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Clinical Study Statistical Analysis Plan (SAP)

PROTOCOL TITLE: A Mult**i**center, Rando**m**ized, Double-blind, Placebo-controlled, **P**arallel-group Study to Evaluate the Efficacy and Safety of JTE-451 **A**dministered for 16 Weeks in Subje**ct**s with Moderate to Severe Plaque **Ps**oriasis (**IMPACT-PS**)

PROTOCOL NUMBER: AE451-G-18-004

SAP DATE: 30 March 2020

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CONFIDENTIAL

Akros Pharma Inc.

Protocol AE451-G-18-004

A Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy and Safety of JTE-451 Administered for 16 Weeks in Subjects with Moderate to Severe Plaque Psoriasis (IMPACT-PS)

Statistical Analysis Plan

Final V1.0
30 March 2020

Signature Page

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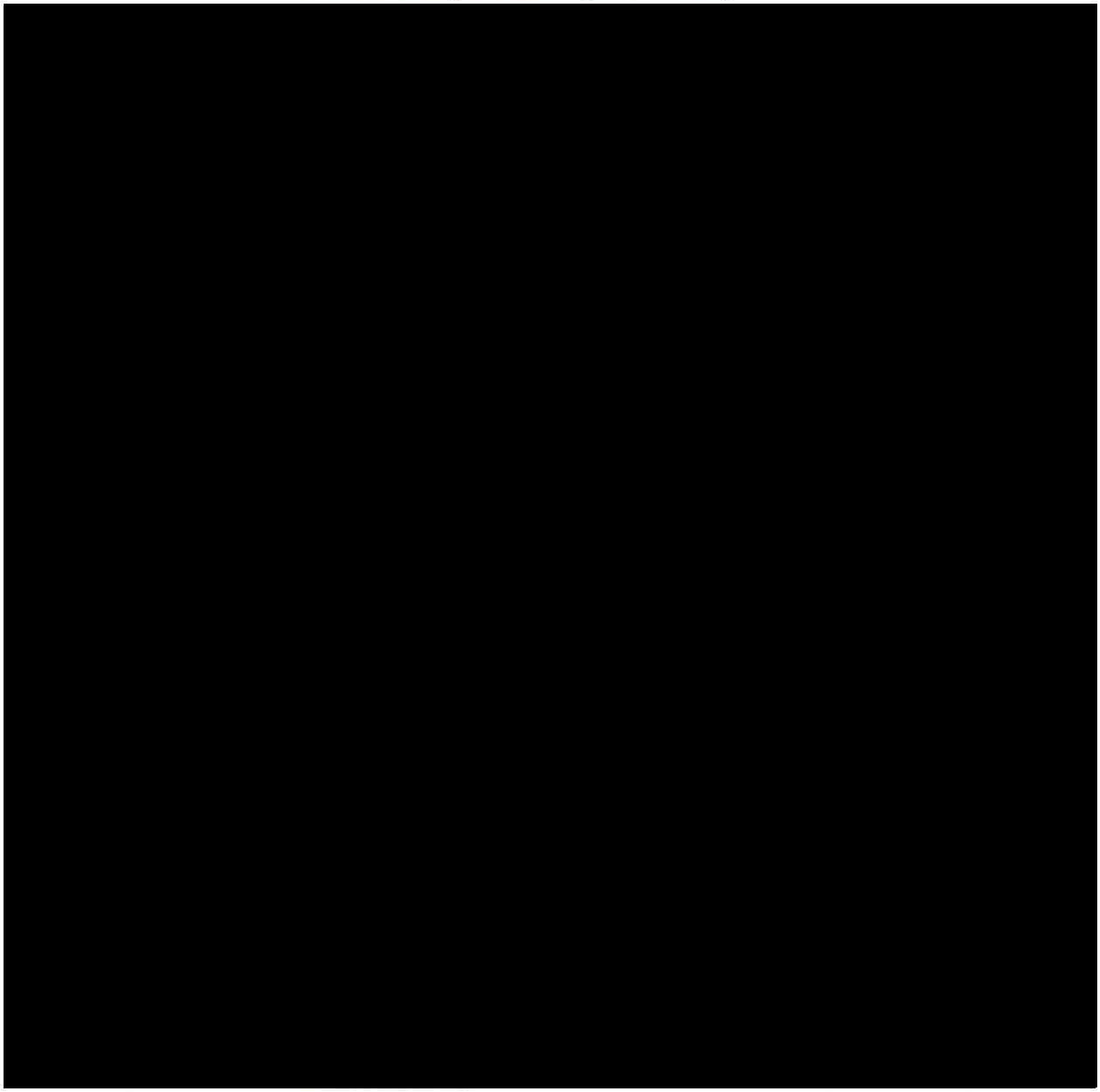

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
ADR	Adverse drug reaction
AE	Adverse event
ATC	Anatomical therapeutic chemical
BLQ	Below the lower limit of quantification
BID	Twice a day
BMI	Body mass index
BSA	Body surface area
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
CRF	Case report form
CTCAE	Common terminology criteria for adverse events
CV%	Coefficient of variation
DB	Double-blind
eCRF	Electronic case report form
ECG	Electrocardiogram
EOT	End of treatment
FSH	Follicle-stimulating hormone
GEE	Generalized estimating equation
ITT	Intent to treat
IWRS	Interactive web response system
LOCF	Last observation carried forward
MCMC	Markov Chain Monte Carlo
MedDRA	Medical dictionary for regulatory activities
MMRM	Mixed effect model with repeated measures
NA	Not applicable
NCS	Not clinically significant
NRS	Numerical rating scale
OR	Odds Ratio
PASI	Psoriasis Area and Severity Index
PBSA	Psoriasis body surface area
PCS	Potentially clinically significant
PD	Pharmacodynamic
PK	Pharmacokinetics
PP	Per protocol
PPK	Population PK
PR	Interval from beginning of the P wave to the beginning of the QRS complex in the frontal plane
[redacted]	
PT	Preferred term

Abbreviation	Definition
QOL	Quality of life
QRS	Duration of QRS complex in the frontal plane
QT	Interval from beginning of the QRS complex to end of the T wave in the frontal plane
QT_cF	Fridericia-corrected QT interval
RR	Interval from beginning of the QRS complex in the frontal plane to the next QRS complex
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SOC	System organ class
SOP	Standard operating procedure
sPGA	Static Physician's Global Assessment
TEAE	Treatment-emergent adverse event
WHO	World health organization

1. INTRODUCTION

This Statistical Analysis Plan (SAP) describes the statistical methods that will be used during the analysis and reporting of data collected for a Phase 2 double-blind (DB), placebo-controlled, parallel-group study evaluating efficacy, safety and pharmacokinetic (PK) of JTE-451 in subjects with moderate to severe plaque psoriasis. This SAP should be read in conjunction with the study protocol. This version of the SAP has been developed using protocol version 3.0 dated 24 June 2019.

2. OBJECTIVES

Primary Objective

To evaluate the efficacy of JTE-451 administered for 16 weeks in subjects with moderate to severe plaque psoriasis compared with placebo.

Secondary Objectives

- To evaluate the safety and tolerability of JTE-451 administered for 16 weeks in subjects with moderate to severe plaque psoriasis.
- To evaluate the pharmacokinetics (PK) of JTE-451 administered for 16 weeks in subjects with moderate to severe plaque psoriasis.

[redacted]

3. STUDY DESIGN

This is a 16-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study in subjects with moderate to severe plaque psoriasis.

Eligible subjects will be randomized at Visit 2 to receive JTE-451 200 mg twice a day (BID) (400 mg/day), 400 mg BID (800 mg/day) or placebo BID for 16 weeks. Approximately 150 subjects are planned to be randomized into 3 treatment groups. Randomized subjects will visit the site at Weeks 2, 4, 8, 12 and 16 during the treatment period. A follow-up visit will take place approximately 4 weeks after the last dose of study drug. Randomization will be stratified based on prior exposure of subjects to biologic therapy (i.e., biologic-naïve vs. biologic-experienced subjects) and body weight (i.e., <90 kg vs. ≥90 kg at Visit 2).

