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Clinical Study Protocol

PROTOCOL TITLE: A **M**ulticenter, Randomized, Double-blind, Placeb**O**-controlled, Parallel-group Study to E**V**aluate the **E**fficacy and Safety of JTE-051 Administered for 12 Weeks to Subjects with Active **R**heumatoid **A**rthritis (MOVE-RA)

PROTOCOL NUMBER: AE051-G-13-003

PROTOCOL DATE: 24 March 2016

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Cover Page

Akros Pharma Inc.

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PROTOCOL NUMBER:	AE051-G-13-003
DATE:	24 March 2016
IND NUMBER:	[redacted]
EUDRACT NUMBER	2015-003140-39
SPONSOR:	Akros Pharma Inc. 302 Carnegie Center, Suite 300 Princeton, NJ 08540
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MEDICAL MONITOR:	[redacted]

Signature Page

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The signatures below indicate approval of the protocol.

Sponsor Representative _____ _____
[redacted] Date

Sponsor Statistician _____ _____
[redacted] Date

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)

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
Ab	Antibody
ACPA	Anti–citrullinated protein antibody
ACR	American College of Rheumatology
ACR20	Percentage of subjects achieving at least 20% improvement from baseline in tender and swollen joint counts and at least 20% improvement in 3 of the 5 remaining ACR core set measures
ACR50	Percentage of subjects achieving at least 50% improvement from baseline in tender and swollen joint counts and at least 50% improvement in 3 of the 5 remaining ACR core set measures
ACR70	Percentage of subjects achieving at least 70% improvement from baseline in tender and swollen joint counts and at least 70% improvement in 3 of the 5 remaining ACR core set measures
ACR-N	Numeric ACR: the lowest percentage improvement from baseline of 3 measures: tender joint count, swollen joint count and median improvement of the remaining 5 core measures.
ADL	Activities of daily living
ADP	Action potential duration
AEs	Adverse events
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
Anti-CCP	Anti-cyclic Citrullinated Peptide
aPTT	Activated partial thromboplastin time
AR	Accumulation ratio
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
$AUC_{0\text{-}24}$	Area under the concentration-time curve from the time of dosing to 24 hours
$AUC_{0\text{-}inf}$	Area under the concentration-time curve from the time of dosing to infinity
AUC_{tau}	Area under the concentration-time curve during the dosing interval
BCG	Bacille Calmette-Guérin
BCRP	Breast cancer resistance protein
BMI	Body mass index

Abbreviation	Definition
BUN	Blood urea nitrogen
CABG	Coronary Artery Bypass Graft
CAIA	Collagen antibody-induced arthritis
CDAI	Clinical Disease Activity Index
CFR	Code of Federal Regulations
CI	Confidence interval
CIA	Collagen-induced arthritis
CL_F	Apparent oral clearance of drug following extravascular administration
C_{max}	Maximum concentration
COX	Cyclooxygenase
CRF	Case report form
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	Trough concentration
CV%	Coefficient of variation
CYP	Cytochrome P450
DAS	Disease Activity Score
DB	Double-blind
DDI	Drug-drug interaction
DIP	Distal interphalangeal
DMARDs	Disease-modifying anti-rheumatic drugs
ECG	Electrocardiogram
EGF	Epidermal growth factor
EOT	End of treatment
EULAR	European League Against Rheumatism
FGFR	Fibroblast growth factor receptor
Flt3	Fms-like tyrosine kinase-3
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GEE	Generalized estimating equation
eGFR	Estimated glomerular filtration rate

Abbreviation	Definition
HAQ-DI	Health Assessment Questionnaire Disability Index
HBc	Hepatitis B core
HBsAg	Hepatitis B virus surface antigen
HCV	Hepatitis C virus
HDL-C	High-density lipoprotein cholesterol
HEENT	Head, Ears, Eyes, Nose, Throat
βhCG	Human chorionic gonadotropin
hERG	Human ether-a-go-go related gene
HIV	Human immunodeficiency virus
hs-CRP	High-sensitivity C-reactive protein
IB	Investigator's brochure
ICH	International Conference on Harmonisation
IC_{50}	Half-maximal inhibitory concentration
IEC	Independent Ethics Committee
IFNγ	Interferon γ
IL-2	Interleukin-2
IL-6	Interleukin-6
IL-17	Interleukin-17
IMP	Investigational Medicinal Product
IP	Interphalangeal
IRB	Institutional Review Board
ITK	Interleukin-2-inducible T-cell kinase
ITT	Intent to treat
IWRS	Interactive web response system
LDL-C	Low-density lipoprotein cholesterol
LOCF	Last observation carried forward
MBI	Mechanism based inhibition
MCMC	Markov chain Monte Carlo
MCP	Metacarpophalangeal
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Definition
MMF	Mycophenolate mofeti
MMP	Matrix metalloproteinase
MOA	Mechanism of action
MTP	Metatarsophalangeal
MTX	Methotrexate
N/A	Not applicable
[redacted]	
NRS	Numerical Rating Scale
NSAIDs	Non-steroidal anti-inflammatory drugs
NYHA	New York Heart Association
PGA	Physician's Global Assessment
P-gp	P-glycoprotein
PI	Posterior interval
PIP	Proximal interphalangeal
PK	Pharmacokinetic(s)
PP	Per protocol
PPD	Purified Protein Derivative
PR	Interval from beginning of the P wave to the beginning of the QRS complex in the frontal plane
PT	Prothrombin Time
PTCA	Percutaneous Transluminal Coronary Angioplasty
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
OCT	Organic cation transporter
QD	Once daily
QOL	Quality of life
QRS	Duration of QRS complex in the frontal plane
QT	Interval from beginning of the QRS complex to end of the T wave in the frontal plane
QTcF	Fridericia-corrected QT Interval
RA	Rheumatoid Arthritis
RF	Rheumatoid Factor

Abbreviation	Definition
[redacted]	
RR	Interval from beginning of the QRS complex in the frontal plane to the next QRS complex
SAA	Serum amyloid
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SDAI	Simplified Disease Activity Index
SGA	Subject's Global Assessment
SNRIs	Serotonin-norepinephrine reuptake inhibitors
SOC	Standard of care
[redacted]	
SSRIs	Selective serotonin reuptake inhibitors
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{1/2}$	Elimination half-life associated with the terminal slope (λz) of a semilogarithmic concentration-time curve
TCR	T cell receptor
TDI	Time-dependent inhibition
TEAE	Treatment-emergent adverse event
TIA	Transient ischemic attack
t_{max}	Time to reach peak or maximum concentration following drug administration
TNF-α	Tumor necrosis factor-α
TNF-RI	Tumor necrosis factor receptor I
[redacted]	
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
USP	United States Pharmacopeia
VCAM-1	Vascular cell adhesion molecule-1
VEGF-A	Vascular endothelial growth factor A
V_F	Apparent volume of distribution following extravascular administration
YKL-40	Human cartilage glycoprotein 39

Protocol Synopsis

STUDY TITLE	A **M**ulticenter, Randomized, Double-blind, Placeb**O**-controlled, Parallel-group Study to E**V**aluate the **E**fficacy and Safety of JTE-051 Administered for 12 Weeks to Subjects with Active **R**heumatoid **A**rthritis (MOVE-RA)
PROTOCOL NUMBER	AE051-G-13-003
CLINICAL PHASE	Phase 2a
STUDY DURATION	Approximately 20-week duration per subject: • Up to a 28-day Screening Period • A 12-week double-blind (DB) Treatment Period • Approximately a 4-week Follow-up Period
STUDY OBJECTIVES	• To evaluate the clinical efficacy of JTE-051 in subjects with active rheumatoid arthritis receiving background non-biologic disease-modifying anti-rheumatic drug therapy. • To evaluate the safety and tolerability of JTE-051 administered for 12 weeks in subjects with active rheumatoid arthritis receiving background non-biologic disease-modifying anti-rheumatic drug therapy. • To evaluate the pharmacokinetics (PK) of JTE-051 in plasma of subjects with active rheumatoid arthritis.
STUDY DESIGN	This is a multicenter, randomized, double-blind, placebo-controlled, parallel-group, 12-week study in biologic and kinase inhibitor treatment-naive rheumatoid arthritis (RA) subjects on stable disease-modifying anti-rheumatic drug (DMARD) therapy, including methotrexate (MTX). 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. Subjects will continue to receive up to two non-biologic DMARDs, including MTX, throughout the study (at a stable background dose and route of administration for at least 12 weeks prior to Visit 2 and throughout the study) and will return for a Follow-up Visit approximately four weeks after the last dose of study drug is administered. Randomization will be stratified by geographical region and by the screening high-sensitivity C-reactive protein (hs-CRP).

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 250 subjects (50 subjects per treatment group).
KEY ELIGIBILITY CRITERIA	• Males and females, 18 to 75 years of age (inclusive) at the time of the Screening Visit; • A diagnosis of RA prior to the Screening Visit, based on the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) 2010 Classification Criteria; • Active disease despite ongoing therapy with up to two non-biologic DMARDs, including MTX at both the Screening and Baseline Visits (Visits 1 and 2), as defined by both: ✧ ≥6 out of 68 tender joints AND ✧ ≥6 out of 66 swollen joints; • Screening hs-CRP ≥1.2 x upper limit of normal (ULN), based on the central laboratory values; • Background treatment with up to two non-biologic DMARDs including MTX (mandatory) and one of the following medications (optional): sulfasalazine ≤3 g/day, hydroxychloroquine ≤400 mg/day or chloroquine: ≤250 mg/day at the time of the Screening Visit; ✧ The MTX dosage must be 15-25 mg/week (or the maximum documented tolerated dose for the subject, not <10 mg/week) and all background therapy must be stable, defined as no change in dose or route of administration for ≥12 weeks prior to the Randomization Visit (Visit 2). • No prior/current exposure to biologic and/or kinase inhibitor therapy; [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, once daily 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 for 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 the JTE-051 tablets) Not applicable (N/A) Oral administration for 12 weeks starting on the day of randomization at Visit 2, once daily 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 for Visit 6, when no study drug will be administered).
EVALUATION CRITERIA	**Primary Efficacy Parameters** • Percentage of subjects achieving at least 20% improvement from baseline in tender and swollen joint counts and at least 20% improvement from baseline in 3 of the 5 remaining ACR core set measures (ACR20 response rate) at end of treatment (EOT) **Secondary Efficacy Parameters** (will be evaluated at Weeks 2, 4, 8, 12 and 16 unless otherwise stated) • Percentage of subjects achieving at least 20, 50 and 70% improvement from baseline in tender and swollen joint counts and at least 20, 50 and 70% improvement from baseline in 3 of the 5 remaining ACR-core set measures, respectively (i.e., ACR20/50/70 response rate)

EVALUATION CRITERIA, Cont.	**Secondary Efficacy Parameters, Cont.** • Change from baseline in Simplified Disease Activity Index (SDAI) • Percentage of subjects who achieved remission based on SDAI (≤3.3) • Percentage of subjects who achieved low disease activity based on SDAI (≤11) • Change from baseline in Clinical Disease Activity Index (CDAI) • Percentage of subjects who achieved remission based on CDAI (≤2.8) • Percentage of subjects who achieved low disease activity based on CDAI (≤10) • Percentage of subjects in Boolean Remission • Change from baseline in Disease Activity Score (DAS) based on hs-CRP (DAS28-CRP) • Percentage of subjects with DAS28-CRP of <2.6 • Percentage of subjects with DAS28-CRP of <3.2 • Percentage of subjects with good EULAR response at Week 12 • Percentage of subjects with moderate EULAR response at Week 12 • The lowest percentage change from baseline of 3 measures: tender joint count, swollen joint count and median change of the remaining 5 core measures (numeric ACR [ACR-N] index) • Change from baseline in the Health Assessment Questionnaire Disability Index (HAQ-DI) • Change from baseline in the number of tender and swollen joint counts (68/66 joints will be counted) • Change from baseline in subject pain score by numeric rating scale (NRS) • Change from baseline in subject global assessment (SGA) of disease activity by NRS • Change from baseline in physician global assessment (PGA) of disease activity by NRS • Change from baseline in hs-CRP

EVALUATION CRITERIA, Cont.	[redacted] Safety Parameters • The number 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 (PK) Parameters • Trough plasma levels of JTE-051 • The relationship between the JTE-051 dose (exposure) and response may be assessed (exploratory)
STATISTICAL METHODS	For the primary efficacy parameter (ACR20 at EOT), the Fisher's exact test will be used to compare each JTE-051 dose group with placebo. Furthermore, the exact Cochran-Armitage trend test will be computed. For dichotomous secondary efficacy parameters, similar analyses as the primary efficacy parameter will be used by time point. [redacted]

STATISTICAL METHODS, Cont.	The model includes effects for treatment, time, treatment by time interaction, and the stratification factors and subject as the repeated factor. 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 factors and the appropriate baseline, and subject as the random effect. A linear trend test at each time point will be computed using appropriate linear contrast. All analyses will be performed at the two-sided α=5% significance level. No formal multiple comparison adjustment will be made. The estimated treatment effect (relative to placebo) from the model, along with a two-sided 95% confidence interval (CI) and p-value, will be tabulated where appropriate. Descriptive statistics of efficacy parameters over time will be presented by treatment. They 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. 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. With respect to the safety data analysis, descriptive statistics of vital signs, ECG parameters, and clinical laboratory data will be presented by treatment. Potentially clinically significant values for vital signs, ECG, and laboratory data will be flagged in data listings and may be summarized as appropriate. For PK data, descriptive statistics of the trough plasma concentration of JTE-051 will be presented by treatment.

1. INTRODUCTION

1.1. Background

1.1.1. Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a systemic autoimmune disease of unknown cause characterized by chronic and persistent joint swelling, joint tenderness and synovial joint destruction that leads to pain and disability.[1] Approximately 1% of the world's population is considered to be suffering from the disease[2] and the number of patients is estimated to be approximately 1.3 million in the US.[3] Females are more likely to suffer from the disease, with a reported ratio of male to female patients of 1:2.5. The disease can occur at any age, but it is most common among those aged 40 to 70 years, its incidence increasing with age.

In rheumatoid arthritis, abnormal activation of various inflammatory cells such as T cells and macrophages causes and exacerbates chronic synovitis. Patients mostly complain of morning stiffness as an initial symptom. The disease is characterized by inflammatory findings that involve multiple joints such as those in the fingers, hands and knees, leading to the development of pain, swelling associated with synovial fluid retention and local warmth. The inflammatory symptoms are mostly experienced in the early stage followed by repeated remissions and relapses, which lead to the destruction of cartilage and bone, with deformation of the joints over time, finally causing severe dysfunction. When the disease is highly active, various clinical symptoms such as general malaise, pyrexia, and anemia are observed as non-joint-related symptoms. It is known that these symptoms markedly impair the activities of daily life and finally worsen life prognosis. It has been reported that insufficient treatment shortens the life of patients with rheumatoid arthritis by 10 to 15 years compared with that of healthy individuals.[4]

1.1.2. Treatment of Rheumatoid Arthritis

The treatment of rheumatoid arthritis aims to maintain the physical functions of the patients and improve their quality of life (QOL) through control of symptoms and prevention of joint destruction.[5] To achieve these aims, drug treatments from an early stage of the disease based on the background of appropriate nonmedical therapies is recommended in US and Europe.[6,7] Currently, as therapeutic agents, disease-modifying anti-rheumatic drugs (DMARDs), non-steroidal anti-inflammatory drugs (NSAIDs), oral use and intraarticular injection of steroids, and biological agents are used. Disease-modifying anti-rheumatic drugs that can inhibit progression of the pathological conditions play a central role in the treatment. Methotrexate (MTX) is prescribed as the standard therapy and immunosuppressive drugs are prescribed as switch or combination therapy. Disease-modifying anti-rheumatic drugs alleviate pain and swelling by correcting the immune abnormality, but their efficacy is not sufficient, leaving some non-responders and those with a reduced response without relief. These drugs may also be able to inhibit the joint destruction, but their inhibitory effect on the progression of destruction of the cartilage and bone is not sufficient in the absence of remission. Since DMARDs are slow-acting, it takes a long time to improve the QOL, and the pathological condition may be allowed to progress if judgment to change the drug for non-responders is delayed. Since

rheumatoid arthritis has a chronic course, long-term therapies are usually required, however, very often, it is difficult to continue sufficient treatment due to adverse events (AEs) such as disorders in gastrointestinal tract associated with NSAID use, blood and liver AEs caused by DMARDs, as well as osteoporosis associated with steroids. Recently, it has been demonstrated that biological agents can quickly alleviate arthritis symptoms and suppress progression of joint destruction by selectively inhibiting the action of cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6).[8-11] However, long-term use of biological agents is also problematic, because they have the potential to increase the risk of infections and induce serious allergic reactions, are expensive and can be administered only by injection. Based on these considerations, new oral therapeutic drugs that can quickly alleviate pain and swelling, inhibit the progression of cartilage and bone destruction, and are superior to existing drugs in terms of safety, convenience, and cost efficiency are desired.

