Protocol Number: KD025-211

Document Title: A Phase 2, Randomized, Double-blind, Placebo-controlled, Dose-finding Study to Evaluate the Safety, Tolerability, and Efficacy of KD025 in Adult Subjects with Moderate to Severe Chronic Plaque Psoriasis Who are Candidates for Systemic Therapy or Phototherapy

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STATISTICAL ANALYSIS PLAN

A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Dose-Finding Study to Evaluate the Safety, Tolerability, and Efficacy of KD025 in Adult Subjects with Moderate to Severe Chronic Plaque Psoriasis who are Candidates for Systemic Therapy or Phototherapy

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Version 1	18-Oct-2019
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SIGNATURE PAGE

Date	Prepared by: Zhongming Yang, PhD Director, Biostatistics Kadmon Holdings, Inc.
Date	Reviewed by: Dr. Sanjay K Aggarwal Senior Vice President, Clinical Development Kadmon Holdings, Inc.

Zhongming Yang

From: Zhongming Yang
Sent: Sunday, April 5, 2020 10:25 AM
To: Kevin Jia [redacted] 'Sune Hao'
Cc: Nicole Martins, MPH
Subject: RE: KD025-211 SAP V1.1
Attachments: KD025-211_SAP_V1.1.docx

Dear All,

I am writing this email to confirm KD0250211 SAP is confirmed by both statistician Zhongming Yang and clinician Sanjay Aggarwal.

Due to Covid 19 circumstance, this email also served as official signature.

Zhongming

[redacted]

DOCUMENT HISTORY

Version	Author	Description
1.0	Zhongming Yang	18-Oct-2019 New Document
1.1	Sune Hao	02-Apr-2020 Minor Revision The primary reasons for this new version include: • Add specification: Efficacy analysis will be performed on blinded period and entire treatment duration. Safety analysis will be performed on blinded period, open-label period and entire treatment duration. • Delete relative dose intensity (RDI) calculation.

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LIST OF ABBREVIATIONS

Abbreviation	Full Term
AE	Adverse event
BID	Twice daily
CI	Confidence Interval
CTCAE	Common terminology criteria for adverse events
CRF	Case report form
DLQI	Dermatology Life Quality Index
ECG	Electrocardiogram
EE	Evaluable for Efficacy
EOT	End of treatment
ICH	International Conference on Harmonization
MedDRA	Medical dictionary for regulatory activities
mITT	Modified Intent-to-treat
PASI	Psoriasis Area and Severity Index
PD	Pharmacodynamics
PGA	Physicians Global Assessment
PK	Pharmacokinetics
PR	Partial response
PT	Preferred term
QD	Once daily
QTcF	Corrected QT interval using Fridericia's formula
SAE	Serious adverse event
SAP	Statistical analysis plan
SOC	System organ class
TEAE	Treatment emergent adverse event
WHO	World Health Organization

1 INTRODUCTION

Psoriasis is an autoimmune disease that affects many parts of the body but is primarily manifested in the skin. It affects 2% to 3% of the population globally, making it a very common inflammatory autoimmune disease. A number of biologic products have been approved for the treatment of moderate to severe chronic plaque psoriasis. However, there are still safety concerns and most of these products are parenterally administered. An oral agent such as KD025, which targets IL-17, could potentially provide an oral treatment option with an improved safety and efficacy profile.

This Statistical Analysis Plan (SAP) describes statistical procedures to be used for study KD025-211 as specified in the protocol (Amendment No. 2, 12-Mar-2019). The pharmacodynamic data will be analyzed and reported separately.

The SAP was written in accordance with the recommendations outlined in the International Conference on Harmonization (ICH) E9 Guideline entitled "Guidance for Industry: Statistical Principles for Clinical Trials" and the most recent ICH-E3 Guideline, entitled "Guidance for Industry: Structure and Content of Clinical Study Reports."

2 STUDY SUMMARY

2.1 Study Objectives

2.1.1 Primary Objective

- To assess the number of subjects that reach Psoriasis Area and Severity Index (PASI) 75 after 16 weeks of dosing with various regimens of KD025 compared with placebo

2.1.2 Secondary Objectives

- To assess changes in absolute PASI scores from baseline to Week 16
- To assess the mean percent change in PASI scores from baseline to Week 16
- To assess safety and tolerability of KD025
- To assess changes in Physicians Global Assessment (PGA)
- To assess changes in Dermatology Life Quality Index (DLQI)
- To assess changes in PASI scores from baseline to Week 48 for subjects receiving 48 weeks of KD025 treatment

- To evaluate the difference in PASI scores between Week 16 and Week 48 for subjects receiving KD025 for a total of 48 weeks

2.1.3 Exploratory Objectives

To evaluate the concentration and changes in IL-17 expression in blood, tissue before and after 16 weeks of dosing with KD025

2.2 Study Design

This is a Phase 2, double blind, randomized, placebo-controlled, dose-finding, safety, tolerability, and efficacy study.

