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

Version Number: Amendment #2

Date of Document: 12 March 2019

NCT Number: NCT02852967

CLINICAL STUDY PROTOCOL

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

Protocol Number:	KD025-211
Study Drug:	KD025
IND Number:	120787
Phase	2
Sponsor:	Kadmon Corporation 450 East 29th Street New York, NY 10016
Medical Monitor:	John L Ryan, PhD, MD
Date of Protocol:	Original, 24 May 2016
Amendment No. 1	**21 February 2017**
Amendment No. 2	**12 March 2019**

PROCEDURES IN CASE OF EMERGENCY

Serious and Unexpected Adverse Events

Any serious adverse event (SAE)* or suspected unexpected serious adverse reaction (SUSAR)** occurring in a subject while receiving study drug or within 30 days of receiving the last dose of study drug, even though the event may not appear to be study drug related, must be promptly reported (within 24 hours) by telephone, e-mail, or telefax to the sponsor (or designee).

Emergency Contact Information

For SAE/SUSAR reporting:	**For any other questions or to contact the medical monitor:**
INC Drug Safety Fax: (877) 464-7787 Email: INCDrugSafety@INCResearch.com	John L Ryan, PhD, MD Kadmon Corporation 450 East 29th Street New York, NY 10016 Telephone: Cell: (617) 230-4764 E-mail: john@kadmon.com

SAE AND SUSAR CRITERIA

* A SAE is any untoward medical occurrence that at any dose results in any of the following outcomes, regardless of relationship to study drug (see Section 11.3.1, Serious Adverse Events for additional information):

- Death
- Life-threatening adverse drug event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- An important medical event that may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed above.

** A SUSAR is any untoward and unintended responses to an investigational product related to any dose administered, of which the nature, or severity, is not consistent with the applicable product information (see also Section 11.3.2 of this document; Suspected Unexpected Serious Adverse Reactions). All suspected adverse reactions related to an investigational medicinal product which occur in the concerned study and that are both unexpected and serious are subject to expedited reporting.

SPONSOR SIGNATURE

I have read and approve this protocol. My signature, in conjunction with the signature of the investigator, confirms the agreement of both parties that the clinical study will be conducted in accordance with the protocol and all applicable laws and regulations including, but not limited to, the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), the Code of Federal Regulations (CFR), and the ethical principles that have their origins in the Declaration of Helsinki.

John L Ryan, PhD, MD
Kadmon Chief Medical Officer

11 Apr 2019
Date of Signature
(DD Mmm YYYY)

INVESTIGATOR SIGNATURE

I have read and approve this protocol. My signature, in conjunction with the signature of the sponsor, confirms the agreement of both parties that the clinical study will be conducted in accordance with the protocol and all applicable laws and regulations including, but not limited to, the International Conference on Harmonisation Guideline for Good Clinical Practice (GCP), the Code of Federal Regulations (CFR), and the ethical principles that have their origins in the Declaration of Helsinki.

Nothing in this document is intended to limit the authority of a physician to provide emergency medical care under applicable regulations.

Investigator Signature	Date of Signature (DD Mmm YYYY)
Name of Investigator (please print)	

1 SYNOPSIS

Study 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
Clinical Phase	2
Number of Study Centers	Up to 20
Study Background	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 of the world, making it a very common inflammatory autoimmune disease. The most common form of psoriasis, called psoriasis vulgaris, accounts for over 80% of the people with psoriasis. This type of psoriasis appears as raised plaques of dry scaly skin that may affect multiple regions of the body. Psoriasis is graded as mild, moderate, or severe based on the percentage of the body affected and the intensity of the inflammation. Several genetic loci have been associated with psoriasis and the major genetic determinant, psoriasis susceptibility, accounts for up to 50% of the hereditary aspects of the disease. This locus encodes several immune functions as well as epidermis-associated proteins that are expressed and up-regulated in psoriasis. The genetic basis of sensitivity to psoriasis is supported by the fact that there is 70% concordance in identical twins. The pathogenesis of psoriasis is not fully understood. However, it has been recognized that the recently discovered T helper 17 (Th17) cells, which represent highly proinflammatory cells that function in the induction of multiple autoimmune diseases as well as enhancing the clearance of extracellular pathogens, play a critical role in the pathogenesis of psoriasis. Th17 cells secrete interleukins IL-17A, IL-17F, and IL-22, which can activate keratinocytes and endothelial cells in the skin. Antibodies directed against IL-17 have been approved by the United States (US) Regulatory Authorities. Secukinumab is a human IL-17A antagonist indicated for the treatment of moderate to severe chronic plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy. It is administered subcutaneously and has demonstrated robust efficacy in 4 well-controlled clinical studies. The primary endpoints for these 4 studies were the proportion of subjects who achieved a reduction in Psoriasis Area and Severity Index (PASI) score of at least 75% (PASI 75) from baseline to Week 12 and treatment success (clear or almost clear) on the Physician's Global Assessment (PGA; modified 2011). An increase of

	infections was reported, as well as a few exacerbations of Crohn's disease and hypersensitivity. Another subcutaneous agent, ustekinumab, has been approved for the same indication. Ustekinumab is a human IL-12 and IL-23 antagonist indicated for the treatment of adult patients (18 years or older) with moderate to severe chronic plaque psoriasis who are candidates for phototherapy or systemic therapy. An increase of infections and a few cases of skin cancer were reported in 2 large placebo-controlled studies. One oral agent, apremilast (an inhibitor of phosphodiesterase 4), has been approved for the treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for phototherapy or systemic therapy. However, safety concerns such as depression, weight decrease, and issues with drug interactions due to a strong cytochrome P450 enzyme induction have been reported. Also, administration requires a titration at initiation due to gastrointestinal (GI) side effects. The efficacy at 16 weeks was relatively less than that observed with secukinumab and ustekinumab. In 2 large controlled studies, efficacy results were PASI 75 of 33.1% and 28.8% versus placebo 5.3% and 5.8%, with the static Physician Global Assessment (sPGA) of "clear" or "almost clear" of 21.7% and 20.4% versus placebo 3.9% and 4.4%. Apremilast is also approved for psoriatic arthritis. Several Janus kinase (Jak) inhibitors have been studied for the therapy of psoriasis as well as other autoimmune diseases. However, none has been approved for the treatment of psoriasis to date. Tofacitinib is an inhibitor of Jak 3 with somewhat less activity against Jak 1 and Jak 2. It has been approved by the Food and Drug Administration (FDA) as a twice daily (BID) oral medication for the therapy of rheumatoid arthritis and is marketed as XELJANZ®, and has multiple severe infectious and immunologic side effects associated with therapy. Monotherapy with tofacitinib was associated with a modest increase in American College of Rheumatology 20% (ACR20) improvement criteria compared with placebo (57% versus 26%). Ruxolitinib is a Jak 1 and Jak 2 inhibitor that has been approved for myelofibrosis. It has also been associated with severe side effects including bone marrow suppression. Both of the above Jak inhibitors have undergone initial clinical testing in psoriasis, but the side effect profile of this class of inhibitors has been troublesome. Several studies have been performed with etanercept and adalimumab, both of which block tumor necrosis factor alpha (TNFα) and have demonstrated efficacy in the therapy of rheumatoid arthritis, but no therapy has been as effective as IL-17 blockade in the therapy of psoriasis.

	A number of biologic products have been approved for the treatment of moderate to severe chronic plaque psoriasis. Interestingly, secukinumab, an IL-17 targeting agent, has shown robust efficacy with rapid onset. However, there are still safety concerns and most of these products are parenterally administered. Apremilast, which does not target IL-17, is an approved oral agent with an acceptable risk benefit. An oral agent such as KD025, which targets IL-17, could potentially provide an oral treatment option with an improved safety and efficacy profile.
Study Rationale	This proof-of-principle, placebo-controlled study is designed to evaluate the safety, tolerability, and efficacy of KD025 administered orally for 16 weeks to subjects with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy. Data collected in this study will be used along with data from previous KD025 studies to further evaluate the safety, tolerability, and efficacy of KD025. Recent studies with KD025 have demonstrated that this molecule has anti-inflammatory activity mediated by the inhibition of secretion of IL-17 and IL-21 by Th17 cells. Since this pathway has emerged as a central inflammatory pathway in psoriasis, it is possible that an oral formulation (e.g., KD025) could offer significant advantages over other available oral formulations. This study will provide safety and efficacy data of the therapeutic response to evaluate the risk/benefit of treating plaque psoriasis with KD025.
Study Objective(s)	**Primary objective** • To assess the number of subjects that reach PASI 75 after 16 weeks of dosing with various regimens of KD025 compared with placebo **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

<table>
<tr><td></td><td>Exploratory objectives
To evaluate the concentration and changes in IL-17 expression in blood, tissue, and other biomarkers in punch biopsy before and after 16 weeks of dosing with KD025</td></tr>
<tr><td>Study Design</td><td>Phase 2, double-blind, randomized, placebo-controlled, dose-finding, safety, tolerability, and efficacy study.</td></tr>
<tr><td>Methodology</td><td>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>
<tr><td>Cohort 1</td><td>22 subjects</td><td>200 mg KD025 once daily (QD)</td></tr>
<tr><td>Cohort 2</td><td>22 subjects</td><td>200 mg KD025 BID</td></tr>
<tr><td>Cohort 3</td><td>22 subjects</td><td>400 mg KD025 QD</td></tr>
<tr><td>Cohort 4</td><td>22 subjects</td><td>600 mg/day KD025 (administered as 400 mg in the morning and 200 mg in the evening)</td></tr>
<tr><td>Cohort 5</td><td>22 subjects</td><td>Matching placebo BID</td></tr>
</table>
Study drug will be orally administered in a double-blind fashion.

During the 16 week, double-blind treatment period, data will be collected for the evaluation of efficacy of KD025.

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). Safety, tolerability, and efficacy of KD025 will be evaluated for the remaining period.

Subject status (relative to PASI) will be collected at screening, Week 1 Day 1 (baseline) and, for the evaluation of primary and secondary study endpoints, response will be assessed by PASI, PGA, and DLQI scores at scheduled time points throughout the study.