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.[12] 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.[13] 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.[14] This information suggest 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]

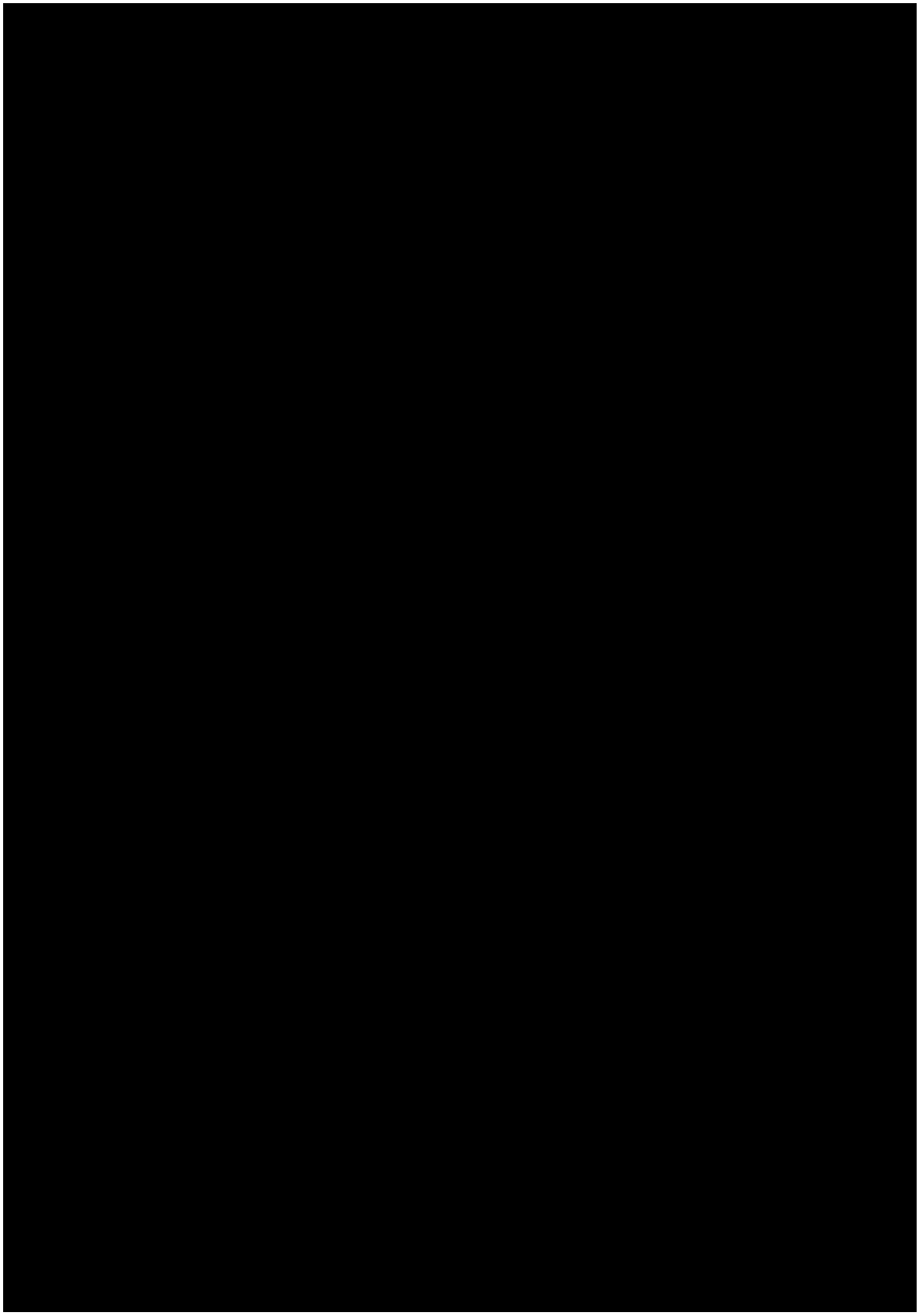
1.2. JTE-051

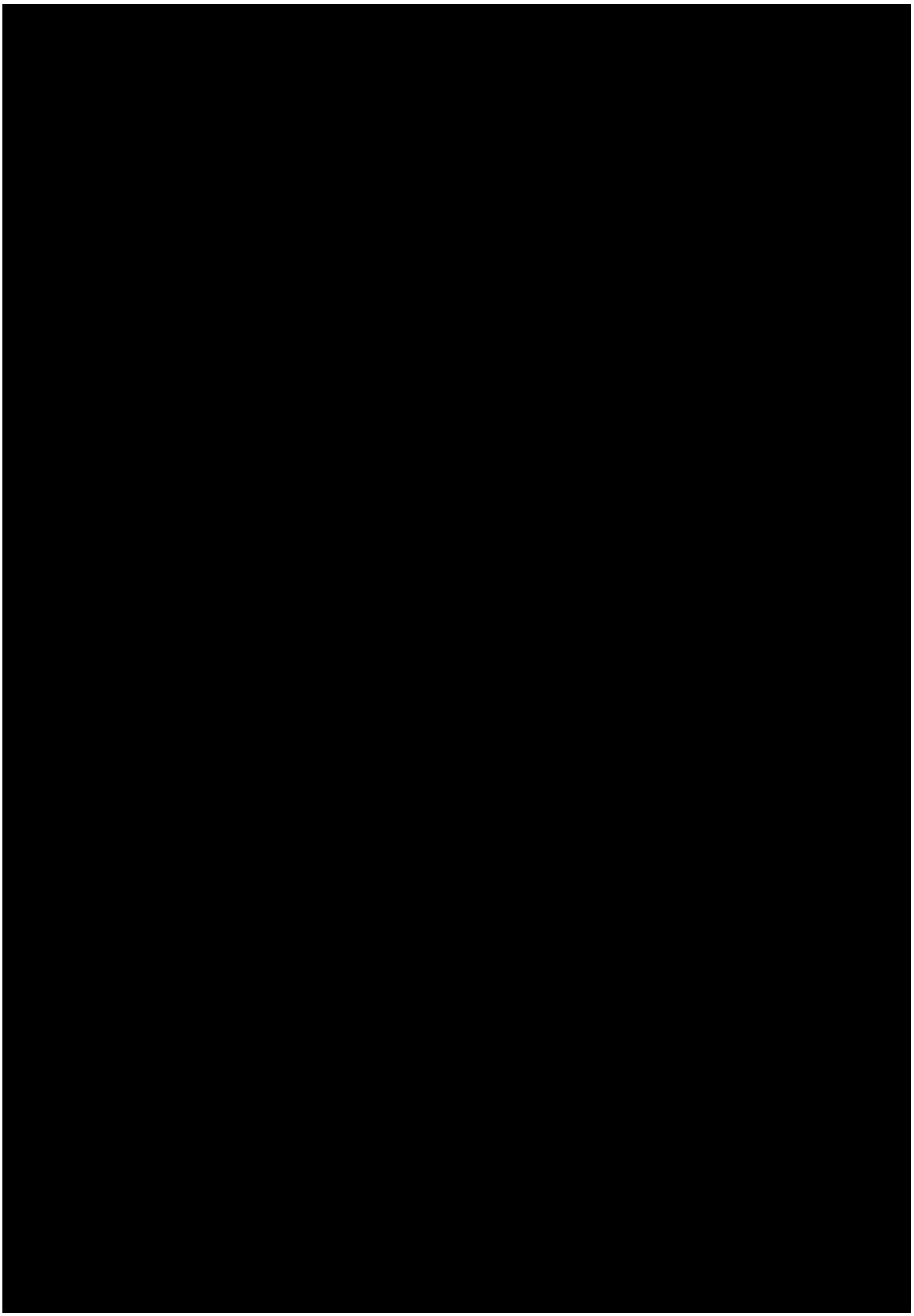
[redacted]

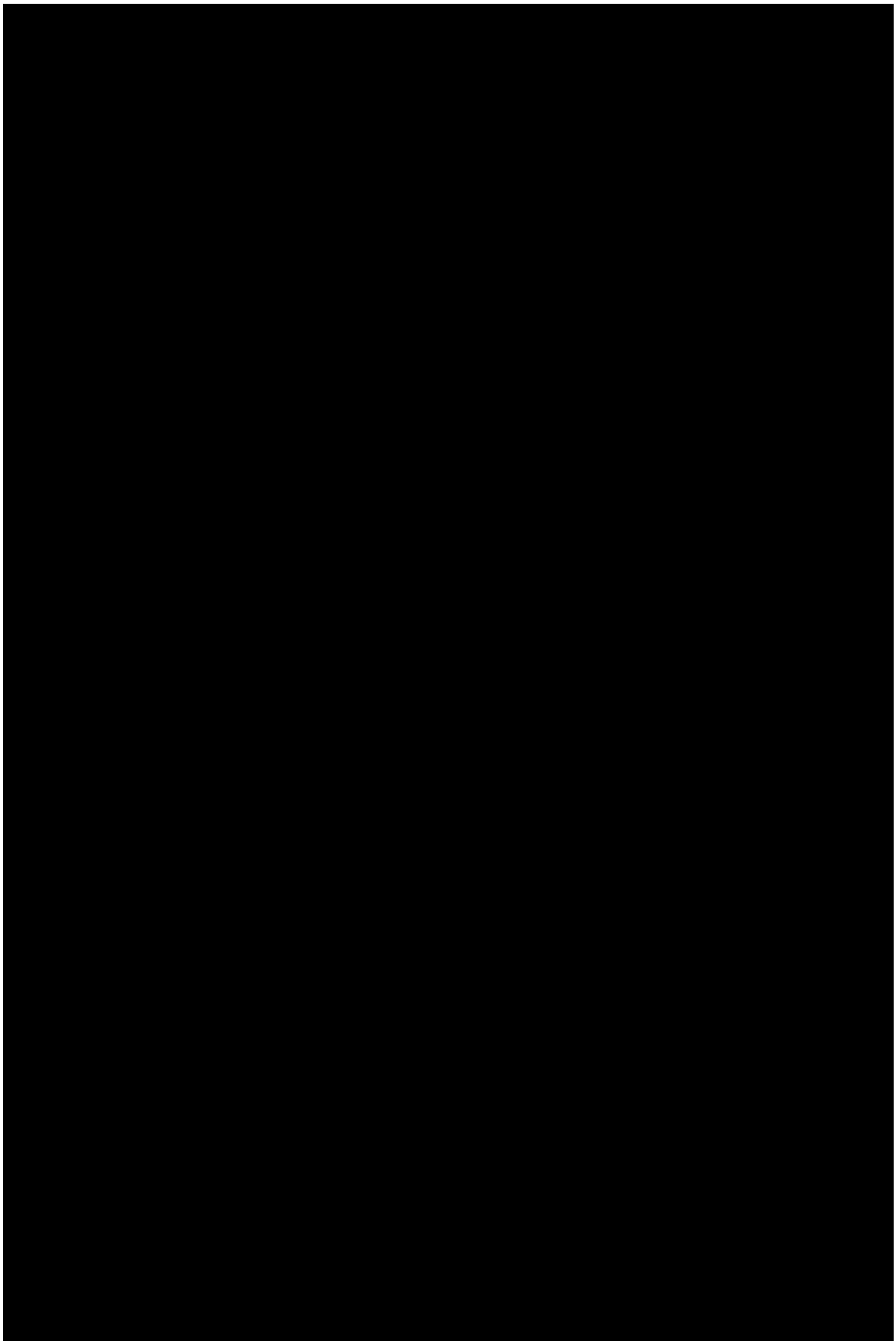
A brief summary of the nonclinical findings to date is included below. Additional details are described in the JTE-051 Investigator's Brochure (IB).

