

Statistical Analysis Plan for Study TLL018-205

A randomized, double-blinded, placebo-controlled, multicenter Phase 2 study evaluating the efficacy and safety of TLL018 in participants with moderate-to-severe plaque psoriasis

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STATISTICAL ANALYSIS PLAN

A randomized, double-blinded, placebo-controlled, multicenter Phase 2 study evaluating the efficacy and safety of TLL018 in participants with moderate-to-severe plaque psoriasis

TLL018-205

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SAP SIGNATURES

I give my approval for the attached SAP entitled *A randomized, double-blinded, placebo-controlled, multicenter Phase 2 study evaluating the efficacy and safety of TLL018 in participants with moderate-to-severe plaque psoriasis* dated 06-Jun-2024.

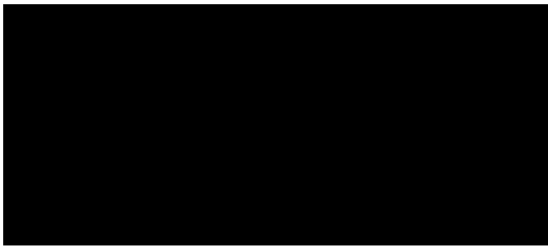
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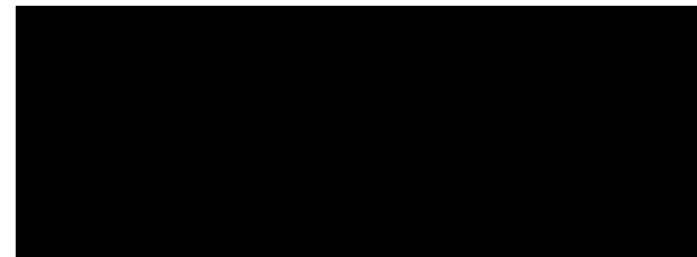
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 Medical Affairs Director, Highlightl Pharma

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TABLE OF CONTENTS

SAP SIGNATURES.....	1
REVISION HISTORY	2
TABLE OF CONTENTS	3
LIST OF ABBREVIATIONS AND DEFINITION OF TERMS	5
1 OVERVIEW AND INVESTIGATIONAL PLAN	8
1.1 STUDY DESIGN AND RANDOMIZATION	8
1.2 OBJECTIVES.....	8
1.2.1 Primary objectives	8
1.2.2 Secondary objectives	8
1.2.3 Exploratory objectives	8
1.3 DETERMINATION OF SAMPLE SIZE	9
1.4 BLINDING	9
1.5 DATA MONITORING COMMITTEE	9
1.6 STUDY PLAN.....	10
2 STATISTICAL AND ANALYTICAL PROCEDURE	13
2.1 ANALYSIS VARIABLES	13
2.1.1 Efficacy variables	13
2.1.1.1 Primary efficacy variable	13
2.1.1.2 Secondary efficacy variables	13
2.1.1.3 Exploratory efficacy variables	14
2.1.2 Safety variables.....	15
2.1.2.1 Adverse events.....	15
2.1.2.2 Laboratory safety variables.....	15
2.1.2.3 Vital signs	16
2.1.2.4 Electrocardiograms	16
2.1.2.5 Physical Examinations findings	17
2.1.3 Pharmacokinetic variables	17
2.1.4 Pharmacodynamic variables	17
2.2 ANALYSIS POPULATIONS	17
2.2.1 Full Analysis Set.....	17
2.2.2 Safety Set.....	17
2.2.3 Per-protocol Set	18
2.3 STATISTICAL METHODS	18
2.3.1 Analysis Conventions	18

2.3.2	Subject Disposition	18
2.3.3	Protocol Deviations	19
2.3.4	Demographics and baseline characteristics.....	19
2.3.5	Medical History	20
2.3.6	Prior/Concomitant Medications and Procedures/Non-Drug Therapies.....	20
2.3.7	Extent of study intervention exposure and compliance	20
2.3.8	Analyses of efficacy variables	21
2.3.8.1	Statistical hypotheses	21
2.3.8.2	Analyses of primary efficacy variable	21
2.3.8.3	Analyses of secondary efficacy variables	22
2.3.8.4	Subgroup Analyses	23
2.3.8.5	Multiplicity issues.....	23
2.3.8.6	Analyses of exploratory efficacy variable(s)	23
2.3.9	Analyses of safety data	24
2.3.9.1	Analyses of adverse events	24
2.3.9.2	Laboratory variables analyses.....	24
2.3.9.3	Analyses of vital sign variables	25
2.3.9.4	Electrocardiograms	25
2.3.9.5	Physical Examination	25
2.3.10	Analyses of pharmacokinetic and pharmacodynamic variables	25
2.3.10.1	Pharmacokinetic	25
2.3.10.2	Pharmacodynamic.....	25
2.4	DATA HANDLING CONVENTIONS	26
2.4.1	Missing data.....	26
2.4.1.1	Handling of Missing data for efficacy endpoints	26
2.4.1.2	Partial Dates for Adverse Events	26
2.4.1.3	Partial Dates for Concomitant therapy.....	26
2.4.1.4	Interval values for Laboratory variables	27
2.4.2	Unscheduled visits	27
2.4.3	Pooling of centers for statistical analyses	27
3	INTERIM ANALYSIS	28
4	SOFTWARE DOCUMENTATION.....	28
5	REFERENCES	28

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse event
AESI	Adverse Events of Special Interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BID	Twice daily
BMI	Body mass index
BQL	Below Quantification Limit
CMH	Cochran-Mantel-Haenszel
COVID-19	Coronavirus disease 2019
CRF	Case report form
CTCAE	Common terminology criteria for adverse event
C _{trough ss}	Trough concentration at steady state
CV	Coefficient of variation
DLQI	Dermatology Life Quality Index
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic case report form
EOT	End of Treatment
ET	Early Termination
FAS	Full Analysis Set
GeoCV	Geometric coefficient of variation
Geomean	Geometric mean
GGT	Gamma glutamyl transferase
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
Hcg	Human chorionic gonadotropin
HCV	Hepatitis C virus
HDL	High density lipoprotein
HIV	Human immunodeficiency virus