All subjects will have pharmacodynamic (PD) blood samples collected over the course of the study.</td></tr>
</table>

	Subjects will undergo medical history evaluations; physical examinations ([PEs] including weight measurements); vital sign measurements; adverse event (AE) assessments; concomitant medication assessments; blood sample collection for hematology, chemistry, coagulation, lipid panel, and thyroid-stimulating hormone (TSH), urinalysis; pregnancy testing for females of childbearing potential; photography (optional); punch biopsy (optional); and electrocardiograms (ECG). If a subject discontinues from the study prior to 16 weeks, an Early-Termination visit will be performed and procedures are to be conducted immediately upon discontinuation. 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.
Approximate Number of Subjects	Approximately 110 subjects (approximately 22 subjects per cohort)
Approximate Overall Duration of Subject Participation	Approximate overall duration will be 56 weeks: 4 weeks for screening, 16 weeks of double-blind treatment, option for an additional 32 weeks of open-label treatment, and 4 weeks of follow-up.
Diagnosis and Main Criteria for Inclusion	**Inclusion Criteria** To be eligible for participation in the study, each subject must meet all of the following criteria: 1. Adult, between the age of 18 and 65 years 2. Able to provide written ICF prior to the performance of any study-specific procedures 3. A diagnosis of moderate to severe chronic plaque psoriasis and a candidate for systemic therapy or phototherapy 4. A PASI of ≥ 12 at screening and prior to the first dose of study drug, confirmed at Week 1 (Day 1) 5. ≥ 10% PASI body surface area involvement at screening and prior to the first dose of study drug, confirmed at Week 1 (Day 1) 6. Willing to avoid tanning devices 7. Adequate bone marrow function: a. Absolute neutrophil count (ANC) > 1500/mm^3 b. Hemoglobin > 9.0 g/dL c. Platelets > 100,000/mm^3 8. Adequate safety laboratory values:

a. Serum total bilirubin within normal limits (WNL)

b. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) < 2 × upper limit of normal (ULN)

c. Serum creatinine < 1.5 × ULN

9. Female subjects of childbearing potential have a negative pregnancy test at screening. Females of childbearing potential are defined as sexually mature women without prior hysterectomy or those who have had any evidence of menses in the past 12 months. However, women who have been amenorrheic for 12 or more months are still considered to be of childbearing potential if the amenorrhea is possibly due to prior chemotherapy, anti-estrogens, or ovarian suppression.

   - Women of childbearing potential (i.e., menstruating women) must have a negative urine pregnancy test (positive urine tests are to be confirmed by serum test) documented within the 24-hour period prior to the first dose of study drug.
   - Sexually active women of childbearing potential enrolled in the study must agree to use 2 forms of accepted methods of contraception during the course of the study and for 3 months after their last dose of study drug. Effective birth control includes (a) intrauterine device plus one barrier method; (b) on stable doses of hormonal contraception for at least 3 months (e.g., oral, injectable, implant, transdermal) plus one barrier method; (c) 2 barrier methods. Effective barrier methods are male or female condoms, diaphragms, and spermicides (creams or gels that contain a chemical to kill sperm); or (d) a vasectomized partner.

10. For male patients who are sexually active and who are partners of premenopausal women: agreement to use 2 forms of contraception, as in criterion 9, bullet 2c above, during the treatment period and for at least 3 months after the last dose of study drug.

11. Willing to complete all study measurements and assessments in compliance with the protocol

Exclusion Criteria

Any subject who meets any of the following criteria will be ineligible for participation in the study:

1. Non-plaque or drug-induced (e.g., antimalarials, lithium) psoriasis (if subject is taking angiotensin II receptor blockers or beta blockers doses must be stable for 6 months prior to study entry)
2. Use of systemic corticosteroid within 12 weeks prior to study entry
3. Use topical corticosteroids except to the face, groin, or scalp

	4. Use of methotrexate, retinoids (such as acitretin), or calcineurin inhibitors (such as cyclosporine) within 4 weeks prior to study entry 5. Phototherapy within 4 weeks prior to study entry 6. Biologic therapies, including antibodies to IL-17, anti-TNFα, anti-IL-12 and IL-23, within 3 months prior to study entry 7. Current use of an inhibitor of inducer of CYP3A4 8. Active viral, fungal, or bacterial skin infection (other than nail fungal infection) 9. Is a pregnant or lactating woman 10. History of GI surgery including any bariatric surgery, or any GI condition that might interfere with drug absorption 11. Current participation in another study with an investigational drug or within 28 days or 5 half-lives of the investigational drug (whichever is longer) of study entry 12. History or other evidence of severe illness or any other conditions that would make the subject, in the opinion of the investigator, unsuitable for the study 13. Has QTc(F) interval (QT interval data corrected using Fridericia's formula) of > 450 msec (average of 3 readings) during screening 14. Regular and/or excessive use of alcohol within the 2 years prior to study entry defined as alcohol intake > 14 drinks per week in a man or > 7 drinks per week in a woman. Approximately 10 g of alcohol equals one "drink" unit. One unit equals 1 ounce of distilled spirits, one 12-ounce beer, or one 4-ounce glass of wine. 15. Exposure to KD025 within the last 6 months prior to study entry, or known allergy/sensitivity to KD025 or any other rho-associated, coiled-coil-containing protein kinase (ROCK)-2 inhibitor 16. History or presence of any of the following: a. ALT or AST > 2.0 × the upper limit of normal (ULN) at screening. (Subjects with an isolated AST elevation of any magnitude, or a ratio of AST:ALT > 1.5 should be interviewed regarding use of alcohol, have levels repeated and participation in the study should be discussed with the medical monitor.) b. Renal disease and/or serum creatinine > 1.5 × ULN at screening
Test Article(s)	KD025 will be provided as 200-mg tablets. Kadmon will provide each investigator with adequate supplies of KD025 and placebo.

<table>
<tr><td>Dosage and Administration</td><td>All study drug will be administered orally with a meal or within 5 minutes of finishing a meal.
<table>
<tr><td colspan="3">Double-Blind Treatment Period</td></tr>
<tr><td>Cohort</td><td>No. of Subjects</td><td>Dose Regimen</td></tr>
<tr><td>Cohort 1</td><td>22 subjects</td><td>200 mg KD025 QD (subjects will receive 1 KD025 200 mg and 1 matching placebo tablet in the morning and a matching placebo in the evening)</td></tr>
<tr><td>Cohort 2</td><td>22 subjects</td><td>200 mg KD025 BID (subjects will receive 1 KD025 200 mg and 1 matching placebo tablet in the morning and KD025 200 mg in the evening)</td></tr>
<tr><td>Cohort 3</td><td>22 subjects</td><td>400 mg KD025 QD (subjects will receive 2 KD025 200 mg tablets in the morning and a matching placebo in the evening)</td></tr>
<tr><td>Cohort 4</td><td>22 subjects</td><td>600 mg/day KD025 (subjects will receive 2 KD025 200 mg tablets in the morning and 1 KD025 200 mg tablet in the evening)</td></tr>
<tr><td>Cohort 5</td><td>22 subjects</td><td>Control (subjects will receive 2 matching placebo tablets in the morning and 1 matching placebo tablet in the evening)</td></tr>
<tr><td colspan="3">32-Week Open-Label Continuation Period (Week 16 through Week 48)</td></tr>
<tr><td colspan="2">All subjects</td><td>400 mg KD025 QD (subjects will receive 2 KD025 200 mg tablets in the morning)</td></tr>
</table></td></tr>
<tr><td>Duration of Treatment</td><td>Up to 48 weeks of treatment: All subjects will receive blinded study drug (either KD025 or placebo) from randomization, for a total of 16 weeks. Subjects randomized to KD025 or placebo will have the option to continue 400 mg of KD025 QD treatment for an additional 32 weeks in the open-label treatment period.</td></tr>
<tr><td>Concomitant Treatment</td><td>Subjects will be counseled to avoid non-prescribed medicines or complementary alternative medicines excluded by the study. Any medications a subject receives from signing ICF through the end-of-study (30-Day Follow-Up visit) will be documented.
Subjects may be receiving low-dose oral corticosteroids (≤ 10 mg daily prednisone or equivalent) at study entry. Oral corticosteroid dose must be</td></tr>
</table>

	stable for at least 1 month prior to study entry and expected to remain stable throughout participation. Any changes in systemic corticosteroid dose will be documented on the electronic Case Report form (eCRF). Topical corticosteroids or immunosuppressive therapies to the face, groin, or scalp are allowed. Prior systemic treatments, including biologics, are to be recorded on the eCRF, including duration of exposure and reason for discontinuation.
Safety Evaluation	Safety assessments will include AEs, serious adverse events (SAEs), PEs (including weight), vital sign measurements (including blood pressure [BP], pulse rate, respiratory rate, and temperature), clinical laboratory evaluations (hematology, chemistry, urinalysis, coagulation, lipid panel, TSH), ECGs, and reasons for treatment discontinuation due to toxicity. The AE reporting period for a subject enrolled in the study begins when the subject signs the ICF and continues through 30 days after the last dose of study drug. All AEs that occur in enrolled subjects during the AE reporting period must be reported on subjects' eCRFs, regardless of the relationship of the AE to study drug. Any known untoward event that occurs beyond the AE reporting period that the investigator assesses as possibly related to study drug also should be reported to the sponsor. Subjects with ongoing AEs/SAEs will be followed until resolution or a new treatment is started.
Efficacy Evaluation	The primary efficacy endpoint for analysis will be the number (%) of subjects with a 75% decrease in PASI at Week 16. The secondary efficacy endpoints for analysis will include the following: 1. A 50% reduction in Week 16 PASI score (PASI 50) 2. The mean Week 16 percent change from baseline in PASI 3. Improvements in PGA of "clear" or "almost clear" at Week 16 4. Improvements in DLQI at Week 16 The exploratory efficacy endpoints are: • To evaluate the concentration and changes in IL-17 expression in blood, tissue, and other biomarkers in punch biopsy after 16 weeks of dosing with KD025 Efficacy analyses will be divided into 2 periods: the double-blind treatment period through database lock at Week 16, and the 32-week, open-label continuation period.
Pharmacodynamics	All subjects will have PD blood samples collected over the course of the study. Subjects who elect to continue therapy will also have PD blood

	samples collected. For any subject who discontinues prematurely, blood for PD evaluation will also be collected at the Early-Termination visit. Samples will be evaluated for the expression of the psoriasis-associated cytokine, IL-17, in plasma.
Statistical Analysis	**Data Presentations/Descriptive Statistics** The sample size will be 110 subjects due to early study termination. Two populations will be employed in the analysis of study data: • The modified intent-to-treat (mITT) population will consist of all subjects who are randomized and take at least 1 dose of study drug. All safety analyses will be performed on the mITT population. • The Evaluable for Efficacy population will consist of subjects who have non-missing baseline and Week 16 PASI scores and do not have a major protocol violation. Demographics, subject disposition, and screening and baseline characteristics will be summarized for mITT populations, where appropriate. Efficacy analyses will include the number (%) of subjects with a 75% decrease in PASI (number of subjects that reach PASI 75) at Week 16 in the KD025 treatment groups compared with the placebo group in a pairwise manner using a Fisher's exact test. The number of subjects who reach PASI 50 at Week 16 will be analyzed similarly. Treatment group differences in DLQI and PGA changes from baseline to Week 16 will be assessed using an analysis of covariance (ANCOVA) model with treatment as a fixed effect and a subject's baseline value as a covariate. No adjustments for multiplicity are being made for this Phase 2 study. The primary safety endpoint will be the percentage of subjects in each treatment group experiencing AEs. Treatment-emergent AEs (TEAEs) will be summarized by treatment group using Medical Dictionary for Regulatory Activities (MedDRA®) System Organ Class (SOC) and preferred term, classified from verbatim terms (Version 18.1 or higher). The incidence and percentage of subjects with at least 1 occurrence of a preferred term will be included, according to the most severe grade using a 5-point scale (mild, moderate, severe, life threatening, or death). The number of events per preferred term will also be summarized. Causality (relationship to study treatment) will be summarized separately.