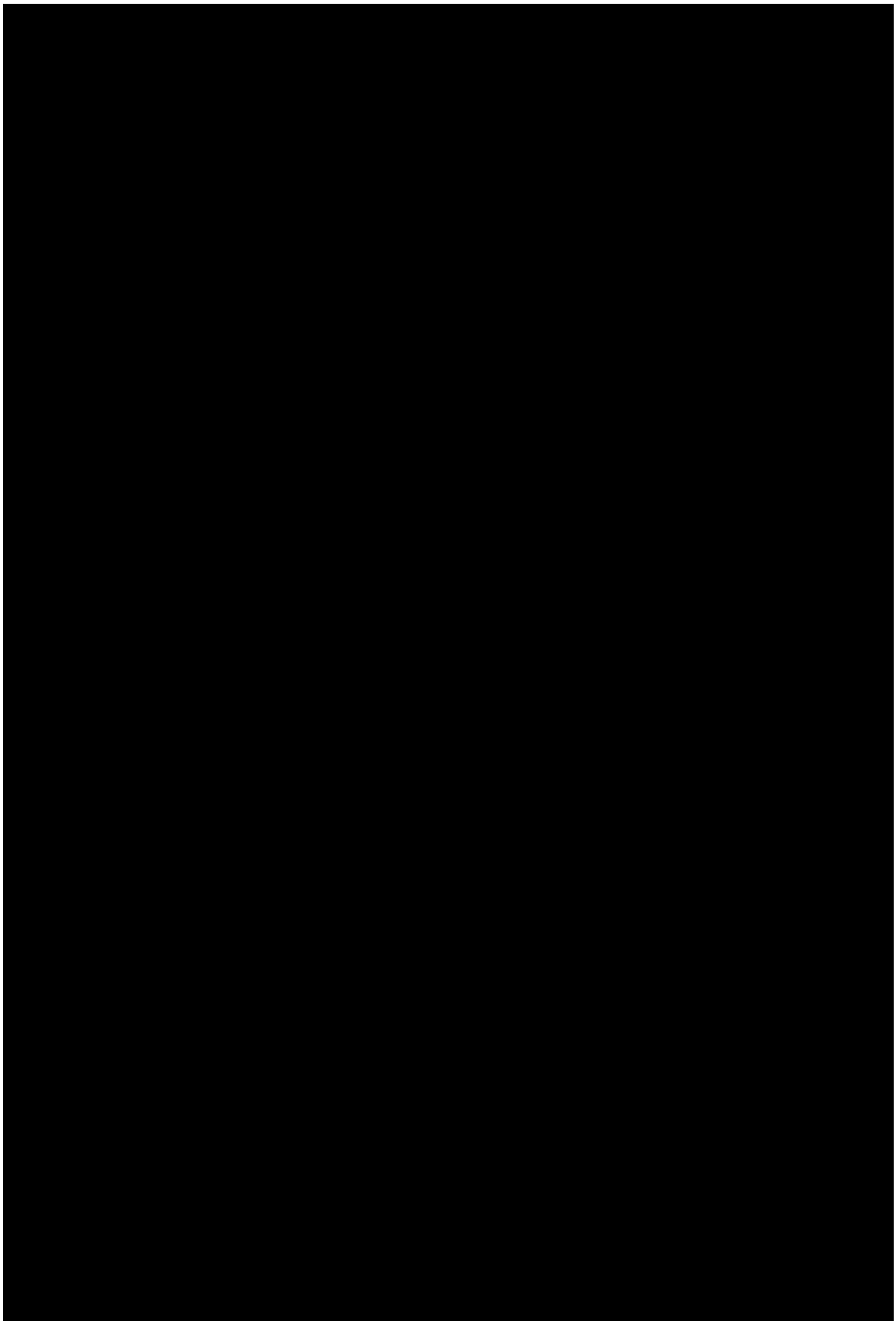
1.2.1. Nonclinical Studies

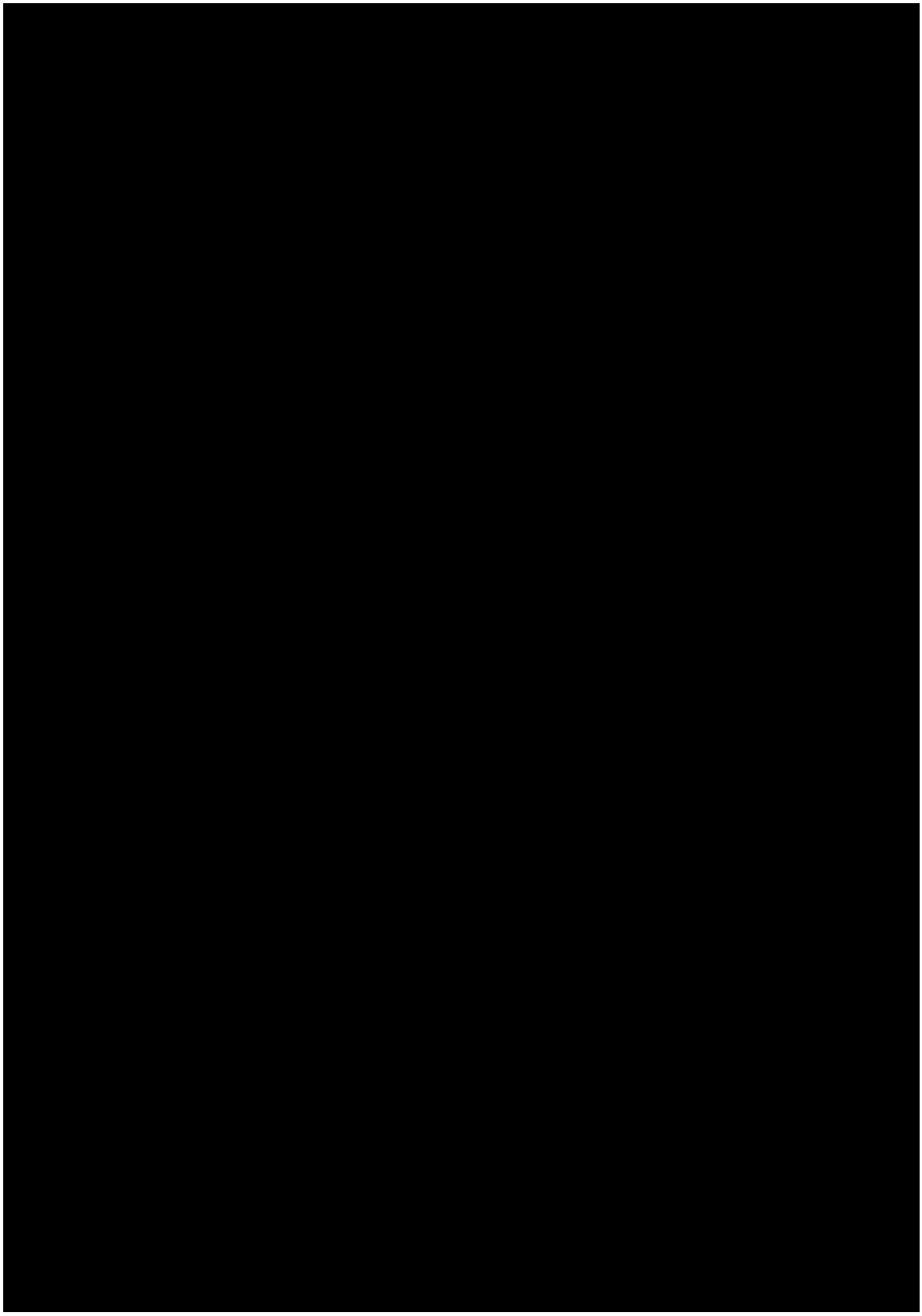
[redacted]

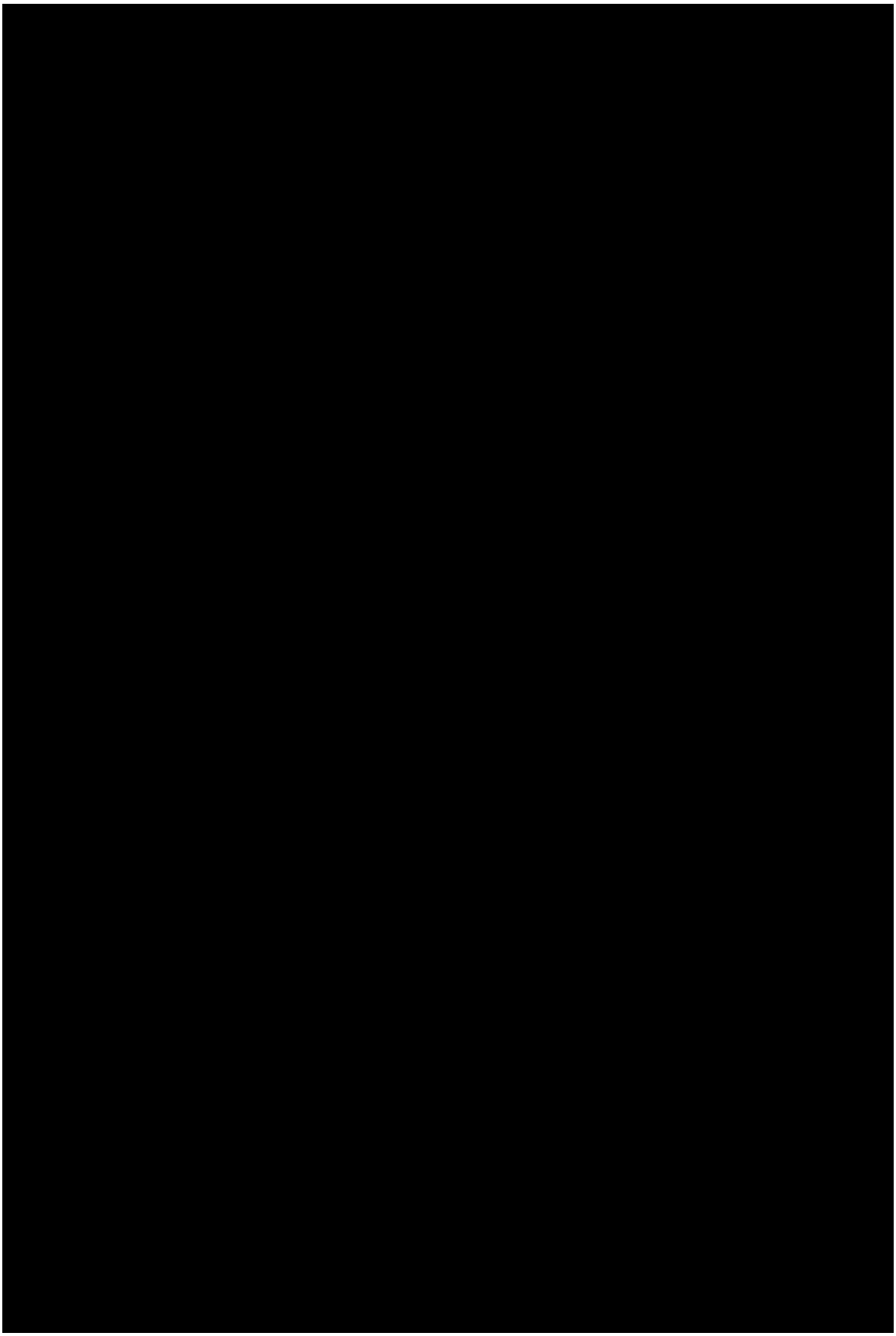


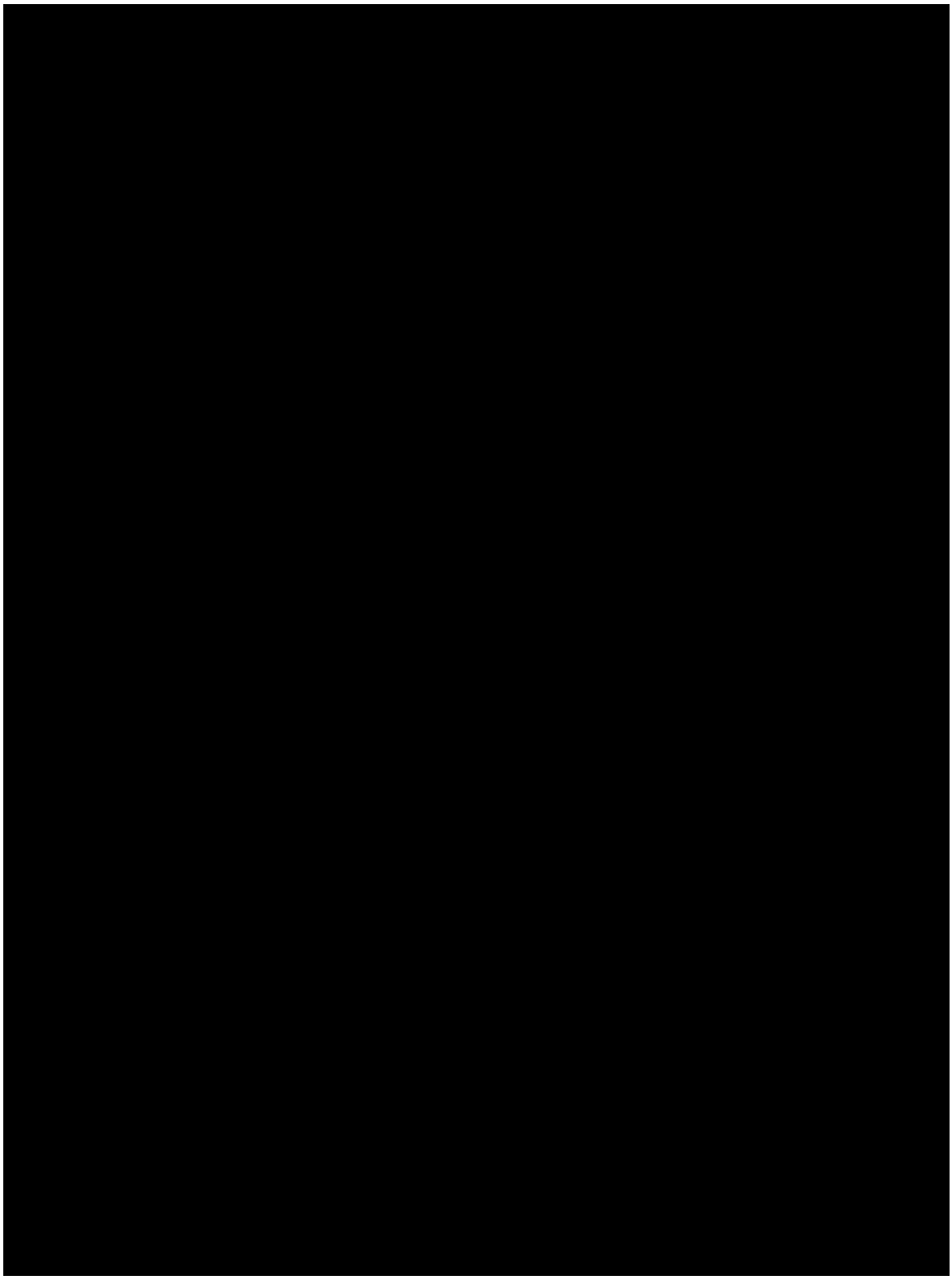












1.3. Justification of Study Population and Dose Selection

Justification for Study Population

[redacted]

Patients with a diagnosis of RA, based on the American College of Rheumatology (ACR)/European League against Rheumatism (EULAR) 2010 Classification Criteria[23] (see Appendix 1), that are MTX-insufficient responders, i.e., have active RA (defined by the number of tender and swollen joints) despite stable dosing of at least 12 weeks with MTX (and up to one additional non-biologic DMARD) will be enrolled in this study (for the purpose of the study, RA patients will be referred to as "subjects" throughout the protocol). The inclusion/exclusion criteria and the restrictions set in this study are based on its objectives, i.e., to demonstrate the clinical efficacy of the compound and to evaluate safety and tolerability of JTE-051 in patients with RA, the stage in development (i.e., early Phase 2 study, first to evaluate clinical efficacy in RA) and the nonclinical/clinical characteristics of JTE-051, based on the data available to date. Efforts have been made to take into account feasibility and enrollment-related considerations while maintaining the scientific integrity of the study and minimizing the risks for the study subjects.

Briefly, from an efficacy perspective, study subjects must have not been exposed to biologic or kinase inhibitor therapy in order to minimize the variability in the efficacy response due to prior exposure to these immunosuppressive/immunomodulator agents in this "first-in patient" study. Additionally, in order to be eligible, subjects would have to have high-sensitivity C-reactive protein (hs-CRP) levels >1.2 x the upper limit of normal (ULN) at study entry, to confirm a sufficient level of disease activity and to allow for an adequate evaluation of the primary efficacy parameter (i.e., the ACR20 response rate at EOT). Considering other parameters of upmost significance for the evaluation of JTE-051's efficacy, such as ACR50 and ACR70, an hs-CRP cut-off above 1.2 x ULN would be ideal from a scientific perspective, however, taking into account feasibility, the current value is considered appropriate with the appropriate stratification criteria set in place, to ensure a comparable distribution of high vs. lower hs-CRP subjects across treatment groups. Minimum of a 12-week stable dosing (with respect to dose and the route of administration) for the background MTX and for the other non-biologic DMARDs permitted by the protocol is mandatory and restrictions pertaining to the anti-inflammatory and anti-pain medications (including corticosteroids and NSAIDs), as well as other anti-RA medications administration have been set, in order to ensure that the maximum efficacy response to these medications has been attained and that the subject is stable by the time of baseline evaluations in this study, and to subsequently

minimize the placebo response, which is known to be significant in studies of similar indication. Also, in an attempt to minimize other confounding factors, subjects with inflammatory and rheumatic conditions other than RA are prohibited from being randomized in the study.

From a safety perspective, study restrictions were 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, as they occur. Thus, subjects at high risk of developing immunosuppression-related AEs, such as infections or malignancies, including those with pre-existing conditions (e.g., clinically-manifest or latent tuberculosis, active infections with hepatitis B or C viruses or the human immunodeficiency virus [HIV] infection) or significant hematological abnormalities (see Exclusion Criterion # 3) are excluded from participating in the study. [redacted] Other, general safety-related restrictions, such as cardiovascular-system-related, hepatic and renal function-related restrictions have been implemented, taking into account the co-administration with MTX (a medication with known significant hepatic and renal-related toxicity), as well as the known safety signals associated with other comparable compounds on the market or in development (e.g., hepatic or lipid-related signals). The procedures set in place to ensure that the appropriate subjects are randomized in this "first-in patient" POC study in subjects with RA, as well as the safety management strategies implemented in the study are discussed in the following section: "Justification for Study Design".

Justification for Study Design

A parallel group, placebo-controlled, add-on therapy 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 active RA. 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 (50 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 (DB) treatment for 12 weeks followed by a four-week Follow-up Period. The single-dose AE051-U-11-001

study data demonstrated no food effect on the PK of JTE-051; thus, study drug will be administered regardless of meals; nonetheless, the protocol requires that the once daily study drug administration to occur in the morning, to ensure an approximately 24-hour period between dosing, based on the PK characteristics of the compound (see Section 1.2.2). The duration of the DB Treatment Period is sufficient to allow for proof of efficacy in subjects with RA, as an initial step in development. Following attainment of this objective, longer-duration (≥6 months) studies, including open-label extensions, as appropriate, are planned. The duration of the Follow-up Period was set to approximately four weeks, standard duration for similar out-patient studies administered an investigational product. Considering the PK characteristics of JTE-051 (see Section 1.2.1), it was determined that this interval is conservative [redacted]

The efficacy parameters assessed in this study are consistent with the standards in the industry in similar RA trials [redacted] Appropriate efficacy analyses are planned, as detailed in Section 3.8.3.2. To minimize the chance for 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. Additionally, although all joint evaluators in the study are expected to be rheumatologists with experience in joint assessments, adequate training on these assessments is planned, to ensure consistency and to minimize intra- and inter-assessor variability. For this reason, the protocol also strongly recommends that the same assessor performs the joint counts for a subject throughout the study duration.

