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Clinical Study Protocol

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

PROTOCOL DATE: 24 June 2019

NCT NUMBER: NCT03832738

Cover Page
Akros Pharma Inc.
Clinical Study Protocol

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PROTOCOL NUMBER:	AE451-G-18-004
DATE:	24 June 2019
IND NUMBER:	[redacted]
EUDRACT NUMBER:	2018-003359-40
SPONSOR:	Akros Pharma Inc. 302 Carnegie Center, Suite 300 Princeton, NJ 08540
SPONSOR CONTACT:	[redacted] Akros Pharma Inc. [redacted]
MEDICAL MONITOR:	[redacted]

Signature Page

Protocol Number: AE451-G-18-004

Protocol Number: 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**)

The signatures below indicate approval of the protocol.

Investigator's Statement of Agreement:

I acknowledge possession of the JTE-451 Investigator's Brochure (IB) and this protocol. Having fully reviewed all the information provided, I consider it ethically justifiable to give the study drug to subjects according to the agreed protocol. I will conduct the study in full accordance with this protocol and all applicable laws and regulations, including but not limited to current Good Clinical Practices.

Investigator _____ _____
(Signature) Date

_____
(Printed Name)

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List of Abbreviations and Definition of Terms

Abbreviation	Definition of term
^{14}C-JTE-451	^{14}C-labeled JTE-451
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AUC_{inf}	Area under the concentration-time curve from the time of dosing to infinity
BA	Bioavailability
BCRP	Breast cancer resistance protein
βhCG	Human chorionic gonadotropin
BID	Twice a day
BMI	Body mass index
BSA	Body surface area
CFR	Code of federal regulations
CI	Confidence interval
CL_F	Apparent oral clearance of drug following extravascular administration (total body clearance)
C_{max}	Maximum concentration
CPRI	Central Pharmaceutical Research Institute
CRF	Case report form
CTCAE	Common terminology criteria for adverse events
CV%	Coefficient of variation
CYP	Cytochrome P450
ECG	Electrocardiogram
eCOA	Electronic clinical outcome assessment
EOT	End of treatment
FSH	Follicle-stimulating hormone
GCP	Good clinical practice
GI	Gastrointestinal
HBc	Hepatic B core
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
hCav1.2	L-type calcium channel
HCV	Hepatitis C virus
hERG	Human *ether-a-go-go*-related gene
HIV	Human immunodeficiency virus
hNav1.5	Human cardiac sodium channel
HPLC-MS/MS	High performance liquid chromatography/tandem mass spectrometry
HR	Hear rate

Abbreviation	Definition of term
IAP	Intestine-originated alkaline phosphatase
IB	Investigator's Brochure
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent ethics committee
IL	Interleukin
IMP	Investigational medicinal product
IRB	Institutional review board
ITT	Intent-to-treat
IWRS	Interactive web response system
K_i	Inhibition constant
LOCF	Last observation carried forward
MATE1	Multidrug and toxin extrusion transporter 1
MATE2-K	Multidrug and toxin extrusion transporter 2K
MDR1	Multidrug resistance protein 1
MedDRA	Medical Dictionary for Regulatory Activities
MOA	Mechanism of action
mRNA	Messenger ribonucleic acid
MTX	Methotrexate
NOAC	Novel anticoagulant agent
NOAEL	No observed adverse effect level
NRS	Numeric rating scale
OAT1	Organic anion transporter 1
OAT3	Organic anion transporter 3
OATP1B1	Organic anion transporting polypeptide 1B1
OATP1B3	Organic anion transporting polypeptide 1B3
OCT2	Organic cation transporter 2
PASI	Psoriasis area and severity index
PK	Pharmacokinetic(s)
PLSS	Psoriatic lesion severity sum
PP	Per protocol
PR	Interval from beginning of the P wave to the beginning of the QRS complex in the frontal plane
[redacted]	
PR	Interval from beginning of the P wave to the beginning of the QRS complex in the frontal plane
PT	Prothrombin time
PUVA	Psoralen plus ultraviolet A
QD	Once a day
QOL	Quality of life
QRS	Duration of QRS complex in the frontal plane

Abbreviation	Definition of term
QT	Interval from beginning of the QRS complex to end of the T wave in the frontal plane
QT_cF	Fridericia-corrected QT interval
ROR	Retinoid-related orphan receptor
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
SPF	Sun protection factor
sPGA	Static Physician's Global Assessment
SUSAR	Suspected unexpected adverse drug reaction
$t_{1/2}$	Elimination half-life associated with the terminal slope (λ_z) of a semilogarithmic concentration-time curve
TB	Tubercle bacillus
TEAE	Treatment-emergent adverse event
Th cells	T helper cells (type 1 [Th1], type 2 [Th2], type 17 [Th17])
TNF	Tumor necrosis factor
ULN	Upper limit of normal
UVA	Ultraviolet A
UVB	Ultraviolet B
V_F	Apparent volume of distribution following extravascular administration

Protocol Synopsis

STUDY 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
CLINICAL PHASE	Phase 2
STUDY DURATION	Approximately 24 weeks duration per subject: • Up to 28-day Screening Period • 16-week double-blind Treatment Period • Approximately 4-week Follow-up Period
STUDY 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]

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. Follow-up visits will take place approximately 4 weeks after the last dose of study drug. 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). The end of the study is defined as the date of the last subject last visit.
PLANNED NUMBER OF SUBJECTS TO BE ENROLLED AND RANDOMIZED	A sufficient number of subjects will be screened to ensure the randomization (in a 1:1:1 ratio) of approximately 150 subjects (approximately 50 subjects in each treatment group).
KEY ELIGIBILITY CRITERIA	• Male or female, ≥18 and ≤70 years of age at Visit 1; • Have had a history of moderate to severe plaque psoriasis for at least 6 months prior to Visit 1; • Subjects with moderate to severe plaque psoriasis covering ≥10% body surface area (BSA), with a psoriasis area and severity index (PASI) ≥12 and static Physician's Global Assessment (sPGA) score ≥3 at Visit 1 and Visit 2; • Body Mass Index (BMI) ≤40 kg/m^2 at Visit 1; [redacted] • Absence of erythrodermic psoriasis, pustular psoriasis, guttate psoriasis, medication-induced psoriasis or other skin conditions (e.g., clinically-significant eczema or severe acne) at Visit 1; • No history or presence of itch due to underlying conditions other than plaque psoriasis which cause or influence pruritus of the skin within 12 months prior to Visit 1; • Negative QuantiFERON®-TB Gold Plus test, negative chest radiographic findings for tubercle bacillus (TB) and no other evidence of active or untreated latent TB;

KEY ELIGIBILITY CRITERIA, Cont.	• No history of a clinically-significant infection (e.g., infection that required oral antimicrobial therapy) within 4 weeks prior to Visit 2; **Note:** Subjects with treated upper respiratory tract infection or urinary tract infection will be permitted if it resolved prior to Visit 2. • No history of infections requiring hospitalization or parenteral antibiotic, antiviral, antifungal or antiparasitic therapy within 3 months prior to Visit 2 and no history of recurrent infections or conditions predisposing to chronic infections (e.g., bronchiectasis, chronic osteomyelitis);
INVESTIGATIONAL PRODUCT (STUDY DRUG), FORMULATION, DOSAGE, ROUTE AND TIME OF ADMINISTRATION	JTE-451 200 mg Tablets 200 mg BID, 400 mg BID 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 at the site under the supervision of the investigator or designee after all study-related procedures have been completed (except at Visit 7, when no study drug will be administered).
REFERENCE PRODUCT (STUDY DRUG), FORMULATION, DOSAGE, ROUTE AND TIME OF ADMINISTRATION	Placebo Tablets (identical in appearance to JTE-451 tablets) Not applicable (N/A) 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 at the site under the supervision of the investigator or designee after all study-related procedures have been completed (except at Visit 7, when no study drug will be administered).

EVALUATION CRITERIA	Primary Efficacy Parameters Proportion of subjects achieving a minimum 75% improvement from baseline in the PASI (PASI-75) at end of treatment (EOT). Secondary Efficacy Parameters The following will be evaluated at Weeks 2, 4, 8, 12, 16, 20 and EOT, unless otherwise stated. • Proportion 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 Numeric Rating Scale (NRS); • Change from baseline in each domain score/questionnaire of the Skindex-16. [redacted] Safety Assessments • Number and proportion of subjects with adverse events (AEs), type and severity of AEs, change from baseline in safety laboratory, vital sign and electrocardiogram (ECG) parameters. Pharmacokinetic Assessments • Trough plasma levels of JTE-451; [redacted]
STATISTICAL METHODS	Appropriate statistical analysis will be performed using the software for statistical analysis by the SAS Windows®.

1 Introduction

1.1 Background

1.1.1 Psoriasis

Plaque psoriasis is the most common form of psoriasis. It is an intractable inflammatory skin disease characterized by raised, well-demarcated, itchy erythematous circular-to-oval plaques covered with adherent silvery white scales. In addition to the skin-related manifestation, concomitant joint- and nail-related signs and symptoms may be experienced by some patients. The number of patients with psoriasis is estimated to be approximately 7.5 million in the US, 7.5 million in the EU and 420 thousands in Japan, and the worldwide prevalence is calculated to be 0.6 to 4.8%.[1-4] It is also known that the quality of life (QOL) of the psoriasis patients is lower than that of patients with cancer or diabetes.[5] As a result, psoriasis markedly restricts the social activities of patients.

Various cytokines produced by Th1 and Th17 cells play a crucial role in the development of psoriasis. Clinical studies of biologics targeting cytokines have revealed that interleukin (IL)-17 produced by Th17 cells and IL-23 responsible for the growth and maintenance of Th17 cells, play highly important roles in the disease progression and exacerbation of psoriasis.[6-9]

1.1.2 Treatment of Psoriasis

The goal of psoriasis treatment is to achieve rapid remission induction, long-term control of skin manifestations and improve the QOL. The pharmacotherapy for psoriasis mainly consists of topical vitamin D3 analogues and topical corticosteroids, and depending on the symptoms, systemic treatment such as cyclosporine and methotrexate (MTX) may be used. For patients with concomitant joint symptoms and those who have not sufficiently responded to conventional systemic treatment, biologics targeting such as tumor necrosis factor (TNF)-α, IL-23 and IL-17 may be prescribed. Cyclosporine and MTX, which form the core of the systemic treatment, exert their actions more rapidly and effectively compared with the topical drugs and can induce remission in many patients.[10] However, these drugs raise many safety concerns: long-term treatment with cyclosporine may cause nephropathy or increase the blood pressure, and MTX may lead to myelosuppression and a wide variety of other side effects. Biologics can achieve complete remission in some patients, making a massive contribution to the advancement in treatment of psoriasis. However, biologics involve many issues that have to be resolved: (1) approximately 30% of the patients do not respond to therapy (2) increased risks for infections and cancer development (3) financial burden is high and (4) the lack of availability of long-term safety data for these compounds.[11] Additionally, it is known that psoriasis significantly impacts the QOL of the patients affected and there is not always a direct correlation between the severity grading of the disease (which is significantly related to the amount of body area covered by the rash) and its impact on the QOL (e.g., if the rash is limited to the face, the severity may be assessed as mild, although the QOL is significantly impaired). Nonetheless, highly efficacious therapeutic options, such as biologics may not be selected in such cases, therefore this issue is not being addressed with the current therapeutic options.

Based on these reasons, next generation of therapeutic drugs for psoriasis are expected to be cost-effective, highly efficacious and safe oral drugs that can induce remission rapidly and achieve

complete remission with high probability. Unlike existing drugs for systemic treatment that are indicated only for severe cases, the cost, as well as the safety profile of the new generation therapeutics must allow prescribing those to any patient regardless of the severity of the disease.

1.1.3 Retinoid-related Orphan Receptor γ (RORγ)

Retinoid-related orphan receptor γ is a nuclear receptor, discovered in 1994[12], but its functions remained unclear for many years. In 2006, it was reported that RORγ is specifically expressed in Th17 cells and that it plays a crucial role in the differentiation of naive T cells into Th17 cells as well as in the activation of Th17 cells.[13] Since then, RORγ has drawn attention as a target molecule for diseases involving Th17 cells. RORγ binds to the ROR binding element following nuclear translocation and enhances the transcriptional activities of target genes such as IL-17 and IL-23 receptors. The molecule is thus considered to be a master regulator playing a central role in the functional regulation of Th17 cells. The biologics targeting IL-17 and IL-23 are currently indicated for some autoimmune diseases in clinical settings. IL-17 is produced by Th17 cells, functions of which are regulated by RORγ and IL-23 plays an important role in the proliferation and maintenance of Th17 cells. These facts suggest that RORγ, a master regulator of Th17 cells, can play an important role in the pathogenesis and exacerbation of various autoimmune diseases.

