

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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Title Page

Protocol Title: 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

Brief Title: A study to investigate the efficacy and safety of TLL018 compared with placebo in participants with moderate-to-severe plaque psoriasis

Compound: TLL018

Indication: Plaque Psoriasis

Study Sponsor: Highlightll Pharmaceutical (USA) LLC
485C US Highway 1 South, Ste 350 – 106
Iselin, New Jersey 08830
United States

Protocol Number: TLL018-205

Study Phase: Phase 2

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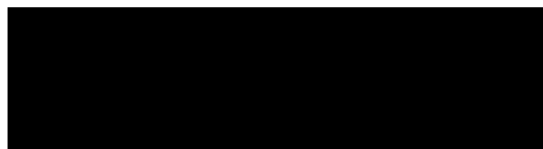
Approval Date: 17-Oct-2023

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Sponsor Signatory:



Oct 17, 2023

, MD, PhD, FACP

Date

Highlightll Pharmaceutical (USA) LLC

Principle Investigator, Medical Monitor names, and contact information will be provided separately.

Protocol Amendment Summary of Changes Table

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Original Protocol*	1.0	01-June-2022
Protocol Amendment	1.1	31-Aug-2022
Protocol Amendment	1.2	17-Nov-2022
Protocol Amendment	1.3	01-Feb-2023
Protocol Amendment	2.0	15-Jun-2023
Protocol Amendment	3.0	17-Oct-2023

* Version 1.0 was not submitted to EC/IRBs or distributed to sites.

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Abbreviations and Definitions

Abbreviation	Description
ADL	activities of daily living
AE	adverse event
AESI	adverse events of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BID	twice daily
BMI	body mass index
BSA	body surface area
CAC	Clinical Adjudication Committee
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
COVID-19	coronavirus disease 2019
CPK	creatine phosphokinase
CRF	case report form
CRO	contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450 enzyme
DC	dendritic cells
DMC	Data Monitoring Committee
DLQI	Dermatology Life Quality Index
DRE	disease-related event
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EOT	End of Treatment
ET	Early Termination
F	female
FAS	full analysis set
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GFR	glomerular filtration rate

Abbreviation	Description
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HIV	human immunodeficiency virus
hs-CRP	high-sensitivity C-reactive protein
HRT	hormonal replacement therapy
IB	Investigator's Brochure
IBD	inflammatory bowel diseases
ICF	informed consent form
ICH	International Conference on Harmonisation
IFN	interferon
IL	interleukin
INR	international normalized ratio
IP-10	interferon inducible protein
IRB	Institutional Review Board
IRT	Interactive Response Technology
IXRS	Interactive Voice/Web Response System
JAK	Janus kinase
LAR	legally authorized representative
M	male
MACE	major adverse cardiovascular events
NCI	National Cancer Institute
NOAEL	no-observed-adverse-effect-level
OTC	over-the-counter
PASI	Psoriasis Area and Severity Index
PD	pharmacodynamic(s)
PGA	Physician's Global Assessment
PK	pharmacokinetic(s)
PP	plaque psoriasis
QD	once daily
RA	rheumatoid arthritis
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SoA	schedule of assessments

Abbreviation	Description
STAT	signal transducer and activator of transcription proteins
SUSAR	suspected unexpected serious adverse reactions
TB	tuberculosis
TEAE	treatment-emergent adverse event
T _{max}	time of maximum concentration
TNF	tumor necrosis factor
TYK	tyrosine kinase
ULN	upper limit of normal
WBC	white blood cell
WOCBP	woman of childbearing potential

Overall Rationale for the Amendment:

The clinical study protocol, dated 16-Oct-2023, is primarily being amended to change the number of participants from 70 patients to approximately 90 patients. Other adjustments and updates were made to inclusion criteria in regard to the (06-Oct-2023) CDC COVID-19 vaccinations guidelines. Also, exclusion criteria defining borderline tuberculosis test results and possible follow up diagnostics. Additional adjustments were made to clarify language but keep the protocol's original intent, e.g., SOA table, removal of 10 mg, discontinuation after positive COVID-19 test results.

A summary of changes is presented in the table below. Deleted text is indicated using ~~strikethrough~~ format and new text is in **bold/underline** format.

Section # and Name	Description of Change	Minor / Substantial
Throughout protocol	Self-evident, grammatical, and formatting updates.	Minor
Throughout protocol	Participant numbers were increased from 70 enrolled to approximately 90 and associated text.	Substantial – ensure adequate sample size.

Section # and Name	Description of Change	Minor / Substantial
Inclusion Criteria #15	Participants must have completed their coronavirus disease 2019 (COVID-19) vaccination in accordance with the latest CDC guidelines, which is based on previous vaccination history. Please reference COVID-19 vaccination guidance for individuals who are moderately or severely immunocompromised (Clinical Guidance for COVID-19 Vaccination CDC). Previous Pfizer-BioNTech, Moderna or Novavax: Must have previously received at least a 1st and 2nd dose, then must have received an updated formulation according to the CDCs dosing requirements; or Novavax or Johnson and Johnson's Janssen: Must have previously received 1 or more doses in combination with any original monovalent or bivalent COVID-19 vaccine doses, then must receive an updated formulation according to the CDCs vaccination guidelines. Participants must have completed their primary series for the coronavirus disease 2019 (COVID-19). Primary series completion in accordance with the CDC guidelines is the following per vaccine manufacturer: a. ——— Pfizer BioNTech, Moderna or Novavax: 1st and 2nd Dose b. ——— Johnson and Johnson's Janssen: 1st Dose	Substantial – eligibility update in accordance with new CDC guidelines.

Section # and Name	Description of Change	Minor / Substantial
	appropriate boosters' vaccinations according to guidelines are recommended	
Exclusion Criteria #9	9. Recent exposure to active tuberculosis (TB). Current evidence of active TB or current evidence of latent TB. Participants with positive TB test (e.g., QuantiFERON) that have been treated for latent TB. A borderline QuantiFERON test should be repeated. If still indeterminant, then a chest x-ray may be performed (positive chest x-ray is exclusionary).	Substantial – clarify process for borderline QuantiFERON results.
Exclusion Criteria #35	35. Previously not completed COVID-19 vaccination in accordance with the CDC guidelines.	Substantial – eligibility update in accordance with new CDC guidelines.
Schedule of Assessments	Deleted the “X” in table for Week 12 Study Drug Administration. Superscript d. If clinically indicated, c 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.	Minor
Section 2.2.1.1	TLL018 will not be administered to participants upon confirmation of any signs or symptoms of and by COVID 19 PCR test. infection.	Minor
Table 6.1	Deleted 10mg from Drug Description/Investigational Drug cell.	Minor

Section # and Name	Description of Change	Minor / Substantial
Section 7.2	In addition, if a participant develops fever or symptoms suggestive of COVID-19 infection during the study, the investigator is advised to discontinue the subject from study drug or rule out COVID 19 disease with an appropriate COVID-19 test. any suspected or confirmed COVID-19 cases will be immediately discontinued from study intervention. The participant will be withdrawn by the Investigator based on discussion with the Sponsor and Medical Monitor.	Minor
Section 9.5	The sample size of 3628 participants for each of the TLL018 BID dose groups and 1814 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.	Substantial – ensure adequate sample size.
Section 10.4.2	Male participants who are sexually active with a WOCBP, even if the male participants have undergone a successful vasectomy, must agree to use effective methods of contraception from the start of TLL018 treatment until at least 13 weeks following the last dose of TLL018.	Minor

Section # and Name	Description of Change	Minor / Substantial
	His female partner(s) must use at least 1 of the contraceptive measures as noted below including a barrier method form of birth control.	
Section 10.4.2	In addition, male participants must refrain from donating sperm for the duration of the study and for 1213-weeks after the last dose of TLL018. Female Participants: Female participants must agree to use highly effective contraception as specified below and have monthly pregnancy testing during exposure to TLL018 and for 1213-weeks following the last dose of TLL018.	Minor

1 Protocol Summary

1.1 Synopsis

Protocol Title: 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.

Brief Title: A study to investigate the efficacy and safety of TLL018 compared with placebo in participants with moderate-to-severe plaque psoriasis.

Sponsor Protocol No.: TLL018-205

Study Phase: 2

Sponsor: Highlightll Pharmaceutical (USA) LLC

Rationale:

TLL018 is a novel, highly potent, and selective Janus kinase 1 (JAK1)/tyrosine kinase 2 (TYK2) inhibitor being developed for the treatment of autoimmune and inflammatory diseases. This study is designed to investigate the efficacy and safety of 2 dose levels of TLL018 for therapy of participants with moderate-to-severe plaque psoriasis (PP). Based on the mechanism of action of TLL018 and clinical experience in the first-in-human Phase 1 study of orally administered TLL018 (TLL018-101 study), TLL018 is hypothesized to be safe and well-tolerated at the doses and regimens proposed in this study, and to have reduced toxicity and improved efficacy compared to currently approved less selective JAK inhibitors.

Objectives and Endpoints:

Objectives	Endpoints
<u>Primary Objective</u> To evaluate the efficacy of TLL018 in the treatment of moderate-to-severe PP	<u>Primary Endpoint</u> Proportion of participants achieving a minimum 75% improvement from Baseline at the end of Week 12 for PASI (PASI-75)
<u>Secondary Objectives</u> - To evaluate the safety of TLL018 in participants 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	<u>Secondary Safety Endpoints</u> - TEAEs^a - SAEs - AESIs - Clinical laboratory tests - Vital signs (blood pressure, pulse rate, respiratory rate, and oral temperature) 12-lead ECGs - Physical examination findings <u>Secondary Efficacy Endpoints</u> - 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
<u>Exploratory Objective</u> - 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	<u>Exploratory Endpoints</u> - Proportion of participants achieving PASI-100 - Changes in [REDACTED] levels from Baseline and their association with TLL018 exposure/levels - Serum C_{trough ss} of TLL018

AE = adverse event, AESI = adverse event of special interest, DLQI = Dermatology Life Quality Index, ECG = electrocardiogram, IL = interleukin, PASI = Psoriasis Area and Severity Index, PD = pharmacodynamics, PGA = Physician's Global Assessment, PP = plaque psoriasis, SAE = serious adverse event, TEAE = treatment-emergent adverse event

- a. An event that emerges during treatment, having been absent pretreatment, or worsens relative to the pretreatment state.

Overall Design:

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 dose levels of TLL018 as therapy in up to approximately 90 participants with moderate-to-severe 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 Day 8), participants who meet eligibility criteria will be randomized in a 2:2:1 ratio to receive 1 of the following study investigational products orally for 12 weeks: TLL018 20 mg BID, TLL018 40 mg BID, or placebo BID.

Participants will be assessed for safety, tolerability, and response to treatment. Samples for pharmacodynamics (PD) biomarker analyses will be collected throughout the study for potential correlation to clinical outcomes. Samples for pharmacokinetics analysis will be collected with the PD samples.

Brief Summary:

The purpose of this study is to evaluate the efficacy and safety of 2 dose levels of TLL018 compared with placebo in participants with moderate-to-severe PP. Study details include:

- Study duration: Up to 4 weeks for Screening, up to 1 week for Baseline period, 12 weeks for Treatment Period.
- Treatment duration: 12 weeks for Treatment Period.
- Visit frequency: Screening visit, Baseline visit, Week 1 (Day 1), Week 4 (Day 28), Week 8 (Day 56), and Week 12 (Day 84) of the Treatment Period and End-of-Treatment (EOT) or Early Termination (ET) visit.
- Planned total study duration will be approximately 4 months.

Number of Participants:

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

Selection of Participants:

Inclusion Criteria:

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

1. Are between the ages of 18 and 75 years, inclusive, at time of informed consent.
2. Capable of giving informed consent and complying with study procedures.
3. Willing and able to adhere to study restrictions.
4. Laboratory and medical history parameters within the protocol defined ranges.
5. Normal renal function (>90 mL/min/ 1.72 m²) or mild renal impairment (Stage 2 mild chronic kidney disease glomerular filtration rate [GFR]=60 to 89 mL/min/ 1.73 m²) as determined by central laboratory.
6. Body mass index (BMI) of 18.0 to 35.0 kg/m² inclusive.
7. Have had a diagnosis of moderate-to-severe PP for at least 6 months prior to Baseline.
8. Participants with moderate-to-severe PP covering $\geq 10\%$ body surface area (BSA), with a Psoriasis Area and Severity Index (PASI) ≥ 12 and a static Physician's Global Assessment (PGA) score ≥ 3 at Baseline.
9. Participants with plaque psoriasis who are systemic treatment naïve or have received one or more of the conventional anti-psoriasis treatments, such as acitretin, phototherapy, methotrexate, cyclosporine, apremilast, or biologic therapy (anti-TNF or anti-IL 12/17/23).
10. Participants who are candidates for systemic treatment for psoriasis at the discretion of the Investigator.
11. Must agree to avoid prolonged exposure (> 15 minutes) to the sun and avoid use of tanning booths or other ultraviolet light sources during the study.

12. Female participants of childbearing potential (See [Section 10.4.1](#) definition of Woman of Childbearing Potential - WOCBP) must have a negative serum human chorionic gonadotropin (hCG) at Screening, and meet one of the following criteria:
 - a. Using a medically acceptable form of birth control ([Appendix 4](#)) for at least 1 month prior to Screening and 3 months after the last dose of study drug (e.g., hormonal contraceptives [oral, patch, injectable or vaginal ring], implantable device [implantable rod or intrauterine device], bilateral tubal occlusion/tubal ligation, azoospermic partner).
 - b. Abstinence as a form of birth control is generally not permitted during the study with the exception of participants who practice abstinence as a preferred and usual lifestyle choice. The Investigator must confirm that abstinence is still in accordance with the participant's lifestyle at regular intervals throughout the study.
13. Male participants with female partners of childbearing potential must agree to use condoms for the duration of the study and until 13 weeks after administration of the study investigational product and must refrain from donating sperm for this same period. In addition, his female partner should agree to use a highly effective method of birth control per [Appendix 4](#) or an additional barrier form of birth control (e.g., diaphragm, cervical cap, spermicide, or sponge).
14. Ability to swallow and retain oral study investigational product.
15. Participants must have completed their coronavirus disease 2019 (COVID-19) vaccination in accordance with the latest CDC guidelines, which is based on previous vaccination history. Please reference COVID-19 vaccination guidance for individuals who are moderately or severely immunocompromised ([Clinical Guidance for COVID-19 Vaccination | CDC](#)).
 - a. Previous Pfizer-BioNTech, Moderna or Novavax: Must have previously received at least a 1st and 2nd dose, then must have received an updated formulation according to the CDCs dosing requirements; **or**
 - b. Novavax or Johnson and Johnson's Janssen: Must have previously received 1 or more doses in combination with any original monovalent or bivalent COVID-19 vaccine doses, then must receive an updated formulation according to the CDCs vaccination guidelines.