The study duration will be of approximately 24 weeks per subject:

- Up to 28-day Screening Period
- 16-week double-blind Treatment Period
- 4-week Follow-up Period

3.1 Study Procedures

The study schema and schedule of study procedures are described in Figure 1 and Table 1, respectively.

Figure 1. Study Schema

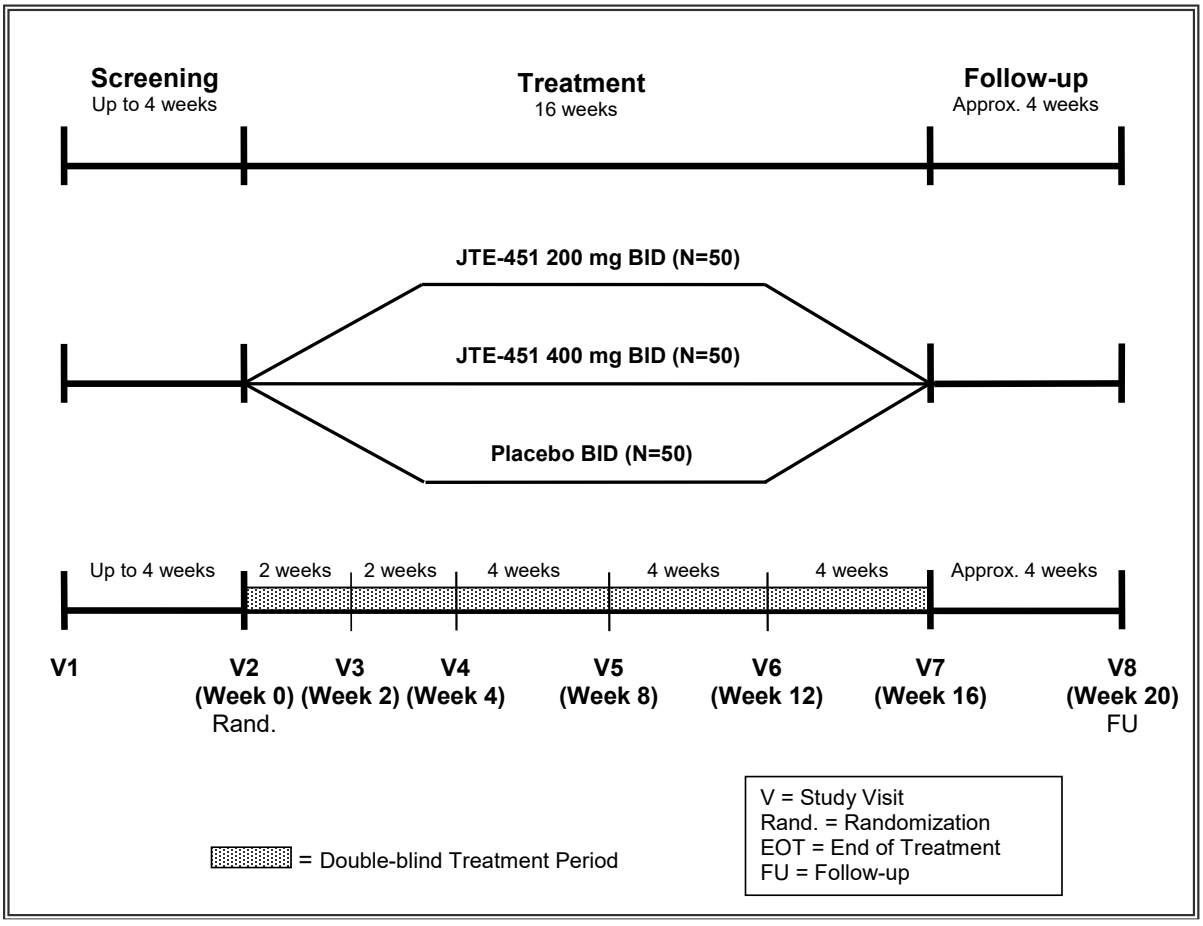


Table 1. Schedule of Study Procedures

	Screening Period	Treatment Period						Follow-up Period
Duration/ Study Week (Day)[a]	Up to 4 weeks	Week 0 (Day 1)	Week 2 (Day 14±2)	Week 4 (Day 28±2)	Week 8 (Day 56±4)	Week 12 (Day 84±4)	Week 16 (Day 112±4)	Week 20 (Day 140±4)
Visit	1	2	3	4	5	6	7	8
Informed Consent[b]	X							
Inclusion/ Exclusion Criteria	X	X						
Medical History	X	X						
Demographic Information	X							
Review Prior/ Concomitant Medications	X	X	X	X	X	X	X	X
Physical Exam	X	X	X	X	X	X	X	
Vital Signs including Weight	X	X	X	X	X	X	X	X
Height and Calculate BMI	X							
12-Lead ECG	X	X		X			X	
Chest Radiography[c]	X							
QuantiFERON-TB Gold-In-Tube	X							
Drugs of Abuse Screen	X							
Viral Serology	X							
FSH[d]	X							
Pregnancy Test[d]	X	X	X	X	X	X	X	X
HbA1c	X							
Serum Biochemistry	X	X	X	X	X	X	X	X
Hematology	X	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X	X
Coagulation	X	X	X	X	X	X	X	X
Psoriasis Body Surface Area	X	X	X	X	X	X	X	X
PASI	X	X	X	X	X	X	X	X
sPGA	X	X	X	X	X	X	X	X
Skindex 16	X	X	X	X	X	X	X	X
Itch NRS[e]	←							→
Digital Photography[f]		X					X	
[redacted]								
Randomization using IWRS		X						
Access IWRS and Dispense Study Drug[i]		X	X	X	X	X		
Collect Study Drug and Check Compliance[j]			X	X	X	X	X	
Study Drug Administration[k]		X	X	X	X	X		
JTE-451 PK Blood Samples[l]		X		X	X	X	X	
Document Adverse Events[m]	X	X	X	X	X	X	X	X

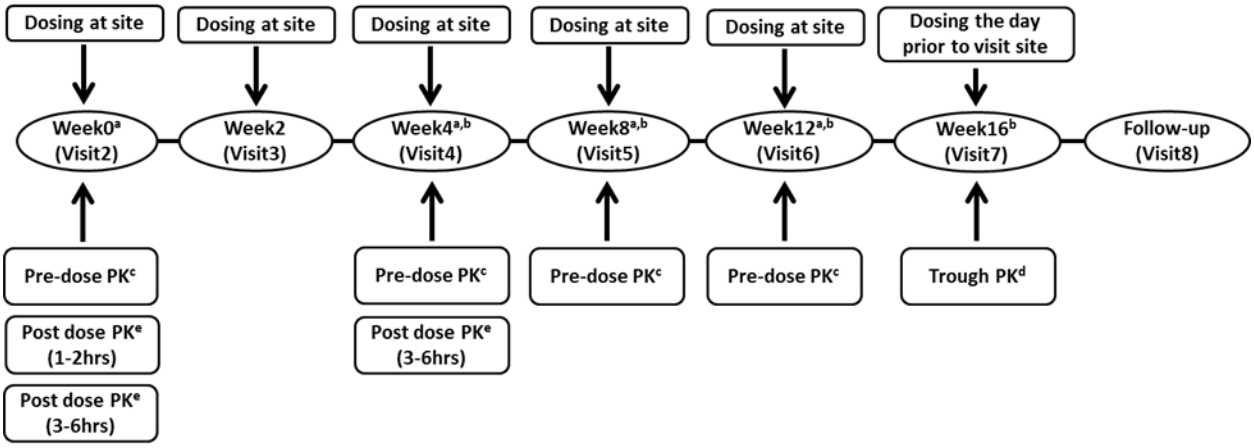
Note: All study procedures should be performed at each study visit prior to study drug administration; except for appropriate PK sample collection procedures as discussed below (see Figure 2). When scheduled at the same time points, ECG and vital sign parameters collection activities should be performed prior to (or at least 15 minutes after) procedures involving venipuncture [redacted]