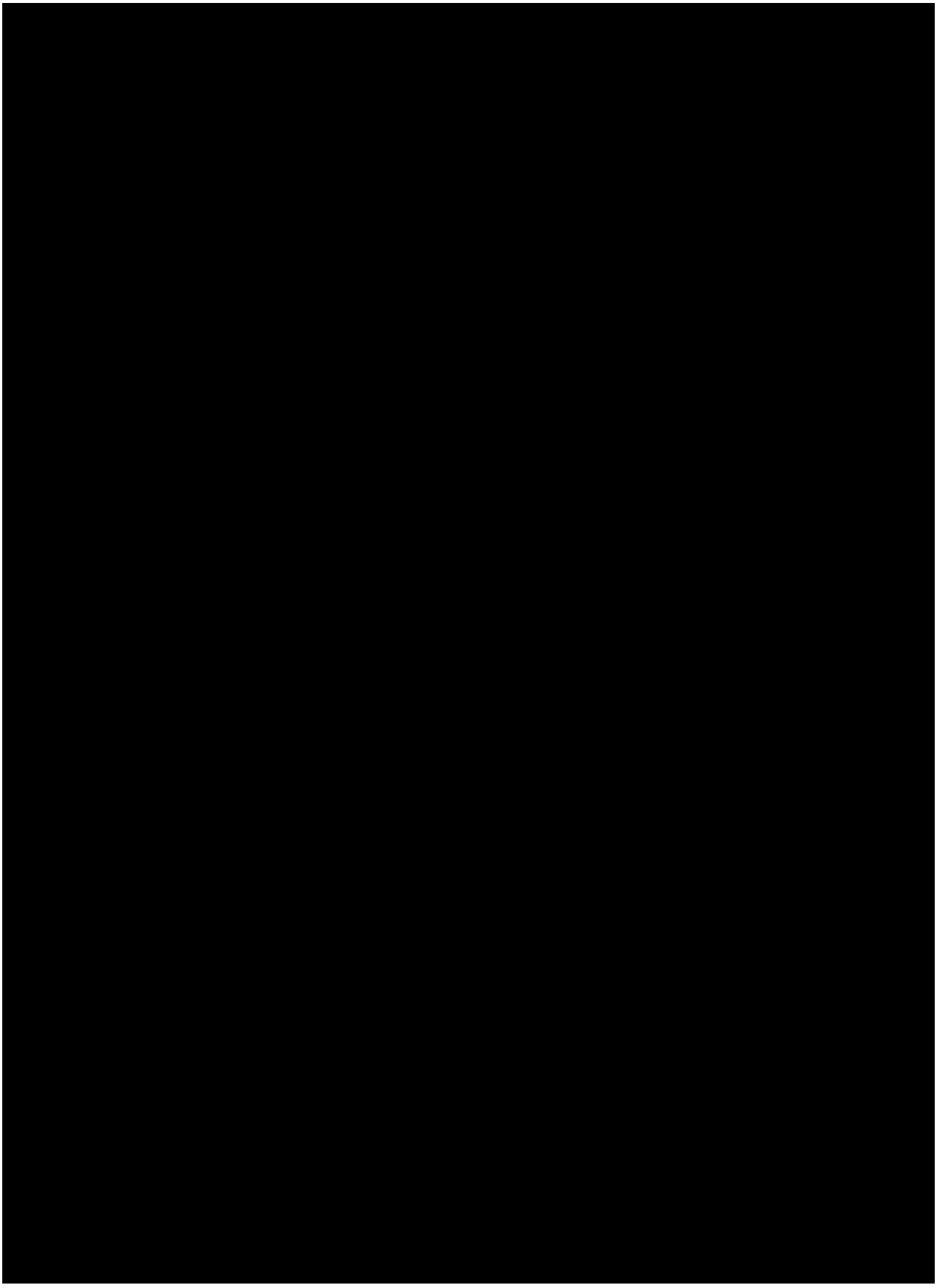
1.2 JTE-451

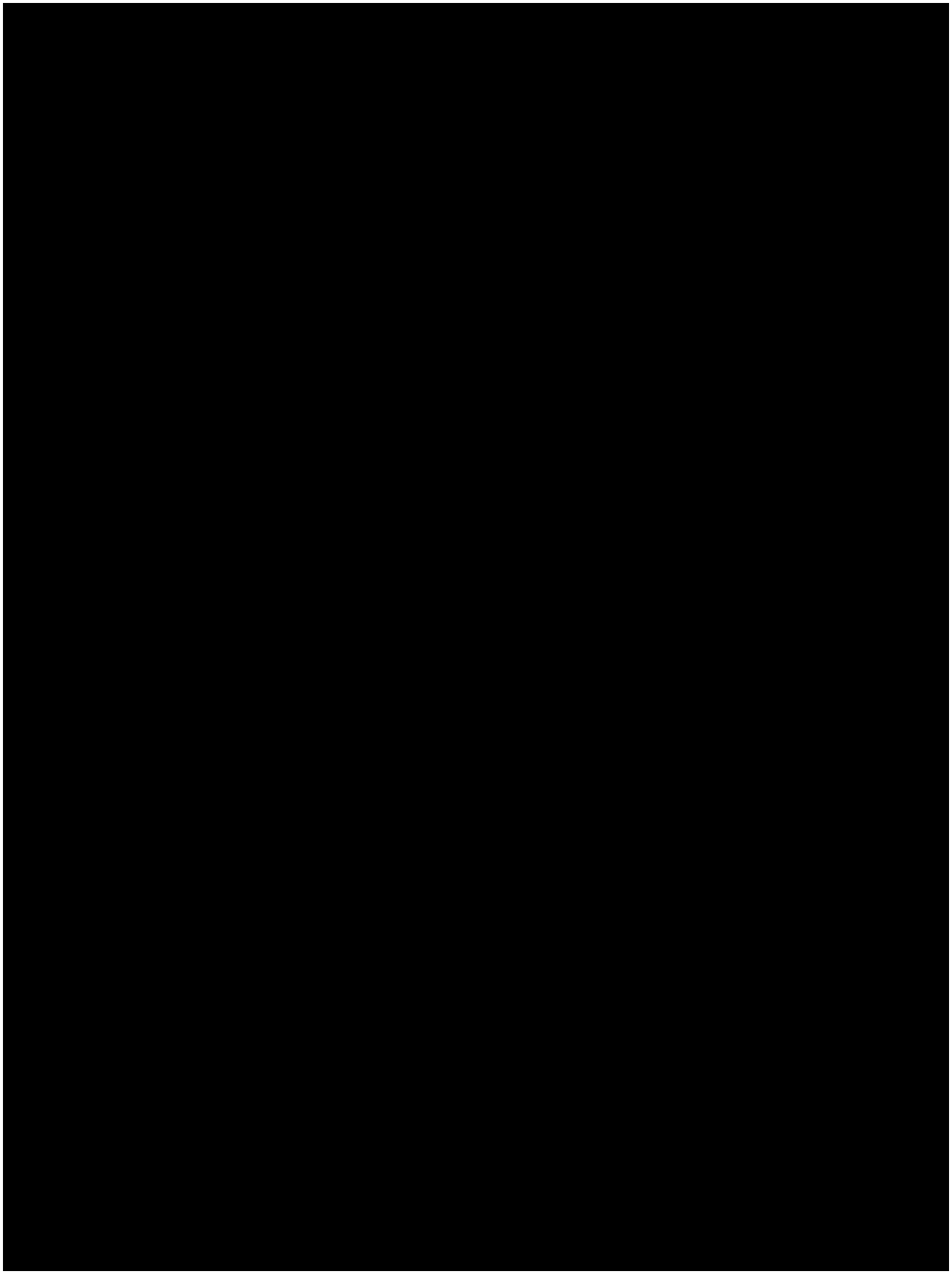
[redacted]

A brief summary of the nonclinical and clinical findings is included below. Additional details are described in the JTE-451 Investigator's Brochure (IB).

1.2.1 Nonclinical Information

[redacted]

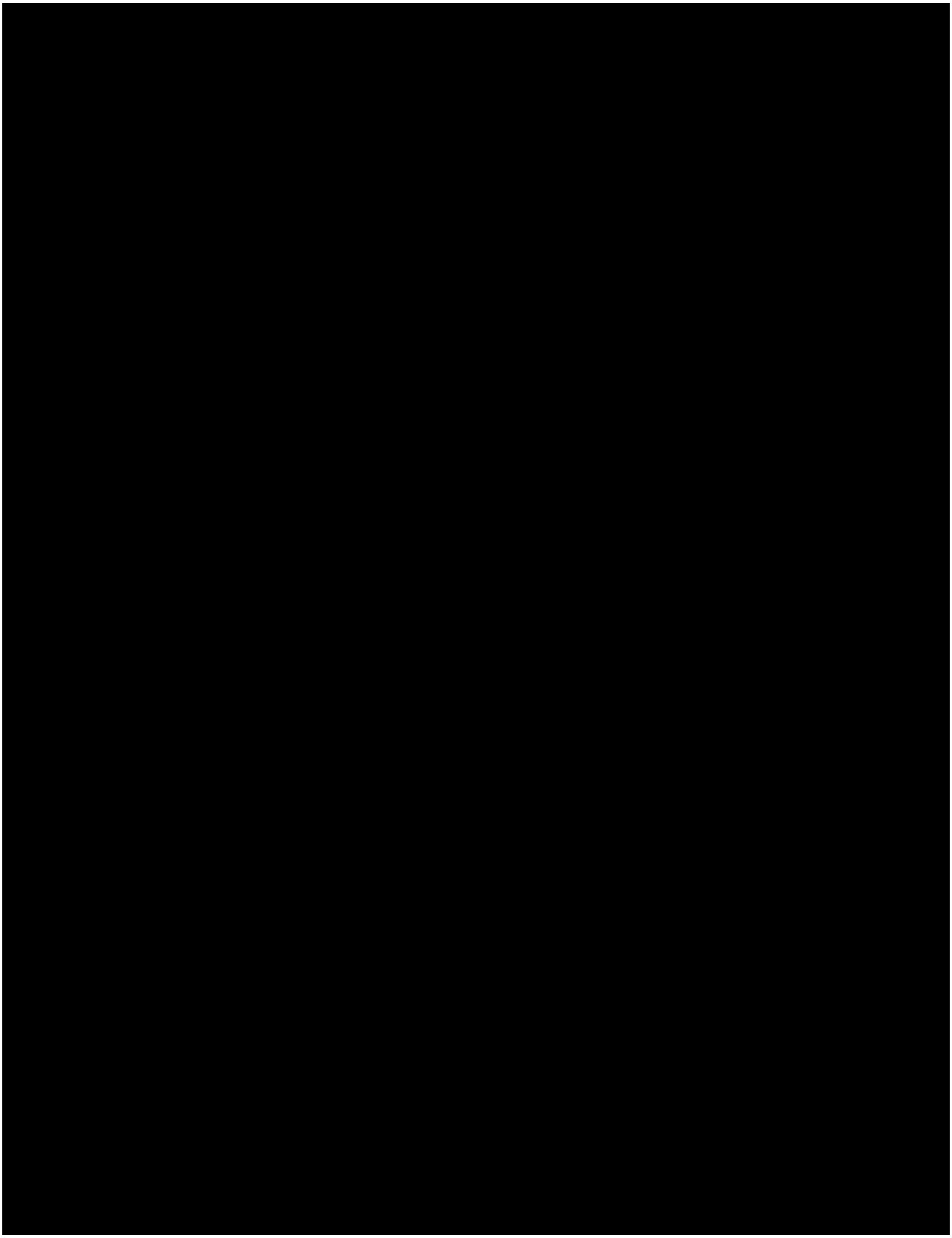




[redacted]

1.2.2 Clinical Information

[redacted]



1.3 Justification of Study Population and Dose Selection

1.3.1 Justification for Study Population

Subjects with moderate to severe plaque psoriasis, based on several psoriasis severity criteria (i.e., psoriasis area and severity index [PASI], sPGA and body surface area [BSA] described in Section 3.3.1) will be enrolled in this study. [redacted]

From a safety perspective, study restrictions will be implemented based on the [redacted] nonclinical and clinical data available to date. These include restrictions aiming to minimize the risk to the participating subjects, to minimize the confounding factors in the assessment process and to monitor and adequately manage any safety-related findings. [redacted] Other general safety-related restrictions such as cardiovascular-system-related, hepatic and renal function-related restrictions, as well as the known safety signals associated with other compounds with similar MOA have been implemented to monitor and adequately manage safety-related findings.

1.3.2 Justification for Study Design

A parallel group, placebo-controlled design will be employed in this study to evaluate the effect of JTE-451 on the efficacy and safety of JTE-451 compared to placebo in subjects with plaque psoriasis. Briefly, upon completion of all protocol-mandated screening procedures, qualified subjects will be randomized at Visit 2 in a 1:1:1 ratio to one of the following three parallel dose groups: JTE-451 200 mg BID (400 mg/day), JTE-451 400 mg BID (800 mg/day) or placebo BID (approximately 50 subjects to be randomized per group) and will receive the double-blind treatment for 16 weeks followed by a 4-week Follow-up Period. To minimize potential confounders in efficacy responses, 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). No clinically meaningful food effect on the PK of JTE-451 was shown in the single ascending dose study [redacted] thus, study drug will be administered regardless of meals. Based on the PK charac eristics of the compound, the protocol requires the study drug administration twice a day, at approximately 12-hour intervals. The duration of the double-blind treatment period is sufficient to obtain the proof-of-efficacy for JTE-451 in subjects with plaque psoriasis. The duration of the Follow-up Period is set to approximately 4 weeks; standard duration for similar outpatient studies administered an

investigational product. Based on the PK characteristics of JTE-451, this period is considered conservative, as JTE-451 clears the human body within approximately one day after the last dose.

