 (key secondary endpoint) was 33% in the 5 mg arm, 58% in the 25 mg arm, 62% in the 100 mg arm, 74% in the 200 mg arm and 2% in the placebo arm. The difference between each active dose versus placebo in terms of PGA response was statistically significant ($p \leq 0.001$). These results demonstrated a clear dose response over the range of doses studied: the 5 and 25 mg doses demonstrated suboptimal efficacy for the PASI 75 and PGA endpoints, the 100 mg dose demonstrated near-maximal efficacy and the 200 mg dose appeared to show maximal efficacy.

The results from the Phase 2 (P05495) dose-ranging study were then used to develop an exposure-response model to analyze PASI 75 and PASI 90 response rates. The model-based analysis of the clinical data from P05495 suggested that the 100 mg dose was near the plateau of the exposure-response relationship for PASI 75. The incremental benefit for 200 mg versus 100 mg was estimated to be ~2% for PASI 75 response and 2% to 6% for PASI 90 response.

These findings were confirmed in two Phase 3 studies (P010 and P011) that further demonstrated that tildrakizumab 200 mg and 100 mg were efficacious and were well tolerated in the treatment of patients with moderate to severe chronic plaque psoriasis. The results for the primary and secondary endpoints in these studies were similar for tildrakizumab 200 mg and 100 mg. The results of the pivotal Phase 3 studies were the basis for the approval of tildrakizumab 100 mg in the United States on 20 March 2018 for the treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy, and in Australia on 06 September 2018 for the treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy.

In considering both clinical data and the model-based analysis, this Phase 3b study will include only a 100 mg dose. The safety/tolerability profile of tildrakizumab to date supports this approach.

4.4 End of Study Definition

A subject is considered to have completed the study if he/she has completed all parts of the study, including the last visit Week 72 (EoS).

The EoS is defined as the date of the last visit of the last subject in the study globally.

5.0 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Subjects are eligible to be included in the study only if all of the following criteria apply:

1. Subjects should be 18 years or older at the time of signing the informed consent during the Screening visit.
2. Subjects with a chronic moderate to severe plaque-type psoriasis for at least 6 months (as determined by subject interview and confirmation of diagnosis through physical examination by Investigator).
3. Subjects must have moderate to severe nail psoriasis at Screening and Baseline, defined by:
    - mNAPSI score of ≥20.
    - ViSENPsO ≥3
4. Subjects must have moderate to severe plaque psoriasis at Screening and Baseline, defined by:
    - s-PGA score of at least 3.
    - Body Surface Area (BSA) involvement of ≥10%.
    - PASI ≥12
5. Subjects must be considered candidates for systemic therapy, meaning psoriasis inadequately controlled by topical treatments (corticosteroids), and/or phototherapy, and/or previous systemic therapy.
6. Subjects have a negative evaluation for tuberculosis (TB) within 4 weeks before initiating study treatment, defined as a negative QuantiFERON® test. Subjects with a positive or 2 successive indeterminate QuantiFERON® tests are allowed if they have all of the following:
    - No history of active TB or symptoms of TB
    - A posteroanterior (PA) chest radiogram (with associated report available at study center) performed within 3 months of Screening with no evidence of active TB (or of any other pulmonary infectious diseases)
    - If prior latent TB infection (LTBI), must have a history of adequate prophylaxis (per local standard of care)
    - If the presence of LTBI is established, then treatment according to local country guidelines must have been followed for 4 weeks prior to inclusion in the study. A maximum of 2 QuantiFERON® tests are allowed. A re-test is only permitted if the first is indeterminate; the result of the second test will then be used.

7. Subjects are unlikely to conceive, as indicated by at least one "Yes" answer to the following questions:

    - Subject is a male
    - Subject is a female and agrees to abstain from heterosexual activity OR use a highly effective method of contraception as per Appendix 5.
    - Male subjects with female partners of childbearing potential who are not using birth control as described above must use a barrier method of contraception (e.g., condom) if not surgically sterile (i.e., vasectomy)
    - Subject is a surgically sterilized female or is documented to be postmenopausal. For contraceptive guidance, see Appendix 5.

8. For women of childbearing potential, a negative serum pregnancy test at Screening and a negative urine pregnancy test within 24 hours prior to Day 1 and on subsequent visits at which study treatment doses are scheduled.
9. Subjects must have results of a physical examination within normal limits or clinically acceptable limits to the Investigator prior to Day 1. The Investigator is encouraged to consult with the Medical Monitor (or appropriate designee) if there are questions regarding the significance of any out-of-range values.
10. Subjects must be capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICF and this protocol.

5.2 Exclusion Criteria

Subjects are excluded from the study if any of the following criteria apply:

1. Subjects who have laboratory abnormalities at Screening, including any of the following:
    - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥2.5 × the upper limit of normal (ULN).
    - Creatinine ≥2 × the ULN.
    - Serum direct bilirubin ≥1.5 mg/dL.
    - White blood cell count $<3.0 \times 10^3/\mu L$.
    - Any other laboratory abnormality which, in the opinion of the Investigator, will prevent the subject from completing the study or will interfere with the interpretation of the study results.
2. Subjects who have predominantly non-plaque forms of psoriasis, specifically erythrodermic psoriasis, predominantly pustular psoriasis, medication-induced or medication-exacerbated psoriasis, or new-onset guttate psoriasis.

3. Subjects with ongoing inflammatory skin diseases other than psoriasis or any other disease affecting the fingernails, which may potentially confound the evaluation of the study treatment.
4. Subjects with fungal nail infection should be excluded from the study. Subjects in whom the Investigator suspects a fungal nail infection* (see Appendix 6) in addition to nail psoriasis should have scrapings sent for direct microscopy and fungal culture. If fungal culture or direct microscopy of nail scrapings turns out to be positive for fungal infection, the subject should be excluded from the study. At the discretion of the investigator, Periodic Acid-Schiff (PAS) staining for nail clippings could also be considered to rule out fungal infection of the nails. Direct microscopy or fungal culture is not required if fungal infection is diagnosed in PAS staining.

   **Subjects with fungal nail infection whose fungal culture will be sent to the laboratory would have a Screening Period of 6 weeks.*
5. Women of childbearing potential who are pregnant, intend to become pregnant (within 6 months of completing the study), or are lactating.
6. Subjects with any infection or history of recurrent infection requiring treatment with systemic antibiotics within 2 weeks prior to screening or severe infection (e.g., pneumonia, cellulitis, bone or joint infections) requiring hospitalization or treatment with intravenous (IV) antibiotics within 6 weeks prior to Screening.
7. Subjects with any previous use of tildrakizumab or other IL-23/Th-17 pathway inhibitors, including p40, p19, and IL-17 antagonists for psoriasis.
   - Prior use of TNF-alpha inhibitors with a wash-out period of 12 weeks would be allowed. However, the number of subjects with prior use of TNF-alpha inhibitors would be capped at 40%, and the analysis will be stratified based on prior use of these biologics.
8. Use of the medications listed below within the indicated washout period prior to Baseline visit:

Excluded Medications/treatments	**Wash-out period prior to randomization**
Topical psoriasis treatment (including medicated nail preparations)	2 Weeks
Conventional systemic psoriasis therapy (e.g. cyclosporine, methotrexate, acitretin, fumaric acid esters) or phototherapy (e.g. ultraviolet [UV] B light phototherapy, Psoralen-UVA (PUVA) therapy, tanning salon or home-administered UVB)	4 Weeks
Treatment with injectable or oral corticosteroids;	4 Weeks
Treatment with a biological agent other than Tildrakizumab or any other IL-23/Th-17 inhibitors, including p40, p19, or IL-17 inhibitors	12 Weeks (or 5 half-lives, whichever is longer)
Treatment with an investigational agent	4 Weeks (or 5 half-lives, whichever is longer)

9. Subjects with a positive human immunodeficiency virus test result, hepatitis B surface antigen, or hepatitis C virus test result. Subjects with Hepatitis C viral (HCV) antibody reactive test could be included if HCV-RNA is negative.
10. Subjects with a prior malignancy or concurrent malignancy (excluding successfully treated basal cell carcinoma, squamous cell carcinoma of the skin in situ, squamous cell carcinoma of the skin with no evidence of recurrence within 5 years or carcinoma in situ of the cervix that has been adequately treated).
11. Subjects who have received live viral or bacterial vaccination within 4 weeks prior to Baseline or who intend to receive live viral or bacterial vaccination during the study.
12. Subjects who are currently participating in another interventional clinical study or have participated in an interventional clinical study within 5 half-lives (of the drug) to wash out prior to randomization. (Subjects participating in observational studies or non-interventional registry studies may be included in the study).
13. Subject or family member is among the personnel of the study center or Sponsor/designee staff directly involved with this study.
14. Subjects who have any concomitant medical condition, which in the opinion of the Investigator, could affect the study outcome or present an unacceptable risk.
15. Subjects who were hospitalized due to an acute cardiovascular event (such as myocardial infarction, cerebrovascular accident, cardiovascular illness [e.g., angina pectoris], or cardiovascular surgery [such as coronary artery bypass]) within 6 months before Screening.
16. Subjects who, in the opinion of the Investigator, will not be reliable participants in the study and those who can confound the results of the study.
17. Subjects who have a history of alcohol or drug abuse in the previous year.
18. Subjects who have a high risk of suicidality at the Screening assessment based on the Investigator's judgment or, if appropriate, as indicated by a response of "yes" within the last 12 months to Questions 4 or 5 in the suicidal ideation section or any positive response in the behavioral section of the C-SSRS.
19. Subjects with any other clinically significant laboratory abnormality, which, in the opinion of the Investigator, will prevent the subject from completing the study or will interfere with the interpretation of the study results.
20. Subjects with a known history of allergy or hypersensitivity to any of the inactive ingredients of the Tildrakizumab or placebo formulations.

5.3 Lifestyle Considerations

Excessive exposure to sunlight should be avoided during the study. Subjects should avoid the use of tanning booths or other ultraviolet light sources for the duration of the study.

5.4 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to

ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. The minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened at the discretion of the Investigator for up to 2 additional times, with a minimum of 2 weeks between each rescreening. When a subject is rescreened, all Screening procedures will be repeated.

Note: If the original ICF was signed within 30 days of the rescreening visit, a new ICF does not need to be completed.

Rescreened subjects should not be assigned the same subject number as for the initial Screening. Any subject who is started on prophylactic treatment for latent TB during the Screening Period may be randomized 4 weeks after initiation of treatment without the need for rescreening. Any subject with a negative fungal nail infection whose fungal culture was sent to the laboratory would have a Screening Period of 6 weeks

6.0 STUDY TREATMENT

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a subject according to the study protocol.

The study treatment in this study is tildrakizumab and placebo. All subjects will be dosed at the same time points to maintain the blind throughout the study. The study arms will receive study treatment during the course of the study as follows:

Arm A:
- Tildrakizumab 100 mg SC injections at Weeks 0, 4, 16, 28, 40, and 52.
- Placebo injections at Weeks 32 and 44.

Arm B:
- Placebo injections at Weeks 0, 4, 16, 40, and 52.
- Tildrakizumab 100 mg SC injections at Weeks 28, 32, and 44.

6.1 Study Treatment Administered

Study treatment details are provided in Table 3.

Table 3: Study Treatment Details

Study Treatment Name:	**Tildrakizumab**	**Placebo**
Dosage Formulation:	Tildrakizumab will be available as a prefilled syringe (PFS) with 100 mg of tildrakizumab and 1 mL solution. Each PFS will contain tildrakizumab solution and the following inactive ingredients: L-Histidine, L-Histidine Hydrochloride Monohydrate, Sucrose, and Polysorbate 80	The placebo formulation is similar to the tildrakizumab without the active ingredient. It will be available in PFS containing 1 mL solution and the following inactive ingredients: L-Histidine, L-Histidine Hydrochloride Monohydrate, Sucrose, and Polysorbate 80.
Unit Dose Strength/Dosage Level:	100 mg	-
Route of Administration	SC	SC
Dosing Instructions:	All the subjects will be dosed at the same time points to maintain the study blinding throughout the study.	
	For SC injections, tildrakizumab/placebo is supplied in a ready-to-use 1 mL PFS with a safety device. Each PFS is assembled with a safety device to prevent accidental needle sticks. Subcutaneous injections should be rotated with each dose and should not be given into moles, scars, tattoos, or areas where the skin is tender, bruised, red, hard, or not intact. Abdominal administration is the preferred site for SC doses.	
Packaging and Labeling	Tildrakizumab will be provided in PFS. Each PFS will be labeled as per country requirements.	Placebo will be available in identical containers with the same excipients (with no active drug)

6.2 Preparation/Handling/Storage/Accountability

1) The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatments received, and any discrepancies are reported and resolved before the use of the study treatment.
2) Only subjects enrolled in the study may receive study treatment, and only authorized study center staff may supply or administer the study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the Investigator and authorized study center staff.
3) The study treatment should be kept in a locked storage area under refrigerated storage at 2°C to 8°C. Study treatment experiencing temperature excursions outside this temperature should be quarantined and can only be released for subject use after consultation with the Sponsor.
4) The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
5) Further guidance and information for the final disposition of unused study treatment will be provided by the study center monitor.