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 [redacted] for summary information and the Investigator's Brochure for detailed information]) and to facilitate further characterization of the safety profile of JTE-051.

Specifically, [redacted] screening procedures were set in place to exclude subjects at high risk of infections (e.g., medical history, chest radiography and serologic screening for tuberculosis, screening for hepatitis B and C, as well as HIV infections) and adequate withdrawal criteria, based on the Common Terminology Criteria for Adverse Events (CTCAE), see Section 3.4, have been implemented.

[redacted]

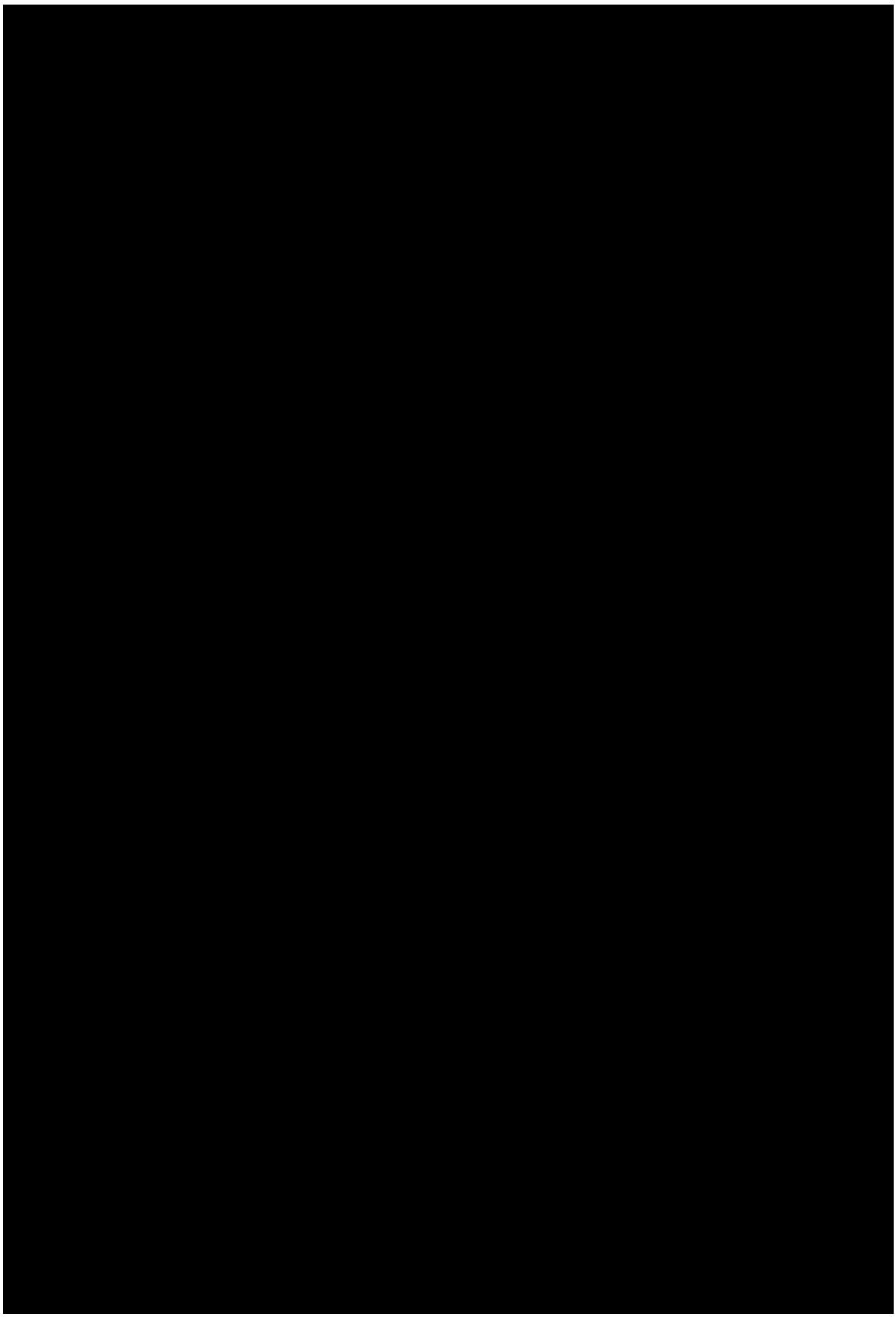
[redacted]

With respect to the musculoskeletal AE, considering the underlying disease of subjects in this study (i.e., RA), it is expected that musculoskeletal-related signs and symptoms will be common; thus, differentiation by the Investigator of the etiology of these events, i.e., underlying disease vs. potential other causes will be required. [redacted] These type of events will be adequately managed through the standard AE collection, processing and reporting procedures, per Good Clinical Practice (GCP) and all actions to ensure the safety of the subjects will be taken by the study investigators. Additionally, the CTCAE withdrawal criteria will be applied to all AEs reported in the study. [redacted] The safety data obtained after the completion for the study will facilitate a better understanding of the compound's safety profile as a stepping stone in the next stage of development.

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]



[redacted]

2 STUDY OBJECTIVES

- To evaluate the clinical efficacy of JTE-051 in subjects with active rheumatoid arthritis receiving background non-biologic disease-modifying anti-rheumatic drug therapy
- To evaluate the safety and tolerability of JTE-051 administered for 12 weeks to subjects with active rheumatoid arthritis receiving background non-biologic disease-modifying anti-rheumatic drug therapy
- To evaluate the pharmacokinetics of JTE-051 in plasma of subjects with active rheumatoid arthritis

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 250 subjects (50 subjects per treatment group).

3.2. Study Design

This is a multicenter, randomized, double-blind, placebo controlled, parallel-group, 12-week study in biologic and kinase inhibitor treatment-naive RA subjects on stable background non-biologic DMARD therapy, including MTX.

Eligible subjects will be randomized at Visit 2 to receive JTE-051 50 mg, 100 mg, 150 mg, 200 mg or placebo once daily for 12 weeks. Subjects will continue to receive up to two non-biologic DMARDs, including MTX throughout the study (at a stable background dose and route of administration for at least 12 weeks prior to Visit 2 and throughout the study) and will return for a Follow-up Visit approximately four weeks after the last dose of study drug is administered. Randomization will be stratified by geographical region and by the screening hs-CRP.

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

- Up to a 28-day Screening Period

  Note: Certain pre-defined exceptions that would allow for a longer duration of the Screening Period to ensure a 28-day pre-randomization stabilization of concomitant medications are permitted, as described in Section 3.5.4.1.

- A 12-week double-blind Treatment Period
- Approximately 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

1. Males and females, 18 to 75 years of age (inclusive) at the Screening Visit (Visit 1);
2. A diagnosis of RA prior to the Screening Visit, based on the ACR/EULAR 2010 Classification Criteria[23] (see Appendix 1);
3. Active disease despite ongoing therapy with up to 2 non-biologic DMARDs, including MTX at both the Screening and Baseline Visits (Visit 1 and Visit 2), as defined by both:
    a. ≥6 out of 68 tender joints **AND**
    b. ≥6 out of 66 swollen joints;
4. Screening hs-CRP ≥1.2 x ULN, based on the central laboratory values;
5. Background treatment with up to 2 non-biologic DMARDs, including MTX (mandatory) and one of the following medications (optional): sulfasalazine ≤3 g/day, hydroxychloroquine ≤400 mg/day or chloroquine: ≤250 mg/day, at the time of the Screening Visit (Visit 1);
    - The MTX dose must be 15-25 mg/week (or the maximum documented tolerated dose for the subject, not <10 mg/week) and all background therapy must be stable, defined as no change in dose or route of administration for ≥12 weeks prior to the Randomization Visit (Day 1). See Section 3.5.4.1 for all concomitant medication-related restrictions.
6. Body Mass Index (BMI): 18 to 40 kg/m^2 (inclusive) at the Screening Visit (Visit 1);
7. Females may participate if they meet one of the following criteria:
    - Surgically sterile (e.g., hysterectomy or bilateral oophorectomy), or
    - Post-menopausal (i.e., history compatible with menopause [i.e., reported lack of menses for ≥12 months prior to Visit 1] and no other biological/surgical cause AND a serum follicle-stimulating hormone (FSH) measurement of ≥40 mIU/mL at Visit 1), or
    - Of childbearing potential and are compliant with at least 2 acceptable forms of birth control (in conjunction with their partner) for the duration of the study and for at least 12 weeks after the last dose of study drug. Acceptable contraceptive methods include the following: intrauterine devices; partner sterilization (with the

appropriate post-vasectomy documentation of the absence of sperm in the ejaculate); condom with a spermicide; diaphragm, cervical cap, vaginal sponge, or "female condom", all with spermicide;

Notes:

- Females with sterilization history limited to tubal ligation will be considered of childbearing potential and must comply with the contraception regimen as described above.
- Females with a history compatible with menopause and have a serum FSH <40 mIU/mL at Visit 1 will be considered of childbearing potential and must agree to comply with a contraceptive regimen as described above.
- Concomitant use of a female condom and a male condom is not considered an acceptable method of contraception for the study.

8. Males with female partners of childbearing potential must agree to practice total abstinence or to utilize 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; additionally, male subjects must not donate sperm for the duration of the study and within 12 weeks of the last dose of study drug;
    - Female partners of male subjects randomized in this study must be surgically sterile, postmenopausal, or use an acceptable form of birth control (see description listed in inclusion criterion # 7; additionally, oral and implantable hormonal contraceptives are considered acceptable in female partners of male subjects) for the duration of the study and for at least 12 weeks after completing the study;
9. 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. Prior/current exposure to biologic and/or kinase inhibitor therapy;
2. Does not meet all study restrictions, including previous/concomitant medication restriction criteria, as described in Section 3.5.4 of the protocol;
3. White blood cell 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 the Screening Visit (Visit 1);
4. Hemoglobin <9 g/dL or platelet count <100,000/mm^3 at the Screening Visit (Visit 1);
5. Alanine aminotransferase (ALT) >1.2 x the ULN; aspartate aminotransferase (AST) >1.2 x the ULN or total bilirubin >1.5 x the ULN at the Screening Visit (Visit 1);

6. Clinical evidence of renal impairment or an estimated glomerular filtration rate (eGFR) ≤60 mL/min/1.73m^2 at the Screening Visit (Visit 1), using the abbreviated Modification of Diet in Renal Disease (MDRD) equation;
7. Serum triglycerides >400 mg/dL at the Screening Visit (Visit 1);
8. Positive viral serology at the Screening Visit (Visit 1) for:
   - Human immunodeficiency virus: positive HIV antibodies (Ab)
   - Hepatitis B virus: positive total hepatitis B core (HBc) Ab or positive hepatitis B surface antigen (HBsAg) or
   - Hepatitis C virus (HCV): positive HCV Ab;
9. Positive drug of abuse and alcohol test results at the Screening Visit (Visit 1);

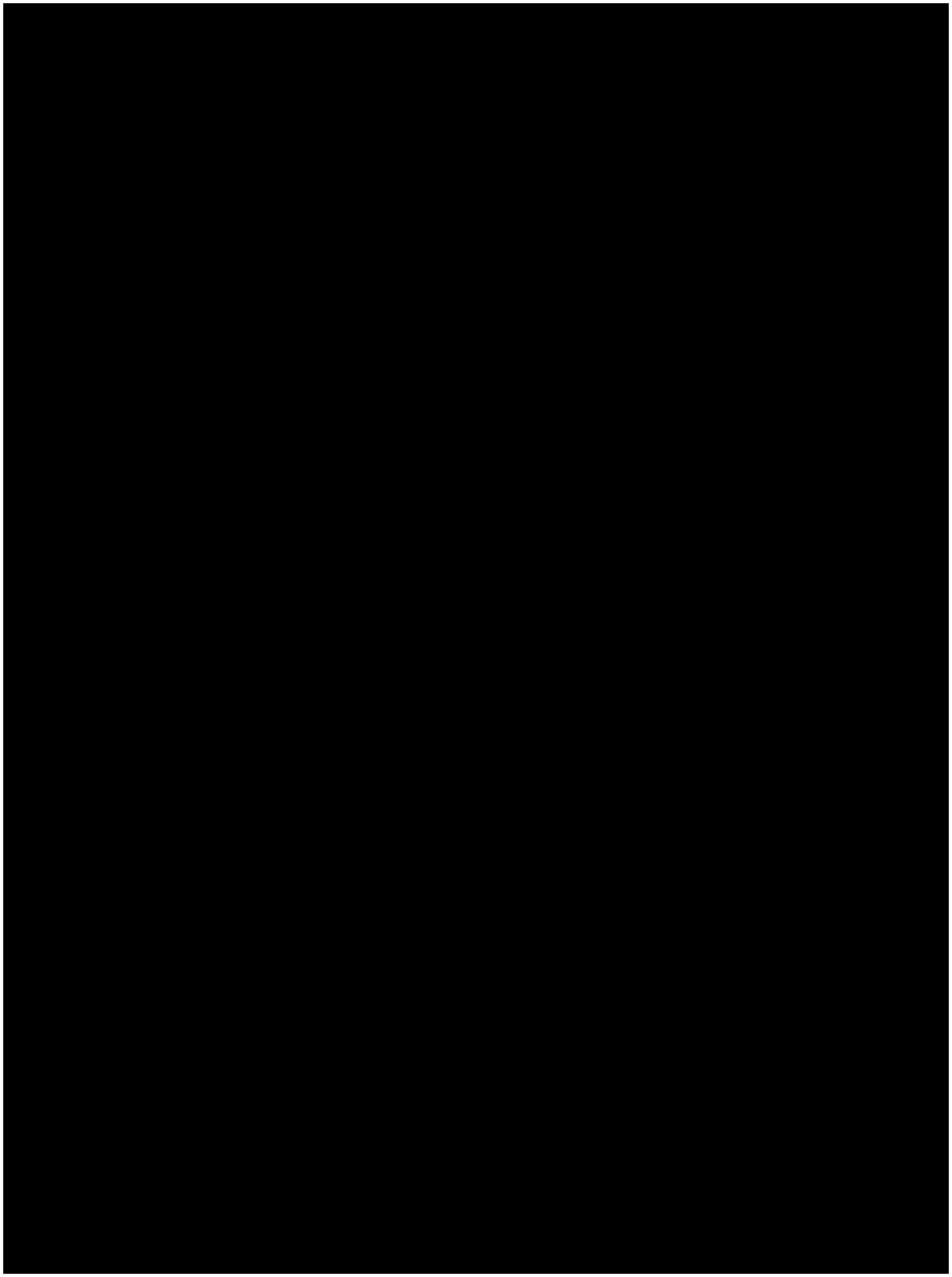
   Note: Adequate (i.e., non-abusive) use of prescription drugs, according to the Investigator's judgment is permitted, provided that the concomitant medications restrictions required by the protocol are met. Positive test results for cannabinoids will result in exclusion of subject from the study.
10. History or presence of substance abuse, drug addiction or alcoholism within 1 year prior to the Screening Visit (Visit 1);
11. Positive Purified Protein Derivative (PPD) or quantiFERON®-TB Gold-In-Tube test (**Note**: either test can be performed, according to the local guidelines), positive chest radiography findings for tuberculosis or any other evidence of tuberculosis;
    - For subjects with a history of Bacille Calmette-Guérin (BCG) vaccination 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.
    - If the quantiFERON®-TB Gold-In-Tube test is performed and it is indeterminate, a retest is allowed if results can be obtained in time prior to Visit 2. If the retest results are also indeterminate, the PPD test may be performed (unless the subject has a history of BCG vaccination) and, if negative, the subject may be randomized into 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 contact with a person with active tuberculosis are excluded, unless documentation of appropriate completion (>12 weeks prior to the Screening Visit) of tuberculosis prophylaxis is provided to the investigator.
12. History of live attenuated vaccination within 6 weeks prior to Day 1 (Visit 2), or have a live attenuated vaccination planned during the course of the study or within 6 weeks after the last dose of study drug;

