ClinicalTrials.gov Posted Document Cover Page

Clinical Study Protocol

PROTOCOL TITLE: A Multicenter, Randomized, Double-blind, Pla**C**ebo-controlled, Parallel-group Study to Eva**L**uate the Safety and **E**fficacy of JTE-051 **A**dministered for 12 Weeks in Subjects with Mode**R**ate to Severe Plaque **PS**oriasis (**CLEAR-PS**)

PROTOCOL NUMBER: AE051-G-16-007

PROTOCOL DATE: 8 October 2018

NCT NUMBER: NCT03358290

Cover Page
Akros Pharma Inc.
Clinical Study Protocol

PROTOCOL TITLE:	A Multicenter, Randomized, Double-blind, Pla**C**ebo-controlled, Parallel-group Study to Eva**L**uate the Safety and **E**fficacy of JTE-051 **A**dministered for 12 Weeks in Subjects with Mode**R**ate to Severe Plaque **PS**oriasis (**CLEAR-PS**)
PROTOCOL NUMBER:	AE051-G-16-007
DATE:	8 October 2018
IND NUMBER:	[redacted]
EUDRACT NUMBER	2018-003209-24
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: AE051-G-16-007

Protocol Number: A Multicenter, Randomized, Double-blind, PlaCebo-controlled, Parallel-group Study to EvaLuate the Safety and Efficacy of JTE-051 Administered for 12 Weeks in Subjects with ModeRate to Severe Plaque PSoriasis (**CLEAR-PS**)

The signatures below indicate approval of the protocol.

[redacted]

Investigator's Statement of Agreement:

I acknowledge possession of the JTE-051 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)

Table of Contents

List of Figures

[redacted]

List of Tables

[redacted]

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition of term
Ab	Antibody
ADAMTSL5	A disintegrin-like and metalloprotease domain containing thrombospondin type 1 motif-like 5
AE	Adverse event
AI-NRS	Average-Itch Numeric Rating Scale
ALB	Albumin
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
$AUC_{0\text{-}inf}$	Area under concentration time curve from the time of dosing to infinity
$AUC_{0\text{-}24}$	Area under the concentration-time curve from the time of dosing until the 24 hour time point
BCRP	Breast cancer resistance protein
BMI	Body mass index
BSA	Body surface area
BUN	Blood urea nitrogen
Caco-2 cells	Human colonic adenocarcinoma cells
CAIA	Collagen antibody-induced arthritis
CFR	Code of Federal Regulations
CI	Confidence interval
C_{max}	Maximum concentration
CPK	Creatinine phosphokinase
CRF	Case report form
CRN	Creatinine
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DDI	Drug-drug interaction
ECG	Electrocardiogram
EOT	End of treatment
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practices
GGT	Gamma-glutamyl transferase
GI	Gastrointestinal
GLP	Good laboratory practice
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus

Abbreviation	Definition of term
Hct	Hematocrit
HCV	Hepatitis C virus
HDL	High density lipoprotein
HEENT	Head, ears, eyes, nose, throat
HEK	Human embryonic kidney
hERG	Human ether-a-go-go-related gene
Hgb	Hemoglobin
HIV	Human immunodeficiency virus
hs-CRP	High sensitivity C-reactive protein
IB	Investigator's brochure
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IFNγ	Interferon γ
IL	Interleukin
IL-1β	Interleukin-1β
IL-2	Interleukin-2
IL-6	Interleukin-6
IL-17	Interleukin-17
IL-23	Interleukin-23
IMP	Investigational medicinal product
IND	Investigational new drug application
IRB	Institutional Review Board
ITK	Interleukin-2-inducible T cell kinase
ITT	Intent-to-treat population
IV	Intravenous
IWRS	Interactive Web Response System
LC-MS/MS	Liquid chromatography/tandem mass spectrometry
LCL	Lower confidence level
LDH	Lactate dehydrogenase
LOCF	Last observation carried forward
LRV	Lower reference value
MedDRA	Medical Dictionary for Regulatory Activities
MOA	Mechanism of action
mRNA	Messenger ribonucleic acid
MTD	Maximum tolerated dose
MTX	Methotrexate
N/A	Not applicable
[redacted]	
NOAEL	No observed adverse effect level
NSAID	Non-steroidal anti-inflammatory drug

Abbreviation	Definition of term
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
OCT	Organic cation transporter
OECD	Organization for Economic Co-operation and Development
PASI	Psoriasis area and severity index
P-gp	P-glycoprotein
pH	Logarithmic measure of hydrogen ion concentration
PI	Principal Investigator
PK	Pharmacokinetic(s)
PP	Per protocol
PR	Interval from beginning of the P wave to the beginning of the QRS complex in the frontal plane
PT	Prothrombin time
QD	Once daily
QOL	Quality of life
QTcF	Fridericia-corrected QT Interval
RA	Rheumatoid arthritis
[redacted]	
RR	Interval from beginning of the QRS complex in the frontal plane to the next QRS complex
SAE	Serious adverse event(s)
SAP	Statistical analysis plan
SAS	Statistical analysis system
SD	Standard deviation
Skindex-16	A 16-item, skin-related quality of life questionnaire
SOC	System organ class(es)
SPF	Sun protection factor
sPGA	Static Physician's Global Assessment
SUSAR	Suspected unexpected serious adverse reaction
TB	Tubercle bacillus
TCR	T cell receptor
TEAE	Treatment-emergent adverse event
TG	Triglycerides
TNSn	Total neuropathy score nurse
Treg	Regulatory T cells
[redacted]	
TSH	Thyroid stimulating hormone
TV	Target value
UCL	Upper confidence level
WI-NRS	Worst-Itch Numeric Rating Scale

Protocol Synopsis

STUDY TITLE	A Multicenter, Randomized, Double-blind, Pla**C**ebo-controlled, Parallel-group Study to Eva**L**uate the Safety and **E**fficacy of JTE-051 Administered for 12 Weeks in Subjects with Mode**R**ate to Severe Plaque **PS**oriasis (**CLEAR-PS**)
PROTOCOL NUMBER	AE051-G-16-007
CLINICAL PHASE	Phase 2a
STUDY DURATION	Approximately 20 weeks duration per subject: • Up to 28-day Screening Period • 12-week double-blind Treatment Period • 4-week Follow-up Period
STUDY OBJECTIVES	• To evaluate the efficacy of JTE-051 administered for 12 weeks in subjects with moderate to severe plaque psoriasis. • To evaluate the safety and tolerability of JTE-051 administered for 12 weeks in subjects with moderate to severe plaque psoriasis. • To evaluate the pharmacokinetics (PK) of JTE-051 administered for 12 weeks in subjects with moderate to severe plaque psoriasis.
STUDY DESIGN	This is a 12-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-051 50 mg, 100 mg, 150 mg, 200 mg or placebo once daily (QD) for 12 weeks. Approximately 85 subjects are planned to be randomized into 5 treatment groups. 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 treatment-naïve vs. biologic treatment-experienced subjects).
PLANNED NUMBER OF SUBJECTS TO BE ENROLLED AND RANDOMIZED	A sufficient number of subjects will be screened to ensure the randomization (in a 1:1:1:1:1 ratio) of approximately 85 subjects (17 subjects in each treatment group).

KEY ELIGIBILITY CRITERIA	• Male or female, 18 to 70 years of age (inclusive) at Visit 1 (Screening Visit) and diagnosed with moderate to severe plaque psoriasis at least 6 months prior to Visit 1; • No medical history of treatment failure to any systemic agents for plaque psoriasis; • Plaque-type psoriasis covering ≥10% of body surface area (BSA) at Visit 1 and Visit 2 (Baseline); • Psoriasis Area and Severity Index (PASI) score ≥12 at Visit 1 and Visit 2; • 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; • Negative QuantiFERON®-TB Gold test or PPD test, negative chest radiographic findings for tubercle bacillus (TB) and no other evidence of active or latent TB; • No history of a clinically-significant infection (e.g., that required oral antimicrobial therapy) within 8 weeks prior to Visit 2; • No history of infections requiring hospitalization or parenteral antibiotic, antiviral, antifungal or antiparasitic therapy within 6 months prior to Visit 2 and no history of recurrent infections or conditions predisposing to chronic infections (e.g., bronchiectasis, chronic osteomyelitis); [redacted]

INVESTIGATIONAL PRODUCT (STUDY DRUG), FORMULATION, DOSAGE, ROUTE AND TIME OF ADMINISTRATION	JTE-051 50 mg tablets 50 mg, 100 mg, 150 mg and 200 mg Oral administration for 12 weeks starting on the day of randomization at Visit 2, QD in the morning, regardless of meals. On study visit days, subjects should take their scheduled study treatment at the clinical research site (site) under the supervision of the investigator or designee after all study-related procedures have been completed (except at Visit 6, 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-051 tablets) Not applicable (N/A) Oral administration for 12 weeks starting on the day of randomization at Visit 2, QD in the morning, 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 6, 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 collected at Weeks 2, 4, 8, 12 and 16 unless otherwise stated: • Percent change from baseline in PASI score; • Proportions of subjects achieving PASI 50, PASI 75, PASI 90 and PASI 100; • Proportion of subjects achieving a sPGA score of 0 or 1; • Change from baseline in sPGA score; • Percent change from baseline in the psoriasis affected BSA; • Change from baseline in the Skindex-16 (a 16-item, skin-related quality of life questionnaire). [redacted] Safety Assessments • Number and proportion of subjects with adverse events (AEs), type and severity of AEs, change from baseline in the safety laboratory, vital sign and electrocardiogram (ECG) parameters. Pharmacokinetic Assessments • Trough plasma levels of JTE-051; • Relationship between the JTE-051 dose (exposure) and response may be assessed (exploratory).
STATISTICAL METHODS	Appropriate statistical analysis will be performed using SAS for Windows® (SAS Institute Inc., Cary, NC 27512-8000, USA).

1 INTRODUCTION

1.1 Background

1.1.1 Psoriasis

Plaque psoriasis is the most common form of psoriasis. It is a mild to severe inflammatory autoimmune disease with primary skin manifestation 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 with psoriatic arthritis and nail psoriasis may be experienced by some patients. Also, it is reported patients consider itch to be the most bothersome symptom of psoriasis and is more likely to cause absence from work and reduced work productivity than psoriasis related pain or scaling.[1] The number of patients with psoriasis is estimated to be approximately 7.5 million in the US, 7.5 million in the EU, 420 thousand in Japan and the worldwide prevalence of psoriasis is calculated to be 0.6 to 4.8%.[2-5] It is also known that the quality of life (QOL) of the psoriasis patients is lower than that of patients with cancer or diabetes.[6] As a result, psoriasis markedly restricts the social activities of patients.

Psoriasis is triggered by the cells and molecules of both, innate and adaptive immune systems. The inflammatory cells infiltration consists mainly of dendritic cells, macrophages and T cells in dermis, and T cells and neutrophils in epidermis. These cells are activated through antimicrobial peptide such as β-defensins and auto-antigens including LL-37 and a disintegrin-like and metalloprotease domain containing thrombospondin type 1 motif-like 5 (ADAMTSL5).[7,8] Various cytokines produced by these immune cells play a crucial role in the development of psoriasis. Clinical studies of biologics targeting cytokines have revealed that Interleukin (IL)-17 and IL-23 play highly important roles in the disease progression and exacerbation of psoriasis.[9-12] [redacted]

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 current pharmacotherapy for psoriasis mainly consists of topical vitamin D3 analogues and topical corticosteroids, and systemic treatments such as cyclosporine and methotrexate (MTX) may be used depending on the symptoms. For patients with concomitant psoriatic arthritis and those who have not sufficiently responded to conventional systemic treatments, biologics targeting tumor necrosis factor-α (TNF-α), IL-23, IL-17, etc. may be used. 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 some patients.[14] 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. Biologic therapies can achieve remission in many patients, making a huge contribution to the advances in psoriasis treatment. However, there are concerns related to biologics, which have yet to be addressed: (1) inadequate response to therapy in approximately 30% of the patients (2) increased risks for infections and cancer development

(3) high financial burden (4) lack of availability of long-term safety data for these compounds (5) hypersensitivity reactions, such as infusion reaction, injection site reaction and (6) generation of neutralizing antibodies.[15,16] Based on these considerations, the next generation therapies for psoriasis are expected to be represented by cost-effective, highly-efficacious and safe oral drugs that can induce remission rapidly and achieve complete remission with high probability. Unlike the existing drugs for systemic treatment that are indicated only for severe cases, 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 Interleukin-2-inducible T-cell Kinase

Interleukin-2-inducible T-cell kinase (ITK) is a non-receptor protein tyrosine kinase that is mainly expressed in T cells, mast cells, and natural killer cells. In the T cells, the molecule plays a role in transmitting stimulation triggered by the antigen via the T cell receptor (TCR) located on the cell membrane.[17] When antigen is presented with the major histocompatibility complex on the antigen-presenting cells such as dendritic cells and macrophages, T cells are activated by recognizing the antigen via the TCR. As a result of activation, T cells produce cytokines such as interleukin-2 (IL-2), interleukin-17 (IL-17) and interferon γ (IFNγ) and accelerate their own proliferation. It is also considered that T cells are significantly involved in the development of tissue inflammation and damage by activation of other inflammatory cells by these cytokines. Findings that indicate a relationship between ITK and pathological changes have been reported. T cells obtained from ITK-knockout mice could not show IL-2 production in response to stimulation mimicking antigen presentation, which led to decreased cell proliferation. Cell proliferation is also less sensitive in the mixed lymphocyte reaction if obtained from mice of a different strain.[18] Furthermore, it has been reported that ITK-knockout mice show impaired response in allergic airway inflammation induced by the antigen: the production of various cytokines in the T cells in lymphoid tissues, the infiltrative inflammatory cell counts in the airway, and the secretion of airway mucus.[19] This information suggests that ITK may be involved in the development of pathological changes in autoimmune diseases, transplant rejection and allergic diseases of which the onset and exacerbation are caused by an excessive immune response to the antigen.