Exclusion Criteria:

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

1. Pregnant or nursing women.
2. Past history of gastrointestinal perforation, history of peptic ulcers and/or regular use of NSAIDs.
3. History of chronic alcohol or drug abuse within 6 months prior to Screening as determined by the Investigator based on medical history and patient interview.
4. Current or recent history of severe, progressive, or uncontrolled renal, hepatic, hematologic, gastrointestinal, metabolic, endocrine, pulmonary, cardiovascular, neurologic, or psychiatric disease.
5. Current and/or recent history (<30 days prior to Screening and/or <45 days prior to randomization) of a clinically significant viral, bacterial, fungal, parasitic, or mycobacterial infection.
6. Subject is currently being treated with or has received strong cytochrome P450 3A (CYP3A4) inhibitors, such as itraconazole, within 4 weeks prior to Baseline (Day 0).
7. Any history of malignancies, except for non-recurrent basal cell skin cancer, squamous cell skin cancer, and cervical cancer *in situ* that are considered to be cured.
8. Tests positive for hepatitis B, hepatitis C, or human immunodeficiency virus (HIV). For Hepatitis B, all subjects will undergo testing for Hepatitis B Surface Antigen (HBsAg) and Hepatitis B Core Antibody (HBcAb). Subjects who are HBsAg positive are not eligible for the study. Subjects who are HBsAg negative and HBcAb positive will subsequently need testing for Hepatitis B virus deoxyribonucleic acid (HBV DNA) and if HBV DNA negative may be enrolled in the study; if HBV DNA is positive, the subject is not eligible for the study. Positive hepatitis C virus result is defined as having a positive hepatitis C antibody test with a positive confirmatory hepatitis C polymerase chain reaction test.
9. Recent exposure to active tuberculosis (TB). Current evidence of active TB or current evidence of latent TB. Participants with positive TB test (e.g., QuantiFERON) that have been treated for latent TB. A borderline QuantiFERON test should be repeated. If still indeterminate, then a chest x-ray may be performed (positive chest x-ray is exclusionary).
10. History of unexplained syncope, symptomatic hypotension, or hypoglycemia.
11. Abnormal D-dimer levels in conjunction with clinical or current and past thrombotic disease.

12. Participants with uncontrolled hypertension, uncontrolled diabetes, untreated or uncontrolled hyperlipidemia (fasting blood triglycerides >500 mg/dL and fasting cholesterol >250 mg/dL).
13. History of any significant cardiac event (e.g., myocardial infarction) within 6 months prior to Screening, including:
 - a. History of long QTc syndrome; history or presence of an abnormal ECG, which, in the Investigator's opinion, is clinically significant.
 - b. History of unstable ischemic heart disease or uncontrolled hypertension.
 - c. Current Class 3 or 4 heart failure per the New York Heart Association Functional Classification.
 - d. Screening and/or Baseline QTcF > 450 msec for males and > 470 msec for females, confirmed by triplicate ECG.
14. Participants with history of thrombosis and/ or thromboembolism, or associated risk factors (e.g., inherited thrombophilias, etc.).
15. Donated or lost >500 mL of blood in the previous 3 months.
16. Participants with chronic kidney disease with eGFR <60 mL/min/1.73 m².
17. Participants with moderate-to-severe hepatic impairment (i.e., Child-Pugh Class B and C).
18. Major surgery within 3 months prior to Screening or participant has a planned major surgery during the course of the study.
19. Participants with any of the following abnormalities in clinical laboratory tests at Screening, as assessed by the study-specific laboratory and confirmed by a single repeat, if deemed necessary:
 - Hemoglobin <100 g/L
 - White blood cell (WBC) count of <3.0 × 10⁹/L
 - Platelet count of <80 × 10⁹/L
 - Absolute neutrophil count of <1.5 × 10⁹/L
 - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) values greater than 3 times the ULN
20. Any uncontrolled clinically significant laboratory abnormality that would affect interpretation of study data or the participant's participation in the study.

21. Previous or current autoimmune diseases (e.g., RA, systemic lupus erythematosus, inflammatory bowel disease, scleroderma, inflammatory myopathy, mixed connective tissue disease overlap syndrome, etc.). Note, psoriatic arthritis patients are allowed.
22. Other types of psoriasis (such as erythrodermic psoriasis, pustular psoriasis, guttate psoriasis, drug-induced psoriasis).
23. Current enrollment in another study protocol or experimental treatment within 30 days or five half-lives (whichever is longer).
24. Received any topical therapy that can affect psoriasis (including topical use of moderate-strong glucocorticoids, retinoids, vitamin D3 derivatives, salicylic acid, anthracene, etc.) within 2 weeks of first study intervention. Low potency topical steroids are permitted for sensitive areas only (e.g., face, axillae, genitalia). Bland emollients without urea or α or β hydroxy acids are permitted.
25. Use of phototherapy (including photochemotherapy, ultraviolet therapy, tanning bed self-therapy) within 4 weeks of first study intervention.
26. Use of systemic oral therapy that can affect psoriasis (including but not limited to, glucocorticoids, retinoids, cyclosporine, methotrexate and apremilast) within 4 weeks of first study intervention.
27. Received intravenous corticosteroids within 4 weeks of first study intervention.
28. Use of antimalarial drugs, interferon- α , lithium and beta-blockers within 4 weeks of first study intervention.
29. Use of Chinese or herbal medicine treatment of psoriasis within 2 weeks of first study intervention.
30. Prior to randomization, washout periods of the following biologics are required: etanercept ≥ 28 days; any s.c. mAb targeting TNF (e.g., infliximab, adalimumab, certolizumab) ≥ 3 months; ustekinumab or drugs that specifically target IL-23 ≥ 6 months; secukinumab, ixekizumab, bimekizumab, brodalumab, or other IL-17 antagonists ≥ 6 months; Any other anti-psoriasis treatments not listed should have a washout period > 5 half-lives. Topical JAK inhibitors should have a washout period > 2 weeks.
31. Prior use of three or more biologic therapies.
32. Use of natalizumab and other drugs that regulate B or T cells within 12 months of first study intervention, such as rituximab, alemtuzumab, and abatacept.

33. Participants who have received live vaccines within 2 months prior to first study intervention or plan to receive live vaccines during the study period. Non-live-attenuated vaccines (e.g., ribonucleic acid [RNA]-based vaccines, inactivated adenovirus-based vaccines, protein-based vaccines), including non-live-attenuated vaccines or boosters for coronavirus disease 2019 (COVID-19) during the study are allowed.
34. Participants who have received COVID-19 vaccines within 2 weeks of Baseline or participants who plan to receive COVID-19 vaccines during the study period (boosters are allowed).
35. Previously not completed COVID-19 vaccination in accordance with the CDC guidelines.
36. Participants who are allergic to any component of the study intervention or who are at risk for allergy as determined by the Investigator during the study.
37. Any condition for which the Investigator considers the participant inappropriate to participate in this study.

Study Intervention Groups and Duration:

Up to 3 parallel dose cohorts are planned in a double-blinded fashion for a 12-week Treatment Period. The planned study investigational product dose is 20 mg BID and 40 mg BID. Dosing instructions will include the number of tablets to be administered at individual dose levels. Participants who meet eligibility criteria will be randomized in a 2:2:1 ratio to 1 of the 3 study intervention groups:

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

Statistical Methods:

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

Statistical analysis:

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.

Further details of the statistical analysis will be provided in the statistical section of the protocol and the statistical analysis plan.

Data Monitoring/Other Committee:

An independent Data Monitoring Committee (DMC) will be established to continuously monitor participant safety, including safety signal detection during the study. The DMC will initially meet at defined intervals of every 2 months or more frequently if indicated to conduct safety reviews of aggregate data after enrollment of a defined number (30) 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.

Clinical Adjudication Committee (reporting to DMC):

There will be 2 Clinical Adjudication Committee (CAC) external panels of independent physicians experienced in assessing cardiovascular, malignancies, and thromboembolic endpoints. One committee will adjudicate cardiovascular/thromboembolic events; the other will adjudicate malignancies. These panels will be blinded to treatment assignments. The members of both CAC's will not be an Investigator in any trial for TLL018-205. A sub-group of the DMC consisting of clinical experts will periodically review the safety data and independently adjudicate adverse events of special interest (AESIs), such as venous and arterial thromboembolic events,

malignancies, and major adverse cardiovascular events (MACE) using standard criteria and processes.

A subset of AESI, listed below, will be adjudicated by the committees to determine the underlying cause and relationship to TLL018:

- All deaths
- MACE
- Thromboembolic events
- Malignancies
- Serious infections (Grade 3 or higher)

The criteria to define clinical cardiovascular, mortality, thromboembolic events, and malignancies will be detailed within the respective CAC charters (MACE, malignancy). All events meeting adjudication criteria as outlined within the CAC charter and this protocol will be collected from the first day of double-blinded treatment through the end of study (including 14 day post last visit reporting period) for all randomized participants who have received at least 1 dose of study investigational product.

Clinical adjudication events occurring between the Screening period (the time of informed consent), the 1-week Baseline period and double-blinded treatment randomization will not be adjudicated as these events will be excluded.

The identification of adjudication events will be made by the study site or by designee. The study site will communicate the event to the designee within 24 hours of awareness of the adjudication event using the appropriate case report form module. The study site will in turn provide the specific documents needed to support the adjudication review conducted by the CACs. Obtaining documentation will be the responsibility of the study site. Documentation will include but is not limited to, any of the following: hospital discharge summaries, operative reports, study site notes, ECGs, diagnostic cardiac enzymes, imaging studies, tumor staging, results of other diagnostic tests, autopsy reports, and death certificate information. The respective adjudication charters will contain additional information on source documents to be collected for event adjudication.

Interim Safety Assessment:

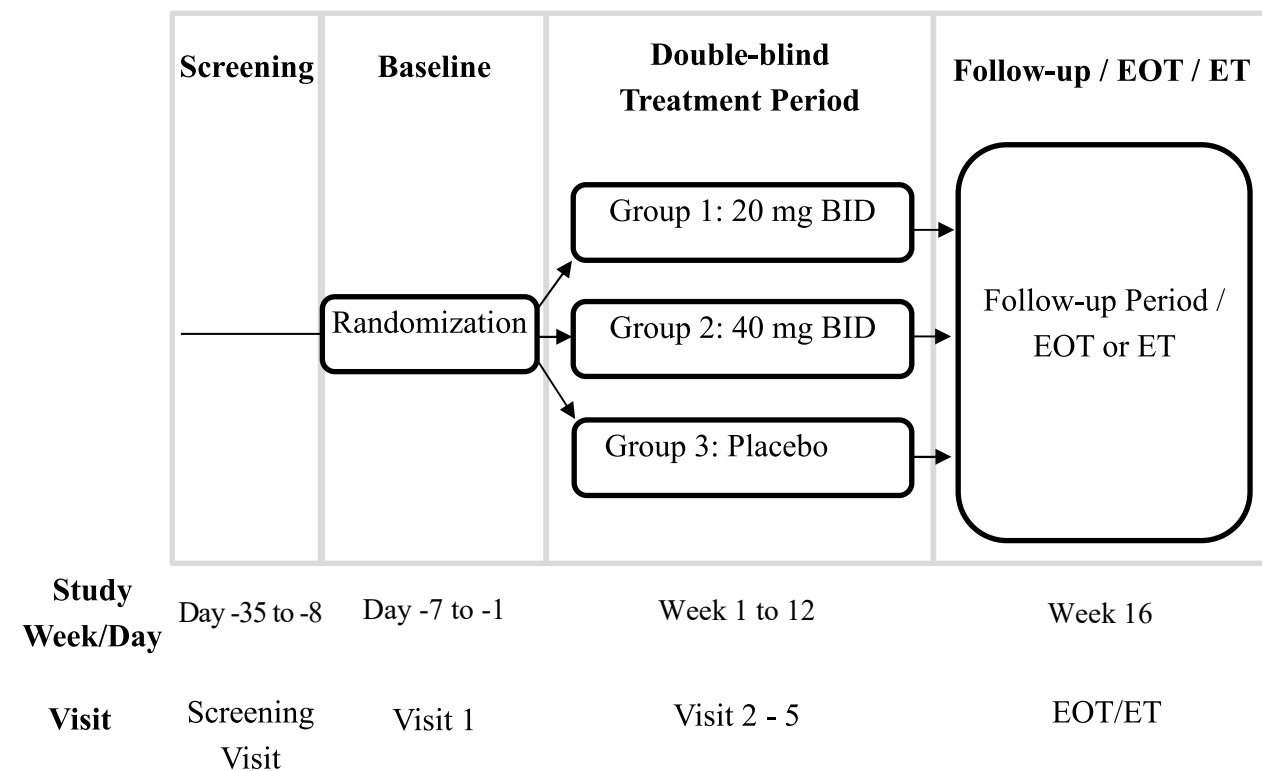
Interim safety assessment will be performed when there are ≥ 5 serious adverse events (SAEs) or when there are ≥ 3 AESIs. The study enrollment will be stopped however treatment may continue for randomized patients, and the DMC should review the data in their entirety and recommend discontinuing the study or reconfiguring the dosing groups if:

- Either ≥ 5 SAEs are deemed related or possibly related to study intervention and $\geq 6\%$ of enrolled participants have related or possibly related SAEs; or
- The ≥ 3 AESIs are adjudicated to be related or possibly related to study intervention.

The structure and operation of the DMC, including the role of its independent member, is detailed in the DMC Charter.

1.2 Schema

Figure 1–1 Study Design



BID=twice daily, EOT=End-of-Treatment, ET=Early Termination

1.3 Schedule of Assessments

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							

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
Serum β-hCG ⁱ	X							
Urine pregnancy test ^j		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 ^m		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	

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
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 Day1 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 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 locally 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 Table 10-1.
- 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 [REDACTED]. PK blood collections are to be at the same time points as all 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 Introduction

TLL018 is a novel, highly potent, and selective Janus kinase 1 (JAK1)/tyrosine kinase 2 (TYK2) inhibitor being developed for the treatment of autoimmune and inflammatory diseases. This study evaluates its potential for the treatment of plaque psoriasis (PP).