IFN	Interferon
Ig	Immunoglobulin
IL	Interleukin
INR	International normalized ratio
IRT	Interactive Response Technology
IXRS	Interactive Voice/Web Response System
LDL	Low density lipoprotein
MedDRA	Medical dictionary for regulatory activities
MMRM	Mixed model repeated measures
NRI	Non-responder imputation
OC	Observed case
PASI	Psoriasis Area and Severity Index
PASI-75	Achieving a minimum 75% improvement from Baseline for PASI
PASI-90	Achieving a minimum 90% improvement from Baseline for PASI
PASI-100	Achieving a 100% improvement from Baseline for PASI
PD	Progressed disease
PEST	Psoriasis Epidemiology Screening Tool
PGA	Physician's Global Assessment
PK	Pharmacokinetics
PP	Plaque psoriasis
PPS	Per-protocol Set
PsAID-9	Psoriatic Arthritis Impact of Disease Questionnaire
PT	Preferred term
PTT	Activated partial thromboplastin time
Q1	Lower quartiles
Q3	Upper quartiles
QTc	corrected QT interval
QTcB	QT intervals corrected by Bazetts's formula
QTcF	QT intervals corrected by Fridericia's formula
REML	Restricted maximum likelihood
RNA	Ribose nucleic acid
SAE	Serious adverse events

SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SOC	System organ class
SS	Safety Set
TB	Tuberculosis
TEAE	Treatment-Emergent Adverse Events
WBC	White blood cell
WHODrug	WHO Drug Dictionary

1 OVERVIEW AND INVESTIGATIONAL PLAN

This statistical analysis plan (SAP) provides a comprehensive and detailed description of strategy and statistical technique to be used to realize the analysis of data for TLL018-205 study protocol V3.0 17-Oct-2023. The purpose of the SAP is to ensure the credibility of the study findings by pre-specifying the statistical approaches to the analysis of study data prior to database lock.

1.1 STUDY DESIGN AND RANDOMIZATION

This is a Phase 2, multicenter, randomized, double-blinded, parallel dose group, placebo-controlled, dose-ranging study to evaluate the efficacy and safety of 2 doses of TLL018 as therapy in up to approximately 90 participants with moderate-to-severe plaque psoriasis (PP).

Up to 3 parallel study intervention cohorts are planned in a double-blinded fashion for a 12-week Treatment Period. The planned study intervention is 20 and 40 mg twice daily (BID). Study investigational product will be administered orally, preferably after or with a meal (breakfast or dinner). Participants will be stratified by previous psoriasis biologic use and diagnosis of psoriatic arthritis.

After a 4-week Screening period (Day -35 to -8), participants who meet eligibility criteria will be randomized in a 2:2:1 ratio to receive 1 of the 3 study interventions for 12 weeks:

- Group 1: TLL018: 20 mg BID orally
- Group 2: TLL018: 40 mg BID orally
- Group 3: Placebo BID

Approximately 90 participants will be evaluated with 72 participants randomized to receive 2 different dose levels of active study intervention and 18 participants randomized to receive placebo in a double-blinded fashion.

Randomization schedules will be prospectively prepared. Automated randomization and study intervention assignment will be performed by an interactive response system (Interactive Voice/Web Response System [IXRS] or Interactive Response Technology [IRT]). Details of the procedure are described in the IXRS/IRT Manual provided to all study sites.

1.2 OBJECTIVES

1.2.1 Primary objectives

- To evaluate the efficacy of TLL018 in the treatment of moderate-to-severe PP.

1.2.2 Secondary objectives

- To evaluate the safety of TLL018 in patients with moderate-to-severe PP
- To evaluate the effect of TLL018 treatment on disease activity and quality of life in participants with moderate-to-severe PP

1.2.3 Exploratory objectives

- To evaluate the effect of TLL018 treatment on disease activity in participants with moderate-to-severe PP

- To evaluate the PD of TLL018 in participants with moderate-to-severe PP
- To evaluate the population PK of TLL018 in participants with moderate-to-severe PP

1.3 DETERMINATION OF SAMPLE SIZE

The sample size of 36 participants for each of the TLL018 BID dose groups and 18 participants in the placebo BID group will provide 85% power for a 1-sided $\alpha = 0.025$, if the proportion of participants achieving a minimum 75% improvement from Baseline in the PASI (PASI-75) compared to placebo at the end of Week 12 is at least 60% in the active group TLL018 BID and around 5% in the placebo group. Considering 20% dropout rate, a total of 90 participants will be enrolled in the study with 36 participants assigned to for each of the TLL018 BID dose groups and 18 participants in the placebo BID group. No adjustment of the type I error α is planned as a hierarchical testing strategy is applied where the highest to the lowest study intervention groups are tested against placebo and testing stops when a comparison is non-significant.

1.4 BLINDING

This is a double-blinded study in which participants and Investigators are blinded to study intervention. The IRT will be programmed with blind-breaking instructions.

Throughout the duration of the study, every effort will be made to maintain the integrity of the study blind based on Blinding Maintenance and Unblinding Plan, the following data must be blinded to patients, sites and blinded study team members, such as sponsor, investigators, data collectors, monitors and analysts:

- Treatment assignment in RTSM system,
- Unblinded PK Results (efficacy endpoints) in external vendor's database,
- Unblinded PD Results (efficacy endpoints) in external vendor's database,
- Unblinded data transfers for DMC review in Q2BI sFTP.

1.5 DATA MONITORING COMMITTEE

Participant safety will be continuously monitored by an independent DMC, which includes safety signal detection at any time during the study. The DMC will meet at defined intervals (initially once every 2 months or more frequently if indicated) to conduct safety reviews of aggregate data after enrollment of a defined number of participants treated for at least 4 weeks. The DMC will recommend to the Sponsor whether to continue, modify, or terminate the study. All Sponsor personnel involved in the adjudication process will remain blinded to treatment allocation throughout the trial. The DMC will be unblinded.