This study will be performed in adult male and female subjects with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy. Subjects who have signed an Institutional Review Boards/Independent Ethics Committees (IRBs/IECs) approved informed consent form (ICF) and have met all of the inclusion/exclusion criteria will be enrolled. Approximately 110 subjects will be randomly assigned to each of the 5 dose cohorts in a 1:1:1:1:1 manner to achieve 22 evaluable subjects at 16 weeks in each cohort.

Table 1: Cohorts

Cohort	Number of Subjects	Treatment
Cohort 1	~22	200 mg KD025 QD
Cohort 2	~22	200 mg KD025 BID
Cohort 3	~22	400 mg KD025 QD
Cohort 4	~22	600 mg/day KD025 (administered as 400 mg in the morning and 200 mg in the evening)
Cohort 5	~22	Matching placebo BID

Study drug will be orally administered in a double-blind fashion for an initial 16 weeks. All subjects will be given the option to receive KD025 400 mg QD for an additional 32-weeks in an open-label treatment period (week 16 through week 48).

For all subjects, including those who discontinue from the study prematurely, a Follow-Up visit will occur 30 days (± 3 days) after the last dose of study drug.

2.3 Visit Schedule and Study Assessment

The flow chart of visit schedule and study assessments is given in study protocol Table 1.

3 STATISTICAL METHODS

3.1 General Methods

3.1.1 Computing Environment

All statistical programming and data analyses will be performed using SAS® Version 9.4 on Windows platform.

3.1.2 General Considerations

General considerations for descriptive statistics and presentation for continuous and categorical data are given below.

Continuous data will be described using descriptive statistics: number of observations (n), mean, standard deviation, median, minimum and maximum. Frequencies and percentages will be used for summarizing discrete (categorical) data. When categorical data are presented, the percent will be suppressed when the count is zero in order to draw attention to the nonzero counts. The denominator for all percentages, unless otherwise specified, will be the number of subjects in the cohort or in the specified analysis population.

Means, medians, standard deviations, and confidence intervals (CI) will be reported to one decimal place more than the data reported on the CRF or by the vendor. Minimum and maximum will be reported to the same number of decimal places displayed on the CRF or by the vendor. P-values will be reported to 4 decimal places.

Efficacy analysis will be performed on blinded period and entire treatment duration. Safety analysis will be performed on blinded period, open-label period and entire treatment duration.

Unless otherwise indicated, all summary tables for blinded period and entire treatment duration will be presented by the following groups: cohort 1, cohort 2,

cohort 3, cohort 4, cohort 5, and all KD025. For open-label period, summary tables will be presented by the actual dose group (400 mg KD025 QD for all subjects).

Because of the exploratory nature of the study, no adjustments will be made for the multiplicity of endpoints.

Last Observation Carried Forward (LOCF) method will be incorporated when applicable.

3.1.3 Study Day

The study day for all assessments prior to the first study drug administration is calculated as the difference between the date of the event or measurement (e.g., AE onset date, assessment date, sample collection date, etc.) and the start date of study treatment. The day before the start of study treatment is Study Day -1.

The study day for all post assessments after the first study drug administration is calculated as the difference between the date of the event or measurement (e.g., AE onset date, assessment date, sample collection date, etc.) and the start date of study treatment, plus one day. The first day of study treatment is Study Day 1.

3.1.4 Baseline

Two different types of baseline are defined considering the different periods in this study.

For blinded period and entire treatment duration, baseline value is defined as the valid and last non-missing value obtained within 28 days prior to subject receiving the first study medication, unless otherwise stated under the related assessment section. Baseline can be the day before the first study medication or on the same day as the first study medication if a pre-dose assessment is available. Subjects without data on a parameter before the first study medication will have a missing baseline for this parameter.

For open-label period, baseline value is defined as the last non-missing assessment value on or before Week 16.

3.1.5 Handling of Incomplete or Missing Data

Missing data will not be imputed in general and will be reported as missing in all listings. For categorical variables, patients with missing data are not included in calculations of percentages unless otherwise specified.