[redacted]

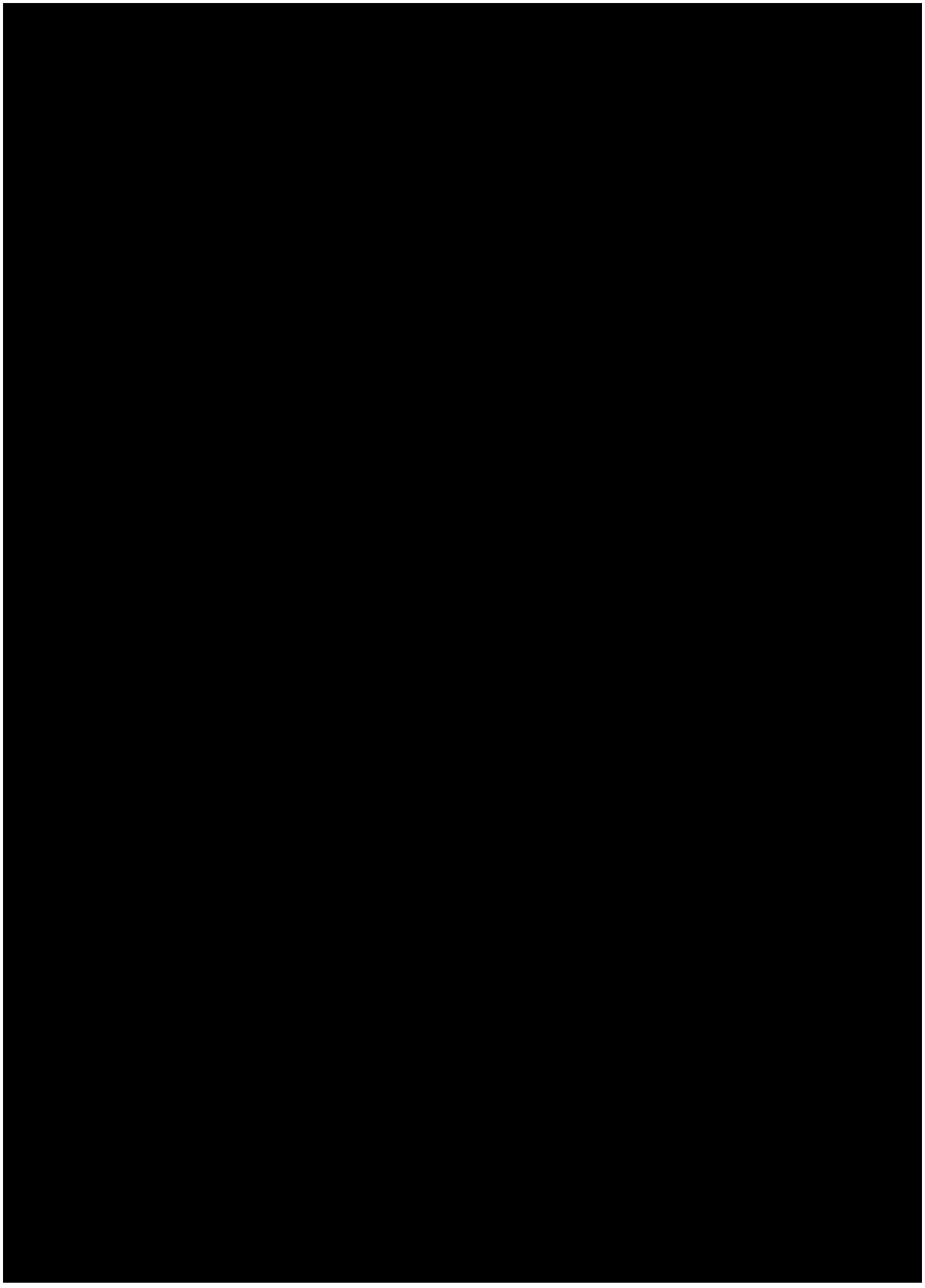
1.2 JTE-051

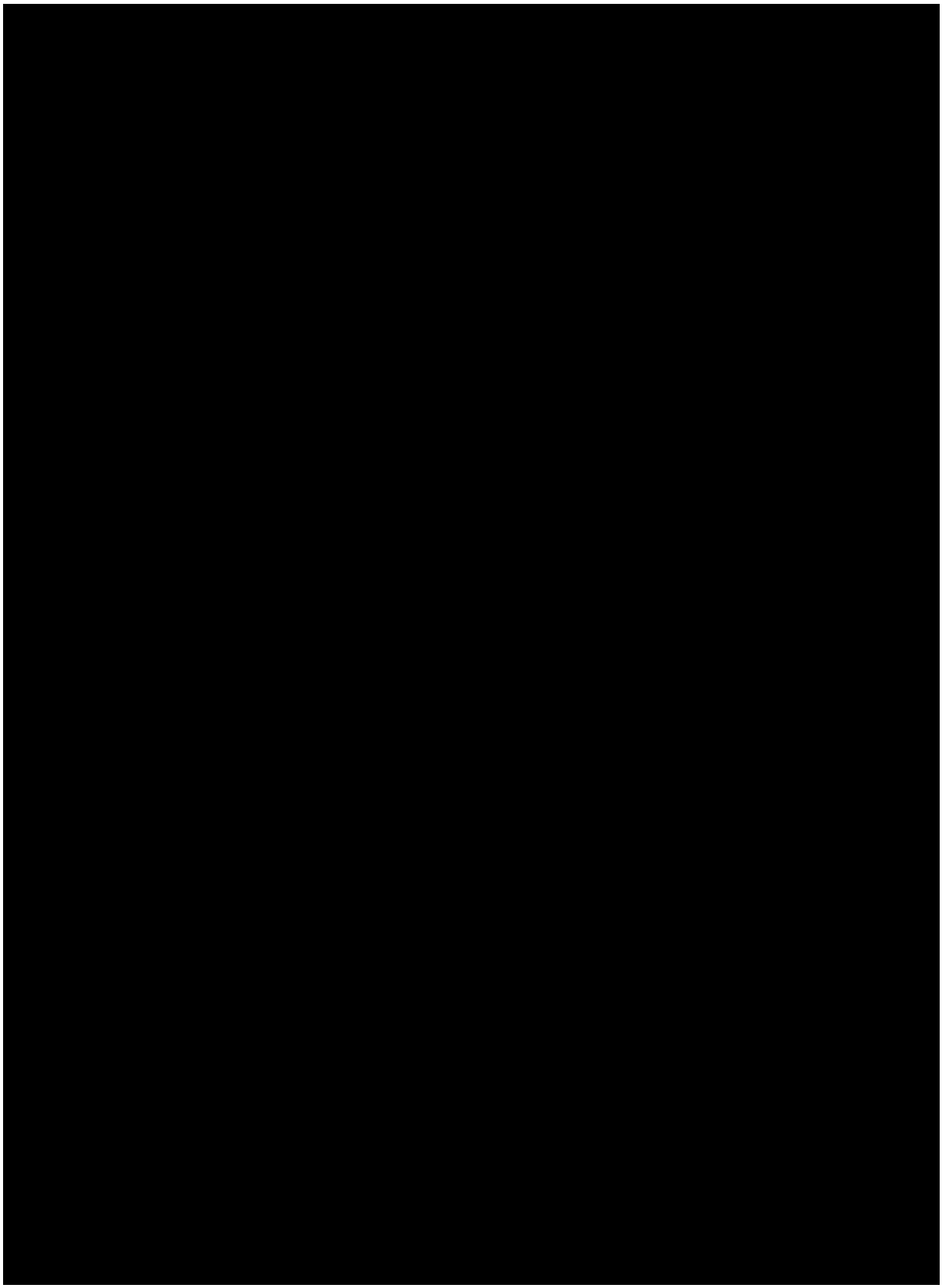
[redacted]

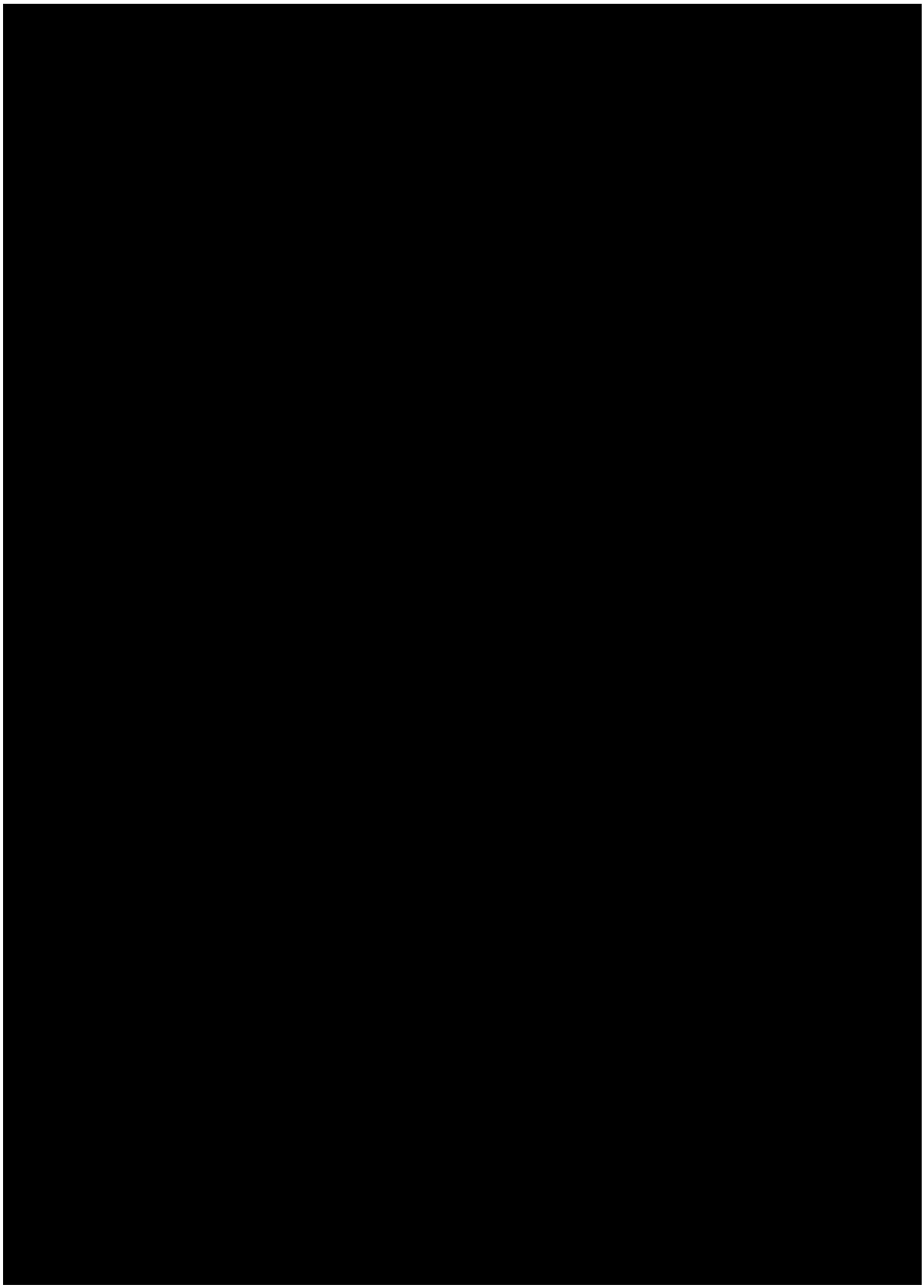
A brief summary of the nonclinical findings to date is included below. Additional details are described in the JTE-051 Investigator's Brochure (IB).

