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Clinical Study Statistical Analysis Plan (SAP)

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

PROTOCOL NUMBER: AE051-G-16-007

SAP DATE: 15 January 2019

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CONFIDENTIAL

Akros Pharma Inc.

Protocol AE051-G-16-007

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

Statistical Analysis Plan

Version 1.0
15 January 2019

Signature Page

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The signatures below indicate approval of this Statistical Analysis Plan.

[redacted]

Table of Contents

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition of term
AE	Adverse event
AI-NRS	Average-itch numeric rating scale
BMI	Body mass index
BSA	Body surface area
CRF	Case report form
CSR	Clinical study report
DB	Double-blind
ECG	Electrocardiogram
ITT	Intent-To-Treat
MedDRA	Medical Dictionary for Regulatory Activities
NRS	Numeric rating scale
PK	Pharmacokinetics
PASI	Psoriasis Area and Severity Index
PP	Per protocol
QD	Once daily
SAE	Serious adverse event
SAP	Statistical analysis plan
sPGA	Static Physician's Global Assessment
TEAE	Treatment-emergent adverse event
WI-NRS	Worst-itch numeric rating scale

1. INTRODUCTION

This Statistical Analysis Plan (SAP) describes the statistical methods and data presentations to be used in the summary tables and listings of study AE051-G-16-007. No figures are planned due to the limited amount of data.

This document has been prepared based on Protocol Amendment 4, Version 5.2 – 8 Oct 2018 and Case Report Form (CRF) Amendment 1, Version 2.0 – 22 May 2018. Details on the study conduct and data collection can be found in the protocol and the CRF.

2. OBJECTIVES

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

3. STUDY DESIGN

This is a 12-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study in subjects with moderate to severe plaque psoriasis.

Eligible subjects will be randomized at Visit 2 to receive JTE-051 50 mg, 100 mg, 150 mg, 200 mg or placebo once daily (QD) for 12 weeks. Approximately 85 subjects are planned to be randomized into 5 treatment groups. A follow-up visit will take place approximately 4 weeks after the last dose of study drug. Randomization will be stratified based on prior exposure of subjects to biologic therapy (i.e., biologic treatment naïve vs. biologic treatment experienced subjects).

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

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

3.1 Study Procedures

The schedule of study procedures is described in the following Figure 1 and Table 1.