The Investigator, a member of the study center staff, or a hospital pharmacist must maintain an adequate record of the receipt and distribution of all study treatments using the Drug Accountability Form.

6.3 Measures to Minimize Bias: Randomization and Blinding

All subjects will be centrally assigned in a 1:1 ratio to receive either tildrakizumab 100 mg or a placebo using an Interactive Web Response System (IWRS). Before the study is initiated, the Login information and directions for the IWRS will be provided to each study center.

This is a double-blind study with limited access to the randomization code. Tildrakizumab and placebo will be identical in physical appearance. The treatment each subject will receive will not be disclosed to the Investigator, study center staff, subject, Sponsor, or study vendors. The treatment codes will be held by the Clinical Supplies Department of the Sponsor or their designated Contract Research Organization (CRO).

Study treatment will be dispensed at the study visits summarized in the SoA (see Section 1.3). All subjects will be dosed at the same time points to maintain the study blinding throughout the study. Returned study treatment should not be re-dispensed to the subjects.

[redacted]

6.4 Study Treatment Compliance

The prescribed dosage, timing, and mode of administration may not be changed. Any departures from the intended regimen must be recorded in the eCRFs.

On Week 0 (Day 1), Weeks 4, 16, 28, 32, 40, 44, and 52 the study treatment will be administered at the study center by appropriately trained staff.

Study treatment accountability and subject compliance will be documented throughout the treatment periods (Part 1 and Part 2) using study-specific study treatment dispensing record forms. If a subject does not receive the scheduled dose, every effort should be made to administer the dose as soon as possible.

6.5 Concomitant Therapy

Any medication or vaccine (including over-the-counter [OTC] or prescription medicines, vitamins, and/or herbal supplements) that the subject is receiving at the time of enrollment or receives during the study must be recorded on the eCRF along with:

- Reason for use.
- Dates of administration, including start and end dates.
- Dosage information, including dose and frequency.

In addition, all prior medications used to treat the disease conditions and any other medications taken within 6 months prior to enrollment must be recorded in the eCRF.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

A list of excluded medications/therapy is provided in Table 4.

Other concomitant medication may be considered on a case-by-case basis by the Investigator in consultation with the Medical Monitor if required.

6.5.1 Rescue Medicine

Not applicable.

6.5.2 Allowed Concomitant Medication

- Acetaminophen (paracetamol) may be used by the subject as needed except within 7 days before a scheduled study efficacy evaluation except EOS/week 72 visit, when nail pain will be recorded on the NRS scale.
- Medications needed to treat pre-existing medical conditions that are not exclusionary to the study.
- Medications necessary to treat adverse events (AEs) or medical emergencies.
- Bland emollients (without α or β-hydroxy acids or keratolytic agents).
- Medicated shampoos that do not contain corticosteroids.
- Vitamins, supplements, antacids, and other over-the-counter medications that are not exclusionary to the study.
- Class VI or VII low-potency topical corticosteroids (such as prednicarbate 0.05%, triamcinolone acetonide 0.025%, fluocinolone acetonide 0.01%, desonide 0.05%, hydrocortisone 2.5% or hydrocortisone 1%) are allowed in Part 2 of the study, but not in Part 1.

Note that the use of any concomitant medication must relate to the documented medical history, prophylaxis, or an AE of the subject.

6.6 Dose Modification

No dose modification is allowed in this study. Study treatment can be interrupted temporarily or permanently if deemed necessary as per the Investigator's discretion.

6.7 Treatment after the End of the Study

The Sponsor will not provide any study treatment to the subjects during the Observational Safety Follow-up period. Patient care should not differ from what is normally expected for subjects with psoriasis.

6.8 Excluded Medication

Excluded medications/therapy is listed below. The concomitant use of an excluded medication/therapy with study treatment is not in compliance with the study protocol and must be recorded in the eCRF.

Table 4: Excluded Medications/treatments

Topical psoriasis treatment (including medicated nail preparations) *
Conventional systemic psoriasis therapy (e.g., cyclosporine, methotrexate, acitretin, fumaric acid esters) or phototherapy (e.g., ultraviolet [UV] B light phototherapy, Psoralen-UVA (PUVA) therapy, tanning salon or home-administered UVB)
Treatment with injectable or oral corticosteroids;
Treatment with a biological agent other than study treatment (including monoclonal antibodies, alefacept)
Treatment with an investigational agent (other than study treatment)
*Any class of topical corticosteroid is prohibited in the base study. Low-potency topical corticosteroids (class VI and VII) are only allowed during Part 2 of the study.

7.0 DISCONTINUATION OF STUDY TREATMENT AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Treatment

Subjects may voluntarily discontinue study treatment for any reason at any time and enter the 20-week wash-out period or completely withdraw from the study (see Section 7.2). Subjects who consent to enter the wash-out period will undergo the Week 52 (EoT) assessment at approximately 4 weeks after administration of the last dose of study treatment.

At any time during Part 1 or Part 2 of the study, the Investigator should discontinue the study treatment of a given subject if, on balance, he/she believes that continuation would be detrimental to the subject's well-being.

The study treatment must be discontinued under the following circumstances, and the further steps need to be discussed with the Medical Monitor:

- An SAE, drug reaction or complication, or an unacceptable AE, whether attributed to study treatment or not, precludes the continuation of treatment with study treatment. This includes the development of allergic reactions or the development of other potentially serious drug reactions to medication required by the protocol.
- Diagnosis of malignancy (except basal or squamous cell carcinoma of the skin) during the study (at the discretion of the subject and Investigator).
- Meets early escape criteria at week 16 or week 28
- Subjects who develop suicidal behavior.
- Evidence of pregnancy.
- Withdrawal of informed consent.
- Lost to follow-up.
- Significant non-compliance of the subject with study procedures.
- Decision of the Sponsor to terminate the subject, study center, or the study.

Subjects who discontinue the study treatment may not be replaced.

Subjects who withdraw from the study will undergo the assessment that corresponds to the end assessment of the study part which they are leaving. Week 52 assessments (EoT) should be conducted approximately 4 weeks after administration of the last dose of study treatment.

See the SoA (see Section 1.3) for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

7.1.1 Temporary Discontinuation

Study treatment can be interrupted temporarily in case of:

- Clinically important laboratory abnormalities.
- Subjects who develop suicidal ideation.
- Other intercurrent illnesses or major surgery.
- Use of prohibited treatment.
- Any other protocol deviation that results in a significant risk to the subject's safety.
- Sponsor decision.

The Medical Monitor should be informed. Re-starting of study treatment at the next scheduled administration study visits can be done after a discussion with the Medical Monitor.

7.2 Subject Discontinuation/Withdrawal from the Study

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time.

Withdrawal of consent occurs when a subject does not want to participate in the study anymore and does not want to attend any further visits or assessments, have further study-related contact, or allow an analysis of already obtained biologic material.

If a subject withdraws consent, the Investigator must make every effort to determine the primary reason for this decision and record this information on the treatment disposition eCRF page. If the subject decides to completely withdraw from the study (refuses any further study participation or contact), all study participation for that subject will cease, and data to be collected at subsequent visits will be considered missing. The study treatment must be discontinued, and no further assessments will be conducted. Further attempts to contact the subject are not allowed unless safety findings require communication or follow-up.

However, for safety reasons, Week 52 (EoT) assessments should be conducted for subjects withdrawing during Part 1 or 2, if the withdrawn subject is willing to undergo the assessments. For subjects withdrawing during Part 3 and willing to undergo final assessments, the Week 72 (EoS) assessments should be conducted approximately 4 weeks after their last visit.

The appropriate personnel from the study center and CRO will assess whether the study treatment should be discontinued for any subject whose treatment code has been broken inadvertently for any reason.

The Investigator must also contact the IWRS to register the subject's discontinuation from the study treatment.

7.3 Lost to Follow-up

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

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

- The study center must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study.

8.0 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (see Section 1.3).
- Some visits may be performed virtually depending on circumstances at the study site and in the community upon discussion with the Sponsor.
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the subject should continue or discontinue the study treatment.
- Adherence to the study design requirements, including those specified in the SoA (see Section 1.3), is essential and required for the study's conduct.
- All Screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The Investigator will maintain a Screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the subject's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilized for Screening or Baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA (see Section 1.3).
- The maximum amount of blood collected from each subject over the duration of the study, including any extra assessments that may be required, will not exceed more than 150 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.
- The efficacy assessments ViSENPsO, NAPSI, mNAPSI, PGA-S, BSA, PASI, and nail pain NRS score will be assessed at each visit during the study. The visits where efficacy assessments are made, the Patient Reported Outcomes (PROs) (in particular the Dermatology Life Quality Index [DLQI], Nail Assessment in Psoriasis and Psoriatic Arthritis Quality of Life [NAPPA-QoL], the nail pain NRS, Patient Global Impression of Change [PGIC], Patient Global Impression of Change for pain [PGIC-P], Patient Global Impression of Severity [PGIS], Patient Global Impression of Severity for pain [PGIS-P], and Columbia Suicidal Severity Rating Scale [C-SSRS]) must be completed by the subject prior to efficacy assessments performed by the Investigator (or designee). s-PGA, CGIS, CGIS will be assessed at visits as defined in the SoA.
- The order of the efficacy assessments evaluated by the Investigator should be the global assessments (e.g., ViSENPsO, s-PGA, PGA-S, CGIC, and CGIS) followed by other efficacy assessments (e.g., mNAPSI, NAPSI, BSA, and PASI).

[redacted]

- To ensure consistency of efficacy assessments over the study duration, it is preferred that the same person/assessor perform the same assessment on the same subject across all visits.
- All study treatments will be administered subcutaneously. All doses of study treatment will be administered at the study center; at home, administration is not permitted.
- All unscheduled visits and assessments performed during the visits will be recorded in the subject's eCRF. During any unscheduled visits, the Investigator will record any AEs and concomitant medications as well as performing any assessments or collecting samples deemed necessary at the discretion of the Investigator.

8.1 Efficacy Assessments

Efficacy assessments after Week 28 are considered exploratory. Time points for efficacy assessments are provided in the SoA (see Section 1.3).

8.1.1 Nail Psoriasis Severity Index (NAPSI)

The Nail Psoriasis Severity Index (NAPSI) is a numeric, reproducible, objective, simple tool for the evaluation of nail psoriasis (see Appendix 7). This scale is used to evaluate the severity of nail bed psoriasis and nail matrix psoriasis by area of involvement in the nail unit. A modified version (mNAPSI) was developed to enhance the face validity and feasibility of this tool (see Appendix 8).

The following items will be assessed:

- Nail pitting
- Nail onycholysis and oil-drop dyschromia
- Nail crumbling
- Nail leukonychia, splinter hemorrhages, hyperkeratosis, red spots in the lunula

A score is 0 if the items are not present, 1 if they are present in 1 quadrant of the nail, 2 if present in 2 quadrants of a nail, 3 if present in 3 quadrants of a nail, and 4 if present in 4 quadrants of a nail. Thus, each nail has a matrix score (0-4) and a nail bed score (0-4), and the total nail score is the sum of those 2 individual scores (0-8) sum of the total score of all involved fingernails is the total NAPSI score for that patient at that time point.

Only the fingernails will be evaluated in this study.

8.1.2 Physician's Global Assessment of Skin - Whole body (PGA-S)

A systematic review to evaluate the degree of correlation between two commonly used psoriasis assessment tools: The Psoriasis Area and Severity Index (PASI) and Physician Global Assessment (PGA). It was recorded and compared the percent of patients achieving both a 75% reduction in PASI score (PASI 75) and PGA 0 or 1 (clear or almost clear) at 8 to 16 weeks, 17 to 24 weeks, and greater than 24 weeks of treatment with the investigational drug. Indeed, the two assessment tools correlate very tightly except at the lower bounds of therapeutic efficacy (39-41). The r(2) values for the correlation between PASI 75 and a score of clear or almost clear on the PGA were 0.9157 at 8 to 16 weeks and 0.892 at 17 to 24 weeks. Indeed, the two assessment tools are substantially redundant and either alone is a sufficient tool for assessing psoriasis severity in patients with moderate to severe disease (39).