13. Have donated or received any blood or blood products within 8 weeks prior to the Screening Visit (Visit 1);
14. History of a clinically-significant infection (e.g., required oral antimicrobial or antiviral therapy) within 8 weeks prior to Day 1 (Visit 2), except for treated urinary tract infections, which will be permitted if resolved >1 week prior to Day 1 (Visit 2);

    Note: Subjects with confirmed Zika infection within 4 weeks **prior to the Screening Visit (Visit 1)** are prohibited to participate in the study, whether or not they have received antiviral therapy.
15. History of opportunistic infections or infection requiring hospitalization or parenteral antibiotic, antiviral, antifungal, or antiparasitic therapy within 6 months prior to Day 1 (Visit 2) or any history of recurrent infections or conditions predisposing to chronic infections (e.g., bronchiectasis, chronic osteomyelitis);
16. History of shingles within 12 months prior to the Screening Visit or any known history of disseminated/complicated herpes zoster;
17. History of acute inflammatory joint disease of an origin other than RA or subject has any other rheumatic disease other than RA (e.g., any arthritis with onset prior to age 16 years, gout, mixed connective tissue disease, seronegative spondylarthropathy, psoriatic arthritis, reactive arthritis or systemic lupus erythematosus) or fibromyalgia;

    Note: Subjects with Sjögren's syndrome secondary to RA are permitted in the study provided that all other inclusion/exclusion criteria are met;
18. History or presence of any lymphoproliferative disorder, such as Epstein Barr Virus-related lymphoproliferative disorder, lymphoma, leukemia, multiple myeloma, etc., 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 the Screening Visit (Visit 1);
20. History of organ transplantation;
21. Acute coronary syndrome (e.g., myocardial infarction or unstable angina), percutaneous coronary intervention (Percutaneous Transluminal Coronary Angioplasty [PTCA] or similar procedures), coronary artery bypass graft (CABG) surgery, cerebrovascular accident or transient ischemic attack (TIA) within 6 months prior to the Screening Visit (Visit 1);
22. Any history or presence of Class III or IV heart failure, as defined by the New York Heart Association (NYHA)[24] or known Rutherford category 4 or higher peripheral arterial disease;
23. Any history or presence of clinically significant arrhythmias or other ECG abnormalities, according to the Investigator's judgment;

24. Uncontrolled arterial hypertension defined as repeated (i.e., up to 3 repeat measurements are allowed) systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥100 mmHg at the Screening Visit (Visit 1);



32. Pregnant or nursing females at Screening Visit or Day 1 (Visit 1 and Visit 2) or subjects who plan to become pregnant or initiate breastfeeding during the study and within 12 weeks after the last dose of study drug;
33. Significant history of drug or other hypersensitivities (e.g., multiple drug allergies or severe allergic reactions, including angioedema);
34. 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 RA, such as type I diabetes) or hematologic (e.g., sickle cell) disease that, in the opinion of the Investigator, may place the subject at unacceptable risk for study participation and may prevent the subject from completing the study (e.g., low life expectancy, high risk of non-compliance) or would interfere with the study conduct or data interpretation, according to the Investigator's judgment;
35. 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[25], 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. Subjects who interrupted study drug administration due to a grade 3 CTCAE finding may be re-started on therapy if the event has resolved and it is considered appropriate by the Investigator and Sponsor or designee.

   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; exceptions on a case-by-case basis may be permitted if approved by Sponsor or designee)

   *Determined at >1 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: the subject was randomized in the study and did not meet all inclusion/exclusion criteria mandated by the protocol (exceptions on a case-by-case basis may be permitted if approved by Sponsor or designee)
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
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 the first dose of study drug on Day 1 will be requested to complete an Early Termination Visit at which time the subject will undergo all the procedures described for Visit 6 (EOT). Every effort should be made to perform the EOT assessments as soon as possible after the decision of discontinuation is made and prior to any changes made in the subject's anti-RA 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

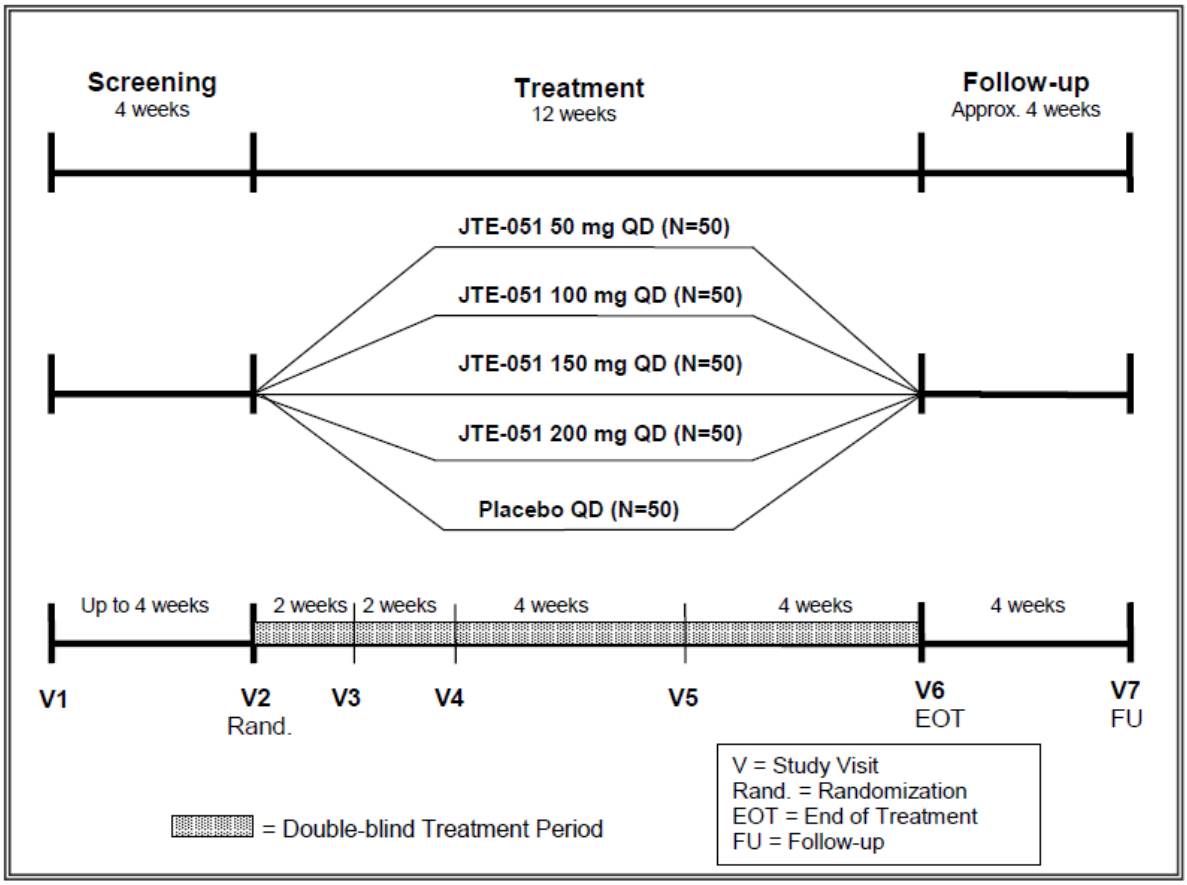


Table 1. Planned Schedule of Study Procedures

	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
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	
Vital Signs, including Weight	X	X	X	X	X	X	X
Height and Calculate BMI	X						
12-Lead ECG	X	X		X		X	
Chest Radiography[c]	X						
TB test (PPD or quantiFERON gold)	X						
Drugs of Abuse Screen	X						
Viral Serology	X						
FSH (post-menopausal females only)	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
25-hydroxyvitamin D	X						
Serum IgG, IgM and IgA		X				X	
RF[e] and Anti-CCP antibodies[f]		X					
Bone-specific ALP	X	X				X	
hs-CRP	X	X	X	X	X	X	X
CRP		X				X	
Tender Joint Count (68)	X	X	X	X	X	X	X
Swollen Joint Count (66)	X	X	X	X	X	X	X
Subject's Assessment of Arthritis Pain	X	X	X	X	X	X	X
Subject's Global Assessment of Arthritis	X	X	X	X	X	X	X
Physician's Global Assessment of Arthritis	X	X	X	X	X	X	X
HAQ-DI	X	X	X	X	X	X	X
Randomization using IWRS		X					
Access IWRS and Dispense Study Drug[g]		X	X	X	X		
Collect Study Drug and Check Compliance[h]			X	X	X	X	
Study Drug Administration[i]		X	X	X	X		
JTE-051 Trough PK Blood Samples			X	X	X	X	
Document Adverse Events[j]	X	X	X	X	X	X	X

a. The target day for each visit timepoint 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.

[redacted]

c. Unless a chest radiography had been performed within 3 months (12 weeks) of the Screening Visit, and documentation is available for review by the Investigator and inclusion in the subject's file.

d. At Visit 1 serum pregnancy test will be performed; at all other visits, urine pregnancy tests will be performed. Pregnancy tests may also be repeated as needed or per request from IRBs/IECs or if required by local regulations.

e. Rheumatoid Factor

f. Anti-cyclic citrullinated peptide antibodies

g. At Visit 2, a back-up drug blister card will be dispensed to all subjects, in addition to the regular study drug blister cards. Subjects will be instructed not to use the back-up blister card unless all drug in the regular blister cards has been used and to bring all used and unused (including back-up) blister cards to each study visit for accountability purposes. At Visit 6, study drug will not be dispensed. If a study subject discontinues study drug prematurely, the appropriate systems will be accessed to record termination as soon as possible after the decision has been made.

h. 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/returned by the subject. The subject is to maintain the back-up blister card for the duration of the Treatment Period.

i. 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). If no tablets from the previously supplied non-back-up blister cards are available, then the subject should dose from the new blister card supplied at that visit. Following completion of accountability and compliance assessments, the back-up blister card will be re-dispensed at Visits 3 through 5 and will be collected at Visit 6 along with all non-back-up drug blister cards. The back-up blister card should only be utilized by subjects if all study drug from the regularly-supplied (i.e., non-back-up) blister cards has been used.

j. Adverse event information will be collected at the specified time points as well as at any time when a clinical research unit staff member becomes aware of an AE after the subject signs the informed consent for the study. However, stable or improving pre-existing conditions that are detected through the screening procedures throughout 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 documented accordingly.

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. 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 with the exception of the blood/urine collection activities may be performed; the subject's remaining procedures will be rescheduled for blood/urine collection on a subsequent day within the visit window and he/she will be reminded to fast overnight.

Please refer to Table 1 for the list of screening procedures to be performed in the study. A one-time repeat of the screening laboratory (except for drugs of abuse and alcohol, viral serology and pregnancy tests), vital sign and ECG assessments is permitted, if considered appropriate by the Investigator, except if stated otherwise (e.g., an up to a three-time repeat of blood pressure measurements at the Screening Visit is permitted). The repeat test(s) results 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 with the exception of the blood/urine collection activities may be performed; the subject's remaining procedures will be rescheduled for blood/urine collection on a subsequent day within the visit window and he/she will be reminded to fast overnight. Exception to this would be Visit 2 (Randomization Visit), 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 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.

Subjects will be administered the first dose of study drug in the clinical research center, upon completion of all pre-dosing procedures and randomization at Visit 2; subsequently, they will be instructed to self-administer study drug once daily, 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. On those days study drug will be administered at the site by the study personnel from the subject's previously supplied non-back-up 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 no tablets from the previously supplied non-back-up blister cards are available, then the subject should dose from the new non-back-up blister card supplied at that visit. Following completion of accountability and compliance assessments, the back-up blister card will be re-dispensed at Visits 3 through 5 and will be collected at Visit 6 along with all non-back-up blister cards. The back-up blister card should only be utilized by subjects if all study drug from the regularly-supplied (i.e., non-back-up) blister cards has been used. 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 last dose prior to the PK sample collection at each visit should be documented.

Study drug will not be administered and all 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 EOT visit (Visit 6) should be performed, if possible, prior to initiation of any change in the anti-RA medication regimen of the subject.

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 four 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 in the study.

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 four weeks after the last dose of study drug.

3.5.4. Study Restrictions

3.5.4.1. Previous and Concomitant Medication Restrictions

Medications PROHIBITED <u>any time prior or during the study</u> (through the Follow-up Visit [Visit 7]):

- Biologics and kinase inhibitor agents;
- Antipsychotic therapy;
- Anti-retroviral therapy and alpha-interferon;
- Anti-cancer chemotherapy;

  Note: Methotrexate, as background treatment for RA is permitted;
- Tacrolimus and mycophenolic acid/mycophenolate mofeti (MMF)

Medications PROHIBITED <u>within 6 months (24 weeks) prior to Day 1 (Visit 2)</u> through the Follow-up Visit (Visit 7):

- Cyclophosphamide.

Medications PROHIBITED <u>within 3 months (12 weeks) prior to Day 1 (Visit 2)</u> through the Follow-up Visit (Visit 7):

- Oral or injectable gold, azathioprine, penicillamine and cyclosporine;
- Leflunomide, unless the subject has undergone cholestyramine washout at least 28 days prior to Visit 2;
- Monoamine oxidase inhibitors;
- Isoniazid.

Medications PERMITTED AT STABLE DOSE <u>for at least 3 months (12 weeks) prior to Day 1 (Visit 2)</u> through the Follow-up Visit (Visit 7):

- All subjects must receive background MTX at stable doses of 15-25 mg/week, or at the maximum documented tolerated dose for the subject, not <10 mg/week. For the purpose of the study "stable" is defined as no change in dose or route of MTX administration for ≥12 weeks prior to the Visit 2. Methotrexate dose and route of administration must not change throughout the study (i.e., until after the Follow-up Visit [Visit 7]);
  - ✧ Supplementation with folic acid or folinic acid (leucovorin), according to the local standard of care (SOC) (i.e., local MTX package insert) is required in all subjects as follows: subjects must receive folic acid between 1 and 5 mg per dose, inclusive, at least four days each week, and at least 7 mg total weekly dose, unless this regimen violates the local MTX label, case when the later should be followed. Alternatively, study subjects may receive folinic acid (leucovorin) up to 5 mg per dose administered 8 to 24 hours after the MTX weekly dose. Dosing regimen for folic acid/folinic acid must be stable for at least 4 weeks (28 days) prior to Visit 2.

Note: If the subject has not been receiving folic acid or folinic acid prior to signing the informed consent, then a prescription for dosing according to the local SOC and MTX package insert must be provided by the investigator at the Screening Visit and subject should initiate administration within two calendar days from signing the Informed Consent. In this case, the duration of Screening Period may be extended by two days, to allow for a 4-week (28-day) stabilization period for folic acid/folinic acid.

- Sulfasalazine ≤3 g/day, hydroxychloroquine ≤400 mg/day and chloroquine: ≤250 mg/day;

  Note:
  - ✧ If a subject has not been on stable treatment with these drugs for at least 12 weeks prior to Visit 1, these must not be initiated until after the Follow-up Visit (Visit 7);
  - ✧ For candidates receiving chloroquine or hydroxychloroquine, fundoscopic and visual field examination results performed within the timeframe consistent with the local SOC, but not exceeding 12 months prior to the Screening Visit must be reviewed by the Investigator and filed in the subject's source documents. If not available, such examinations should be performed (as part of SOC) and results should be reviewed/filed by the investigator prior to randomization;
- Selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), bupropion (Wellbutrin) and tricyclic or tetracyclic antidepressants.