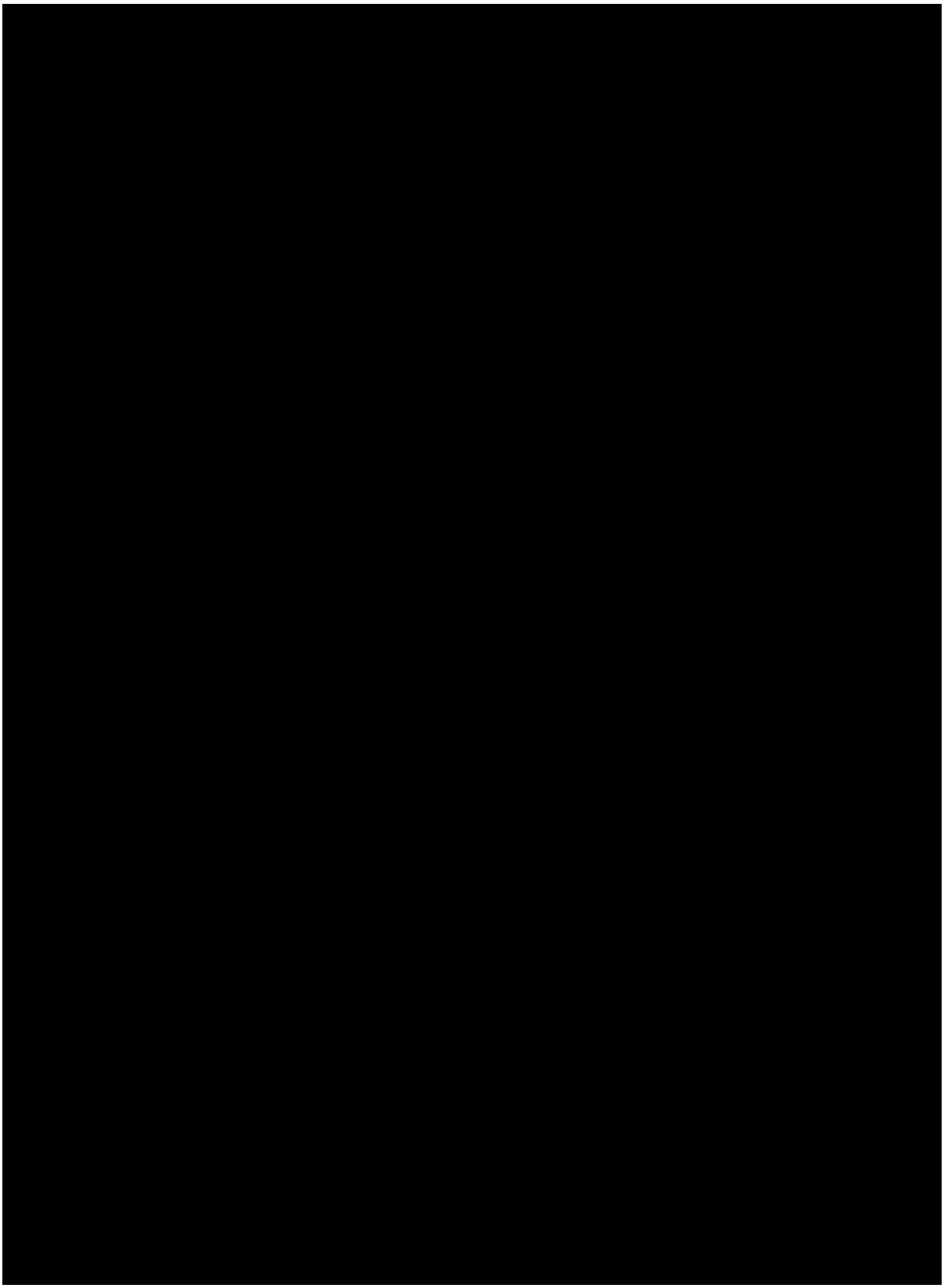
1.2.1 Nonclinical Studies

[redacted]





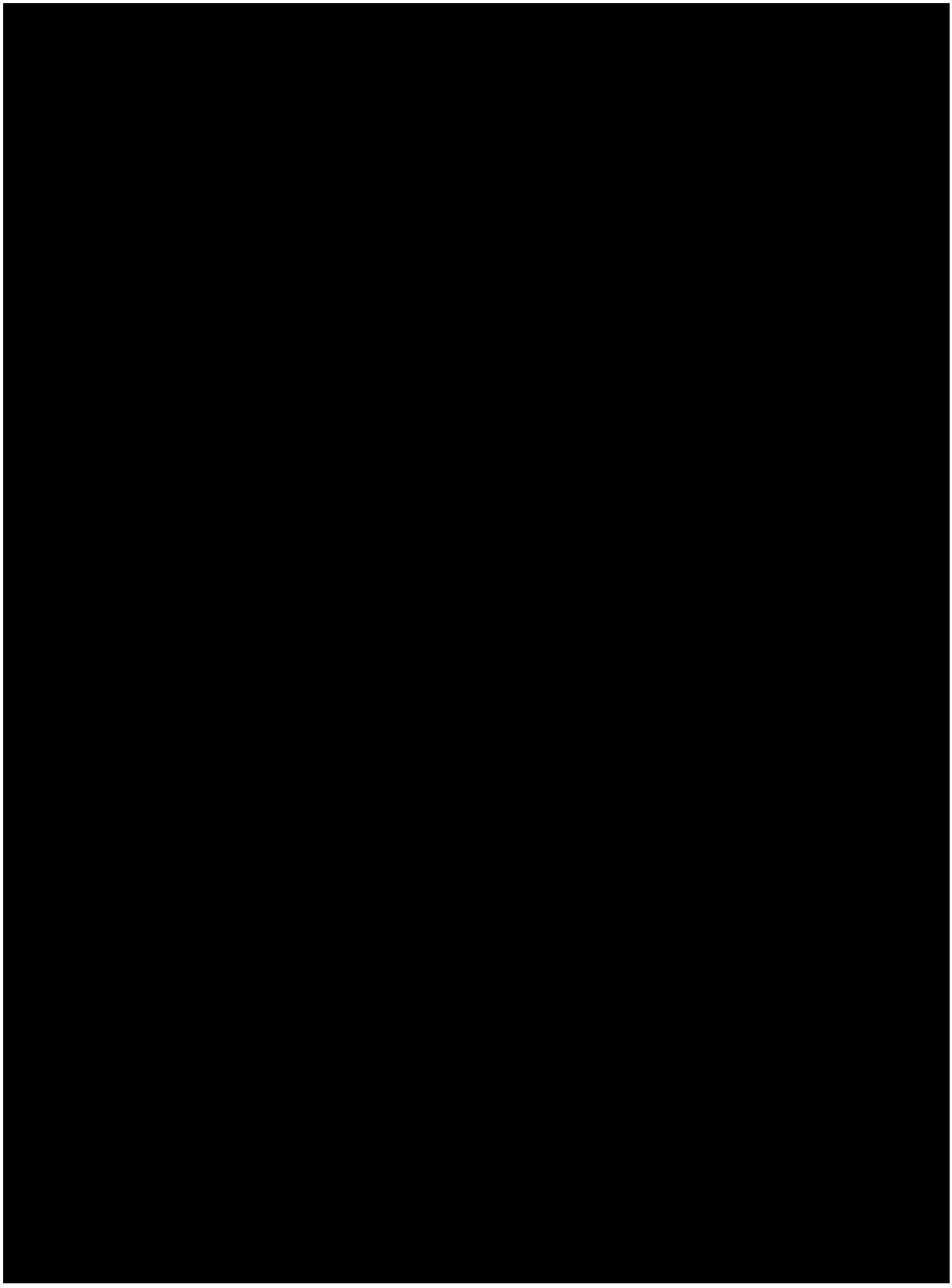


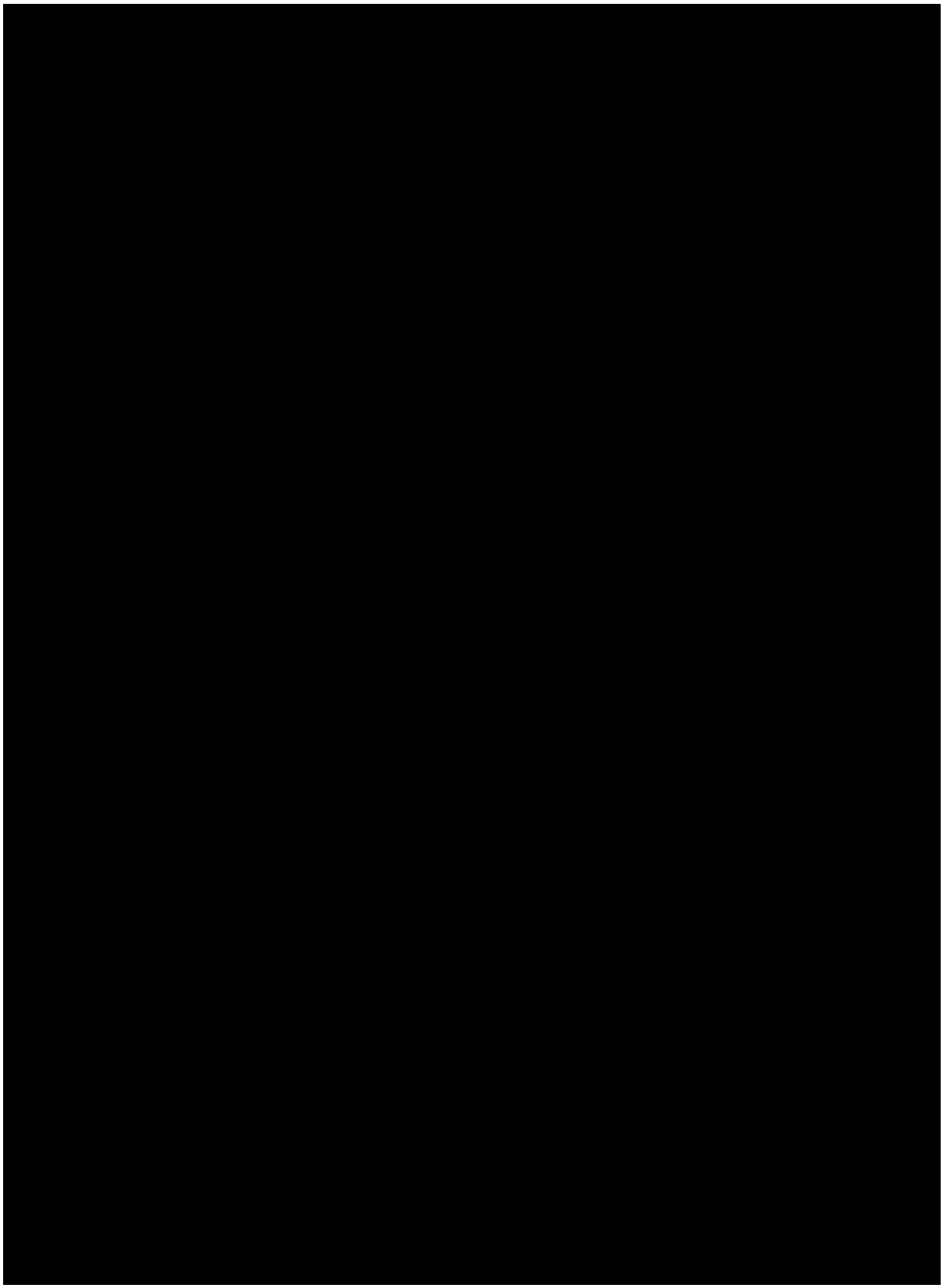


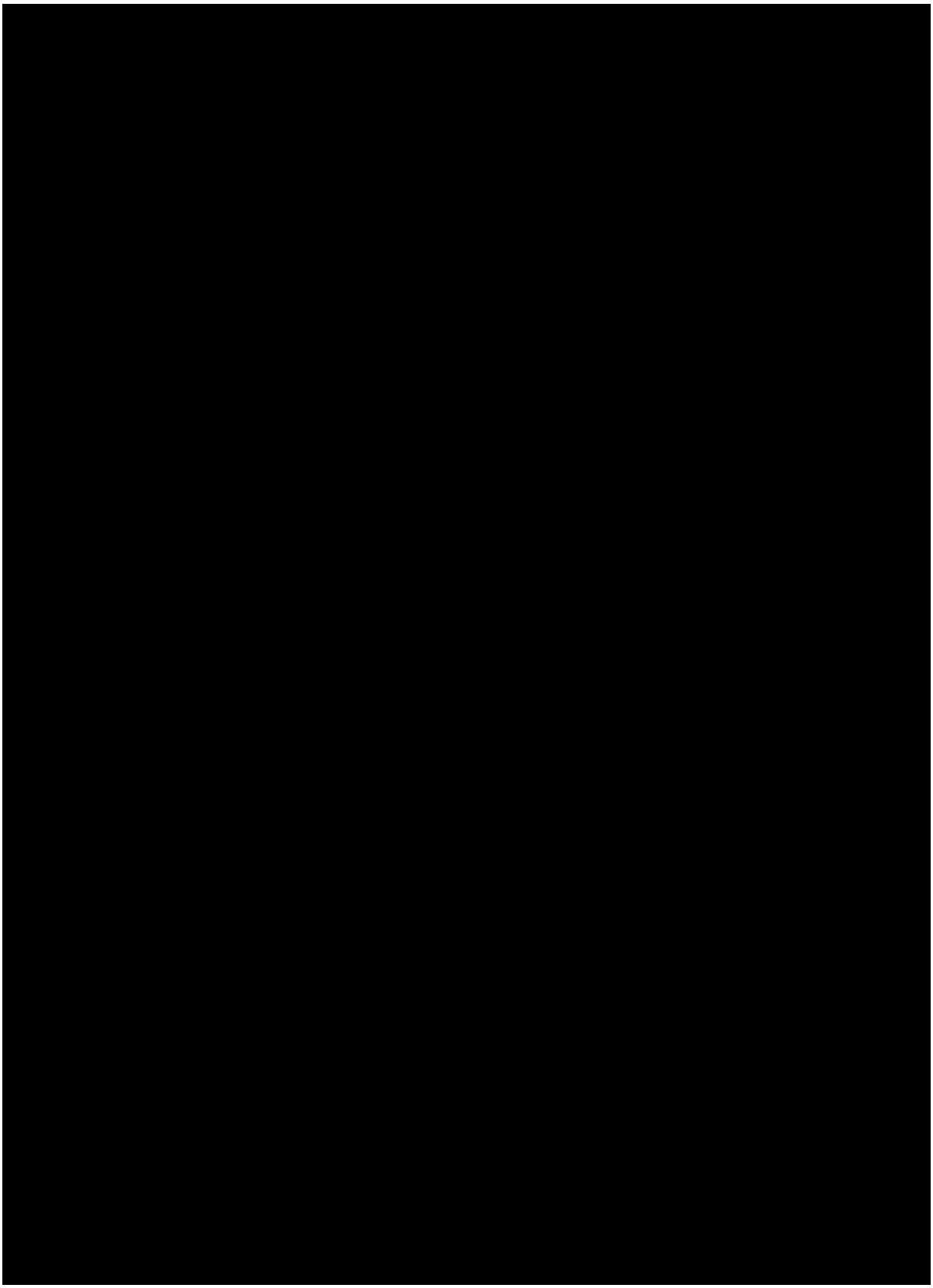
[redacted]

1.2.2 Clinical Information

[redacted]







[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 the extent of psoriasis severity criteria (i.e., BSA, PASI and sPGA) described in Section 3.3.1 will be enrolled in this study. Subjects with other types of psoriasis will be excluded from the study to ensure a homogenous study population. Furthermore, to minimize potential confounders in the efficacy response, subjects must have no history of treatment failure following any systemic treatment.