The term “study intervention” throughout the protocol, refers to TLL018 or placebo.

2.1 Study Rationale

This study is to investigate the efficacy and safety of 2 doses of TLL018 for therapy of participants with moderate-to-severe PP. Based on the mechanism of action of TLL018 and clinical experience in the first-in-human Phase 1 study of orally administered TLL018 (TLL018-101 study), TLL018 is expected to be safe and well-tolerated at the doses and regimens proposed in this study, and to have reduced toxicity and improved efficacy compared to currently approved JAK inhibitors (Section 4.2).

2.2 Background

TLL018 is a novel, highly potent small molecule JAK1/TYK2 inhibitor. JAK1 and TYK2 are the key regulators of pro-inflammatory cytokines (Murray 2007, Schwartz et al 2016). Cytokines are important drivers of autoimmune and inflammatory diseases, such as PP. The JAK-signal transducer and activator of transcription proteins (STAT) pathway plays a central role in the physiologic regulation of a large number of pro-inflammatory cytokines in these diseases. JAKs (JAK1, JAK2, JAK3, and TYK2) belong to a family of intracellular, non-receptor tyrosine kinases that transduce cytokine-mediated signals via the JAK-STAT pathway (Schwartz et al 2016, Winthrop 2017). Cytokine-targeting therapies such as IL-17, IL-23, and tumor necrosis factor (TNF)- α neutralizing antibodies have been approved and used to treat patients with certain autoimmune diseases including rheumatoid arthritis (RA) and psoriasis. However, not all patients respond adequately to or can tolerate these therapies. In recent years, small molecule JAK inhibitors have also been developed and shown promising clinical activities in the treatment of many autoimmune diseases such as RA, psoriasis, psoriatic arthritis, inflammatory bowel disease (IBD), graft-versus-host disease, alopecia areata, atopic dermatitis, systemic lupus erythematosus, systemic sclerosis, and uveitis (Murray et al., 2007, Schwartz et al 2016, Winthrop 2017, Krueger et al 2022).

TLL018 has demonstrated excellent pharmacologic activities and efficacy in commonly established animal arthritis models, while being well-tolerated. In a Phase 1 study in healthy volunteers, TLL018 was dosed from 4 mg up to 120 mg as single doses and 7-day multiple doses, including 32 mg twice daily (BID). The drug was well-tolerated and there were no adverse events

(AEs) attributable to TLL018 as assessed by the Investigator. Furthermore, TLL018 treatment up to 120 mg daily for 7 days did not cause any effects on vital signs, electrocardiograms (ECG), hematology, laboratory chemistry, and urinalysis parameters and there was no cytopenia (anemia, leukopenia, and neutropenia), no increased lipids, no increased creatine phosphokinase (CPK) or creatinine, no infections or serious infections that were commonly observed with other less selective JAK inhibitors such as tofacitinib, baricitinib, and upadacitinib. In addition, orally administered TLL018 exhibited approximately linear pharmacokinetics (PK) with rapid absorption (time of maximum concentration [T_{max}] values of 0.5 to 1 hour), large volume of distribution (>135 L), and substantial renal clearance (up to 50% of the drug dose is recovered as parent drug in the urine). Food effects were observed with approximately 30% reduction of maximum plasma concentration and delayed absorption (T_{max} of 3 hours) following a high-fat meal. The overall exposure, based on area under the curve values, was not significantly changed. TLL018 treatment caused a consistent transient decrease of absolute neutrophil cell counts and a consistent transient increase of absolute lymphocyte cell counts. [REDACTED]

[REDACTED]

Phase 1 study data suggest that TLL018 has a favorable safety and activity profile indicative of a potentially better therapeutic window compared to some of other JAK inhibitors, and further support its development in clinical studies of patients with relevant autoimmune/inflammatory diseases, including PP.

A detailed description of the chemistry, pharmacology, biologic activity, and safety of TLL018 is provided in the Investigator's Brochure (IB).

2.3 Benefit/Risk Assessment

2.3.1 Risk Assessment

Potential risks associated with TLL018 and study procedures and measures to control the risks are summarized in [Table 2-1](#). More detailed information about the known and expected benefits and risks and reasonably expected AEs of TLL018 may be found in the IB.

Table 2-1 Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention: TLL018		
Serious infections	Infections are common AEs with JAK inhibitors. TLL018 could increase the risk of infection.	Avoid use of TLL018 in participants with active, serious infection, including localized infections. Evaluate and test participants for latent or active TB prior to administration of TLL018.
Malignancy	Malignancy, such as lymphoma and other cancers have been reported in patients with RA treated with certain JAK inhibitors, but there is no indication that the risk was significantly increased compared to placebo or biologic disease-modifying antirheumatic drugs.	Exclude participants with a known history of malignancy.
Thrombosis	According to the US FDA black box warning for tofacitinib (FDA Drug Safety Communication 2019), an increased risk of thrombosis and even death was observed in patients taking 10 mg BID tofacitinib compared with 5 mg BID or a TNF blocker, consistent with the preclinical finding that tofacitinib can inhibit all 3 JAKs, including JAK2 at high doses.	Exclude participants who may be at increased risk of thrombosis or have a history of thrombosis. Promptly evaluate participants with symptoms of thrombosis and treat appropriately.
Major adverse cardiovascular events	MACE are defined as incident myocardial infarction, stroke, heart failure, coronary revascularization, atrial fibrillation, or cardiovascular death. FDA Drug Safety Communication dated February 4, 2021 (FDA Drug Safety Communication 2021) indicated that tofacitinib showed a higher occurrence of serious heart-related events.	Participants experiencing MACE events Grade 2 and above will be discontinued from study treatment. Also, participants with significant cardiac events within 6 months of Screening as well as participants with risk factors including uncontrolled hypertension and diabetes will be excluded from the study. Safety assessments will include cardiac death, nonfatal myocardial infarction, and fatal or nonfatal stroke, whichever occurred first (composite cardiovascular endpoint). See Section 10.3.3 for MACE definition.
Gastrointestinal perforations	Relatively rare SAEs of gastrointestinal perforation have been reported in the clinical studies, although the toxicity may be directly associated with individual JAK inhibitors or inhibition of specific JAK family members.	Use with caution in participants who may be at increased risk with a history of stomach ulcers/ upper intestinal ulcers.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention: TLL018		
Potential changes in lymphocytes, neutrophils, hemoglobin, liver enzymes and lipids	Relatively rare SAEs, such as cytopenia have been reported in the clinical studies, although the toxicity may be directly associated with individual JAK inhibitors or inhibition of specific JAK family members.	Perform laboratory monitoring.
Embryo-fetal toxicity	TLL018 may cause fetal harm based on animal studies of other JAK inhibitors. Effects of TLL018 on fetal development are being evaluated preclinically.	Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception. Men with partners of childbearing potential must be willing to abide by protocol-specified methods to avoid fathering a child from the time of Screening throughout the study period.
Vaccinations	JAK inhibitors have immunosuppressive activity.	Avoid use of TLL018 with live vaccines 2 months before and after the administration of TLL018.
Hypersensitivity	As with any drug, rare allergic reactions, including anaphylaxis, to TLL018 or excipients included in formulations of the drug are possible.	Perform laboratory monitoring.

AE=adverse event, BID=twice daily, FDA=Food and Drug Administration, JAK=Janus kinase, MACE=major adverse cardiovascular events, PP=plaque psoriasis, RA=rheumatoid arthritis, SAE=serious adverse event, TB=tuberculosis, TNF=tumor necrosis factor, US=United States

2.3.1.1 Risk Assessment for Coronavirus Disease 2019 Pandemic

There is an ongoing pandemic of respiratory disease (coronavirus disease 2019 [COVID-19]) caused by a novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Appropriate medical measures have been implemented into this protocol to detect COVID-19 disease to confirm eligibility of participants and to safely conduct the study.

TLL018 is a molecule inhibitor and is believed to cause immune suppression. However, to date, there are no data suggesting that JAK inhibitors increase the risk of COVID-19 infection and its complications. Measures to mitigate the additional risks caused by COVID-19 are as follows:

- This study is going to start enrolling only when the Sponsor and contract research organization (CRO) in collaboration deem it is safe to start the study.
- Current national laws and local recommendations for prevention of the pandemic will be strictly adhered to.

- Participants will be closely monitored for any signs and symptoms of COVID-19 throughout the study, including fever, dry cough, dyspnea, sore throat, and fatigue. If clinical signs of infection are reported by participants, the Investigator needs to determine whether samples can be collected, and safety data can be recorded at the study site. If not, AEs and concomitant medications will be obtained via phone calls. Body temperature measurements will be taken during outpatient visits.
- TLL018 will not be administered to participants upon confirmation of any signs or symptoms and by COVID-19 PCR test.
- Confirmation of COVID-19 infection by optional laboratory assessment will be conducted based on availability (test capacity and turnaround time) of approved tests and at Investigators' discretion.
- The probability of virus transmission will be controlled as much as possible by:
 - Advice for participants to adhere to local requirements for reduction of public exposure while ambulatory.
 - The study site should follow local / institutional guidelines related to COVID-19 prior to every patient visit.
 - Physical distancing and person-to-person contact restrictions will be applied during study site visits and in-house confinement.
 - Where physical distancing is not possible, personal protective equipment will be used by the participants (surgical face mask, gloves) and personnel (for example, but not limited to, masks, gloves, protectors, and medical suits) if deemed appropriate by the Investigators and site personnel and guided by local requirements.
 - Logistical improvements of the study site and structural measures of the study site building will be implemented to further improve physical distancing.

2.3.2 Benefit Assessment

TLL018 has been shown to be a potent and highly selective small molecule inhibitor of JAK1 and TYK2 based on a series of enzymatic and cellular assays as well as a large panel kinase profiling. Since JAK1 and TYK2 are key regulators of pro-inflammatory cytokines, this exclusive selectivity for JAK1/TYK2 offers an opportunity to assess the potential clinical benefit and safety of specific and dual inhibition of JAK1 and TYK2 in patients with autoimmune and inflammatory diseases where drug safety or tolerability is of special importance. The hypothesis is that a highly selective JAK1/TYK2 inhibitor may reduce or potentially eliminate some reported severe toxicities

associated with JAK2 and/or JAK3 inhibition while maintaining equal or better clinical benefits in patients.

2.3.3 Overall Benefit/Risk Conclusion

Considering the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with TLL018 are justified by possible benefits that may be afforded to patients with PP.

3 Objectives and Endpoints

Study objectives and endpoints are summarized in [Table 3-1](#).

Table 3-1 Objectives and Endpoints

Objectives	Endpoints
<u>Primary Objective</u> To evaluate the efficacy of TLL018 in the treatment of moderate-to-severe PP	<u>Primary Endpoint</u> Proportion of participants achieving a minimum 75% improvement from Baseline at the end of Week 12 for the PASI (PASI-75)
<u>Secondary Objectives</u> - 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	<u>Secondary Safety Endpoints</u> - TEAEs^a - SAEs - AESIs - Clinical laboratory tests - Vital signs (blood pressure, pulse rate, respiratory rate, and oral temperature) 12-lead ECGs - Physical examination findings <u>Secondary Efficacy Endpoints</u> - 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

Objectives	Endpoints
	- 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
<u>Exploratory Objective</u> - 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	<u>Exploratory Endpoints</u> - Proportion of participants achieving PASI-100 - Changes in [REDACTED] levels from Baseline and their association with TLL018 exposure/levels - Serum C_{trough ss} of TLL018

AE=adverse event, AESI=adverse event of special interest, DLQI=Dermatology Life Quality Index, ECG=electrocardiogram, IL=interleukin, PASI=Psoriasis Area and Severity Index, PD=pharmacodynamics, PGA=Physician's Global Assessment, PP=plaque psoriasis, SAE=serious adverse event, TEAE=treatment-emergent adverse event

- a. A TEAE is defined as an event that emerges during treatment, having been absent pretreatment, or worsens relative to the pretreatment state.

4 Study Design

4.1 Overall Design

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 approximately 90 participants with moderate-to-severe 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 range is 20 mg BID and 40 mg BID. Study interventions 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 2:1:1 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 70 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.

Participants will be assessed for safety, tolerability, and response to treatment. Samples for PD biomarker analyses will be collected throughout the study according to the Schedule of Assessments (SoA; [Table 1-1](#)) for potential correlation to clinical outcomes. PK samples will be collected with the PD samples. Planned total study duration will be approximately 4 months.

4.2 Scientific Rationale for Study Design

Psoriasis is a common, chronic, inflammatory, T cell-mediated disease [[Krueger et al, 2022](#)]. It is typically characterized by erythematous, scaly, thick plaque on the skin. The majority of patients with psoriasis have only skin and nail involvement, although joint disease, i.e., psoriatic arthritis, is common, occurring in approximately 30% of patients with psoriasis. Many reports show that psoriasis patients are at high risk for other co-morbidities as well, including cardiovascular disease, diabetes, metabolic syndrome, and depression. The precise cause and pathogenesis of psoriasis are still unknown, although it is believed that environmental factors trigger/drive abnormal inflammatory responses in genetically susceptible individuals.

Psoriasis may affect any race, age group, and gender and its prevalence is similar in men and women. Approximately two-thirds of patients have disease onset before the age of 40 years and the disease is more severe in winter and milder during the summer in most patients. In addition to genetic factors, environmental factors (such as humidity, trauma, alcohol use), and mental stress also contribute to the development of psoriasis. It is also associated with obesity, metabolic syndrome, and cardiovascular disease. In adults, the prevalence of psoriasis in the United Kingdom is estimated to be 1.30% [[O'Neill and Kelly, 1996](#); [Parisi et al, 2013](#)]. This is thought to be among the lowest in Europe. For example, prevalence of psoriasis in Denmark was estimated to be 3.73% [[Brandrup and Green, 1981](#)]. Estimates of psoriasis prevalence in the United States are as high as 3.15% [[Kurd and Gelfand, 2009](#)].