1.6 STUDY PLAN

Table 1-1 Schedule of Assessments

Study Procedure	Screening*	Baseline	Treatment Period Weeks 1 to 12					Follow-up Period
Visit Identifier	Day -35 to Day -8	Day -7 to Day -1	Day 1 Week 1 ^a	Week 4 ±3 Days	Week 8 ±3 Days	Week 12 ±3 Days	ET/EOT ^b	28 ±7 Days After the Last Dose
Informed consent	X							
Demography	X							
Medical history	X							
QuantiFERON ^c	X							
Inclusion criteria	X	X						
Randomization			X					
Covid-19 testing ^d		X						
Covid-19 site precautions ^e	X	X	X ^e	X	X	X	X	X
Physical examination, height/weight, vital signs ^f	X	X		X	X	X	X	X
ECG ^g	X	X		X	X	X	X	X
D-Dimer ^h	X							
HIV, HBV, HCV	X							
Serum β-hCG ⁱ	X							

Study Procedure	Screening*	Baseline	Treatment Period Weeks 1 to 12					Follow-up Period
Visit Identifier	Day -35 to Day -8	Day -7 to Day -1	Day 1 Week 1 ^a	Week 4 ±3 Days	Week 8 ±3 Days	Week 12 ±3 Days	ET/EOT ^b	28 ±7 Days After the Last Dose
Urine pregnancy test ⁱ		X		X	X	X	X	X
Hematology, blood chemistry, fasting lipid panel, urinalysis, coagulation ^k	X	X		X	X	X	X	X
DLQI ^l		X		X	X	X	X	
PASI	X	X		X	X	X	X	X
BSA	X	X		X	X	X	X	X
PGA	X	X		X	X	X	X	X
PEST		X						
PsAID-9 ^m		X		X	X	X	X	X
MSK ⁿ		X		X	X	X	X	X
PD ⁿ bloods		X		X		X		
PK ⁿ bloods		X		X		X		
Study intervention administration			X	X ^o	X			
Collect study intervention and compliance				X	X	X	X	
AE Collection ^p		X		X	X	X	X	X
ConMed Collection	X	X		X	X	X	X	X

AE=adverse event, AST=aspartate aminotransferase, BMI=body mass index, DLQI=Dermatology Life Quality Index, DNA=Deoxyribonucleic acid, ECG=electrocardiograph, EOT=End-of-Treatment, ET=Early Termination, HBV=hepatitis B virus, hCG=human chorionic gonadotropin, HCV=hepatitis C virus, HIV=human immunodeficiency virus, PASI=Psoriasis Area and Severity Index, PD=pharmacodynamics, PGA=Physician's Global Assessment, RNA=ribose nucleic acid,

* Screening procedures may be completed up to Day 1 Week 1, if completed within 7 days of Day 1 Week 1, then they are not to be repeated for Baseline.

- a. It is not necessary for this to be a separate visit, however randomization and dosing must be completed within 24 hours of Baseline completion.
- b. For ET, the participant should complete EOT visit within 2 weeks. For participants who finish the study normally until the end of the Week 12, the Week 12 visit will be the EOT visit.
- c. Positive QuantiFERON result is a screen failure. Two borderline/indeterminate QuantiFERON tests also become a screen failure.
- d. If clinically indicated, confirm a possible coronavirus infection with a rapid test. If tested positive, then do not administer the study drug. May also confirm with a PCR test from central lab. A positive test result from the COVID-19 test will be reported to a health authority as required by the local regulation.
- e. The study site should follow local / institutional guidelines related to COVID-19 prior to every patient visit. Day 1/Week 1 is not necessary if Day 1/Week 1 is incorporated into Baseline.
- f. Body weight will be recorded only at Screening and Week 12 or at the EOT visit to calculate BMI; vital signs should be checked before blood collection and after 5 minutes rest. Vital signs include oral temperature, blood pressure, pulse rate, respiratory rate. Complete physical examination at Screening and focused physical examination at all other visits.
- g. Single ECGs will be performed after 5 minutes rest at Screening/Baseline and the end of Week 4, 12 and/or ET/EOT, and the Follow-Up visits. At any timepoint, if the subject experiences a QTc prolongation, then hold drug and confirm results by triplicate ECG. If confirmed, discontinue subject with CTCAE grade 3 or above. Otherwise, the subject may continue treatment with ECGs in triplicate at all subsequent visits. Discontinued subjects should be followed by triplicate ECGs until QTc prolongation is resolved.
- h. Serum D-dimer: measured during Screening.
- i. For all female participants with reproductive potential (18 years to 12 months after menopause), serum pregnancy tests will be performed during the Screening period. If a Screening serum pregnancy test is performed within 7 days of Day Week 1, then a Baseline urine pregnancy does not have to be completed. Serum pregnancy tests are centrally tested. If the serum pregnancy test is near the positive threshold, then the test should be repeated. If the serum pregnancy test is still near the positive threshold after 3 days, then the patient is screen failed.
- j. Baseline urine is local tested. If the urine pregnancy test is positive, stop administration of study investigational product and a serum pregnancy test should be performed. Participants who have confirmed pregnancy must discontinue the study.
- k. Tests performed centrally. See Section 2.1.2.2.
- l. Complete the DLQI at Baseline or on the day of study intervention administration (Day 1).
- m. Given to patients with known PSA at baseline or PEST score 3 or more at baseline.
- n. PD blood collection will be performed within 30 minutes prior to the first study intervention administration (PD baselines). PD blood collection will also be performed at the end of Week 4, and Week 12. PK blood collections are to be at the same time points as PD samples.
- o. Please skip the at home morning dose during Week 4 visit as study drug should be taken after the trough level and PD markers are drawn in the clinic for this day.
- p. Safety information of all participants may be collected through telephone follow-up, including follow-up of any prior and new AEs.

2 STATISTICAL AND ANALYTICAL PROCEDURE

2.1 ANALYSIS VARIABLES

2.1.1 Efficacy variables

2.1.1.1 Primary efficacy variable

The primary endpoint is the proportion of participants achieving a minimum 75% improvement from Baseline at the end of Week 12 for PASI (PASI-75)

The PASI is a measure of the average redness (erythema), thickness (induration), and scaliness (scaling); each graded on a 0 to 4 scale of the lesions, weighted by the area of involvement. All assessments for a given participant should be made by the same observer, wherever possible. The PASI score is a composite score ranging from 0 (no psoriasis) to 72 (severe psoriasis).