a. The target day for each visit after randomization will be calculated relative to the date of Visit 2. Every attempt should be made to have the subject attend each visit within the windows specified in the table. The study site is encouraged to make a reminder phone call to the subject before the scheduled visit. However, if a subject is unable to attend a visit within the specified windows, the visit should be scheduled as closely as possible to these windows. A subject should not skip a protocol-specified visit due to scheduling difficulties.
b. Written informed consent must be obtained prior to performing any study-related procedures including washout of previous medications prior to or at the Screening Visit to participate in the study.
c. Chest radiography may not be performed if it has been performed within 12 weeks of the Screening Visit and documentation is available for review by the Investigator and inclusion in the subject's file.
d. At Visit 1, serum pregnancy test will be performed for all female subjects. At Visits 2 through 8 (or Follow-up Visit), urine pregnancy tests will be performed only for female subjects of childbearing potential. At Visit 1, female subjects with a documented history of lack of menses for ≥12 consecutive months with no other reversible medical etiology will be considered post-menopausal. Only for the female with a history of lack of menses but onset has been within 12 months prior to Visit 1, an FSH testing is required at Visit 1, then an FSH >40 mIU/mL will be considered post-menopausal, otherwise subject is considered of childbearing potential.
e. The Itch NRS during a 24-hour recall period will be recorded in the e-diary by the subject once daily from the day of screening through the last visit. Site will dispense the e-diary device at Screening Visit and train the subject on how to use the device.
f. If collecting photographs is raised as the reason for not participating in the study, the subject still can be part of the study without collecting photographs. Subjects who do not raise this objection will be required to take photographs of four half-body views (i.e., upper anterior, lower anterior, upper posterior and lower posterior).

[redacted]

i. At Visit 2 through Visit 6, randomized subjects will receive sufficient study drug blister cards for the period between visits. At Visit 7, study drug will not be dispensed. If a subject discontinues study drug prematurely after receiving at least one dose of study drug, the termination should be recorded as soon as possible after the decision has been made.
j. Subjects will be instructed to bring all used and unused blister cards to each study visit for accountability purposes. Study drug compliance will be calculated by the site at each visit during the Treatment Period starting at Visit 3, based on the number of tablets dispensed or returned by the subject.
k. Oral administration for 16 weeks starting on the day of randomization at Visit 2, BID, at approximately 12-hour intervals, regardless of meals. On study visit days, subjects should take their scheduled study treatment from their existing study drug supply (if available) at the site, under the supervision of the investigator or designee after all required procedures prior to administration have been performed (except for Visit 7, when no study drug will be administered, as the last dose will be taken the day prior to the visit).
l. See Figure 2 for a detailed description of PK sampling time points.
m. Adverse event information will be collected at the specified time points as well as at any time when a site staff member becomes aware of an AE after the subject signs the informed consent for the study. However, stable or improving pre-existing conditions detected through the screening procedures at Visit 1 (e.g., abnormalities in ECG, physical examination, vital signs and laboratory tests) are considered medical history and should be documented accordingly.

Figure 2. Dosing and Pharmacokinetic Sample Collection Time



a. Exact date and time of dose at each visit at the site will be collected.
b. Exact date and time of the last two doses prior to the pre-dose/trough PK sample collection will be collected.
c. The pre-dose PK sample collections (i.e., samples obtained prior to the dosing of the study drug at the site) are mandatory in all subjects at all sites. The sample collection date and time will be recorded.
d. The trough PK sample collections (relative to dosing of the study drug on the day prior to the visit) are mandatory in all subjects at all sites. The sample collection date and time will be recorded.
e. Three post-dose PK samples per subject (relative to the dosing of the study drug at the site) should be collected from at least 34 randomized subjects. The samples will consist of one sample from 1 to 2 hours window at Week 0 (Visit 2), one sample from 3 to 6 hours window at Week 0 (Visit 2), and one sample from 3 to 6 hours window at Week 4 (Visit 4). The relative sampling time of the two samples of 3 to 6 hours window at Visit 2 and Visit 4 should be separated by at least 1 hour. The sample collection date and time will be recorded.

3.2 Randomization

Approximately 150 eligible subjects with moderate to severe plaque psoriasis will be randomized into this study. Subjects will be randomized in a 1:1:1 ratio (approximately 50 subjects per treatment group) to receive JTE-451 200 mg BID (400 mg/day), JTE-451 400 mg BID (800 mg/day) or placebo BID. Randomization will be stratified based on prior exposure to biologic therapy (i.e., biologic-naïve vs. biologic-experienced subjects) and body weight (i.e., <90 kg vs. ≥90 kg at Visit 2).

An Interactive Web Response System (IWRS) will be employed for the randomization activities. It will use a stratified randomization algorithm that takes into account the strata specified above.

The randomization code will be controlled by an unblinded member of the Sponsor or designee who will provide the randomization code to select laboratories (see Protocol Section 3.7.8).

4. SUBJECT POPULATIONS

4.1 Safety Population

The safety population consists of the randomized subjects who receive at least one dose of the study drug.

4.2 Intent-To-Treat (ITT) Population

The ITT population consists of all subjects who are randomized at Visit 2. Subjects will be analyzed according to the treatment to which they were assigned, even if subjects do not take the assigned treatment, do not receive the correct treatment, or otherwise do not follow the protocol.

4.3 Per Protocol (PP) Population

The PP population is a subset of the ITT population in which subjects do not have any major protocol deviations as listed below:

1. Dosing compliance not in 80%-120% (based on actual dosing period)
2. Subject's last dose not between Days 90-134
3. Subject did not take 360-536 tablets in total
4. >4 days between last dose and last non-follow-up efficacy assessment
5. Not meeting Inclusion Criterion #2, #3 or #4
6. Meeting Exclusion Criterion #1, #2, #3, #4, #5 (details shown below) or #10
7. Subject took "key" prohibited concomitant medications or had unstable background therapy that could potentially affect efficacy results/interpretation
   - Use of restricted medications listed in Table 2 of the protocol in the prohibited period
   - Use of prohibited medications listed in Table 4 and Table 5 of the protocol in the prohibited period. The exclusion decision will be made based on the review of the individual case and will be documented
8. Subject took incorrect study medication, e.g. due to incorrect drug dispense
9. Significant procedural deviations/non-compliance that could potentially affect efficacy results/interpretation

A pre-analysis meeting will take place after all data have been entered into the database and cleaned, but before the release of the randomization code, to identify the PP population. The decisions made to select the PP population will be documented.

4.4 Pharmacokinetic (PK) Population

The PK population consists of the randomized subjects who receive at least one dose of JTE-451 and have at least one usable JTE-451 plasma concentration measurement.

5. ANALYSIS PARAMETERS

5.1 Demographic and Baseline Characteristics

Demographic variables include age, gender, ethnic group, country, race, body weight, height and body mass index (BMI) at Screening Visit.

Baseline (last non-missing value prior to first dose) subject characteristics include but not limited to the following parameters: prior biologic therapy use (naïve or experienced), weight category (<90 kg or ≥90 kg), age category (<65 years or ≥65 years), prior exposure to oral systemic non-biologic therapies (yes or no), number of prior anti-psoriasis systemic treatment (biologic or non-biologic; 0, 1 or ≥2), time from diagnosis, itch numeric rating scale (NRS, week average at one week prior to Day 1 dosing, i.e., Day -6 to Day 1), psoriasis body surface area (BSA), psoriasis area and severity index (PASI) score, static physician's globa sessmen (PGA) score, Skindex-16 questionnaire scale scores and overall score[redacted]

Summary tables for demographic and baseline characteristics will be generated for the safety, ITT and PP populations, respectively.

5.2 Efficacy Parameters

5.2.1 Primary Efficacy Parameter

The primary efficacy parameter is the proportion of subjects achieving PASI-75 at end of treatment (EOT).