Plaque psoriasis will be assessed using a 6-point Physician's Global Assessment of Skin scale to determine the overall severity of a subject's psoriasis lesions at a given time point (see Appendix 9). The Investigator should select the category that best represents the condition of all the psoriasis lesions:

0 = Cleared, except for residual discoloration

1 = Minimal - majority of lesions have individual scores for Thickness (T) + Erythema (E) + Scaling (S)/3 that averages 1,

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

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

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

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

8.1.3 Psoriasis Area and Severity Index (PASI)

Psoriasis Area and Severity Index will be used to determine the treatment response (PASI 75, PASI 90, and PASI 100) in subjects with nail psoriasis. The PASI includes scores on erythema, thickness, scaling, and percentage of BSA affected (see Appendix 10).

8.1.4 Nail Pain Numeric Rating Scale (NRS)

The NRS is a simple assessment tool that subjects will use to report the intensity of their pain during the study (see Appendix 11). An improvement of 30% in Nail Pain NRS score from Baseline at Week 28 is an achievement that follows other biological product's outcomes in nail psoriasis studies. (42) There are numerous precedents in pain measurement across conditions for the use of a 30% threshold using the "worst pain" item. In this study, a decrease in absolute nail pain NRS score of at least 3 points will be assessed.

- On a scale of 0 to 10, with 0 being 'no pain' and 10 being the 'worst nail pain imaginable', how would you rate the worst nail pain you experienced during the previous 24 hours?

Patients will complete pain assessments by responding at each Visit, on a scale of 0 to 10, with 0 being 'no pain' and 10 being the 'worst nail pain imaginable', how would he/she rate the worst nail pain experienced during previous 24 hours, on each of the seven consecutive days leading up to the visit. However, at the Screening, pain NRS will be assessed once. The complete observation will be performed on the average score for each visit that will be based on the seven daily scores. The complete score at a given visit will be based on an average of no less than four of the seven prompted valid daily recall observations.

No imputation of missing daily recalls will be used, and the change in averaged scores at Baseline and Week 28 will provide the basis for analysis. The analysis will be conducted with complete observations, to be detailed in the SAP.

The subject should complete the nail pain NRS at the time points indicated in the SoA (see Section 1.3). Subjects will be instructed to record their nail pain NRS scores in the patient diary.

Only the fingernails will be evaluated in this study.

Acetominphen (allowed pain medication) cannot be taken for the 7 days when nail pain will be recorded on NRS scale.

8.1.5 Total Body Surface Area (BSA)

The BSA will be used to measure the severity of overall psoriasis. It is defined as the percentage of the total BSA affected by psoriasis. The overall BSA affected by psoriasis will be measured at time points specified in the SoA (see Section 1.3). The BSA will be measured using the palm method where the palm of the subject's hand (including the palmar aspects of the fingers) represents 1% of the BSA. The affected areas are then calculated by their size compared to the subject's palm.

8.1.6 Visual Medical Scale to Evaluate Nail Psoriasis Severity (ViSENPsO)

ViSENPsO is a new, simpler, and visual-based clinician-reported outcome (ClinRO) scale, assessing nail psoriasis severity. In addition to being used as the key secondary efficacy endpoint, the scale will promote well-defined and reliable evaluations of nail psoriasis treatment

outcomes in studies where a biological product is used; it will be validated in this study (see Appendix 12).

8.1.7 static Physician's Global Assessment (s-PGA)

An s-PGA has many variations, including 5, 6, or 7-point scoring ranging from 'clear' to 'severe'. In our specific study, we are using a simple, 6-point scale to evaluate subjects meeting early escape conditions, as better explored in Appendix 20.

This study will utilize s-PGA to determine if there is worsening of disease that warrants the discontinuation of the subject from the study.

8.1.8 Clinician Global Impression of Change (CGIC)

The Clinician Global Impression of Change is a simple questionnaire that reflects a clinician's belief about the efficacy of treatment (see Appendix 21).

8.1.9 Clinician Global Impression of Severity (CGIS)

The Clinician Global Impression of Severity is a global index that is used by clinicians to rate the severity of a specific condition in patients (a single-state scale) (see Appendix 22).

8.1.10 Quality of life

8.1.10.1 Dermatology Life Quality Index (DLQI)

The DLQI questionnaire will be used to assess treatment response on the subject's quality of life. The aim of this questionnaire is to measure how much the nail psoriasis has affected the subject's life during the previous week (see Appendix 13)

Subjects will be asked to recall their experiences during the previous week by responding to 10 questions. The DLQI will be completed by the subject in the PRO prior to any safety or efficacy evaluations. The questionnaire is self-explanatory and handed to the subject, who is asked to fill it in without the need for a detailed explanation.

8.1.10.2 Nail Assessment in Psoriasis and Psoriatic Arthritis QoL (NAPPA-QoL)

The NAPPA-QoL questionnaire will describe the QoL with nail psoriasis on the hands and/or feet over the past week (see Appendix 14).

Only the fingernails will be evaluated in this study.

8.1.10.3 Patient Global Impression of Change (PGIC)

The Patient Global Impression of Change is a simple questionnaire that reflects a patient's belief about the efficacy of treatment (see Appendix 15).

8.1.10.4 Patient Global Impression of Change for pain (PGIC-P)

Since the Patient Global Impression of Change is a versatile, global index that may be used to rate the change of any clinical condition, it will also be used in this protocol to evaluate change of nail pain (see Appendix 16), which will be called PGIC-P, and it will be recorded at the visits wherein PGIC will also be recorded.

8.1.10.5 Patient Global Impression of Severity (PGIS)

The Patient Global Impression of Severity is a global index that may be used to rate the severity of a specific condition (a single-state scale) (see Appendix 17).

8.1.10.6 Patient Global Impression of Severity for pain (PGIS-P)

Since the Patient Global Impression of Severity is a versatile global index that may be used to rate the severity of any clinical condition, it will also be used in this protocol to evaluate the intensity of nail pain (see Appendix 18), which will be called PGIS-P, and it will be recorded at the post-baseline visits wherein PGIS will also be recorded.

8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoA (see Section 1.3).

8.2.1 Physical Examinations

- A complete physical examination will include assessments of general appearance; skin; head/neck; pulmonary, cardiovascular, gastrointestinal, external genitourinary, lymphatic, and musculoskeletal system; extremities; eyes (inspection and vision control); nose; throat; and neurologic status.
- A detailed examination of the skin should be performed at the time points indicated in the SoA (see Section 1.3) for the efficacy assessments (e.g., ViSENPsO, NAPSI, PGA-S, PASI, BSA, etc.).
- Height and weight will also be measured and recorded at Baseline before administration of the study treatment.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2 Vital Signs

- Oral body temperature, pulse rate, blood pressure, and respiratory rate will be assessed at the time points specified in the SoA (see Section 1.3).
- Blood pressure and pulse measurements will be assessed in the supine position.
- Blood pressure and pulse measurements should be preceded by approximately 5 minutes of rest for the subject in a quiet setting without distractions (e.g., television, cell phones).
- Vital signs (to be taken before blood collection for laboratory tests) will consist of pulse and blood pressure measurement using a validated device.

8.2.3 Assessment of Suicidal Ideation and Behavior

- The subjects will be assessed for suicidal ideation and behavior at Screening using Screening Columbia-Suicide Severity Rating Scale (C-SSRS), at Baseline (using Baseline C-SSRS), and each subsequent visit using the C-SSRS Since Last Visit version (seeAppendix 18). There are 5 questions relating to levels of suicidal ideation which prompt questioning about suicidal behavior or intensity of ideation, depending on response.
- Subjects acknowledging active thoughts of self-harm but lacking an articulated plan for doing so are classified at the intermediate risk level; those presenting a defined self-harm plan or lacking needed impulse control are judged to be at the high-risk level.
- Subjects who have a high risk of suicidality at the Screening assessment based on the Investigator's judgment or, if appropriate, as indicated by a response of "yes" within the last 12 months to Questions 4 or 5 in the suicidal ideation section or any positive response in the behavioral section of the C-SSRS should not be enrolled in the study.
- Those subjects who develop suicidal ideation during the study rated as high risk according to the above classification must be temporarily discontinued from receiving study treatment and referred promptly for psychiatric evaluation.
- Subjects rated as displaying the intermediate level of suicidal ideation should receive psychological support and be assessed on an individual basis.
- All individuals assessed as exhibiting suicidal behavior, except preparatory acts, must discontinue study treatment permanently. The presence of non-suicidal self-injurious behavior should be assessed on an individual basis.

8.2.4 Electrocardiograms

- A single 12-lead electrocardiogram (ECG) will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, RR, QRS, QT, and QTc intervals.
- The ECG will be reviewed by an ECG vendor, and the instructions and guidelines for collection (e.g., equipment), transmission, and archiving of ECG data will be provided in the ECG Manual.

8.2.5 Tuberculosis Testing

- During the Screening Period, it must be determined and documented that a subject does not show evidence of active infection with TB.
- The subject must have a negative evaluation for TB within 4 weeks before initiating study treatment, defined as a negative QuantiFERON® test.
- Subjects with a positive or 2 successive indeterminate QuantiFERON® tests are allowed to enter the study if they have no history of active TB or symptoms of TB and a PA chest radiogram is performed (and with a report available at the study center) within 3 months of Screening with no evidence of TB (or of any other pulmonary infectious diseases).
- If there is evidence of prior LTBI, subjects must have a history of adequate prophylaxis per the local standard of care. If the presence of LTBI is established, treatment according to

local country guidelines must have been followed for at least 4 weeks prior to inclusion in the study.

8.2.6 Chest X-ray

A chest X-ray will be performed at Screening if the subject has a positive or 2 indeterminate QuantiFERON results unless it has been taken and documented within the 3 months prior to Screening (the X-ray and associated report must be available at the study center). There must be no evidence of active TB or other pulmonary infectious diseases for the subject to be eligible for the study.

8.2.7 Clinical Safety Laboratory Assessments

- See Appendix 2 for the list of clinical laboratory tests to be performed and the SoA (see Section 1.3) for the timing and frequency of the tests.
- A central laboratory will perform all laboratory tests except urine pregnancy dipstick, which will be assessed by the center staff. However, local laboratory tests will be allowed in the event that the central laboratory results will not be available immediately, and the Investigator needs to make an immediate decision for any safety concerns based on the laboratory results.
- The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease unless judged by the Investigator to be more severe than expected for the subject's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study including the subject's last EoS visit should be repeated until the values return to normal or Baseline or until stabilized or are no longer considered clinically significant by the Investigator or Medical Monitor.

If such values do not return to normal/Baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, if possible, and the Sponsor notified.

All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the Laboratory Manual and the SoA (see Section 1.3).

8.3 Adverse Events

The safety and tolerability of subjects will be assessed by the incidence of treatment-emergent adverse events (TEAEs), laboratory test results, vital signs, ECGs, and physical examination findings.

The definitions of an AE or SAE can be found in Appendix 3.

The Investigator will document all AEs in the subject's source document and eCRF. All entries should contain an event term, date of onset, date of resolution, severity, action taken, outcome, relationship to study treatment, and a seriousness assessment.

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

Any relevant observations made before the end of the Screening and Baseline visit (prior to the first dose of study treatment) are to be recorded on the AE eCRF, but will not be considered TEAEs and will be reported separately from TEAEs. Any relevant observations made after the first dose of study treatment will be recorded as an AE in the subject's AE eCRF (see Section 1.3).

In view of the long half-life of tildrakizumab at doses previously studied, subjects will continue to be monitored throughout the 20-week Observational Safety Follow-up period following the EoT (Week 52) visit. For the purposes of this study, any detrimental change in the subject's condition after the first dose of study treatment and up to the completion of the EoS visit should be considered an AE. For those subjects who may withdraw during the Observational Safety Follow-up period or wash-out period, at least 2 attempts should be made to collect the AEs.

A hospitalization planned by the subject prior to signing the ICF is considered a therapeutic intervention and not the result of a new SAE and should be recorded as medical history. If the planned hospitalization or procedure is executed as planned, the record in the subject's medical history is considered complete. However, if the event/condition worsens during the study, it must be reported as an AE.

Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the AE section of the eCRF however will not be considered as TEAEs.