	AEs, SAEs, related AEs, related SAEs, ≥ Grade 3 AEs, related ≥ Grade 3 AEs, and AEs leading to withdrawal, or treatment discontinuation will be summarized by treatment group according to SOC and preferred terms. AEs will also be presented in listings. Duration of AEs will be determined and included in listings, along with action taken and outcome. Laboratory results will be classified using the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Studies and summarized. Incidence of laboratory abnormalities will be summarized by treatment group. The worst on-study grade after the first dose of study drug will be summarized by treatment group. The incidence of ≥ Grade 3 laboratory abnormalities under treatment and shifts in toxicity grading from baseline to highest grade post-baseline will be displayed. Vital sign measurements will be summarized at each scheduled time point using descriptive statistics. The exploratory endpoints are to evaluate changes in blood and punch biopsy PD markers.

Table 1-1 Schedule of Assessments

Assessments	Screening	Double-Blind Treatment Period					32-Week Open-Label Continuation Period						Unscheduled or Early Termination[b] Visit (±3 days)	30-Day Follow-Up[c] (±3 days)
		Week 1	Week 4	Week 8	Week 12	Week 16[a]	Week 20	Week 24	Week 30	Week 36	Week 42	Week 48		
Visit	1	2	3	4	5	6	7	8	9	10	11	12		
Day	-28 to -1	1 (Baseline)	28 (±3 days)	56 (±3 days)	84 (±3 days)	112 (±3 days)	140 (±3 days	168 (±3 days)	210 (±3 days)	252 (±3 days)	294 (±3 days)	336 (±3 days)		
Informed consent	X													
Demographics and Medical history	X													
Physical examination[d]	X	X				X		X		X		X	X	X
Vital signs[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology and serum chemistry[f]	X[g]	X	X	X	X	X	X	X	X	X	X	X	X	X
Lipid panel[h]	X[g]	X				X	X	X		X		X	X	X
PT, PTT, INR	X[g]	X				X	X	X		X		X	X	X
TSH	X[g]	X				X	X	X		X		X	X	X
Urinalysis	X[g]	X	X	X	X	X	X	X	X	X	X	X	X	X
Supine 12-Lead ECG[i]	X	X				X						X	X	
Pregnancy test[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization[k]		X												
Photographs (optional)[l]		X				X						X	X	X
Punch Biopsy (optional)[m]		X				X								
PD whole blood sample[n]		X		X		X						X	X	X

Assessments	Screening	Double-Blind Treatment Period					32-Week Open-Label Continuation Period						Unscheduled or Early Termination[b] Visit (±3 days)	30-Day Follow-Up[c] (±3 days)
		Week 1	Week 4	Week 8	Week 12	Week 16[a]	Week 20	Week 24	Week 30	Week 36	Week 42	Week 48		
Visit	1	2	3	4	5	6	7	8	9	10	11	12		
Day	-28 to -1	1 (Baseline)	28 (±3 days)	56 (±3 days)	84 (±3 days)	112 (±3 days)	140 (±3 days	168 (±3 days)	210 (±3 days)	252 (±3 days)	294 (±3 days)	336 (±3 days)		
PASI Scoring	X[o]	X	X	X	X	X		X		X		X	X	
PGA Scoring		X	X	X	X	X		X		X		X	X	
DLQI	X	X	X	X	X	X		X		X		X	X	
Study drug administration[p]		X		X		X						X		
Dispense/Collect study drug Diary[q]		X				X						X	X	
Concomitant medications		*To be collected from the date that the informed consent form is signed until 30 days after last dose of study drug.*												
Adverse events														

DLQI = Dermatology Life Quality Index; ECG = electrocardiogram; INR = international normalized ratio; PASI = Psoriasis Area and Severity Index; PD = pharmacodynamics; PGA = Physicians Global Assessment; PT = prothrombin time; PTT = partial thromboplastin time; TSH = thyroid-stimulating hormone.

a. After Week 16 assessments in the double-blind treatment period, subjects will be given the option to receive KD025 400 mg QD for an additional 32-weeks in an open-label treatment period (end of week 16 assessments through week 48).
b. Unscheduled visits and the assessments performed are at the investigator's discretion, but may include any or all of those listed. An Early-Termination visit will be scheduled for all subjects who discontinue prematurely from study drug during the double-blind or open-label treatment periods and procedures are to be conducted immediately upon discontinuation.
c. For all subjects, including those who discontinue from the study prematurely, a Follow-Up visit should occur 30 days (± 3 days) after their last dose of study drug.
d. Physical examinations will include weight. Height is to be collected only at the Screening visit.
e. Vital sign measurements will include sitting blood pressure (BP), heart rate, respiratory rate, and temperature after 5 minutes of rest. Refer to Section 7.2.4 for appropriate BP measuring technique.
f. Refer to Section 7.2.5 for a complete list of required hematology and serum chemistry assessments. If increases in liver enzymes are observed at any time in a subject, refer to Section 9.4.
g. If laboratory assessments are done within 14 days of Day 1, they do not need to be repeated on Day 1.

h. Lipid panel to include total cholesterol, triglycerides, high density lipoprotein (HDL) cholesterol, and low density lipoprotein (LDL) cholesterol.
i. ECGs are to be performed immediately prior to blood sample collection (tolerance window: -240 minutes to 0 hour) and to be obtained in triplicate after 5 minutes of resting in the supine position (see Section 7.2.5 for additional information).
j. Pregnancy tests will be done using urine samples in women of childbearing potential. Subject must have a negative urine pregnancy test documented within the 24-hour period prior to the first dose of study drug. Confirm with serum testing if urine sample is positive.
k. On Day 1 (Week 1), prior to dosing, subjects will be randomized to receive 200 mg KD025 once daily (QD), 200 mg KD025 twice daily (BID), 400 mg KD025 QD, 600 mg/day KD025, or matching placebo. On Day 112 (Week 16) after all assessments are complete in the double-blind treatment period, subjects will be given the option to continue in the 32-week open-label treatment period, during which all participating subjects will receive KD025 400 mg QD for 32weeks.
l. Photos will be taken of affected area(s) if the subject agrees to them. Detailed instructions will be provided.
m. Punch biopsies from clear unaffected skin and a selected lesion will be collected predose on Day 1 (Week 1) and from the selected lesion on Day 112 (Week 16). Subjects have the option to decline the punch biopsy.
n. PD blood samples to be collected predose and 6 hours postdose on Day 1 of Weeks 1 and 8. PD blood samples to be collected predose on Day 1 of Week 16; predose on Day 1 of Week 48 (for those subjects receiving KD025 during the 32-week continuation period), and at the 30-Day Follow-Up visit.
o. To be eligible for the study, subjects must have a PASI of $\geq$ 12 at screening and prior to the first dose of study drug, confirmed at Day 1 (Week 1).
p. Subjects will take the first dose of study drug in the clinic and at each visit when PD blood samples are collected. Then study drug will be dispensed for home administration. Study drug is to be taken with a meal or within 5 minutes of finishing a meal.
q. Subjects will be required to keep study drug diaries in which they will record the date of study drug administrations. These diaries will be dispensed at the Day 1 (Week 1) visit. Final collection will be at Week 16 for those who do not wish to continue into the open-label period. For subjects that continue to the open-label treatment period, a new diary will be distributed at the Week 16 visit and will be collected at the Week 48 visit. For subjects who discontinue the study prematurely, the diary will be collected at the Early-Termination visit.

2 TABLE OF CONTENTS

LIST OF TABLES

List of Appendices

3 LIST OF ABBREVIATIONS

AE	adverse event
ACR20	American College of Rheumatology 20%
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical
AUC	area under the curve
BA/BE	bioavailability/bioequivalence
BID	twice daily
BP	blood pressure
CFR	Code of Federal Regulations
C_{max}	maximum plasma concentration
DLQI	Dermatology Life Quality Index
DBP	diastolic blood pressure
ECG	electrocardiogram
eCRF	electronic case report form
EMEA	European Medicines Agency
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	gastrointestinal
GGT	gamma-glutamyl transpeptidase
HDL	high density lipoprotein
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IGA	Investigator's Global Assessment
IND	Investigation New Drug
INR	international normalized ratio
IRB/IEC	institutional review board/independent ethics committee
IRT	Interactive Response Technology
Jak	Janus kinase
LDL	low density lipoprotein
LFT	liver functions test
MAD	multiple ascending dose

MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
PASI	Psoriasis Area and Severity Index
PD	pharmacodynamics
PE	physical examinations
PGA	Physician's Global Assessment
PK	pharmacokinetics
PT	prothrombin time
PTT	partial thromboplastin time
QD	once daily
QTc(F)	QT interval corrected using Fridericia's formula
ROCK	Rho-associated, coiled-coil-containing protein kinase
SAD	single-ascending dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SOC	System Organ Class
sPGA	static Physician Global Assessment
SD	standard deviation
SUSAR	suspected unexpected serious adverse reaction
SBP	systolic blood pressure
TEAE	treatment-emergent adverse event
Th17	T-helper 17 cell
TID	three times daily
TNFα	tumor necrosis factor alpha
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
US	United States
WHO	World Health Organization
WNL	within normal limits

4 BACKGROUND AND RATIONALE

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 of the world, making it a very common inflammatory autoimmune disease. The most common form of psoriasis, called psoriasis vulgaris, accounts for over 80% of the people with psoriasis. This type of psoriasis appears as raised plaques of dry scaly skin that may affect multiple regions of the body. Psoriasis is graded as mild, moderate, or severe based on the percentage of the body affected and the intensity of the inflammation. Several genetic loci have been associated with psoriasis and the major genetic determinant, psoriasis susceptibility, accounts for up to 50% of the hereditary aspects of the disease. This locus encodes several immune functions as well as epidermis-associated proteins that are expressed and up-regulated in psoriasis. The genetic basis of sensitivity to psoriasis is supported by the fact that there is 70% concordance in identical twins.

The pathogenesis of psoriasis is not fully understood. However, it has been recognized that the recently discovered T helper 17 (Th17) cells, which represent highly proinflammatory cells that function in the induction of multiple autoimmune diseases as well as enhancing the clearance of extracellular pathogens, play a critical role in the pathogenesis of psoriasis. Th17 cells secrete IL-17A, IL-17F, and IL-22, which can activate keratinocytes and endothelial cells in the skin. Antibodies directed against IL-17 have been approved by United States (US) Regulatory Authorities. Secukinumab is a human IL-17A antagonist indicated for the treatment of moderate to severe chronic plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy. It is administered subcutaneously and has demonstrated robust efficacy in 4 well-controlled clinical studies. The primary endpoints for these 4 studies were the proportion of subjects who achieved a reduction in Psoriasis Area and Severity Index (PASI) score of at least 75% (PASI 75) from baseline to Week 12 and treatment success (clear or almost clear) on the Physicians Global Assessment (PGA; modified 2011). An increase of infections was reported, as well as a few exacerbations of Crohn's disease and hypersensitivity.