Activation of the IL-23/IL-17 immunologic pathway is crucial psoriasis pathogenesis. Indeed, treatments targeting either IL-23 or IL-17 are highly efficacious for psoriasis patients. The skin contains a complex network of dendritic cells (DCs) mainly composed of epidermal Langerhans cells, bone-marrow-derived dermal conventional DCs, plasmacytoid DCs, and inflammatory DCs. DCs and inflammatory macrophages are the main cell sources of interferon (IFN)- α , TNF- α , IL-12, and IL-23, and play key roles in psoriasis. IL-23 promotes survival and proliferation of Th-17 and Tc-17 cells and stimulates these cells to become activated, proliferate, and produce excessive pro-inflammatory cytokines, including IL-17A, IL-17F, and IL-23. These cytokines drive abnormal differentiation and proliferation of keratinocytes [Krueger et al, 2022]. IL-23 is overexpressed in human psoriatic skin and injection of IL-23 into the skin of wild-type mice can cause psoriasis-like lesions. Discovery of its key role in the pathogenesis of psoriasis was translated into the development of anti-IL-23 monoclonal antibody therapies, which show excellent efficacy in treating psoriasis. JAK1, JAK2, JAK3, and tyrosine kinase (TYK2) are intracellular tyrosine kinases. They are activated by binding of cytokines to cytokine receptors, leading to JAK phosphorylation. This in turn leads to recruitment, phosphorylation, and activation of STAT proteins, which control transcription of many genes associated with innate and adaptive immunity, hematopoiesis, and cellular processes, including cell growth, survival, differentiation, and migration.

TLL018 under development by Hangzhou Highlightll Pharmaceutical Co., Ltd. is a novel, potent, and selective small molecule JAK1/TYK2 inhibitor. JAK1 and TYK2 are main key regulators of pro-inflammatory cytokines. Studies have showed that JAK1 and TYK2 synergistically mediated signal transduction of many pro-inflammatory cytokines, including IL-2, IL-4, IL-6, IL-10, IL-15, IL-23, IL-24, IL-31 and IFN- γ , IFN- α , IFN- β , and IFN- λ . TYK2 has also been demonstrated to phosphorylate IL-12, IL-23, and STAT proteins downstream of type I IFN receptors, and these proteins are associated with many autoimmune disorders, such as psoriasis, IBD, RA, and lupus. Additionally, TYK2 variant I684S was found to be psoriasis-protective [Enerback et al, 2022] and a selective TYK2 inhibitor deucravacitinib has shown impressive efficacy in psoriasis patients [Krueger 2022]. Therefore, highly selective JAK1 and TYK2 inhibitors may have potential for treating various autoimmune and inflammatory diseases and minimize or avoid some of the toxicities related to JAK2 and JAK3 inhibition. The latest published toxicologic and clinical safety findings of JAK inhibitors appear mainly related to inhibition of JAK2. Moreover, TLL018 has good absorption, distribution, metabolism, and excretion properties in humans and in experimental animals.

4.3 Justification for Dose

In the Phase 1 TLL018-101 study, TLL018 was tested up to 120 mg QD for 7-day multiple ascending doses. TLL018 was well-tolerated and there were no AEs of any grades attributable to TLL018 by the Investigator. In addition, TLL018 of 7-day treatment did not cause significant effects on vital signs, ECG, hematology, laboratory chemistry, urinalysis parameters and there was no cytopenia (anemia, leukopenia, and neutropenia), no increased lipids, no increased CPK or creatinine, no infections or serious infections that have previously been reported with other less selective JAK inhibitors, such as tofacitinib, baricitinib, and upadacitinib. The Phase 1 results support studying a low dose of TLL018 at 10 mg BID and a high dose of at least 40 mg BID for the duration of this Phase 2 study with PP patients. In addition, 3-month Good Laboratory Practices toxicity studies in rats and dogs have identified no-observed-adverse-effect-levels (NOAELs) of at least 10 and 5 mg/kg/day in rats and dogs, respectively, and both doses were the highest doses administered in those studies.

In the 3-month dog study, TLL-018 dosed up to 5 mg/kg/day was well tolerated with no mortality or morbidity, no effects on clinical observations (body weight, food consumption, ophthalmology, ECG) or anatomic pathology parameters. In the 9-month, TLL018 related pyogranulomatous inflammation in the skin of males and females given 5 mg/kg/day was considered adverse, and the NOAEL was determined to be 1.5 mg/kg/day.

In the 3-month rat study, TLL018 was dosed at 0.2, 2, and 10 mg/kg/day and there were no treatment-related effects on clinical observations. The only TLL-018 related clinical pathology changes were confined to hematology, including non-adverse minimally to mildly lower mean values for total leukocyte and lymphocyte counts. TLL-018 related organ weight changes consisted of non-adverse decreases in spleen, thymus, and uterus with cervix on Day 92. In the 6-month rat study, no adverse test article-related effects were observed, and the NOAEL was determined to be 10 mg/kg/day.

Clinical trials in rheumatoid arthritis patients from China suggest that 10mg BID is not an effective dose. In addition to the favorable data for TLL-018 in the Phase 1 trial, the Phase 2 rheumatoid arthritis trial and toxicity studies, experience with other selective or non-selective JAK1 and/or TYK2 inhibitors in clinical trials, including psoriasis trials, are also considered. Thus, Highlightll Pharmaceutical (USA) proposes to investigate TLL018 at 20 and 40 mg BID in this Phase 2 study with PP patients and suggests that TLL018 will be safe at the doses proposed.

In the trial, hematologic parameters will be routinely monitored, and strict pregnancy Screening/testing and the use of effective contraception will be implemented to avoid potential reproductive risk in the studied participants.

4.4 End-of-Study Definition

The end of the study is defined as the date of the last scheduled procedure shown in the SoA (Table 1-1) for the last participant in the study.

A participant is considered to have completed the study if he/she has completed all periods of the study, including the last scheduled procedure shown in the SoA (Table 1-1).

5 Study Population

5.1 Inclusion Criteria

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

1. Are between the ages of 18 and 75 years, inclusive, at time of informed consent.
2. Capable of giving informed consent and complying with study procedures.
3. Willing and able to adhere to study restrictions.
4. Laboratory and medical history parameters within the protocol defined ranges.
5. Normal renal function (>90 mL/min/1.72 m²) or mild renal impairment (Stage 2 mild chronic kidney disease glomerular filtration rate [GFR] = 60 to 89 mL/min/1.73 m²) as determined by central laboratory.
6. Body mass index (BMI) of 18.0 to 35.0 kg/m² inclusive.
7. Have had a diagnosis of moderate-to-severe PP for at least 6 months prior to Baseline.
8. Participants with moderate-to-severe PP covering $\geq 10\%$ body surface area (BSA), with a Psoriasis Area and Severity Index (PASI) ≥ 12 and a static Physician's Global Assessment (PGA) score ≥ 3 at Baseline.
9. Participants with plaque psoriasis who are systemic treatment naïve or have received at least one of the conventional anti-psoriasis treatments such as acitretin, phototherapy, methotrexate, cyclosporine, apremilast, or biologic therapy (anti-TNF or anti-IL-12/17/23).
10. Participants who are candidates for systemic treatment for psoriasis at the discretion of the Investigator.
11. Must agree to avoid prolonged exposure (> 15 minutes) to the sun and avoid use of tanning booths or other ultraviolet light sources during the study.

12. Female participants of childbearing potential (See [Section 10.4.1](#) definition of Woman of Childbearing Potential - WOCBP) must have a negative serum human chorionic gonadotropin (hCG) at Screening, and meet one of the following criteria:
 - a. Using a medically acceptable form of birth control ([Appendix 4](#)) for at least 1 month prior to Screening and 3 months after the last dose of study drug (e.g., hormonal contraceptives [oral, patch, injectable or vaginal ring], implantable device [implantable rod or intrauterine device], bilateral tubal occlusion/tubal ligation, azoospermic partner).
 - b. Abstinence as a form of birth control is generally not permitted during the study with the exception of participants who practice abstinence as a preferred and usual lifestyle choice. The Investigator must confirm that abstinence is still in accordance with the participant's lifestyle at regular intervals throughout the study.
13. Male participants with female partners of childbearing potential must agree to use condoms for the duration of the study and until 13 weeks after administration of the study intervention and must refrain from donating sperm for this same period. In addition, his female partner should agree to use a highly effective method of birth control per [Appendix 4](#) or an additional barrier form of birth control (e.g., diaphragm, cervical cap, spermicide, or sponge.)
14. Ability to swallow and retain oral study intervention.
15. Participants must have completed their coronavirus disease 2019 (COVID-19) vaccination in accordance with the latest CDC guidelines, which is based on previous vaccination history. Please reference COVID-19 vaccination guidance for individuals who are moderately or severely immunocompromised ([Clinical Guidance for COVID-19 Vaccination | CDC](#)).
 - a. Previous Pfizer-BioNTech, Moderna or Novavax: Must have previously received at least a 1st and 2nd dose, then must have received an updated formulation according to the CDCs dosing requirements; **or**
 - b. Novavax or Johnson and Johnson's Janssen: Must have previously received 1 or more doses in combination with any original monovalent or bivalent COVID-19 vaccine doses, then must receive an updated formulation according to the CDCs vaccination guidelines.

5.2 Exclusion Criteria

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

1. Pregnant or nursing women.
2. Past history of gastrointestinal perforation, history of peptic ulcers and/or regular use of NSAIDs.
3. History of chronic alcohol or drug abuse within 6 months prior to Screening as determined by the Investigator based on medical history and patient interview.
4. Current or recent history of severe, progressive, or uncontrolled renal, hepatic, hematologic, gastrointestinal, metabolic, endocrine, pulmonary, cardiovascular, neurologic, or psychiatric disease.
5. Current and/or recent history (<30 days prior to Screening and/or <45 days prior to randomization) of a clinically significant viral, bacterial, fungal, parasitic, or mycobacterial infection.
6. Subject is currently being treated with or has received strong cytochrome P450 3A (CYP3A4) inhibitors, such as itraconazole, within 4 weeks prior to Baseline (Day 0).
7. Any history of malignancies, except for non-recurrent basal cell skin cancer, squamous cell skin cancer, and cervical cancer in situ that are considered to be cured.
8. Tests positive for hepatitis B, hepatitis C, or human immunodeficiency virus (HIV). For Hepatitis B all subjects will undergo testing for Hepatitis B Surface Antigen (HBsAg) and Hepatitis B Core Antibody (HBcAb). Subjects who are HBsAg positive are not eligible for the study. Subjects who are HBsAg negative and HBcAb positive will subsequently need testing for Hepatitis B virus deoxyribonucleic acid (HBV DNA) and if HBV DNA negative may be enrolled in the study; if HBV DNA is positive, the subject is not eligible for the study. Positive hepatitis C virus result is defined as having a positive hepatitis C antibody test with a positive confirmatory hepatitis C polymerase chain reaction test.
9. Recent exposure to active tuberculosis (TB). Current evidence of active TB or current evidence of latent TB. Participants with positive TB test (e.g., QuantiFERON) that have been treated for latent TB. A borderline QuantiFERON test should be repeated. If still indeterminant, then a chest x-ray may be performed (positive chest x-ray is exclusionary).
10. History of unexplained syncope, symptomatic hypotension, or hypoglycemia.
11. Abnormal D-dimer levels in conjunction with clinical or current and past thrombotic disease.

12. Participants with uncontrolled hypertension, uncontrolled diabetes, untreated or uncontrolled hyperlipidemia (fasting blood triglycerides >500 mg/dL and fasting cholesterol >250 mg/dL).
13. History of any significant cardiac event (e.g., myocardial infarction) within 6 months prior to Screening, including:
 - a. History of long QTc syndrome; history or presence of an abnormal ECG, which, in the Investigator's opinion, is clinically significant.
 - b. History of unstable ischemic heart disease or uncontrolled hypertension.
 - c. Current Class 3 or 4 heart failure per the New York Heart Association Functional Classification.
 - d. Screening and/or Baseline QTcF > 450 msec for males and > 470 msec for females, confirmed by triplicate ECG.
14. Participants with history of thrombosis and/ or thromboembolism, or associated risk factors (e.g., inherited thrombophilias, etc.).
15. Donated or lost >500 mL of blood in the previous 3 months.
16. Participants with chronic kidney disease with eGFR <60 mL/min/1.73 m².
17. Participants with moderate-to-severe hepatic impairment (i.e., Child-Pugh Class B and C).
18. Major surgery within 3 months prior to Screening or participant has a planned major surgery during the course of the study.
19. Participants with any of the following abnormalities in clinical laboratory tests at Screening, as assessed by the study-specific laboratory and confirmed by a single repeat, if deemed necessary:
 - Hemoglobin <100 g/L
 - White blood cell (WBC) count of <3.0 × 10⁹/L
 - Platelet count of <80 × 10⁹/L
 - Absolute neutrophil count of <1.5 × 10⁹/L
 - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) values greater than 3 times the ULN
20. Any uncontrolled clinically significant laboratory abnormality that would affect interpretation of study data or the participant's participation in the study.

21. Previous or current autoimmune diseases (e.g., RA, systemic lupus erythematosus, IBD, scleroderma, inflammatory myopathy, mixed connective tissue disease overlap syndrome, etc.). Note, psoriatic arthritis patients are allowed.
22. Other types of psoriasis (such as erythrodermic psoriasis, pustular psoriasis, guttate psoriasis, drug-induced psoriasis).
23. Current enrollment in another study intervention protocol or experimental treatment within 30 days or five half-lives (whichever is longer).
24. Received any topical therapy that can affect psoriasis (including topical use of moderate-strong glucocorticoids, retinoids, vitamin D3 derivatives, salicylic acid, anthracene, etc.) within 2 weeks of first study intervention. Low potency topical steroids are permitted for sensitive areas only (e.g., face, axillae, genitalia). Bland emollients without urea or α or β -hydroxy acids are permitted.
25. Use of phototherapy (including photochemotherapy, ultraviolet therapy, tanning bed self-therapy, etc.) within 4 weeks of first study intervention.
26. Use of systemic oral therapy that can affect psoriasis (including but not limited to glucocorticoids, retinoids, cyclosporine, methotrexate and apremilast) within 4 weeks of first study intervention.
27. Received intravenous corticosteroids within 4 weeks of first study intervention.
28. Use of antimalarial drugs, interferon- α , lithium and beta-blockers within 4 weeks of first study intervention.
29. Use of Chinese or herbal medicine treatment of psoriasis within 2 weeks of first study intervention.
30. Prior to randomization, washout periods of the following biologics are required: etanercept ≥ 28 days; any s.c. mAb targeting TNF (eg., infliximab, adalimumab, certolizumab) ≥ 3 months; ustekinumab or drugs that specifically target IL-23 > 6 months; secukinumab, ixekizumab, bimekizumab, brodalumab or other IL-17 antagonists ≥ 6 months; any other anti-psoriasis treatments not listed within 5 half-lives. Topical JAK inhibitors should have a washout period > 2 weeks.
31. Prior use of three or more biologic therapies.
32. Use of natalizumab and other drugs that regulate B or T cells within 12 months of first study intervention, such as rituximab, alemtuzumab, and abatacept.