Medications PROHIBITED <u>within 4 weeks (28 days) prior to Day 1 (Visit 2)</u> through the Follow-up Visit (Visit 7):

- Parenteral or intra-articular corticosteroids, as well as oral prednisone/prednisolone or steroid equivalent at doses >10 mg/day;

  Note: Topical or inhaled corticosteroids for indications other than RA are permitted as needed throughout the study
- Doxycycline and minocycline;
- Pentoxifylline;
- Sulfamethoxazole/Trimethoprim (Bactrim), sulfones (e.g., Dapsone), colchicine and systemic metronidazole;
- Vitamin B6 at doses >100 mg/day;
- Cannabinoids, including marijuana.

Medications PROHIBITED <u>within 4 weeks (28 days) *PRIOR TO VISIT 1 (SCREENING VISIT)*</u> through the Follow-up Visit (Visit 7):

- Investigational drugs: prohibited within 4 weeks <u>or 5 PK half-lives</u> prior to the Screening Visit (Visit 1), whichever is longer;

- ✧ Subjects cannot participate in any other investigational or long-term observational studies related to an investigational medication after signing the AE051-G-13-003 consent form through the Follow-up Visit (Visit 7);

  Note: Participation in registries and long-term population-based studies (e.g., nurse health studies) is permitted.
- ✧ If the investigational drug was a biologic or a kinase inhibitor, the subject cannot be randomized in the study regardless of the timing of exposure.

Medications PERMITTED AT STABLE DOSE <u>for at least 4 weeks (28 days) prior to Day 1 (Visit 2)</u> through the Follow-up Visit (Visit 7):

- Oral prednisone/prednisolone or steroid equivalent at doses ≤10 mg/day;
- Daily doses of oral NSAIDs, cyclooxygenase (COX)-2 inhibitors, opioids and acetaminophen/paracetamol;
  - ✧ Subjects with occasional use (i.e., not more than two consecutive days) of the above medications for indications other than RA (e.g., headache) may be permitted in the study pending discussion with the Medical Monitor, provided that the intake of such drugs did not occur within 1 week (i.e., 7 days) of Visit 2 and all other inclusion/exclusion criteria are met.
- Hormone replacement, lipid-lowering, antihypertensive and anti-osteoporosis agents;
  - ✧ Following receipt of screening lipoprotein assessment results, the investigator may initiate lipid lowering drug therapy, as appropriate, according to the local SOC and his/her judgment; such action should be taken as soon as possible, but not >2 business days from the time of receipt of the results and in these cases the Screening Period may be extended with the number of days necessary to meet the 4-week (28-day) prior to Visit 2 stability requirement.
- Over-the-counter, herbal, traditional, ayurvedic therapy, including vitamins, minerals and supplements.
- Vitamin D supplementation at doses according to the local standard of care is to be initiated in patients with Vitamin D concentrations below the lower limit of normal at the Screening Visit. Dosing must be initiated immediately after the deficiency is identified and should be stable for at least 4 weeks prior to JTE-051 dosing initiation and throughout the study (in this situation, the duration of Screening Period may be extended beyond 28 days to ensure a duration of Vitamin D stability of 28 days).
- Generally, every effort should be made to ensure that all other permitted chronically-administered concomitant medications are taken by subjects at stable dose/route of administration for at least 4 weeks (28 days) prior to Day 1, unless a change in dose/route of administration is considered medically necessary.

[redacted]

[redacted]

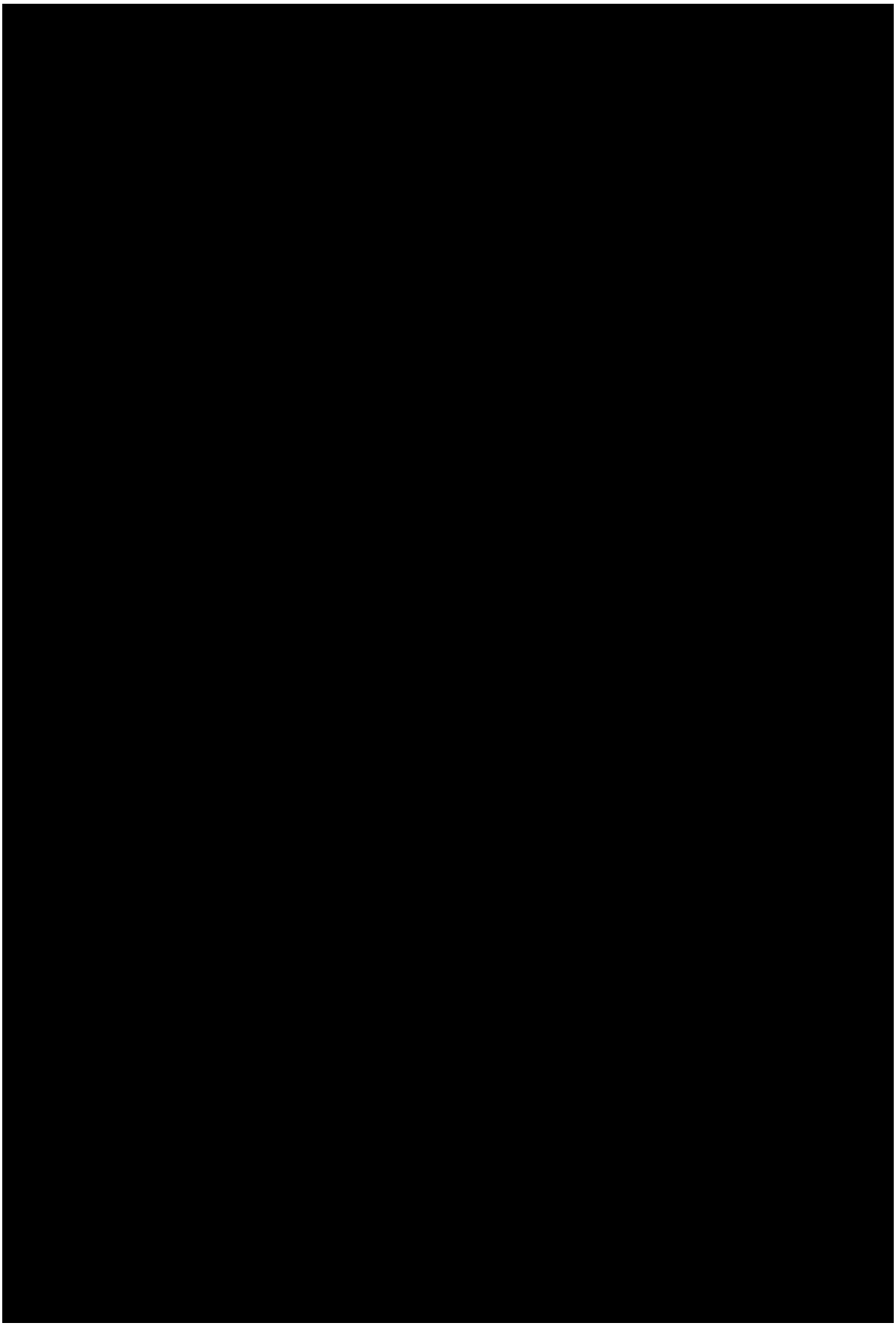
General Medication-related Protocol Instructions:

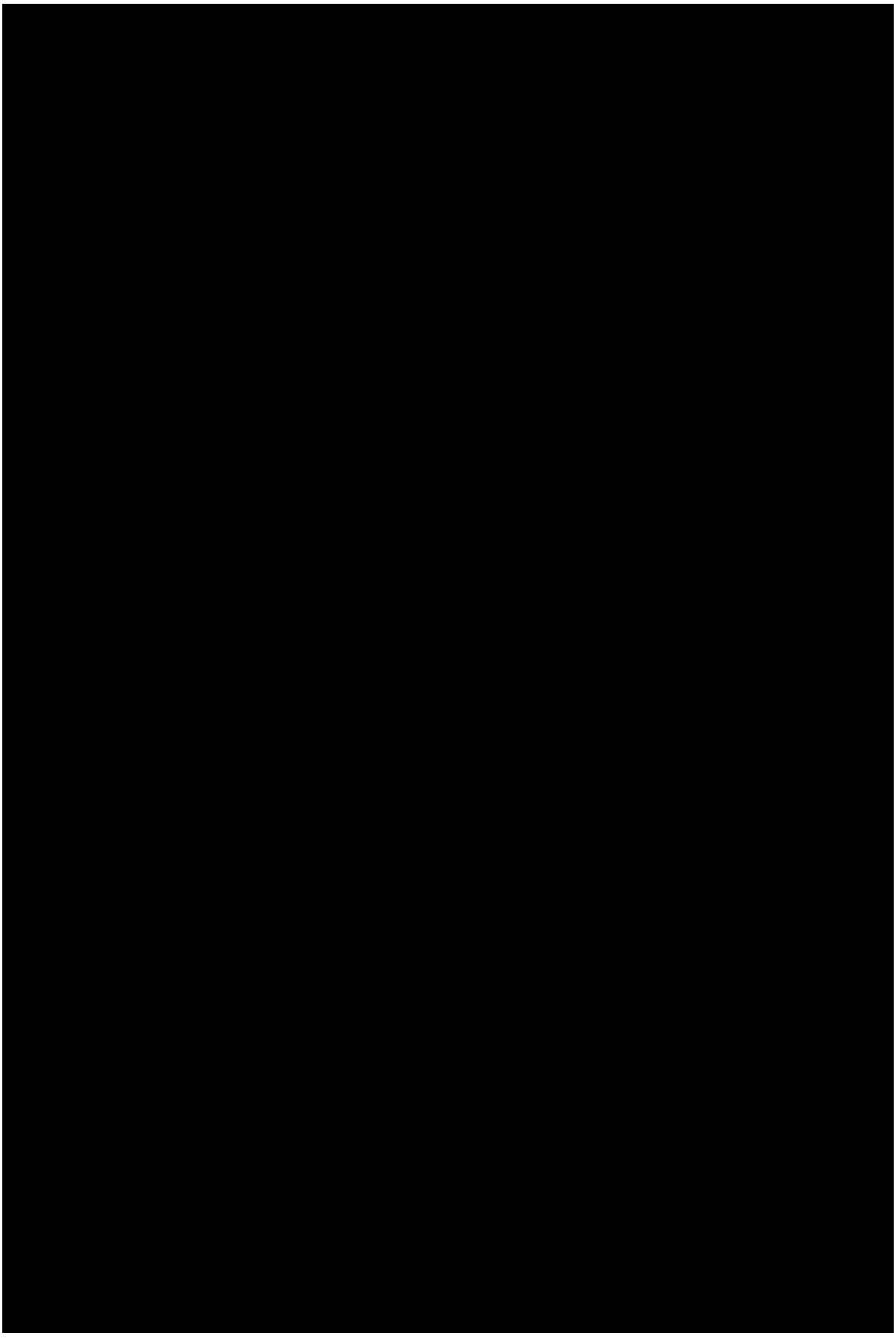
[redacted]

- 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, case when any appropriate action, according to the Investigator's judgment should be taken;
- 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. General Restrictions

- Joints that have been injected with corticosteroid medications within <6 weeks of the assessment, were replaced or are fused will not be included in the assessments.
- 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.
- 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.





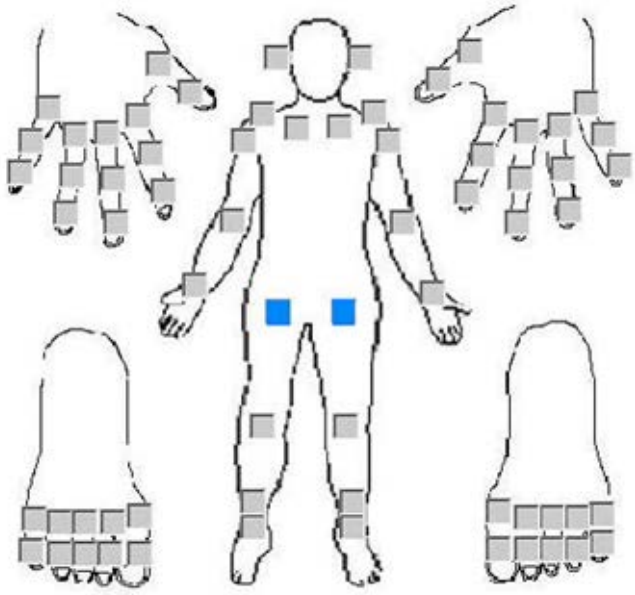
3.5.6. Procedure Definitions

3.5.6.1. Efficacy Assessments

3.5.6.1.1. Quantitative Joint Assessments (68/66)

Standardized 68 and 66 joint counts will be performed for assessment of the number of tender and swollen joints, respectively, according to the schedule summarized in Table 1. See Figure 3 for a diagram of joints to be assessed as part of the 68/66 tender and swollen joint counts. Every effort should be made to ensure that the quantitative joint assessments is performed by an experienced, trained independent assessor, different from the Principal Investigator/Sub-investigator who is performing overall evaluation of the subject. The independent assessor must have medical training (e.g., he/she may be a medical doctor, physician assistant, nurse practitioner or registered nurse), must have performed RA joint assessments for clinical studies prior to the current study and must have undergone the joint count training provided by Akros or designee, as applicable. The same assessor should perform the counting for a specific subject throughout the study (scheduling of study subjects should take into account the assessor's availability). In exceptional circumstances, if conditions do not permit the availability of the same assessor, an alternate assessor may perform the quantitative joint assessment provided that he/she meets that experience/training requirements as described above. These exceptions should be documented and communicated to the medical monitor. Additionally, every effort will be made to limit the number of assessors within a site (ideally, the same assessor will perform the quantitative joint assessments for all subjects at a site). See Section 3.5.4.2 for the restrictions pertaining to the joints to be included in these assessments.

Figure 3. Tender and Swollen Joint Counts (68/66)



3.6.6.1.1.1 Tender/Painful Joint Counts (68)

Sixty-eight (68) joints will be assessed to determine the number of joints that are considered tender or painful. Artificial/missing/fused joints or joints that have received corticosteroid injection within 6 weeks of the assessment must not be included in the assessment.

The 68 joints to be assessed are:

- **Upper Body**: temporomandibular (2), sternoclavicular (2), acromioclavicular (2);
- **Upper Extremity**: shoulder(2), elbow (2), wrist (2) (includes radiocarpal, carpal and carpometacarpal considered as one unit), metacarpophalangeals (MCP I[2], II[2], III[2], IV[2], V[2]), thumb interphalangeal (IP) (2), proximal interphalangeals (PIP II[2], III[2], IV[2], V[2]), distal interphalangeals (DIP II[2], III[2], IV[2], V[2]);
- **Lower Extremity**: hip(2), knee(2), ankle(2), tarsus (includes subtalar, transverse tarsal and tarsometatarsal considered as one unit) (2), metatarsophalangeals (MTP I[2], II[2], III[2], IV[2], V[2]), great toe IP (2), proximal and distal interphalangeals combined (PIP II[2], III[2], IV[2], V[2]).

3.6.6.1.1.2 Swollen Joint Counts (66)

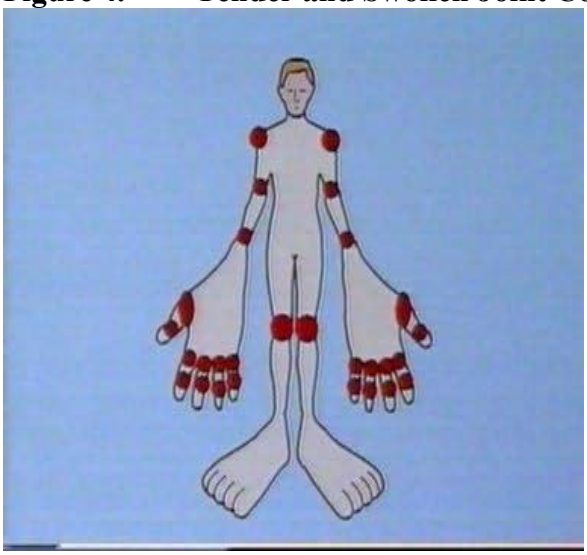
The joint assessor will also assess joints for swelling. Artificial/missing/fused joints or joints that have received corticosteroid injection within 6 weeks of the assessment must not be included in the assessment.