5.2.2 Secondary Efficacy Parameters

The secondary efficacy parameters (for which data will be evaluated at Weeks 2, 4, 8, 12, 16, 20 and EOT unless otherwise stated) are:

- Proportions of subjects achieving PASI-50/PASI-75/PASI-90;
- Percent change from baseline in PASI;
- Proportion of subjects achieving sPGA score of 0 or 1;
- Change from baseline in sPGA score;
- Percent change from baseline in BSA;
- Change from baseline in Skindex-16;
- Change from baseline in Itch NRS;
- Change from baseline in each domain score/questionnaire of Skindex-16.

[redacted]

5.2.4 Efficacy Parameters Calculation

5.2.4.1 Psoriasis Area and Severity Index (PASI)

The PASI is a quantitative rating score to assess the severity of psoriatic lesions based on the area coverage and plaque appearance. The PASI score will be derived as indicated in Table 2 below (refer to protocol Section 3.5.6.2 for further details).

Table 2. The PASI Scoring

Body region	Erythema (E)	Thickening (plaque elevation, induration, I)	Scaling (desquamation, D)	Area score (based on true area %, A)*
Head (H)†	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0 = 0% 1 = 1-9% 2 = 10-29% 3 = 30-49% 4 = 50-69% 5 = 70-89% 6 = 90-100%
Trunk (T)‡	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0 = 0% 1 = 1-9% 2 = 10-29% 3 = 30-49% 4 = 50-69% 5 = 70-89% 6 = 90-100%
Upper limbs (U)	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0 = 0% 1 = 1-9% 2 = 10-29% 3 = 30-49% 4 = 50-69% 5 = 70-89% 6 = 90-100%
Lower limbs (L)§	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0 = 0% 1 = 1-9% 2 = 10-29% 3 = 30-49% 4 = 50-69% 5 = 70-89% 6 = 90-100%

Percentage (not score) of body region (not whole body) affected will be entered in the CRF

† Neck is assessed as part of the Head (H) body region.

‡ Axillae and groin are assessed as part of the Trunk (T) body region.

§ Buttocks are assessed as part of the Lower limbs (L) body region.

The PASI score is calculated using the following formula:

PASI = 0.1(EH+IH+DH)AH + 0.2(EU+IU+DU)AU + 0.3(ET+IT+DT)AT + 0.4(EL+IL+DL)AL

The PASI scores can range from 0, corresponding to no signs of psoriasis, up to a theoretic maximum of 72.0, corresponding to maximal signs of psoriasis. The calculated composite PASI score will be directly available in the corresponding database.

5.2.4.2 The PASI-50/PASI-75/PASI-90 Response Rate

The PASI-50/PASI-75/PASI-90 response rate will be calculated for Visits 3 through EOT respectively based on the PASI score collected by the Investigator.

The PASI-50/PASI-75/PASI-90 response is a dichotomous variable with a positive (= responder) or negative (= non-responder) outcome.

- PASI-50 is ≥50% improvement from baseline
- PASI-75 is ≥75% improvement from baseline
- PASI-90 is ≥90% improvement from baseline

5.2.4.3 Static Physician's Global Assessment (sPGA)

The sPGA is used to determine the severity of subject's psoriatic lesion at a given time point. The psoriatic lesion will be graded for induration, erythema and scaling based on the scales below. The sPGA will be derived by the sponsor for all study visits.

The sum of the 3 scales will be divided by 3 to obtain the final sPGA score.

Induration (I)
0 = no evidence of plaque elevation
1 = barely palpable
2 = slight but definite elevation, indistinct edge
3 = elevated with distinct edges
4 = marked plaque elevation, hard/sharp borders

Erythema (E)
0 = no evidence of erythema (post inflammatory hyperpigmentation and/or hypopigmentation may be present)
1 = faint erythema
2 = light red coloration
3 = red coloration
4 = dusky to deep red coloration

Scaling (S)
0 = no evidence of scaling
1 = occasional fine scale
2 = fine scale predominates
3 = coarse scale predominates
4 = thick, coarse scale predominates

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

Physician's Static Global Assessment based upon above Total Average
0 = Cleared, except for residual discoloration
1 = Minimal – majority of lesions have individual scores for I+E+S/3 that averages 1
2 = Mild – majority of lesions have individual scores for I+E+S/3 that averages 2
3 = Moderate – majority of lesions have individual scores for I+E+S/3 that averages 3
4 = Severe – majority of lesions have individual scores for I+E+S/3 that averages 4

Note: Scores should be rounded to the nearest whole number (e.g., if the total is <1.50, the score should be 1; if the total is ≥1.50, the score should be 2) except if the score is >0 and <1, score should be treated as 1.

5.2.4.4 Psoriasis Body Surface Area (BSA)

The total BSA affected by plaque-type psoriasis will be estimated from the percentages of areas affected, including head, trunk, upper limbs and lower limbs. The psoriasis BSA will be derived by the Sponsor for all study visits.

The following calculations will be done: each reported percentage will be multiplied by its respective body region corresponding factor (head = 0.1, trunk = 0.3, upper limbs = 0.2, lower limbs = 0.4). The resulting 4 values will be added up to estimate the total BSA affected by plaque-type psoriasis.

5.2.4.5 Skindex-16

Skindex-16 is a 16-item, skin-related quality of life (QOL) questionnaire (refer to Appendix 2 of the protocol) and has three domain scores: symptoms, emotions, and functioning. Each 16-item QOL questionnaire will be reported on a scale of 0 to 6. Each raw score will be multiplied by 16.667, thus all responses will be transformed to a linear scale of 100 (i.e., from 0 [no effect] to 100 [effect experienced all the time]). A scale score is the average of non-missing items in a given scale as follows.

- Symptom scale score: average of items 1-4
- Emotions scale score: average of items 5-11
- Functioning scale score: average of items 12-16
- Overall score: average of 16 items

5.2.4.6 Itch Numeric Rating Scale (NRS)

The Itch NRS is a validated, self-reported instrument for measurement of itch intensity. It uses a 24-hour recall period and asks subjects to rate the worst itch intensity on an 11-point scale ranging from 0 (no itch) to 10 (worst itch imaginable).

The Itch NRS scores will be recorded by the subject using the e-diary once daily (before study drug administration once the subject is randomized) preferably at the same time of the day each day from Screening through the last visit.

5.3 Safety Parameters

5.3.1 Adverse Events (AEs)

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

Serious AE (SAE) is the AE that meets a criterion of the SAE definition per protocol. The severity of an AE is graded by Investigators referring to Common Terminology Criteria for Adverse Events (CTCAE) and translated into mild, moderate and severe and causality of AE is assessed in three categories “not related”, “possibly related” or “related”.

The Medical Dictionary for Regulatory Activities (MedDRA) Version 23.0 will be used to map verbatim AEs to preferred terms and their respective system organ classes. Adverse events will be characterized as either pre-treatment or treatment-emergent according to the criteria described in the following sections.

5.3.2 Pre-Treatment Adverse Events

A pre-treatment AE is the AE with an onset time that is prior to the treatment period, but after the informed consent is obtained.

5.3.3 Treatment-Emergent Adverse Events

The treatment-emergent AE (TEAE) is defined as one of the following;

- An AE that occurred during the treatment period or the follow-up period. In the process of collecting the onset dates of AEs, an AE that occurs after the initiation of trial medication on Day 1 (the first day of the treatment period) should be treated as a TEAE. All AEs occurring on the day of first dose will be considered as TEAE if the time of AE occurrence relative to the dosing is unknown.
- An AE present prior to the treatment period that worsened in severity during the treatment period or the follow-up period.
- Any events that are present prior to the treatment period and have recovered, but recurred during the treatment period or the follow-up period should be considered as new TEAEs.

5.3.4 Medical History

A complete medical history will be obtained at the Screening Visit (Visit 1) and will include evaluations for past or present conditions. Specifically, any known history of psoriatic arthritis and scalp psoriasis will be documented at Visit 2.

Any pre-existing conditions detected at Visit 1 (e.g., abnormalities in ECG, physical examination, vital signs and laboratory tests) are considered medical history.