2.1.1.2 Secondary efficacy variables

Secondary endpoints include:

- Proportion of participants achieving PGA score of 0 or 1
- Proportion of participants achieving PASI-75 (except Week 12)
- Proportion of participants achieving PASI-90
- Mean percent change from Baseline in PASI
- Percent of subjects with PGA 0 or 1 and a 2-point improvement from baseline at week 12
- Change from Baseline in DLQI
- Change from baseline in PsAID-9 in patients who are PEST positive or have a rheumatologist's diagnosis of PSA at baseline
- Proportion of PSA or PEST-positive patients achieving a PsAID-9 score of less than or equal to 4 at week 12
- Change from baseline in MSK in all study participants

PGA

The PGA is an observer rating system for psoriasis lesions with scores ranging from 0 to 4 as listed below:

- 0 Clear: No signs of psoriasis, but post-inflammatory discoloration may be present.
- 1 Almost clear: Only minimal plaque elevation, scaling, and erythema.
- 2 Mild: Slight plaque elevation, scaling, and erythema.
- 3 Moderate: Moderate plaque elevation, scaling, and erythema.
- 4 Severe: Very marked plaque elevation, scaling, and erythema.

PASI-90

PASI-90 is defined as a minimum 90% improvement from Baseline for PASI.

DLQI

The DLQI is a 10-question validated questionnaire. It is calculated by summing the score of each question resulting in a maximum of 30 and a minimum of 0. The higher the score, the more quality of life is impaired.

PEST

The PEST ^[1] is a 5-question validated questionnaire. Three or more affirmative answers is a positive psoriatic arthritis diagnosis.

PsAID-9

The PsAID-9 ^[2] is a 9-question validated questionnaire to assess psoriatic arthritis symptom severity. Higher values indicate worse symptoms. It is calculated by the formula below:

PsAID Score =

$$\begin{aligned} & (\text{PsAID1 (pain) value (range 0-10)} * 0.174) \\ & + (\text{PsAID2 (fatigue) value (range 0-10)} * 0.131) \\ & + (\text{PsAID3 (skin) value (range 0-10)} * 0.121) \\ & + (\text{PsAID4 (Work and/or leisure activities) value (range 0-10)} * 0.110) \\ & + (\text{PsAID5 (function) value (range 0-10)} * 0.107) \\ & + (\text{PsAID6 (discomfort) value (range 0-10)} * 0.098) \\ & + (\text{PsAID7 (sleep) value (range 0-10)} * 0.089) \\ & + (\text{PsAID8 (coping) value (range 0-10)} * 0.087) \\ & + (\text{PsAID9 (anxiety) value (range 0-10)} * 0.085) \end{aligned}$$

IDEOM MSK

The IDEOM MSK ^[3] is a questionnaire utilizing 9 questions across two parts to assess musculoskeletal symptoms and quality of life. Higher values indicate worse symptoms or diminished quality of life. It is calculated by three Sub-scores as described below:

- MSK Symptoms Sub-score (range 0-30): (Question 1 (pain) NRS value (range 0–10)) + (Question 2 (joint swelling) NRS value (range 0–10)) + (Question 3 (joint stiffness) converted NRS* value (range 0–10)).
- Impact of MSK Symptoms Sub-score (range 0-50): (Question 4 (Work and/or school activities) NRS value (range 0–10)) + (Question 5 (Family, social, and/or leisure activities) NRS value (range 0–10)) + (Question 6 (Physical activities) NRS value (range 0–10)) + (Question 7 (Sleep) NRS value (range 0–10)) + (Question 8 (Emotional state) NRS value (range 0–10)).
- Fatigue Sub-score (range 0-10): Question 9 (Fatigue) NRS value (range 0–10).

2.1.1.3 Exploratory efficacy variables

The exploratory efficacy variable is proportion of participants achieving PASI-100, defined as a 100% improvement from Baseline for PASI.

2.1.2 Safety variables

2.1.2.1 Adverse events

- **Treatment-emergent adverse event (TEAE):** an AE began or worsened (increased in severity) on or after the date of the first dose of the study intervention, but will not be counted if the AE occurs more than 30 days after the last dose of study intervention or EOT.
- **Serious Adverse Event (SAE):** an AE that meets the definition in Section 10.3.2 from protocol.
- **Adverse Events of Special Interest (AESI):** an AE that meets the definition in Section 10.3.3 from protocol.
- **TEAE requiring treatment:** an TEAE that meets other action taken with Concomitant Medication or Procedures and Non-Drug Therapies per CRF.

All adverse events will be coded using MedDRA (version 25.1 or higher). Severity of adverse events rated by the investigators as 5 grades based on Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. Causality of adverse events follows binary decision choice (Related or Not related).

For details on handling missing data and partial dates, see [2.4.1.2](#).

2.1.2.2 Laboratory safety variables

All protocol-required laboratory tests, as defined in below table:

Laboratory Tests	Parameters
Hematology	Hemoglobin Reticulocytes RBC count WBC count and classifications (including absolute neutrophils, eosinophils, basophils, lymphocyte count) Platelet count D-dimer
Clinical chemistry	Creatinine Urea or urea nitrogen Total protein Albumin Total and direct bilirubin Alkaline phosphatase Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Gamma glutamyl transferase (GGT) Total cholesterol Triglyceride High density lipoprotein (HDL) Low density lipoprotein (LDL) Fasting blood-glucose Sodium Potassium Calcium Phosphorus Troponin
Coagulation	Prothrombin Time (PT) International Normalized Ratio (INR) Activated partial thromboplastin time (PTT)

Laboratory Tests	Parameters
Routine urinalysis	Specific gravity Color and appearance [*] Urine protein [*] Urine glucose [*] Urine ketone [*] Urine red blood cells and urine white blood cells; by semiquantitative dipstick [*] Microscopic urinary sediment analysis: cells, casts, crystals [*]
Pregnancy testing	Serum hCG pregnancy test at Screening (centrally) Urine (completed locally) at Baseline and all timepoints except Screening
Other Screening tests	FSH (as needed in women of non-childbearing potential only) Serology (HIV antibody, HBsAg, HBcAb and HCV antibody) [*]. Subsequent testing (if required) for Hepatitis B DNA and Hepatitis C RNA. QuantiFERON-TB for screen [*]
COVID-19 testing	(Optional, if requested by PI) SARS-CoV-2 RT-PCR [*] SARS-CoV-2 antibody assay (IgG, IgA, or IgM) [*] Rapid Test

[*] Non-quantitative laboratory results marked

2.1.2.3 Vital signs

- Oral temperature (C)
- Pulse rate (beats/min)
- Respiratory rate (breaths/min)
- Systolic/diastolic blood pressure (mmHg)

Vital signs (measured before blood collection for laboratory tests) will consist of 3 pulse and 3 blood pressure measurements (after the participant has been sitting for 5 minutes, 3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute). The average of the 3 blood pressure and average of the 3 pulse readings will be recorded.