The sixty-six (66) joints that will be assessed for swelling are the same as those listed above for tenderness/pain, except that the right and left hip joints are not included in the swollen joint count.

3.5.6.1.2. Quantitative Joint Assessments (28)

The 28 joints utilized for the calculation of certain efficacy parameters, such as Disease Activity Score (DAS)28, Clinical Disease Activity Index (CDAI) and Simplified Disease Activity Index (SDAI), see Appendix 5, are a sub-set of the 68/66 joints assessed per the instructions in Section 3.5.6.1.1 (see Figure 4); thus, the results of the above-described 68/66 joint assessments applicable to the 28 joints should be utilized when reporting the 28-joint assessment results (i.e., no re-assessment of the 28 joints will be done).

Figure 4. Tender and Swollen Joint Counts (28)



3.5.6.1.2.1. Tender/Painful Joint Counts (28)

The twenty-eight tender/painful joint count includes the following joints: shoulders (2), elbows (2), wrists (2), MCP joints (10), PIP joints (10) and knees (2).

3.5.6.1.2.2. Swollen Joint Counts (28)

The twenty-eight swollen joint count includes the same joints as those included in the tender joint counts.

3.5.6.1.3. Subject's Assessment of Arthritis Pain

Subjects will assess the severity of their arthritis pain according to the schedule summarized in Table 1 using a numeric rating scale (NRS) with 0 representing "no pain" and 10 representing "pain as bad as it can be". See Appendix 3 for a template in English of the NRS for subject pain assessment. Whenever available, the local language-validated tool will be utilized.

3.5.6.1.4. Subject's Global Assessment (SGA) of Disease Activity

Using a 0 to 10 NRS format, subjects will assess their disease activity according to the schedule summarized in Table 1. See Appendix 3 for a template in English of the subject's global assessment of disease activity scale. Whenever available, the local language-validated tool will be utilized.

3.5.6.1.5. Physician's Global Assessment (PGA) of Disease Activity

The Investigator will assess the subject's overall arthritis activity according to the schedule summarized in Table 1 using a 0 to 10 NRS format. This is an evaluation based on the subject's disease signs, functional capacity and physical examination, and should be independent of the SGA of disease activity. See Appendix 3 for a template in English of the PGA of disease activity scale. Whenever available, the local language-validated tool will be utilized.

3.5.6.1.6. Health Assessment Questionnaire Disability Index (HAQ-DI)

The HAQ-DI assesses the extent of the subject's functional ability by assessing the degree of difficulty a subject has experienced during the past week in eight categories of daily living activities: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and common daily activities. Each category has at least two sub-category questions. The subjects report the amount of difficulty they have in performing some of these activities. The HAQ-DI is designed to assess the subject's usual ability during the past week, not a particularly good or bad day. This questionnaire should be completed by the subject prior to any procedures being performed at the visit, if possible. The form should then be checked by the site staff for completeness. See Appendix 4 for the Stanford University School of Medicine, Division of Immunology & Rheumatology Health Assessment Questionnaire Worksheet and for instructions on handling the responses by the Investigator, as well as the scoring process that will be performed by the Sponsor.

3.5.6.1.7. High-sensitivity C-reactive Protein

The blood samples for hs-CRP measurements will be collected according to the schedule summarized in Table 1 and will be analyzed by the central laboratory.

3.5.6.1.8. C-reactive Protein

The blood samples for CRP measurements utilizing the non-high sensitivity method will be collected at Visit 2 and Visit 6 and will be analyzed by the central laboratory.

3.5.6.2. Medical History

A complete medical history will be obtained at the Screening Visit (Visit 1) and will include evaluations for past or present conditions. [redacted] Stable or improving pre-existing conditions that are detected as part of the screening procedures (e.g., ECG, physical examination, [redacted] vital signs, and laboratory test abnormalities) are considered to be medical history.

3.5.6.3. 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.

With respect to the use of corticosteroids, detailed information (including but not limited to dose, route, indication, duration of administration) will be obtained. Every effort should be made to document this information from the time of first use by the subject, with focus on chronic use of these agents (i.e., having a duration of ≥ 2 weeks);

nonetheless, for the period within 30 days prior to Visit 1, all corticosteroid use (including short-term) will be documented.

3.5.6.4. Physical Examination

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.

3.5.6.6. Height and Weight Measurements, and BMI Calculation

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 weight. Body mass index will be calculated at the Screening Visit (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.

3.5.6.7. Vital Signs

Vital sign assessments including blood pressure, pulse rate, respiratory rate and body temperature (°C) will be performed in a 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 pulse rate assessments.

3.5.6.8. 12-Lead ECG

Twelve-lead ECG recordings and conduction intervals including the interval from beginning of the QRS complex in the frontal plane to the next QRS complex (RR), the interval from beginning of the P wave to the beginning of the QRS complex in the frontal

plane (PR), duration of QRS complex in the frontal plane (QRS), interval from beginning of the QRS complex to end of the T wave in the frontal plane (QT), and Fridericia-corrected QT interval (QTcF) will be obtained according to the schedule summarized in Table 1. Subjects will lay supine for at least 5 minutes prior to the 12-lead ECG assessments.

3.5.6.9. Hematology

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

3.5.6.10. Serum Biochemistry

Blood samples to assess serum ALT, albumin, alkaline phosphatase (ALP), AST, bilirubin, BUN, calcium, carbon dioxide, chloride, creatine kinase, creatinine, gamma-glutamyl transferase, globulin, glucose, lactate dehydrogenase, phosphate, potassium, protein, sodium and urate will be obtained according to the schedule summarized in Table 1. The eGFR will be calculated at each study visit by the central laboratory using the MDRD equation.

3.5.6.11. Bone-specific Alkaline Phosphatase

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

3.5.6.12. 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.

3.5.6.13. 25-hydroxyvitamin D

Blood samples to measure 25-hydroxyvitamin D will be obtained at the Screening Visit.

3.5.6.14. Rheumatoid Factor, Anti-cyclic citrullinated peptide antibodies, Serum Immunoglobulins G, M and A

Blood samples to measure the rheumatoid factor (RF), anti-cyclic citrullinated peptide (anti-CCP) antibodies and serum immunoglobulins G, M and A (IgG, IgM and IgA) will be obtained at the Screening Visit.

3.5.6.15. Coagulation

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

3.5.6.16. Viral Serology

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

3.5.6.17. Pregnancy Test

Pregnancy tests to assess βHCG levels will be performed for all female subjects. Blood samples will be collected at the Screening Visit (Visit 1) for a serum pregnancy test. At Visits 2 through 7, urine pregnancy tests will be performed at the site. Pregnancy tests may also be repeated as needed, per request from IRBs/IECs or if required by local regulations.

3.5.6.18. Follicle-stimulating Hormone

Blood samples to assess the menopausal status will be collected at the Screening Visit (Visit 1) from all female subjects who report a history compatible with menopause with no other identified biological/surgical cause.

3.5.6.19. Drugs of Abuse and Alcohol Screen

Urine samples to assess amphetamine, barbiturates, benzodiazepine, cannabinoids, cocaine, ethanol, opiates, oxycodone and methadone will be obtained at the Screening Visit (Visit 1).

3.5.6.20. Tuberculosis Screening

The Mantoux skin test (also known as the PPD test) or the Quantiferon®-TB Gold-In-Tube test (according to the local SOC) may be used as tuberculosis screening tools for the study during the Screening Period.

If the Mantoux test is selected, 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 Mantoux 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 up to one time if results can be obtained in time prior to Visit 2. If the retest is also indeterminate, the PPD test may be performed and, if negative, the subject may be randomized into the study, however 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 administered.

3.5.6.21. 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 the Screening Visit and documentation (including interpretation of TB status) is available and is provided to the Investigator to review and file in the subject's file, that 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.

3.5.6.22. Urinalysis

Urine samples to assess bilirubin, occult blood, color, glucose, ketones, leukocyte esterase, nitrite, pH, protein, specific gravity, turbidity, and urobilinogen, as well as for a microscopic exam (in case of positive macroscopic findings only) will be obtained under fasted conditions according to the schedule summarized in Table 1.

[redacted]

3.5.6.24. Pharmacokinetic Procedures

3.5.6.24.1. 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. Trough PK blood samples will be collected in the fasted state at pre-specified study visits.

The actual date and time of the last dose of study drug prior to the PK sample collection, as well as the sample collection date and time will be documented for PK data analysis. Refer to the laboratory manual for specific instructions for the collection, processing, storing and shipping of blood samples for PK assessments.

3.5.6.24.2. Analysis of JTE-051 in Plasma

JTE-051 in plasma will be analyzed using a validated 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:

3.6. Adverse Events

3.6.1. Safety Definitions

Akros complies with the following International Conference on Harmonisation (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., Investigator's Brochure).

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, the de-challenge/re-challenge response (if available) 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. 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 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 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

At the Screening Visit (Visit 1), 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

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 once daily in the morning, regardless of meals. On the day of scheduled study visits, subjects should not take study drug prior to arriving to the study site. At the site, study drug will be administered from the previously supplied non-back-up blister card, if available, after all study procedures have been completed. If no tablets from the previously supplied non-back-up blister cards are available, then the subject should dose from the new non-back-up blister card supplied at that visit. The back-up study drug blister card should only be utilized by subjects if all study drug from the regularly-supplied (non-back-up) blister cards has been used.

Randomized subjects will receive two study drug blister cards at Visits 2 and 3, respectively. Subjects will receive four blister cards each on Visits 4 and 5. Additionally, at Visit 2, all subjects will receive a back-up blister card (identical in appearance with the other blister cards) for use as needed throughout the study. The back-up blister card may be identified at the site level and subjects will be instructed to utilize all tablets from the other (non-back-up) blister cards before initiating tablet use from the back-up blister card. The subjects will be instructed to return the clinical supplies (full, partially full, and empty blister cards, including the back-up blister card) at Visits 3, 4, 5 and 6 for accountability and compliance assessment. Following completion of accountability and compliance assessments, the back-up blister card will be re-dispensed at Visits 3 through 5 and will be collected at Visit 6 along with all non-back-up blister cards.

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 GCP.

3.7.7. Randomization

Approximately 250 eligible subjects with active RA will be randomized into this study. Subjects will be randomized in a 1:1:1:1:1 ratio (50 subjects per treatment group) to receive JTE-051 50 mg, JTE-051 100 mg, JTE-051 150 mg, JTE-051 200 mg or placebo once daily. Randomization will be stratified by region and by the screening hs-CRP level (the qualifying hs-CRP value must be utilized).

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 3.5.6.24).

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 designated members of pharmacovigilance group 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 and safety parameters. A formal SAP will be developed at a later time. Statistical issues not addressed in the present 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, 100 mg QD, 150 mg QD, 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 (the actual received drug will be considered).

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.

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 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 250 eligible subjects (50 in each treatment group) will be randomized into the DB treatment period of this study.

The primary efficacy evaluation will be to compare the ACR20 response rate between JTE-051 with placebo at EOT. From one study comparing marvilimumab with placebo in combination with stable methrotrexate[26], the ACR20 of marvilimumab and placebo at Week 12 were 0.69 and 0.40, respectively. Assuming the ACR20 of at least one of the JTE-051 doses to be at least 0.30 above placebo, the following sample size per group will be needed to detect a statistical significant difference at the 5% level with about 80% power (using 2-sided Fisher's exact test):

Placebo ACR20	0.25	0.35	0.45
Sample size per group	47	48	47

About 50 randomized subjects per group would therefore give at least an 80% power for a range of placebo responses. The sample size calculation was carried out using the software SiZ 6.2 (Cytel Inc., 2013).

3.8.2. Interim Analysis

No interim analysis is planned for the 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 parameter analyses using the PP population and/or other sub-population may be performed if deemed appropriate.

3.8.3.1. Efficacy Parameters

The primary efficacy parameter is the ACR20 response rate at EOT.

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

- Percentage of subjects achieving ACR20/50/70 response rate
- Change from baseline in SDAI
- Percentage of subjects who achieved remission based on SDAI (≤3.3)
- Percentage of subjects who achieved low disease activity based on SDAI (≤11)
- Change from baseline in CDAI
- Percentage of subjects who achieved remission based on CDAI (≤2.8)
- Percentage of subjects who achieved low disease activity based on CDAI (≤10)
- Percentage of subjects achieving Boolean Remission
- Change from baseline in DAS28-CRP

- Percentage of subjects with DAS28-CRP of <2.6
- Percentage of subjects with DAS28-CRP of <3.2
- Percentage of subjects with good EULAR response at Week 12
- Percentage of subjects with moderate EULAR response at Week 12
- The ACR-N index
- Change from baseline in HAQ-DI
- Change from baseline in the number of tender and swollen joint counts (68/66 joints will be counted)
- Change from baseline in subject pain score by NRS
- Change from baseline in SGA of disease activity by NRS
- Change from baseline in PGA of disease activity by NRS
- Change from baseline in hs-CRP

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 DB treatment period after the first dose of study drug without any treatment intervention. For subjects who receive rescue treatment, the last value prior to the intervention will be defined as the EOT.

For the primary efficacy parameter (ACR20 at EOT), the Fisher's exact test will be used to compare each JTE-051 dose group with placebo. Furthermore, the exact Cochran-Armitage trend test[27] will be computed, using the ordinal score for treatment, e.g., score 1 for placebo, score 2 for the lowest JTE-051 dose, etc.

For dichotomous secondary efficacy parameters, similar analyses as the primary efficacy parameter will be used by time point, i.e., the Fisher's exact test for pairwise comparisons with placebo and the Cochran-Armitage test for trend.

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 factors 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., SDAI at Week 0 for the analysis of change from baseline in SDAI. 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.

[redacted]

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[28] 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. They 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 region and by the screening hs-CRP level. 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. The region effect will be included in the analysis model where appropriate.

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

Some efficacy parameters are a composite value derived from a complex instrument. The chance that one of its components is missing increases greatly due to various reasons. In order to minimize missing data, algorithms will be prepared to compute the derived value where reasonable in case some of the components are missing. These algorithms will be described in the SAP.

There will be missing data however, either intermittent like a missing visit or due to 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.

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 Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized by system organ class and preferred term.

Other safety parameters will be summarized as appropriate.

3.8.5. Pharmacokinetic Analyses

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

3.8.5.1. Pharmacokinetic Parameters

The PK measurements are:

- Trough concentrations (C_{trough}) of JTE-051 will be measured at each visit during the Treatment Period;
- Population PK parameters for JTE-051 may be generated using population PK analysis.

3.8.5.2. Pharmacokinetic Data Analysis

If data allow, population PK analysis will be performed using plasma concentration data 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 intra- and inter-subject variability of these parameters will be characterized. The effect of demographics/covariates (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 relationship between exposure of JTE-051 and response (e.g., efficacy) may also be explored. Descriptive statistics of plasma concentration data for JTE-051 will be presented by treatment with N, arithmetic mean, geometric mean, SD, coefficient of variation (CV%), median, minimum and maximum.

The population PK analysis results may be reported in a separate report.

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 clinical 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 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 or the subject's legally acceptable representative 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 or, if the subject is unable to provide informed consent, the subject's legally acceptable representative, 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 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 each subject randomized in 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.

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 the 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.

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7 APPENDICES

Appendix 1. ACR/EULAR Classification Criteria for Rheumatoid Arthritis

JOINT DISTRIBUTION (0-5)	
1 large joint	**0**
2-10 large joints	**1**
1-3 small joints (large joints not counted)	**2**
4-10 small joints (large joints not counted)	**3**
>10 joints (at least one small joint)	**5**
SEROLOGY (0-3)	
Negative RF AND negative Anti–citrullinated protein (ACPA)	**0**
Low positive RF OR low positive ACPA	**2**
High positive RF OR high positive ACPA	**3**
SYMPTOMS DURATION (0-1)	
<6 weeks	**0**
≥6 weeks	**1**
ACUTE PHASE REACTANTS (0-1)	
Normal CRP AND normal Erythrocyte Sedimentation Rate	**0**
Abormal CRP AND abnormal Erythrocyte Sedimentation Rate	**1**

If the cumulative score is ≥6 = definite RA; when the score is <6 a patient might fulfill the criteria (a) prospectively over time (cumulatively) or (b) retrospectively is data on all four domains have been adequately recorder in the past.