33. Participants who have received live vaccines within 2 months prior to first study intervention or plan to receive live vaccines during the study period. Non-live-attenuated vaccines (e.g., ribonucleic acid [RNA]-based vaccines, inactivated adenovirus-based vaccines, protein-based vaccines), including non-live-attenuated vaccines or boosters for coronavirus disease 2019 (COVID-19) during the study are allowed.
34. Participants who have received COVID-19 vaccines within 2 weeks of Baseline or participants who plan to receive COVID-19 vaccines during the study period (boosters are allowed).
35. Previously not completed COVID-19 vaccination in accordance with the CDC guidelines.
36. Participants who are allergic to any component of the study intervention or who are at risk for allergy as determined by the Investigator during the study.
37. Any condition for which the Investigator considers the participant inappropriate to participate in this study.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

There are no restrictions on meals and diet. Although, high fat meals should be avoided prior to and with dosing.

5.3.2 Alcohol Consumption and Marijuana Use

During each dosing session, participants will be advised to abstain from alcohol for 48 hours prior to visit until after collection of the final PK and/or PD sample.

Recreational and therapeutic use of marijuana will be permitted.

5.3.3 Activity

Participants will be advised to abstain from strenuous exercise for duration of study.

5.4 Screen Failures

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, reason for screen failure (e.g., eligibility

requirements failed), and documentation of any medical occurrences that qualify as serious adverse events (SAEs).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once. Rescreened participants should be assigned a new participant number for every Screening/rescreening event.

5.4.1 Screening and Enrollment Log and Participant Identification Numbers

The participant's enrollment will be recorded in the Screening and Enrollment Log.

Upon enrollment, each participant will receive a unique participant identification number. Participant numbers must not be re-used for different participants.

6 Study Interventions and Concomitant Therapy

Study intervention is defined as any investigational treatments intended to be administered to a study participant according to the study protocol. Study drug will be given as BID dosing preferably within a window of 8 – 12 hours. Suggested times are after breakfast and after dinner. If a dose is missed and known within 4 hours, then it can be taken. However, if recognized after 4 hours, then the participant should skip this dose and just take the next regular dose.

6.1 Study Interventions Administered

Study interventions and study groups are summarized in [Table 6-1](#) and [Table 6-2](#), respectively.

Table 6-1 Study Interventions Administered

Drug Label	Investigational Drug	Reference Therapy
Drug Name	TLL018	Placebo
Drug Description	TLL018 is a film-coated tablet with 10 mg strength, consisting of TLL018, [REDACTED] TLL018 will be given orally at 20, or 40 mg BID. Dosing instructions will include the number of tablets to be administered at individual dose levels.	The compositions of matching placebos are the same except that there is no TLL018, and [REDACTED] is adjusted accordingly to have the same tablet weight. TLL018 matching placebos will be given orally BID.
Type	Drug	Drug
Dosage Formulation	Tablet	Tablet
Unit Dose Strength	10 mg per tablet	N/A
Dosage Level(s)	20, or 40 mg BID	20, or 40 mg matching placebo BID

Drug Label	Investigational Drug	Reference Therapy
Route of Administration	Oral	Oral
Use	Experimental	Placebo comparator
IMP or NIMP	IMP	NIMP
Sourcing	Provided centrally by the Sponsor or designee.	Provided centrally by the Sponsor or designee.
Packaging and Labeling	Study intervention will be provided in blister packs. Each blister pack will be labeled as required per country requirement.	Study intervention will be provided in blister packs. Each blister pack will be labeled as required per country requirement.

BID=twice daily, IMP=investigational medicinal product, N/A=not applicable, NIMP=non-investigational medicinal product

Table 6-2 Study Groups

Arm Title	Group 1	Group 2	Group 3
Arm Type	Experimental	Experimental	Placebo
Arm Description	Participants will receive TLL018 20 mg BID daily for 12-weeks in the Treatment Period.	Participants will receive TLL018 40 mg BID daily for 12-weeks in the Treatment Period.	Participants will receive TLL018 matching placebo BID daily for 12-weeks in the Treatment Period.
Associated Drug Labels	Study intervention	Study intervention	Reference therapy

BID=twice daily

6.2 Preparation, Handling, Storage, and Accountability

The Investigator or designee must maintain a log to confirm appropriate temperature conditions have been maintained during transit for all study interventions received, and any discrepancies are reported and resolved before use of the study intervention.

Study intervention must be stored at controlled room temperature between 20 to 25 °C (68 to 77 °F). Excursions between 15 °C and 30 °C (59 °F and 86 °F) that are experienced in pharmacies, hospitals, and warehouses, and during shipping are allowed.

Only participants enrolled in the study may receive study intervention, and only authorized site personnel may supply or administer study intervention. All study interventions 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 site personnel.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study intervention are provided in the Pharmacy Manual.

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 intervention using the Drug Accountability Form. These forms must be available for inspection at any time.

6.3 Assignment to Study Intervention

Approximately 90 participants will be randomized 2:2:1 to receive 20 mg BID, 40 mg BID, or placebo BID, respectively, resulting in 72 participants per active study intervention group and 18 participants in placebo. Randomization will be stratified by previous psoriasis biologic use and diagnosis of psoriatic arthritis.

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.

Study intervention will be administered/dispensed at the study visits as summarized in the SoA ([Table 1-1](#)).

6.4 Blinding/Masking

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. In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a participant's study intervention assignment is warranted. Participant's safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, the Investigator should make every effort to contact the Sponsor prior to unblinding a participant's study intervention assignment unless this could delay emergency treatment for the participant. If a participant's study intervention assignment is unblinded, the Sponsor must be notified within 24 hours of this occurrence. The date and reason for the unblinding must be recorded.

Sponsor safety staff may unblind the study intervention assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to 1 or more regulatory agencies, a copy of the report, identifying the participant's study intervention assignment, may be sent to Investigators in accordance with local regulations and/or Sponsor policy.

6.5 Study Treatment Compliance

When participants are administered study intervention at the study site, they will receive study intervention directly from the Investigator or designee, under medical supervision. The date and time of each study intervention administered in the study site will be recorded in the source documents. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site personnel other than the person administering the study intervention.

When participants self-administer study intervention at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed by direct questioning and counting returned tablets during the study site visits and documented in the source documents and relevant form. Deviations from the prescribed dosage regimen should be recorded.

A record of the quantity of TLL018 or placebo dispensed to and administered by each participant must be maintained and reconciled with study treatment and compliance records. For compliance recording, participants will be given a dosing diary and asked to document their daily dosing. The diary will be returned for inclusion in source documents. Study intervention start and stop dates, including dates for study intervention delays and/or dose reductions will also be recorded. Non-compliance will be defined as < 85% of the monthly prescribed doses.

6.6 Dose Modification

The decision on dose modification may be made by the Data Monitoring Committee (DMC) based on safety and tolerability.

6.7 Continued Access to Study Intervention After the End of the Study

Participants will not have continued access to TLL018 following the end of the study.

6.8 Treatment of Overdose

There is no experience with overdose of TLL018 in humans to date. Adverse effects in animals at high doses may also occur in humans. Refer to Section 6.9 of the IB for more details.

For this study, any dose of study intervention given, greater than the highest dose at a single dosing day specified in this protocol may be considered an overdose.

In the event of an overdose, the Investigator or treating physician should:

- Contact the Medical Monitor immediately;

- Closely monitor the participant for AE/SAE and laboratory abnormalities;
- Document the quantity of the excess dose in the electronic case report form (eCRF).

6.9 Prior and Concomitant Therapy

Any medication, vaccine (including OTC or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) or non-drug therapy that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

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

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

The Investigator or qualified designee will review prior medication use and record prior medications taken by the participant within 2 months prior to Screening.

The Investigator or qualified designee will record medication, if any, taken by the participant during the study through the last visit. Concomitant medications will be recorded for 5 days after the last dose of study intervention (or longer if related to an SAE).

Concomitant topical creams of potencies 5 and 6, i.e., fluocinolone (5), cortisone (6), hydrocortisone (6) Bland emollients without urea or α / β hydroxy acids are permitted if not used within 24 hours of PASI assessments. These creams are permitted for sensitive areas only (e.g., face, axillae, genitalia). The bland emollients without urea or α or β hydroxy acids are permitted, as long as not within 24 hours of PASI assessment.

6.9.1 Prohibited Concomitant Therapies

Prohibited concomitant therapies include biologics, glucocorticoids, retinoids, cyclosporine, tacrolimus, corticosteroids (oral, parenteral, or topical (except as permitted in Section 6.9), methotrexate, and apremilast. Inhaled steroids are allowed, e.g., asthma.

Live vaccines (2 months before and after the administration of TLL018) are prohibited.

Patients that must receive a prohibited therapy due to worsening condition must be discontinued from study.

7 Discontinuation of Study Intervention and Participant Discontinuation

Discontinuation of specific study sites or of the study as a whole are handled as part of the appendix on Governance, [Appendix 1](#), Section [10.1.9](#) and upon recommendation of the DMC.

7.1 Discontinuation of Study Treatment

It may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant will not remain in the study. See the SoA ([Table 1-1](#)) for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

7.1.1 Individual Stopping Criteria

Individual participant stopping criteria include, but are not limited to, the following criteria according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (Section [10.3.4](#) in [Appendix 3](#)):

Adverse events of special interest:

1. Thromboembolic event – Grade 2 or higher
2. Infection, including fever – Grade 3 or higher
3. Hypertension – Grade 3 or higher
4. Major adverse cardiovascular event (MACE) – Grade 2 or higher (See Section [10.3.3](#) for MACE definition)
5. Malignancy

Abnormal clinical laboratory parameters (refer to [CTCAE version 5.0](#)):

1. ALT or AST – Grade 3 or higher
2. Bilirubin – Grade 3 or higher
3. Creatinine increase – Grade 3 or higher
4. Anemia – Grade 3 or higher
5. Leukopenia – Grade 3 or higher
6. Neutropenia – Grade 3 or higher
7. Thrombocytopenia – Grade 3 or higher
8. CPK – Grade 3 or higher

9. Hemoglobin decrease – Grade 3 or higher
10. Cholesterol and total cholesterol – Grade 3 or higher
11. Low density lipoprotein – Grade 3 or higher

In addition, participants who experience the following should be discontinued from the study.

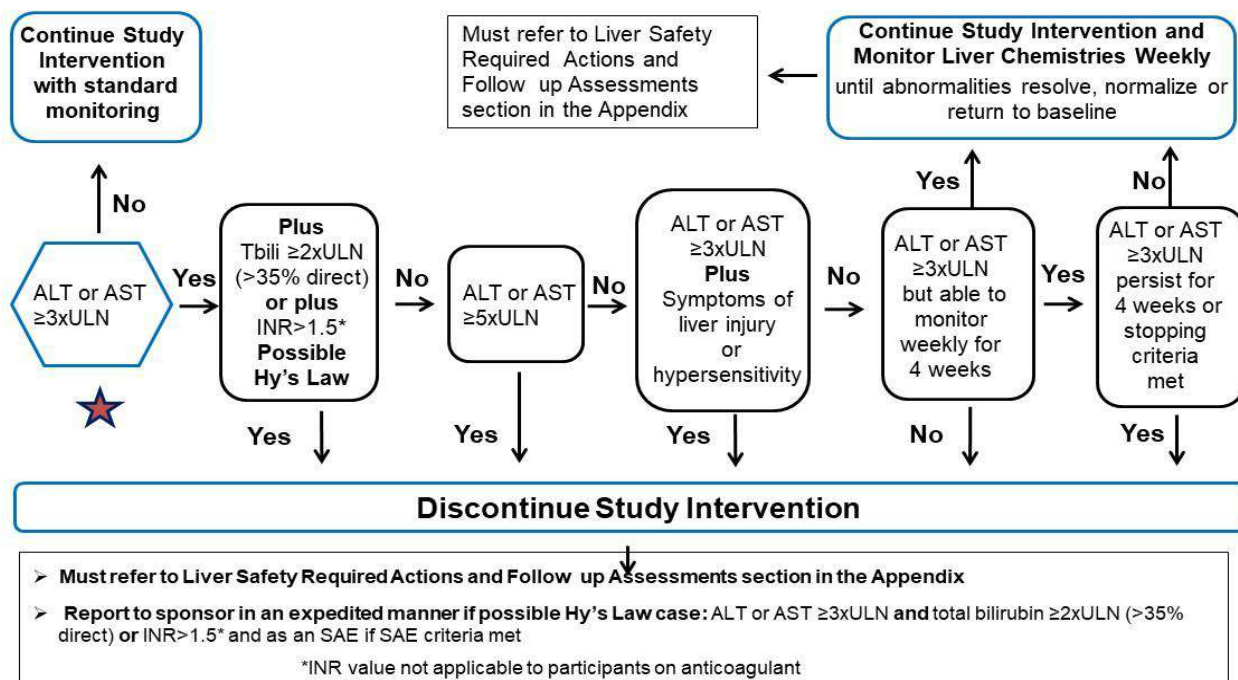
1. Grade 3 or higher AE related to or possibly related to study intervention (abnormal laboratory results should be confirmed)
2. Pregnancy
3. SAEs of hypersensitive reactions and
4. Gastrointestinal perforations

Participants who meet any of these criteria will undergo an Early Termination (ET) visit (Section 7.2). The Investigator or designee will closely follow the participants until resolution or stabilization of the AE and will make an appropriate medical referral if required. Both the final visit procedures and follow-up care will be documented in the eCRF.

7.1.1.1 Liver Chemistry Stopping Criteria

Discontinuation of study intervention for abnormal liver tests is required by the Investigator when a participant meets one of the conditions outlined below.

Study intervention will be discontinued for a participant if liver chemistry stopping criteria are met.



ALT=alanine transaminase; AST=aspartate transaminase, INR=international normalized ratio; SAE=serious adverse event; Tbili=total bilirubin, ULN=upper limit of normal

Liver Safety: Suggested Actions and Follow-up Assessments are provided in [Appendix 5](#).