2.1.2.4 Electrocardiograms

ECGs will be performed using an ECG monitor (Single or Triplicate) that automatically calculates with following variables:

- Heart Rate (beats/min)
- PR (ms)
- RR (ms)
- QRS Duration (ms)
- QT Intervals (ms)
- QTc Intervals (ms)
- ECG Result (Normal, Abnormal NCS, Abnormal CS, Not Done)

If the QTc value collected is calculated based on Bazett's correction or other formula, QTcF will be calculated using the formula $QT \times (HR/60)^{1/3}$.

The QTcF will be categorized into below categories:

- ≤ 450 ms
- $>450 - 480$ ms
- $>480 - 500$ ms
- > 500 ms

The QTcF change from baseline will be categorized as below:

- Increase from baseline ≤ 30 ms
- Increase from baseline $> 30 - 60$ ms
- Increase from baseline > 60 ms

2.1.2.5 Physical Examinations findings

A complete physical examination will be conducted at Screening and will include, at a minimum, assessments of the following variables:

- Cardiovascular System (Normal, Abnormal NCS, Abnormal CS, Not Done)
- Respiratory System (Normal, Abnormal NCS, Abnormal CS, Not Done)
- Gastrointestinal System (Normal, Abnormal NCS, Abnormal CS, Not Done)
- Neurological System (Normal, Abnormal NCS, Abnormal CS, Not Done)
- Other parts System (Normal, Abnormal NCS, Abnormal CS, Not Done)

A focused physical examination will be conducted at all other visits and will include clinical signs and symptoms related to previous PE findings.

2.1.3 Pharmacokinetic variables

Serum $C_{trough\ ss}$ of TLL018.

2.1.4 Pharmacodynamic variables

Changes in [REDACTED] from Baseline and their association with TLL018 exposure/levels.

2.2 ANALYSIS POPULATIONS

2.2.1 Full Analysis Set

The Full Analysis Set (FAS) is defined as all participants who are randomized into the study, including participants who randomized to TLL 10mg BID per Protocol version 1.0. The primary analysis of efficacy will be based on the FAS.

2.2.2 Safety Set

The Safety population is defined as all participants who have taken at least 1 dose of study intervention, including participants who randomized to TLL 10mg BID per Protocol version 1.0. The safety analyses will be based on the safety set (SS).

2.2.3 Per-protocol Set

The per-protocol set (PPS) will include a subset of FAS. Participants who meet the major protocol deviations will not be included into PPS. Per-protocol set will be used for primary efficacy endpoint as a sensitivity analysis.

2.3 STATISTICAL METHODS

2.3.1 Analysis Conventions

Demographics and other Baseline assessments will be summarized based on full analysis set. Safety, PK and PD analyses will be based on safety set for TLL018 groups.

The Baseline for a given parameter is defined as the last assessment for this parameter before the first study intervention administration.

Unless otherwise specified, all data analyses will be presented by study intervention groups. Continuous variables will be presented by descriptive statistics: n (number of participants), mean, standard deviation, lower quartiles (Q1), upper quartiles (Q3), median and range (minimum and maximum). Categorical variables will be summarized by counts and percentages of participants.

In general, each numeric value should not exceed 4 decimal places. Minimum and maximum will be reported to the same number of decimal places as the original data collected. The mean, geometric mean (Geomean) and quantiles (such as median, Q1 and Q3) will be reported to one decimal place more than the original data. The standard deviation, coefficient of variation (CV) and geometric coefficient of variation (GeoCV) will be reported to one decimal place more than the original data. Percentages will be rounded to one decimal place (when count is 0, percentage will not be displayed, when percentage is 100%, no decimal place will be displayed). P-values (after rounded to 4 decimal places) ≥ 0.0001 and ≤ 0.9999 will be reported to 4 decimal places; p-values less than 0.0001 will be reported as " < 0.0001 "; p-values more than 0.9999 will be reported as " > 0.9999 ".

All efficacy estimates will be presented with two-sided 95% confidence intervals.

2.3.2 Subject Disposition

For all screened subjects, number and percentage of subjects in the following categories will be summarized:

- Screened subjects
- Screen failure subjects and reasons for screen failures
- Randomized subjects

For all enrolled subjects, number and percentage of subjects in the following categories will be summarized:

- Subjects in each analysis set (FAS, PPS, SS)
- Subjects who completed study treatment
- Subjects who discontinued study treatment, including the reason for discontinuation
- Subjects who completed study
- Subjects who exited the study and primary reasons subject exited the study

Listings for subject disposition, subject eligibility and inclusion/exclusion will also be provided.

2.3.3 Protocol Deviations

All recorded major and minor protocol deviations will be summarized by study intervention groups and by category based on FAS. All protocol deviations including major and minor deviations will be listed.

2.3.4 Demographics and baseline characteristics

The demographic and baseline characteristics will be summarized descriptively based on FAS and SS.

Demographic

- Age (years)
- Age Category (years) (< 40, <=65 and >=40, > 65)
- Sex (Male, Female [childbearing potential, post-menopausal])
- Ethnicity (“Not of Hispanic, Latino/a, or Spanish origin”, “Mexican, Mexican American, Chicano/a”, “Puerto Rican”, “Cuban”, “Another Hispanic, Latino/a or Spanish origin”, “Other”)
- Race (“American Indian or Alaska Native”, “Asian”, “Black or African American”, “Native Hawaiian or Other Pacific Islander”, “White”, “Other”)
- Height (cm)
- Weight (kg)
- BMI (kg/m²)
- BMI Category (kg/m²) (< 24, <28 and >=24, >=28)

Baseline disease characteristics

- Duration of Disease (Month)
- Severity at screening (Moderate, Severe, Unknown, Other)
- PASI Score
- Body Surface Area (%)
- PGA Score Category (3 - Moderate, 4 - Severe)
- DLQI Score
- PEST Score
- PSA or PEST-positive (Yes or No)
 - A participant is considered as PSA if he/she has a diagnosis of psoriatic arthritis prior to study for plaque psoriasis history; a participant is considered as PEST-positive if he/she has a three or more affirmative answers on assessment of PEST at baseline.
- PsAID-9 Score
- IDEOM MSK Score
 - IDEOM MSK Score includes MSK Symptoms Sub-score, Impact of MSK Symptoms Sub-score and Fatigue Sub-score.
- Stratification Factor 1 - Previous Psoriasis Biologic Use (Yes or No)
- Stratification Factor 2 - Diagnosis of Psoriatic Arthritis (Yes or No)

- Serology (Positive, Negative, Not Done) [HBsAg, HBcAb, HCV antibody, HIV antibody]
- QuantiFERON-TB Test (Positive, Negative, Borderline, Indeterminate, Not Done)
- Covid-19 testing (Positive, Negative, Not Done) [SARS-CoV-2 RT-PCR, IgG, IgA, IgM; Rapid Test]

The demographic and baseline characteristics will be listed.