Missing start and end dates for AE and concomitant medication (CM).

The assumption will be the worst or most conservative judgment when imputing AE and CM start and end dates. The purpose of imputing a start date is to help define whether the AE/CM started while taking study drug.

For a partial or missing start date:

- If the day is missing, the first day of the month will be imputed. If the missing day is the same as the month of first dose of study drug, then the first dose date will be imputed.
- If the day and month are missing, the first day of January will be imputed. If the year is the same as the first dose date, then the first dose date will be imputed.
- If the day is completely missing, the first dose date will be imputed. If the end date suggests it could have started prior to this, the first day of January of the same year as the end date will be imputed.
- When imputing a start date, the start date will ensure that the new imputed date is sensible, i.e., is prior to the end date of the AE or CM.

For a partial or missing end date:

- If the day is missing, the last day of the month or the last assessment date, whichever is earlier, will be imputed.
- If the day and month are missing, the 31st of December or the last assessment date, whichever is earlier, will be imputed
- If the date is completely missing, there will be a need to look at whether the AE/CM is still ongoing before imputing a date. If the ongoing flag is missing, then it will be assumed that AE is still present, or CM is still being taken (i.e., do not impute a date). If the AE/CM has stopped, then the last assessment date will be imputed.

These data imputations are for categorization purpose only and will not be used in the listings.

If the assessment of the relationship of the AE to KD025 is missing, then it will be assumed that the AE is related to KD025 and the AE considered as such in the frequency tables of possibly related AEs. No imputation should be done at the data level.

3.2 Analysis Populations

Modified Intent-to-treat (mITT) Population: Modified Intent-to-treat (mITT) Population is defined as all subjects who receive at least 1 dose of study medication.

The mITT Population will be used for tables of demography, baseline characteristics and efficacy analyses.

Safety: The safety population is defined as all subjects who receive at least one dose of study medication. In this study, safety population is equivalent to mITT population.

3.3 Subject Disposition and Evaluability

Subjects with screen failure (i.e., subjects who signed the informed consent were screened but never started the study treatment, their basic demographics and any AE after signing the informed consent may have been collected in the CRF) will be excluded from any populations defined in section 3.2, therefore these subjects will be excluded in any summary tables or listings.

The number of subjects discontinuing from the study and the primary reason for discontinuation will be summarized.

3.4 Protocol Deviations

All protocol deviations will be identified and classified as major or minor (as defined below) before the clinical database lock, and will be presented in a listing.

Major Deviation: Protocol deviation that may impact the accuracy, and/or reliability of the study data or that may impact subject rights, safety or well-being.

Minor Deviation: Protocol deviation that does not impact the accuracy, and/or reliability of the study data or subject rights, safety or well-being.

Serious non-compliance: Serious non-compliance presents a significant risk to the safety of study patients or significantly affects the scientific value of the reported results of the study. This classification may include fraud, scientific misconduct and serious breaches of ethical conduct. Persistent clinical investigator site noncompliance, even if not serious, is also considered within this definition.

3.5 Demographics and Baseline Characteristics

3.5.1 Demographics

Subject demographics and baseline characteristics will be summarized for the mITT population. Descriptive statistics will be provided for age, height, weight, and body mass index (BMI). Frequencies and percentages will be tabulated for sex, race, and ethnicity.

3.5.2 Medical History

Medical history will be summarized by primary system organ class and preferred term. Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA, Version 20.1 or higher) terminology.

3.6 Prior and Concomitant Medications

Concomitant medications will be coded using WHO Drug Dictionary. Prior medications are those that started and stopped before the start of study treatment; concomitant medications are all medications taken after the start of study treatment, during each study period, including those started before but ongoing at the start of study treatment. Where a medication start date is partially or fully missing, and it is unclear as to whether the medication is prior or concomitant, it will be assumed that it is concomitant.

Number and percentage of incidence of prior and concomitant medication will be summarized according to ATC class and preferred drug name.

3.7 Treatment Compliance and Exposure

The duration of exposure is defined as,

Duration of exposure (days) = Date of last dose – Date of Study Day 1 + 1.

The descriptive summary statistics of the treatment duration will be presented.

3.8 Efficacy Analysis

3.8.1 Primary Endpoint

- The number (%) of subjects with a 75% decrease in PASI by Week 16

  In addition to the descriptive statistics (n, %, CI) for each group, the difference of the percentage of subjects with a 75% decrease in PASI by Week 16 between each treatment and control group will be analyzed with Fisher's exact method.