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. Thus, subjects at high risk of developing immunosuppression-related AEs, such as infections or malignancies, including those with pre-existing conditions (e.g., clinically-manifested or latent TB, active infections with HBV, HCV or HIV) or significant hematological condition are excluded from participating in the study. [redacted]

[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 mechanism of action on the market or in development, have been implemented.

1.3.2 Justification for Study Design

A parallel group, placebo-controlled design will be employed in this study, to assess the effect of JTE-051 on the efficacy parameters and to evaluate the safety of JTE-051, compared to placebo in subjects with plaque psoriasis. Briefly, upon completion of all protocol-mandated screening procedures, the qualified subjects will be randomized at Visit 2 in a 1:1:1:1:1 ratio to one of the following five parallel dose groups: JTE-051 50 mg QD, JTE-051 100 mg QD, JTE-051 150 mg QD, JTE-051 200 mg QD or placebo QD (17 subjects to be randomized per arm; see Section 3.8.1.6 for considerations related to sample size calculation), and will receive the double-blind treatment for 12 weeks followed by a 4-week Follow-up Period. The single ascending dose study (AE051-U-11-001) data demonstrated no food effect on the PK of JTE-051; thus, study drug will be administered regardless of meals; nonetheless, based on the PK characteristics of the compound, the protocol requires the study drug administration in the morning to ensure an approximately 24-hour period between dosing, (see Section 1.2.2). The duration of the double-blind treatment period is sufficient to obtain proof-of-efficacy in subjects with plaque psoriasis, as an initial step in development. The duration of the Follow-up Period is set to approximately 4 weeks, standard duration for similar out-patient studies administered an investigational product. Based on the PK characteristics of JTE-051 (see Section 1.2.1), this period is considered conservative, [redacted]

The efficacy parameters assessed in this study are consistent with the standards in the industry in similar psoriasis trials; appropriate efficacy analyses are planned, as detailed in Section 3.8.3.2. 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 safety, adequate procedures have been implemented to minimize the risks to the study subjects (based on the compound's MOA and the nonclinical and clinical data available to date [see Sections 1.2.1, 1.2.2 for summary information and the IB for detailed information]) and to facilitate further characterization of the safety profile of JTE-051.

1.3.3 Justification for Dose Selection

The selection of JTE-051 doses in this study is based on the collective data from nonclinical pharmacology/toxicology studies and Phase 1 clinical studies.

[redacted]

2 STUDY OBJECTIVES

- To evaluate the efficacy of JTE-051 administered for 12 weeks in subjects with moderate to severe plaque psoriasis.
- To evaluate the safety and tolerability of JTE-051 administered for 12 weeks in subjects with moderate to severe plaque psoriasis.
- To evaluate the pharmacokinetics (PK) of JTE-051 administered for 12 weeks in subjects with moderate to severe plaque psoriasis.

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 1:1:1:1:1 ratio) approximately 85 subjects (17 subjects per treatment group).

3.2 Study Design

This is a 12-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-051 50 mg, 100 mg, 150 mg, 200 mg or placebo QD for 12 weeks. Approximately 85 subjects are planned to be randomized into 5 treatment groups. 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 treatment-naïve vs. biologic treatment-experienced subjects).

The study duration will be of approximately 20 weeks per subject:

- Up to a 28-day Screening Period
- A 12-week double-blind Treatment Period
- A 4-week Follow-up Period

3.3 Selection of Study Population

Written informed consent must be obtained prior to performing any study-related procedures. 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 had a diagnosis of moderate to severe plaque psoriasis for at least 6 months prior to Visit 1;
3. Plaque-type psoriasis covering ≥10% of Body Surface Area (BSA) at Visit 1 and Visit 2 (Baseline);
4. Psoriasis Area and Severity Index (PASI) score ≥12 at Visit 1 and Visit 2;
5. Static Physician's Global Assessment (sPGA) score ≥3 at Visit 1 and Visit 2;

6. Body Mass Index (BMI) ≤40 kg/m^2 at Visit 1;
7. Females may participate if they meet one of the following criteria:
   - Surgically sterile (e.g., hysterectomy or bilateral oophorectomy),
   - At Visit 1, females with a documented history of lack of menses for ≥12 consecutive months with no other reversible medical etiology will be considered postmenopausal.
   - At Visit 1, if positive for lack of menses but onset <12 months, then an FSH >40 will be required to define post-menopausal status, otherwise subject is considered of childbearing potential, or
   - If of childbearing potential, with a negative pregnancy test at Visit 1 and if participates in heterosexual intercourse, agrees to be compliant with the consistent and correct use of acceptable methods of contraception as described below. Acceptable methods of birth control for this study are:
     a) one highly effective contraceptive method of birth control, which includes intrauterine devices, partner sterilization (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate), tubal ligation, bilateral tubal occlusion, intrauterine hormone-releasing systems, **in addition to**
     b) one effective method of birth control, which includes male condom, female condom, cervical cap, diaphragm or contraceptive sponge all with spermicide (hormonal methods are not allowed).

     The above described contraception methods must be maintained for the duration of the study and for at least 30 days after the last dose of study drug.
8. Male subjects must agree to use a barrier contraceptive method with spermicide for the duration of the study and for at least 12 weeks 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 12 weeks after the last dose of study drug. Counseling on the appropriate contraception methods for their female partners should be given as follows: female partners of male subjects randomized in this study must be post-menopausal or in case of female partner of childbearing potential, unless surgically sterile, they must agree to use at least one form of an acceptable form of birth control (in addition to the method utilized by the male subject) for the duration of the study and for at least 12 weeks after the last dose of study drug. Please see inclusion criterion # 7 for a list of acceptable forms of birth control for the study (hormonal methods will be allowed for females partners of male subjects);

   Additionally, male subjects must not donate sperm for the duration of the study and within 12 weeks of the last dose of study drug.
9. [redacted]
10. Able and willing to complete an [redacted] questionnaire responses on a mobile device on a daily basis for the duration of the study;
11. 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. Medical history of treatment failure to any systemic agents (including biologic and non-biologic systemic agents) for plaque psoriasis;
2. Presence of erythrodermic psoriasis, pustular psoriasis, guttate psoriasis, medication-induced psoriasis or other skin conditions at (e.g., clinically-significant eczema or severe acne) that could interfere with study evaluations at Visit 1;
   Note: Subjects with psoriatic arthritis will not be excluded from the study provided that criteria for cutaneous severity of psoriasis, as well as all other study restrictions required by the protocol are met.
3. Presence or history 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;
4. Does not meet all study restrictions, including previous/concomitant medication restriction criteria, as described in Section 3.5.4.1;
5. 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; Hemoglobin <11 g/dL or platelet count <100,000/mm^3 at Visit 1;
6. ALT >2.0 X the upper limit of normal (ULN) or AST >2.0 X the ULN at Visit 1;
7. Evidence of renal impairment; serum creatinine >1.5 X the ULN at Visit 1;
8. Hemoglobin A1c (HbA1c) >8.5% at Visit 1;
9. Serum triglycerides >400 mg/dL at Visit 1;
10. Positive viral serology at Visit 1 for:
    - Human immunodeficiency virus (HIV): positive HIV antibodies (Ab) or
    - Hepatitis B virus (HBV): positive total hepatitis B core (HBc) Ab or positive hepatitis B surface antigen (HBsAg) or
    - Hepatitis C virus (HCV): positive HCV Ab;
11. Positive drug of abuse test results at Visit 1;
    Note: Non-abusive use of prescription drugs, according to the Investigator's judgment is permitted, provided that the concomitant medications restrictions required by the protocol are met.
12. Positive Purified Protein Derivative (PPD) test or QuantiFERON®-TB Gold-In-Tube test , positive chest radiographic findings for tubercle bacillus (TB) or any other evidence of active or latent TB;
    - For subjects with a history of Bacille Calmette-Guérin (BCG) vaccination or in case PPD test fails, the QuantiFERON®-TB Gold-In-Tube test should be performed;
    - A PPD test is considered positive if, at 48 to 72 hours of administration, the induration (not erythema) obtained is ≥5 mm. The reaction must be read between 48 and 72 hours after administration (a subject that does not return after 72 hours must be rescheduled for a repeat PPD test);

- If QuantiFERON®-TB Gold-In-Tube 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;
- The QuantiFERON®-TB Gold-In-Tube test should not be performed within ≤4 weeks from the date of a live vaccination;
- Subjects who have had household contact with a person with active TB are excluded, unless appropriate and documented prophylaxis for TB was administered.

13. History of live vaccination within 4 weeks prior to Visit 2 or have a live vaccination planned during the course of the study or within 6 weeks after the last dose of study drug;
14. Have donated or received blood or blood products within 4 weeks prior to Visit 1;
15. History of a clinically-significant infection (e.g., infection that required oral antimicrobial or antiviral therapy) within 8 weeks prior to Visit 2, except for treated urinary tract infections, which will be permitted if resolved >1 week prior to Visit 2;
16. History of opportunistic infections or infection requiring hospitalization or parenteral antibiotic, antiviral, antifungal or antiparasitic therapy within 6 months prior to Visit 2 or history of recurrent infections or conditions predisposing subject to chronic infections (e.g., bronchiectasis, chronic osteomyelitis);
17. History of shingles within 12 months prior to Visit 1 or known history of disseminated/complicated herpes zoster;
18. 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;
19. History of or current 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 >6 months prior to Visit 1;
20. History of organ transplantation;
21. A history of substance abuse, drug addiction or alcoholism within 12 months prior to Visit 1. 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);
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;

[redacted]

[redacted]

[redacted]

29. Pregnant or nursing at Visit 1 or Visit 2 or plan to become pregnant or initiate breastfeeding during the study and within 12 weeks after the last dose of study drug;
30. Significant history of drug or other hypersensitivities per the investigator (e.g., multiple drug allergies or severe allergic reactions, including angioedema);
31. History or presence of any other clinically relevant medical condition or disease or laboratory abnormality including hepatic, renal, gastroenterologic, respiratory, cardiovascular, endocrinologic, [redacted], psychiatric (e.g., schizophrenia, manic-depressive disorder, treatment-resistant major depression), immunologic (e.g., immunocompromised subjects or subjects with autoimmune conditions other than psoriasis, such as type I diabetes), [redacted] or hematologic (e.g., sickle cell) disease that, in the opinion of the Investiga or, 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;
32. Cannot communicate reliably with the Investigator (including inability to complete the self-assessment questionnaires) 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. 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 the adverse event.

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 [ADL] such as bathing, dressing, undressing, feeding self, using the toilet, taking medication, but not bedridden), according to the CTCAE[29], are noted in a subject, he/she must be promptly evaluated by the Investigator (including repeat tests, evaluation of the baseline parameters, concomitant medications, etc.) for potential withdrawal from the study. Every effort should be made to discuss with the study's Medical Monitor prior to final decision, unless not feasible, based on safety considerations.

   Notes:

   - The investigator may decide to evaluate or withdraw the subject from the study based on findings of lesser than grade 3 severity, according to his/her judgment.

   [redacted]

3. Consistent 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 is to counsel the subject and ensure steps are taken to improve compliance.

4. Inclusion/Exclusion Criteria Not Met: If a subject who did not meet any of the study inclusion or exclusion criteria is identified after the randomization, the Investigator, Medical Monitor and Sponsor will review that subject profile, including the medical history, prior and current concomitant medications, physical examination, vital signs, 12-lead ECGs and clinical laboratory test results. Since such deviations are usually noted after randomization, the decision to be made is to allow the subject to continue the study or not. For such cases, 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. Some of the examples where case-by-case basis exceptions may be allowed are as follows:

- A subject who had a minor deviation from the inclusion/exclusion criteria defined for the efficacy evaluation purpose (e.g., inclusion criteria 1 through 6, exclusion criteria 1 through 4).
- A subject who had a minor deviation in clinical laboratory test results from the cut-off values defined in exclusion criteria 6 through 11.

5. Protocol Violation: the subject is non-compliant with regard to this protocol (other than the withdrawal criteria 3 and 4 listed above), as determined by Sponsor or the Investigator on a case-by-case basis.
6. Lost to Follow-up
7. Death
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 those already mentioned (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 6. Every effort should be made to perform the Visit 6 assessments 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 as described at Visit 7 should be performed.