2.3.5 Medical History

Medical history will be coded using the MedDRA (version 25.1 or higher), which will be summarized and listed by system organ class (SOC) and preferred term (PT) based on FAS.

2.3.6 Prior/Concomitant Medications and Procedures/Non-Drug Therapies

Prior and Concomitant Medications

- Prior Medications are defined as all medications stop prior to the first dose of study drug;
- Concomitant Medications are defined as all medications taken on or after the first dose of study drug.

Prior or Concomitant medications will be coded using the WHODrug Global B3 September 2022 (or higher version), and will be summarized and listed by ATC3 class and preferred term based on FAS. Within each level of summarization, a subject will be counted once if he/she takes one or more medications.

Prior and Concomitant Procedures/Non-Drug Therapies

- Prior Procedures/Non-Drug Therapies are defined as all procedures and non-drug therapies stop prior to the first dose of study drug;
- Concomitant Procedures/Non-Drug Therapies are defined as all procedures and non-drug therapies taken on or after the first dose of study drug.

Prior and concomitant Procedures/Non-Drug Therapies will be coded using the MedDRA (version 25.1 or higher), and will be summarized and listed by SOC and PT based on FAS. Within each level of summarization, a subject will be counted once if he/she takes one or more medications.

2.3.7 Extent of study intervention exposure and compliance

Participants may be administered study intervention either at the study site or at home. Study drug administration at study site as well as supply accountability log during each study site visits will be recorded in the source documents.

Extent of study intervention exposure and compliance will be summarized descriptively and listed based on SS with respect to:

- Treatment duration (weeks) = (last treatment date – first treatment date + 1) / 7
- Total tablets received
 - Calculated by summing the number of capsules taken per visit
- Dose Intensity (tablets/ day) = total tablets received / (treatment duration * 7)
- Number of subjects with any dose adjustment [Adjustment type, Adjustment reason for subjects with dose permanently discontinued]
- Number of subjects with any doses missed

- Days of missed dose (day)
- Number of subjects with any overdose
- Days of overdose (day)
- Compliance = Total tablets received / Scheduled tablets * 100%
 - Scheduled tablets = (last dose date – first dose date + 1) * daily tablet frequency.
 - Compliance will be summarized in the following categories: “<80%”, “=<120% and >=80%”, “>120%”.

2.3.8 Analyses of efficacy variables

2.3.8.1 Statistical hypotheses

The null hypothesis for the primary objective of this study is that the proportion of participants achieving a minimum 75% improvement from Baseline in the PASI (PASI-75) compared to placebo at the end of Week 12 is not different in the TLL018 dose groups compared to placebo (treatment difference between dose arms of TLL018 [p_{20} , p_{40} , and placebo $p_0=0$]). The alternative hypothesis is that the two active dose arms of TLL018 show a higher proportion of participants achieving a minimum 75% improvement from Baseline at the end of week 12 (treatment difference between dose arms of TLL018 and placebo >0)

$$H_0: p_{40}-p_0=0, p_{20}-p_0=0$$

$$H_1: p_{40}-p_0>0, p_{20}-p_0>0$$

where p_{20} , p_{40} , and p_0 represent the proportion of participants in the 2 dose arms of TLL018 or placebo respectively, achieving a minimum 75% improvement from Baseline in the PASI (PASI-75) at the end of Week 12.

2.3.8.2 Analyses of primary efficacy variable

Primary analysis

In the primary efficacy analysis, data from all subjects based on FAS will be analyzed according to randomized treatment group regardless of the treatment was actually received.

The primary endpoint to be analyzed is the proportion of participants achieving PASI-75 at week 12. Non-responder imputation (NRI) will be considered, in which case participants with missing response but included in FAS will be considered as non-responders. The treatment comparison will be performed using the Cochran-Mantel-Haenszel (CMH) test stratified by previous psoriasis biologic use (Yes or No) and diagnosis of psoriatic arthritis (Yes or No). The magnitude of the treatment difference will be estimated by the difference in response rates between the TLL018 dose groups and placebo group with a 95% confidence interval (CI) calculated based on Miettinen-Nurminen (score). 95% confidence interval (CI) for response rate within each dose groups and placebo group will be calculated based on Clopper-Pearson (Exact).

Sensitivity analysis

1. A sensitivity analysis will be performed similarly to the primary analysis based on PPS.
2. A sensitivity analysis will be performed similarly to the primary analysis considered with last observation carried forward (LOCF) instead of NRI, in which case participants with missing response but included in FAS will be imputed using the last measured outcome value from the previous visit.

2.3.8.3 Analyses of secondary efficacy variables

Analysis of secondary efficacy variable will be conducted based on FAS.

PGA scores and DLQIs values will be summarized by visit and dose group, including placebo. Change from Baseline in PGA and DLQIs values will be summarized by visit and dose group. Percentage of participants achieving PGA scores of 0 or 1 will be presented by visit and dose group. PASIs as proportion of participants achieving PASI-75 or PASI-90 will be displayed by visit and dose group. Average percent changes from Baseline in PASI will be evaluated by visit and dose group. Descriptive statistics by visit for each secondary endpoint will be provided. PEST, PsAID-9, and IDEOM MSK will be summarized by visit and dose group including placebo.

For all continuous secondary efficacy variables, treatment comparison will be performed using a Mixed-Effect Model Repeated Measures (MMRM). Mean percent change from baseline/change from baseline will be the dependent variable. The model will include treatment, previous psoriasis biologic use (Yes or No), diagnosis of psoriatic arthritis (Yes or No), visit (three post baseline visits, Week 4, 8 and 12), and treatment-by-visit interaction as independent fixed factors, and subjects will be included as a random effect. An unstructured covariance structure will be used to model the within-subject variability, if the unstructured covariance matrix results in a lack of convergence, the heterogeneous compound symmetry structure, followed by the compound symmetry structure will be used until convergence. The parameters in the MMRM model will be estimated using the restricted maximum likelihood (REML) method. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. The treatment differences between the TLL018 dose groups and placebo group will be estimated by the difference in the least squares means (LSmeans). The 95% confidence interval (CI) for the differences in LSmeans and p-values will be calculated based on the MMRM.