Figure 1. Planned Study Schema

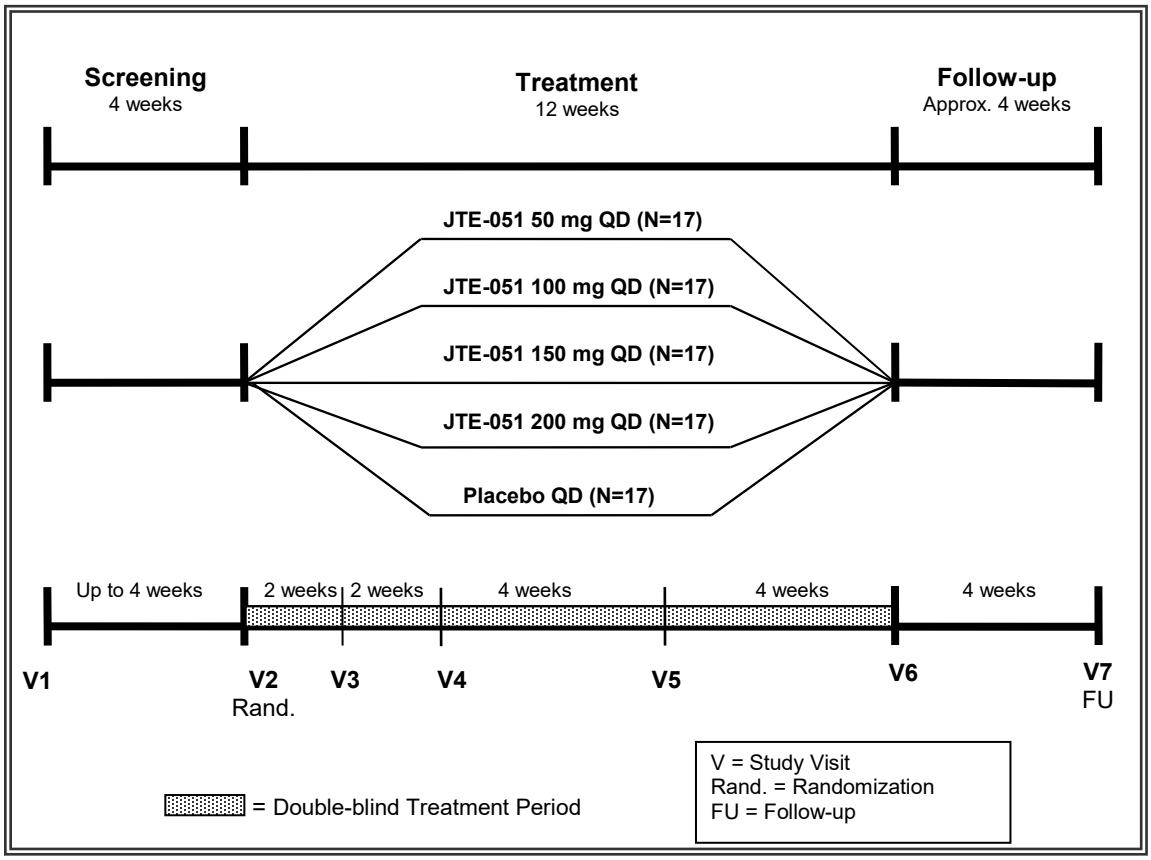


Table 1. Planned Schedule of Study Procedures

	Screening Period	Treatment Period					Follow-up Period
Duration/ Study Week (Day)[a]	Up to 4 weeks	Week 0 (Day 1)	Week 2 (Day 14±2)	Week 4 (Day 28±2)	Week 8 (Day 56±2)	Week 12 (Day 84±2)	Week 16 (Day 112±2)
Visit	1	2	3	4	5	6	7
Sign Informed Consent	X						
Inclusion/ Exclusion Criteria	X	X					
Medical History	X						
Demographic Information	X						
Review Prior/ Concomitant Medications	X	X	X	X	X	X	X
Physical Exam	X	X	X	X	X	X	
[redacted]							
Vital Signs	X	X	X	X	X	X	X
Body Weight	X	X				X	
Height and Calculate BMI	X						
12-Lead ECG	X	X		X		X	
Chest Radiography[c]	X						
TB test (quantiFERON gold OR PPD Test)	X						
Drugs of Abuse Screen & alcohol	X						
Viral Serology (HBs Ag, HCV Ab, HIV Ab)	X						
FSH[d]	X						
HbA1c	X						
Pregnancy Test (all females)[d]	X	X	X	X	X	X	X
Serum Biochemistry	X	X	X	X	X	X	X
Hematology	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X
Coagulation	X	X		X		X	X
Lipid Profile	X	X		X		X	X
Serum IgG, IgM and IgA		X				X	
25-hydroxyvitamin D	X						
Psoriasis Body Surface Area	X	X	X	X	X	X	X
Bone-specific ALP	X	X				X	
PASI	X	X	X	X	X	X	X
sPGA	X	X	X	X	X	X	X
Skindex 16		X	X	X	X	X	X
Itch NRS [redacted]	←						→
[redacted]							
Digital Photography[g]		X				X	
Randomization using IWRS		X					
Access IWRS and Dispense Study Drug[h]		X	X	X	X		
[redacted]							
Collect Study Drug and Check Compliance[j]			X	X	X	X	
Study Drug Administration[k]		X	X	X	X		
JTE-051 PK Blood Samples[l]		X	X	X	X	X	
Document Adverse Events[m]	X	X	X	X	X	X	X

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

a. The target day for each visit after randomization will be calculated relative to the date of Randomization Visit (Visit 2) and not relative to the date of the previous visit. All visits should be performed within the windows specified in the table. Every attempt should be made to have the subject attend each visit as scheduled. The investigational site is encouraged to a make a reminder phone call to the subject approximately a day or two before the scheduled visit. However, if a subject is unable to attend a visit within the specified windows, the visit should be scheduled as closely as possible to these windows. A subject should not skip a protocol-specified visit due to scheduling difficulties.