Another subcutaneous agent, ustekinumab, has been approved for the same indication. Ustekinumab is a human IL-12 and IL-23 antagonist indicated for the treatment of adult patients

(18 years or older) with moderate to severe chronic plaque psoriasis who are candidates for phototherapy or systemic therapy. An increase of infections and a few cases of skin cancer were reported in 2 large placebo-controlled studies.

One oral agent, apremilast (an inhibitor of phosphodiesterase 4), has been approved for the treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for phototherapy or systemic therapy. However, safety concerns such as depression, weight decrease, and issues with drug interactions due to a strong cytochrome P450 enzyme induction have been reported. Also, administration requires a titration at initiation due to gastrointestinal (GI) side effects. The efficacy at 16 weeks was relatively less than that observed secukinumab and ustekinumab. In 2 large controlled studies, efficacy results were PASI 75 of 33.1% and 28.8% versus placebo 5.3% and 5.8%, with the static Physician Global Assessment (sPGA) of "clear" or "almost clear" of 21.7% and 20.4% versus placebo 3.9% and 4.4%, respectively. Apremilast is also approved for psoriatic arthritis.

Several Janus kinase (Jak) inhibitors have been studied for the therapy of psoriasis as well as other autoimmune diseases. However, none has been approved for the treatment of psoriasis to date. Tofacitinib is an inhibitor of Jak 3 with somewhat less activity against Jak 1 and Jak 2. It has been approved by the Food and Drug Administration (FDA) as a twice daily (BID) oral medication for the therapy of rheumatoid arthritis and is marketed as XELJANZ®, and has multiple severe infectious and immunologic side effects associated with therapy. Monotherapy with tofacitinib was associated with a modest increase in American College of Rheumatology 20% (ACR20) improvement criteria compared with placebo (57% versus 26%). Ruxolitinib is a Jak 1 and Jak 2 inhibitor that has been approved for myelofibrosis. It has also been associated with severe side effects including bone marrow suppression. Both of the above Jak inhibitors have undergone initial clinical testing in psoriasis, but the side effect profile of this class of inhibitors has been troublesome.

Several studies have been performed with etanercept and adalimumab, both of which block tumor necrosis factor alpha (TNFα) and have demonstrated efficacy in the therapy of rheumatoid arthritis, but no therapy has been as effective as IL-17 blockade in the therapy of psoriasis.

A number of biologic products have been approved for the treatment of moderate to severe chronic plaque psoriasis. Interestingly, secukinumab, an IL-17 targeting agent, has shown robust efficacy with rapid onset. However, there are still safety concerns and most of these products are parenterally administered. Apremilast, which does not target IL-17, is an approved oral agent with an acceptable risk benefit. An oral agent such as KD025, which targets IL-17, could potentially provide an oral treatment option with an improved safety and efficacy profile.

4.1 Study Rationale

This proof-of-principle, placebo-controlled study is designed to evaluate the efficacy, safety, and tolerability of KD025 administered orally for 16 weeks to subjects with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy. Data collected in this study will be used along with data from previous KD025 studies to further evaluate the safety, tolerability, and efficacy of KD025.

Recent studies with KD025 have demonstrated that this molecule has anti-inflammatory activity mediated by the inhibition of secretion of IL-17 and IL-21 by Th17 cells. Since this pathway has emerged as a central inflammatory pathway in psoriasis, it is possible that an oral formulation (e.g., KD025) could offer significant advantages over other available oral formulations. This study will provide safety and efficacy data of the therapeutic response to evaluate the risk/benefit of treating plaque psoriasis with KD025.

4.2 Selection of Doses in this Study

The only Rho kinase inhibitor that has published human dosing data is fasudil. Fasudil is a moderately selective kinase inhibitor but in contrast to KD025 has activity against both Rho-associated, coiled-coil-containing protein kinase (ROCK1 and ROCK2). The potency of fasudil against ROCK2 is similar to KD025. Fasudil has been marketed in Japan for more than 10 years as an intravenous drug for the prevention of cerebrovascular spasm after stroke. Fasudil was also under development for the treatment of chronic angina. In a Phase 2 clinical study in the US (Vicari et al, 2005), fasudil was dosed from 20 mg three times a day (TID) up to 80 mg TID over 8 weeks. At all doses tested, the adverse events (AEs) in the treatment arm were

reported as no different from placebo. In a separate study to examine endothelial function in subjects and healthy subjects (Nohria et al, 2006), fasudil was dosed at 40 mg TID for 30 days.

The single-ascending dose (SAD)/multiple-ascending dose (MAD) (KD025-101) and MAD (KD025-102) studies support daily dosing with KD025 and have shown a safety profile that allows daily dosing up to 1000 mg per day. In addition, in Study KD025-103, a Phase 1, placebo-controlled study examining the safety, tolerability, and pharmacokinetics (PK) of 500 mg of KD025 administered BID for 28 days in healthy male and post-menopausal female subjects for up to 28 days, the regimen was generally well tolerated.

Pharmacodynamic (PD) studies in these normal healthy subjects have shown biological activity in inhibition of secretion of IL-17 and IL-21 by TH-17 cells in ex vivo stimulated peripheral blood mononuclear cells at the 120-, 240-, and 320-mg dose levels. Thus, the dosing selected in the proposed study (200 mg once daily [QD], 200 mg BID, 400 mg QD, and 600 mg/day) should be both safe and at a level at which biological activity has been measured.

4.3 Previous Clinical Experience with KD025

A Phase 1 fed or fasted study (KD025-105) was conducted to evaluate the food effect as well as to further evaluate the safety and PK of a single 500-mg dose of KD025 administered orally to fed and fasted healthy males.

Study results showed approximately a 3-fold higher exposure (maximum serum concentration [C_{max}] and area under the curve [AUC]) in the fed state compared with the fasted state. There were no treatment emergent adverse events (TEAEs) and no treatment-related AEs were reported in any subject after receiving KD025 in either the fed or fasted state. There were no clinically relevant changes in vital signs, physical examination (PE) findings, or electrocardiogram (ECG) parameters. There were no clinically relevant changes and no clinically meaningful trends in hematology, chemistry, and urinalysis laboratory results attributable to study drug during this study. Plasma concentrations achieved in this study were comparable to plasma levels achieved in previous studies at similar dose levels, where breakfast was provided immediately after dose administration. These studies support dosing KD025 with food.

KD025-205 was a Phase 2a, open-label study in 8 adult subjects with moderately severe psoriasis vulgaris who have failed first-line therapy. As with the other studies, 200 mg QD KD025 administered daily for 28 days was generally safe and well tolerated.

KD025-206 was a Phase 2a, open-label, dose-finding study in 36 adult subjects with moderately severe psoriasis vulgaris who have failed first-line therapy. The study was a 3-month, open-label study with 3 cohorts (200 mg BID, 400 mg QD, and 400 mg BID). KD025 was well tolerated in all subjects and demonstrated activity as measured by PASI. The only adverse experience was related to elevated alanine aminotransferase (ALT)/ aspartate aminotransferase (AST) levels in approximately 20% of the subjects. The KD025 400-mg BID group showed the highest (Grade 3) elevations. The 400-mg BID dose will not be pursued in future studies.

The Investigator's Brochure (IB) 2015 includes additional nonclinical and clinical information about this agent.

4.4 KD025 Nonclinical Toxicology

KD025 nonclinical toxicology has been characterized in multiple species using a variety of dosing regimens. Details are found in the IB 2015.

4.5 Compliance Statement

This study will be conducted in compliance with Good Clinical Practice (GCP), including International Conference on Harmonisation (ICH) Guidelines, and in general, consistent with the most recent version of the Declaration of Helsinki. In addition, the investigator agrees to adhere

to all applicable local laws and regulatory requirements relevant to the use of new therapeutic agents in the countries involved.

The study is to be conducted in compliance with the protocol. The appropriate Institutional Review Boards/Independent Ethics Committees (IRBs/IECs) must approve the protocol and any amendments and the subject informed consent form (ICF) prior to implementation.

Freely given written ICF must be obtained from every subject prior to participation in this clinical study. The rights, safety, and well-being of participating subjects are the most important considerations and should prevail over interests of science and society.

Study personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective task(s). This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct of fraud (e.g., loss of medical licensure, debarment).

5 STUDY OBJECTIVES

5.1 Primary Objectives

The primary objective of the study is as follows:

- To assess the number of subjects that reach PASI 75 after 16 weeks of dosing with various regimens of KD025 compared with placebo

5.2 Secondary Objectives

The following are the secondary objectives of the study:

- 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 PGA
- To assess changes in 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

5.3 Exploratory Objective

The exploratory objective for the study is as follows:

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

5.4 Study Sites

This study will be conducted at approximately 20 sites in the US.

5.5 Study Endpoints

The primary safety endpoint will be the percentage of subjects in each treatment group experiencing AEs.

The primary efficacy endpoint for analyses will be the number (%) of subjects with a 75% decrease in PASI by Week 16.

The secondary efficacy endpoints for analysis will include the following:

- A 50% reduction in Week 16 PASI score (PASI 50)
- The mean Week 16 percent change from baseline in PASI
- Improvements in PGA of "clear" or "almost clear" at Week 16
- Improvements in DLQI at Week 16

The exploratory efficacy endpoint is:

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

5.6 Overview of Study Design

This will be 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 IRB/IEC-approved ICF and 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 patients at 16 weeks in each cohort (Table 5-1).

Table 5-1: Dosing Cohorts

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

Abbreviations: BID = twice daily; QD = once daily

Study drug will be orally administered in a double-blind fashion.

During the 16 week, double-blind treatment period, data will be collected for the evaluation of efficacy of KD025.

All subjects will be given the option to receive KD025 400 mg QD for 32weeks in an open-label treatment period. Safety, tolerability, and efficacy of KD025 will be evaluated for the remaining period in the study.

Subject status (relative to PASI) will be collected during the study for the evaluation of primary and secondary study endpoints. Response will be assessed by PASI, PGA, and DLQI scores at scheduled time points throughout the study.

All subjects will have PD blood samples collected over the course of the study.

Subjects will undergo medical history evaluations; PEs (including weight measurements); vital sign measurements; AE assessments; concomitant medication assessments; blood sample collection for hematology, chemistry, coagulation, lipid panel, and thyroid-stimulating hormone (TSH), urinalysis; pregnancy testing for females of childbearing potential; photography (optional); punch biopsy (optional); and ECGs. If a subject discontinues from the study prior to Week 16, an Early-Termination visit will be performed. All procedures are to be conducted immediately upon discontinuation.

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

See Table 1-1 (Schedule of Assessments) for specific assessment time points.

5.7 Randomization and Blinding

This is a double-blind, randomized study. An Interactive Response Technology (IRT) system will be used for randomization and drug supply management.

6 STUDY POPULATION

6.1 Target Population

Approximately 110 adult male and female subjects (approximately 22 subjects per cohort) will participate in the study. Subjects will be eligible for enrollment as defined by the following inclusion and exclusion criteria.