The efficacy parameters assessed in this study are consistent with the standards in the industry in similar psoriasis trials (e.g., PASI, sPGA, BSA). [redacted]. To minimize the chances of errors, all calculations of derived parameters will be done by the Sponsor based on the appropriate core data points collected and documented by the Investigators.

With respect to study entry restrictions, [redacted] screening procedures and exclusion criteria to mitigate and minimize the risk of infections, including tuberculosis and viral infections have been included to ensure the safety of subjects. To minimize the risks to the subjects and to facilitate further characterization of the safety profile of JTE-451, standard safety evaluations, such as AE collection, physical examination, vital sign, laboratory (including biochemistry, hematology, coagulation and urinalysis) and ECG assessments are included in the study as part of ongoing safety monitoring activities. Data for these parameters will be collected throughout the study and will be evaluated on an ongoing basis.

1.3.3 Justification for Dose Selection

Selection of JTE-451 doses in this study (200 mg BID and 400 mg BID) is based on the collective data from nonclinical studies and Phase 1 clinical studies in healthy subjects [redacted] and in subjects with plaque psoriasis [redacted]

[redacted]

2 Study 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 Investigational Plan

3.1 Number of Sites and Subjects

Multiple sites will be employed to ensure screening of sufficient number of subjects to randomize (in a 1:1:1 ratio) approximately 150 subjects (approximately 50 subjects per treatment group).

3.2 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 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

The end of the study is defined as the date of the last subject last visit.

3.3 Selection of Study Population

Written informed consent must be obtained prior to performing any study-related procedures including washout of previous medications to participate in the study. A copy of the informed consent will be provided to the subject.

3.3.1 Inclusion Criteria

To qualify for the study, the subject must satisfy the following criteria:

1. Male or female, ≥18 and ≤70 years of age at the time of Visit 1 (Screening Visit);
2. Have a history of moderate to severe plaque psoriasis for at least 6 months prior to Visit 1;
3. Subjects with moderate to severe plaque psoriasis covering ≥10% BSA, with a PASI ≥12 and sPGA score ≥3 at Visit 1 and Visit 2 (baseline);
4. Body Mass Index (BMI) ≤40 kg/m^2 at Visit 1;
5. Female subjects may participate if they meet one of the following criteria:
   - Surgically sterile (e.g., hysterectomy or bilateral oophorectomy),
   - Post-menopausal;
     - Female subjects with a documented history of lack of menses for ≥12 consecutive months prior to Visit 1 with no other reversible medical etiology,
     - Female subjects with a history of lack of menses but onset <12 months prior to Visit 1 and a serum follicle-stimulating hormone (FSH) >40 mIU/mL, or
   - If of childbearing potential (all female subjects other than above), with a negative pregnancy test at Visit 1 and Visit 2, and if participates in heterosexual intercourse, agrees to be compliant with consistent and correct use of acceptable methods of contraception as described below for the duration of the study and for at least 30 days after the last dose of study drug. Acceptable methods of birth control for this study are:

     a) <u>at least one highly effective contraceptive method</u>, which includes intrauterine devices, tubal ligation, bilateral tubal occlusion, partner sterilization (with appropriate post-vasectomy documentation of the absence of sperm in the ejaculate), intrauterine hormone-releasing systems, or

     b) <u>at least two effective methods</u>, which include male condom, female condom, cervical cap, diaphragm or contraceptive sponge; all with spermicide

     Notes:
     - Female subjects of childbearing potential must agree to undergo urine pregnancy testing from Visit 2 until Visit 8.
     - Hormonal methods (except for intrauterine hormone-releasing systems) are <u>not</u> considered an acceptable method of contraception for the study.
     - Concomitant use of a female condom and a male condom is not considered an acceptable method of contraception for the study.

   Note: Female subjects must not donate eggs for the duration of the study and for at least 12 weeks after the last dose of study drug.
6. Male subjects must agree to practice abstinence from heterosexual intercourse, use a barrier contraceptive method with spermicide if his partner is of childbearing potential for the duration

of the study and for at least 30 days after the last dose of study drug or be sterilized (with appropriate post-vasectomy documentation of the absence of sperm in the ejaculate):

- Male subjects should be informed about the risks involved if pregnancy in female partners occurs while he is taking an investigative product and for at least 30 days after the last dose of study drug.
- Counseling on appropriate contraception methods for their female partners should be given as follows: female partners of male subjects randomized in this study must be surgically sterile or post-menopausal, or in case of female partner of childbearing potential, they must agree to use at least one effective method of birth control (in addition to the method utilized by the male subject) for the duration of the study and for at least 30 days after the last dose of study drug. Please see inclusion criterion # 5 a) and # 5 b) for a list of acceptable forms of birth control for the study (hormonal methods will be allowed as one of two effective method for female partners of male subjects);
- Male subjects must not donate sperm for the duration of the study and within 12 weeks of the last dose of study drug.

7. Able and willing to give written informed consent.

3.3.2 Exclusion Criteria

The following criteria will exclude a subject from participating in the study:

1. [redacted]
2. [redacted]
3. Presence of erythrodermic psoriasis, pustular psoriasis, guttate psoriasis, medication-induced psoriasis or other skin conditions (e.g., clinically-significant eczema or severe acne) that could interfere with study evaluations at Visit 1;
   [redacted]
4. History or presence of any itch due to underlying conditions other than plaque psoriasis which cause or influence pruritus of the skin (e.g., drug-induced pruritus, significant other systemic diseases with itch) within 12 months prior to Visit 1;
5. Does not meet all study restrictions, including previous/concomitant medication restriction criteria, as described in Section 3.5.5.1;
6. Leucocyte count of <3.0 X 10^9/L (<3000/mm^3), absolute neutrophil count of <1.5 X 10^9/L (<1500/mm^3) or absolute lymphocyte count <0.8 X 10^9/L (<800/mm^3) at Visit 1;
7. Hemoglobin <11 g/dL or platelet count <100,000/mm^3 at Visit 1;
8. ALT >2.0 X the upper limit of normal (ULN) or AST >2.0 X the ULN at Visit 1;
9. Serum creatinine >1.5 X the ULN at Visit 1;

10. Hemoglobin A1c (HbA1c) >8.5% at Visit 1;

11. Positive viral serology at Visit 1 for:
    - HIV: positive HIV antibodies (Ab),
    - HBV: positive hepatitis B surface antigen (HBsAg),
    - HCV: positive HCV Ab;

    Note: Subjects who test negative for HBsAg and test positive for hepatic B core (HBc) Ab will not be excluded from the study.

12. Positive drug of abuse test results at Visit 1, unless results are due to a medically relevant reason;
    Note: Subjects who test positive for only cannabinoids or opiates, and have had no evidence of substance dependence or substance abuse problem that could interfere with study evaluations may participate in the study according to the Investigator's judgment, if all other study restrictions required by the protocol are met.

13. History or presence of substance abuse, drug addiction or alcoholism within 1 year prior to Visit 1;
    Note: Alcoholism is defined as the consumption of more than 28 units of alcohol a week (an alcohol unit is defined as 300 mL of beer, 100 mL of wine, or 25 mL of hard liquor).

14. Positive QuantiFERON®-TB Gold Plus test, positive chest radiographic findings for tubercle bacillus (TB) or any other evidence of active or untreated latent TB;
    - The QuantiFERON®-TB Gold Plus test should not be performed within 4 weeks from the date of a live vaccination;
    - If QuantiFERON®-TB Gold Plus test is indeterminate, a retest is allowed if results can be obtained within the timeframe allowed between Visit 1 and Visit 2. If the retest is also indeterminate, the subject will be excluded from the study;
    - Subjects with positive QuantiFERON®-TB Gold Plus test and a history of treated latent TB who have documented evidence of completed adequate treatment at least 12 months prior to Visit 2 may participate in the study, if all other study restrictions required by the protocol are met;
    - Subjects who have had household contact with a person with active TB are excluded, unless appropriate and documented prophylactic treatment for TB, as recommended by local guidelines, was completed at least 30 days prior to Visit 2.

15. History of live vaccination within 4 weeks prior to Visit 2 or have a live vaccination planned during the study or within 6 weeks after the last dose of study drug;

16. Have donated or received blood or blood products within 4 weeks prior to Visit 1;

17. History of a clinically-significant infection (e.g., infection that required oral antimicrobial or antiviral therapy) within 4 weeks prior to Visit 2;
    Note: Subjects with treated upper respiratory tract infection or urinary tract infection will be permitted if the infection resolved prior to Visit 2.

18. History of opportunistic infections or infection requiring hospitalization or parenteral antibiotic, antiviral, antifungal or antiparasitic therapy within 3 months prior to Visit 2 or history of recurrent infections or conditions predisposing subject to chronic infections (e.g., bronchiectasis, chronic osteomyelitis);

19. History or presence of any lymphoproliferative disorder (e.g., Epstein Barr Virus-related lymphoproliferative disorder, lymphoma, leukemia, multiple myeloma) or signs and symptoms suggestive of current lymphatic disease, such as Hodgkin's or Non-Hodgkin's lymphoma;
20. History or presence of malignancies with the exception of adequately treated or excised non-metastatic basal cell or squamous cell carcinoma of the skin or cervical carcinoma in situ more than 6 months prior to Visit 1;
21. History of organ transplantation;
22. History of decompensated heart failure, fluid overload, myocardial infarction, uncontrolled arterial hypertension or evidence of ischemic heart disease or other serious cardiac disease within 12 months prior to Visit 1;
23. Pregnant or nursing at Visit 1 or Visit 2 or plan to become pregnant or initiate breastfeeding during the study or within 30 days after the last dose of study drug;
24. History of clinically-significant hypersensitivities (e.g., multiple drug allergies or severe allergic reactions, including angioedema);
25. History or presence of significant uncontrolled depressive disorder (e.g., manic-depressive disorders, treatment-resistant major depression), history of suicidal ideation or behavior or presence of risk for suicide by Investigator’s judgment;
26. History or presence of any other clinically relevant medical condition or disease or laboratory abnormality including hepatic, renal, gastroenterologic, respiratory, cardiovascular, endocrinologic, neurologic (e.g., epilepsy), psychiatric (e.g., schizophrenia), immunologic (e.g., immunocompromised subjects or subjects with autoimmune conditions other than psoriasis, such as rheumatoid arthritis, systemic lupus erythematosus, type I diabetes), metabolic bone (e.g., osteoporosis) or hematologic (e.g., sickle cell) disease that, in the opinion of the Investigator, may place the subject at unacceptable risk for study participation and may prevent the subject from completing the study (e.g., low life expectancy, high risk of non-compliance) or would interfere with the study conduct or data interpretation, according to the Investigator’s judgment;
27. Cannot communicate reliably with the Investigator (including inability to complete the self-assessment questionnaire) or are unlikely to cooperate with the requirements of the study.

3.4 Removal of Subjects from the Study

A subject will not participate further in the study under the following conditions:

1. Death
2. Adverse Event: a clinical or biological adverse event or intercurrent condition(s), requiring study drug discontinuation, whether or not related to the study drug.

   If grade 3 findings (defined as severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living such as bathing, dressing, undressing, feeding self, using the toilet, taking medication, but not bedridden), according to the common terminology criteria for adverse events (CTCAE)[14], are noted in a subject, he/she must be promptly evaluated by the Investigator (e.g., repeat tests, evaluation of the baseline parameters, concomitant medications) for potential withdrawal from the study. Every effort should be made to discuss this with the Medical Monitor prior to final decision, unless not feasible, based on safety considerations.
3. Withdrawal by Subject: subjects have the right to withdraw from the study at any time. However, if a subject withdraws consent because of experiencing an adverse event, the reason for subject termination should be documented as an adverse event.
4. Non-compliance with Study Drug (i.e., <80% or >120% compliance at two consecutive study visits; exceptions on a case-by-case basis may be permitted if approved by Sponsor or designee).
   Note: Compliance will be evaluated at every study visit during the Treatment Period. If compliance of <80% or >120% is identified at a study visit, the Investigator or designee should counsel the subject and ensure steps are taken to improve compliance.
5. Inclusion/Exclusion Criteria Not Met: If a subject who did not meet one or more of the study inclusion or exclusion criteria is identified after randomization, the Investigator, Medical Monitor and Sponsor will review that subject profile, including the medical history, prior and concomitant medications, physical examination, vital signs, 12-lead ECGs and clinical laboratory test results. An exception may be permitted on a case-by-case basis if the subject was randomized into the study due to a minor error determined to be of no clinical and/or safety risk to the subject.
6. Protocol Violation: the subject is non-compliant with regard to this protocol (other than the withdrawal criteria 4 and 5 listed above), as determined by Sponsor, Medical Monitor or the Investigator on a case-by-case basis.
7. Lost to Follow-up: the subject does not come for a scheduled visit and site staff makes at least 3 attempts, including a formal letter, to contact the subject over 4 weeks from a scheduled visit with no success.
8. Study Terminated by Sponsor: the Sponsor may suspend or terminate the study or part of the study at any time for any reason.
9. Pregnancy
10. Investigator Decision: the Investigator decides a subject should be discontinued for any reasons other than listed above (actual reason must be documented by site).
11. Other: actual reason must be documented by site.