7.1.1.2 QTc Stopping Criteria

If a clinically significant finding is identified (including, but not limited to, changes from Baseline in QT interval corrected using Bazett's formula or Fridericia's formula) after enrollment, the Investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. The review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

QTc prolongation is defined as:

- QTc ≥ 500 msec confirmed on repeat ECG (triplicate)
- QTc change >60 msec from Baseline confirmed on repeat ECG (triplicate).

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.

7.1.2 Temporary Discontinuation

Study intervention interruption may be performed if any of the following applies:

- Severe laboratory abnormalities.
- Severe infections.
- SAE that is considered related to or possibly related to the study intervention.
- Per Investigator's discretion if significant AE is considered related to or possibly related to the study intervention.

However, even when the case does not meet any of the criteria, the study intervention may be interrupted upon discussion with the Sponsor if the Investigator considers it clinically necessary (see [Section 10.1.5](#)).

7.1.3 Re-challenge

If a participant needs to stop study intervention temporality, re-challenge may be allowed if the temporary discontinuation of study intervention is due to an AE that is transient at the Investigator's discretion and upon discussion with the Sponsor/DMC. Re-challenge may not be performed if participants missed > 7 consecutive days of dosing.

7.2 Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study at any time at their own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, or compliance reasons. The participant will be permanently discontinued from the study intervention and the study at that time.

In addition, if a participant develops fever or symptoms suggestive of COVID-19 infection during the study, the investigator is advised to discontinue the subject from study drug or rule out COVID 19 disease with an appropriate COVID-19 test. Confirmed COVID-19 cases will be immediately discontinued from study intervention. The participant will be withdrawn by the Investigator based on discussion with the Sponsor and Medical Monitor.

If a participant develops fever or symptoms suspected of being a result of COVID-19 during the study, they will be instructed to follow-up with their regular healthcare provider or follow the instructions for suspected COVID-19 cases per their local health authority. Withdrawal of a participant under such conditions is at the discretion of the Investigator and DMC/CAC.

If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the study site records.

At the time of discontinuing from the study, if possible, an Early Termination (ET) visit should be conducted. The ET visit includes all final visit procedures (i.e., procedures scheduled for Week 24±3 days). Refer to the SoA ([Table 1-1](#)) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

If participant is permanently discontinued due to a TLL018-associated AE, the participant will follow the normal follow-up procedure as below.

The Investigator should take all appropriate measures to ensure the safety of the participant, including referral to a specialist if indicated. The Investigator should follow-up on the outcome of any AE until the event has resolved or stabilized, or for 30 days after last administration of study intervention.

Any SAE brought to the attention of the Investigator within 30 days after cessation of study intervention and considered by him/her to be caused by the study intervention with a reasonable possibility, should be reported through the SAE reporting process (Section [10.3.5](#) in [Appendix 3](#)).

7.3 Lost to Follow-Up

A participant will be considered lost to follow-up if they repeatedly fail to return for scheduled visits and are unable to be contacted by the study site.

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- In cases where the participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record/eCRF.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

- Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented, and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

8 Study Assessments and Procedures

Study procedures and their timing are summarized in the SoA ([Table 1-1](#)). Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All Screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a Screening log to record details of all participants screened and to confirm eligibility or record reasons for Screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of the informed consent form (ICF) may be used for Screening purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoA. Values for clinical chemistry, hematology and urinalysis evaluations at Baseline and during the study should be obtained from the designated central laboratory.

Safety and laboratory results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 450 mL.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Participant identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of efficacy and safety parameters as required by the protocol; record of all AEs and follow-up of AEs; concomitant medication; related study intervention: receipt/ dispensing/return records; study intervention administration information; and date of study completion and reason for early discontinuation of study intervention or withdrawal from the study, if applicable, must be recorded in eCRF.

8.1 Administrative and Baseline Procedures

Participant Identification Card:

All participants will be given a participant identification card identifying them as participants in a research study. The card will contain study site contact information (including direct telephone numbers) to be used in the event of an emergency. The Investigator or qualified designee will provide the participant with a participant identification card immediately after the participant provides written informed consent. At the time of study intervention allocation/randomization, site personnel will add the study intervention/randomization number to the participant identification card.

The participant identification card also contains contact information for the emergency unblinding call center so that a healthcare provider can obtain information about study intervention in emergency situations where the Investigator is not available.

Medical History:

Medical history will be obtained by the Investigator or qualified designee. The medical history including medical conditions of interest such as a significant cardiac event (e.g., myocardial infarction or stroke), will be collected within 6 months and cancer diagnosis within 5 years prior to Screening that the Investigator considers to be clinically relevant. Details regarding psoriasis history and treatment including duration of previous biologic(s) and reason for discontinuing previous biologic(s) will be recorded separately and not listed as medical history.

8.2 Efficacy Assessments

8.2.1 Psoriasis Area and Severity Index (PASI)

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 secondary endpoints also related to PASI. 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 ([Feldman et al., 2005](#)). All assessments for a given participant should be made by the same observer, wherever possible.

8.2.2 Physician's Global Assessment (PGA)

The secondary endpoints related to PGA will include proportion of participants achieving PGA score of 0 or 1 and change from Baseline in PGA score ([Vanessa et al, 2015](#)).

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.

8.2.2.1 Assessment of Dermatology Life Quality Index (DLQI)

The secondary endpoint related to DLQI will include change from Baseline in 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. The DLQI could also be expressed as a percentage of the maximum possible score of 30 [[Finlay et al, 1994](#)].

8.2.2.2 Assessment of Psoriatic Epidemiology Screening Tool (PEST), Psoriatic Arthritis Impact of Disease Questionnaire (PsAID-9) and IDEOM MSK

The secondary endpoint related to PEST, PsAID-9 and IDEOM MSK will assess change from Baseline. The PEST [[Ibrahim GH et al 2009](#)] is a 5-question validated questionnaire. Three or more affirmative answers is a positive psoriatic arthritis diagnosis. The PsAID-9 [[Perez-Chada LM et al 2020](#)] is a 9-question validated questionnaire to assess psoriatic arthritis symptom severity. Higher values indicate worse symptoms. The IDEOM MSK [[Perez-Chada LM et al 2021](#)] is a questionnaire utilizing 8 questions across two parts to assess musculoskeletal symptoms and quality of life. Higher values indicate worse symptoms or diminished quality of life.

8.3 Safety Assessments

Planned time points for all safety assessments are provided in the SoA ([Table 1-1](#)).

8.3.1 Physical Examinations

A complete physical examination will be conducted at Screening and will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurologic systems.

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

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.2 Height and Weight

Height and weight will be measured and recorded. Body weight is taken only at Screening and Week 12 or at the End-of-Treatment (EOT) visit to calculate BMI.

8.3.3 Vital Signs

Body temperature (oral), pulse rate, respiratory rate, and blood pressure (systolic/diastolic) will be assessed.

Blood pressure, pulse rate, and respiratory rate measurements will be assessed in a supine or seated position with a completely automated device. Manual techniques will be used only if an automated device is not available.

Blood pressure, pulse rate, and respiratory rate measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).

Vital signs will be measured on dosing days before the study drug administration and before blood collection for laboratory tests. Participants take study drug, then will be monitored (vitals monitored but not recorded unless AE occurs) for another 1 to 2 hours. Participants can leave the site after 1 hour if vital signs are in normal range and the participants are clinically stable.

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.

8.3.4 Electrocardiograms

ECGs will be performed as outlined in the SoA ([Table 1-1](#)) using an ECG monitor that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section [7.1.1.2](#) for QTc stopping criteria. Participants will be supine at least 5 minutes prior to the assessment.

8.3.5 Clinical Safety Laboratory Tests

Refer to [Appendix 2](#) for the list of clinical laboratory tests to be performed and the SoA ([Table 1-1](#)) for the timing and frequency.

The Investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents.

Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the Investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered to be abnormal and clinically significant during participation in the study or within 5 days after the last study intervention should be repeated until the values return to normal or Baseline or are no longer considered clinically significant by the Investigator or Medical Monitor.

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

All protocol-required laboratory tests, as defined in [Appendix 2](#), must be conducted in accordance with the Laboratory Manual and the SoA ([Table 1-1](#)).

If laboratory values from laboratory tests not specified in the protocol and performed at the institution's local laboratory result in the need for a change in participant management or are considered clinically relevant by the Investigator (e.g., are considered to be an SAE or an AE or require study intervention modification), then the results must be recorded.

8.3.6 Pregnancy Testing

A serum pregnancy test will be performed for woman of childbearing potential (WOCBP) at Screening, and a urine pregnancy test at Baseline. 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. Urine pregnancy tests will be performed at all other visits as specified in the SoA ([Table 1-1](#)). Postmenopausal status will be confirmed by serum FSH levels at Screening.

8.4 Adverse Events, Serious Adverse Events, and Other Safety Reporting

The definitions of AEs and SAEs are provided in [Appendix 3](#).

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or a legally authorized representative [LAR]).

The Investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or the study, or that caused the participant to discontinue the study intervention (see [Section 7](#)).

AE questioning will include specific questions regarding symptoms of COVID-19: fever, cough, dry throat, difficulty breathing, and potential exposure in the past 2 weeks. Confirmed COVID-19 infection will disqualify the participant from the study.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in [Appendix 3](#).

8.4.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All AEs and SAEs will be collected from the signing of ICF to the end of the study at the time points specified in the SoA ([Table 1-1](#)). Participants who completed the study will return within 4 weeks to complete a follow up visit including AE assessments.

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours of awareness, as indicated in [Section 10.3.5](#) in [Appendix 3](#). The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obliged to actively seek information on AEs or SAEs after the conclusion of study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor.

8.4.2 Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence. Exceptions are permitted when following local / institutional guidelines for Covid-19.

8.4.3 Follow-up of Adverse Events and Serious Adverse Events

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and non-serious AESIs (as defined in Section 8.4.7), will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Section 10.3.4 in [Appendix 3](#).

8.4.4 Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification (within 24 hours, see Section 10.3.5 in [Appendix 3](#)) by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB), and Investigators.

An Investigator who receives an Investigator Safety Report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB, if appropriate according to local requirements.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

8.4.5 Pregnancy

Details of all pregnancies in female participants and, if indicated, partners of male participants will be collected until after the delivery. While on study and 4-weeks after study completion, male participants of pregnant female partners are expected to use condoms.

If a pregnancy is reported, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the female participants or partner

of male participant (after obtaining the necessary signed informed consent from the partner) pregnancy and should follow the procedures outlined in [Appendix 5](#).

While pregnancy itself is not considered an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered SAEs and will be reported as such.

The participant or pregnant partner will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant or pregnant partner and the neonate, and the information will be forwarded to the Sponsor.

Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section [8.4.4](#). While the Investigator is not obligated to actively seek this information in former study participants or pregnant partners, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study will be withdrawn from the study.

8.4.6 Disease-related Events and/or Disease-related Outcomes Not Qualifying as Adverse Events or Serious Adverse Events

Because these events are typically associated with the disease under study, they will not be reported according to the standard process for expedited reporting of SAEs even though the event may meet the definition of a SAE. These events will be recorded within 3 days.

NOTE: However, if either of the following conditions applies, then the event must be recorded and reported as an AE/SAE (instead of a DRE):

- The event is, at the discretion of the Investigator, of greater intensity, frequency, or duration than expected for the individual participant.
- The Investigator considers that there is a reasonable possibility that the event was related to study intervention.

8.4.7 Adverse Events of Special Interest

Refer to Section [10.3.3](#) for the definition of AESI.

AESIs are required to be reported by the Investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event) regardless of their causality to the study intervention. The most appropriate diagnosis or if a diagnosis cannot be established, the abnormal laboratory values should be recorded on the eCRF and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a SAE or an AESI.

8.5 Pharmacokinetics

Plasma samples will be collected at the time points specified in the SoA (Table 1-1) for measurement of plasma concentrations of TLL018. Instructions for the collection and handling of biologic samples will be found in the Laboratory Manual. The actual date and time (24-hour clock time) of each sample will be recorded on the eCRF.

Samples will be used to evaluate the PK of TLL018. Samples collected for analyses of TLL018 plasma concentration may also be used to evaluate safety or efficacy aspects that address concerns arising during or after the study.

Genetic analyses will not be performed on these plasma samples. The Sponsor may store samples for up to 15 years after the end of the study to achieve study objectives. Additionally, with participants' consent, samples may be used for further research by the Sponsor or others, such as universities or other companies, to contribute to the understanding of PP or other diseases, the development of related or new treatments, or research methods.

8.6 Pharmacodynamics

See Section 8.8.

8.7 Genetics

Not applicable.

8.8 Biomarkers

Serum samples will be collected to evaluate exploratory PD biomarkers. PD samples will be collected at Baseline and 30 minutes prior to first study intervention administration on the last day of Weeks 4 and 12, with a total of 3 PD blood collection sites per participant. PD biomarkers will include changes in [REDACTED] levels from Baseline and their association with TLL018 exposure/levels. Samples will be collected at the time points specified in the SoA (Table 1-1) and as detailed in the Laboratory Manual.

The Sponsor may store samples for up to 15 years after the end of the study to achieve study objectives. Additionally, with participants' consent, samples may be used for further research by the Sponsor or others such as universities or other companies, to contribute to the understanding of PP or other diseases, the development of related or new treatments, or research methods.

8.9 Immunogenicity Assessments

Not applicable.

8.10 Medical Resource Utilization and Health Economics

Medical resource utilization and health economics parameters are not evaluated in this study.

9 Statistical Considerations

The statistical analysis plan (SAP) will be finalized prior to database lock, and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints, including primary and key secondary endpoints.

9.1 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.

9.2 Analysis Sets

9.2.1 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.

9.2.2 Safety Population

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 population.

9.2.3 Per-protocol Population

The per-protocol population will include a subset of FAS. The detailed criteria for inclusion into the per-protocol population will be defined in the SAP.

9.3 Statistical Analyses

9.3.1 General Considerations

All data analyses will be presented by treatment groups.

Demographics and other Baseline assessments, including, efficacy, safety, and biomarker data will be summarized based on FAS population. Safety and biomarker analyses will be based on safety population. Efficacy analyses will be based on the FAS. Per-protocol population will be used for primary efficacy endpoint as a sensitivity analysis.

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

Continuous variables will be presented by descriptive statistics: n (number of participants), mean, standard deviation or standard error, median and range (minimum and maximum). Categorical variables will be summarized by counts and percentages of participants.

9.3.2 Primary Endpoint Analysis

9.3.2.1 Primary Endpoint

The primary endpoint is 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.