6.2 Inclusion Criteria

To be eligible for participation in the study, each subject must meet all of the following criteria:

1. Adult, between the ages of 18 and 65 years
2. Able to provide written ICF prior to the performance of any study specific procedures
3. A diagnosis of moderate to severe chronic plaque psoriasis and is a candidate for systemic therapy or phototherapy
4. A PASI of $\geq$ 12 at screening and prior to the first dose of study drug, confirmed at Week 1 (Day 1)
5. $\geq$ 10% PASI body surface area involvement at screening and prior to the first dose of study drug, confirmed at Week 1 (Day 1)
6. Willing to avoid tanning devices
7. Adequate bone marrow function
    a. Absolute neutrophil count (ANC) > 1500/mm^3
    b. Hemoglobin > 9.0 g/dL
    c. Platelets > 100,000/mm^3
8. Adequate safety laboratory values
    a. Serum total bilirubin within normal limits (WNL)
    b. AST and ALT < 2 × upper limit of normal (ULN)
    c. Serum creatinine < 1.5 × ULN
9. Female subjects of childbearing potential have a negative pregnancy test at screening. Females of childbearing potential are defined as sexually mature women without prior

hysterectomy or those who have had any evidence of menses in the past 12 months. However, women who have been amenorrheic for 12 or more months are still considered to be of childbearing potential if the amenorrhea is possibly due to prior chemotherapy, anti--estrogens, or ovarian suppression.

- Women of childbearing potential (i.e., menstruating women) must have a negative urine pregnancy test (positive urine tests are to be confirmed by serum test) documented within the 24-hour period prior to the first dose of study drug.
- Sexually active women of childbearing potential enrolled in the study must agree to use 2 forms of accepted methods of contraception during the course of the study and for 3 months after their last dose of study drug. Effective birth control includes (a) intrauterine device plus one barrier method; (b) on stable doses of hormonal contraception for at least 3 months (e.g., oral, injectable, implant, transdermal) plus one barrier method; (c) 2 barrier methods. Effective barrier methods are male or female condoms, diaphragms, and spermicides (creams or gels that contain a chemical to kill sperm); or (d) a vasectomized partner.

10. For male patients who are sexually active and who are partners of premenopausal women: agreement to use 2 forms of contraception as in criterion 9, bullet 2c above, during the treatment period and for at least 3 months after the last dose of study drug
11. Willing to complete all study measurements and assessments in compliance with the protocol

6.3 Exclusion Criteria

Any subject who meets any of the following criteria will be ineligible for participation in the study:

1. Non-plaque or drug-induced (antimalarials, lithium) psoriasis (if subject is taking angiotensin II receptor blockers or beta blockers, doses must be stable for 6 months prior to study entry)
2. Use of systemic corticosteroid within 12 weeks prior to study entry
3. Use topical corticosteroids except to the face, groin, or scalp
4. Use of methotrexate, retinoids (such as acitretin), or calcineurin inhibitors (such as cyclosporine) within 4 weeks prior to study entry
5. Phototherapy within 4 weeks prior to study entry
6. Biologic therapies, including antibodies to IL-17, anti-TNFα, anti-IL-12 and IL-23, within 3 months prior to study entry
7. Current use of an inhibitor, inducer, or CYP3A4 (see Appendix G)
8. Active viral, fungal, or bacterial skin infection (other than nail fungal infection)
9. Is a pregnant or lactating woman
10. History of GI surgery including any bariatric surgery, or any GI condition that might interfere with drug absorption
11. Current participation in another study with an investigational drug or within 28 days or 5 half-lives of the investigational drug (whichever is longer) of study entry
12. History or other evidence of severe illness or any other conditions that would make the subject, in the opinion of the investigator, unsuitable for the study
13. Has QTc(F) interval (QT interval data corrected using Fridericia's formula) of > 450 msec (average of 3 readings) during screening (Appendix B)

14. Regular and/or excessive use of alcohol within the 2 years prior to study entry defined as alcohol intake > 14 drinks per week in a man or > 7 drinks per week in a woman. Approximately 10 g of alcohol equals one "drink" unit. One unit equals 1 ounce of distilled spirits, one 12-ounce beer, or one 4-ounce glass of wine.
15. Exposure to KD025 within the last 6 months prior to study entry, or known allergy/sensitivity to KD025 or any other ROCK-2 inhibitor
16. History or presence of any of the following:
    a. ALT or AST > 2.0 × ULN at screening. (Subjects with an isolated AST elevation of any magnitude, or a ratio of AST:ALT > 1.5 should be interviewed regarding use of alcohol, have levels repeated and participation in the study should be discussed with the medical monitor.)
    b. Renal disease and/or serum creatinine > 1.5 × ULN at screening

7 STUDY ASSESSMENTS AND PROCEDURES

Screening assessments outlined in this section and in Table 1-1 will be performed after obtaining a signed ICF.

The timing for these study assessments is presented in Table 1-1 while a listing of clinical laboratory parameters to be measured is presented in Table 7-1.

7.1 General Study Procedures

A description for each phase of the study is provided in this section.

Confirmation that the most current IRB/IEC-approved ICF has been signed should occur before any study-specific procedures are performed. All subjects who are enrolled and receive KD025 or undergo study-specific procedures should be re-consented with any updated versions of IRB/IEC-approved ICFs during study participation as applicable and per institutional guidelines.

7.1.1 Screening Enrollment

Informed consent must be obtained before completing any study-specific procedures.

After written informed consent has been obtained, subjects will be screened to assess eligibility for study participation. All screening assessments are to be performed within **28 days** prior to first study drug dose, unless otherwise specified.

If significant changes from baseline are noted during the course of the study, additional unscheduled clinic visits may be undertaken by the investigator, or requested by the sponsor, in order to determine both the relevance of the finding(s) and the duration of the event(s).

Subjects who meet the eligibility criteria will be eligible to be enrolled in the study.

7.1.2 Double-Blind Treatment Period

Study Day 1 is defined as the date the subject takes the first dose of study drug, with subsequent visits numbered sequentially thereafter. Subjects satisfying eligibility requirements will be enrolled and should receive the first dose of study drug on Day 1 of the study.

Procedures will be completed during the treatment period from Week 1 to Week 16 at the times designated in the Schedule of Assessments (Table 1-1).

7.1.3 32-week Open-Label Continuation Period

Procedures will be completed during the 32-week continuation period from Week 16 (after the completion of assessments in the double-blind treatment period) to Week 48 at the times designated in the Schedule of Assessments (Table 1-1).

7.1.4 Early-Termination Visit

An Early-Termination visit will be scheduled for all subjects who discontinue prematurely from the study during the double-blind or open-label treatment periods and procedures are to be conducted immediately upon discontinuation (refer to Table 1-1).

7.1.5 Unscheduled Visit

Unscheduled visits and the assessments performed at those visits are at the investigator's discretion, but may include any or all of those listed in Table 1-1.

7.1.6 30-day Follow-up Visit

Approximately 30 days (± 3 days) after the subjects last dose of study drug, all subjects will complete a 30-day Follow-Up visit (Table 1-1).

7.2 Description of Study Procedures

Refer to Table 1-1 for an outline of the procedures required at each study visit. Informed Consent Form.

All subjects must take part in the ICF process. Adequate time must be allowed for the subject to ask questions and make a voluntary decision. No protocol-specific procedures, including screening procedures, are to be performed until the subject has signed and dated an IRB/IEC-approved ICF.

7.2.1 Demographics and Medical History

A complete medical history will include demographic information, prior medical illnesses and conditions, and surgical procedures.

7.2.2 Physical Examination

Physical examinations (PE) will include assessment of skeletal (i.e., muscle aches), neurological (i.e., gait) systems, height (screening only) and weight. All procedures will be performed by a physician or staff member who is qualified to perform such examinations (e.g., physician's assistant, nurse practitioner).

Any abnormal or clinically significant findings from the PE must be recorded in the appropriate electronic case report form (eCRF).

7.2.3 Vital Sign Measurements

Vital sign measurements will be collected after the subject has been sitting for 5 minutes. Vital sign assessments will include measurements of a sitting BP (mmHg), heart rate (beats per minute), respiratory rate (breaths per minute), and temperature (Fahrenheit).

Note that BP measurements are to be performed using appropriate technique (per guidelines of the American Heart Association). Subjects must be seated quietly for at least 5 minutes in a chair with their backs supported, feet flat on floor (legs uncrossed), and arms bared on a hard surface, with the arm slightly abducted and bent, with palm up and the midpoint of upper arm at heart level. Correct cuff and bladder size should be utilized. Two or more readings separated by 1 to 2 minutes should be averaged. If the first 2 readings differ by more than 5 mmHg, additional readings should be obtained and averaged. Record cuff size, arm used, and subject's position (if not seated).

7.2.4 Laboratory Assessments

A central laboratory will analyze hematology, serum chemistry, coagulation, lipid panel, TSH, urinalysis, and biomarker tests. The results will be provided to the investigator (Table 7-1). Blood and urine samples for hematology, serum chemistry, coagulation, lipid panel, TSH, antibody, and urinalysis will be obtained using standard procedures.

Table 7-1: Clinical Laboratory Panels

Hematology	Serum Chemistry	Urinalysis
• white blood cell count with differential (including at minimum: neutrophils, basophils, eosinophils, lymphocytes, monocytes) • red blood cell count • hemoglobin • hematocrit • platelet count • MCV	• albumin • alkaline phosphatase • ALT • AST • BUN • calcium • carbon dioxide • chloride • cholesterol • creatinine • CPK • direct bilirubin • GGT • globulin • glucose • lactate dehydrogenase • magnesium • phosphorus • potassium • sodium • total bilirubin • total protein • uric acid	• appearance • color • pH • specific gravity • ketones • protein • glucose • bilirubin • nitrite • urobilinogen • occult blood (microscopic examination of sediment will be performed only if the results of the urinalysis dipstick evaluation are positive)
Coagulation	**Thyroid**	
• INR • PT • PTT	• TSH	
Lipid Panel	**Biomarkers**	
• Total cholesterol • Triglycerides • HDL cholesterol • LDL cholesterol	• IL-17	

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CPK = creatine phosphokinase; GGT = gamma glutamyl transpeptidase; HDL= high density lipoprotein; INR = international normalized ratio; LDL = low density lipoprotein; MCV = mean corpuscular volume; PT = prothrombin time; PTT = partial thromboplastin time; TSH = thyroid-stimulating hormone

Abnormalities in clinical laboratory tests that lead to a change in subject management (e.g., dose delay, discontinuation, requirement for additional medication or monitoring) are considered clinically significant for the purposes of this study, and will be recorded on the AE eCRF page. With the exception of LFTs, laboratory results will be classified using the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Studies (see Appendix A). Laboratory results for ALT, AST, alkaline phosphatase, GGT, and

bilirubin will be classified according to Table 9-2 in Section 9.4. If laboratory values constitute part of an event that meets criteria defining it as serious, the event (and associated laboratory values) must be reported as an SAE (see Section 11.3.1).

7.2.5 12-Lead Electrocardiogram

Supine 12-lead ECGs will be obtained prior to blood sample collection (tolerance window: -240 minutes to 0 hour).