Subjects who are removed from the study or withdraw consent to participate in the study after receiving at least one dose of study drug will be requested to complete an Early Termination Visit at which time the subject will undergo all the procedures described for Visit 7. Every effort should be made to perform the Visit 7 procedures as soon as possible after the last dose of study drug and the decision of discontinuation is made and prior to any changes made in the subject's anti-psoriasis therapy. Additionally, at approximately 4 weeks after study drug discontinuation, subject should return for a Follow-up Visit, where all procedures described for Visit 8 should be performed.

3.5 Study Procedures

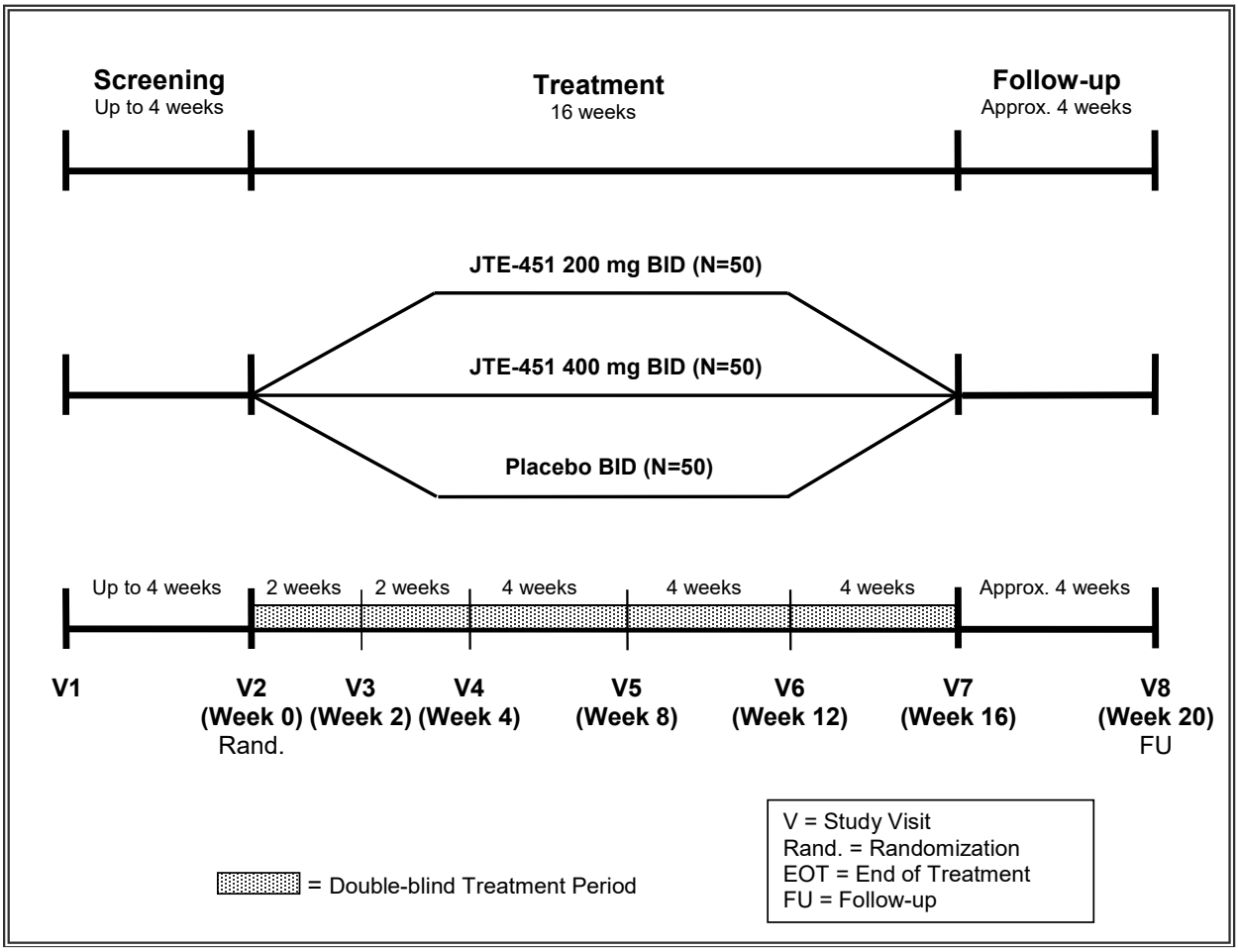


Figure 1. Study Schema

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 Plus Test	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]								
[redacted]								
[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]

[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.

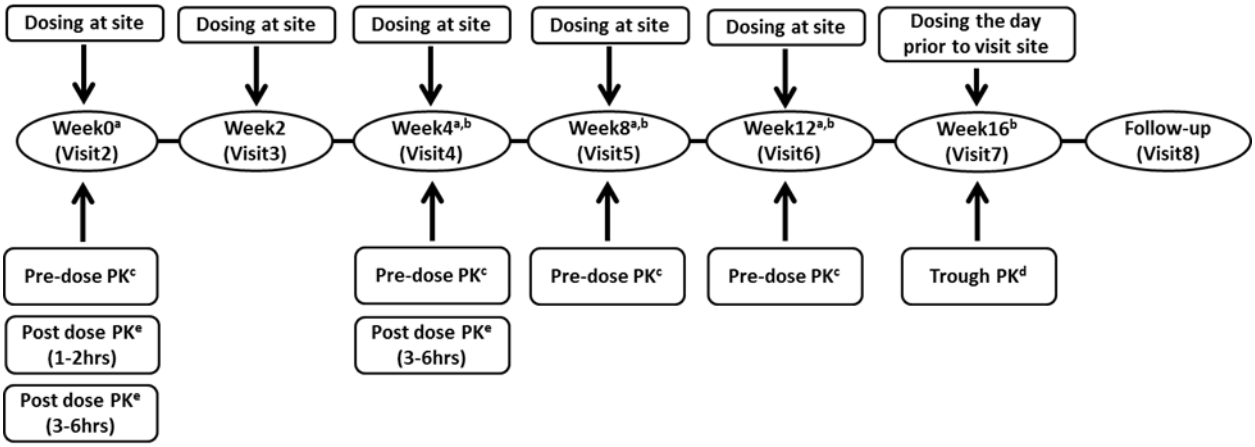


Figure 2. Dosing and Pharmacokinetic Sample Collection Time

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.

3.5.1 Informed Consent

Written informed consent must be obtained prior to performing any study-related procedures including washout of previous medications to participate in the study. A copy of the informed consent will be provided to the subject. Washout of previous medications to participate in the study will be started once the subject signs the informed consent regardless of the 28-day window of the Screening Period.

3.5.2 Screening Period

Day -28 (Visit 1) to Day 1 (Visit 2)

Following signing of the informed consent for the study, screening procedures to confirm eligibility may be performed across multiple days, as needed, during the Screening Period. If a subject arrives for a visit not having fasted (fasted at least 10 hours prior to blood and urine sample collection), all study procedures except the blood/urine collection activities may be performed; the blood/urine collection will be rescheduled on a subsequent day within the visit window and the subject will be reminded to fast at least 10 hours.

Please refer to Table 1 for the list of screening procedures to be performed in the study. A one-time repeat of the screening laboratory (except for drugs of abuse and alcohol, and viral serology), vital sign and ECG assessments is permitted, if considered appropriate by the Investigator, except stated otherwise (e.g., up to three-time repeat of blood pressure measurements at the Screening Visit is permitted). The repeat test result(s) will be utilized for subject qualification purposes. If the repeat test results are outside the protocol-required range, the subject should be excluded from the study.

Re-screening of subjects may be permitted on a case-by-case basis, pending discussion and approval by the Medical Monitor.

3.5.3 Double-blind Treatment Period

Day 1 (Visit 2) to Day 112±4 (Visit 7/Week 16)

Please refer to Table 1 for the by-visit list of procedures to be performed in the study during this period.

All visits during the Double-blind Treatment Period, including Visit 2 (Randomization Visit), should be performed under fasted conditions (fasted at least 10 hours prior to blood and urine sample collection). If a subject arrives for a visit not fasted, then all study procedures except the blood/urine collection activities may be performed; the blood/urine collection will be rescheduled on a subsequent day within the visit window and the subject will be reminded to fast at least 10 hours. Exception to this would be Visit 2, at which all study procedures should be completed within the same session, therefore, if the subject is not fasted at Visit 2, the full visit should be rescheduled. Every effort should be made to collect blood/urine samples at similar times throughout the study.

All visits should be performed within the windows specified in Table 1. Every attempt should be made to have the subject attend each visit as scheduled. The site is encouraged to make a reminder phone call to the subject approximately a day or two 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.

Subjects will be administered the first dose of study drug at the site, upon completion of all pre-dosing procedures and randomization at Visit 2; subsequently, they will be instructed to self-administer study drug BID, at approximately 12-hour intervals, regardless of meals. However, subjects should not take study drug on the day of a study visit until after all study procedures have been completed (except for post-dose PK samples collection as shown in Figure 2). On study visit days, subjects should take their scheduled study treatment 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). If the subject inadvertently took study drug on the day of the study visit, prior to all required procedures, he/she may complete the visit and the actual date and time of the last dose prior to the PK blood samples collection will be accurately recorded.

Exact date and time of the last two doses prior to the pre-dose/trough PK sample collection at Visits 4 through 7 and the dosing time at the site should be documented at each visit during the Treatment Period (i.e., Visits 2 through 6).

Study drug will not be administered and all remaining study drug will be collected from the subjects at Visit 7.

If a subject discontinues the study prematurely after receiving at least one dose of study drug, an Early Termination Visit should be completed at which all procedures listed for the Visit 7 should be performed, if possible, prior to any changes made in the subject's anti-psoriasis therapy.

3.5.4 Follow-up Period

Day 112±4 (Visit 7/Week 16) to Day 140±2 (Visit 8/Week 20)

The Follow-up Visit will occur approximately 4 weeks after the last dose of study drug. Subjects should arrive under fasted conditions (i.e., overnight fast, at least 10 hours prior to blood and urine sample collection). Please refer to Table 1 for the list of follow-up procedures to be performed.

For subjects who discontinue the study prematurely after receiving at least one dose of study drug, follow-up procedures, as described for Visit 8 should be performed approximately 4 weeks after the last dose of study drug.

3.5.5 Study Restrictions

3.5.5.1 Previous and Concomitant Medication Restrictions

3.5.5.1.1 Prohibited Psoriasis Therapy and Immunomodulation Therapy

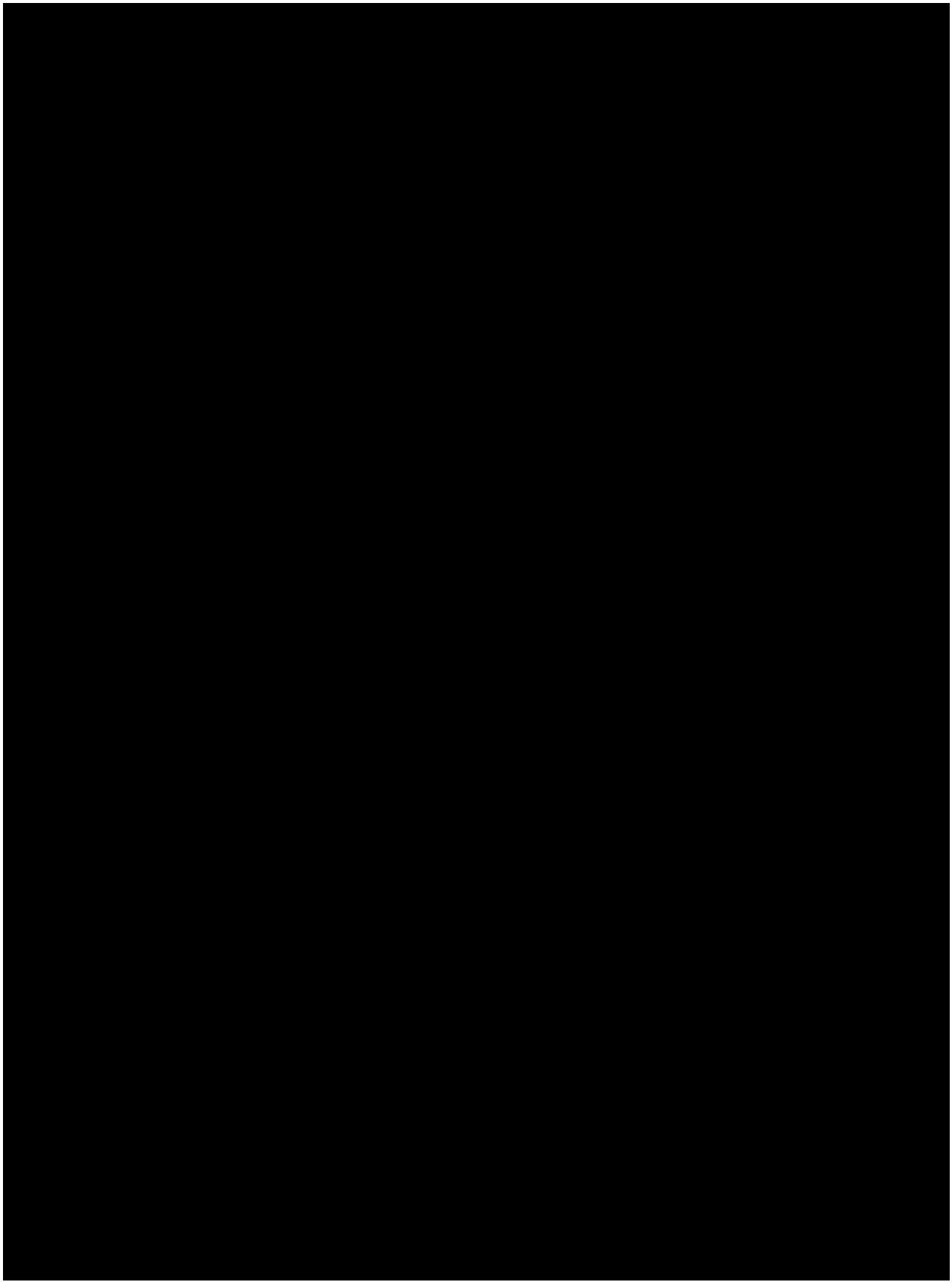
Use of the following therapies will NOT be allowed during the Prohibited Period as described in Table 2.