  Patients without Week 16 assessment will be counted as failed to reach 75% decrease.

3.8.2 Secondary Endpoints

- The Week 16 change from baseline in PASI scores

  The descriptive statistics (n, mean, 95% CI) of Week 16 change from baseline in PASI scores will be summarized and tabulated by treatment groups.

- The Week 16 percent change from baseline in PASI

  The descriptive statistics (n, mean, 95% CI) of Week 16 percent change from baseline in PASI scores will be summarized and tabulated by treatment groups.

- Improvements in PGA of "clear" or "almost clear" (excellent) at Week 16

  Use the same approach with primary endpoint analysis in section 3.8.1.

- Improvements in DLQI at Week 16

  The descriptive statistics (n, mean, 95% CI) of DLQI changes from baseline to Week 16 will be summarized and tabulated by treatment.

- The Week 48 change from baseline in PASI scores

  The descriptive statistics (n, mean, 95% CI) of Week 48 change from baseline in PASI scores will be summarized and tabulated by treatment groups.

- The Week 48 percent change from baseline in PASI

  The descriptive statistics (n, mean, 95% CI) of Week 48 percent change from baseline in PASI scores will be summarized and tabulated by treatment groups.

- The Week 48 change from Week 16 in PASI scores

  The descriptive statistics (n, mean, 95% CI) of Week 48 change from Week 16 in PASI scores will be summarized and tabulated by treatment groups.

3.8.3 Exploratory Endpoints

- Descriptive statistics for concentration and change from baseline in IL-17, will be tabulated.

3.9 Safety Analysis

Safety assessments include AEs, serious adverse events (SAEs), vital sign measurements, clinical laboratory evaluations (hematology and chemistry), and ECGs. Unscheduled visits for safety assessments will not be presented in summary tables, but will be presented in listings. All safety analyses will be performed using the safety population.

3.9.1 Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary (Version 20.0 or higher). TEAEs for blinded period and entire treatment duration are any AEs occurring or worsening in severity after the first administration of study medication. TEAEs for open-label period are any AEs occurring or worsening in severity after Week 16. All AEs (including SAEs) will be graded using the 5-point CTCAE V5.0 scale (mild, moderate, severe, life threatening, or death); their causality with KD025 will be classified into following 5 classes: definitely related, probably related, possibly related, unlikely related, not related. The Investigator will further assess the relationship of adverse events to cGVHD or the underlying disease.

The number and percentage of patients who experienced at least one TEAE as well as the number and percentage of patients who experienced adverse events of each specific system organ class (SOC) and preferred term (PT) will be presented. For the presentation of AE incidences, the SOCs and the PTs within each SOC will be presented by decreasing total frequency. Tabulation by maximum severity and relationship to KD025 will also be included by treatment group.

TEAEs, Grade ≥3 TEAEs, SAEs and TEAEs leading to dose modification / discontinuation will be summarized according to treatment arm, system-organ-class, and preferred terms. These analyses will be repeated for events considered related (definitely related / probably related / possibly related) to KD025.

Subject listings will be provided for SAEs, AEs resulting in study drug discontinuation and deaths.

AEs will also be presented in listings. Time to onset and duration of AEs will be included in listings, along with action taken and outcome.

3.9.2 Clinical Laboratory Evaluation

The summary statistics (including number, mean, standard deviation, median, minimum and maximum) of all laboratory variables and changes from baseline will be calculated for each visit or study assessment by treatment group. For parameters of WCC, neutrophils (absolute count), lymphocytes (absolute count), monocytes (absolute count), Hb, platelets, ALP, ALT, AST, GGT, total bilirubin, GFR, plots of mean / mean changes from baseline with the corresponding standard error will be displayed.

For shift tables, laboratory results will be classified using the CTCAE V5.0. All graded laboratory parameters will be summarized separately for hematology and biochemistry. Corresponding shift tables to compare baseline to the worst post-baseline grade within the treatment period will be provided.

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3.9.3 Vital Signs

Descriptive statistics for vital signs (weight, temperature, blood pressure, pulse rate, and respiratory rate) values and the change from baseline will be presented for each scheduled assessment time point.

3.9.4 ECG

Descriptive statistics for ECG parameters (i.e., PR interval, QRS interval, and QTcF interval) at each time point with triplicate ECGs will be presented for the values and change from baseline scores (note: Fridericia's correction: $QTcF = QT/RR^{1/3}$).