All SAEs will be recorded and reported to the CRO within 24 hours, as indicated in Appendix 3. The Investigator will submit any updated SAE data to the CRO within 24 hours of it being available. The Investigator is responsible for informing the Ethics Committee of the SAE as per local requirements. All AEs/SAEs have to be reported to the Sponsor, whether or not considered causally related to the study treatment or to the study procedures.

Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, if the Investigator learns of any SAE, including death, at any time after a subject has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the Investigator must promptly notify the CRO.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

8.3.2 Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each subject at subsequent visits/contacts. Subjects who are discontinued from treatment because of SAEs, and non-serious AEs of special interest (AESI) (as defined in Section 8.3.6), will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 3.

8.3.4 Regulatory Reporting Requirements for SAEs

All SAEs must be reported according to ICH GCP or local regulations, applying the regulation with the stricter requirements. The report will contain as much available information concerning the SAE to enable the Sponsor's designated pharmacovigilance personnel/CRO to file a report which satisfies regulatory reporting requirements. The SAE report will be notified by Investigator within 24 hours of his/her awareness to the Sponsor's designated pharmacovigilance personnel/CRO. These timelines apply to initial reports of SAEs and to all follow-up reports. All SAEs will be recorded on the SAE report form in the eCRF and source documents.

The following minimum information must be included in the SAE form:

- Name, address and telephone number of the reporting Investigator,
- Study treatment details,
- Subject identification number, initials, gender, and date of birth,
- Description of the SAE, measures taken, and outcome.

Relevant pages from the eCRF may be provided in parallel (e.g., medical history, concomitant drugs). Additional documents may be provided by the Investigator, if available (e.g., laboratory results, hospital report, autopsy report).

The Investigator must respond to any request for follow-up information (e.g., additional information, outcome, final evaluation, other records where needed) or to any question, the Sponsor's designated pharmacovigilance personnel/CRO may have on the SAE. This is necessary to ensure prompt assessment of the event by the Sponsor's designated pharmacovigilance personnel to allow the Sponsor to meet strict regulatory timelines associated with expedited safety reporting obligations.

8.3.5 Pregnancy

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study treatment may have interfered with the effectiveness of the contraceptive medication. If a pregnancy is reported for a subject, no further study treatment will be administered to this subject, and the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented. Follow-up should be performed up to delivery and examination of the newborn, after which a follow-up report should be sent with any new information regarding the pregnancy and the outcome of the birth.

The pregnancy shall be followed every 3 months during pregnancy until its outcome and 1 month post-delivery. If there are abnormalities present at delivery, the newborn will be followed for an appropriate period, or up to 3 months, to assess the functional and health status of the child.

All congenital abnormalities/birth defects should be classified as SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as SAEs but should be reported as a follow-up report for the pregnancy. All outcomes of pregnancy must be reported to the Sponsor on a Pregnancy Outcomes Report Form.

Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the female partner.

Pregnancies must be reported to IQVIA Clinical Pharmacovigilance and Safety Services using the reporting details provided in Appendix 3 within 24 hours of becoming aware of the pregnancy.

8.3.6 Adverse Events of Special Interest

Injection site reactions, including injection site urticaria, pruritus, pain, reaction, erythema, inflammation, edema, swelling, bruising, hematoma, and hemorrhage, can be observed with the use of tildrakizumab. In general, these AE are well-tolerated and tend to disappear spontaneously, but if any of those occur in this study, they will be captured as AEs of special interest.

The events of severe infections, malignancies (including non-melanoma and melanoma skin cancer), major adverse cardiovascular events (MACE)s, and study treatment-related hypersensitivity reactions (see Appendix 3) will be identified as AESIs for summarizing in this study. Major Adverse Cardiovascular Events include non-fatal stroke, non-fatal myocardial infarction, and cardiovascular death. An AESI must be reported to the sponsor as if it were an SAE.

8.3.7 Events of Clinical Interest

An Event of Clinical Interest (ECI) is a non-serious AE or occurrence that is designated to be of special interest and must be reported to the Sponsor as though it were an SAE.

The following events are considered ECIs for this study:

- An overdose of study treatment. An overdose that is not associated with clinical symptoms or abnormal laboratory results is to be reported as a non-serious ECI, using the terminology "accidental or intentional overdose without adverse effect."
- An elevated AST or ALT laboratory value that is ≥ 3 × the ULN and an elevated total bilirubin laboratory value that is ≥ 2 × ULN and, at the same time, an alkaline phosphatase laboratory value that is < 2 × ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.
- Infections that require IV or IM antibiotics but do not meet the definition of an SAE will be designated a closely monitored AE for this study.
- Depression, suicidal ideation, and other behavior events.

8.4 Treatment of Overdose

A drug overdose is defined as the accidental or intentional use of a drug or medicine or an administration error in an amount that is higher than is normally used. Every overdose must be reported to IQVIA Clinical Pharmacovigilance and Safety Services within 24 hours of awareness, irrespective of whether the overdose was associated with an AE/SAE.

Overdose in this study is specifically defined as any dose greater than the intended protocol dose (see Section 6.1). In case of overdose, it is recommended that the subject be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment be instituted immediately.

8.5 Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7 Genetics

Genetics are not evaluated in this study.

8.8 Biomarkers

Biomarkers are not evaluated in this study.

8.9 Health Economics or Medical Resource Utilization and Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

9.0 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

The primary efficacy endpoint for this study is the proportion of subjects who achieve at least a 75% improvement from baseline in total-mNAPSI at Week 28. The key secondary efficacy endpoint is the proportion of subjects with a score of "0 - normal" or "1 – minimal nail psoriasis" and at least a 2-point decrease from baseline at Week 28 as measured by the ViSENPsO.For each endpoint, the tildrakizumab 100 mg dose will be compared with the placebo at Week 28.

The overall study Type 1 error will be controlled for the primary and secondary efficacy endpoints using the step-down sequential procedure to control the overall type I error rate at 0.05 level. The hierarchical order of testing the endpoints will follow the sequence provided below:

[redacted]

9.2 Sample Size Determination

Conservatively assuming the mNAPSI75 response rates between active drugs and placebo of 35 vs 10 (Results from a similar therapeutic agent, Adalimumab had shown response rates of 46 vs 3 (43)) and assuming Normal Approximation and a Z-test (pooled) for proportions and a two-sided alpha (α) of 0.05 approximately 43 subjects per treatment arm (for a total 86) will need to be randomized in a 1:1 ratio, stratified for prior use of TNF-alpha inhibitors (yes/no) and baseline body weight (≤90 kg or >90 kg). Under these assumptions, 48 subjects in each arm, after accounting for up to 10% dropout, will yield at least 80(43)% power.

At 80% power and alpha of 0.05, evaluable per arm subjects shall be 43. Considering 10% dropout study shall enroll 96 subjects [48 per arm]

9.3 Populations for Analyses

For purposes of analysis, the analysis sets in Table 5 are defined.

Table 5: Analysis Sets

Analysis Set	Description
Intent-to-Treat (ITT)	All randomized subjects who were dispensed study treatment, regardless of whether treatment was taken by the subject or not. The primary efficacy population will be the ITT.
Per Protocol Set (PPS)	All subjects in the ITT population who complete the 28-week placebo-controlled treatment without any major protocol deviations. Details of exclusion criteria for the PPS will be specified in the Statistical Analysis Plan (SAP). The composition of the PPS will be determined in blind reviews of the database conducted prior to the analysis at Week 28.
Safety Analysis Set (SAF)	All randomized subjects who have taken at least 1 dose of study treatment. Subjects will be analyzed according to the treatment they actually received. Safety endpoints will be analyzed descriptively based on the SAP.

9.4 Statistical Analyses

Statistical analyses will be performed using SAS® Version 9.4 or higher. All details regarding the statistical analysis and the preparation of tables, figures, and listings will be described in the SAP. The SAP will be developed and finalized before the unblinded interim analysis for analysis after all subjects complete Week 28 visit. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

The following descriptive statistics will be used as applicable to summarize the study data unless otherwise specified:

- Continuous variables: sample size (n), mean, standard deviation (SD), median, minimum (min), and maximum (max).
- Categorical variables: frequencies and percentages.

Unless otherwise specified, “Baseline” is defined as the last observed value of the parameter of interest prior to the first intake of study treatment (this includes unscheduled visits). For numerical variables, change from Baseline will be calculated as the difference between the post-baseline value and the corresponding Baseline value.

Statistical comparisons for the primary and key secondary endpoints will be performed for inferential purpose following the testing approach described in Section 9.1; other statistical comparisons will be performed for descriptive purpose. COVID-19 related analyses will be specified in the SAP.

Individual subject data will be presented in listings.

9.4.1 Efficacy Analyses

Table 6: Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary and Key Secondary Efficacy Endpoints	
• The proportion of subjects who achieve at least a 75% improvement from Baseline in total modified Nail Psoriasis Severity Index (mNAPSI) at Week 28. (Primary efficacy endpoint) • The proportion of subjects with a score of "0 - normal" or "1 – minimal nail psoriasis" and at least a 2-point decrease from baseline at Week 28 as measured by the ViSENPsO. (Key secondary endpoint)	The primary and key secondary analyses will be a comparison between the responders at Week 28 across the tildrakizumab 100 mg and placebo treatment arms using a Cochran-Mantel-Haenszel test, incorporating prior use of TNF-alpha inhibitors (yes/no) and Baseline body weight (≤90 kg or >90 kg) as stratification factors. In addition, M&N common risk (the response rate) difference between tildrakizumab 100 mg and placebo arm along with the 95% confidence interval will be estimated. These analyses will be based on the ITT population. All analyses will also be conducted for the PPS populations as supportive. For the primary endpoint, subjects with missing values will be imputed using non-responder imputation. The estimand framework for the primary and key secondary efficacy endpoints will be based on composite strategy approach and details will be described in the SAP. The following sensitivity analyses will be performed: • PPS, using Observed Cases only. • Other sensitivity analyses based on multiple imputation methods, in addition to a tipping point analysis, will be described in the SAP.
Secondary and Exploratory Endpoints	
• The proportion of subjects with, at least 3 point decrease from Baseline in nail pain NRS score at Week 28 in subjects with baseline nail pain NRS score of ≥ 3* • The proportion of subjects achieving total-fingernail mNAPSI 90, and mNAPSI 100 at Week 28. • The proportion of subjects achieving total fingernail NAPSI 75, NAPSI 90 and NAPSI 100 at Week 28 • Change in total-fingernail mNAPSI score from Baseline at Week 28.	All secondary and exploratory efficacy endpoints will be analyzed using the ITT population. Binary endpoints up to Week 28 will be analyzed based on the methods described for the primary endpoint. For change-from-baseline at Week 28 (continuous), secondary efficacy endpoints, MMRM model with treatment, visit (Weeks 4, 8,12,16,20,24,28), prior use of TNF-alpha inhibitors (yes/no), baseline body weight (≤90 kg or >90 kg), treatment-by-visit interaction as factors and corresponding baseline value as a covariate will be performed. Secondary and Exploratory efficacy endpoints obtained from

Endpoint	Statistical Analysis Methods
• Change in total-fingernail NAPSI score from Baseline at Week 28. • Change in patient-reported nail pain NRS score • Clinician-assessed proportions of ViSENPsO category results at Week 28 compared between treatment groups. • The proportion of subjects achieving PASI 75, PASI 90, and PASI 100 at Week 28. • The proportion of subjects achieving a PGA-S score of "clear" or "almost clear" with at least 2-point reduction from Baseline at Week 28. • Percentage change in total BSA involvement from Baseline at Week 28. • Change from Baseline in mNAPSI, NAPSI, Nail Pain NRS, BSA, PGA-S, s-PGA, PASI and the proportions of ViSENPsO category results at measured time points through Week 52. • Change from Baseline in DLQI score (total and domain scores), NAPPA-QoL score, CGIC, CGIS, PGIC, PGIC-P, PGIS, and PGIS-P at measured time points through Week 52. • The proportion of subjects with, at least, 30% decrease in Nail Pain NRS score from Baseline at Week 28 in subjects with a baseline nail pain NRS score of > 3	Week 28 to Week 52 will be evaluated using summary statistics.