Table 2. Psoriasis Therapy and Immunomodulation Therapy Restrictions

Prohibited Period	Medication(s)
24 weeks prior to Visit 2 till after the last study visit (Visit 8)	• IL-12/IL-23p40 inhibitor (e.g., ustekinumab) • IL-23p19 inhibitor (e.g., guselkumab, mirikizumab, risankizumab, tildrakizumab)
12 weeks (or 5 times the PK half-life, whichever is longer) prior to Visit 2 till after the last study visit (Visit 8)	• Biologic agents other than above (including marketed or investigational) • Investigational systemic therapies
28 days or **5 times the PK half-life** (whichever is longer) prior to Visit 2 till after the last study visit (Visit 8)	• Acitretin • Methotrexate • Cyclosporine • Apremilast • Oral/parental corticosteroids (including intramuscular or intraarticular administration) • Tofacitinib • Fumaric acid ester • Other immunomodulating systemic treatment • Psoralen plus ultraviolet A (PUVA) therapy • Ultraviolet A (UVA) therapy • Ultraviolet B (UVB) therapy • Investigational topical therapies
14 days prior to Visit 2 till after the last study visit (Visit 8)	• Topical corticosteroids • Topical vitamin A or D analog preparations • Anthralin • Topical calcineurin inhibitors (e.g., cyclosporine)

Use of one (1) topical non-medical moisturizer (e.g., Cetaphil®) will be allowed during the study, however it will be prohibited within 12 hours prior to the study visit.

Note: If a subject develops significant clinical exacerbation of their psoriasis at any time during the entire duration of the study, study drug may be withdrawn and the subject will be treated clinically per existing standard of care.



3.5.5.1.3 Permitted Medications to be used with Caution

Permitted medications (Appendix 1) are based on nonclinical and clinical drug-drug interaction data with JTE-451. [redacted]

3.5.5.1.4 General Medication-related Protocol Instructions:

- Generally, changes in medication dose/route of administration or initiation of new medications during the conduct of the study is not recommended unless such actions are considered medically necessary;
- All medications taken by the subject, including over-the-counter, herbal, traditional, ayurvedic compounds (whether permitted or excluded by the protocol) must be documented in the case report form (CRF), as described in Section 3.5.6.10;
- Contact the Medical Monitor with questions regarding prior/concomitant therapy.

3.5.5.2 Dietary Restrictions

Grapefruit juice and grapefruit are not permitted for at least 3 days prior to Visit 2 and during the Treatment Period.

3.5.5.3 UV-Related Restrictions

Every effort should be made to minimize/eliminate unnecessary sun exposure during the study. If sun exposure is unavoidable, sunscreen with a sun protection factor (SPF) of minimum 30 should be utilized. Intentional tanning is prohibited throughout the study.

3.5.5.4 General Restrictions

- Following enrollment in the study, subjects should continue all non-pharmacological therapies, such as physical therapy, as indicated and deemed appropriate for his/her physical condition.
- Subjects should not donate blood or receive any blood or blood products within 4 weeks prior to Visit 1 and throughout the study duration.
- Routine household contact with children or others vaccinated with live vaccine components (e.g., varicella, or attenuated typhoid fever, oral polio, attenuated rotavirus or inhaled flu vaccines) should be avoided during the study and for 6 weeks after the last dose of study drug.
- Travel to countries with known high prevalence of tuberculosis should be avoided from the time of signing the informed consent through the Follow-up Visit.

3.5.6 Procedure Definitions

3.5.6.1 Static Physician's Global Assessment (sPGA)

The sPGA will be performed on psoriatic lesions overall by the Investigator according to the schedule summarized in Table 1.

The sPGA is used to determine the severity of subject's psoriatic lesion at a given time point. Every effort should be made to perform the sPGA assessments by the same evaluator throughout the study. The psoriatic lesion will be graded for induration, erythema and scaling based on the scales below. The sum of the 3 scales will be divided by 3 to obtain 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 ≤1.49, 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.

3.5.6.2 Psoriasis Body Surface Area (BSA) and Psoriasis Area and Severity Index (PASI)

The BSA assessment will be performed according to the schedule summarized in Table 1.

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 (see below for PASI assessment). 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.

Psoriasis area and severity index (PASI), a quantitative rating score to assess the severity of psoriatic lesions based on the area coverage and plaque appearance will be performed according to the schedule summarized in Table 1.

Every effort should be made to perform the BSA and PASI assessments by the same evaluator throughout the study.

The PASI score will be derived as indicated in Table 8.

The head, trunk, upper limbs and lower limbs are assessed separately for erythema, thickening (plaque elevation, induration) and scaling (desquamation). The average degree of severity of each sign in each of the four body regions is assigned a score of 0 to 4. The area covered by lesions on each body region is estimated as a percentage of the total area of that particular body region. Listed below are further practical details to help with the assessment:

1. The neck is assessed as part of the head.
2. The axillae and groin are assessed as part of the trunk.
3. The buttocks are assessed as part of the lower limbs.
4. When scoring the severity of erythema, scales should not be removed.

Because the head and neck, upper limbs, trunk and lower limbs correspond to approximately 10%, 20%, 30% and 40% of the body surface area, respectively, the PASI score is calculated using the following formula:

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

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.

Table 8. 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.

3.5.6.3 Skindex-16

Subjects will complete Skindex-16 questionnaire according to the schedule summarized in Table 1.

Skindex-16 is a 16-item, skin-related QOL questionnaire (see Appendix 2) and has 3 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]). If more than 25% of the responses missing, the scale is considered missing. An item with multiple answers is considered missing.

3.5.6.5 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. Site will dispense the e-diary device at Screening Visit and train the subject on how to use the device.

[redacted]

3.5.6.7 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.

3.5.6.8 Height and Weight Measurements and Body Mass Index Calculation

The height and weight measurements will be performed according to the schedule summarized in Table 1. Subjects will remove their shoes and wear light clothing to be consistent between measurements of height and/or weight. The BMI will be calculated at Visit 1 using the following equation: (weight (kg)/[height $(m)^2$]), where the weight in kilograms will be documented to one decimal place and the height in centimeters will be rounded to the nearest whole number.

3.5.6.9 Medical History

A complete medical history will be performed at Visit 1 and will include evaluations for past or present conditions. [redacted]

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

3.5.6.10 Prior and Concomitant Medications

Information pertaining to all medications use (including prescription, over-the-counter, supplements, vitamins and minerals) will be collected for the period of at least 30 days prior to Visit 1 and throughout the study.

Information regarding any prior/current psoriasis therapies and/or immunomodulating therapies, as listed in Section 3.5.5.1.1 will be collected according to the schedule summarized in Table 1.

3.5.6.11 Vital Signs

Vital sign assessments including blood pressure, heart rate, respiratory rate and body temperature (°C) will be performed in sitting position according to the schedule summarized in Table 1. Subjects must rest in a sitting position for at least 5 minutes in preparation for blood pressure and heart rate assessments.

3.5.6.12 12-Lead ECG

12-lead ECG recordings and conduction intervals including RR, PR, QRS, QT and Fridericia-corrected QT interval (QT_cF) will be obtained according to the schedule summarized in Table 1. The Investigator or designee will review and assess each individual ECG report and the interpretation of the actual findings, rather than the automatic printout, results on the ECG tracing will be documented. Subjects will lay supine without pillows for at least 5 minutes prior to the 12-lead ECG assessment.

3.5.6.13 Hematology

Blood samples to assess complete blood count including erythrocytes, hematocrit, hemoglobin, platelets, leucocytes and differential (percent and absolute [neutrophil, eosinophil, basophil, lymphocyte, monocyte]) will be obtained under fasted conditions according to the schedule summarized in Table 1.

3.5.6.14 Serum Biochemistry

Blood samples to assess ALP, albumin, ALT, AST, bilirubin, blood urea nitrogen, calcium, carbon dioxide, chloride, creatinine phosphokinase, creatinine, gamma-glutamyl transferase, globulin, glucose, C-reactive protein, lactate dehydrogenase, low-density lipoprotein cholesterol, phosphate, potassium, protein, sodium, total cholesterol, triglyceride, urate will be obtained under fasted conditions according to the schedule summarized in Table 1.

3.5.6.15 Coagulation

Blood samples to assess thromboplastin time (PT) and activated partial thromboplastin time (aPTT) will be obtained as measures of blood coagulation according to the schedule summarized in Table 1. International normalized ratio will also be calculated.

3.5.6.16 Viral Serology

Blood samples to assess HBc antibodies, HBsAg, HCV antibodies and HIV antibodies will be obtained at Visit 1.

3.5.6.17 Drugs of Abuse and Alcohol Screen

Urine samples to assess amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine metabolites, opiates, ethanol, methadone, methylenedioxymethamphetamine and oxycodone will be obtained at Visit 1.

3.5.6.18 Urinalysis

Urine samples to assess bilirubin, occult blood, color, glucose, ketone, leukocyte esterase, nitrite, pH, protein, specific gravity, turbidity and urobilinogen, as well as for a microscopic exam (to be performed only if the macroscopic exam is abnormal), including bacteria, cast, crystals, epithelial cells, mucus threads, erythrocytes, leukocytes and budding yeast will be obtained under fasted conditions according to the schedule summarized in Table 1.

3.5.6.19 Glycosylated Hemoglobin

Blood samples to measure glycosylated hemoglobin (HbA1c) will be obtained at Visit 1.

3.5.6.20 Pregnancy Test

Blood samples from all female subjects will be collected at Visit 1 for a serum pregnancy test to assess human chorionic gonadotropin (βHCG) levels. At Visits 2 through 8, urine pregnancy tests will be performed only for female subjects of childbearing potential.

3.5.6.21 Follicle-stimulating Hormone

Blood samples to assess the menopausal status will be collected at Visit 1 only from female subjects who report a history of for lack of menses but onset within 12 months with no other identified biological/surgical cause.

3.5.6.22 QuantiFERON®-TB Gold Plus Test

The QuantiFERON®-TB Gold Plus test (according to the local standard of care) may be used as tuberculosis screening tools for the study during the Screening Period. Blood samples will be collected, processed and shipped during the Screening Period, according to the laboratory instructions. In case of an indeterminate QuantiFERON®-TB Gold Plus test, the test may be repeated one time if results can be obtained in time prior to Visit 2. If the retest is also indeterminate, subject will not be eligible for the study.

Subjects with positive QuantiFERON®-TB Gold Plus test and a history of treated latent TB who have documented evidence of completed adequate treatment at least 12 months prior to Visit 2 may participate in the study, if all other study restrictions required by the protocol are met.

Subjects who have had household contact with a person with active tuberculosis are excluded, unless appropriate and documented prophylactic treatment for TB, as recommended by local guidelines, was completed at least 30 days prior to Visit 2.

3.5.6.23 Chest Radiography

Chest radiography to include two views (anterior-posterior and lateral) will be obtained during the Screening Period in all subjects. If adequate chest radiography has been performed within 3 months (12 weeks) prior to Visit 1 and documentation (including interpretation of TB status) is available, it will be provided to the Investigator for review and documented in the subject's record. This radiography may be utilized to determine eligibility of the subject. To be considered eligible for the study, the radiography must be negative for active tuberculosis infection; however, the Investigator may decide to exclude the subjects based on clinically-significant chest radiography findings other than tuberculosis (e.g., due to an acute or chronic inflammatory process), according to his/her judgment.

[redacted]

3.5.6.25 Photography

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] according to the schedule presented in Table 1. In all collected photographs, subject identification (e.g., eye, mouth, tattoos) will be blinded. Please refer to the photography manual for detailed instructions regarding collection, processing, storage and transmission of photographs.

3.5.6.26 Blood Samples for Pharmacokinetic Assessments

Blood samples for quantification of JTE-451 in plasma will be obtained according to the schedule summarized in Table 1 and Figure 2.