The number and percentage of subjects with observed QTcF values that satisfy the following conditions will be presented by treatment group and study visit:

- ≤ 450 ms
- >450 - 480 ms
- >480 - 500 ms

- > 500 ms

The number and percentage of subjects having change from baseline QTcF values that satisfy the following conditions will be presented by treatment group and study visit:

- ≤ 0 ms
- >0 to ≤ 30 ms
- >30 to ≤ 60 ms
- > 60 ms

3.10 Pharmacokinetic Analysis

No pharmacokinetic analysis will be conducted.

3.11 Pharmacodynamic Analysis

Pharmacodynamics endpoints are included in exploratory analysis (section 3.8.3).

3.12 Sample Size Justification

A sample size of 36 subjects per cohort receiving KD025 will provide approximately 90% probability of 1 or more subjects in the cohort experiencing an AE that has an underlying rate of ≥ 6% and approximately an 80% probability of 1 or more subjects in the cohort experiencing an AE that has an underlying rate of ≥ 4%.

An evaluable sample size of 30 subjects per cohort will provide approximately 85% power to detect a difference in the number of subjects that reach PASI 75 rates at Week 16 between a KD025 group and placebo, assuming rates of 33% and 5%, respectively, at a 5% 2-sided significance level using Fisher's Exact test. This assumes an observed case analysis with approximately 17% of subjects not having a Week 16 PASI score.

But due to newly available plaque psoriasis treatment, this study was terminated early with 110 subjects.

3.13 Interim Analysis

There is no interim analysis.

3.14 Primary CSR Analysis

A primary CSR analysis will be conducted after conclusion of the study.

4 List of Tables, Figures and Listings

In all tables, figures and listing, results will be presented by treatment cohorts and overall, unless be otherwise specified.

Table 2: Demographics and Baseline Characteristics TLFs

T/F/L	Title	Population
T	Subject disposition	mITT
L	Subject disposition	mITT
L	Protocol deviations	mITT
T	Demographics and baseline characteristics	mITT
L	Demographics and baseline characteristics	mITT
T	Medical histories by primary system organ class and preferred terms	mITT
L	Medical history	mITT

Table 3: Efficacy TLFs

T/F/L	Title	Population
PASI		
T	The number (%) of subjects with a 75% decrease in PASI by Week 16	mITT
T	The number (%) of subjects with a 75% decrease in PASI by Week 48	mITT
T	PASI score, change and % change from baseline by visit	mITT
T	PASI change and % change from Week 16 to Week 48 visit	mITT
PGA		
T	The number (%) of subjects with "clear" and "almost clear" (excellent) in PGA at Week 16, 48	mITT
DLQI		

T/F/L	Title	Population
T	DLQI score, change and % change from baseline by visit	mITT
Exploratory Endpoints		
T	Descriptive statistics for IL-17 by visit	mITT

Table 4: Safety TLFs

T/F/L	Title	Population
T	Concomitant medications	mITT
L	Concomitant medications	mITT
T	Treatment exposure and compliance	mITT
L	Treatment exposure and compliance	mITT
T	Dose modifications and interruption	mITT
L	Dose modifications and interruption	mITT
T	Overall summary of TEAEs	Safety
T	TEAEs by Soc/PT	Safety
T	TEAEs by PT	Safety
T	TEAEs by severity and PT	Safety
T	Treatment related AEs by PT	Safety
T	Serious TEAEs by Soc/PT	Safety
T	Serious TEAEs by PT	Safety
T	Treatment related SAEs by PT	Safety
T	Grade 3-5 TEAEs by Soc/PT	Safety
T	Grade 3-5 TEAEs by PT	Safety
T	Treatment related grade 3-5 AEs by Soc/PT	Safety
L	AEs	Safety
L	AE Leading to treatment discontinuation	Safety
L	Death	Safety
T	Lab values and their change from baseline	Safety
F	Lab values by visit	Safety
T	Shifts in CTC grade from baseline to highest grade post-baseline of laboratory	Safety
L	Lab values with CTC grade ≥ 3	Safety

T	Vital signs and their change from baseline	Safety
L	Vital signs	Safety
T	ECG parameters and their change from baseline	Safety
F	ECG parameters by visit	Safety
T	Number and percentage of subjects with QTcF by visit a) absolute ranges and b) change from baseline	Safety
T	QTcF abnormalities	Safety
L	ECG values	Safety