[redacted]

c. Chest radiography may not be performed if it has been performed within 12 weeks of Visit 1 and documentation is available for review by the Investigator and inclusion in the subject's file.
d. At Visit 1, serum pregnancy test will be performed for all female subjects. At Visits 2 through 7, urine pregnancy tests will be performed only for female subjects of child bearing potential. At Visit 1, females with a documented history of lack of menses for ≥12 consecutive months with no other reversible medical etiology will be considered postmenopausal. If the female is positive for lack of menses but onset has been <12 months, then an FSH >40 will be required to define post-menopausal status, otherwise subject is considered of childbearing potential.
e. Both worse-itch numeric rating scale (WI-NRS) and average-itch numeric rating scale (AI-NRS) during a 24-hour recall period will be recorded by the subject once daily from screening through the last visit.

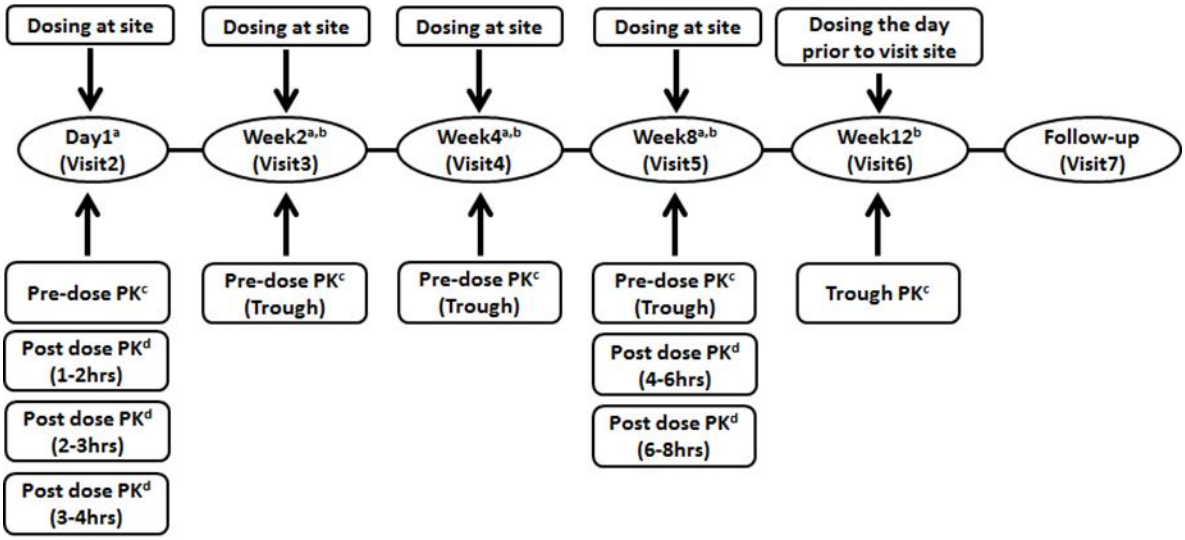
[redacted]

g. All subjects will be required to take photographs of the [redacted] four half-body views (i.e., upper anterior, lower anterior, upper posterior, and lower posterior). However, if collecting photographs is raised as the reason for not participating in the study, the subject still can be part of the study without collecting photographs. In all the photographs, subject identification will be blinded.
h. At Visit 2 through Visit 5, randomized subjects will receive sufficient study drug blister cards for the period between visits. At Visit 6, study drug will not be dispensed. If a study subject discontinues study drug prematurely, the termination should be recorded as soon as possible after the decision has been made.