9.3.2.2 Analysis of Primary Endpoint

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.

Further details of the statistical analysis will be provided in the SAP.

9.3.3 Secondary Endpoints Analysis

9.3.3.1 Secondary Endpoints

The 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 PET 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.

9.3.3.2 Analysis of Secondary Endpoints

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. 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.

9.3.4 Exploratory/Other Endpoints Analysis

PK and PD data will be analyzed with appropriate, standard, non-linear analytic software.

The population PK parameters will be summarized for each active dosing group. Trough concentration at steady state ($C_{\text{trough,ss}}$) will be presented graphically for each dosing group. All PK parameters will be analyzed by appropriate PK methodology.

The exploratory PD and biomarker endpoint include changes in [REDACTED] from Baseline and their association with TLL018 exposure/levels. The PD/biomarker endpoints will be summarized by study intervention groups at each visit and presented in by-participant listings.

PASIs as proportion of participants achieving PASI-100 will be displayed by visit and dose group.

9.3.5 Safety Analyses

Safety analyses will be performed on the safety population for each study intervention group and across TLL018 dose groups.

9.3.5.1 Analysis of Adverse Events

An AE will be considered a treatment-emergent adverse event (TEAE) if the AE began or worsened (increased in severity) on or after the date of the first dose of the study intervention. However, an AE that occurs more than 30 days after the last dose of study intervention or EOT will not be counted as a TEAE.

An AE will be considered a treatment-emergent SAE if it is a TEAE that additionally meets any SAE criterion.

An overall summary of TEAEs will be provided. The number and percentage of participants who experience any of the following will be provided:

- TEAEs
- TEAEs of grade ≥ 3
- Treatment-related TEAEs
- Serious TEAEs
- Serious treatment-related TEAEs
- TEAEs with a fatal outcome
- TEAEs leading to study intervention discontinuation
- TEAEs of study interest

The TEAEs will be coded according to the Medical Dictionary for Regulatory Activities dictionary. Summary tables will be presented by system organ class and preferred term.

The definitions of AE, SAE, and AESI are provided in [Appendix 3](#).

9.3.5.2 Other Safety Analyses

Other safety parameters will include clinical laboratory test values, vital sign assessments, and ECG results.

All safety data will be summarized descriptively. Detailed specifications of the statistical reporting will be provided in the SAP.

9.4 Interim Analyses

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.

9.5 Sample Size Determination

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.

10 Supporting Documentation and Operational Considerations

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with:

- 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 Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines.
- Applicable laws and regulations.

The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB by the Investigator and reviewed and approved by the IRB before the study is initiated.

Any amendments to the protocol will require IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB.
- Notifying the IRB of SAE or other significant safety findings as required by IRB procedures.
- Overall conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH GCP guidelines, the IRB, and all other applicable local regulations.
- Periodic presentations of safety data to the DMC and implementation of DMC recommendations.

10.1.2 Financial Disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations 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.

10.1.3 Informed Consent Process

The Investigator or their representative will explain the nature of the study, including the risks and benefits, to the participant or the participant's LAR and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants or the participant's LAR will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy, and data protection requirements, where applicable, and the IRB or study center.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Participants 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 participant or the participant's LAR.

A participant who is rescreened is not required to sign another ICF if there is no change to the ICF.

If a protocol amendment is required, the ICF may need to be revised to reflect the changes to the protocol. If the ICF is revised, it must be reviewed and approved by the appropriate IRB and signed by all participants subsequently enrolled in the study as well as those currently enrolled in the study.

10.1.4 Data Protection

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.

The participants must be informed that their 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 participant who will be required to give consent for their data to be used as described in the informed consent.

The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB members, and by inspectors from regulatory authorities.

10.1.5 Committee Structure - 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.

Clinical Adjudication Committee:

There will be 2 Clinical Adjudication Committee (CAC) external panels of independent physicians experienced in assessing cardiovascular, malignancies, and thromboembolic endpoints. One committee will adjudicate cardiovascular/thromboembolic events; the other will adjudicate malignancies. These panels will be blinded to treatment assignments. The members of both CAC's will not be an Investigator in any trial for TLL018-205. A sub-group of the DMC consisting of clinical experts will periodically review the safety data and independently adjudicate AESIs, such as venous and arterial thromboembolic events, malignancies, and MACE, using standard criteria and processes. A subset of AESI, listed below (Section 10.3.3), will be adjudicated by the CAC committees to determine the underlying cause and relationship to TLL018:

- All deaths
- MACE
- Thromboembolic events
- Malignancies
- Serious infections (Grade 3 or higher)

The criteria to define clinical cardiovascular, mortality, thromboembolic events, and malignancies are detailed within the respective CAC charters (MACE, malignancy). All events meeting adjudication criteria as outlined within the CAC charter and this protocol will be collected from the first day of double-blinded study intervention through the end of study (including 14 day post last visit reporting period) for all randomized participants who have received at least 1 dose of study intervention.

Clinical adjudication events occurring between the Screening period (the time of informed consent), the 1-week Baseline period and double-blinded treatment randomization will not be adjudicated as these events will be excluded as per Section 8.3.1.

The identification of adjudication events will be made by the study site or by designee. The site will communicate the event to the designee within 24 hours of awareness of the adjudication event using the appropriate case report form (CRF) module. The site will in turn provide the specific documents needed to support the adjudication review conducted by the CACs. Obtaining documentation will be the responsibility of the study site. Documentation will include, but is not limited to, any of the following: hospital discharge summaries, operative reports, clinic notes, ECGs, diagnostic cardiac enzymes, imaging studies, tumor staging, results of other diagnostic tests, autopsy reports, and death certificate information. The respective adjudication charters will contain additional information on source documents to be collected for event adjudication.

Interim Safety Assessment:

Interim safety assessment will be performed when there are ≥ 5 SAEs or when there are ≥ 3 AESIs. The study enrollment will be stopped however treatment may continue for randomized patients, and the DMC should review the data in their entirety and recommend discontinuing the study or reconfiguring the dosing groups if

- Either ≥ 5 SAEs are deemed related or possibly related to study intervention and $\geq 6\%$ of enrolled participants have related or possibly related SAEs; or
- The ≥ 3 AESIs are adjudicated to be related or possibly related to study intervention.

The structure and operation of the DMC, including the role of its independent member, will be detailed in the DMC Charter.

10.1.6 Dissemination of Clinical Study Data

A summary of the results of the clinical study together with a summary that is understandable to a layperson will be provided after the global end (or ET) of the study in all countries concerned to ensure full availability of all clinical data under this protocol, within 12 months.

10.1.7 Data Quality Assurance

All participant data relating to the study will be recorded on printed or eCRFs unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Guidance on completion of eCRFs will be provided in the eCRF Completion Instructions.

The Investigator must permit study-related monitoring, audits, IRB review, and Regulatory Agency inspections and provide direct access to source data documents.

Monitoring details describing strategies, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality, such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.

The Sponsor or designee is responsible for the data management of this study, including quality checking of the data.

The Sponsor assumes accountability for actions delegated to other individuals (e.g., CROs).

Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the Investigator for 2 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

All data generated by the site personnel will be captured electronically at each study site using eCRFs. Data from external sources (such as laboratory data) will be imported into the database. Once the eCRF clinical data have been submitted to the central server at the independent data center, corrections to the data fields will be captured in an audit trail. The reason for change, the name of the person who performed the change, together with the time and date will be logged to provide an audit trail.

If additional corrections are needed, the responsible monitor or data manager will raise a query in the electronic data capture (EDC) application. The appropriate staff at the study site will answer queries sent to the Investigator. The name of the staff member responding to the query, and time and date stamp will be captured to provide an audit trail. Once all source data verification is complete and all queries are closed, the monitor will freeze the eCRF page.

The specific procedures to be used for data entry and query resolution using the EDC system/eCRF will be provided to study sites in a training manual. In addition, site personnel will receive training on the EDC system/eCRF.

10.1.8 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the study site.

Data reported in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.9 Study and Site Start and Closure

First Act of Recruitment:

The study start date is the date the clinical study will be open for recruitment of participants.

The first act of recruitment is considered when the first site is activated and allowed to screen participants, which will be the study start date.

Study/Site Termination:

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

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

The Investigator may initiate study site 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 site by the Sponsor or Investigator may include, but are not limited to:

For study termination:

- Discontinuation of further study intervention development.

For site termination:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB or local health authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the Investigator.
- Total number of participants included earlier than expected.

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.10 Publication Policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.1.11 Protocol Approval and Amendment

Before the start of the study, the study protocol and/or other relevant documents will be approved by the IRB/Competent Authorities, in accordance with local legal requirements. The Sponsor must ensure that all ethical and legal requirements have been met before the first participant is enrolled in the study.

This protocol is to be followed exactly. To alter the protocol, amendments must be written, receive approval from the appropriate personnel, and receive IRB/Competent Authority approval prior to implementation (if appropriate). In the US: following approval, the protocol amendment(s) will be submitted to the Investigational New Drug recorded for the study.

Administrative changes (not affecting the participant benefit/risk ratio) may be made without the need for a formal amendment. All amendments will be distributed to all protocol recipients, with appropriate instructions.

10.1.11.1 Liability and Insurance

The Sponsor will take out reasonable third-party liability insurance cover in accordance with all legal requirements. The civil liability of the Investigator, the persons instructed by him or her and the hospital, practice, or institute where they are employed and the liability of the Sponsor with respect to financial loss due to personal injury and other damage that may arise as a result of carrying out of this study are governed by the applicable law.

The Sponsor will arrange for participants participating in this study to be insured against financial loss due to personal injury caused by the pharmaceutical products being tested or by medical steps taken in the course of the study.

10.1.11.2 Access to Source Data

During the study, a monitor will make site visits to review protocol compliance, compare EDC entries and individual participant's medical records, assess drug accountability, and ensure that the study is being conducted according to pertinent regulatory requirements. EDC entries will be verified with source documentation. The review of medical records will be performed in a manner to ensure that participant confidentiality is maintained.

Checking of the EDC entries for completeness and clarity, and cross-checking with source documents, will be required to monitor the progress of the study. Moreover, regulatory authorities of certain countries, IRBs, IECs, and/or the Sponsor's Clinical Quality Assurance Group may wish to carry out such source data checks and/or on-site audit inspections. Direct

access to source data will be required for these inspections and audits; they will be carried out giving due consideration to data protection and medical confidentiality. The Investigator assures the Sponsor, and Contract Research Organization (CRO) if involved in monitoring/data management, of the necessary support at all times.

10.2 Appendix 2: Clinical Laboratory Tests

The tests detailed in [Table 10-1](#) will be performed by the central laboratory unless otherwise noted.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in [Section 5.1](#) and [Section 5.2](#) 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 10-1 Protocol-required Safety Laboratory Tests

Laboratory Tests	Parameters
Hematology	Hemoglobin Reticulocytes RBC count WBC count and classifications (including neutrophils, eosinophils, basophils, absolute lymphocyte count) Platelet count D-dimer
Clinical chemistry	Creatinine Urea or urea nitrogen Total protein Albumin Total and direct bilirubin Alkaline phosphatase AST/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	PT/INR, 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 urine sediment analysis will be performed if indicated by dipstick analysis (hematuria, leukocyturia) (Microscopic urinary sediment analysis: cells, casts, crystals).
Pregnancy testing	Serum hCG pregnancy test at Screening (centrally). Urine (<u>completed locally</u>) at Baseline and all timepoints except Screening.
Other Screening tests	FSH (<u>as needed in women of non-childbearing potential only</u>) 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	(<u>Optional, if requested by PI</u>) SARS-CoV-2 RT-PCR ³ SARS-CoV-2 antibody assay (IgG, IgA, or IgM) ³
NOTES: 1. If alkaline phosphatase is elevated, consider fractionating. 2. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB. 3. To be assessed by local convention but preference with a PCR test.	

ALT=alanine aminotransferase, AST=aspartate aminotransferase, FSH=follicle-stimulating hormone, HBsAg=hepatitis B surface antigen, HBcAb=hepatitis B core antibody, hCG=human chorionic gonadotropin, HCV=hepatitis C virus, HDL=high-density lipoprotein, HIV=human immunodeficiency virus, Ig=immunoglobulin, INR=international normalized ration,, PD=pharmacodynamic, PK=pharmacokinetic, PT=prothrombin time, PTT=activated partial thromboplastin time, RBC=red blood cell, SARS-CoV-2=severe acute respiratory syndrome coronavirus 2, WBC=white blood cell

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

10.3.1 Definition of Adverse Event

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

Events Meeting the AE Definition
Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiologic scans, vital signs measurements), including those that worsen from Baseline, considered clinically significant in the medical and scientific judgment of the Investigator (e.g., not related to progression of underlying disease). Exacerbation of a chronic or intermittent pre-existing condition, including either an increase in frequency and/or intensity of the condition. New condition detected or diagnosed after study intervention 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 intervention 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 pharmacologic 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 that are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant'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 participant's condition.

Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.

Situations where 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.

Definition of Unsolicited and Solicited AE

An unsolicited adverse event is an adverse event that was not solicited using a participant diary and that is communicated by a participant/participant's LAR who has signed the informed consent. Unsolicited AEs include serious and non-serious AEs.

Potential unsolicited AEs may be medically attended (i.e., symptoms or illnesses requiring a hospitalization, or emergency room visit, or visit to/by a healthcare provider). The participant/participant's LAR will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of the participant/participant's LAR concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records.

Unsolicited AEs that are not medically attended nor perceived as a concern by the participant/participant's LAR will be collected during an interview with the participant/participant's LAR and by review of available medical records at the next visit.

10.3.2 Definition of Serious Adverse Event

An SAE is an AE that:
a. Results in death
b. Is life-threatening The term life-threatening in the definition of serious refers to an event that places the participant at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or intervention that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious. Hospitalization for elective intervention of a pre-existing condition that did not worsen from Baseline is not considered an AE.
d. Results in persistent or significant disability/incapacity The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) that may interfere with or prevent everyday life functions, but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations Medical or scientific judgment should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations, such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

10.3.3 Definition of Adverse Events of Special Interest

The events listed below are defined as AESI. If any of the events are also reported as SAEs, there is no need to complete a separate AESI form.