3.5 Study Procedures

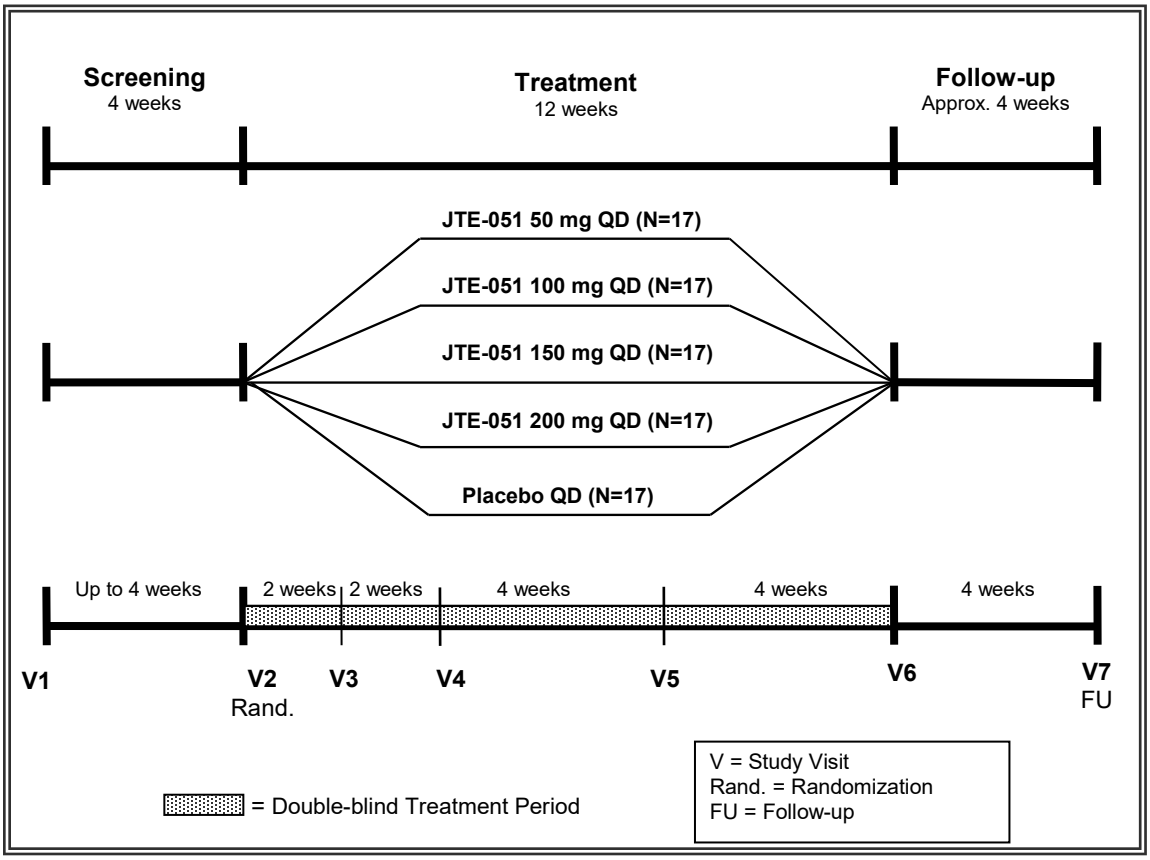


Figure 1. Planned Study Schema

Table 1. Planned 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±2)	Week 12 (Day 84±2)	Week 16 (Day 112±2)
Visit	1	2	3	4	5	6	7
Sign Informed Consent	X						
Inclusion/ Exclusion Criteria	X	X					
Medical History	X						
Demographic Information	X						
Review Prior/ Concomitant Medications	X	X	X	X	X	X	X
Physical Exam	X	X	X	X	X	X	
[redacted]							
Vital Signs	X	X	X	X	X	X	X
Body Weight	X	X				X	
Height and Calculate BMI	X						
12-Lead ECG	X	X		X		X	
Chest Radiography[c]	X						
TB test (quantiFERON gold OR PPD Test)	X						
Drugs of Abuse Screen & alcohol	X						
Viral Serology (HBs Ag, HCV Ab, HIV Ab)	X						
FSH[d]	X						
HbA1c	X						
Pregnancy Test (all females)[d]	X	X	X	X	X	X	X
Serum Biochemistry	X	X	X	X	X	X	X
Hematology	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X
Coagulation	X	X		X		X	X
Lipid Profile	X	X		X		X	X
Serum IgG, IgM and IgA		X				X	
25-hydroxyvitamin D	X						
Psoriasis Body Surface Area	X	X	X	X	X	X	X
Bone-specific ALP	X	X				X	
PASI	X	X	X	X	X	X	X
sPGA	X	X	X	X	X	X	X
Skindex 16		X	X	X	X	X	X
Itch NRS [redacted]	←						→
[redacted]							
[redacted]							
Digital Photography[g]		X				X	
Randomization using IWRS		X					
Access IWRS and Dispense Study Drug[h]		X	X	X	X		
[redacted]							
Collect Study Drug and Check Compliance[j]			X	X	X	X	
Study Drug Administration[k]		X	X	X	X		
JTE-051 PK Blood Samples[l]		X	X	X	X	X	
Document Adverse Events[m]	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 samples 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 procedures involving venipuncture [redacted].

a. The target day for each visit after randomization will be calculated relative to the date of Randomization Visit (Visit 2) and not relative to the date of the previous visit. All visits should be performed within the windows specified in the table. Every attempt should be made to have the subject attend each visit as scheduled. The investigational site is encouraged to a 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.

b. [redacted]

c. Chest radiography may not be performed if it has been performed within 12 weeks of Visit 1 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 7, urine pregnancy tests will be performed only for female subjects of child bearing potential. At Visit 1, females with a documented history of lack of menses for ≥12 consecutive months with no other reversible medical etiology will be considered postmenopausal. If the female is positive for lack of menses but onset has been <12 months, then an FSH >40 will be required to define post-menopausal status, otherwise subject is considered of childbearing potential.

e. Both WI-NRS and AI-NRS during a 24-hour recall period will be recorded by the subject once daily from screening through the last visit.

f. [redacted]

g. All subjects will be required to take photographs of the [redacted] four half-body views (i.e., upper anterior, lower anterior, upper posterior, and lower posterior). However, 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. In all the photographs, subject identification will be blinded.

h. At Visit 2 through Visit 5, randomized subjects will receive sufficient study drug blister cards for the period between visits. At Visit 6, study drug will not be dispensed. If a study subject discontinues study drug prematurely, the termination should be recorded as soon as possible after the decision has been made.

i. [redacted]

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 to and returned by the subject.

k. Oral administration for 12 weeks starting on the day of randomization at Visit 2, QD in the morning, 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 study-related procedures have been performed (except for Visit 6, 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 dosing and 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 during the Screening Period (e.g., abnormalities in ECG, physical examination, [redacted], vital signs and laboratory tests) are considered to be medical history and should be documen ed accordingly.

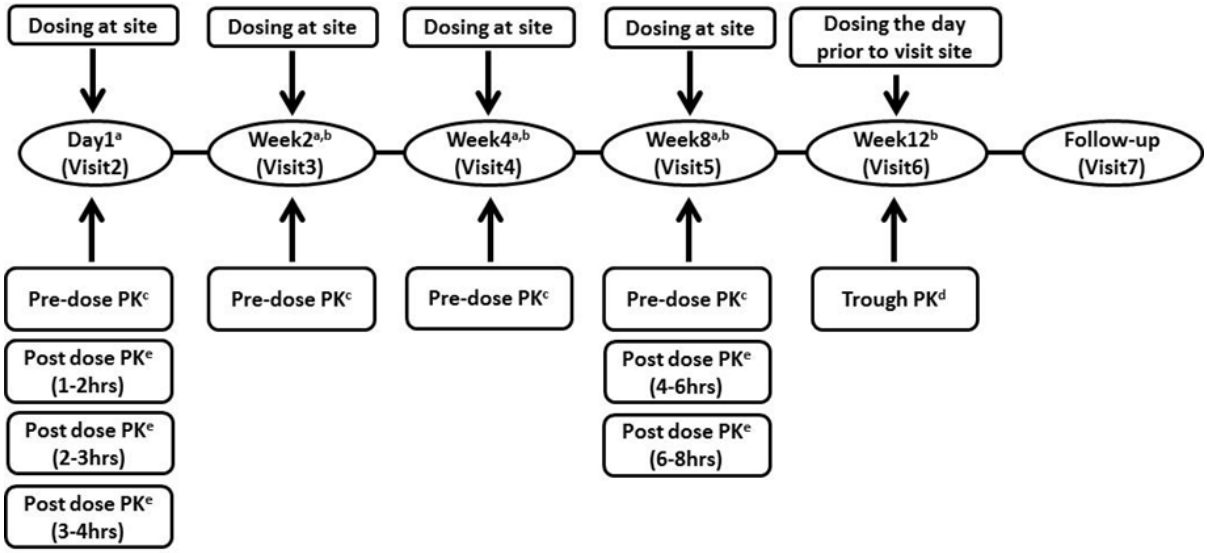


Figure 2. Dosing and Pharmacokinetic Sample Collection Time

a. The exact date and time of dose at each visit at the site will be collected.
b. The exact date and time of the last three doses prior to the PK sample collection will be collected.
c. The PK samples at pre-dose point (i.e., samples obtained prior to the morning dosing of the study drug at the site) are mandatory in all subjects at all sites. Sample collection date and time will be collected.
d. The PK samples at trough point (relative to dosing of the study drug at the day prior to the visit) are mandatory in all subjects at all sites. Sample collection date and time will be collected.
e. Every effort should be made to collect post-dose PK samples (relative to the morning dosing of the study drug at the site) from as many subjects/treatment as possible. Sample collection date and time will be collected.
f. The sampling time between post dose blocks (boxes in Figure 2) should be separated by at least 1 hour.

3.5.1 Screening Period

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

Following signature of the informed consent for the study, screening procedures to confirm eligibility may be performed across multiple days, as needed, during the Screening Period. Washout of previous medications can begin once the subject signs the informed consent regardless of the 28 day screening period. If a subject arrives for a visit not having fasted (overnight fast, 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 overnight.

Please refer to Table 1for 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, viral serology and pregnancy tests), 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(s) result(s) are to 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.

3.5.2 Double-blind Treatment Period

Day 1 (Visit 2) to Day 84 ±2 (Visit 6/Week 12)

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 (i.e., including Visit 2 [Randomization Visit]), should be performed under fasted conditions (overnight fast, 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 overnight. Exception to this would be Visit 2, at which all study procedures have to be completed within the same session, therefore, if the subject is not fasted, the full visit should be rescheduled.

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 a 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 QD, in the morning, regardless of food. However, subjects should not take study drug in the morning of the day of a study visit until after all study procedures

have been completed (except for appropriate PK samples collection procedures as discussed in Figure 2). On those days, study drug will be administered at the site by the study personnel from the subject's previously supplied study drug blister cards, if available, except for Visit 6, 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 the visit, 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.

The exact date and time of the last three doses prior to the PK sample collection and the dosing time after the initial (trough) PK sample collection at each visit during the Treatment Period (i.e., Visits 2 through 6) should be documented.

Study drug will not be administered and all remaining study drug will be collected from the subjects at Visit 6.

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 6 should be performed, if possible, prior to any changes made in the subject's anti-psoriasis therapy.

3.5.3 Follow-up Period

Day 84 ±2 (Visit 6/Week 12) to Day 112 ±2 (Visit 7/Week 16)

The Follow-up Visit will occur approximately 4 weeks after the last dose of study drug. Similar to all other study visits, 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 7 should be performed approximately 4 weeks after the last dose of study drug.

3.5.4 Study Restrictions

3.5.4.1 Previous and Concomitant Medication Restrictions

Please refer to the tables below for the list.

Table 2. Psoriasis Therapy Restrictions

Prohibited Period	Medication(s)
Within 12 weeks (or 5 times the PK half-life, whichever is longer) prior to Visit 2 and through Visit 7	• Biologic agents (marketed or investigational) • Investigational systemic therapies
Within 28 days prior to Visit 2 and through Visit 7	• Investigational topical therapies • Acitretin • Methotrexate • Cyclosporine • Apremilast • Fumaric acid ester • Oral/parental corticosteroids (including intramuscular, intradermal or intraarticular administration) • Psoralen plus ultraviolet A (PUVA) therapy • Ultraviolet A (UVA) therapy • Ultraviolet B (UVB) therapy
Within 14 days prior to Visit 2 and through Visit 7	• Topical steroids • Topical vitamin A or D analog preparations • Anthralin • Topical calcineurin inhibitors (e.g., cyclosporine) • Topical salicylic acid

Use of one (1) topical moisturizer (e.g., Cetaphil®) will be allowed during the study. This may not be used 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 can be withdrawn and the subject will be treated clinically per existing standard of care.