For all binary secondary efficacy variables, non-responder imputation (NRI) will be considered, in which case participants with missing response but included in FAS will be considered as non-responders. Treatment comparison will be performed using the Cochran-Mantel-Haenszel (CMH) test stratified by previous psoriasis biologic use (Yes or No) and diagnosis of psoriatic arthritis (Yes or No). The magnitude of the treatment difference will be estimated by the difference in response rates between the TLL018 dose groups and placebo group with a 95% confidence interval (CI) calculated based on Miettinen-Nurminen (score). 95% confidence interval (CI) for response rate within each dose groups and placebo group will be calculated based on Clopper-Pearson (Exact).

All efficacy measures at each visit will be listed.

Secondary efficacy variables are listed as below:

Measure	Variable	Type of Variable	Analysis Method	Time Point
PASI	Proportion of PASI-75	Binary	CMH	Week 4, Week 8
	Proportion of PASI-90	Binary	CMH	Week 4, Week 8, Week 12
	Mean percent change from Baseline in PASI	Continuous	MMRM	Week 4, Week 8, Week 12
PGA	Proportion of achieving PGA score of 0 or 1	Binary	CMH	Week 4, Week 8, Week 12

Measure	Variable	Type of Variable	Analysis Method	Time Point
	Percent of subjects with PGA 0 or 1 and a 2-point improvement from baseline	Binary	CMH	Week 4, Week 8, Week 12
DLQI	Change from Baseline in DLQI	Continuous	MMRM	Week 4, Week 8, Week 12
PsAID-9	Change from baseline in PsAID-9 in PSA or PEST-positive patients	Continuous	MMRM	Week 4, Week 8, Week 12
	Proportion of PSAID-9 less than or equal to 4 in PSA or PEST-positive patients	Binary	CMH	Week 4, Week 8, Week 12
MSK	Change from baseline in MSK	Continuous	MMRM	Week 4, Week 8, Week 12

2.3.8.4 Subgroup Analyses

Subgroup analyses will be performed on the endpoints: proportion of PASI 75, proportion of PASI 90 and proportion of achieving PGA score of 0 or 1 using FAS (at Week4, Week 8, Week 12). Non-responder imputation (NRI) and Last observation carried forward (LOCF) imputation will be applied respectively.

Treatment comparison will be performed using the Cochran-Mantel-Haenszel (CMH) test stratified by previous psoriasis biologic use (Yes or No) and diagnosis of psoriatic arthritis (Yes or No). The magnitude of the treatment difference will be estimated by the difference in response rates between the TLL018 dose groups and placebo group with a 95% confidence interval (CI) calculated based on Miettinen-Nurminen (score).

The following subgroups will be considered:

- Previous psoriasis biologic use (Yes or No),
- PGA Score at Baseline (3 - Moderate or 4 - Severe).

2.3.8.5 Multiplicity issues

No adjustment of the type I error α is planned as a hierarchical testing strategy is applied where the highest to the lowest study intervention groups are tested against placebo and testing stops when a comparison is non-significant.

2.3.8.6 Analyses of exploratory efficacy variable(s)

Analyses of proportion of participants achieving PASI-100 at each planned visit will follow the same way as binary secondary efficacy variables in [2.3.8.3](#).

2.3.9 Analyses of safety data

Analysis of safety data will be performed based on SS and conducted with descriptive summary by study intervention groups and across TLL018 dose groups.

2.3.9.1 Analyses of adverse events

The incidence of the following AE categories will be summarized at subject level and also by system organ class (SOC) and preferred term (PT) in descending order of frequency:

- TEAEs
- Highest Grade TEAE
- Treatment Related TEAEs
- TEAEs of grade ≥ 3
- Treatment-related TEAEs of grade ≥ 3
- Serious TEAEs
- Serious and treatment-related TEAEs
- TEAEs with a fatal outcome
- Treatment-related TEAEs with a fatal outcome
- TEAEs leading to study drug discontinuation
- Treatment-related TEAEs leading to study drug discontinuation
- TEAEs of special interest
- Treatment-related TEAEs of special interest
- TEAEs requiring treatment
- Treatment-related TEAEs requiring treatment

A subject experienced with multiple adverse events for a given SOC or PT will be counted only once under each SOC or PT, and performed as the most severe occurrence. Missing severity rating will not be imputed.

All reported AEs will be presented in listings. A separate listing of all deaths during the conduct of the study with information regarding the death will be provided.

2.3.9.2 Laboratory variables analyses

For hematology, clinical chemistry, coagulation and routine urinalysis, descriptive summary for the actual values and changes from baseline will be tabulated for quantitative laboratory variables by study intervention groups at each planned visit, including maximum value observed post-treatment.

The shift tables of CTCAE Grade as well as clinical significance from baseline to the worst post-treatment will be tabulated for accessible laboratory variables.

Interval value such as “< x” or “> x” will be imputed for descriptive summary (see [2.4.1.4](#)) and keep the original results in listings.

All laboratory test performed in [2.1.2.2](#) will be listed.

2.3.9.3 Analyses of vital sign variables

All of vital sign parameters (see 2.1.2.3) observed values and change from baseline, will be summarized descriptively by study intervention groups at each planned visit, including maximum value observed post-treatment. The shift tables of clinical significance from baseline to the worst post-treatment will be tabulated for vital sign variables.

For subjects with multiple measurements for the same visit in terms of systolic/diastolic blood pressure and pulse, the average value and average clinical significance for the visit will be used to perform analyses. Original results and the derived results from multiple measurements will be listed simultaneously.

All assessments of vital sign will be presented in listings.

2.3.9.4 Electrocardiograms

A descriptive summary of ECG parameters (see 2.1.2.4) observed values and change from baseline will be presented by study intervention groups at each planned visit. The shift table of clinical significance from baseline to the worst post-treatment will be tabulated for ECG result.

For subjects with multiple measurements for the same visit, the average value for the visit will be used to perform analysis, and the clinical significance for the visit will carry the worst result (Abnormal CS > Abnormal NCS > Normal) to perform analysis. Original results and the derived results from multiple measurements will be listed simultaneously.