Abbreviations: BSA = body surface area; CGIC = Clinician Global Impression of Change; CGIS = Clinician Global Impression of Severity; DLQI = Dermatology Life Quality Index; ITT = Intent to treat; LOCF = Last-Observation-Carried-Forward; MMRM = Mixed Model Repeated Measures; mNAPSI = modified Nail Psoriasis Severity Index; NAPPA-QoL = Nail Assessment in Psoriasis and Psoriatic Arthritis Quality of Life; NAPSI = Nail Psoriasis Severity Index; NRS = Numeric Rating Scale; PASI = Psoriasis Area and Severity Index; PGA-S = Physician Global Assessment-Skin; PGIC = Patient Global impression of Change; PGIC-P = Patient Global impression of Change for pain; PGIS = Patient Global Impression of Severity; PGIS-P = Patient Global Impression of Severity for pain; PPS = Per Protocol Set; s-PGA = static Physicians' Global Assessment TNF = tumor necrosis factor; ViSENPsO = Visual Medical Scale to Evaluate Nail Psoriasis Severity

9.4.2 Safety Analyses

All safety analyses will be performed on the Safety Analysis Set based on the actual treatment they received. All the safety will be summarized by the treatment arm, and by-subject listings will be provided.

9.4.2.1 Adverse Events and Serious Adverse Events

Treatment-emergent adverse events are defined as AEs that first occurred or worsened in severity after the first administration of study treatment.

Adverse events will be coded using the most current version of the Medical Dictionary for Regulatory Activities (MedDRA). For each study treatment, the numbers of TEAEs and incidence rates will be tabulated by preferred term and system organ class.

Treatment-emergent AEs by maximum severity, TEAEs by relationship to study treatment, SAEs, TEAEs leading to death, and TEAEs leading to discontinuation of study treatment will be tabulated for each treatment arm. Commonly occurring TEAEs, i.e., those that occur in 5% or more of the subjects in either treatment arm, will be summarized using descriptive statistics.

The safety of tildrakizumab will be evaluated and reported as the percentage of subjects for the following TEAEs:

- Incidence, seriousness, and severity of all AEs, death cases, and discontinuations from the study.
- Percentage of subjects with severe infections, defined as any infection meeting the regulatory definition of an SAE or any infection requiring IV antibiotics whether or not reported as a serious event as per the regulatory definition.
- Percentage of subjects with malignancies (excluding carcinoma in situ of the cervix).
- Percentage of subjects with non-melanoma skin cancer.
- Percentage of subjects with melanoma skin cancer.
- Percentage of subjects with MACE (see Section 8.3.6).
- Percentage of subjects with study treatment-related hypersensitivity reactions (e.g., anaphylaxis, urticaria, angioedema, etc.).
- Percentage of subjects with injection site reactions (e.g., pain, erythema, edema, etc.).

9.4.2.2 Physical Examinations, 12-Lead ECG, Vital Signs, and Clinical Safety Laboratory Tests (Hematology, Biochemistry, and Urinalysis)

Summaries and listings of data for physical examination findings, vital signs, hematology, biochemistry, and urinalysis laboratory tests will be presented. Appropriate descriptive statistics will be presented for the observed value at each scheduled assessment and for the corresponding change from Baseline.

For hematology and biochemistry tests, listings of subject data will also flag any abnormal or out-of-range values. Clinically significant changes in the laboratory test parameters will be summarized and listed. Hematology and clinical laboratory data will be reported using Conventional Units.

Descriptive statistics will be used to present the safety outcomes, including physical examination results, weight, body mass index, 12-Lead ECG, vital signs measurements, and clinical laboratory test results.

Change from Baseline will also be summarized for vital signs measurements and clinical laboratory test results.

All ECG data results (normal/abnormal) will be summarized using frequency and percentages. Clinically significant abnormalities will be presented in by-subject listings.

The incidence of treatment-emergent abnormal laboratory, vital signs, and ECG values will also be summarized using descriptive statistics.

9.4.3 Other Analyses

No other analyses are planned for this study.

9.4.4 Missing Data

Data from subjects who withdraw from the study, including AEs and any follow-up, will be included in the analyses as applicable.

Handling of missing data is described in Table 6 of Section 9.4.1.

9.5 Interim Analyses (IA)

An interim analysis may be performed. An external program-independent Data Monitoring Committee (DMC) may be established to conduct this unblinded interim analysis, review the unblinded results and make recommendations regarding the continuation of the study. To maintain the scientific reliability of possible final results and guard from introducing any potential bias into the conduct of the study and analysis, individuals involved in the interim analysis will not be involved in any operational aspect of the study. Further details of the unblinded interim analysis, in particular, its scope, the processes put in place to maintain study integrity, team structures, and responsibilities, will be documented in the Data Monitoring Committee Charter and/or a separate document. The interim analysis could include an unblinded sample size re-estimation (SSRE). The sample size of the study could be increased as a result of this SSRE. In the event of an increase in sample size, the total sample size of the study will not exceed a total of approximately 282 randomized subjects.

Following the last subject's Week 28 visit (or early termination prior to Week 28), a primary analysis may be conducted on available data to evaluate safety and efficacy and develop a clinical study report based on the data evaluated up to Week 28 visit. This analysis will be performed by the CRO; the Sponsor, and the DMC may not be involved in this analysis.

In the event of such an analysis, subjects who complete Part 1, all assessments of efficacy and safety before or on the date of injection at Week 28 (or Day 210 for subjects who do not have Week 28 injection), will be fully evaluated. Study centers, subjects, and study team members directly involved in study activities will remain blinded to study treatment assignments until the last subject completes their active treatment period (Week 52) and wash-out period. A separate document will provide further details related to the unblinding of personnel involved in reporting activities for the IAs. Sharing of subject-level unblinded information for the IAs will be confined to a designated unblinded study team.

The SAP will describe the planned IAs in greater detail.

9.6 Monitoring Committee

An independent Data Monitoring Committee may be established for periodic review of safety data from the study. The composition and responsibilities of the DMC will be described in the DMC Charter. The DMC will have access to unblinded data, including the interim analysis performed before the primary analysis.

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11.0 APPENDICES

Appendix 1: Regulatory, Ethical and Study Oversight Considerations

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines.
  - Applicable International Council for Harmonisation Good Clinical Practice (ICH GCP) Guidelines.
  - Applicable laws and regulations.
- The protocol, protocol amendments, informed consent form (ICF), Investigator Brochure, and other relevant documents (e.g. advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) before the study is initiated.
- Any amendments to the protocol will require IRB/IEC and regulatory authority approval, when applicable, before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to subjects.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC. Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
  - Providing oversight of the conduct of the study at the study center and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.
- After reading the protocol, each Investigator will sign the protocol signature page and send a copy of the signed page to the Sponsor or representative (Appendix 23:). The study will not start at any study center at which the Investigator has not signed the protocol.

Financial Disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Insurance

Sponsor will provide insurance in accordance with local guidelines and requirements as a minimum for the subjects in this study. The terms of the insurance will be kept in the study files.

Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the subject or his/her legally authorized representative and answer all questions regarding the study.
- Subjects must be informed that their participation is voluntary. Subjects or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability, and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the subject was entered in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the subject or the subject's legally authorized representative.
- A subject who is rescreened is not required to sign another ICF if the rescreening occurs within 30 days from the previous ICF signature date.

Data Protection

- Subjects will be assigned a unique identifier by the Sponsor. Any subject records or datasets that are transferred to the Sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.
- The subject must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject.
- The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Dissemination of Clinical Study Data

The results of the study should be reported within 1 year from the end of the clinical study. Irrespective of the outcome, the Sponsor will submit to the European Union (EU) database a summary of the results of the clinical study within 1 year from the end of the clinical study. It shall be accompanied by a summary written in a manner that is understandable to laypersons.

Quality Control and Quality Assurance

According to the Guidelines of GCP (CPMP/ICH/135/95), IQVIA is responsible for implementing and maintaining quality assurance and quality control systems with written standard operating procedures (SOPs). Quality control will be applied to each stage of data handling.

The following steps will be taken to ensure the accuracy, consistency, completeness, and reliability of the data:

- Central laboratories for clinical laboratory parameters.
- Study center Initiation visit.
- Early study center visits post-enrollment.
- Routine study center monitoring.
- Ongoing study center communication and training.
- Data management quality control checks.
- Continuous data acquisition and cleaning.
- Internal review of data.
- Quality control check of the final clinical study report (CSR).

In addition, Sponsor and/or IQVIA Quality Assurance Department may conduct periodic audits of the study processes, including, but not limited to study center, central laboratories, vendors, clinical database, and final CSR. When audits are conducted, access must be authorized for all study-related documents, including medical history and concomitant medication documentation to authorized Sponsor's representatives and regulatory authorities.

Monitoring

Sponsor has engaged the services of a Contract Research Organization (CRO), IQVIA, to perform all monitoring functions within this clinical study. IQVIA' monitors will work in accordance with IQVIA' SOPs. The monitor will establish and maintain regular contact between the Investigator and Sponsor.

The monitor will evaluate the competence of the study center, informing Sponsor about any problems relating to facilities, technical equipment, or medical staff. During the study, the monitor will check that written informed consent has been obtained from all subjects correctly and that data are recorded correctly and completely. The monitor is also entitled to compare entries in the electronic case report forms (eCRFs) with corresponding source data and to inform the Investigator of any errors or omissions. The monitor will also assess and control adherence to the protocol and ICH/GCP guidelines at the study center. The monitor will arrange for the supply of study treatment, ensure proper study treatment dispensing/accountability, and appropriate storage conditions are maintained.

Monitoring visits will be conducted according to all applicable regulatory requirements and standards. Regular monitoring visits will be made to each center while subjects are enrolled in the study.

During monitoring visits, all entries in the eCRFs will be compared with the original source documents (source data verification). For the following and all other items, this check will be 100%:

- Subject identification number.
- Subject consent obtained.
- Subject eligibility criteria (inclusion and exclusion criteria).
- IMP administration.
- Efficacy variables (not directly entered into electronic patient-reported outcome [ePRO]).
- Safety variables.
- Medical record of adverse event (AE).

Quality Management

A system should be implemented to manage quality throughout all stages of the study process with the focus on study activities essential to ensuring human subject protection and the reliability of study results. The methods used to assure and control the quality of the trial should be proportionate to the risks inherent in the trial and the importance of the information collected. All aspects of the study should be operationally feasible and should avoid unnecessary complexity, procedures, and data collection.

During protocol development, processes, and data that are critical to ensure human subject protection and the reliability of trial results should be identified. Risks should be considered at both the system level (e.g., SOPs, computerized systems, and personnel) and clinical trial level (e.g., trial design, data collection, informed consent process). The approach used to reduce risk to an acceptable level should be proportionate to the significance of the risk. Predefined quality tolerance limits should be established, taking into consideration the medical and statistical characteristics of the variables as well as the statistical design of the trial, to identify systematic issues that can impact subject safety or reliability of trial results. Detection of deviations from the predefined quality tolerance limits should trigger an evaluation to determine if action is needed.

Quality management activities should be documented and communicated to those who are involved in or affected by such activities, to facilitate risk review and continual improvement during clinical trial execution.

Data Management/Coding

Data generated within this clinical study will be handled according to the relevant SOPs of the Data Management and Biostatistics departments of IQVIA.

Electronic data capture (EDC) will be used for this study, meaning that all eCRF data will be entered in electronic forms at the study centers. Data collection will be completed by authorized study center staff designated by the Investigator. Appropriate training and security measures will be completed with the Investigator and all designated study center staff prior to the study being initiated and any data being entered into the system for any study subjects.

All data must be entered in English. The eCRFs should always reflect the latest observations on the subjects participating in the study. Therefore, the eCRFs are to be completed as soon as possible during or after the subject's visit. To avoid inter-observer variability, every effort should be made to ensure that the same individual who made the initial Baseline determinations completes all efficacy and safety evaluations. The Investigator must verify that all data entries in the eCRFs are accurate and correct. If some assessments are not done, or if certain information is not available or not applicable or unknown, the Investigator should indicate this in the eCRF. The Investigator will be required to electronically sign off on the clinical data when all the data is clean prior to database lock.

The monitor will review the eCRFs and evaluate them for completeness and consistency. The eCRF will be compared with the source documents to ensure that there are no discrepancies between critical data. The monitor cannot enter data in the eCRFs. All entries, corrections, and alterations are to be made by the responsible Investigator or his/her designee. If additional corrections are needed, the responsible monitor or Data Manager will raise a query in the EDC application. The appropriate study center staff will answer queries sent to the Investigator. This will be audit trailed by the EDC application, meaning that the name of investigational staff, time, and date stamp are captured.