5.3.5 Study Medication Compliance

Total number of tablets taken will be recorded in the eCRF for the corresponding intervals as scheduled in Table 1. Compliance of the study medication will be calculated as follows:

$$\text{Compliance (\%)} = \frac{\text{Total tablets taken}}{\text{Treatment duration} \times 4} \text{ x } 100\%$$

Compliance will be calculated for the treatment duration by visits, and the entire treatment period.

5.3.6 Clinical Laboratory Results

Hematology, coagulation, serum biochemistry and urinalysis are collected as scheduled in Table 1. The following information will be derived for each of the hematology, coagulation, serum biochemistry, urinalysis and other parameters:

- Change from baseline at all post-baseline visits
- Classification relative to the normal range (‘Low’, ‘Normal’ or ‘High’)
- Treatment-Emergent potentially clinically significant (PCS) abnormalities, if applicable

In addition, viral serology, drugs of abuse and alcohol screen, glycosylated hemoglobin (HbA1c), pregnancy test, Follicle-stimulating Hormone (FSH), QuantiFERON®-TB Gold-In-Tube test and chest radiography will also be obtained at the corresponding scheduled visit, respectively.

5.3.7 Vital Signs

Vital signs and body weight are collected as scheduled in Table 1. Vital signs include systolic/diastolic blood pressure, heart rate, respiratory rate and body temperature (°C). Subjects must rest in a sitting position for at least 5 minutes in preparation for blood pressure and heart rate assessments. The following information will be derived for all vital signs and body weight:

- Change from baseline at all post-baseline visits
- Treatment-emergent PCS abnormalities, if applicable

5.3.8 12-Lead ECG

Twelve-lead ECG recordings and conduction intervals including RR, PR, QRS, QT and Fridericia-corrected QT interval (QT_cF) are obtained according to the schedules summarized in Table 1. The QT_cF (Fridericia's formula, $QT_cF = QT/RR^{1/3}$) will be derived and reported in the database.

The following information will be calculated for each of the 12-lead ECG measurements:

- Change from baseline to all post-baseline visits
- Treatment-emergent PCS abnormalities, if applicable

The overall clinical interpretation of an ECG is assessed as follows: normal, abnormal not clinically significant or abnormal clinically significant.

5.3.9 Physical Examination

The physical examinations will be performed by a physician or a qualified designee according to the schedule summarized in Table 1 and will include examination of the following body systems: general appearance, skin (including hair and nails), HEENT (head, ears, eyes, nose, throat), neck/thyroid, chest/lungs, cardiovascular, gastrointestinal, neurological, psychiatric/emotional, lymphatic and musculoskeletal systems.

Clinically significant abnormal physical examination findings will be recorded as medical history or AE where appropriate.

5.4 Pharmacokinetic (PK) Parameters

The pharmacokinetic parameters are:

- Trough plasma levels of JTE-451;

[redacted]

[redacted]

5.6 Medications/Procedures

At each study visit, investigators will review concomitant medications and procedures with the patients. The World Health Organization (WHO) Drug Dictionary version Global B3 March 2020 or later will be used to classify medications by preferred term, chemical ingredient names and WHO Level 3 Anatomical Therapeutic Chemical (ATC) classification of trade name. Medication

records will be characterized as prior medication and/or concomitant medication based on the subjects' start and end date of the study drug.

5.6.1 Prior Medications/Procedures

Prior medications/procedures are defined as any medications/procedures started and ended before the first dose of the study drug.

5.6.2 Concomitant Medications/Procedures

Any medications/procedures that begin before the start of the first dose of study drug and continue past that, or that begins on or after the first dose of study drug and up to 28 days after last dose of the study drug will be considered as concomitant medications/procedures.

6. STATISTICAL METHODOLOGY

Titles and headers of all statistical analysis tables will indicate the corresponding study population; the number of subjects for the population and for each treatment will be presented in the tables. Summary statistics for continuous parameters will include the number of subjects with non-missing data (n), mean, standard deviation (SD), median, minimum and maximum. For plasma concentrations, summary statistics will also include the coefficient of variation (CV%). Summary statistics for discrete parameters will include frequency count and percentage of which the denominator will be clearly indicated in the analysis table.

For efficacy and safety summaries, mean and median will be presented to 1 more decimal than the source data; SD will be presented to 2 more decimals than the source data; minimum and maximum will be presented in the same precision as the source data. Percentages including response rate will be presented to 1 decimal, e.g., xx.x%. P-values will be presented to 3 decimals. P-values greater than 0.999 will be presented as >0.999; p-values less than 0.001 will be presented as <0.001.

For figures, the corresponding study population will be displayed in the titles. All collected observations will be included in the related listings.

Baseline value is defined as the last non-missing value prior to the first dose. If the scheduled Day 1 value (i.e., not unscheduled or repeat measurement on Day 1) is available, the scheduled Day 1 value will be the baseline, as all procedures are to be performed before dosing at each visit.

The determination of baselines and EOT values for both efficacy and safety variables will be based on available scheduled assessments and unscheduled assessments. Only assessments from scheduled visits will be used for the by-visit summary tables, however, data collected from both scheduled and unscheduled visits will appear in the subject listings.

When calculating percent change from baseline in efficacy analyses, if the baseline value is 0 and the post-baseline value is also 0, then the percent change from baseline is set to 0. If the baseline value is 0 or missing and the post-baseline value is non-zero or missing, then the percent change from baseline is set to missing.

6.1 Sample Size

Approximately 150 eligible subjects (50 subjects in each treatment group) will be randomized into the double-blind treatment period.

The sample size estimation is based on the primary efficacy parameter of the proportion of subjects achieving PASI-75 at EOT. [redacted]

Taking into consideration a 15-20% treatment discontinuation rate, about 50 subjects per group will be randomized into the double-blind treatment period.

6.2 Subject Disposition Summary

Subject disposition will be summarized and tabulated by treatment group and in total. The number and percentage of subjects in the safety, ITT, PP and PK populations will be tabulated. Discontinued patients and the reasons for discontinuation will be summarized. The number of subjects at each scheduled visit will be tabulated for the ITT population by treatment group and in total.

6.3 Demographics and Baseline Characteristics

Demographics and baseline characteristics as defined in Section 5.1 will be presented by treatment group with descriptive statistics for the safety, ITT and PP populations.

6.4 Efficacy Analysis

Analyses of primary and secondary efficacy parameters will be performed for both the ITT and PP populations, respectively. [redacted]

For efficacy analyses, the JTE-451 treatment period is defined as the time period from the first dose of study drug to the last dose of study drug plus 4 days. The EOT value is defined as the last value taken during the JTE-451 treatment period. For PASI-50/75/90 and sPGA response analyses at EOT, if 10% or more subjects take any other psoriasis treatment that is listed in the protocol Section 3.5.5.1.1, a sensitivity analysis will be conducted using an alternative EOT value. The data used for the alternative EOT value determination will be up to and excluding the start of the other psoriasis treatment. The alternative EOT value will be the last value within 4 days after the last dose of JTE-451 in this data cutoff.

All analyses will be performed two-sided at the 5% significance level. No formal multiple comparison adjustment will be made for secondary efficacy parameters. The estimated treatment

effect (relative to placebo) from the model, along with a two-sided 95% confidence interval (CI) and p-value, will be tabulated where appropriate.

Graphical presentations of the treatment profile will be provided for the primary and secondary efficacy parameters. Sensitivity analysis and model fit assessment may be conducted, and data transformation may be employed if appropriate.

6.4.1 Analyses of Primary Efficacy Parameter

The primary efficacy parameter (PASI-75 response rate at EOT) will be compared for each JTE-451 dose group with placebo using the Cochran-Mantel-Haenszel (CMH) test, stratified by prior exposure to biologic therapy (Yes or No) and body weight (<90 kg or ≥90 kg at Visit 2). The adjusted odds ratio for each active treatment group to the placebo group along with 95% CIs and p-value will be reported.