Notes:

- **These are "classification", not "diagnostic" criteria; the diagnosis is made by the rheumatologist.**
- **The target population for the criteria must meet the following two requirements:**
  - Patient with at least one joint with definite clinical synovitis (swelling)
  - Synovitis is not better explained by another disease

See reference 23 for additional details pertaining to these classification criteria.

Appendix 3. Numeric Rating Scale Templates

SUBJECT PAIN ASSESSMENT NRS TEMPLATE

SUBJECT ASSESSMENT OF PAIN

Circle the number that best describes the **pain** you felt due to arthritis **DURING THE PAST 3 DAYS?**

0	1	2	3	4	5	6	7	8	9	10
no pain										severe pain

SUBJECT GLOBAL ASSESSMENT OF DISEASE ACTIVITY NRS TEMPLATE

SUBJECT ASSESSMENT OF GLOBAL DISEASE ACTIVITY

Considering all the ways arthritis has affected you **DURING THE PAST 3 DAYS**, circle the number that best describes how **you have been doing**.

0	1	2	3	4	5	6	7	8	9	10
very well										very poor

PHYSICIAN'S GLOBAL ASSESSMENT OF DISEASE ACTIVITY NRS TEMPLATE

PHYSICIAN ASSESSMENT OF GLOBAL DISEASE ACTIVITY

Make a **global assessment** of the subject's **disease activity** by circling one number on the scale below.

0	1	2	3	4	5	6	7	8	9	10
No Disease Activity										Extremely Active Disease

Appendix 4. Health Assessment Questionnaire

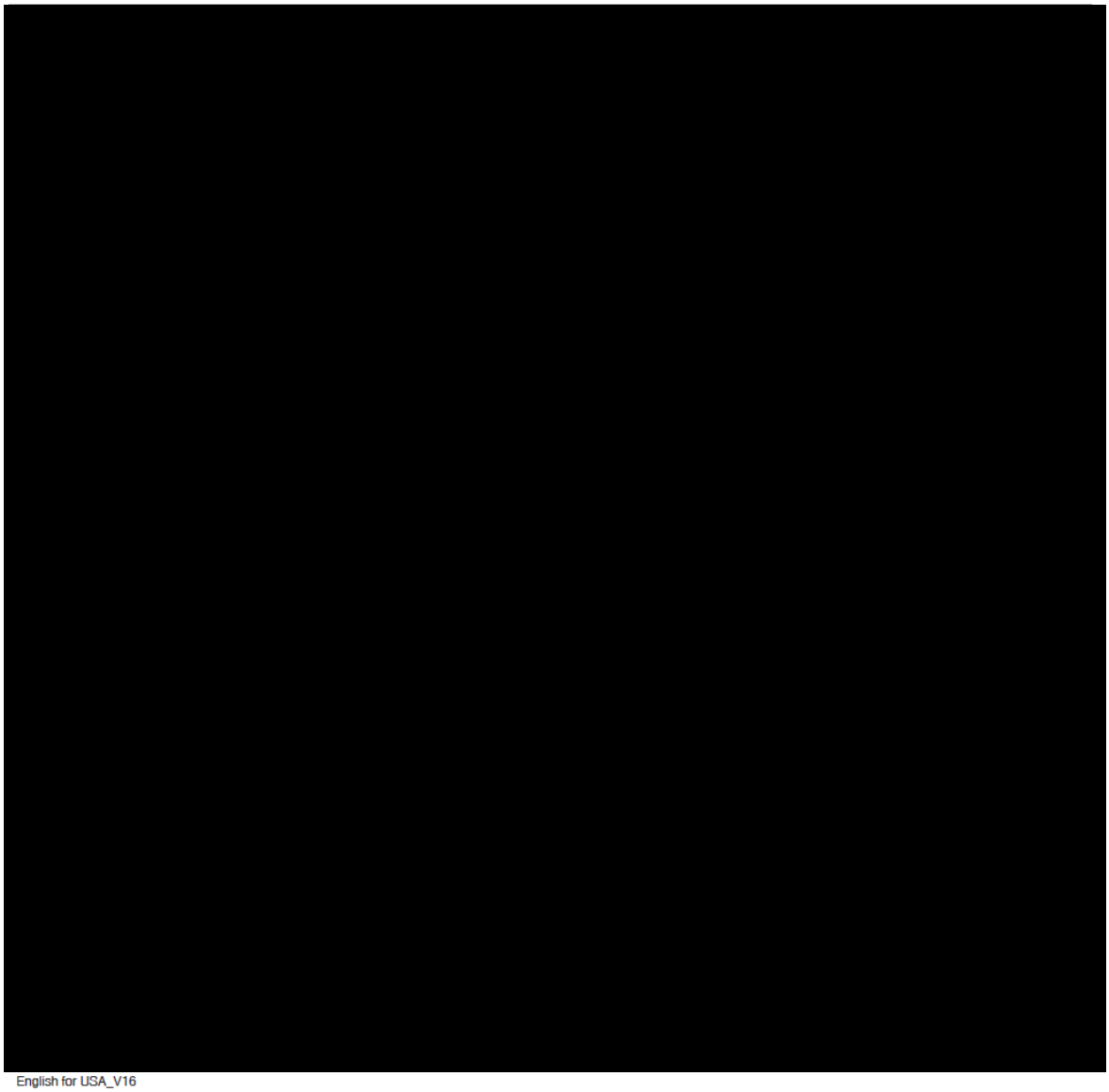
AKROS MOVE-RA STUDY **PROTOCOL NUMBER AE051-G-13-003**

Subject Number | | | | | - | | | |

Visit Number | | |

Visit Date | | | - | | | | - | | | | |
D D - M M M - Y Y Y Y

HAQ1-4



English for USA_V16

Akros Pharma Inc. – Princeton, New Jersey, USA

AKROS MOVE-RA STUDY **PROTOCOL NUMBER AE051-G-13-003**

Subject Number | | | | | - | | | |

Visit Number | |

Visit Date | | | - | | | | - | | | | |
D D - M M M - Y Y Y Y

HAQ2-4

[redacted]

English for USA_V16

Akros Pharma Inc. – Princeton, New Jersey, USA

AKROS MOVE-RA STUDY **PROTOCOL NUMBER AE051-G-13-003**

Subject Number | | | | | - | | | |

Visit Number | | |

Visit Date | | | - | | | | - | | | | |
D D - M M M - Y Y Y Y

HAQ3-4

[redacted]

English for USA_V16

Akros Pharma Inc. – Princeton, New Jersey, USA

AKROS MOVE-RA STUDY **PROTOCOL NUMBER AE051-G-13-003**

Subject Number | | | | | - | | | |

Visit Number | | |

Visit Date | | | - | | | | - | | | | |
D D - M M M - Y Y Y Y

HAQ4-4

[redacted]

Akros Pharma Inc. – Princeton, New Jersey, USA

Handling Responses (by the Investigator)

For each question in the questionnaire, the level of difficulty is scored from 0 to 3 with 0 for "Without ANY difficulty," 1 for "With SOME difficulty," 2 for "With MUCH difficulty," and 3 for "UNABLE to do".

- The HAQ-DI questionnaire should be completed by the study subject, following receipt of detailed instructions from the Investigator/study staff. After the subject completes the questionnaire and prior to the subject leaving the study site, the study staff should perform a detailed review of the answers, discuss why any questions were not answered, and what was intended when answers were marked outside the box or more than one box was marked for a question.
- Each subject should answer the questions according to his/her personal situation. Thus, the ratings, "Without ANY difficulty", "With SOME difficulty", "With MUCH difficulty", and "UNABLE to do", are deliberately not defined for subjects. For example, if a subject asks what "SOME" means, an appropriate response would be "Whatever you think 'SOME' means to you".
- When a sub-category item does not apply, e.g., when a subject does not use shampoo (or perhaps has no hair), the subject should give the response that represents the ability the subject believes he/she would have had in attempting the activity.
- When a subject uses aids or devices (e.g., crutches, jar openers), the subject should answer the question based on the usual equipment or way of performing the activity. If the subject has no difficulty doing an activity when using aids/devices, the subject should mark the "Without ANY difficulty" option. In scoring, the use of aids/devices results in an adjusted score for that item.
- **Notes about Aids/Devices:** The assignment of devices to particular disability categories assumes that the devices are used only for their intended purposes as shown in Table 2 below. For example, when a subject indicates use of a cane, it is presumed that the cane is used as an aid in walking.
  - If the subject informs the Investigator/site personnel that a device listed is being used for a different activity other than those shown in Table 2, (e.g., a cane is used for getting up from bed but not walking), or if a different device, not listed on the HAQ-DI form is utilized by the subject, then the Investigator must confirm for which activity category the specific device is utilized and a device from the list that is specific for that same activity category should be checked. This may be a different device than the one actually used (e.g., "built up or special chair" should be checked instead of "cane" in this example).
  - If a device is used for any activity in the "ACTIVITIES" category, as listed on Page 4 of the HAQ-DI questionnaire, only the "Errands and chores" under "HELP FROM ANOTHER PERSON" should be checked (i.e., none of the AIDS and DEVICES listed on Page 4 should be checked). This will ensure the appropriate adjustment to the score for the "ACTIVITY" category (this is done programmatically).

- **Items left blank or multiple answers:** If all component questions are blank or if more than one answer is given, then follow-up with the subject at the time of the visit is required.
- **Improperly Marked Items:** If the subject's mark is outside the answer box, then move it to the closest one. If it's directly between the two, move it to the answer with greater difficulty. However, follow-up with the subject and confirmation of intended answer should be done at the time of the visit, and all items should be marked appropriately before the subject leaves the study center.
  NOTE: A HAQ-DI score cannot be calculated validly when there are scores for less than six of the eight categories.

Scoring (performed by the Sponsor)

The HAQ-DI's scoring conventions allow for the computation of two disability indices:
1. The Standard HAQ-DI is the preferred and traditional scoring method which takes into account the use of aids/devices.
2. The Alternative Disability Index does not take into account the use of aids/devices.

A subject must have a score for at least six of the eight categories. Otherwise a HAQ-DI score cannot be validly computed. For the purpose of the current study, the standard computing method will be applied.

Computing the Standard HAQ-DI Score (With Aids/Devices): There are three steps:

1. Sum the 8 category scores by using the highest sub-category score from each category (for example, in the category "EATING" there are three sub-category items. If a subject responds with a 1, 2, and 0, respectively; the category score is 2).
2. Adjust for use of aids/devices and/or help from another person when indicated. Table 2 identifies the Aid/Devices companion variable for each HAQ-DI category.

Table 2. Companion Aids/Device Items for HAQ-DI Categories

HAQ-DI Category	Companion Item
Dressing & Grooming	Devices used for dressing
Arising	Built up or special chair
Eating	Built up or special utensils
Walking	Cane walker, crutches, wheelchair
Hygiene	Raised toilet seat, bathtub seat, bathtub bar Long handled appliances in bathroom
Reach	Long handled appliances for reach
Grip	Jar opener (for jars previously opened)

- Adjust the score for a category by increasing a zero or a one to a two.
- If a subject's highest score for that sub-category is a two it remains a two, and if a three, it remains a three.

3. Divide the summed category scores by the number of categories answered (must be a minimum of 6) to obtain a HAQ-DI score of 0-3 (3=worst functioning).

Appendix 5. Efficacy Endpoints Calculation

Numeric ACR (ACR-N) Index

The ACR-N will be derived by the Sponsor for Visits 3 through 7 based on the ACR core set measures collected by the Investigator. See Section 3.5.6.1 for the description of the ACR core set measures assessments by the Investigator.

This is a continuous variable expressing the percentage improvement from baseline a subject has experienced, defined as the minimum of percent improvement in swollen joints, tender joints and the median percent change in the other five ACR core set measures:

1. Subject's Assessment of Arthritis Pain.
2. Subject's Global Assessment of Disease Activity.
3. Physician's Global Assessment of Disease Activity.
4. Health Assessment Questionnaire Disability Index (HAQ-DI)
5. Acute phase reactant (hs-CRP)

Thus, and ACR-N of X means that the subject has achieved a change of at least X% in the tender and swollen joint counts and a change of at least X% in the median of the other five other parameters. ACR-N will take a negative value if a there is a worsening in either the swollen joint count, tender joint count and the median of the other five ACR core set measures (i.e., a subject can have a negative ACR-N despite improving in two of the three components).

The ACR20/50/70 Response Rate

The ACR20/50/70 response rate will be calculated by the Sponsor for Visits 3 through 7 based on the ACR core set measures collected by the Investigator.

This composite parameter measures improvement in tender (68) and swollen (66) joint counts and improvement in at least three of the following five ACR core set measures as listed above.

The ACR20/50/70 response rate is a dichotomous variable with a positive (= responder) or negative (= non-responder) outcome.

ACR20 is ≥20% improvement

ACR50 is ≥50% improvement

ACR70 is ≥70% improvement

Simple Disease Activity Index

The SDAI will be calculated by the Sponsor for all study visits. See Section 3.5.6.1.2 for the list of 28 joints included in the SDAI scoring.

The scoring of SDAI will be done as follows:

Variable	Range	Value
Tender joint score	(0-28)	
Swollen joint score	(0-28)	
Patient global score	(0-10)	
Provider global score	(0-10)	
C-reactive protein (mg/dL)	(0-10)	
Add the above values to calculate the SDAI score	**(0-86)**	

Interpretation of scoring will be done as follows:

SDAI Score Interpretation	
0.0 – 3.3	Remission
3.4 – 11.0	Low Activity
11.1 – 26.0	Moderate Activity
26.1 – 86.0	High Activity

Clinical Disease Activity Index

The CDAI will be calculated by the Sponsor for all study visits. See Section 3.5.6.1.2 for the list of 28 joints included in the CDAI scoring.

The scoring of CDAI will be done as follows:

Variable	Range	Value
Tender joint score	(0-28)	
Swollen joint score	(0-28)	
Patient global score	(0-10)	
Provider global score	(0-10)	
Add the above values to calculate the CDAI score	**(0-76)**	

Interpretation of scoring will be done as follows:

CDAI Score Interpretation	
0.0 – 2.8	Remission
2.9 – 10.0	Low Activity
10.1 – 22.0	Moderate Activity
22.1 – 76.0	High Activity

Disease Activity Score (DAS) 28[29]

The DAS assessment is a derived measurement with differential weighting given to each component. The DAS 28 (CRP) will be calculated by the Sponsor at all study visits. See Section 3.5.6.1.2 for the list of 28 joints included in the DAS calculation.

The components of the DAS 28 arthritis assessment include:

1. Tender/Painful Joint Count (28)
2. Swollen Joint Count (28)
3. CRP
4. Subject's Global Assessment of Disease Activity

DAS28(CRP) = 0.56 X √(TJC28) + 0.28 X √(SJC28) + 0.36 X Ln(CRP+1) + 0.014 X SGA + 0.96

Percentage of Subject achieving Boolean Remission

This secondary efficacy parameter will be calculated by the Sponsor, based on the following definition:

- Tender joint count (TJC) (28) ≤1
- Swollen joint count (SJC) (28) ≤1
- C-reactive protein ≤1 mg/dL
- Subject's global assessment (SGA) of disease activity ≤1 (on a 0 - 10 scale)

EULAR Response Criteria

The EULAR response criteria will be assessed by the Sponsor.

This parameter takes into account both the change in DAS28 between two timepoints, as well as DAS28 value at a specific timepoint.

DAS28-CRP will be utilized in calculating the EULAR response in the study subjects.

DAS28 improvement → / Present DAS28↓	>1.2	>0.6 and ≤1.2	≤0.6
≤3.2	good response	moderate response	no response
>3.2 and ≤5.1	moderate response	moderate response	no response
>5.1	moderate response	no response	no response

Note: High-sensitivity CRP (hs-CRP) will be utilized in all primary and secondary endpoints calculations [redacted]