The eCRF is essentially considered a data entry form and should not constitute the original (or source) medical records unless otherwise specified. Source documents are all documents used by the Investigator or hospital that relate to the subject's medical history, that verify the existence of the subject, the inclusion and exclusion criteria and all records covering the subject's participation in the study. They include but are not limited to laboratory notes, electrocardiogram (ECG) results, memoranda, pharmacy dispensing records, subject files, etc. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Any changes to the source documents or cancellations should be signed and initialed with a date. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g., via an audit trail).

The Investigator is responsible for maintaining source documents. These will be made available for inspection by the study monitor at each monitoring visit. The Investigator must submit a completed eCRF for each subject who is screened and enrolled in the study, regardless of duration. All supportive documentation submitted with the eCRF, such as a laboratory or hospital records, should be clearly identified with the study and subject number. Any personal information, including subject name, should be removed or rendered illegible to preserve individual confidentiality.

User Roles and Responsibilities:

Once clinical data of the eCRF have been submitted to the central server, corrections to the data fields will be audit trailed, meaning that the reason for the change, the name of the person who performed the change, together with time and date will be logged. Roles and rights of the study center staff responsible for entering the clinical data into the eCRF will be determined in advance.

Electronic case report form records will be automatically appended with the identification of the creator, by means of their unique User ID. Specified records will be electronically signed by the Investigator to document his/her review of the data and acknowledgement that the data are accurate. This will be facilitated by means of the Investigator's unique User ID and password; date and time stamps will be added automatically at time of electronic signature.

Data Handling and Record Keeping

The Investigator must maintain essential study documents (protocol and protocol amendments, completed eCRFs, signed ICFs, relevant correspondence, and all other supporting documentation). The study center should plan on retaining such documents for approximately 15 years after study completion. The study center should retain such documents 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 applications in an ICH region or at least 2 years after the formal discontinuation of clinical development of the study treatment. These documents should be retained for a longer period if required by the applicable regulatory requirements or the hospital, institution, or private practice in which the study is being conducted. Subject identification codes (subject names and corresponding study numbers) will be retained for this same period of time. These documents may be transferred to another responsible party, acceptable to Sponsor, who agrees to abide by the retention policies. Written notification of transfer must be submitted to Sponsor. The Investigator must contact Sponsor prior to disposing of any study records.

Direct Access to Source Documents

The Investigator will prepare and maintain adequate and accurate source documents to record all observations and other pertinent data for each subject randomized into the study.

The Investigator will allow Sponsor, IQVIA, and authorized regulatory authorities to have direct access to all documents pertaining to the study, including individual subject medical records, as appropriate. Such information must be kept confidential and must have locked facilities that allow for this. Subject identification number will be recorded on all documents related to the study.

Study and Study Center Closure

The Sponsor designee reserves the right to close the study center or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study centers will be closed upon study

completion. A study center is considered closed when all required documents and study supplies have been collected, and a study center closure visit has been performed.

The Investigator may initiate study center closure at any time, provided there is reasonable cause, and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study center by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of subjects by the Investigator.
- Discontinuation of further study treatment development.

Publication Policy

The data generated by this study are confidential information of the Sponsor. [redacted]

Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 7 will be performed by the ACM Global Laboratories. The time points are specified in the Schedule of Activities (SoA) (see Section 1.3).
- Local laboratory tests will be allowed in the event that the central laboratory results will not be available immediately and the Investigator needs to take an immediate decision for any safety concerns. If a local sample is required, it is important that the sample for central analysis is obtained at the same time.
- Local laboratory results must be entered into the eCRF.
- Urine pregnancy test will be performed at the study center prior to study treatment administration.
- Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Section 5.0 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

- Investigators must document their review of each laboratory safety report.

Table 7: Protocol-required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**	
Hematology	Hemoglobin	White Blood Cell Count (WBC)*
	Hematocrit	* WBC with Differential only if WBC is abnormal
	Platelet count	
Clinical Chemistry	Alanine aminotransferase (ALT)	Creatinine
	Albumin	Gamma glutamyl transferase (GGT)
	Alkaline phosphatase (ALP)	Glucose
	Aspartate aminotransferase (AST)	Potassium
	Bicarbonate	Phosphate (Inorganic)
	Bilirubin (Total)	Protein (Total)
	Bilirubin (Direct-only if the total is elevated)	Sodium
	Calcium	Blood urea nitrogen (urea)
	Chloride	Creatine Kinase
	Uric acid	Triglycerides
	Lactate dehydrogenase	
Lipids (fasting)	Total Cholesterol (fractions)	Triglycerides
Serum pregnancy [a]	Human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)	
Follicle-stimulating hormone (FSH)	As needed in a postmenopausal woman aged over 45 years with at least 1 year of amenorrhea without an alternative medical cause.	

Laboratory Assessments	**Parameters**	
Urinalysis	Bilirubin	pH
	Blood	Protein
	Glucose	Specific gravity
	Ketones	Urobilinogen
	Leukocyte esterase (if it is abnormal, a full microscopic examination may be performed)	Microbiology (At the discretion of Investigator based on urinalysis results)
	Nitrites	Microscopy (At the discretion of Investigator based on urinalysis results)
Viral serology[a]	Hepatitis B surface antigen	
	Hepatitis C Antibody	
	HIV antibodies	
Tuberculosis (TB) Screening[a]	QuantiFERON® test	

NOTES:
[a] Only during Screening
- The results of each test must be entered into the electronic case report form (eCRF). The date and exact time of sample collection must be recorded.
- Blood samples are to be collected (prior to study treatment administration), after an electrocardiogram (ECG) and vital sign measurements. At visits where lipids are to be assessed, the blood samples are to be collected (prior to study treatment administration) after 12 hours fasting, following ECG and vital sign measurements.

Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

An AE is any untoward medical occurrence in a patient or subject, temporally associated with the use of study treatment, whether or not considered related to the study treatment.

NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study treatment.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from Baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or severity of the condition.
- New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.

- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Pregnancy itself is not regarded as an AE unless there is suspicion that the study treatment may have interfered with the effectiveness of a contraceptive medication. If a pregnancy is reported for a subject, no further study treatment will be administered to this subject and the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented. Follow-up should be performed up to delivery and examination of the newborn, after which a follow-up report should be sent with any new information regarding the pregnancy and the outcome of the birth.
- All congenital abnormalities/birth defects should be classified as SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as SAEs but should be reported as a follow-up report for the pregnancy. All outcomes of pregnancy must be reported to the Sponsor on a Pregnancy Outcomes Report Form.
- Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the female partner.
- The pregnancy shall be followed every 3 months during pregnancy till until its outcome and 1 month post-delivery. If there are abnormalities present at delivery, the newborn will be followed for an appropriate period, or up to 3 months, to assess the functional and health status of the child
- Pregnancies must be reported to IQVIA Clinical Pharmacovigilance and Safety Services using the reporting details provided in Section 8.3.5 within 24 hours of awareness.

Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g. hospitalization for signs/symptoms of the disease under study, death due to the progression of disease).

An SAE is defined as, but is not limited to, an event that:

a) Results in death

Death is not an AE in itself, but an outcome. The cause of death is the AE, which resulted in death.

b) Is life-threatening

Life-threatening means that the subject was at immediate risk of death at the time of the SAE; it does not refer to an SAE that hypothetically might have caused death if it had been more severe.

c) Requires in-patient hospitalization or prolongs existing hospitalization

Hospitalization is defined as at least 1 overnight formal admission into hospital, usually in order to perform additional tests, provide treatment which it is not possible to provide at home and/or due to an unstable medical condition which requires specific monitoring of the subject. Pre-planned hospitalizations (known already prior to signing the ICF) for pre-existing condition, or a procedure required by the Clinical

Investigation Plan, without a serious deterioration in health or if the hospitalization is clearly not associated with an AE (e.g. social hospitalization) will not be considered an SAE, unless any of the above criteria are fulfilled over the course of the hospitalization due to unplanned complications. Any Hospitalization due to logistic reason will not be considered as SAE. “Social” hospitalization whereby it is administratively impossible to release the subject home is not necessarily an SAE. Complications that occur during hospitalizations are AEs unless they would qualify as an SAE for any of the above criteria. If the complication delays subject release from hospital, then the AE becomes an SAE. Hospitalizations which are not performed due to an AE are not regarded as SAEs.

d) Results in persistent or significant disability/incapacity

The term significant disability refers to any condition that impairs physical/physiological well-being to the extent that the subject is unable to function normally. Physical disability may include, but is not limited to, permanent disability of locomotion or motility, but also systemic permanent dysfunction including heart failure, liver insufficiency or pulmonary fibrosis.

e) Is a congenital anomaly/birth defect

f) Is an important medical event:

Important medical events that may not result in death, be life-threatening or require hospitalization may be considered as an SAE when, based on appropriate medical judgment, they may jeopardize the subject, or the subject may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Recording and Follow-up of AE and/or SAE Definition of the Adverse Event Reporting Period

The AE/SAE reporting period for safety surveillance begins after subject signs ICF. The safety surveillance continues until 20 weeks from last dos

e of study treatment administration. Any AE/SAE occurred post 20 weeks from last dose of study treatment administration will be reported if it is considered related to study treatment by the Investigator.

Unexpected Adverse Event

Any adverse event that is not identified in nature, severity, frequency, or outcome in Investigator Brochure (IB) will be considered as unexpected. Most recent version of IB will serve as reference safety information for assessment of expectedness of SAEs.

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g. hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the eCRF. Each event must be recorded separately.
- It is not acceptable for the Investigator to send photocopies of the subject's medical records to IQVIA Clinical Pharmacovigilance and Safety Services in lieu of completion of the AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by IQVIA Clinical Pharmacovigilance and Safety Services. In this case, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the medical records before submission to IQVIA Clinical Pharmacovigilance and Safety Services.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Severity

The Investigator will make an assessment of severity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the severity of an event; and both AEs and SAEs can be assessed as severe.
  An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality:

The Investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE. The AE must be characterized as certainly/definitely related, unrelated, unlikely to be related, possibly related, or probably related.

- "Certainly/definitely related" suggests that a clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (de-challenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory re-challenge procedure if necessary.
- "Probably related" conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- "Possibly related" suggests that the association of the AE with the study treatment is unknown; however, the AE is not reasonably supported by other conditions.
- "Unlikely to be related" suggests that only a remote connection exists between the study treatment and the AE. Other conditions, including chronic illness, progression or expression of the disease state or reaction to concomitant therapy, appear to explain the reported AE.
- "Unrelated" is used if there is not a reasonable possibility that the study treatment caused the AE.

- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration, will be considered and investigated.
- The Investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report to IQVIA Clinical Pharmacovigilance and Safety Services. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to IQVIA Clinical Pharmacovigilance and Safety Services.
- The Investigator may change his/her opinion of causality in light of follow-up information and send a
- SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Action Taken with respect to study treatment

Action taken is categorized as “none”, “study treatment discontinued permanently”, “study treatment discontinued temporarily and restarted”, or unknown.

Event Outcome

Event outcome recorded and categorized as “Fatal”, “Resolved”, “Resolved with sequelae”, “Resolving”, “Not Resolved”, “Unknown”.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by IQVIA Clinical Pharmacovigilance and Safety Services to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a subject dies during participation in the study or during a recognized follow-up period, the
- Investigator will provide IQVIA Lifecycle Safety with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed eCRF.
- The Investigator will submit any updated SAE data to the IQVIA Clinical Pharmacovigilance and Safety Services within 24 hours of receipt of the information.

Follow-up of unresolved AEs and SAEs

Any AE/SAE unresolved at end of study visit will be followed until resolution/stabilization or as per medical judgment of the Investigator.

Reporting of SAEs

SAE Reporting to IQVIA Clinical Pharmacovigilance and Safety Services via Paper Case Report Form (CRF)

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the IQVIA Clinical Pharmacovigilance and Safety Services.
- In rare circumstances and the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE CRF pages within the designated reporting time frames.

Safety Reporting to Sponsor

IQVIA Clinical Pharmacovigilance and Safety Services will forward the SAE and Pregnancy report to the Sponsor's safety representatives within 1 business day or 3 calendar days (whichever is earlier) of becoming aware of it.

Appendix 4: Anaphylaxis

The clinical criteria for diagnosing anaphylaxis are as follows:

Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:
• Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula) • AND AT LEAST ONE OF THE FOLLOWING: o Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia) o Reduced BP or associated symptoms of end-organ dysfunction (e.g. hypotonia [collapse], syncope, incontinence)
• Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours): o Involvement of the skin-mucosal tissue (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula) o Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia) o Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence) Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
• Reduced BP after exposure to known allergen for that patient (minutes to several hours): o Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP o Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

Abbreviations: BP = blood pressure; PEF = peak expiratory flow

Data source: (44) Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: Summary report – Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol* 2006;117:391-397.