A sample SAS code as below:

- Cochran-Mantel-Haenszel test (Run by K=2, 3 separately):

```
PROC FREQ DATA=<input>;
    TABLES  <biologic therapy> * <body weight > * <TRTn> *<PASI75> / CMH;
    WHERE <TRTn> IN (1, K);
RUN;
```

Note:

- <*biologic therapy*>=0 represents 'Biologic-naïve';
  <*biologic therapy*> =1 represents 'Biologic-experienced';
- <*body weight* >=0 represents 'Body weight < 90 kg';
  <*body weight* >=1 represents 'Body weight >= 90 kg';
- <*TRTn*>=1 for placebo, <*TRTn*>=2 for JTE-451 200 mg, <*TRTn*>=3 for JTE-451 400 mg,
- <*PASI75*> =0 represents a non-responder, <*PASI75*> =1 represents a responder;

In addition, logistic regression model-based supportive analyses will be performed for the pairwise comparisons between JTE-451 and placebo groups (as shown in Model 1 below) and for the evaluation of dose response relationship (as shown in Model 2 below). The logistic regression models will include baseline PASI value and two stratification factors (prior biologic therapy and body weight) as covariates.

Sample SAS codes as below:

- Model 1 (pairwise treatment vs placebo comparison)

```
PROC LOGISTIC DATA=<input> DESCENDING;
   CLASS <biologic therapy> <body weight >;
   MODEL <PASI75> = <Dose_200>  < Dose_400>  <Baseline X>
                        <biologic therapy>  <body weight > ;
RUN;
```

- Model 2 (dose-response analysis)

```
PROC LOGISTIC DATA=<input> DESCENDING;
   CLASS <biologic therapy> <body weight >;
```

```
    MODEL <PASI75> = <Dose> <Baseline X>
                        <biologic therapy> <body weight >;
    ODDSRATIO <Dose>;
RUN;
```

Note:

- In Model 1, <*Dose_x*> = 1 if dose=x; otherwise. <*Dose_x*>=0; i.e., <*Dose_x*> is a dummy variable.
- In Model 2, <*Dose*> = 0, 200, 400 for placebo and each JTE-451 dose level, respectively.
- <*Baseline X*> denotes baseline PASI value.
- <*PASI75*> =1 represents a responder; <*PASI75*> =0 represents a non-responder.
- <*biologic therapy*> =0 represents 'Biologic-naïve';
  <*biologic therapy*> =1 represents 'Biologic-experienced';
- <*body weight*>=0 represents 'Body weight < 90 kg';
  <*body weight*>=1 represents 'Body weight >= 90 kg';
  From the model fitting, one obtains adjusted odds ratios and corresponding p-values for the respective pairwise treatment comparison versus placebo.

6.4.2 Analyses of Secondary Efficacy Parameters

For dichotomous secondary efficacy parameters at defined single time point, similar analyses used for the primary efficacy parameter above will be performed as appropriate. For assessing dichotomous efficacy parameter measured at multiple time points, a generalized estimating equation (GEE) method on the logit scale will be used. The model includes effects for treatment, time, treatment by time interaction, stratification factors, appropriate baseline and subject as the repeated factor. The odds ratio (OR) of each JTE-451 dose group relative to placebo at the same time point will be estimated.

A sample SAS code as below:

- Model: (Generalized estimating equation (GEE) method on the logit scale)

```
PROC GENMOD DATA=<input>;
    CLASS <usubjid> <visit>(REF="Week 0") <TRTn>(REF=1)
          <biologic therapy>(REF =0)  < body weight >(REF =0);
    MODEL <SAPE> = <TRTn> <visit> <TRTn>*<visit> <Baseline> <biologic therapy> < body weight >
                    /DIST=BINOMIAL LINK=LOGIT;
    REPEATED SUBJECT=<usubjid>(<TRTn>) / TYPE=UN CORRW;
RUN;
```

Note:

- <*usubjid*> denotes subject ID;
- <*SAPE*> denotes any dichotomous efficacy parameter;
- <*TRTn*>=1 for placebo, <*TRTn*>=2 for JTE-451 200 mg, <*TRTn*>=3 for JTE-451 400 mg;
- <*Baseline*> denotes appropriate baseline corresponding to the efficacy parameter;
- <*biologic therapy*> =0 represents 'Biologic-naïve';
  <*biologic therapy*> =1 represents 'Biologic-experienced';
- <*body weight*>=0 represents 'Body weight < 90 kg';
  <*body weight*>=1 represents 'Body weight >= 90 kg';

For assessing the continuous efficacy parameter measured at multiple time points, a mixed effect model with repeated measures (MMRM) will be used. The model includes fixed effects for treatment, time, treatment by time interaction, stratification factors, appropriate baseline and

measurements within each subject as repeated measures. The treatment difference of each JTE-451 dose group relative to placebo at the same time point will be estimated as well as the corresponding 95% CI.

A sample SAS code is displayed below:

- Model: (Mixed-effect model with repeated measures (MMRM))

```
PROC MIXED DATA=<input>;
    CLASS <usubjid> <visit> <TRTn>(REF=1)  <biologic therapy>(REF =0)  < body weight >(REF =0);
    MODEL <PCHG> = <Baseline>  <TRTn>  < visit > <TRTn>*<visit>
                        <biologic therapy> < body weight >;
    REPEATED/SUBJECT=<usubjid>(<TRTn>)  TYPE=UN;
    LSMEANS < TRTn >/PDIFF CL;
RUN;
```

Note:

- <*PCHG*> denotes change from baseline or percent change from baseline in any continuous efficacy parameter;
- <*TRTn*>=1 for placebo; <*TRTn*>=2 for JTE-451 200 mg; <*TRTn*>=3 for JTE-451 400 mg;
- <*Baseline*> denotes appropriate baseline corresponding to the efficacy parameter;
- <*biologic therapy*> =0 represents 'Biologic-naïve';
  <*biologic therapy*> =1 represents 'Biologic-experienced';
- <*body weight*>=0 represents 'Body weight < 90 kg';
  <*body weight*>=1 represents 'Body weight >= 90 kg';

The assessments from the follow-up visit and derived EOT will not be included in the GEE or MMRM models.

The Itch NRS scores will be summarized descriptively by each JTE-451 dose group and placebo group, and analyzed in an MMRM for weekly averages (by-visit only) as described above.

Observed values and changes from the weekly average at one week prior to Week 0 to the weekly average at one week prior to each scheduled visit which includes the day of scheduled visit and a 6-day collection before the scheduled visit will be derived and analyzed by each study visit from Week 0 to the Follow-up visit (including EOT) using both the ITT and PP populations, respectively. The data used for by-visit average score derivation in the treatment period (not including the Follow-up visit) will be up to the day of last dose plus 4 days. For the Follow-up visit, the weekly average will use the collection at the day of Follow-up visit and the 6-day collection before the Follow-up visit.

In addition, the Itch NRS scores will be derived and analyzed by each JTE-451 dose group and placebo as following:

- Observed values and changes from baseline (one week prior to Week 0) in weekly average score will be analyzed by each week from Week 0 to Week 20 using the ITT population only. For early-terminated subjects, the data used for weekly average score derivation will be up to the day of last dose plus 4 days.

- Descriptive statistics of observed values and changes from Day 1 in daily score will be presented by each day from Day -6 to Day 28 using the ITT population only. For early-terminated subjects, the data used for daily score summary will be up to the day of last dose plus 4 days.

[redacted]

6.4.4 Treatment by Center Effect

The randomization in this study is stratified by prior exposure to biologic therapy (i.e., biologic-naïve vs. biologic-experienced subjects) and body weight (i.e., <90 kg vs. ≥90 kg at Visit 2). Center effect is not considered due to the expectation that many centers will be used and only a small number of subjects will be enrolled in most centers.

6.4.5 Treatment by Baseline Covariate Effect

The treatment-by-baseline effect will be assessed as appropriate. The baseline will be included in the respective parametric analysis model of the efficacy parameters where appropriate.