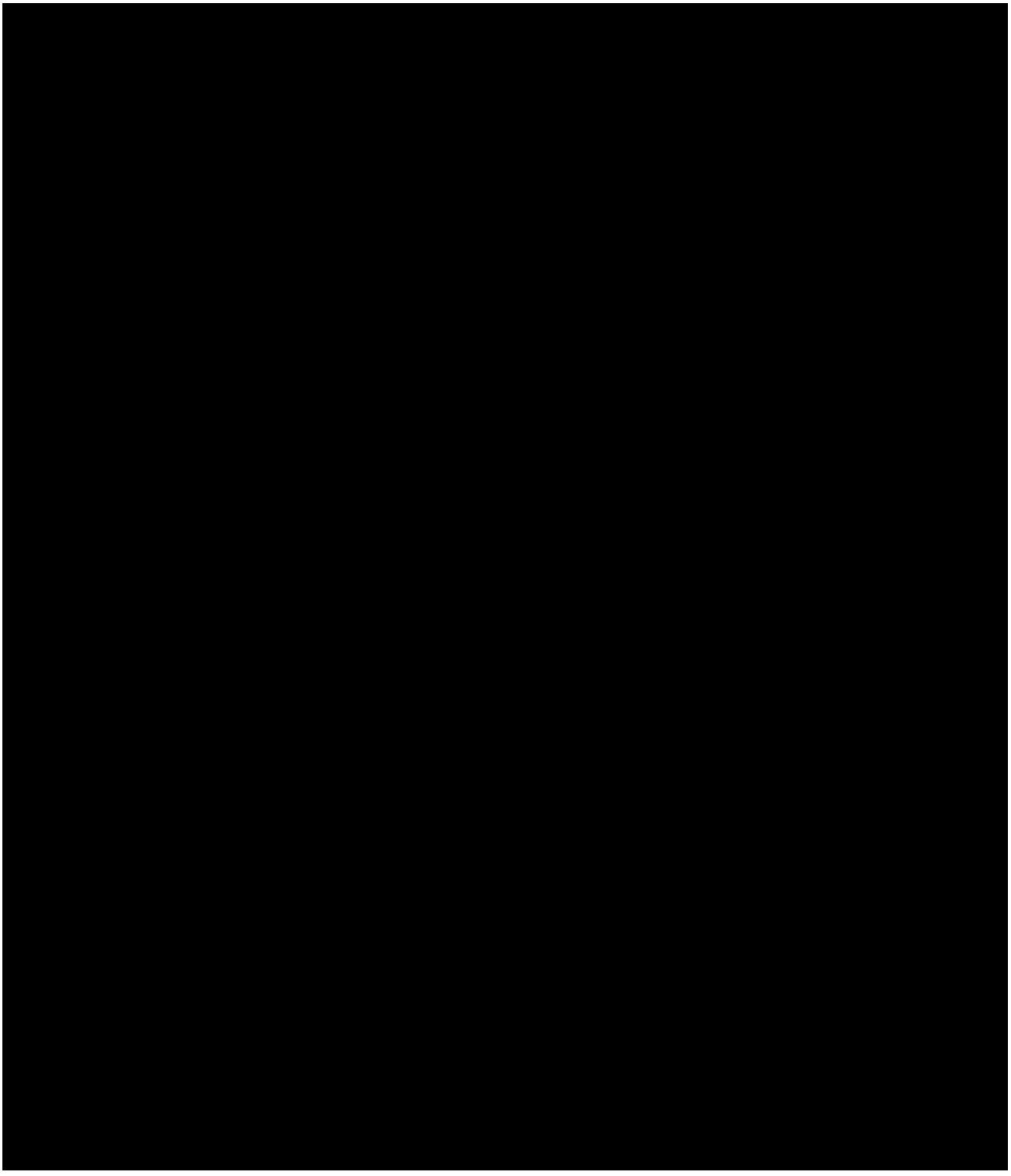
At each study visit during the treatment period (i.e., Visit 2 through Visit 7 [except for Visit 3, when no PK sample collection will be performed]), the actual dose time, as well as the sample collection time will be documented for PK data analysis. Refer to the laboratory manual for specific instructions regarding collection and processing of blood samples for PK assessments.

3.5.6.27 Analysis of JTE-451 in Plasma

JTE-451 will be analyzed in plasma using a validated high performance liquid chromatography/tandem mass spectrometry (HPLC-MS/MS) method.

The laboratory performing the JTE-451 assessments will be unblinded to facilitate analysis of only the samples from JTE-451-administered subjects. Plasma samples from placebo subjects may be analyzed as needed.

3.5.7 Clinical Institutions and Laboratories



3.6 Adverse Events

3.6.1 Safety Definitions

Akros complies with the following International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) AE definitions:

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

Serious Adverse Event (SAE): An SAE is defined as any untoward medical occurrence at any dose that meets any of the following criteria:

- results in death
- is life-threatening
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability or incapacity
- is a congenital anomaly or birth defect
- other important medical event

Note: Important medical events that may not immediately result in death, be life-threatening, or require hospitalization but may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the patient or subject or may require medical or surgical intervention to prevent one of the outcomes listed in this definition above. Examples of such important medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalization, or the development of drug dependency or drug abuse.

Adverse Drug Reaction: All noxious and unintended responses to an investigational medicinal product (IMP)-related to any dose administered.
Note: The phrase "responses to a medicinal product" means that a causal relationship between the medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

Unexpected Adverse Drug Reaction: An adverse drug reaction, the nature (specificity) or severity of which is not consistent with the applicable product information (e.g., IB).

Death: Death represents an outcome, not an event term. The medical condition with the fatal outcome should be reported unless the cause of death is unknown, in which case the term “Death” is acceptable.

Inpatient Hospitalization/Prolongation of Hospitalization: Any admission (even if less than 24 hours) to a healthcare facility. Admission also includes transfer within the hospital to an acute/intensive care unit (e.g., medical floor to the coronary care unit). Initial and prolonged hospitalizations that **do not** meet this SAE criterion include those due to social and/or convenience reasons (e.g., lack of personal care at home, unable to transfer to non-acute facility), admission to rehabilitation/hospice/skilled nursing facilities, emergency room visits,

same-day/outpatient/ambulatory procedures, and those for pre-planned, elective procedures for a pre-existing condition that did not worsen after the informed consent has been signed (no AE present). However, if the hospitalization was prolonged due to a complication of a pre-existing condition, the complication (same diagnosis) would qualify as an SAE.

Disability: A substantial disruption of a person's ability to conduct normal life functions.

Life-threatening: Any AE that places the patient or subject, in the view of the Investigator, at immediate risk of death, i.e., it does not include an event that had it occurred in a more severe form, might have caused death.

Physical Examination, Vital Signs, Laboratory Test and ECG Abnormalities: Any abnormalities fulfilling the criteria for an SAE should be reported as such, in addition to being recorded as an AE in the CRF. Any abnormal vital sign, physical finding or laboratory/ECG result which is clinically-significant (i.e., meets one or more of the following conditions) should be recorded as a single diagnosis on the AE page in the CRF:

- Accompanied by clinical symptoms
- Leads to permanent discontinuation of study drug
- Requires a change in concomitant therapy (e.g., addition of, interruption of, discontinuation of, or any other change in a concomitant medication, therapy or treatment).

This does not apply to abnormal vital signs, physical finding or laboratory/ECG results that do not meet the clinical-significance criteria or parameters that are a result of an AE, which has already been reported.

Pre-existing conditions detected at the Screening Visit (Visit 1), including abnormalities in ECG, physical examination, vital signs and laboratory tests, are considered to be medical history.

3.6.2 Assessing Adverse Events

When completing appropriate forms for reporting the AE, the Investigator will be asked to assess the AE as follows:

Seriousness of Adverse Event:

- Serious: The AE meets a criterion of the SAE definition.
- Not Serious: The AE does not meet a criterion of the SAE definition.

Severity of Adverse Event:

The severity of an AE will be graded as one of the following three grades: mild, moderate or severe. To determine the severity of AEs, refer to CTCAE, and translate Grade 1, Grade 2 and Grade 3 or higher grades of CTCAE[14] into mild, moderate and severe, respectively. The investigator should determine the severity taking into account the general status of the subject, baseline values, outcomes as well as the severity grade into consideration. An AE of Grade 4 or Grade 5 should be assessed whether it should be reported as an SAE according to the SAE definition shown in Section 3.6.1.

- Mild: The AE is transient and may require only minimal treatment or therapeutic intervention. The AE does not generally interfere with usual activities of daily living.
- Moderate: The AE is alleviated with additional specific therapeutic intervention. The AE interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.
- Severe: The AE interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

Relationship of Adverse Event (Causality):

The Investigator's causality assessment is the determination whether there is a reasonable possibility that the IMP caused or contributed to the adverse event. Generally, the facts (evidence) or arguments to suggest causal relationship should be documented. Factors to be taken into consideration when assessing causality include: subject's underlying and pre-existing conditions, prior/concomitant medications, timing of onset relative to study drug administration, the known PK characteristics of JTE-451, the currently-known safety profile of JTE-451, known class effects of similar MOA drugs and any other information that is considered relevant by the Investigator.

The relationship of an AE to the study drug will be assessed using the following three categories:

- Not Related: The AE precedes the first administration of the study drug, or sufficient information exists to indicate that the etiology is clearly related to a cause other than the study drug.
- Possibly Related: The AE follows a reasonable temporal sequence from the administration of the study drug and follows a known or plausible response pattern to the study drug, but could readily have been produced by a number of other factors.
- Related: The AE follows a reasonable temporal sequence from the administration of the study drug; follows a known or expected response pattern to the study drug; is confirmed by improvement on stopping or reducing the dosage of the study drug (de-challenge) and reappearance of the event on repeat exposure (re-challenge); and cannot be reasonably explained by the participant's clinical state.

Action Taken with Regard to Study Drug:

The evaluation of the action taken with the study drug will be assessed using the following four definitions:

- Dose Not Changed: The subject was on treatment with the study drug when the AE occurred, and the study drug dosing was maintained at the same dose level
- Drug Interrupted: The subject was on treatment with the study drug when the AE occurred, and the study drug dosing was temporarily discontinued and then re-started
- Drug Withdrawn: The subject was on treatment with the study drug when the AE occurred, and the study drug dosing was permanently discontinued
- Not Applicable: The subject was not receiving treatment with the study drug when the AE occurred (i.e., AE occurred before the first study drug administration or after the last study drug administration), or if the subject died.

Other Action Taken:

- None
- Additional Treatment Given for the AE
- Therapeutic/ Diagnostic Procedure
- Other (including discontinuation/reduction of a concomitant medication due to the AE)

Outcome to Date:

- Not Recovered/Not Resolved: The subject has not yet recovered from the AE; the event has not improved (follow-up of all serious AEs will be continued until the overall clinical outcome has been ascertained).
- Recovering/Resolving: The subject has not yet recovered from the AE, however, the event is improving (follow-up of all serious AEs will be continued until the overall clinical outcome has been ascertained).
- Recovered/Resolved: The subject recovered from the AE with no sequelae.
- Recovered/Resolved with Sequelae: The subject recovered from the AE with sequelae.
- Fatal: The subject's death was a result of the AE.

3.6.3 Reporting Adverse Events

Adverse Events Reporting

Adverse events occurring (initial occurrence or a worsening of a pre-existing condition) after the informed consent has been signed and up to 4 weeks (28 days) after the last dose of study drug will be reported and included in the appropriate study database. However, pre-existing conditions detected as part of the screening procedures should be documented as medical history.

Worsening of the underlying condition (i.e., plaque psoriasis) or signs/symptoms associated with this condition should not be reported as an AE unless they meet at least one SAE criterion.

Adverse events for the randomized subjects will be reported on the AE CRF page.

Serious Adverse Event Reporting

Reporting by Investigators

Detailed instruction regarding SAE reporting will be provided in the appropriate documents outside of this protocol. A brief, non-all-inclusive summary is provided below.

Any SAE experienced by a study subject after signing the informed consent up to 28 days after the last dose of study drug will be reported to the Sponsor or designee. Additionally, SAEs that occur after this period will also be reported to the Sponsor or designee if the Investigator considers the SAE possibly related or related to the study drug.

Serious adverse events (both initial reports and follow-up information) must be reported to the Sponsor or designee within 24 hours of the Investigator's (site's) awareness or notification of the event.

The Investigators should make every effort to provide complete information when reporting the SAE (both for initial reports, as well as for follow-ups).

Notes:

- The investigators should make every effort to assess the causality of the SAE prior to transmission of the initial SAE report, even if the investigators have minimal information. The SAE report should be amended, if the Investigators change his/her opinion of causality based on the follow-up information.
- Personal information that could potentially identify the patient **MUST NOT** be included in any document that is sent to Sponsor or designee as per ICH GCP Principles 2.11, EU General Data Protection Regulation (GDPR) and other applicable laws and legislations.

The Investigator must continue to follow the subject until the SAE has subsided, the condition becomes chronic in nature, the condition stabilizes (in case of persistent impairment), or the subject dies. Within 24 hours of receipt of follow-up information, the Investigator must submit it to the Sponsor or designee.

The Investigator is also required to submit SAE reports to the IRB/IEC in accordance with local requirements. All investigators involved in studies using the same IMP will receive all Suspected Unexpected Serious Adverse Reaction (SUSAR) reports for onward submission to their local IRB/IEC as required. All SUSAR reports sent to investigators will be blinded.

Reporting by the Sponsor

Competent authorities and IRBs/IECs will be informed by the Sponsor or designee of SUSARs according to the local requirements. Additionally, the Sponsor or designee will report all SUSARs into the EudraVigilance system, as appropriate. Cases will be unblinded by designated personnel for reporting purposes as required.