Appendix 5: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
   a) Documented hysterectomy.
   b) Documented bilateral salpingectomy.
   c) Documented bilateral oophorectomy.

   Note: Documentation can come from the study center personnel's: review of the subject's medical records, medical examination, or medical history interview.
3. Postmenopausal female:
   a) A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
   b) Females on HRT and whose menopausal status is in doubt will be required to use 1 of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

Male subjects

- Male subjects with female partners of childbearing potential are eligible to participate if they agree to ONE of the following during the study and for 6 months after the last dose of study treatment:
  - Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.
  - Agree to use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.

- In addition, male subjects must refrain from donating sperm for the duration of the study and for 6 months after the last dose of study treatment.
- Male subjects with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration for the duration of the study and for 6 months after the last dose of the study treatment.

Female subjects

Female subjects of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly, as described in the table below.

Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
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.
Highly Effective Methods That Are User Independent [a]
Implantable progestogen -only hormonal contraception associated with inhibition of ovulation Intrauterine device. Intrauterine hormone-releasing system (IUS). Bilateral tubal occlusion.
Vasectomized partner *A vasectomized partner is a highly effective birth control method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional, highly effective method of contraception should be used.*
Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.*
NOTES: [a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies.

Pregnancy Testing:

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive serum pregnancy test at Screening and urine pregnancy test on Day 1 (prior to study treatment administration).
- Additional pregnancy testing should be performed as mentioned in SoA (see Section 1.3).

- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected. Positive urine pregnancy test result should be confirmed with serum test.

Collection of Pregnancy Information

Male subjects with partners who become pregnant

- The Investigator will attempt to collect pregnancy information on any male subject's female partner who becomes pregnant while the male subject is in this study. This applies only to male subjects who receive study treatment.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be every 3 months during pregnancy until its outcome and 1 month post-delivery. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female Subjects who become pregnant

- The Investigator will collect pregnancy information on any female subject who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a subject's pregnancy. The subject will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the subject and the neonate and the information will be forwarded to the Sponsor. Generally, follow-up will be every 3 months during pregnancy until its outcome and 1 month post-delivery. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure. The method of reporting pregnancy will be similar to SAE reporting as mentioned in Appendix 3.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any post-study pregnancy related SAE considered reasonably related to the study treatment by the Investigator will be reported to the Sponsor as described in Section 8.3.4. While the Investigator is not obligated to actively seek this information in former subjects, he or she may learn of an SAE through spontaneous reporting.
- Any female subject who becomes pregnant while participating in the study will discontinue study treatment or be withdrawn from the study.

- The pregnancy shall be followed every 3 months during pregnancy till its outcome and 1 month post-delivery. If there are abnormalities present at delivery, the newborn will be followed for an appropriate period, or up to 3 months, to assess the functional and health status of the child.

Appendix 6: Definition and Diagnosis of Fungal Nail Infection

Definition
Fungal nail infections (Onychomycosis) are common infections of the fingernails or toenails that can cause the nail to become discolored, thick, and more likely to crack and break.
• Physical findings in fungal nail infection: o Thickening o Discoloration o Friability o Deformed o Hypertrophic or hyperkeratotic o Subungual debris If any of the above physical findings are seen, nail scrapings should be sent for direct microscopy or fungal culture
• Laboratory findings: o Direct microscopy: Identification of hyphae, pseudohyphae, or spores o Fungal culture: Negative or positive

Appendix 7: Nail Psoriasis Severity Index (NAPSI)

The nail is divided with imaginary horizontal and longitudinal lines into quadrants. Each nail is given a score for nail bed psoriasis (0-4) and nail matrix psoriasis (0-4) depending on the presence of any of the features of nail psoriasis in that quadrant.

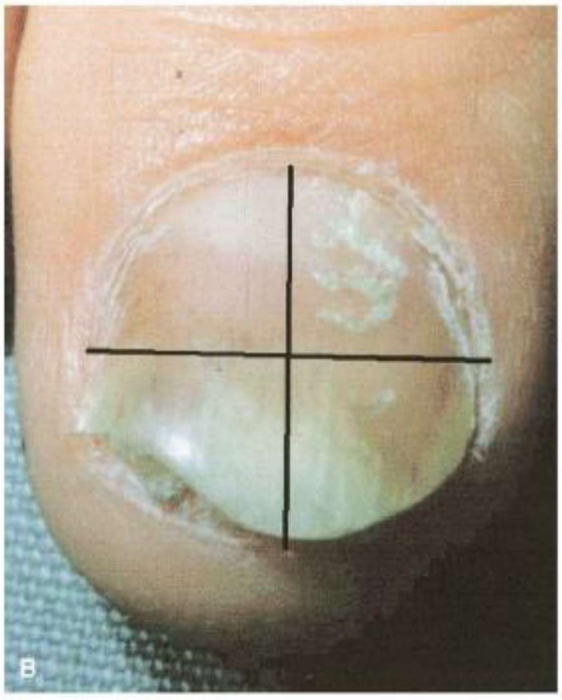
1. Evaluation 1: **Nail matrix.** In each quadrant of the nail, nail matrix psoriasis is evaluated by presence of any of the nail matrix features (pitting, leukonychia red spots in the lunula, crumbling):

0 for none, 1 if present in 1 quadrant of the nail, 2 if present in 2 quadrants of the nail, 3 if present in 3 quadrants of the nail, and 4 if present in 4 quadrants of the nail.

2. Evaluation 2: **Nail bed.** Nail bed psoriasis is evaluated by the presence of any of the nail bed features (onycholysis, splinter hemorrhages, subungual hyperkeratosis, “oil drop” (salmon patch dyschroma): 0 for none, 1 for 1 quadrant only, 2 for 2 quadrants, 3 for 3 quadrants, and 4 for 4 quadrants.

3. Each nail gets a matrix score and a nail bed score, the total of which is the score for that nail (0-8).

4. Each nail is evaluated, and the sum of all the nails is the total NAPSI score. The sum of the scores from all fingernails is 0-80.



Reference: Rich P and Scher RK. J Am Acad Dermatol 2003 Aug; 49(2):206-12 (45)

Appendix 8: modified Nail Psoriasis Severity Index (mNAPSI)

This tool will ask you to assess each nail abnormality for each of a subject's nails. If you question which grade to give, your answer should be the lower of the grades. Three features or groups of features (pitting, onycholysis and oil-drop dyschromia, and crumbling) of each fingernail will be graded on a scale from zero to 3, according to the directions below. Four features (leukonychia, splinter hemorrhages, hyperkeratosis, and red spots in the lunula) will be graded as either present or absent for each fingernail.

Nail Features	Score and Description
Onycholysis and oil-drop (salmon patch) dyschromia	0: No onycholysis or oil drop dyschromia present 1: 1–10% of the nail has onycholysis or oil-drop dyschromia 2: 11–30% of the nail has onycholysis or oil-drop dyschromia 3: > 30% of the nail has onycholysis or oil-drop dyschromia
Pitting	0: No pitting 1: 1–10 pits 2: 11–49 pits 3: ≥ 50 pits
Nail plate crumbling	0: No crumbling 1: 1–25% of the nail has crumbling 2: 26–50% of the nail has crumbling 3: > 50% of the nail has crumbling
Leukonychia	0: Absent 1: Present
Splinter hemorrhages	0: Absent 1: Present
Hyperkeratosis	0: Absent 1: Present
Red spots in the lunula	0: Absent 1: Present
TOTAL SCORE RANGE	0-130 (maximum of 13 for each fingernail)

Reference: Cassell SE, Bieber JD, Rich P et al. J Rheumatol 2007; 34: 123-129 (46)

Appendix 9: Physician's Global Assessment of Skin (Whole Body) (PGA-S)

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

Thickness (T) (averaged across all lesions)	
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)	T =
Erythema (E) (averaged across 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	E =
Scaling (S) (averaged across 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 predominates 5 = severe; very thick tenacious scale predominates	**S** =
Total - Add T + E + S	Total =
Divide Total by 3	Average =
PGA (Round average to the nearest whole number) For example, if Average <1.49, PGA would be 1; if Average >1.50, PGA would be 2.	PGA =

0 = Cleared, except for residual discoloration
1 = Minimal – majority of lesions have individual scores for T+E+S / 3 that average 1
2 = Mild – majority of lesions have individual scores for T+E+S / 3 that average 2
3 = Moderate – majority of lesions have individual scores for T+E+S / 3 that average 3
4 = Marked – majority of lesions have individual scores for T+E+S / 3 that average 4
5 = Severe – majority of lesions have individual scores for T+E+S / 3 that average 5

Appendix 10: Psoriasis Area and Severity Index (PASI)

PASI consists of two major steps:
1) Calculating the BSA covered with lesions and
2) Assessment of the severity of lesions, including assessing the erythema (redness), induration (thickness) and scaling.

All calculations are combined into a single PASI score in the range of 0 (no psoriasis on the body) and up to 72 (the most severe case of psoriasis).

Intensity
A representative area of psoriasis is selected for each body region. The intensity of redness, thickness and scaling of the psoriasis is assessed as none (0), mild (1), moderate (2), severe (3) or very severe (4).

Calculation for intensity
The three intensity scores are added up for each of the four body regions to give subtotals A1, A2, A3, A4.
Each subtotal is multiplied by the body surface area represented by that region.
A1 x 0.1 gives B1
A2 x 0.2 gives B2
A3 x 0.3 gives B3
A4 x 0.4 gives B4

Area
The percentage area affected by psoriasis is evaluated in the four regions of the body (see below). In each region, the area is expressed as nil (0), 1-9% (1), 10-29% (2), 30-49% (3), 50-69% (4), 70-89% (5) or 90-100% (6):

Head and neck
Upper limbs
Trunk
Lower limbs

Calculations for area
Each of the body area scores is multiplied by the area affected.
B1 x (0 to 6)= C1
B2 x (0 to 6)= C2
B3 x (0 to 6)= C3
B4 x (0 to 6)= C4

Total score
The PASI score is C1 + C2 + C3 + C4.

Appendix 11: Numeric Rating Scale (NRS)

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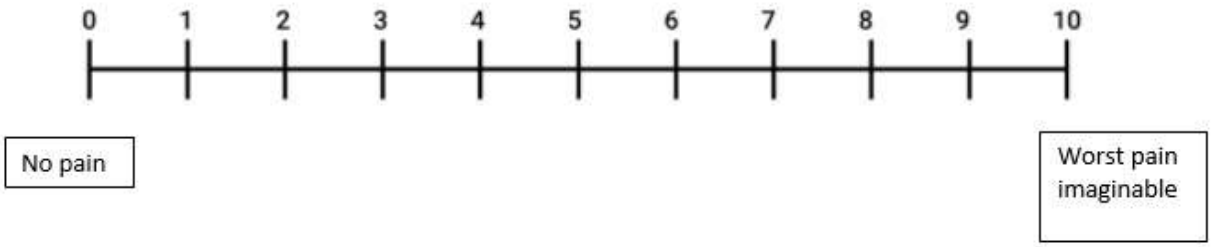

Reference:

https://www.painscale.com/article/numeric-rating-scale-nrs.

[redacted]

Appendix 13: Dermatology Life Quality Index (DLQI)

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 ❒

Please check you have answered EVERY question. Thank you.

Appendix 14: Nail Assessment in Psoriasis and Psoriatic Arthritis QoL (NAPPA-QoL)

QUALITY OF LIFE (NAPPA-QoL)

This questionnaire serves to describe your quality of life with nail psoriasis on hands and/or feet over the past week.

Please answer the questions carefully, yet spontaneously. All responses will be treated confidentially and analyzed anonymously.