Digital 12-lead ECG measurements are to be taken with the subject in a supine position and having rested in this position for at least 5 minutes before each reading. The ECG is to be repeated 3 times consecutively within 30 minutes (with a required interval of at least 1 to 2 minutes between ECGs). At each visit, and when possible, the ECG is to be performed immediately prior to any blood sample collection.

The following ECG parameters will be collected: PR interval, RR interval, QRS interval, QT interval, and QTc interval (QTc[F]; Fridericia's correction, see Appendix B for formula). The ECG findings will be evaluated by a qualified physician for the presence of abnormalities (qualitative assessment). The physician will assess each ECG as normal, abnormal/not clinically significant, or abnormal/clinically significant.

Abnormalities in the ECG that lead to a change in subject management (e.g., dose interruption or delay, requirement for additional medication or monitoring) or result in clinical signs and symptoms are considered clinically significant for the purposes of this study and will be recorded on the AE eCRF. If ECG abnormalities meet criteria defining them as serious, they must be reported as an SAE (see Section 11.3.1).

7.2.6 Pregnancy Testing

Urine pregnancy tests will be collected for women of childbearing potential. Positive results will be confirmed with serum testing.

7.2.7 Randomization

Following the completion of screening assessments, eligible, consenting subjects will be randomized to 1 of 5 dose cohorts. See Section 5.7 for further details.

7.2.8 Punch Biopsy (Optional)

Punch biopsies will be obtained from at least 75% of the subjects. Subjects have the option to decline the punch biopsy. Punch biopsies will be taken from clear unaffected skin and a selected lesion will be collected predose on Day 1 (Week 1) and from the selected lesion on Day 112 (Week 16). Biopsies will be obtained through a standard punch biopsy procedure. These biopsies will be analyzed for PD markers associated with psoriasis and with Rho Kinase inhibition.

7.2.9 Blood Sampling for Pharmacodynamics

Blood sample collection for PD will be performed at all sites (refer to Table 1-1 for time points). All subjects will have PD blood samples collected over the course of the study. Subjects who elect to continue therapy will also have PD blood samples collected.

For any subject who discontinues prematurely, blood for PD evaluation will be collected at the Early Termination visit.

Samples will be evaluated for the expression of the psoriasis-associated cytokine, IL-17, in plasma. Detailed instructions for sample collection and preparation will be provided in a separate manual.

7.2.10 Psoriasis Area and Severity Index Scoring

The PASI is a measure of the psoriasis disease severity using the average redness, thickness, and scaliness of the lesions (each graded on a 0–4 scale), weighted by the area of involvement

(Wozel et al, 2005). PASI combines the assessment of the severity of lesions and the area affected into a single score in the range 0 (no disease) to 72 (maximal disease).

To score the PASI, the body is divided into 4 sections

- head (H): 10% of a person's skin
- arms (A): 20%) of a person's skin
- trunk (T): 30%) of a person's skin
- legs (L): 40% of a person's skin

Each of these areas is scored by itself, and then the 4 scores are combined into the final PASI. For each section, the percent of area of skin involved, is estimated and then transformed into a grade from 0 to 6:

- Grade 0: 0% of involved area
- Grade 1: < 10% of involved area
- Grade 2: 10%–29% of involved area
- Grade 3: 30%–49% of involved area
- Grade 4: 50%–69% of involved area
- Grade 5: 70%–89% of involved area
- Grade 6: 90%–100% of involved area

Within each area, the severity is estimated by 3 clinical signs: erythema (redness), induration (thickness), and desquamation (scaling). Severity parameters are measured on a scale of 0 to 4, from none to maximum.

The sum of all 3 severity parameters is then calculated for each section of skin, multiplied by the area score for that area and multiplied by weight of respective section (0.1 for head, 0.2 for arms, 0.3 for body, and 0.4 for legs).

7.2.11 Relative Physician's Global Assessment

The relative PGA documents the physician's assessment of the subject's psoriasis status (Robinson 2012). Consideration should be given to the percent of body involvement as well as overall induration, scaling, and erythema (refer to Appendix C).

The DLQI is a skin disease-specific instrument designed to assess the impact of the disease on a subject's quality of life (Finlay et al, 1994). Refer to Appendix D for the complete questionnaire.

7.2.12 Photography (Optional)

Subjects have the option to participate in the photography of selected lesions. The same lesions should be photographed throughout the study. Further information can be found in the Kadmon photography manual.

7.2.13 Study Drug Administration

Subjects will receive an adequate supply of study drug for the intervals between the visits scheduled for study drug administration. During the double-blind treatment period, study drug will be dispensed in a blinded fashion and each subject will receive 2 tablets to take each morning and 1 tablet to take each evening. During the 32-week continuation period, all subjects will receive open-label 400 mg KD025 QD, as two 200 mg tablets to be taken in the morning.

At each designated visit, subjects will receive the morning dose (2 tablets) of study drug in the clinic. Subjects will self-administer the balance of daily doses of study drug at home.

Each dose of study drug should be taken together with a meal or within 5 minutes of finishing a meal. See Section 9.1 for further information regarding the dosing schedule and Section 9.3 for guidance regarding missed doses.

7.2.14 Subject Drug Diaries

Subjects will be required to keep study drug diaries in which they will record the date of study drug administrations. These diaries will be dispensed at the Day 1 (Week 1) visit. Final collection will be at Week 16 for those who do not wish to continue into the open-label period. For subjects that complete the open-label treatment period the diary will be collected at the Week 48 visit. For subjects who discontinue the study prematurely, the diary will be collected at the Early-Termination visit. Prior and Concomitant Medications

All concomitant medications, including corticosteroids and changes in corticosteroid usage during the study, will be collected from the time the subject signs the ICF throughout the subject's participation in the study.

7.2.15 Adverse Event Assessments

Information regarding the occurrence of AEs will be collected from the time subjects sign the ICF throughout their participation in the study, including a period of 30 days after last dose of study drug.

> **Note**: AEs resulting in a subject's permanent discontinuation from the study, regardless of seriousness or relationship to study drug, **MUST** be promptly reported to the sponsor.

See Section 8.2 for stopping rules for this study. Also, if significant increases (> 2 × ULN of ALT or AST) in liver enzymes are observed at any time, refer to Section 9.4 for additional information and recommended procedures.

8 REMOVING SUBJECTS FROM STUDY

Every reasonable effort will be made to keep the subject in the study; however, in the event that a subject is withdrawn from the study, every effort will be made by the investigator to complete and report the reasons for withdrawal as thoroughly as possible. This evaluation should include final observations, as required by the protocol at the time of the subject's withdrawal. The reason(s) for termination must be clearly documented on the appropriate page of the eCRF. A termination eCRF must be completed for any subject who is enrolled in the study.

8.1 Subject Withdrawal

A subject's participation in the study may be discontinued for any of the following reasons:

8.1.1 Treatment Discontinuation

- An AE requires permanent discontinuation of study drug
- Voluntary withdrawal by subject
- Noncompliance to protocol

8.1.2 Study Discontinuation

In the event of premature discontinuation, every effort should be made to have the subject come to the clinic for an Early-Termination and 30-day Follow-Up visit in order for the investigator to collect all clinical and laboratory data as scheduled. (Refer to Table 1-1, Schedule of Assessments for a complete list of procedures to be performed.) If a subject dies, Kadmon will actively seek to know the date of death.

Subjects who are withdrawn from this study due to toxicity are to be followed until:

- Resolution or stabilization of toxicity
- The subject is lost to follow-up
- The event is otherwise explained

If there is an ongoing toxicity due to KD025, subjects must be followed with appropriate medical management until resolution or stabilization.

A reasonable effort should be made to contact any subject lost to follow-up during the course of the study in order to complete assessments and retrieve any outstanding data. If the subjects are

unreachable by telephone after 3 attempts, a certified registered return receipt letter should be sent requesting that contact be made with the investigator to report updated information.

8.2 Stopping Rules

Stopping criteria will be assessed using the Clinical Symptom Adverse Event Grading scale (Appendix E) and will include clinically significant changes with respect to BP, dyspepsia, nausea or vomiting, or other treatment-emergent AEs that are Grade 2 (moderate) or higher.

8.2.1 Adverse Events Stopping Criteria

- AEs of clinical concern
- Grade 2 (moderate) or higher TEAEs that are determined by the investigator to be possibly, probably, or definitely related to study drug (with the exception of liver-related adverse events, see Section 9.4);
- Clinically significant elevation of ALT or AST. See Section 9.4 for risk management of LFTs changes observed during the study.

8.2.2 Blood Pressure Stopping Criteria

BP is to be measured with the subject in a sitting position according to the guidelines in Section 7.2.4. BP measurements meeting stopping criteria should be repeated once, to confirm the measurement. The repeat measurement will be used to determine whether the subject meets the stopping criteria.

Clinically significant BP decreases will be defined as follows:

- An absolute systolic BP (SBP) < 85 mmHg at any time point, or a decrease > 30 mmHg in SBP from baseline with accompanying symptoms of hypotension at any time point, or an asymptomatic decrease > 30 mmHg from baseline on any 2 consecutive time points

OR

- An absolute diastolic BP (DBP) < 45 mmHg at any time point, or a decrease > 20 mmHg in DBP from baseline with accompanying symptoms of hypotension at any time point, or an asymptomatic decrease > 20 mmHg in DBP from baseline on 2 consecutive time points.

Clinically significant BP increases are defined as:

- An absolute SBP > 180 mmHg at any time point, or an increase > 30 mmHg in SBP from baseline with accompanying symptoms of hypertension at any time point, or an asymptomatic increase > 30 mmHg from baseline on any 2 consecutive time points

OR

- An absolute DBP > 110 mmHg at any time point, or an increase > 20 mmHg in DBP from baseline with accompanying symptoms of hypertension at any time point, or an asymptomatic increase > 20 mmHg in DBP from baseline on 2 consecutive time points.

8.3 Study Termination

Kadmon Corporation has the right to terminate or to stop the study at any time. Reasons for study discontinuation may include, but are not limited to the following:

- The incidence or severity of AEs in this or other related studies indicates a potential health hazard to subjects
- Subject enrollment is unsatisfactory
- Drug supply issues
- Data recording is inaccurate or incomplete
- Excessive subject self-withdrawal
- Significant protocol violations (e.g., violation of eligibility criteria, dosing errors, missing data for study endpoint analysis)

8.4 Replacements

Subjects withdrawn from the study prior to receiving any study drug will be replaced by enrolling additional subjects into the study.

9 STUDY DRUG

9.1 Dose and Schedule of Study Drug and Reference Therapy

After the completion and review of all screening and baseline procedures, eligible, consenting subjects will be randomly assigned to 1 of 5 dose cohorts in a 1:1:1:1:1 manner (see Table 9-1). Study drug will be orally administered in a double-blind fashion for 16 weeks.

Study drug will be dispensed by the site pharmacist, or designee. KD025 will be supplied as 200-mg tablets. Doses to be studied are 200 mg KD025 QD, 200 mg KD025 BID, 400 mg KD025 QD, and KD025 600 mg/day (administered as 400 mg in the morning and 200 mg in the evening). Placebo will be supplied as matching tablets.