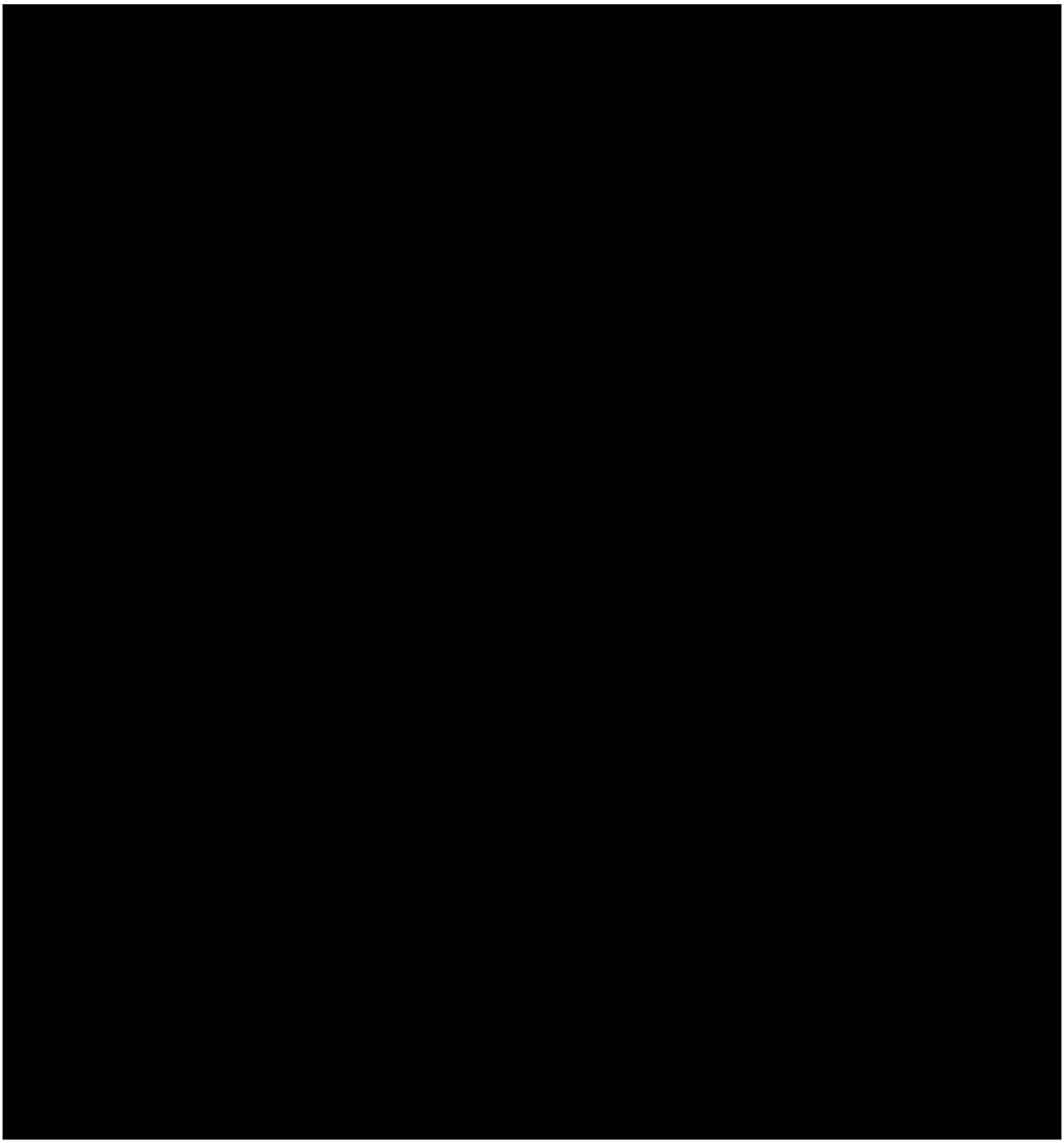
Table 3. Other Medications Restrictions

Prohibited Period	Medication(s)
Any time prior to or during the study (through Visit 7)	• Antipsychotic therapy • Anti-retroviral therapy and alpha-interferon • Anti-cancer chemotherapy
Within 12 weeks prior to Visit 2 and through Visit 7	• Monoamine oxidase inhibitors • Isoniazid
Within 28 days prior to Visit 2 and through Visit 7	• Doxycycline and minocycline • Pentoxifylline • Sulfones (e.g., Dapsone) • Colchicine and systemic metronidazole • Vitamin B6 at doses >100 mg/day • Cannabinoids, including marijuana. [redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Chronic use*	• NSAIDs

*NSAID cannot be used for more than 3 days in a week; low dose prophylactic use of aspirin is allowed.

[redacted]

[redacted]



General Medication-related Protocol Instructions:

[redacted]

[redacted]

- Generally, medication dose/route of administration changes 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);
- Contact the Medical Monitor with questions regarding prior/concomitant therapy.

3.5.4.2 Dietary Restrictions

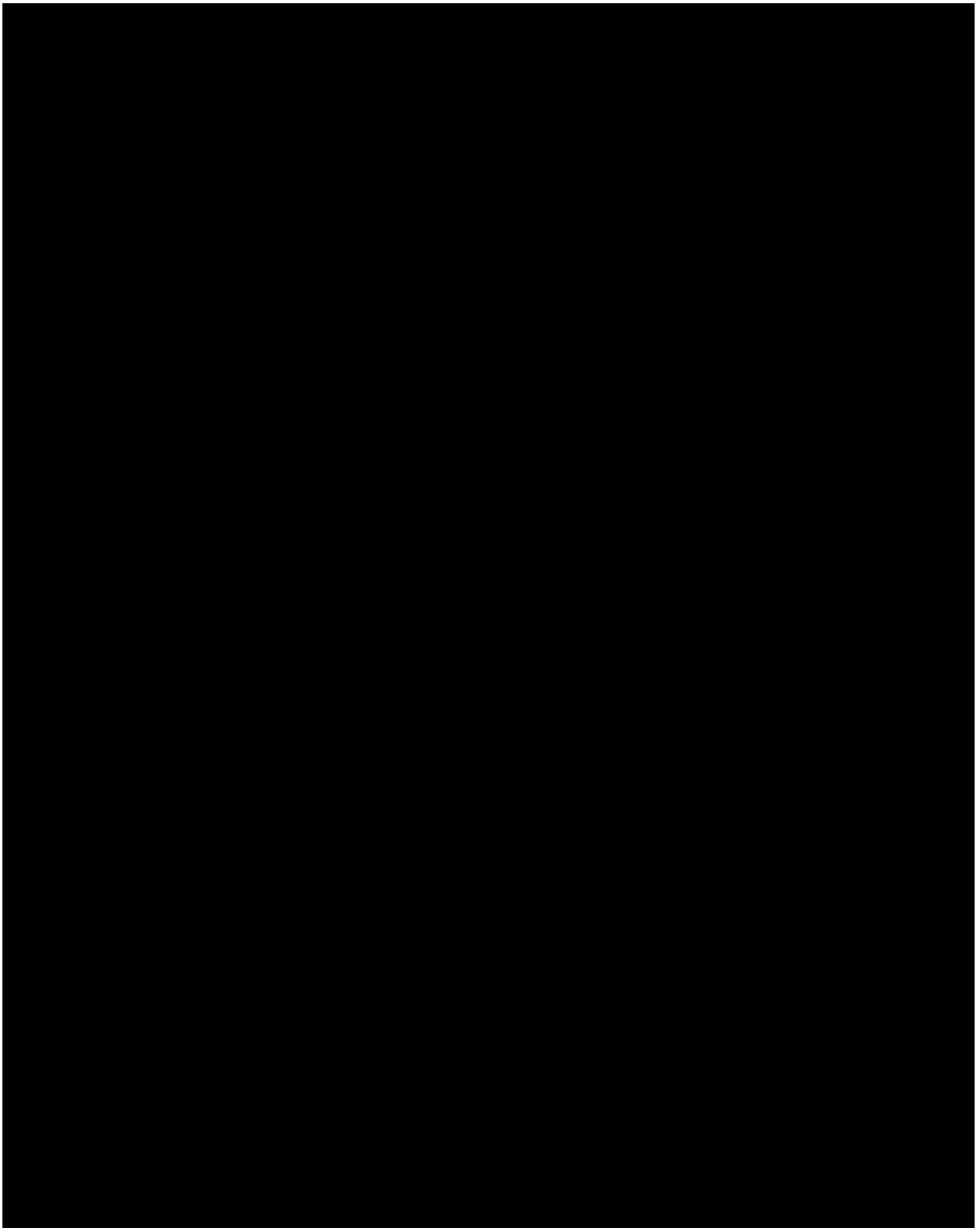
Grapefruit juice, grapefruit and sour oranges are not permitted for at least 3 days before beginning the Treatment Period and during the Treatment Period.

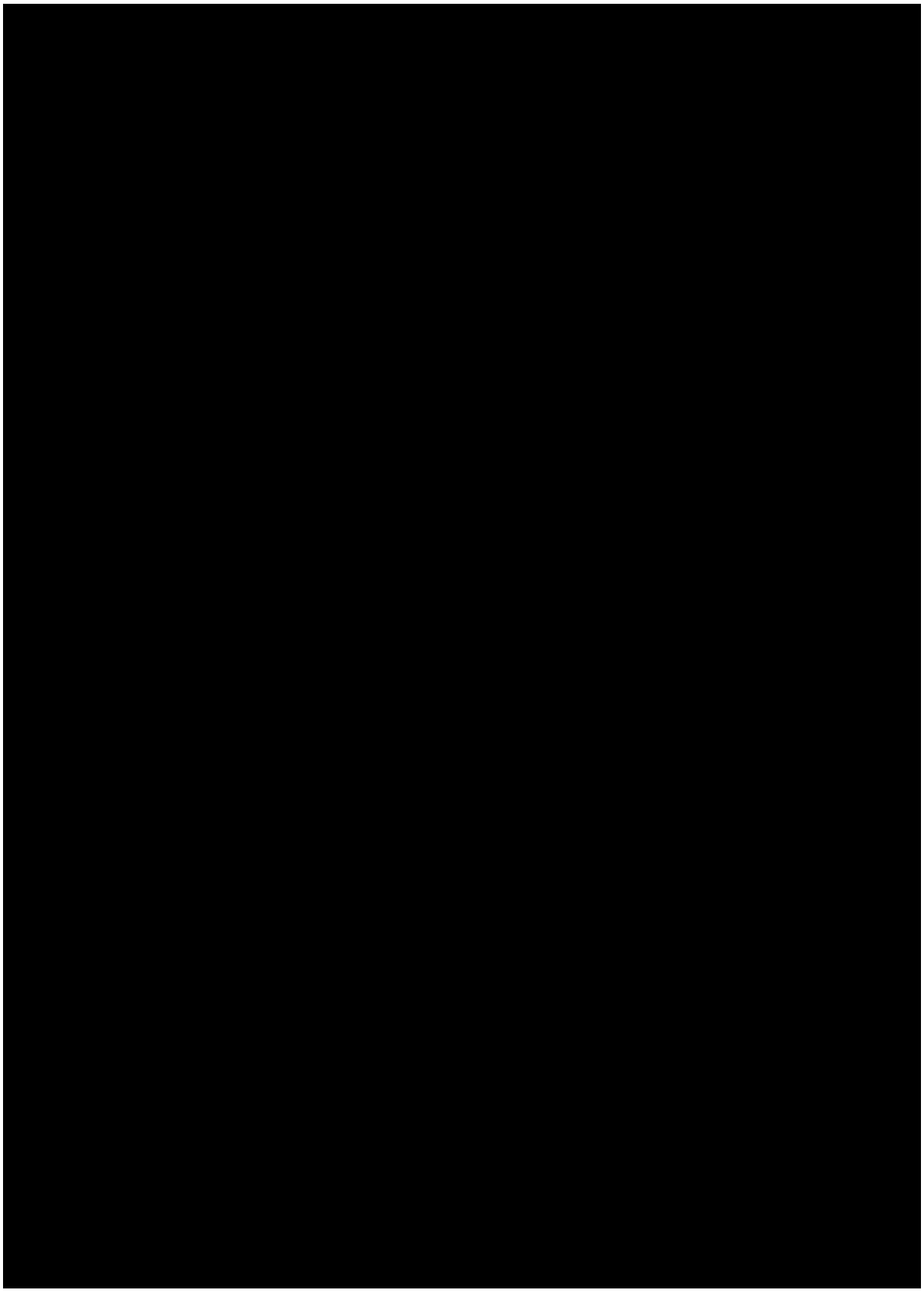
3.5.4.3 UV Related Restrictions

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

3.5.4.4 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 throughout the study duration (i.e., from Visit 2 through the Follow-up Visit).
- 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.
- Local standard recommendations (e.g., insect repellents) should be followed to minimize the risk of infection with the Zika virus in subjects enrolled in the study.





3.5.6 Procedure Definitions

3.5.6.1 Static Physician's Global Assessment

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

The sPGA assessments should be performed on all psoriatic lesions by the same evaluator throughout the study. The sPGA is used to determine the severity of subject's psoriatic lesion at a given time point. The psoriatic lesion will be graded for induration, erythema and scaling based on the scales below. The 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 = minimal plaque elevation, ~0.25 mm
2 = mild plaque elevation, ~0.5 mm
3 = moderate plaque elevation, ~0.75 mm
4 = marked plaque elevation, ~1 mm
5 = severe plaque elevation, ~1.25 mm or more

Erythema (E)
0 = no evidence of erythema, hyperpigmentation may be present
1 = faint erythema
2 = light red coloration
3 = moderate red coloration
4 = bright red coloration
5 = dusky to deep red coloration

Scaling (S)
0 = no evidence of scaling
1 = minimal; occasional fine scale over less than 5% of the lesion
2 = mild; fine scale dominates
3 = moderate; coarse scale dominates
4 = marked; thick, nontenacious scale dominates
5 = severe; very thick tenacious 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 = Marked – majority of lesions have individual scores for I+E+S/3 that averages 4
5 = Severe – majority of lesions have individual scores for I+E+S/3 that averages 5
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 Area and Severity Index

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.