[redacted]

j. Subjects will be instructed to bring all used and unused blister cards to each study visit for accountability purposes. Study drug compliance will be calculated by the site at each visit during the Treatment Period starting at Visit 3, based on the number of tablets dispensed to and returned by the subject.
k. Oral administration for 12 weeks starting on the day of randomization at Visit 2, QD in the morning, regardless of meals. On study visit days, subjects should take their scheduled study treatment from their existing study drug supply (if available) at the site, under the supervision of the investigator or designee after all study-related procedures have been performed (except for Visit 6, when no study drug will be administered, as the last dose will be taken the day prior to the visit).
l. See Figure 2 for a detailed description of dosing and PK sampling time points.
m. AE information will be collected at the specified time points as well as at any time when a site staff member becomes aware of an AE after the subject signs the informed consent for the study. However, stable or improving pre-existing conditions detected through the screening procedures during the Screening Period (e.g., abnormalities in ECG, physical examination, [redacted], vital signs and laboratory tests) are considered to be medical history and should be documented accordingly.

Figure 2. Dosing and Pharmacokinetic Sample Collection Time



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

4. SUBJECT POPULATIONS

The Intent-To-Treat (ITT) population, the Per Protocol (PP) population and the PK population are mentioned in the protocol but will not be identified in the final analyses due to the early termination of the study and the limited amount of data.

4.1 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 placebo QD.

4.2 Safety Population

The safety population consists of the randomized subjects who receive at least one dose of JTE-051 or placebo after the randomization, including those who did not complete the study.

5. STATISTICAL ANALYSIS

The study was terminated early due to the results of another study on the same compound and slow enrollment in this study. Therefore, the planned sample size of 85 eligible subjects (17 in each treatment group) was not achieved. With only 13 subjects randomized until the early study termination, there will not be enough data to analyze the planned efficacy and safety endpoints. No inferential tests will be performed. Most of the data will be displayed in listings only.

Titles and headers of all statistical analysis tables will indicate the corresponding study population; the number of subjects for the population and for each treatment will be presented in the tables.

Percentages will be presented to 1 decimal, e.g., xx.x%.

Baseline is defined as the last non-missing value prior to the first dose of study drug. Missing data will not be imputed in this study.

Unless otherwise noted, all records collected in the study database, including CRF data and any external data transfers (such as clinical laboratory results) will be displayed in listings, regardless of whether the subject is randomized or not.

All analysis will be performed using SAS® Version 9.4.

5.1 Disposition

Subject disposition will be summarized and tabulated by treatment group and in total. The number and percentage of subjects in the randomized and safety populations will be tabulated. Number of discontinued subjects and the reasons for discontinuation during the double-blind (DB) treatment period will be tabulated for the randomized population.

5.2 Safety

The Medical Dictionary for Regulatory Activities (MedDRA) Version 21.0 will be used to map verbatim AEs to preferred terms and their respective primary system organ classes.

A treatment-emergent AE (TEAE) is defined as any AE with an onset date on or after the first dose of study drug.

The number and percentage of subjects experiencing TEAEs will be tabulated by treatment in an overall summary as well as by preferred term and system organ class for the safety population. Listings will be provided for serious adverse events (SAEs) and AEs leading to study discontinuation.

5.3 Efficacy

For Psoriasis Area and Severity Index (PASI), Static Physician's Global Assessment (sPGA) and Skindex-16 questionnaire, change from baseline will be derived. In addition, percentage change from baseline will be derived for PASI score and psoriasis affected Body Surface Area (BSA).

Skindex-16 questionnaire is reported in a scale of 0 to 6. Each raw score will be multiplied by 16.667, thus all responses will be transformed to a linear scale of 100 (i.e., from 0 [no effect] to 100 [effect experienced all the time]). Scale scores are the average of non-missing items in a given scale as follows. If any scale has more than 25% of the responses missing, the scale is missing.