6.4.6 Subgroup Analysis

As exploratory analyses, further subgroup analyses may be conducted for selected parameters. The subgroups that may be examined include, but are not limited to, the following:

- Prior biologic therapy (naïve vs. experienced)
- Body weight (<90 kg vs. ≥90kg at Visit 2)

6.4.7 Handling of Dropouts and Missing Data

There may be missing data intermittently (e.g., a missing visit or subject dropout). For PASI-50/-75/-90 and sPGA (achieving score of 0 or 1) responses, subjects with missing EOT data will be imputed as non-responders at EOT; for analyses by scheduled time points, missing data will not be imputed. For analysis with multiple time points, any missing data will be imputed using the last observation carried forward (LOCF) method. For parameters analyzed both by time point and with multiple time points, these two approaches would strengthen the findings when they are similar.

For efficacy analysis of continuous parameters, missing data will not be imputed. This is because the statistical models employed (e.g., mixed effect model) generally provide valid estimates if the missing data mechanism is so-called “missing at random,” a common assumption made as the first approach for analysis.

For the Itch NRS, 4 completed days are necessary to derive a weekly score (1-3 missed days, consecutive or non-consecutive, are allowed). Any missing individual items are treated as missing data. When a weekly score in post-dose time point cannot be calculated (less than 4 completed days), the time point will not be included in the analysis. If a baseline weekly score cannot be derived (i.e., less than 4 completed days from Day -6 to Day 1), the Itch NRS score of the subject will not be included in the analysis.

For the Skindex-16, if more than 25% of the responses are missing, the scale is considered missing. An item with multiple answers is considered missing. The skindex-16 score will be derived for all study visits.

Additional sensitivity analyses of the primary efficacy parameter, i.e., PASI-75 at EOT, may be performed using other missing data handling procedures or approaches.

6.5 Safety Analysis

All safety analyses will be summarized based on the Safety population.

Potentially clinically significant (PCS) abnormalities will be defined according to the Akros Safety Reporting Standards as of 18 Oct, 2004. The PCS values for vital signs, ECG and laboratory data will be flagged in data listings.

Treatment-emergent PCS abnormalities are values that meet the specified criteria after the initiation of study drug (see Section 10.1 for detailed clinically significant criteria).

Treatment-emergent PCS values will be summarized, presenting the number and percentage of subjects who had at least one PCS value on or after the first dose of study drug (JTE-451 or placebo). The denominator is always the number of subjects in the safety population, regardless of whether the subject had any post-baseline measurements. The numerator is the number of subjects in the safety population with any PCS value in the treatment-emergent period. Note that for the purpose of determining PCS abnormalities, baseline is always the last non-missing value before the first dose of study drug. As all procedures will be performed before dosing at each scheduled visit, the values of the scheduled Day 1 collection will be baseline and will not be treatment-emergent PCS.

All safety data will be presented in the data listings, and will be flagged for events of interest (e.g., out of range laboratory data) as appropriate.

6.5.1 Adverse Events (AEs)

AEs will be summarized by MedDRA system organ class (SOC) and preferred term (PT) in descending order unless otherwise specified. For the summary of number of subjects, if a subject reports more than one AE that was coded to the same SOC or PT, the subject will be counted only once for that specific system organ class or preferred term. For the summary of number of AEs, all AEs will be counted.

The number and percentage of subjects experiencing TEAEs will be tabulated by treatment according to the following categories:

- Overall summary of TEAEs.
- TEAEs by system organ class and preferred term.
- TEAEs by system organ class, preferred term and maximum severity.
- TEAEs by system organ class, preferred term and causality.
- TEAEs by preferred term (in order of descending frequency in the total JTE-451 group).
- TEAEs leading to study discontinuation by system organ class and preferred term.
- Serious AEs (SAEs) by system organ class and preferred term.

- SAEs leading to study discontinuation by system organ class and preferred term.

In addition, adverse drug reactions (ADRs) will be summarized. Per ICH E2A guidance, all noxious and unintended responses to a medicinal product related to any dose should be considered ADRs. The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out. For the purpose of analysis, all TEAEs that are related, possibly related or has missing relationship to the study drug will be considered as ADRs. The following summaries of ADRs will be presented:

- Number of ADRs by system organ class, preferred term and maximum severity.
- Number of subjects with ADRs by preferred term (in order of descending frequency in the total JTE-451 group)

Listings will be provided for AEs, SAEs and AEs leading to study discontinuation.

6.5.2 Medical History

Subjects with significant medical history conditions and/or surgeries, the corresponding system organ class and preferred term coded from the MedDRA (Version 23.0) will be presented in the data listing.

6.5.3 Prior and Concomitant Medications

Prior medications and concomitant medications will be listed in the data listings. Concomitant medications will be summarized by ATC Level 3 term, drug preferred term and treatment group.

6.5.4 Clinical Laboratory Tests

Descriptive statistics of observed results and change from baseline for hematology, serum biochemistry, coagulation and continuous urinalysis will be presented by time point and treatment group. Frequency and percentage of the distribution of discrete urinalysis tests will be presented by time point. Number and percentage of subjects with treatment-emergent PCS abnormal values will be summarized by treatment group.

The number and percentage of subjects with post-baseline abnormalities in liver tests will be summarized by treatment group according to Table 3.

Table 3. Criteria for Categorical Analysis in Liver Tests

Parameter	Specified Value			
ALT	ALT ≥ULN×3	ALT ≥ULN×5	ALT ≥ULN×10	ALT ≥ULN×20
AST	AST ≥ULN×3	AST ≥ULN×5	AST ≥ULN×10	AST ≥ULN×20
ALT and AST	ALT and AST ≥ULN×3	ALT and AST ≥ULN×5	ALT and AST ≥ULN×10	ALT and AST ≥ULN×20
ALT or AST	ALT or AST ≥ULN×3	ALT or AST ≥ULN×5	ALT or AST ≥ULN×10	ALT or AST ≥ULN×20
T-Bil	T-Bil >ULNx1.5		T-Bil >ULN×2	
ALP	ALP > ULN×1.5			
ALT and T-Bil	ALT ≥ULN×3 and T-Bil ≥ULN×1.5		ALT ≥ULN×3 and T-Bil ≥ ULN×2	
AST and T-Bil	AST ≥ULN×3 and T-Bil ≥ULN×1.5		AST ≥ULN×3 and T-Bil ≥ ULN×2	
ALT, AST, ALP and T-Bil	ALT ≥ULNx3, AST ≥ULNx3, ALP ≥ULN×2 and T-Bil ≥ULN×2			
ALT and AST	ALT or AST > ULN×3 at any treatment visit and any of the following AEs: Nausea, Vomiting, Anorexia, Abdominal pain or Fatigue, reported within +/- 14 days of the abnormal AT values.			

Other clinical laboratory tests (e.g., drug abuse, alcohol screen, viral serology, pregnancy) will be listed in the data listings.

Qualitative urine parameters are generally reported by a descriptive score, which may differ between laboratories. For pooling the data, the qualitative results will be mapped to a four-point scale. A clinical review will be performed on the mapping of the descriptive scores to the four-point scale; and the descriptive scores will be remapped where appropriate. The four-point scale will be used in the determination of the PCS abnormalities.

The mean profile may be presented for selected laboratory parameters.

6.5.5 Vital Signs

Descriptive statistics of observed results and change from baseline for vital signs and body weight will be presented by time point and treatment group. Number and percentage of subjects with treatment-emergent PCS abnormal values will be presented by treatment group.

6.5.6 12-Lead ECG

Descriptive statistics of observed results and change from baseline will be presented by time point and treatment group for RR, PR, QRS, QT and QT_cF intervals. The number and percentage of subjects with treatment-emergent PCS abnormal values will be presented by treatment group. Clinical interpretation of overall ECG findings will be summarized by time point and treatment group.

6.5.7 Study Medication Exposure and Compliance

A summary of total duration of study medication exposure, which is calculated as (last dose date of study drug – first dose date of study drug + 1), will be presented by treatment group. Average daily dose will also be summarized by treatment group, which is calculated as (total dose of study drug taken/total duration of study medication exposure), where the total dose is calculated as [(total number of tablets/4) × daily dose level in the treatment group (0, 400 mg or 800 mg)].