All ECG result will be presented in listing.

2.3.9.5 Physical Examination

A descriptive summary of physical examination findings (see 2.1.2.5) will be presented by study intervention groups at for each planned visit. The shift tables of clinical significance from baseline to the worst post-treatment will be tabulated for physical examination findings.

All physical examination findings will be presented in listings.

2.3.10 Analyses of pharmacokinetic and pharmacodynamic variables

Analyses of pharmacokinetic and pharmacodynamic variables will be performed based on SS.

2.3.10.1 Pharmacokinetic

PK blood concentrations of TLL018 will be summarized descriptively for active dosing groups at each planned visit for n (number of participants), BQL, mean, standard deviation, median and range (minimum and maximum), quartiles (Q1 and Q3), CV, Geomean, GeoCV. Below plots for each active dosing groups will be generated to show changes of concentration over time.

- Mean concentration (+/- SD) over time.
- For each patient, a line plot for concentration over time will be generated to show individual patient's concentration profile.

Collection and assessment about PK blood concentrations will be listed.

2.3.10.2 Pharmacodynamic

PD biomarker [REDACTED] observed values, change from baseline will be summarized descriptively by study intervention groups at each planned visit.

Collection and assessment about PD biomarker will be listed.

2.4 DATA HANDLING CONVENTIONS

2.4.1 Missing data

Except the situations listed below, missing data will not be imputed for descriptive statistics.

2.4.1.1 Handling of Missing data for efficacy endpoints

The primary, secondary and exploratory efficacy variable with missing value at planned visit for comparative analysis will be handled as below:

- For the continues efficacy data such as change from baseline in PASI at Week 12, all available data will be used, missing data will not be imputed.
- For the binary efficacy data, generally, non-responder imputation (NRI) will be considered, in which case participants with missing response but included in FAS will be considered as non-responders . In addition, for the sensitivity analysis of primary efficacy variable (PASI-75 response at Week 12) and subgroup analysis, last observation carried forward (LOCF) will be considered, in which case participants with missing response but included in FAS will be imputed using the last measured outcome value from the previous visit.

2.4.1.2 Partial Dates for Adverse Events

To determine if the AE is treatment-emergent, the AE partial start date will be imputed as below:

- If only day is missing
 - If year and month are earlier than the corresponding part of first dose date of study drug, then impute with the last day of the month of the event.
 - If year and month are the same as the corresponding part of first dose date of study drug, then impute with the first dose date of study drug.
 - If year and month are later than the corresponding part of first dose date of study drug, then impute with the first day of the month of the event.
- If both month and day are missing
 - If year is earlier than the year of first dose date of study drug, then impute with 31Dec.
 - If year is the same as the year of first dose date of study drug, then impute with the first dose date of study drug.
 - If year is later than the year of first dose date of study drug, then impute with 01Jan.
- If day, month and year are all missing, then impute with first dose date of study drug.
- If imputed start date is later than the end date, then it will be replaced by the AE end date.
- Otherwise, set to missing.

2.4.1.3 Partial Dates for Concomitant therapy

To determine if the medications/non-drug therapies are concomitant. Partial therapy start and end date will be imputed.

Partial therapy start date will be imputed as below:

- If only day is missing, then impute with the first day of the corresponding month.
- If both month and day are missing, then impute with 01Jan.
- If imputed start date is later than the end date or death date, then it will be replaced by the end date or death date.

Partial therapy end date will be imputed as below:

- If only day is missing, then impute with the last day of the corresponding month.
- If both month and day are missing, then impute with 31Dec.
- If day, month and year are all missing, then not impute.

2.4.1.4 Interval values for Laboratory variables

Laboratory values collected by the form of “< x” (e.g. below the lower limit of quantification) or “> x” (e.g. above the upper limit of quantification) will be imputed for descriptive summary.

Laboratory values of “< x” will be imputed as below:

- If x is an integer, imputed with $[x - 1]$, only if $x = 1$, then it will be imputed to 0.9
- If x has one decimal places, imputed with $[x - 0.1]$, only if $x = 0.1$, then it will be imputed to 0.09
- If x has two decimal places, imputed with $[x - 0.01]$, only if $x = 0.01$, then it will be imputed to 0.009
- If x has more than two decimal places, imputed following similar rule above, i.e. imputed with $[x - 1 * \text{decimal precision of } x]$, but imputed to $[x - 0.1 * \text{decimal precision of } x]$ if only x is equal to its decimal precision

Laboratory values of “> x” will be imputed as below:

- If x is an integer, imputed with $[x + 0.1]$
- If x has one decimal place, imputed with $[x + 0.01]$
- If x has two decimal places, imputed with $[x + 0.001]$
- If x has more than two decimal places, imputed following similar rule above, i.e. imputed with $[x - 0.1 * \text{decimal precision of } x]$

2.4.2 Unscheduled visits

Repeat or unscheduled visit may be taken for safety reasons or for other technical issues. Unscheduled data will be included into corresponding analysis as far as possible.

2.4.3 Pooling of centers for statistical analyses

Not Applicable.

3 INTERIM ANALYSIS

There is no interim analysis for efficacy planned for this study. Periodic safety analyses will be presented to the DMC to allow for review of aggregate safety data. The Sponsor will remain blinded to all data presented to the DMC.

4 SOFTWARE DOCUMENTATION

The statistical software package SAS Version 9.4 (SAS Institute, Cary, NC, USA) will be used to perform all analyses and to summarize data.

5 REFERENCES

- 1 Ibrahim GH, Buch MH, Lawson C, Waxman R, Helliwell PS. Evaluation of an existing screening tool for psoriatic arthritis in people with psoriasis and the development of a new instrument: the Psoriasis Epidemiology Screening Tool (PEST) questionnaire. Clin Exp Rheumatol 2009; 27:469-74.
- 2 Perez-Chada LM, Gottlieb AB, Cohen J, Mease P, Duffin KC, Garg A, et al. Measuring psoriatic arthritis symptoms: a core domain in psoriasis clinical trials. J Am Acad Dermatol 2020; 82:54-61.
- 3 Perez-Chada LM et al. Report of the Skin Research Working Groups from the GRAPPA 2020 Annual Meeting. The Journal of Rheumatology Supplemental June: 2021; 97: 10-16.