Events Meeting the AESI Definition
• Thromboembolic event – Grade 2 or higher • Infection, including fever – Grade 3 or higher • Hypertension – Grade 3 or higher • MACE – Grade 2 or higher. MACE are defined as incident myocardial infarction, stroke, heart failure, coronary revascularization, atrial fibrillation, or cardiovascular death. Death from cardiac causes includes sudden cardiac death, death due to congestive heart failure, fatal myocardial infarction, death due to coronary disease during or within 28 days after the study. All other deaths attributable to coronary artery disease will be included • Malignancy

10.3.4 Recording and Follow-up of AE and SAE

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, and diagnostics reports) related to the event. The Investigator will then record all relevant AE/SAE information. It is not acceptable for the Investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the Sponsor-required form. There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor. The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The Investigator will assess intensity for each AE/SAE reported during the study and assign it to categories based on the Common Terminology Criteria for Adverse Events (CTCAE) v5.0. Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.

Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**. Please note, Severe is a category used for rating the intensity of an event; both AEs and SAEs can be assessed as severe. An event is defined as 'serious' when it meets at least one of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.

Grade 4 Life-threatening consequences; urgent intervention indicated.

Grade 5 Death related to AE.

A Semi-colon indicates 'or' within the description of the grade.

Activities of Daily Living (ADL)

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Reference:

Common Terminology Criteria for Adverse Events (CTCAE) Version 5. Published: November 2017. US Department of Health and Human Services, National Institutes of Health, National Cancer Institute

Assessment of Causality

The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The Investigator will use clinical judgment to determine the relationship.

A reasonable possibility of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.

The Investigator will also consult the IB and/or Product Information, for marketed products, in their 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 where an SAE has occurred, and the Investigator has minimal information to include in the initial report in the electronic data collection tool. However, **it is very important that the Investigator always assess causality for every event and discuss with the Sponsor as soon as possible, The initial transmission of the SAE data to the electronic data collection tool then follows.**

The Investigator may change their opinion of causality in light of follow-up information and discussion with the Sponsor and send an SAE follow-up report with the updated causality assessment.

The following “binary” decision choice will be used by the Investigator to describe the initial causality assessment:

- Related: Reasonable possibility of a relatedness
- Not related: No reasonable possibility of relatedness.

The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathologic examinations, or consultation with other health care professionals.

If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor with a copy of any post-mortem findings, including histopathology.

New or updated information will be recorded in the originally completed form.

The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.5 Reporting of SAE

SAE Reporting via Electronic Data Collection Tool

The Investigator must report any SAEs to the Sponsor's designated safety services within 24 hours of becoming aware of the event.

The primary mechanism for reporting an SAE will be the electronic data collection tool.

If the electronic system is unavailable, then the site will use the paper SAE data collection tool to report the event within 24 hours.

The site will enter the SAE data into the electronic system as soon as it becomes available.

When calling to report an SAE, state that you are reporting an SAE and give the Investigator's name, your name, the telephone number where you can be reached, and the protocol number and title.

The Investigator and the Sponsor (or Sponsor's designated agent) will review each SAE report and the Sponsor/CRO will evaluate the seriousness and the causal relationship of the event to study intervention. In addition, the Sponsor (or Sponsor's designated agent) will evaluate the expectedness according to the Reference Safety Information (IB or Summary of Product Characteristics). Based on the Investigator and Sponsor's assessment of the event, a decision will be made concerning the need for further action.

After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.

If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form or by telephone.

Suspected Unexpected Serious Adverse Reactions (SUSARs)

Any AE that is serious, associated with the use of the study intervention, and unexpected (SUSAR) has additional reporting requirements, as described below.

If the SUSAR is fatal or life-threatening, associated with study intervention, and unexpected, regulatory authorities and IRBs will be notified within 7 calendar days after the Sponsor learns

of the event. Additional follow-up (cause of death, autopsy report, and hospital report) information should be reported within an additional 8 days (15 days total).

If the SUSAR is not fatal or life-threatening, but is otherwise serious, associated with study intervention, and unexpected, regulatory authorities and IRBs will be notified within 15 calendar days after the Sponsor learns of the event.

The Sponsor will notify the Investigators in a timely fashion of relevant information about SUSARs that could adversely affect the safety of participants. Follow-up information may be submitted if necessary.

The Sponsor will also provide annual safety updates to the regulatory authorities and IRBs responsible for the study. These updates will include information on SUSARs and other relevant safety findings.

10.4 Appendix 4: Contraceptive and Barrier Guidance

10.4.1 Definitions

Woman of Childbearing Potential (WOCBP)

Women in the following categories are considered WOCBP (fertile):

1. Following menarche.
 2. From the time of menarche until becoming postmenopausal unless permanently sterile:
 - a. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
 - A high 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, confirmation with more than 1 FSH measurement for defining postmenopausal state] is required.
 - 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.
 - b. Permanent sterilization methods (for the purpose of this study) include:
 - Documented hysterectomy
 - Documented bilateral salpingectomy
 - Documented bilateral oophorectomy
 - For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), Investigator discretion should be applied to determining study entry.
- Note:** Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
- c. If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of TLL018, additional evaluation should be considered.

10.4.2 Contraception Guidance

Male Participants:

Male participants who are sexually active with a WOCBP, even if the male participants have undergone a successful vasectomy, must agree to use effective methods of contraception from the start of TLL018 treatment until at least 13 weeks following the last dose of TLL018. His female partner(s) must use at least 1 of the contraceptive measures as noted below including a barrier method form of birth control.

In addition, male participants must refrain from donating sperm for the duration of the study and for 13-weeks after the last dose of TLL018.

Female Participants:

Female participants must agree to use highly effective contraception as specified below and have monthly pregnancy testing during exposure to TLL018 and for 13-weeks following the last dose of TLL018.

CONTRACEPTIVES¹ ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods² That Have Low User Dependency Failure rate of <1% per year when used consistently and correctly.
Implantable progestogen-only hormone contraception associated with inhibition of ovulation³
Intrauterine device
Intrauterine hormone-releasing system
Bilateral tubal occlusion
Azoospermic partner (vasectomized or due to a to medical cause) Azoospermia is a highly effective contraceptive method provided that the partner is the sole 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. Spermatogenesis cycle is approximately 90 days. Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

Highly Effective Methods² That Are User Dependent 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 ○ Injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation ○ Oral ○ Injectable
• 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 intervention. 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 participant.

1. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.
2. Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.
3. Male condoms must be used in addition to hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group guidelines, acceptable contraceptive methods are limited to those that inhibit ovulation as the primary mode of action.

Note: Periodic abstinence (calendar, symptothermal, and post ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure from friction).

10.5 Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments

Liver chemistry stopping criteria are designed to assure participant safety and to evaluate liver event etiology.

Liver Chemistry Stopping Criteria and Follow-Up Assessments

Liver Chemistry Stopping Criteria	
ALT or AST-absolute	ALT or AST $>5 \times$ ULN
ALT or AST Increase	ALT or AST $>3 \times$ ULN persists for 4 weeks
Bilirubin ^{1,2}	ALT or AST $>3 \times$ ULN and total bilirubin $2 \times$ ULN ($>35\%$ direct bilirubin)
INR ²	ALT or AST $>3 \times$ ULN and INR >1.5
Cannot Monitor	ALT or AST $>3 \times$ ULN and cannot be monitored weekly for 4 weeks
Symptomatic ³	ALT or AST $>3 \times$ ULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity
Suggested Actions, Monitoring, and Follow-up Assessments	
Actions	Follow-up Assessments
• Immediately discontinue study intervention. • Report the event to the Sponsor within 24 hours. • Complete the liver event/expedited reporting form and complete an SAE CRF if the event also met the criteria for an SAE². • Perform follow-up assessments as described in the Follow-Up Assessment column. • Monitor the participant until liver chemistry test abnormalities resolve, stabilize, or return to Baseline.	• Viral hepatitis serology⁴ • Obtain serum CPK, LDH, GGT, GLDH, and serum albumin • Fractionate bilirubin, if total bilirubin $>2 \times$ ULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the liver event/expedited reporting form • Record use of concomitant medications (including acetaminophen, herbal remedies, and other over-the-counter medications) on the concomitant medications CRF • Record alcohol use on the liver event alcohol intake form

MONITORING: <u>If ALT or AST >3 x ULN AND total bilirubin >2 x ULN or INR >1.5:</u> - Repeat liver chemistry tests (include ALT, AST, alkaline phosphatase, total bilirubin, and INR) and perform liver event follow-up assessments within 24 hours - Monitor participant twice weekly until liver chemistry test abnormalities resolve, stabilize, or return to Baseline - A hepatology consultation is recommended <u>If ALT or AST >3 x ULN AND total bilirubin <2 x ULN and INR >1.5:</u> - Repeat liver chemistry tests (include ALT, AST, alkaline phosphatase, total bilirubin, and INR) and perform liver chemistry follow-up assessments within 24 to 72 hours - Monitor participants weekly until liver chemistry abnormalities resolve, stabilize, or return to Baseline Do not restart/re-challenge participant with study intervention unless allowed per protocol and Sponsor approval is granted	If ALT or AST >3 x ULN AND total bilirubin >2 x ULN or INR >1.5 obtain the following in addition to the assessments listed above: - Antinuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total IgG, or gamma globulins - Serum acetaminophen adduct assay, when available, to assess potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week - Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease, complete liver imaging form - Liver biopsy may be considered and discussed with local specialist if available, for instance: - In participants when serology raises the possibility of autoimmune hepatitis - In participants when suspected DILI progresses or fails to resolve on withdrawal of study intervention - In participants with acute or chronic atypical presentation - If liver biopsy conducted complete liver biopsy form
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- Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation testing is unavailable, **record the absence/presence of detectable urinary bilirubin on dipstick**, which is indicative of direct bilirubin elevations suggesting liver injury.
- All events of ALT or AST >3 x ULN **and** total bilirubin >2 x ULN (>35% direct bilirubin) or ALT or AST >3 x ULN **and** INR >1.5 may indicate severe liver injury (**possible ‘Hy’s Law’**) **and must be reported to Sponsor in an expedited manner and as an SAE if SAE criteria met (excluding studies of hepatic impairment or cirrhosis)**. The INR stated threshold value will not apply to participants receiving anticoagulants.
- New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or hypersensitivity (such as fever, rash, or eosinophilia).
- Includes: hepatitis A IgM antibody; hepatitis B surface antigen and hepatitis B core antibody; hepatitis C RNA; cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, heterophile antibody or monospot testing); and hepatitis E IgM antibody.

ALT=alanine aminotransferase, AST=aspartate aminotransferase, CRF=Case Report Form, CPK=creatine phosphokinase, DILI=drug-induced liver injury, GGT=gamma glutamyltransferase, GLDH=glutamate dehydrogenase, IgG=immunoglobulin G, IgM=immunoglobulin M, INR=international normalized ratio, LDH=lactate dehydrogenase, RNA=ribonucleic acid, SAE=serious adverse event, ULN=upper limit of normal

Liver Chemistry Increased Monitoring Criteria with Continued Study Intervention

Liver Chemistry Increased Monitoring Criteria and Actions with Continued Study Intervention	
Criterion	Actions
ALT or AST $>3 \times \text{ULN}$ and $<5 \times \text{ULN}$ and total bilirubin $<2 \times \text{ULN}$, or INR <1.5 , without symptoms believed to be related to liver injury or hypersensitivity, and who can be monitored weekly for 4 weeks	• Notify the Sponsor within 24 hours of learning of the abnormality to discuss participant safety. • Participant can continue study intervention. • Participant must return weekly for repeat liver chemistry tests (ALT, AST, alkaline phosphatase, total bilirubin) until the abnormalities resolve, stabilize, or return to Baseline. • If at any time, the participant meets liver chemistry stopping criteria, proceed as described in Section 7.1.1.1. If, after 4 weeks of monitoring, ALT or AST $<3 \times \text{ULN}$ and total bilirubin $<2 \times \text{ULN}$, monitor participants twice monthly until liver chemistry tests resolve, stabilize, or return to Baseline.

ALT=alanine aminotransferase, AST=aspartate aminotransferase; INR=international normalized ratio, ULN=upper limit of normal

10.6 Appendix 6: Dermatology Life Quality Index (DLQI)

DERMATOLOGY LIFE QUALITY INDEX

Hospital No:

Date:

Name:

Score:

Address:

Diagnosis:

DLQI

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.

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PSORIASIS AREA AND SEVERITY INDEX (PASI) WORKSHEET

HOSPITAL NO.:

PATIENT NAME:

DATE OF VISIT:

The Psoriasis Area and Severity Index (PASI) is a quantitative rating score for measuring the severity of psoriatic lesions based on area coverage and plaque appearance.

Plaque characteristic	Lesion score	Head	Upper Limbs	Trunk	Lower Limbs
Erythema	0 = None				
	1 = Slight				
Induration/Thickness	2 = Moderate				
	3 = Severe				
Scaling	4 = Very severe				
Add together each of the 3 scores for each body region to give 4 separate sums (A).					
Lesion Score Sum (A)					

Percentage area affected	Area score	Head	Upper Limbs	Trunk	Lower Limbs
Area Score (B) <i>Degree of involvement as a percentage for each body region affected (score each region with score between 0-6)</i>	0 = 0%				
	1 = 1% - 9%				
	2 = 10% - 29%				
	3 = 30% - 49%				
	4 = 50% - 69%				
	5 = 70% - 89%				
	6 = 90% - 100%				
Multiply Lesion Score Sum (A) by Area Score (B), for each body region, to give 4 individual subtotals (C).					
Subtotals (C)					
Multiply each of the Subtotals (C) by amount of body surface area represented by that region, i.e. x 0.1 for head, x 0.2 for upper body, x 0.3 for trunk, and x 0.4 for lower limbs.					
Body Surface Area		x 0.1	x 0.2	x 0.3	x 0.4
Totals (D)					
Add together each of the scores for each body region to give the final PASI Score.					

PASI Score =

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Investigator Agreement Page

Declaration of the Investigator

Title: 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

All documentation for this study that is supplied to me and that has not been previously published will be kept in the strictest confidence. This documentation includes this study protocol, Investigator's Brochure (IB), electronic data capture (EDC) system/electronic CRF (eCRF), and other scientific data.

The study will not be commenced without the prior written approval of a properly constituted Institutional Review Board (IRB). No changes will be made to the study protocol without the prior written approval of the Sponsor and the IRB, except where necessary to eliminate an immediate hazard to the participants.

I have read and understood and agree to abide by all the conditions and instructions contained in this protocol.

Responsible Investigator of the Local Study Center

Signature

Date

Name (block letters)

Title (block letters)

Institution (block letters)

Phone number