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

[redacted]

6. APPENDICES

6.1 List of Summary Tables

Number	Title
14.1.1	Subject Disposition, Randomized Population
14.3.1.1	Overall Summary of Treatment-emergent Adverse Events (TEAEs), Safety Population
14.3.1.2	Number (%) of Subjects with TEAEs by System Organ Class and Preferred Term, Safety Population
14.3.2.1	Listing of Serious Adverse Events, Safety Population
14.3.2.2	Listing of Adverse Events Leading to Study Discontinuation, Safety Population
14.3.3	Clinical Laboratory Normal Ranges in Reported SI Units and Conventional Units

6.2 List of Data Listings

Number	Title
16.1.7	Randomization
16.2.1.1	Subject Disposition
16.2.1.2	Screen Failure Reasons
16.2.2	Subject Eligibility
16.2.4.1	Demographics
16.2.4.2	Plaque Psoriasis History
16.2.4.3	Medical History
16.2.4.4	Reproductive Status
16.2.4.5	Drugs of Abuse/Alcohol Screen
16.2.4.6	Serum Pregnancy Test and FSH (Females only)
16.2.4.7	Viral Serology at Screening
16.2.4.8	Prior Anti-psoriasis Medications
16.2.4.9	Prior and Concomitant Medications
16.2.4.10	Prior and Concomitant Procedures
16.2.5.1	Study Medication Dispensation
16.2.5.2	Study Medication Administration
16.2.5.3	JTE-051 Plasma Concentration
16.2.6.1	Psoriasis Area and Severity Index (PASI) and Psoriasis Affected Body Surface Area (BSA)
16.2.6.2	Static Physician's Global Assessment (sPGA)
16.2.6.3	Skindex-16, Section 1 of 2
16.2.6.4	Skindex-16, Section 2 of 2
16.2.6.5	Itch Numeric Rating Scale
[redacted]	
16.2.6.7	Digital Photography Collection
16.2.7	Adverse Events
16.2.8.1.1	Clinical Laboratory Test Results – Hematology: Erythrocytes and Platelets
16.2.8.1.2	Clinical Laboratory Test Results – Hematology: Leukocytes, Section 1 of 2
16.2.8.1.3	Clinical Laboratory Test Results – Hematology: Leukocytes, Section 2 of 2
16.2.8.2.1	Clinical Laboratory Test Results – Serum Biochemistry: Liver Function
16.2.8.2.2	Clinical Laboratory Test Results – Serum Biochemistry: Electrolytes/Blood Gases/Glucose
16.2.8.2.3	Clinical Laboratory Test Results – Serum Biochemistry: Lipids/Protein/Inflammation
16.2.8.2.4	Clinical Laboratory Test Results – Serum Biochemistry: Renal Function/Urate/Creatine Kinase
16.2.8.2.5	Clinical Laboratory Test Results – Serum Biochemistry:

Number	Title
	Clinical Laboratory Test Results – Serum Biochemistry: Bone-Specific Alkaline Phosphatase, C Reactive Protein, 25-Hydroxyvitamin D and Hemoglobin A1c
16.2.8.3	Clinical Laboratory Test Results – Serum Immunoglobulins
16.2.8.4	Clinical Laboratory Test Results – Coagulation
16.2.8.5.1	Clinical Laboratory Test Results – Urinalysis: Macroscopic
16.2.8.5.2	Clinical Laboratory Test Results – Urinalysis: Macroscopic and Microscopic
16.2.8.5.3	Clinical Laboratory Test Results – Urinalysis: Microscopic
16.2.8.5.4	Clinical Laboratory Test Results – Urinalysis: Crystals
16.2.8.5.5	Clinical Laboratory Test Results – Urinalysis: Casts
16.2.8.6	Clinical Laboratory Test Comments
16.2.8.7	Vital Signs and Body Weight
16.2.8.8	12-Lead ECG

6.3 Table and Listing Mockups