Study drug compliance will be summarized between visits and overall for each treatment group. Study drug compliance will also be presented as categories <80%, 80%-120% and >120%.

6.6 Pharmacokinetic Analysis

All PK data will be summarized or analyzed based on the PK population.

6.6.1 Method of PK Data Representation

The PK data including individual data and descriptive statistics for plasma drug concentrations will be represented with 3 significant values except for CV% which will be represented to 1 decimal place. The ratio values (see Section 6.6.2) will be displayed to 2 decimal places.

6.6.2 Descriptive Statistics of Plasma Concentrations

Descriptive statistics of plasma concentration data for JTE-451 will be presented by treatment and visit (nominal time point) with n, arithmetic mean, geometric mean, SD, CV%, median, minimum and maximum. The mean ratio of trough concentration relative to the lowest dose will be calculated. Mean plasma concentration-time profiles will be plotted by treatment on linear scales. Below the limit of quantification (BLQ) concentrations will be treated as zero for descriptive statistics.

[redacted]

6.6.4 Population Pharmacokinetic Analysis

Population PK (PPK) analyses may be performed. Population PK analysis plan will be specified in a separate analysis document and the results of PPK analyses will be presented in a standalone report separately from the Clinical Study Report.

[redacted]

7. SUBJECT DATA LISTING

Subject listings of all the data collected in the study database, including eCRF data and any external data transfers (such as clinical laboratory results), will be presented by treatment group and subject number.

If a subject prematurely discontinues the study, additional subjects may be enrolled at the discretion of the Sponsor, as appropriate.

8. SOFTWARE AND QUALITY CONTROL

All analysis will be performed using SAS® Version 9.4 or higher. The SOPs of [redacted] will be followed in the creation and quality control of all tables, listings and analysis.

9. REFERENCES

Please see the references in protocol.

10. APPENDICES

10.1 General Clinically-Significant Criteria for Safety Parameters

Parameter (Full Names)	Reporting Unit	Clinically Significant Criteria [1]	
		Low	High
Hematology			
Hematocrit	%	Male ≤37% Female ≤32%	NA
Hemoglobin	g/dl	Male ≤11.5 Female ≤9.5	NA
White blood cell	E3/mm3	≤2.8	≥16.0
Platelets	E3/mm3	≤75	≥700
Mean corpuscular hemoglobin	pg/cell	--	--
Mean corpuscular hemoglobin concentration	g/dl	--	--
Mean corpuscular volume	fl	--	--
Red blood cell	E6/mm3	≤3.5	NA
Differential			
Bands or (Band neutrophil (stab))	%	NA	≥10%
Basophil (absolute)	E3/mm3	NA	≥0.4
Basophil (%)	%	NA	≥5%
Lymphocytes (absolute)	E3/mm3	≤0.5	≥4.5
Lymphocytes (%)	%	≤10%	≥80%
Monocytes (absolute)	E3/mm3	NA	≥1.5
Monocytes (%)	%	NA	≥ 20%
Neutrophils (absolute)	E3/mm3	≤1.0	
Neutrophils (%)	%	≤15%	≥90%
Eosinophils (absolute)	E3/mm3	NA	≥0.7
Eosinophils (%)	%	NA	≥10%
Coagulation			
Prothrombin time	seconds	NA	≥16
International Normalized Ratio	ratio	NA	≥2.00
Partial thromboplastin time	Seconds	NA	≥50

[1] Can be revised as appropriate, but should be consistent within the project.

Parameter (Full Names)	Reporting Unit	Clinically Significant Criteria [1]	
		Low	High
Heart Function			
Aspartate transaminase	IU/l	NA	≥3 x UNL
Lactic dehydrogenase	U/L	NA	≥3 x UNL
CPK (MB Fraction)	µg/L	--	--
Liver Function			
Alkaline Phosphatase	IU/l	NA	≥3 x UNL
Alanine transaminase	IU/l	NA	≥3 x UNL
Total Bilirubin	mg/dl	NA	≥2.0
Gamma-glutamyltransferase	IU/l	NA	≥3 x UNL
Total Protein	g/dl	≤4.5	≥9.0
Albumin	g/dl	≤2.5	≥6.5
Renal Function			
Blood urea nitrogen	mg/dl	NA	≥30
Creatinine	mg/dl	NA	≥2.0
Thyroid Function			
T_3 Uptake, total	nmol/L	--	--
Reverse T_3	nmol/L	--	--
Thyroxine (T_4)	nmol/L	--	--
Human chorioic gonadotropin	IU/L	--	--
Free T_4	pmol/L	--	--
Thyroid- stimulating hormone	mU/L	--	--
Follicle- stimulating hormone	--	--	--
Lipid Chemistry			
Total cholesterol	mg/dl	NA	≥300
LDL cholesterol	mg/dl	--	--
HDL cholesterol	mg/dl	--	--
Ratio (LDL/HDL)	Fraction	--	--
Triglycerides	mg/dl	NA	≥300

Parameter (Full Names)	Reporting Unit	Clinically Significant Criteria [1]	
		Low	High
Electrolytes			
Chloride	MEq/l	≤90	≥112
Potassium	MEq/l	≤3.0	≥5.8
Sodium	MEq/l	≤130	≥150
Bicarbonate	MEq/L	--	--
Metabolic			
Calcium	mg/dl	≤7.0	≥15.5
Phosphate	mg/dl	≤1.5	≥6.0
Blood Glucose	mg/dl	≤50 (fasting)	≥180 (fasting)
Uric Acid	mg/dl	NA	Male ≥10.5 Female ≥8.5
Cancer			
Prostate-specific antigen	--	--	--
Alpha-fetoprotein	--	--	--
Viral tests			
HIV	--	--	--
HIV_2	--	--	--
Hepatitis A virus	--	--	--
Hepatitis A antibody	--	--	--
Hepatitis B virus	--	--	--
Hepatitis B surface Antigen	--	--	--
Hepatitis B core antigen	--	--	--
Hepatitis C virus	--	--	--
Urinalysis			
(Urine) protein		NA	Increase≥2
(Urine) glucose		NA	Increase≥2
(Urine) bilirubin		NA	Increase≥2
Occult blood		NA	Increase≥2
Color		NA	Increase≥2
Ketone		NA	Increase≥2
Leukocyte esterase		NA	Increase≥2
pH		Decrease≥2	Increase≥2
Turbidity		NA	Increase≥2
Urobilinogen		NA	Increase≥2
Specific gravity		≤1.005	NA

[1] Can be revised as appropriate, but should be consistent within the project.

Parameter (Full Names)	Reporting Unit	Clinically Significant Criteria [1]	
		Low	High
Vital Sign			
Systolic blood pressure	mmHg	≤90 and ≥20 decrease	≥180 and ≥20 increase
Diastolic blood pressure	mmHg	≤50 and ≥15 decrease	≥105 and ≥15 increase
Pulse rate	bpm	≤50 and ≥15 decrease	≥120 and ≥15 increase
Body Temperature	C°	NA	≥1.11 C° Increase
Respiration rate	#/min	≤ 10	--
Height	cm	--	--
Weight	kg	≥7% decrease	≥7% increase
Body mass index	kg/m^2		
Hip Circumference	cm		
Waist Circumference	cm		
ECG			
Heart rate	bpm	<50	>100
R-R interval	msec	--	--
PR interval	msec	NA	>200 msec and >Baseline
QRS interval	msec	NA	>120 msec and >Baseline
QT interval	msec	NA	>450 and >30 increase
QTc interval	msec	<=350 and Baseline<375	>450 or >480 or >500 with Baseline <450
QTc interval[1]	msec	NA	>30 increase or >60 increase

10.2 Mock Summary Tables

The mock summary tables will be created in a separate document.

10.3 Mock Data Listings

The mock summary listings will be created in a separate document.

10.4 Mock Figures

The mock summary figures will be created in a separate document.

[1] Can be revised as appropriate, but should be consistent within the project.