For a given subject, the PASI assessments should be performed by the same evaluator throughout the study.

The PASI score will be derived as indicated in Table 7.

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. Further practical details help 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:

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

Where,

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 7. 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 Psoriasis Body Surface Area Assessment

The BSA assessment will be performed by the same Investigator throughout the study 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. 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. For a given subject, the BSA assessments should be performed by the same evaluator throughout the study.

3.5.6.4 Skindex-16

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

Skindex-16 is a 16-item, skin-related quality of life questionnaire (QOL) and has 3 domain scores: symptoms, emotions and functioning. Each 16-item QOL questionnaire will be reported as a scale 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

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 intensity of their itch on an 11-point scale ranging from 0 (no itch) to 10 (worst itch imaginable). Higher scores indicate greater itch intensity. In this study, both worst itch intensity (WI-NRS) and average itch intensity (AI-NRS) during a 24-hour recall period will be captured using the [redacted].

The Itch NRS score will be recorded by the subject using the [redacted] 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.

3.5.6.6 Physical Examination

The physical examinations will be performed by a physician or 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, [redacted], psychiatric/emotional, lymphatic and musculoskeletal systems.

3.5.6.7 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 in order 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.

3.5.6.8 Medical History

A complete medical history will be performed at Visit 1 and will include evaluations for past or present conditions. Specifically, any known history of psoriatic arthritis will be documented.

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

3.5.6.9 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.

3.5.6.10 12-Lead ECG

12-lead ECG recordings and conduction intervals including RR, PR, QRS, QT and Fridericia-corrected QT interval (QTcF) 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 3 minutes prior to the 12-lead ECG assessment.

3.5.6.11 Hematology

Blood samples to assess complete blood count including erythrocytes, hematocrit (Hct), hemoglobin (Hgb), 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.

3.5.6.12 Serum Biochemistry

Blood samples to assess ALT, ALB, ALP, AST, bilirubin, blood urea nitrogen (BUN), calcium, carbon dioxide, chloride, creatinine phosphokinase (CPK), creatinine (CRN), gamma-glutamyl transferase (GGT), globulin, glucose, CRP, lactate dehydrogenase (LDH), phosphate, potassium, protein, sodium, urate, will be obtained under fasted conditions according to the schedule summarized in Table 1.

3.5.6.13 Bone Specific ALP

Blood samples to measure bone specific ALP will be obtained according to the schedule summarized in Table 1.

3.5.6.14 Lipid Panel

Blood samples to measure cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglycerides will be obtained according to the schedule summarized in Table 1.

3.5.6.15 Serum Immunoglobulins

Blood samples to measure Serum IgG, IgM and IgA will be obtained according to the schedule summarized in Table 1.

3.5.6.16 25-hydroxyvitamin D

Blood samples to measure 25-hydroxyvitamin D will be obtained according to the schedule summarized in Table 1.

3.5.6.17 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.

3.5.6.18 Viral Serology

Blood samples to assess HbcAb (HBsAg), HCV Ab and HIV Ab will be obtained at the Visit 1.

3.5.6.19 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.

3.5.6.20 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.

3.5.6.21 Glycosylated Hemoglobin

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

3.5.6.22 Pregnancy Test

Blood samples will be collected at Visit 1 for a serum pregnancy test to assess human chorionic gonadotropin (βHCG) levels for all female subjects. At Visits 2 through 7, urine pregnancy tests will be performed only for female subjects of childbearing potential.

3.5.6.23 Follicle-stimulating Hormone

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

3.5.6.24 PPD Test and QuantiFERON®-TB Gold Test

The PPD skin test (also known as Mantoux test) or the QuantiFERON®-TB Gold (Gold-In-Tube test according to the local standard of care) may be used as tuberculosis screening tools for the study during the Screening Period. For subjects with a history of Bacille Calmette-Guérin (BCG) vaccination or in case PPD test fails, the QuantiFERON®-TB Gold-In-Tube test should be performed.

If the PPD test is conducted, the reaction must be read between 48 and 72 hours after administration (a subject that does not return after 72 hours must be rescheduled for a repeat PPD test). The reaction will be measured in millimeters of the induration (palpable, raised, hardened area or swelling). The reader will not measure erythema (redness). The diameter of the indurated area will be measured across the forearm (perpendicular to the long axis). An induration of 5 or more millimeters is considered positive.

If the QuantiFERON®-TB Gold-In-Tube test is performed, blood samples will be collected, processed and shipped during the Screening Period, according to the laboratory instructions. In the case of an indeterminate QuantiFERON®-TB Gold-In-Tube 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 (screening failure) and re-training of the applicable parties at the site and/or central laboratory level should be considered.

Subjects who have had household contact with a person with active tuberculosis are excluded, unless appropriate/documented prophylaxis for tuberculosis was successfully administered.

3.5.6.25 Chest Radiography

Chest radiography to include two views (anterior-posterior and lateral) will be obtained during the Screening Period in all subjects. If an 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]

3.5.6.28 Photography

All subjects will be required to take photographs of [redacted] four half-body views (i.e., upper anterior, lower anterior, upper posterior, and lower posterior) according to the schedule presented in Table 1. However, 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. In all the photographs, subject identification will be blinded. Additionally, the photography manual will include detailed procedures on photograph masking is to be done hence assuring protection of subject privacy.

3.5.6.29 Prior Biologics

Information pertaining to prior biologics use will be collected.

3.5.6.30 Prior/Concomitant Medications

Information pertaining to all medication use (including prescription, over-the-counter, supplements, vitamins and minerals) will be collected for the period of at least 30 days prior to the Screening Visit (Visit 1) and throughout the study. For medications excluded for a longer than a 30-day period, as described in Section 3.5.4.1, the timeframe for collecting this information will be extended to cover at least the exclusion period.

[redacted]

[redacted]

3.5.6.32 Pharmacokinetic Procedures

3.5.6.32.1 Blood Samples for Pharmacokinetic Assessments

Blood samples for the quantification of plasma JTE-051 will be collected, according to the schedules summarized in Table 1 and Figure 2. Trough PK blood samples will be collected in the fasted state at pre-specified study visits.

At each study visit during the treatment period (i.e., Visits 2 through 6), the actual dosing date and time, as well as the sample collection date and time will be documented for PK data analysis (see Figure 2). Refer to the laboratory manual for specific instructions for the collection, processing, storing and shipping of blood samples for PK assessments.

3.5.6.32.2 Analysis of JTE-051 in Plasma

JTE-051 in plasma will be analyzed using a validated high-performance liquid chromatography/tandem mass spectrometry (LC-MS/MS) method.

The laboratory performing the JTE-051 plasma concentration assessments will be unblinded to facilitate analysis of only the samples from the JTE-051-treated subjects. Plasma samples from placebo subjects may be analyzed as needed.

3.5.7 Clinical Institutions and Laboratories

This study will be conducted by:

[redacted]

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: As provided by the ICH criteria, an SAE is any adverse drug experience occurring at any dose that results in any of the following outcomes:

- death
- a life-threatening adverse drug experience
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant disability/incapacity
- a congenital anomaly/birth defect
- other important medical event

Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience 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. Examples of such 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 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 reaction, the nature (specificity) or severity of which is not consistent with the applicable product information (e.g., IB).

Death: Death represents an outcome and a SAE criterion, 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 (diagnosis of same) would qualify as an SAE.

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

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

Physical Examination, [redacted], 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 [redacted] 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 those which are a result of an AE which has already been reported.

Pre-existing conditions that are detected at the Screening Visit (Visit 1), including abnormalities in ECG, physical examination, [redacted], 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:

- Mild: No interference with functioning.
- Moderate: No significant interference with functioning.
- Severe: Significant interference with functioning.

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-051, the currently-known safety profile of JTE-051, known class effects of similar MOA drugs and any other information that is considered relevant by the Investigator.

Akros Pharma Inc. evaluates the relationship of an AE to the study drug using the following three categories:

- Not Related
- Possibly Related
- Related

Action Taken with Regard to Study Drug:

Akros Pharma Inc. evaluates the action taken with the treatment product and/or interacting product 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)

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 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 serious criterion; in such case when they would be reported as both an AE and an SAE. Adverse events 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).

The Investigator must continue to follow the subject until the SAE has subsided, the condition becomes chronic in nature, stabilizes (in the 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 any Suspected Unexpected Serious Adverse Reaction (SUSAR) reports for onward submission to their local IRB/IEC as required. All 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, all SUSARs will be reported by the Sponsor or designee 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

28 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 will 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 by any confirmed use of blinded study medication of more than four tablets once a day. If such situations occur, 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-051, thus appropriate symptomatic and/or supportive care is to 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 overdoses 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 the overdose as soon as possible, but not later than the timeframe requested by the Sponsor or designee after the investigator or qualified designee first becomes aware of the overdose. Instructions will be provided on how to collect this information.

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 study 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

[redacted]

3.7.3 Storage and Handling Procedures

The JTE-051 and placebo tablets should be stored at room temperature between 20 and 25°C (United States Pharmacopeia [USP]) and in a secure location with restricted access.

3.7.4 Clinical Supplies Packaging

Each site will receive a supply of double-blind study drug packaged as blister cards corresponding to 8 days of QD dosing. Each blister card will contain a total of 32 JTE-051 tablets.

Study drug blister cards may be labeled with the following information, as appropriate:

- Sponsor identity and protocol number
- Card number
- Dosing instructions
- Spaces for site personnel to add subject number and subject initials
- Spaces for site personnel to add visit number, site number and Investigator name
- Spaces for site personnel to add the card identifier, as appropriate
- Quantity and identity of contents
- Lot number and storage conditions
- Expiration date
- For investigational use only statement

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

Treatment Group	Tablet 1	Tablet 2	Tablet 3	Tablet 4
JTE-051 50 mg	JTE-051 50 mg	JTE-051 Placebo	JTE-051 Placebo	JTE-051 Placebo
JTE-051 100 mg	JTE-051 50 mg	JTE-051 50 mg	JTE-051 Placebo	JTE-051 Placebo
JTE-051 150 mg	JTE-051 50 mg	JTE-051 50 mg	JTE-051 50 mg	JTE-051 Placebo
JTE-051 200 mg	JTE-051 50 mg	JTE-051 50 mg	JTE-051 50 mg	JTE-051 50 mg
Placebo	JTE-051 Placebo	JTE-051 Placebo	JTE-051 Placebo	JTE-051 Placebo

3.7.5 Administration of Study Drug

During the Treatment Period, beginning on the day of Visit 2, subjects will self-administer one dose of study drug (4 tablets) daily for 12 weeks. Study drug will be taken QD in the

morning, 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 samples 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.

Randomized subjects will receive three study drug blister cards at Visits 2 and two study drug blister cards at Visit 3. Subjects will receive four blister cards each on Visits 4 and 5. The subjects will be instructed to use the blister cards on a first-in/first-out basis and to return all study drug blister cards from the former visit for accountability and compliance assessment at Visits 3, 4, 5 and 6 for accountability and compliance assessment. Following completion of accountability and compliance assessments, any unused blister card or a partially used blister card with the study drug available will be returned to the subject. At Visit 6, study drug will not be dispensed.

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 also ensures that all study drug will be dispensed only to study 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 85 eligible subjects with moderate to severe plaque psoriasis will be randomized into this study. Subjects will be randomized in a 1:1:1:1:1 ratio (17 subjects per treatment group) to receive JTE-051 50 mg, JTE-051 100 mg, JTE-051 150 mg, JTE-051 200 mg or placebo QD. Randomization will be stratified based on prior exposure of subjects to biologic therapy (i.e., biologic treatment-naïve vs. biologic treatment-experienced subjects).

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). The JTE-051 50 mg tablets, as well as the placebo tablets will be supplied as unbranded tablets which are identical in appearance.

The laboratory performing the JTE-051 plasma concentration assessments will be unblinded to facilitate analysis of only the samples from the JTE-051-treated subjects. Plasma samples from placebo-treated subjects may be analyzed as needed (see Section 3.5.6.32.2).

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 Sponsor's Medical Monitor prior to breaking the code. If this is not possible and 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 Sponsor's 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. A formal SAP will be developed at a later time. Statistical issues 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 Randomized Population

The randomized population consists of all subjects who are randomized at Visit 2 to one of the five treatment groups: JTE-051 50 mg QD, JTE-051 100 mg QD, JTE-051 150 mg QD, JTE-051 200 mg QD and matching placebo QD.

3.8.1.2 Safety Population

Safety population consists of the randomized subjects who receive at least one dose of the study drug and have at least one post-randomization safety data.

3.8.1.3 Intent-To-Treat (ITT) Population

The ITT population consists of the randomized subjects who receive at least one dose of the study drug per randomization and have at least one post-randomization efficacy data.