Table 9-1 Dosing Cohorts

Cohort	No. of Subjects	Dose Regimen
Cohort 1	22 subjects	200 mg KD025 QD (subjects will receive 1 KD025 200 mg and 1 matching placebo tablet in the morning and a matching placebo in the evening)
Cohort 2	22 subjects	200 mg KD025 BID (subjects will receive 1 KD025 200 mg and 1 matching placebo tablet in the morning and KD025 200 mg in the evening)
Cohort 3	22 subjects	400 mg KD025 QD (subjects will receive 2 KD025 200 mg tablets in the morning and a matching placebo in the evening)
Cohort 4	22 subjects	600 mg/day KD025 (subjects will receive 2 KD025 200 mg tablets in the morning and 1 KD025 200 mg in the evening)
Cohort 5	22 subjects	Control (subjects will receive 2 matching placebo tablets in the morning and 1 matching placebo tablet in the evening)

Each dose of study drug should be taken together with a meal or within 5 minutes of finishing a meal.

Subjects will return to the clinic as outlined in the Schedule of Assessments (Table 1-1), and will receive the morning dose of study drug (2 tablets) during visits when PD samples are to be drawn. Subjects will self-administer the balance of daily doses of study drug at home.

9.2 32-Week Open-Label KD025 Therapy (Week 16 through Week 48)

Subjects randomized to KD025 or placebo will have the option to continue 400 mg of KD025 QD treatment for an additional 32 weeks in the open-label treatment period.

9.3 Missed Doses

- Subjects should make every effort to take the study drug at the same scheduled times daily, morning and evening. In the event that the subject misses the planned dose of study drug, the following protocol should be followed: If less than 6 hours of time have elapsed after the scheduled dose, the drug should be taken and the subject should resume their dosing schedule with the next dose.
- If more than 6 hours of time have elapsed after the scheduled dose, the dose should be skipped. The subject should resume the regular planned dosing schedule.

If the subject skips more than 7 consecutive days of drug, the subject should be discontinued from the study. If the subject cannot take KD025 for more than 7 consecutive days due to a toxicity, the subject is allowed to re-start study drug.

9.4 Evaluation of Liver-Related Blood Tests

Clinically significant elevations of liver-related blood tests as defined below require immediate drug termination.

1. ALT or AST > 5 ×ULN
2. ALT or AST > 3 ×ULN and (total bilirubin > 2 ×ULN or INR >1.5)
3. ALT or AST > 3 ×ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
4. If the total bilirubin is > 2 ×ULN then obtain direct bilirubin

If ALT or AST > 2.0 ×ULN, the subject should remain on study drug with **close observation** which includes:

1. Repeating liver enzyme, every 48 to 72 hours

   (Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the study drug has been discontinued and the subject is asymptomatic.)
2. Obtaining a more detailed history of symptoms and prior or concurrent diseases

3. Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets
4. Ruling out acute viral hepatitis types A, B, and C
5. Obtaining a history of exposure to environmental chemical agents

Table 9-2: Grading of Liver-Related Laboratory Abnormalities

FEATURE	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
ALT	<1.25 ULN	1.25-2.5 ULN	>2.5-5.0 ULN	>5.0-10 ULN	>10 ULN
AST	<1.25 ULN	1.25-2.5 ULN	>2.5-5.0 ULN	>5.0-10 ULN	>10 ULN
Alkaline Phosphatase	<1.25 ULN	1.25-2.5 ULN	>2.5-5.0 ULN	>5.0-10 ULN	>10 ULN
GGT	<1.25 ULN	1.25-2.5 ULN	>2.5-5.0 ULN	>5.0-10 ULN	>10 ULN
Bilirubin	Normal	>1.0-1.5 ULN	>1.5-2.5 ULN	>2.5-5 ULN	>5 ULN

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Note: A Grade 2 elevation of ALT, for example, does not connote a Grade 2 TEAE and the above evaluation should guide stopping rules.

For further details, see IB 2015, Summary of Data and Guidance for the Investigator.

9.5 Identity of Investigational Products

Table 9-3 Investigational Products

Product	Strength	Dosage Form	Route
KD025	200 mg	Yellow to pale yellow oval shaped tablet	Oral
Placebo		Yellow to pale yellow oval shaped tablet	Oral

KD025 and placebo will be supplied by Kadmon.

9.6 Study Drug Packaging and Labeling

KD025 and placebo will be packaged and labeled by the sponsor or designee. The label attached to each bottle will provide the following information:

- Description of contents (number and strength of tablets) and route of administration
- Directions for use

- Storage conditions
- Product identification code
- Lot number identification
- Bottle number
- Name of protocol sponsor
- The statement, "Caution: New Drug – Limited by Federal Law to Investigational Use"
- The statement, "Keep out of the reach of children and pets"

9.7 Dispensing of Study Drug and Dosing Compliance

The amount of study drug dispensed to the subject at the beginning of each dosing month should be sufficient to allow for 1 month of dosing. In the 32-week continuation period, the amount of KD025 dispensed at each visit will be sufficient to allow for dosing until the next visit.

The investigator (or designee) will be responsible for recording this information on the appropriate study drug inventory. This inventory will be maintained throughout the duration of the study and will be periodically reviewed by a representative of the sponsor.

The investigator (or designee) will instruct the subject that all dispensed bottles must be returned at each follow-up visit, at which time a tablet count will be conducted to assure subject dosing compliance.

Additionally, subjects will be required to keep study drug diaries in which they will record the details of study drug administrations. These diaries will be dispensed and/or collected according to the Schedule of Assessments (Table 1-1).

9.8 Study Drug Storage

All supplies of study drug are to be stored at United States Pharmacopeia controlled room temperature of 20°C to 25°C (66°F to 77°F) with excursions permitted between 15°C and 30°C (59°F and 86°F). At the clinic, the study drugs are to be stored in a securely locked area, accessible to authorized persons only, until needed for dosing.

9.9 Study Drug Accountability

The US FDA and other regulatory agencies require accounting for the disposition of all investigational drugs received by each clinical site. Information on drug disposition required by law consists of the date received, date administered, quantity administered, and the subject to whom the drug was administered. The principal investigator is responsible for the accounting for all unused study drugs and all used study drug containers. The investigator must maintain a complete and current dispensing and inventory record that has been supplied by the sponsor.

9.10 Study Drug Handling

At the termination of the study, a final drug accountability review and reconciliation must be completed and any discrepancies must be investigated and their resolution documented.

9.10.1 Disposition of Used Supplies

At the completion of a subject's participation in the study, all partially used and empty pill bottles must be returned to the investigator (or designee) so that a final subject-dosing inventory may be conducted. This information will be recorded on the Drug Dispensing Log.

9.10.2 Inventory of Unused Supplies

Periodically throughout and at the conclusion of the study, an inventory of unused bottles of study drug will be conducted by a representative of the sponsor.

10 CONCOMITANT MEDICATION AND TREATMENT

Subjects will be counseled to avoid non-prescribed medicines or complementary alternative medicines excluded by the study. Any medications a subject receives from signing ICF through the end of study (30-Day Follow-Up visit) will be documented. After discontinuation of study drug, any concomitant medication used in response to an AE is to be recorded on the appropriate eCRF.

Administration of acid-reducing medications should be avoided during the study as these agents may decrease exposure to KD025. If acid-reducing agents are needed, H-2 antagonists or antacids will be recommended rather than proton pump inhibitors. Administration of acid-reducing agents such as H-2 antagonists or antacids, if required, should take place no less than 2 hours before or after dosing with KD025.

Subjects may be receiving low-dose oral corticosteroids ($\leq$ 10 mg daily prednisone or equivalent) at study entry. Oral corticosteroid dose must be stable for at least 1 month prior to study entry and expected to remain stable throughout participation. Any changes in systemic corticosteroid dose will be documented on the eCRF. Topical corticosteroids or immunosuppressive therapies to the face, groin, or scalp are allowed.

Prior systemic treatment, including biologics, is to be recorded on the eCRF, including duration of exposure and reason for discontinuation.

The concomitant medication names will be coded by the sponsor according to the World Health Organization (WHO) Drug Dictionary and classified by anatomical therapeutic chemical (ATC) categories.

11 SAFETY

11.1 Safety Parameters

The Clinical Symptom and Adverse Event Grading Scale will be used for grading toxicities (see Appendix E). With the exception of LFTs, laboratory results will be classified using the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Studies (see Appendix A). LFTs will be classified using Table 9-2 in Section 9.4. Subjects will be monitored throughout the treatment and follow-up period for occurrence of AEs, as well as for changes in clinical status, vital sign measurements, and laboratory data.

11.2 Adverse Event Definition

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. AEs include:

- Suspected adverse drug reactions (abbreviated as either SADR or SAR). This may be serious or not serious
- Reactions from drug overdose, abuse, withdrawal, sensitivity, or toxicity
- Significant changes or abnormalities, when compared with baseline, in structure (sign), function (symptom), clinical laboratory results, ECG results, or physiological testing. This includes any worsening of a pre-existing condition temporally associated with the use of study drug
- Other medical events, regardless of their relationship to the study drug, such as injury, surgery, accidents, extensions of symptoms, or apparently unrelated illnesses

For the purpose of data collection, all untoward events that occur after ICF through 30 days after last dose of study treatment are to be recorded on eCRFs by the investigational site.

11.3 Evaluating Adverse Events

The investigator will determine the seriousness, intensity, and causality of an AE associated with the use of the study drug (i.e., events where there is a reasonable possibility that the event may have been caused by the study drug) based on the definitions that follow.

11.3.1 Serious Adverse Events

(Notify sponsor or designee within 24 hours; document on eCRF)

The SAE definition and reporting requirements are in accordance with Title 21 Part Code of Federal Regulations (CFR) 312.32 and the Guidance for Industry and Investigators Safety Reporting Requirements for Investigational New Drug (IND) applications and bioavailability/bioequivalence (BA/BE) studies.

SAE: An adverse event is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- **Death:** This includes any death that occurs while the subject is "on study" as well as any death that occurs within 30 days after study drug administration.

  Note: Death is an outcome of an AE, and not an AE in itself. The event(s) that caused death (e.g., illness, accident) is the SAE. Death due to any other cause(s) must also be reported as an outcome of the reportable SAE.

- **Life-threatening AE:** An AE or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.
- **Inpatient hospitalization or prolongation of existing hospitalization:**

  In the absence of an AE, the investigator should not report hospitalization or prolongation of hospitalization. This is the case in the following situations:

  - Hospitalization or prolongation of hospitalization is needed for a procedure required by the protocol
  - Hospitalization or prolongation of hospitalization is part of routine procedure followed by study center
  - Hospitalization for survey visits or annual physicals

In addition, a hospitalization planned before the start of the study for a pre-existing condition which has not worsened does not count as an SAE.

- **Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions**
- **Congenital anomaly/birth defect**
- **Important medical event:** An event that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, it may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition.