Exposure *in Utero* Reporting:

If a female subject becomes pregnant or the female partner of a male subject participating in the study becomes pregnant after the subject receives the first dose of study drug, or within 30 days of discontinuing study drug, the Investigator should report the pregnancy to the Sponsor or designee within 24 hours of being notified.

The subject/partner should be followed by the Investigator until completion of the pregnancy. If the pregnancy ends for any reason before the anticipated date, the Investigator should notify the Sponsor or designee. At the completion of the pregnancy, the Investigator should document the outcome of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting an SAE as described above.

Overdose Reporting:

An overdose is a significant variation from the recommended/scheduled dosage for a product. For the purposes of this study, overdose is defined as any confirmed use of blinded study drug of more than two tablets per dose and/or twice a day. If such situation occurs, the Investigator should provide additional training to the subject on study drug dosing instructions and emphasize the importance of compliance. Currently there is no known antidote to JTE-451, thus appropriate symptomatic and/or supportive care should be provided at the Investigator's discretion, as needed. The subject's continued eligibility will be left to the judgment of the Investigator.

Information on overdose in subjects is collected by the Sponsor or designee. Should a subject experience an overdose during the course of the study, the investigator or qualified designee must report it as soon as possible after he/she first becomes aware of it. If an overdose led to SAE, it will be reported to Sponsor or designee according to the Section 3.6.3.

3.7 Identification of Treatments

3.7.1 Method of Assigning Subjects to Treatment Groups

After subject signs the informed consent, each site will assign potential subjects an eight-character subject number. This number will consist of a four-digit site number (with the first two digits representing the country-specific number and the next two digits representing the site-specific number) and a three-digit subject number assigned in a sequential manner. The hyphen between the site and subject number will account for the eighth character. This number will represent the subject's identifier throughout the study. Following confirmation of eligibility at Visit 2, the Interactive Web Response System (IWRS) will be contacted by the site and it will assign the subject a four-digit randomization number that will correspond to a randomly assigned treatment group.

3.7.2 Identity of Investigational Products

3.7.3 Storage and Handling Procedures

The JTE-451 and placebo tablets should be stored at room temperature between 20 and 25°C (United States Pharmacopeia [USP]) in a secure location with restricted access. Please refer to the IMP Handling Directions for detailed instructions.

3.7.4 Clinical Supplies Packaging

Each site will receive a supply of double-blind study drug packaged as blister cards corresponding to 7 days of BID dosing. Each blister card will contain total 28 tablets.

Labels will bear appropriate text as required by local regulation.

The planned blister card allocation of tablets for each dose, broken down by treatment group, is provided below.

Treatment Group	Daily Dose 1		Daily Dose 2	
	Tablet 1	Tablet 2	Tablet 3	Tablet 4
JTE-451 200 mg BID (Total daily dose: 400 mg)	JTE-451 200 mg	Placebo	JTE-451 200 mg	Placebo
JTE-451 400 mg BID (Total daily dose: 800 mg)	JTE-451 200 mg	JTE-451 200 mg	JTE-451 200 mg	JTE-451 200 mg
Placebo BID	Placebo	Placebo	Placebo	Placebo

3.7.5 Administration of Study Drug

During the Treatment Period, beginning on the day of Visit 2, subjects will self-administer two doses of study drug (2 tablets/dose, twice a day) daily for 16 weeks. Study drug will be taken BID, at approximately 12-hour intervals, regardless of meals. On the scheduled study visit days, subjects should not take study drug prior to arriving to the site. At the site, study drug will be administered from the previously supplied blister card, if available, after all study procedures have been completed (except for appropriate PK sample collection procedures as discussed in Figure 2). If no tablets from the previously supplied blister cards are available, then the subject should dose from the new blister card supplied at that visit. Study drug will not be administered on the day of Visit 7.

At Visit 2, three study drug blister cards will be dispensed to all subjects. From Visit 3 onwards, the subjects will be asked to return all study drug blister cards from the former visit for accountability and compliance assessment. At each visit, an unused blister card or a partially used blister card with the study drug available which was dispensed at the previous visit will be returned to the subjects. In addition, new study drug blister cards will be dispensed so that the subjects will receive enough study drug for the period between site visits. The subject will be instructed to use the blister cards on a first-in/first-out basis. At Visit 7, study drug will not be dispensed. If a subject discontinues study drug prematurely, the termination should be recorded as soon as possible after the decision has been made.

In the event that the subject does not take the study drug on a given day during the Treatment Period, the subject should not take more than the daily dosage on the following treatment day.

3.7.6 Management of Clinical Supplies

The Investigator will have responsibility for the control and proper distribution of all study drug (including any investigational product or reference product) in accordance with this protocol. The Investigator is responsible for ensuring that all study drug will be stored at the site at recommended storage temperatures and conditions, in a secured area, free of environmental extremes, with restricted access. The Investigator should also ensure that all study drug will be dispensed only to subjects who have provided written informed consent and have met all entry criteria.

Study drug accountability will be performed by the Investigator or designee at each study visit during the Treatment Period, according to the schedule of procedures presented in Table 1. Study drug compliance will be assessed and documented per the Good Clinical Practices (GCP).

3.7.7 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 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 Section 3.7.8).

3.7.8 Blinding

This study is double-blind (i.e., the treatment assigned to each subject will not be disclosed to the Sponsor members or designees involved in the study, study staff at the site or to the subject). JTE-451 200 mg tablets, as well as placebo tablets will be supplied as unbranded tablets, which are identical in appearance.

The laboratory performing JTE-451 plasma concentration assessments will be unblinded to facilitate analysis of only the samples from the JTE-451-treated subjects. Plasma samples from placebo-treated subjects may be analyzed as needed (see Section 3.5.6.27).

3.7.9 Breaking the Blind

The study drug code may be broken by the Investigator for a particular subject only in the event of a serious adverse experience, which the Investigator feels cannot be adequately treated without knowing the identity of the study drug by using the IWRS. Every effort must be made to contact the Medical Monitor prior to breaking the code. If the situation is an emergency, the Investigator may break the blind to identify the treatment assignment for the specific subject only and must contact the Medical Monitor as soon as possible thereafter. The Sponsor may also elect to break the blind for cause. If the blind is broken, appropriate documentation should be completed as soon as possible.

Additionally, breaking of the blind may be performed by sponsor-designated independent member not involved in the clinical conduct of the study for regulatory reporting purposes, as appropriate.

3.8 Statistical Methods

This section provides an abbreviated statistical analysis plan (SAP) for the efficacy, safety and PK evaluations. A formal SAP will be developed before the database lock. Statistical matters not addressed in this section may be developed in the formal SAP. The plans outlined in this section may be modified in the SAP; however, any major modifications of the primary endpoint definition and/or its analysis may also be reflected in a protocol amendment, as appropriate. Other deviations to the SAP will be discussed in the study report.

3.8.1 Subject Population for Analysis

3.8.1.1 Safety Population

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

3.8.1.2 Intent-To-Treat (ITT) Population

The ITT population consists of all subjects who are randomized at Visit 2.

3.8.1.3 Per Protocol (PP) Population

The PP population is a subset of the ITT population in which subjects do not have any major protocol deviations. 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.

3.8.1.4 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.

3.8.2 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.

3.8.3 Interim Analysis

No interim analysis is planned in this study.

3.8.4 Efficacy Analyses

The ITT population will be used for all efficacy data analysis. The analysis of the primary efficacy parameter will be repeated on the PP population if it excludes 20% or more of the subjects from the ITT population. Additional efficacy analyses using the PP population may be performed if deemed appropriate.

3.8.4.1 Efficacy Parameters

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

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]

3.8.4.2 Efficacy Data Analysis

The primary efficacy analyses will compare the proportion of subjects achieving PASI-75 response in JTE-451 dose groups (200 mg BID and 400 mg BID) with placebo at EOT, respectively. Cochran-Mantel-Haenszel test stratified by prior exposure to biologic therapy (biologic-naïve or biologic-experienced) and body weight (i.e., <90 kg or ≥90 kg at Visit 2) will be used for the primary comparisons. A multiple testing procedure (e.g., step-down procedure) will be considered the primary efficacy analyses of PASI-75. For supportive analyses of PASI-75, a logistic regression model-based analysis will be performed for the pairwise comparisons between a JTE-451 dose group and placebo, and for the evaluation of the dose response relationship. The logistic regression models will include the stratifying factors and baseline values of key efficacy parameters as covariates. The details will be described in the SAP.

For dichotomous secondary efficacy parameters, similar analyses as those for the primary efficacy parameter above will be performed at EOT or by a defined time point as appropriate.

For continuous efficacy parameter analysis with multiple time points, a mixed effect model will be employed. It includes fixed effects for treatment, time, treatment by time interaction, the stratification factor, appropriate baseline and subject as random effect. Appropriate baseline will be the parameter from which the efficacy parameter is derived, (e.g., PASI at Week 0 for the analysis of percent change from baseline in PASI). The treatment effect of each JTE-451 dose group relative to placebo at the same time point will be estimated. A linear trend test at each time point will be computed using appropriate linear contrast.

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. [redacted]

Descriptive statistics of efficacy parameters over time will be presented by treatment. It will include number of subjects (N), arithmetic mean, standard deviation (SD), median, minimum and maximum for continuous parameters, and frequency for dichotomous parameters.

3.8.4.3 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.

3.8.4.4 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.

3.8.4.5 Subgroup Analysis

Subgroup analyses may be performed if appropriate.

3.8.4.6 Handling of Dropouts or Missing Data

There may be missing data intermittently (e.g., a missing visit or subject dropout). For efficacy analysis of dichotomous parameters by scheduled time point, subjects with missing data will not be included in the analysis. For analysis with multiple time points, any missing data will be imputed using the last observation carried forward (LOCF) method except for subjects who withdraw for reasons related to treatment in which case any value after the withdrawal will be imputed as treatment failure. 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.

[redacted]

3.8.5 Safety Analyses

The safety population will be used for the safety data analysis unless otherwise stated.

3.8.5.1 Safety Parameters

The safety parameters are:

- Adverse events
- Clinical laboratory safety tests
- Vital signs
- ECG parameters

3.8.5.2 Safety Data Analysis

Descriptive statistics of vital signs, ECG parameters and clinical laboratory data will be presented by treatment in tabular form with N, arithmetic mean, SD, median, minimum and maximum, or in frequency tabulation form as appropriate. For continuous parameters, change from baseline will be summarized by treatment as appropriate. Potentially clinically-significant values for vital signs, ECG and laboratory data will be flagged in data listings and may be summarized as appropriate.

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.

Adverse events will be coded using the current version of Medical Dictionary for Regulatory Activities (MedDRA), and will be summarized by system organ class and preferred term.

Other safety parameters will be summarized as appropriate.

3.8.6 Pharmacokinetic Analyses

The PK population will be used for the PK data analysis unless otherwise stated.

3.8.6.1 Trough Concentration

Trough (pre-dose) plasma concentrations of JTE-451 at Weeks 2, 4, 8 and 12 will be summarized in terms of the number of subjects, arithmetic mean, standard deviation, coefficient of variation (CV%), median, minimum and maximum by treatment and visit. The relationship between the dose and trough plasma concentrations of JTE-451 will also be assessed.

3.8.6.2 Exposure-Response Relationship

[redacted]

3.8.6.3 Population Pharmacokinetic Analysis

Preliminary population PK analysis will be performed using plasma concentration of JTE-451. Population estimates of PK parameters of JTE-451 such as the apparent oral clearance of drug following extravascular administration (CL_F) and apparent volume of distribution following extravascular administration (V_F) will be estimated and inter-subject variability of these parameters will be characterized. The effect of intrinsic/extrinsic factors (e.g., age, body weight, gender, race, use of concomitant medications) on the PK of JTE-451 will be evaluated. Other PK parameters will be determined and reported as deemed appropriate. The analysis may be carried out using the data combined with plasma concentration of JTE-451 obtained in other clinical studies. The population PK analysis plan and the report may be prepared separately when appropriate.

3.9 Quality Control and Quality Assurance

This study will be conducted in compliance with the protocol, GCP as defined by the US Code of Federal Regulations (CFR) 21 Parts 50, 56 and 312, Sponsor/designee policies and procedures and all applicable local and national regulations.

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

a) Routine site monitoring;
b) CRF review against source documents;
c) Data management quality control checks;
d) Statistical quality control checks;
e) Continuous data acquisition and cleaning; and
f) Quality control of final report.

A representative from the Sponsor and/or authorized representatives may conduct periodic audits of the sites and study processes, including, but not limited to, the clinical database and the final report. The study may also be subject to inspection by regulatory authorities. The Investigator hereby agrees to allow access to required subject records and other documentation and facilities related to the review and conduct of the study.

4 Investigator Obligations

4.1 Institutional Review/Independent Ethics Committee

An Investigator shall ensure that an IRB/IEC that complies with the requirements set forth in the US CFR 21 Part 56 or in the applicable local regulations for countries outside US, as applicable, will be responsible for the initial and continuing review and approval of the proposed clinical study. The Investigator shall also assure that he/she will promptly report to the IRB/IEC all changes in the research activity and all unanticipated problems involving risk to human subjects or others, and that he or she will not make any changes in the research without IRB/IEC approval, except where necessary to eliminate apparent immediate hazards to human subjects.