3.8.1.4 Per Protocol (PP) Population

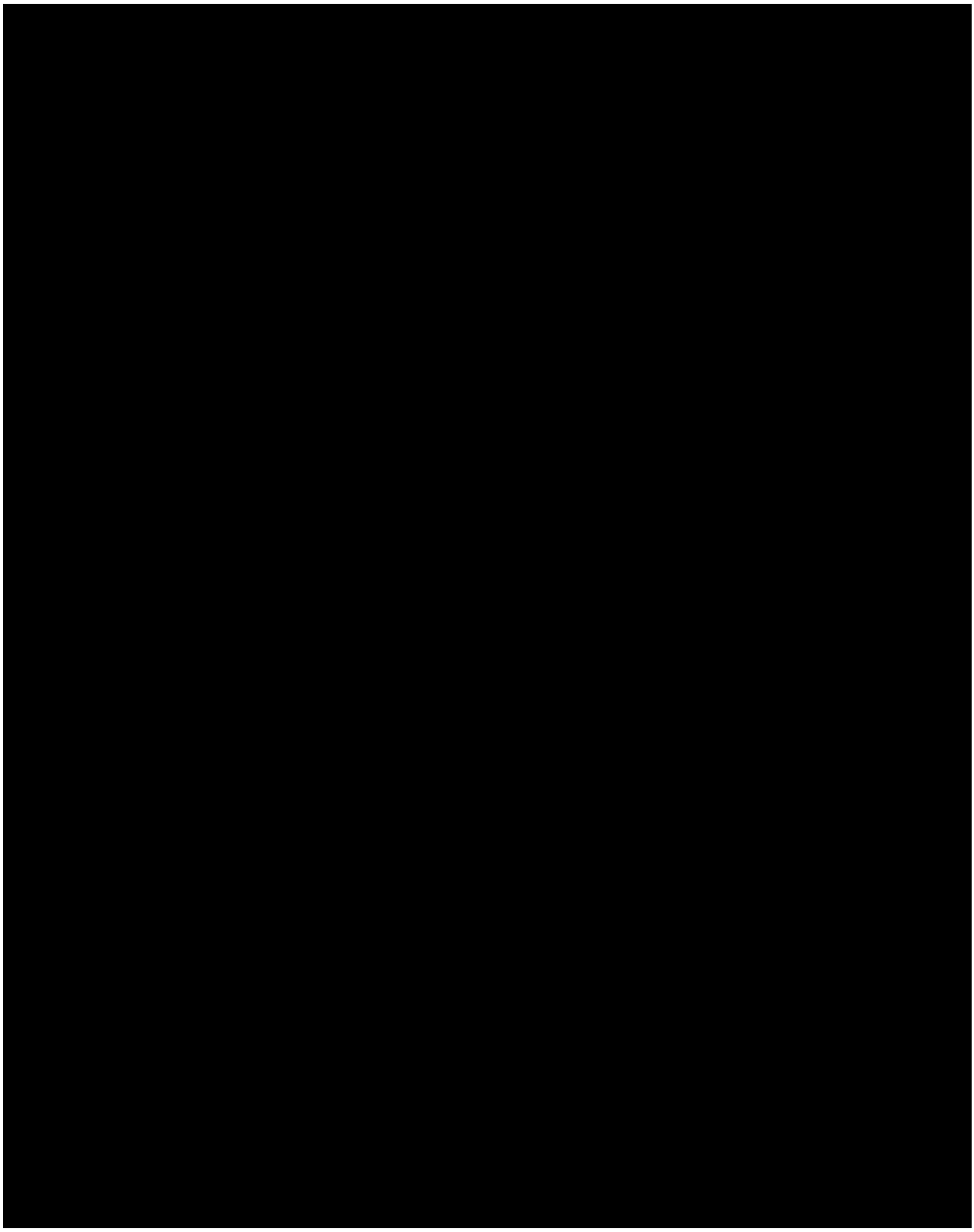
The PP population is a subset of the ITT population in which subjects do not have any major protocol deviations. A pre-analysis meeting will take place after all data have been entered into the database and cleaned, but before the release of the randomization code, to identify the PP population. The decisions made to select the PP population will be documented.

3.8.1.5 Pharmacokinetic (PK) Population

The PK population consists of the randomized subjects who receive at least one dose of JTE-051 and have at least one usable JTE-051 plasma concentration measurement.

3.8.1.6 Sample Size

Approximately 85 eligible subjects (17 subjects in each treatment group) will be randomized into the treatment period of this study.



3.8.2 Interim Analysis

No interim analysis is planned in this study.

3.8.3 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.

3.8.3.1 Efficacy Parameters

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

The secondary efficacy parameters are (evaluated at Weeks 2, 4, 8, 12 and 16, unless otherwise stated):

- Percent change from baseline in PASI score;
- Proportions of subjects achieving PASI 50, PASI 75, PASI 90 and PASI 100;
- Proportion of subjects achieving a sPGA score of 0 or 1;
- Change from baseline in sPGA score;
- Percent change from baseline in the psoriasis affected BSA;
- Change from baseline in Skindex-16;

[redacted]

3.8.3.2 Efficacy Data Analysis

For the purpose of efficacy analysis, the EOT value is defined as the last value taken during the double-blind treatment period after the first dose of study drug, without any treatment intervention.

[redacted]

Conventional statistical evaluations for efficacy parameters will also be conducted as described below:

For the primary efficacy parameter (PASI 75 at EOT), the Fisher's exact test will be used to compare each JTE-051 dose group with placebo. [redacted]

For dichotomous secondary efficacy parameters, similar analyses as the primary efficacy parameter will be used by time point, [redacted]

[redacted]

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 and the appropriate baseline and subject as the random effect. The appropriate baseline will be the parameter from which the efficacy parameter is derived, e.g., PASI score at Week 0 for the analysis of percent change from baseline in PASI score. The treatment effect of each JTE-051 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, therefore, results should be interpreted with the multiplicity in mind. The estimated treatment effect (relative to placebo) from the model, along with a two-sided 95% CI and p-value, will be tabulated where appropriate. The Newcombe's CI of the rate difference between JTE-051 dose and placebo will be computed when performing the Fisher's exact test. Graphical presentations of the treatment profile may be depicted. Sensitivity analysis, model fit assessment may be conducted and data transformation may be employed if appropriate.

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

[redacted]

3.8.3.3 Treatment by Center Effect

The randomization of this study is stratified by prior exposure to biologic therapy. 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.

3.8.3.4 Treatment by Baseline Covariate Effect

The treatment-by-baseline effect is not considered, however the baseline will be included in the respective parametric analysis model of the efficacy parameters where appropriate.

3.8.3.5 Subgroup Analysis

Subgroup analyses may be performed if appropriate.

3.8.3.6 Handling of Dropouts or Missing Data

There may be missing data intermittently (i.e., a missing visit or subject dropout). For dichotomous efficacy parameters analysis by 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 the latter case, any value after 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 continuous efficacy parameters, no imputation will be employed. This is because the mixed effect model gives valid estimates if the missing data mechanism is "missing at random", a common assumption made as the first approach for analysis.

For the sensitivity analysis of the primary efficacy parameter, i.e., PASI 75 at EOT, missing data may be imputed by all possible combinations of success and failure. The robustness of the finding can be evaluated using the tipping point analysis based on the plausibility of the imputed values.

Other missing data imputation methods may be employed for additional sensitivity analysis if deemed necessary.

3.8.4 Safety Analyses

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

3.8.4.1 Safety Parameters

The safety parameters are:

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

3.8.4.2 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 SOC and preferred term.

Other safety parameters will be summarized as appropriate.

3.8.5 Pharmacokinetic Analyses

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

3.8.5.1 Trough Concentration

Trough (pre-dose) plasma concentrations of JTE-051 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-051 will also be assessed.

3.8.5.2 Exposure-Response Relationship

The relationship between the exposure to JTE-051 (e.g., trough concentration of JTE-051) and response (e.g., the proportion of subjects achieving PASI 75 at EOT) may be explored.

3.8.5.3 Population Pharmacokinetic Analysis

Preliminary population PK analysis will be performed using plasma concentration of JTE-051. Population estimates of PK parameters of JTE-051 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 pharmacokinetics of JTE-051 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-051 obtained in other clinical studies. The population pharmacokinetic 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 or 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, provided that 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 a person designated by the Investigator, 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 and in all required reports.

Additionally, laboratory, photography and itch data may be received by Clinical Data Management from the appropriate Clinical Laboratory in electronic format. These data files may be merged with the clinical database.

4.3.1 Case Report Forms

Electronic CRFs 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 signed informed consent for the study and will be reviewed by the Clinical Monitor and verified against source documents. The CRFs 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 can be found 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 to be 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 in Canada, the Investigator shall retain records required to be maintained under this part for a period of twenty-five years following completion of the clinical trial in accordance with the local 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, the 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 or her personal physician or other appropriate medical personnel responsible for his or her welfare.

Data generated by this study must be available for inspection on request by representatives of regulatory authorities, the Sponsor or designee, and the 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. In order 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 any and 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 or designee for the 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 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

1. Valenzuela F, Paul C, Mallbris L, Tan H, Papacharalambous J, Valdez H, et al. Tofacitinib versus etanercept or placebo in patients with moderate to severe chronic plaque psoriasis: patient-reported outcomes from a phase 3 study. *J Eur Acad Dermatol Venereol*. 2016 Oct;30(10):1753-9.
2. Rachakonda TD, Schupp CW, Armstrong AW. Psoriasis prevalence among adults in the United States. *J Am Acad Dermatol*. 2014 Mar;70(3):512-6.
3. Huntley C. Psoriasis Epidemiology (Report Reference:DMKC0144470) Datamonitor Healthcare. Published on 22/09/2015:1-26.
4. Kubota K, Kamijima Y, Sato T, Ooba N, Koide D, Iizuka H, et al. Epidemiology of psoriasis and palmoplantar pustulosis: a nationwide study using the Japanese national claims database. *BMJ Open.* 2015 Jan 14;5(1):e006450.
5. Parisi R, Symmons DP, Griffiths CE, Ashcroft DM. Global epidemiology of psoriasis: a systematic review of incidence and prevalence. *J Invest Dermatol*. 2013 Feb;133(2):377-85.
6. Rapp SR, Feldman SR, Exum ML, Fleischer AB Jr, Reboussin DM. Psoriasis causes as much disability as other major medical diseases. *J Am Acad Dermatol*. 1999;41:401-7.
7. Büchau AS, Gallo RL. Innate immunity and antimicrobial defense systems in psoriasis. *Clin Dermatol*. 2007 Nov-Dec;25(6):616-24.
8. Arakawa A, Siewert K, Stöhr J, Besgen P, Kim SM, Rühl G, et al. Melanocyte antigen triggers autoimmunity in human psoriasis. *J Exp Med*. 2015 Dec 14;212(13):2203-12.
9. Langley RG, Elewski BE, Lebwohl M, Reich K, Griffiths CE, Papp K, et al. Secukinumab in plaque psoriasis - results of two phase 3 trials. *N Engl J Med.* 2014 Jul 24;371(4):326-38.
10. Leonardi C, Matheson R, Zachariae C, Cameron G, Li L, Edson-Heredia E, et al. Anti-interleukin-17 monoclonal antibody ixekizumab in chronic plaque psoriasis. *N Engl J Med*. 2012 Mar 29;366(13):1190-9.
11. Krueger JG, Ferris LK, Menter A, Wagner F, White A, Visvanathan S, et al. Anti-IL-23A mAb BI 655066 for treatment of moderate-to-severe psoriasis: safety, efficacy, pharmacokinetics, and biomarker results of a single-rising-dose, randomized, double-blind, placebo-controlled trial. *J Allergy Clin Immunol.* 2015 Jul;136(1):116-24.
12. Papp K, Thaçi D, Reich K, Riedl E, Langley RG, Krueger JG, et al. Tildrakizumab (MK-3222), an anti-interleukin-23p19 monoclonal antibody, improves psoriasis in a phase IIb randomized placebo-controlled trial. *Br J Dermatol*. 2015 Oct;173(4):930-9.

[redacted]

14. Heydendael VM, Spuls PI, Opmeer BC, de Borgie CA, Reitsma JB, Goldschmidt WF, et al. Methotrexate versus cyclosporine in moderate-to-severe chronic plaque psoriasis. *N Engl J Med*. 2003;349(7):658-65.

15. Patel RV, Clark LN, Lebwohl M, Weinberg JM. Treatments for psoriasis and the risk of malignancy. *J Am Acad Dermatol*. 2009 Jun;60(6):1001-17.

16. Corominas M, Gastaminza G, Lobera T. Hypersensitivity reactions to biological drugs. *J Investig Allergol Clin Immunol*. 2014;24(4):212-25.

17. Sahu N, August A. ITK inhibitors in inflammation and immune-mediated disorders. *Cur Top Med Chem*. 2009;9(8):690-703.

18. Liao XC, Littman DR. Altered T cell receptor signaling and disrupted T cell development in mice lacking Itk. *Immunity*. 1995 Dec;3:757-69.

19. Mueller C, August A. Attenuation of immunological symptoms of allergic asthma in mice lacking the tyrosine kinase ITK. *J Immunol*. 2003 May 15;170:5056-63.

[redacted]

25. Pfizer. Tanezumab Arthritis Advisory Committee Briefing Document. 2012 Feb 08.

[redacted]

27. Gimbel JS, Kivitz AJ, Bramson C, Nemeth MA, Keller DS, Brown MT, et al. Long-term safety and effectiveness of tanezumab as treatment for chronic low back pain. *Pain.* 2014 Sep;155(9):1793-801.

[redacted]

29. U.S. Department of Health and Human Services. National Institutes of Health. National Cancer Institute. Common terminology criteria for adverse events (CTCAE) Version 4.0. 2009 May 28 (v4.03: 2010 June 14).