■ **In the past week**, how much did the nail psoriasis make you suffer from....		not at all	somewhat	moderately	quite a bit	very
1	...itchy fingers/toes	O	O	O	O	O
2	...pain or other abnormal sensations in the fingers/toes	O	O	O	O	O
3	...reduced strength of the nails (e.g. brittle, thin, atrophied or coming off)	O	O	O	O	O
4	...symptoms such as hardened, thickened or raised nails	O	O	O	O	O
5	...changed appearance of your nails	O	O	O	O	O
6	...difficulty in gripping things	O	O	O	O	O
7	How different do your nails now look?	O	O	O	O	O

■ In each line, please mark the box that best describes how the statement applied to you **in the past week**.		not at all	somewhat	moderately	quite a bit	very
8	My nail psoriasis makes care of my nails difficult.	O	O	O	O	O
9	I often catch my nails on things.	O	O	O	O	O
10	My nail psoriasis makes working with my hands difficult.	O	O	O	O	O
11	I cannot lead a normal working life because of my nail psoriasis.	O	O	O	O	O
12	My leisure and sports activities are restricted by my nail psoriasis.	O	O	O	O	O
13	Nail psoriasis is a burden on my relationship. Or: O currently not in a relationship.	O	O	O	O	O
14	I avoid touching other people because of the nail psoriasis.	O	O	O	O	O
15	I try to hide my nails.	O	O	O	O	O
16	I am embarrassed by the way my nails look.	O	O	O	O	O
17	My nails look ugly.	O	O	O	O	O
18	I have the feeling that other people react negatively to me because of my nail psoriasis.	O	O	O	O	O
19	I have the feeling that other people stare at my nails.	O	O	O	O	O
20	I feel depressed or less self-confident due to the nail psoriasis.	O	O	O	O	O

Please check once more to ensure that you have marked each statement with an "x".

Appendix 15: Patient Global Impression of Change (PGIC)

Please choose the response below that best describes the overall change in your nail psoriasis since you started taking the study medication.

□ Much better
□ A little better
□ No change
□ A little worse
□ Much worse

Reference:

https://www.fda.gov/media/116281/download.

Appendix 16: Patient Global Impression of Change for pain (PGIC-P)

Please choose the response below that best describes the overall change in your nail pain since you started taking the study medication.

□ Much better
□ A little better
□ No change
□ A little worse
□ Much worse

Reference:

https://www.fda.gov/media/116281/download.

Appendix 17: Patient Global Impression of Severity (PGIS)

Please choose the response below that best describes the severity of your nail psoriasis over the past week.

□ None
□ Mild
□ Moderate
□ Severe
□ Very severe

References:

https://www.fda.gov/media/116281/download.

Coon CD, Cappelleri JC. Interpreting change in scores on patient-reported outcome instruments. Therapeutic Innovation & Regulatory Science 2016; 50(1):22-29.

Appendix 18: Patient Global Impression of Severity for pain (PGIS-P)

Please choose the response below that best describes the severity of your nail pain over the past week.

□ None
□ Mild
□ Moderate
□ Severe
□ Very severe

References:

https://www.fda.gov/media/116281/download.

Coon CD, Cappelleri JC. Interpreting change in scores on patient-reported outcome instruments. Therapeutic Innovation & Regulatory Science 2016; 50(1):22-29.

Appendix 19: Columbia-Suicide Severity Rating Scale

1) C-SSRS Screening

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Screening

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

C-SSRS-Screening - United States/English - Mapi.
ID040351 / C-SSRS-Screening_AU5.1_eng-USori.doc

SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.

Past X Months

1. Wish to be Dead
Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.
Have you wished you were dead or wished you could go to sleep and not wake up?
If yes, describe:

Yes ☐ No ☐

2. Non-Specific Active Suicidal Thoughts
General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan.
Have you actually had any thoughts of killing yourself?
If yes, describe:

Yes ☐ No ☐

3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it.....and I would never go through with it."*
Have you been thinking about how you might do this?
If yes, describe:

Yes ☐ No ☐

4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."*
Have you had these thoughts and had some intention of acting on them?
If yes, describe:

Yes ☐ No ☐

5. Active Suicidal Ideation with Specific Plan and Intent
Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.
Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?
If yes, describe:

Yes ☐ No ☐

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal.

Most Severe Ideation: _____ _____

Type # (1-5) ***Description of Ideation***

Most Severe

Frequency
How many times have you had these thoughts?
(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day

_____

Duration
When you have the thoughts, how long do they last?
(1) Fleeting - few seconds or minutes
(2) Less than 1 hour/some of the time
(3) 1-4 hours/a lot of time
(4) 4-8 hours/most of day
(5) More than 8 hours/persistent or continuous

_____

Controllability
Could/can you stop thinking about killing yourself or wanting to die if you want to?
(1) Easily able to control thoughts
(2) Can control thoughts with little difficulty
(3) Can control thoughts with some difficulty
(4) Can control thoughts with a lot of difficulty
(5) Unable to control thoughts
(0) Does not attempt to control thoughts

_____

Deterrents
Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?
(1) Deterrents definitely stopped you from attempting suicide
(2) Deterrents probably stopped you
(3) Uncertain that deterrents stopped you
(4) Deterrents most likely did not stop you
(5) Deterrents definitely did not stop you
(0) Does not apply

_____

Reasons for Ideation
What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?
(1) Completely to get attention, revenge or a reaction from others
(2) Mostly to get attention, revenge or a reaction from others
(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain
(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(0) Does not apply

_____

C-SSRS—Screening (Version 1/14/09)

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Past X Years or Lifetime**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	**Yes** ☐ **No** ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	**Yes** ☐ **No** ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes** ☐ **No** ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes** ☐ **No** ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

C-SSRS—Screening (Version 1/14/09)
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C-SSRS Baseline

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.

Lifetime: Time He/She Felt Most Suicidal

1. Wish to be Dead
Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.
Have you wished you were dead or wished you could go to sleep and not wake up?
Yes ☐ No ☐
If yes, describe:

2. Non-Specific Active Suicidal Thoughts
General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan.
Have you actually had any thoughts of killing yourself?
Yes ☐ No ☐
If yes, describe:

3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."*
Have you been thinking about how you might do this?
Yes ☐ No ☐
If yes, describe:

4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."*
Have you had these thoughts and had some intention of acting on them?
Yes ☐ No ☐
If yes, describe:

5. Active Suicidal Ideation with Specific Plan and Intent
Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.
Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?
Yes ☐ No ☐
If yes, describe:

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal.

Most Severe Ideation: ____ _____

Type # (1-5) ***Description of Ideation***

Most Severe

Frequency
How many times have you had these thoughts?
(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day
____

Duration
When you have the thoughts, how long do they last?
(1) Fleeting - few seconds or minutes
(2) Less than 1 hour/some of the time
(3) 1-4 hours/a lot of time
(4) 4-8 hours/most of day
(5) More than 8 hours/persistent or continuous
____

Controllability
Could/can you stop thinking about killing yourself or wanting to die if you want to?
(1) Easily able to control thoughts
(2) Can control thoughts with little difficulty
(3) Can control thoughts with some difficulty
(4) Can control thoughts with a lot of difficulty
(5) Unable to control thoughts
(0) Does not attempt to control thoughts
____

Deterrents
Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?
(1) Deterrents definitely stopped you from attempting suicide
(2) Deterrents probably stopped you
(3) Uncertain that deterrents stopped you
(4) Deterrents most likely did not stop you
(5) Deterrents definitely did not stop you
(0) Does not apply
____

Reasons for Ideation
What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?
(1) Completely to get attention, revenge or a reaction from others
(2) Mostly to get attention, revenge or a reaction from others
(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain.
(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(0) Does not apply
____

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Page 1 of 2

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes** ☐ **No** ☐ Total # of Attempts _____ **Yes** ☐ **No** ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes** ☐ **No** ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes** ☐ **No** ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

2) C-SSRS Since Last Visit

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

C-SSRS Since Last Visit - United States/English - Mapi.
C-SSRS-SinceLastVisit_AU5.1_eng-USori.doc

SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.

Since Last Visit

1. Wish to be Dead
Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.
Have you wished you were dead or wished you could go to sleep and not wake up?
If yes, describe:
Yes ☐ No ☐

2. Non-Specific Active Suicidal Thoughts
General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period.
Have you actually had any thoughts of killing yourself?
If yes, describe:
Yes ☐ No ☐

3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it.....and I would never go through with it".*
Have you been thinking about how you might do this?
If yes, describe:
Yes ☐ No ☐

4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them".*
Have you had these thoughts and had some intention of acting on them?
If yes, describe:
Yes ☐ No ☐

5. Active Suicidal Ideation with Specific Plan and Intent
Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.
Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?
If yes, describe:
Yes ☐ No ☐

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e.,1-5 from above, with 1 being the least severe and 5 being the most severe).

Most Severe Ideation: _____ _____

Type # (1-5) ***Description of Ideation***

Most Severe

Frequency
How many times have you had these thoughts?
(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day
____

Duration
When you have the thoughts how long do they last?
(1) Fleeting - few seconds or minutes
(2) Less than 1 hour/some of the time
(3) 1-4 hours/a lot of time
(4) 4-8 hours/most of day
(5) More than 8 hours/persistent or continuous
____

Controllability
Could/can you stop thinking about killing yourself or wanting to die if you want to?
(1) Easily able to control thoughts
(2) Can control thoughts with little difficulty
(3) Can control thoughts with some difficulty
(4) Can control thoughts with a lot of difficulty
(5) Unable to control thoughts
(0) Does not attempt to control thoughts
____

Deterrents
Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?
(1) Deterrents definitely stopped you from attempting suicide
(2) Deterrents probably stopped you
(3) Uncertain that deterrents stopped you
(4) Deterrents most likely did not stop you
(5) Deterrents definitely did not stop you
(0) Does not apply
____

Reasons for Ideation
What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?
(1) Completely to get attention, revenge or a reaction from others
(2) Mostly to get attention, revenge or a reaction from others
(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain
(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(0) Does not apply
____

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Since Last Visit**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you_____?*** ***Or Did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes** ☐ **No** ☐ Total # of Attempts _____ **Yes** ☐ **No** ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*. Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes** ☐ **No** ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes** ☐ **No** ☐
Suicide:	**Yes** ☐ **No** ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage: medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

Appendix 20: static Physician's Global Assessment (s-PGA):

	[a]Induration (averaged over all lesions)	[b]Erythema (averaged over all lesions)	[c]Scaling (averaged over all lesions)
0	No evidence of plaque elevation	No evidence of erythema; hyperpigmentation may be present	No evidence of scaling
1	Minimal plaque elevation (≈ 0.5 mm)	Faint erythema	Minimal, occasional fine scale over less than 5% of the lesions
2	Mild plaque elevation (≈ 1 mm)	Light red coloration	Mild, fine scale predominates
3	Moderate plaque elevation (≈ 1.5 mm)	Moderate red coloration	Moderate, coarse scale predominates
4	Marked plaque elevation (≈ 2 mm)	Bright red coloration	Marked, thick, non-tenacious scale predominates
5	Severe plaque elevation (≈ 2.5 mm or more)	Dusky to deep red coloration	Severe, very thick tenacious scale predominates

Static Physician's Global Assessment Score (averaged over all lesions):
0 = clear, except for residual discoloration
1 = almost-clear, lesions have individual scores for induration[a] erythema[b] and scaling[c] (IES) of at least 1
2 = Lesions have individual scores for IES of at least 2
3 = Lesions have individual scores for IES of at least 3
4 = Lesions have individual scores for IES of at least 4
5 = Lesions have individual scores for IES of at least 5

Note: When required for comparison purposes, we converted the sPGA numerical range of 0 to 5 to clear = 0, almost-clear = 1, mild = 2, moderate = 3, marked = 4, and severe = 5.

Reference: Chow C, Simpson MJ, Luger TA, Chubb H, Ellis CN. Comparison of three methods for measuring psoriasis severity in clinical studies (Part 1 of 2): change during therapy in Psoriasis Area and Severity Index, Static Physician's Global Assessment and Lattice System Physician's Global Assessment. J Eur Acad Dermatol Venereol. 2015 Jul;29(7):1406-14.

Appendix 21: Clinician Global Impression of Change (CGIC)

Please choose the response below that best describes the overall change in your patient's nail psoriasis since he/she started taking the study medication.

□ Much better
□ A little better
□ No change
□ A little worse
□ Much worse

Appendix 22: Clinician Global Impression of Severity (CGIS)

Please choose the response below that best describes the severity of your patient's nail psoriasis today.

□ None
□ Mild
□ Moderate
□ Severe
□ Very severe

Appendix 23: Signature of Investigator

PROTOCOL TITLE: A Multicenter, Randomized, Double-blind, Placebo-controlled Clinical Study to Assess the Efficacy and Safety of Tildrakizumab in the Treatment of Moderate to Severe Nail Psoriasis.

PROTOCOL NO: TILD-18-19

VERSION: Amendment 3, 23 Dec 2022

This protocol is a confidential communication of Sun Pharmaceutical Industries Limited. I confirm that I have read this protocol, I understand it, and I will work according to this protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from the Sponsor.

I have read this protocol in its entirety and agree to conduct the study accordingly:

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

_____

_____