All advertisements used in conjunction with this study must be reviewed and approved by the Sponsor or designee prior to use and the IRB/IEC, if applicable. The IRB/IEC's approval will be documented in writing and sent to the Investigator. The Investigator will forward a copy of the IRB/IEC approval document to the Sponsor or designee.

The Investigator will not begin the study until the Sponsor or designee has authorized release of investigational drug product.

Any amendments to the protocol must be approved in writing by the IRB/IEC prior to implementation by the Investigator. However, any change to the protocol to eliminate an apparent immediate hazard to the subjects may be implemented immediately, if the IRB/IEC is subsequently notified in accordance with the US 21 CFR Part 56.104 (c) or the applicable regulations in countries outside US.

The Investigator will also provide the IRB/IEC with a current copy of the IB at the start of the study, as well as an updated version of each if revised during the study.

A progress report will be submitted by the Investigator to the IRB/IEC at intervals established by the IRB/IEC. The Investigator will retain a copy of this report in the Investigator's Documentation File. After completion or termination of the study, the Investigator will submit a final documentation to the IRB/IEC. A copy of all reports will be sent to the Sponsor or designee.

4.2 Subject Consent

In obtaining and documenting informed consent, the Investigator should comply with the applicable regulatory requirement(s), i.e., US 21 CFR Part 50 in the US and any applicable regulations in countries outside the US, and should adhere to GCP. Prior to the beginning of the trial, the Investigator should have the IRB/IEC written approval of the written informed consent form and any other written information to be provided to subjects.

The written informed consent form and any other written information to be provided to subjects must be revised whenever important new information becomes available that may be relevant to the subject's consent. Any revised written informed consent form, and written information must receive the IRB/IEC approval in advance of use. The subject must be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information should be documented.

The Investigator or designee should fully inform the subject of all pertinent aspects of the trial including the written information and the approval by the IRB/IEC. A copy shall be given to the person signing the form.

4.3 Data Collection

It is the Investigator's responsibility to ensure that data are collected and reported according to the study protocol. The Investigator will ensure the accuracy, completeness and timeliness of the data reported on the CRF, IWRS and in all required reports.

Additionally, data for efficacy parameters, laboratory, photography and information regarding screening and randomization may be received by Clinical Data Management from appropriate clinical laboratories in electronic format. These data files may be merged with the clinical database.

4.3.1 Case Report Forms

Electronic CRFs (including eCOA and e-diary) will be produced according to protocol requirements, and access/training will be provided to the site in order for the research staff to record the data obtained on each subject during the study.

The CRFs must be completed for all subjects who have been randomized for the study and will be reviewed by the Clinical Monitor and verified against source documents and must be kept up-to-date so that they always reflect the latest observations on the subjects enrolled in the study. All records should be kept in conformance to applicable national and local laws, and regulations.

4.3.2 Source Documents

It is the responsibility of the Investigator to collect and record all study data on source documents. The Investigator must provide access to source data/documents for study-related monitoring, audits, IRB/IEC review and regulatory inspection.

4.4 Adherence to Protocol

By signing the Signature Page of this protocol, the Investigator confirms in writing that he/she has read, understands and will strictly adhere to the study protocol. This study will be conducted in accordance with GCP regulations. Additional information regarding management of protocol amendments is provided in Section 5.2.

4.5 Reporting Adverse Events

For details regarding AE and SAE reporting, see Section 3.6.3.

4.6 Investigator's Final Report

Upon completion of the study, the Investigator will provide the Sponsor or designee with a copy of the summary of the study's outcome provided to the IRB/IEC.

4.7 Records Retention

An Investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity and use by subjects. When the investigation is terminated, suspended, discontinued or completed, the Investigator shall return the unused supplies of the drug to the sponsor, or otherwise provide for disposition of the unused supplies of the drug under the US 21 CFR Part 312.59 and all applicable local regulations.

An Investigator shall retain records required to be maintained under this part for a period of two years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is filed or if the application is not approved for such indication, until two years after the investigation is discontinued and the FDA is notified.

For sites outside of the US, the Investigator shall retain records required to be maintained under this part for a period in accordance with applicable local and national regulations.

The Sponsor or designee should inform the Investigator(s)/institution(s) in writing of the need for record retention and should notify the Investigator(s)/institution(s) in writing when the trial-related records are no longer needed.

Custody of the records may be transferred to another responsible party, acceptable to the Sponsor, who agrees to abide by the retention policies. Written notice of transfer must be submitted to the Sponsor or designee. The Investigator must contact and obtain prior written permission of the Sponsor prior to disposing of or transferring any study records.

4.8 Confidentiality

The Investigator, Medical Monitor, Sponsor and its representatives, agree to protect the privacy and confidentiality of the protected health information in accordance with applicable laws and regulations.

Subject medical information obtained by the study is confidential and disclosure to third parties other than those noted below is prohibited unless required by law. The Investigator shall retain all such information and any other information designated by the Sponsor as confidential, or is otherwise of reasonably confidential nature, in confidence and shall not use such information for any purpose other than the performance of obligations pursuant to the agreement with the Sponsor

and designated affiliates or contractors, as the case may be, without prior written authorization from the Sponsor.

At the subject's request, medical information may be given to his/her personal physician or other appropriate medical personnel responsible for his/her welfare.

Data generated in this study must be available for inspection on request by representatives of regulatory authorities, Sponsor or designee, and IRB(s)/IEC(s) if appropriate.

4.9 Publications

The Investigator agrees that all data, calculations, interpretations, opinions and recommendations regarding the study shall be the sole and exclusive property of the Sponsor, and that the Sponsor may make any use thereof at its discretion without obligation to Investigator. The Investigator agrees to consider the results as information subject to confidential and use restrictions.

In the event that the study results are published in the scientific literature by the Sponsor, acknowledgment will be made to the Investigator(s) in the accepted style, as appropriate. The names of the Investigators or their representatives shall not be used by the Sponsor in publications, for advertising, for other commercial purposes, or otherwise, without appropriate written permission, unless required by law or government regulation.

Individual study center manuscript(s) for publication, text for talks, abstracts of papers, poster presentations and similar material will be submitted to the Sponsor for review and comment prior to publication or disclosure. To ensure that the Sponsor will be able to make comments and suggestions where pertinent, material for public dissemination will be submitted to the Sponsor for review at least sixty (60) days prior to submission for publication, public dissemination or review by a third party committee. The Sponsor will have sixty (60) days from receipt of such information to review and comment on and discuss the contents thereof with the Investigator. If the Sponsor requests, the Investigator will remove all confidential information (other than study results) prior to submitting or presenting the materials. Upon the Sponsor's request, the Investigator will delay submitting or presenting the materials for a further sixty (60) days to permit the Sponsor to take necessary actions to protect its confidential information, including the filing of patent applications thereon.

5 Study Management

5.1 Monitoring

Monitoring visits will be conducted by the Sponsor or designee according to applicable regulations and guidelines for GCP. The Investigator will permit the Sponsor and/or designated representative(s) to make regular site visits during the study. The frequency of monitoring visits will be agreed upon by the Sponsor and/or designee. At each visit, the Investigator and staff will be expected to cooperate with the Sponsor and/or designee for review and verification of protocol compliance, AE reporting, CRFs, source documents, clinical supplies and inventory records, and any additional records as may have been previously arranged between the Investigator and Akros or designated representative(s).

The Investigator and/or other designated study personnel are expected to contact the study monitor of the Sponsor or designee as needed regarding study concerns and/or questions.

5.2 Management of Protocol Amendments and Deviations

With the exception of emergency situations, implementation of any change in the protocol that affects the safety of the subjects, the scope of the investigation or the scientific quality of the study will not be permitted until the Sponsor and the Investigator have approved the protocol amendment and the IRB/IEC responsible for review and approval of the study has reviewed and approved the protocol change.

Implementation of changes that do not affect the safety of the subjects, the scope of the investigation, or the scientific quality of the study cannot be made until the protocol changes are reviewed and approved by Akros and the Investigator. The IRB/IEC must be notified of these protocol changes.

The Investigator will not deviate from the protocol without prior written approval from the Sponsor or designee.

5.3 Study Termination

The study may be terminated at any time at the request of the Sponsor or the Investigator with proper and timely notification of all parties concerned. The IRB/IEC will be informed promptly and reasons for the termination or suspension will be provided by the Investigator, as specified by the applicable regulatory requirements. The study can be considered complete and/or terminated after the Sponsor or designee has received the following data and materials:

- Laboratory findings, clinical data and all special test results from screening through the end of the follow-up
- CRFs properly completed by appropriate study personnel (including correctly answered and closed system or manually-generated edit checks) and signed by the Investigator
- Completed Drug Accountability Records
- Statement of outcome for each SAE reported
- Approval/notification of protocols and protocol amendments from IRB/IEC as well as relevant health authorities (if applicable)

5.4 Sponsor's Final Report

A final report will be prepared by the Sponsor or a designee at the conclusion of this clinical study.

6 References

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14. Common Terminology Criteria for Adverse Events. Quick Reference, Version 5.0, National Institutes of Health, National Cancer Institutes. November 27, 2017.

7 Appendices

Appendix 1. Permitted Medications to be used with Caution

Use of the following medications are permitted during the study; however, caution should be used when the medications [redacted] are co-administered with JTE-451. Please refer to Section 3.5.5.1.3 for detail of cautions.

Strong CYP3A4 inhibitor				
Diltiazem	--	--	--	--
Sensitive and/or Narrow Therapeutic Index CYP2C8 substrates				
Montelukast	Pioglitazone	Repaglinide[a]	Rosiglitazone	--
Sensitive and/or Narrow Therapeutic Index CYP2C9 substrates				
Celecoxib	Diclophenac	Glimepiride	Tolbutamide	--
Sensitive and/or Narrow Therapeutic Index CYP3A4 substrates				
Alfuzosin	Alprazolam	Atorvastatin[b]	Avanafil	Buspirone
Colchicine	Dihydroergotamine	Eletriptan	Eplerenone	Ergotamine
Felodipine	Lovastatin	Midazolam	Nisoldipine	Tadalafil
Triazolam	Sildenafil	Simvastatin[b]	--	--
Other restricted Medications[c]				
Amlodipine	Benzonatate	Bupropion	Citalopram	Clotrimazole
Cyclobenzaprine	Diazepam	Escitalopram	Fluconazole	Fluoxetine
Guaifenesin	Hydroxyzine	Levothyroxine	Losartan	Meloxicam
Nitrofurantoin	Pravastatin	Sertraline	Tamsulosin	Trazodone
OATP1B1/1B3 substrates				
Atorvastatin[b]	Bosentan	Ezetimibe	Fluvastatin	Glyburide
Pitavastatin	Pravastatin	Repaglinide[a]	Rosuvastatin	Simvastatin[b]
P-gp substrate with Narrow Therapeutic Index				
Apixaban	Dabigatran etexilate		Digoxin	Edoxaban

a. A CYP2C8 and OATP1B1/1B3 substrates.
b. A CYP3A4 and OATP1B1/1B3 substrates.
c. The plasma concentration may decrease due to induction potential of JTE-451 for CYP.

Appendix 2. Skindex-16 Questionnaire

Skindex16
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THESE QUESTIONS CONCERN THE SKIN CONDITION WHICH HAS BOTHERED YOU THE MOST DURING THE PAST WEEK

During the past week, how often have you been bothered by:	Never Bothered ↓			•			Always Bothered ↓
1. Your skin condition **itching**	☐0	☐1	☐2	☐3	☐4	☐5	☐6
2. Your skin condition **burning** or **stinging**	☐0	☐1	☐2	☐3	☐4	☐5	☐6
3. Your skin condition **hurting**	☐0	☐1	☐2	☐3	☐4	☐5	☐6
4. Your skin condition **being irritated**	☐0	☐1	☐2	☐3	☐4	☐5	☐6
5. The **persistence / reoccurrence** of your skin condition	☐0	☐1	☐2	☐3	☐4	☐5	☐6
6. **Worry** about your skin condition (For example: that it will spread, get worse, scar, be unpredictable, etc)	☐0	☐1	☐2	☐3	☐4	☐5	☐6
7. The **appearance** of your skin condition	☐0	☐1	☐2	☐3	☐4	☐5	☐6
8. **Frustration** about your skin condition	☐0	☐1	☐2	☐3	☐4	☐5	☐6
9. **Embarrassment** about your skin condition	☐0	☐1	☐2	☐3	☐4	☐5	☐6
10. **Being annoyed** about your skin condition	☐0	☐1	☐2	☐3	☐4	☐5	☐6
11. **Feeling depressed** about your skin condition	☐0	☐1	☐2	☐3	☐4	☐5	☐6
12. The effects of your skin condition on your **interactions with others** (For example: interactions with family, friends, close relationships, etc)	☐0	☐1	☐2	☐3	☐4	☐5	☐6
13. The effects of your skin condition on your **desire to be with people**	☐0	☐1	☐2	☐3	☐4	☐5	☐6
14. Your skin condition making it hard to **show affection**	☐0	☐1	☐2	☐3	☐4	☐5	☐6
15. The effects of your skin condition on your **daily activities**	☐0	☐1	☐2	☐3	☐4	☐5	☐6
16. Your skin condition making it hard to **work or do what you enjoy**	☐0	☐1	☐2	☐3	☐4	☐5	☐6

Have you answered every item? Yes ☐ No ☐

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