11.3.2 Suspected Unexpected Serious Adverse Reaction

(Notify sponsor or designee within 24 hours of first awareness; document on eCRF)

A suspected unexpected serious adverse reaction (SUSAR) is any adverse drug event, the specificity or severity of which is not consistent with those noted in the current protocol and/or IB. This refers to any AE that has not been previously observed (e.g., included in the IB), rather than from the perspective of such an event not being anticipated from the pharmacological properties of the product.

11.3.3 Unexpected Adverse Events

An AE is considered "unexpected" if it is not listed in the IB or is not listed at the specificity or severity that has been observed; or, if an IB is not required or available, is not consistent with the risk information described in the General Investigational Plan or elsewhere in the current application. The term also refers to AEs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

11.3.4 Non-Serious Adverse Events

All other AEs, not fulfilling the previous definitions, are classified as non-serious.

11.3.5 Protocol-Related Adverse Events

AEs that are not study drug related may nevertheless be considered by the investigator or the medical monitor to be related to the conduct of the clinical study. That is, the event may be related to the fact that a subject is participating in the study. For example, a protocol-related AE

may be an event that occurs during a washout period or that is related to a procedure required by the protocol.

11.3.6 Relationship to Study Drug

The investigator will attempt to assess the relationship of the event to study drug using a 5-point scale (not related, unlikely related, possibly related, probably related, or definitely related; see Appendix F; Clinical Adverse Events: Determining Relationship to Study Drug).

11.3.7 Recording Adverse Events

All AEs (including SAEs) are to be accurately recorded on the Adverse Event page of the subject's eCRF during the subject's participation in the study. The severity of each AE will be graded using a 5-point scale (mild, moderate, severe, life threatening, or death; see Appendix E). The date of onset as well as the end date of the event also should be recorded or the event should be entered as "ongoing". In addition, the method used to treat the AE and the outcome of the AE also will be noted. The investigator will assess the relationship of the event to study drug.

11.3.8 Hospitalization

In the absence of an AE, the investigator should not report hospitalization or prolongation of hospitalization. This is the case in the following situations:

- Hospitalization or prolongation of hospitalization is needed for a procedure required by the protocol.
- Hospitalization or prolongation of hospitalization is part of routine procedure followed by study center.
- Hospitalization for survey visits or annual physicals.

In addition, a hospitalization planned before the start of the study for a pre-existing condition that has not worsened does not count as an SAE.

11.3.9 Serious Adverse Event Reporting

11.3.9.1 Governing Regulatory Requirements

Compliance with this request for prompt reporting is essential in that the sponsor is responsible for informing the US FDA as well as all other participating investigators of the event.

Under FDA ruling (Title 21 CFR Part 312.32) and the Guidance for Industry and Investigators Safety Reporting Requirements for INDs and BA/BE Studies, the sponsor is required to submit written documentation, in the form of an IND safety report, detailing:

- Any event associated with the use of the drug, that is both serious and unexpected, or
- Any findings from clinical, epidemiological, or pooled analysis of multiple studies or any findings from animal or in vitro testing that suggest a significant risk in humans exposed to the drug.

Written submission must be made by the sponsor to the FDA and the IRBs as soon as possible and in no event later than 15 calendar days after the sponsor's initial receipt of notification of the event. Any unexpected death or life-threatening suspected adverse reaction must be reported to FDA no later than 7 calendar days after the sponsor's initial receipt of the information. The sponsor shall also inform all investigators.

11.3.9.2 Time-Frame for Reporting

Any death, pregnancy, SAE, or unexpected (and severe) AE experienced by a subject after ICF or within 30 days of receiving study drug, regardless of relationship to study drug, or any death that occurs more than 30 days after receiving study drug, and is believed to be study drug-related, must be promptly reported (within 24 hours of the investigator becoming aware of the event) by e-mail to the sponsor (or sponsor's designee).

Contact information for **SAE/SUSAR** reporting:

INC Drug Safety
Fax: (877) 464-7787
Email: INCDrugSafety@INCResearch.com

Additionally, the investigator will be able to contact the **medical monitor** at all times:

John L Ryan, PhD, MD
Kadmon Corporation
450 East 29th Street
New York, NY 10016
Telephone: Cell: (617) 230-4764
E-mail: john@kadmon.com

11.3.9.3 Information to be Provided by the Investigator

SAEs for all enrolled subjects must be recorded on both the SAE form and the AE eCRF page. This requirement includes all SAEs that occur after the subject signs the ICF and through 30 days after last dose of study treatment, and in addition, any SAEs that are assessed as possibly related to study treatment by the investigator, even if the SAE occurs more than 30 days after the last dose of study treatment must be reported to the Kadmon Pharmacovigilance Department.

The minimum information required for SAE reporting includes identity of investigator, site number, subject number, an event description, SAE term(s), onset date, the reason why the event is considered to be serious (i.e., the seriousness criteria) and the investigator's assessment of the relationship of the event to study treatment. Additional SAE information including medications or other therapeutic measures used to treat the event, action taken with the study treatment due to the event, and the outcome/resolution of the event will be recorded on the SAE form. Forms for reporting SAEs will be provided to the study sites.

In all cases, the investigator should continue to monitor the clinical situation and report all material facts relating to the progression or outcome of the SAE. Furthermore, the investigator may be required to provide supplementary information as requested by the Kadmon Drug Safety personnel or designee.

When reporting an SAE, the following additional points should be noted:

- When the diagnosis of an SAE is known or suspected, the investigator should report the diagnosis or syndrome as the primary SAE term, rather than as signs or symptoms. Signs and symptoms may then be described in the event description. For

example, dyspnea should not be used as an SAE term if the diagnosis which caused the dyspnea is known to be malignant pleural effusion.

- Death should not be reported as an SAE, but as an outcome of a specific SAE, unless the event preceding the death is unknown. In the exceptional case where the events leading to death are unknown, then death may be used as an event term. If an autopsy was performed, the autopsy report should be provided.
- While most hospitalizations necessitate reporting of an SAE, some hospitalizations do not require SAE reporting, as follows:
    - Elective or previously scheduled surgery (e.g., a previously scheduled ventral hernia repair)
    - Procedures for pre-existing conditions that have not worsened after initiation of treatment
    - Pre-specified study hospitalizations for observation
    - Events that result in hospital stays of less than 24 hours and that do not require admission (e.g., an emergency room visit for hematuria that results in a diagnosis of cystitis and discharge to home on oral antibiotics)
- SAEs must, however, be reported for any surgical or procedural complication resulting in prolongation of the hospitalization.

11.3.9.4 Regulatory Reporting

Kadmon Drug Safety (or designee) will process and evaluate all SAEs as soon as the reports are received. For each SAE received, Kadmon will make a determination as to whether the criteria for expedited reporting have been met.

Kadmon (or designee) will submit SAEs that meet the criteria for expedited reporting to the Regulatory Authorities in accordance with local regulations governing safety reporting. Reporting of SAEs by the investigator to his or her IRB will be done in accordance with the standard operating procedures and policies of the IRB. Adequate documentation must be maintained showing that the IRB was properly notified.

As a general rule, treatment codes will be broken by authorized member of the sponsor and/or designee Drug Safety staff before reporting an SAE that meets the criteria for expediting

reporting to the Regulatory Authorities. The investigator and sponsor staff that are not part of the Drug Safety Department will remain blinded to the treatment assignment.

The blind should ordinarily be broken for IND safety reports submitted to the FDA. If a sponsor has concerns that unblinding of AEs will compromise the integrity of the study, the sponsor can propose in advance an alternative reporting format or frequency to maintain the blind that must be agreed to by the director of the review division in FDA with responsibility for review of the IND (21 CFR 312.32(c)(3)). Other Safety Considerations

11.3.10 Laboratory Data

All laboratory data obtained during the course of the study should be reviewed. Any abnormal value that leads to a change in subject management (e.g., dose delay, requirement for additional medication or monitoring) or is considered to be of clinical significance by the investigator should be reported as an AE and/or SAE as appropriate, unless this value is consistent with the subject's present disease state or is consistent with values obtained prior to entry into the study.

With the exception of LFTs, laboratory results will be classified using the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Studies (see Appendix A). LFTs will be classified using Table 9-2 in Section 9.4.

11.3.11 Medication Errors

Any medication error that results in an AE, even if it does not meet the definition of serious, requires reporting within 24 hours to the safety monitor.

11.3.12 Follow-Up of Adverse Events

Any SAE or AE assessed as possibly related that led to treatment discontinuation (including clinically significant abnormal laboratory values that meet these criteria) and is ongoing 30 days after last dose of study treatment must be followed until either resolution of the event or determination by the investigator that the event has become stable or irreversible. This follow-up guidance also applies to possibly related SAEs that occur more than 30 days after last dose of study treatment. The status of all other continuing AEs will be documented as of 30 days after last dose of study treatment.

12 STATISTICAL CONSIDERATIONS

All descriptive and inferential statistical analyses will be performed using SAS statistical software (Version 9.4), unless otherwise noted. For categorical variables, the number and percent of each category within a parameter will be calculated for non-missing data. For continuous variables, the mean, median, and standard deviation (SD), as well as the minimum and maximum values, will be presented.

Statistical significance will be declared when the p-value is found to be ≤ 0.05, unless otherwise noted. Missing data will not be imputed unless otherwise stated. All clinical data captured will be provided in data listings.

Complete details of the planned analysis will be documented in the SAP.

12.1 General Design

All data for enrolled subjects will be presented in data listings by subject number. For those summary tables in which baseline and change from baseline measurements will be presented, the last observed measurement prior to the initial dose of KD025 will be considered the baseline measurement.

Continuous data will be described using descriptive statistics: number of observations (n), mean, SD, 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 non-zero counts. The denominator for all percentages, unless otherwise specified, will be the number of subjects in the specified analysis population. Two-sided 95% confidence interval employing the exact binomial method will be provided for efficacy activity endpoints.

Hypothesis testing, if appropriate, will be carried out at the 5% (2-sided) significance level. Due to the exploratory nature of the study, no adjustments may be made for the multiplicity of endpoints. Non-parametric tests may be used in preference to parametric tests if the underlying distributions of the data are not known. Missing values will not be imputed. If a subject does not have sufficient data for a particular analysis, then, that subject will be excluded from that

analysis. Endpoints defined as an average of multiple measurements will be used for those data points that were non-missing, and the denominator will be adjusted accordingly.

12.2 Sample Size Justification

The sample size will be 110 subjects due to early study termination.

12.3 Study Populations

Two populations will be employed in the analysis of study data:

- The modified intent-to-treat (mITT) population will consist of all subjects who are randomized and take at least 1 dose of study drug. All safety analyses will be performed on the mITT population. The Evaluable for Efficacy population will consist of subjects who have non-missing baseline and Week 16 PASI scores and do not have a major protocol violation.

Demographics, subject disposition, and screening and baseline characteristics will be summarized for mITT populations, where appropriate.

12.4 Subject Accountability, Demographics, and Baseline Characteristics

Subject disposition will be tabulated by treatment group. Similarly, subject demographic information and baseline characteristics will be displayed.

12.5 KD025 Exposure

The amount of KD025 administered by visit and overall will be tabulated by treatment group and presented by subject in data listings. In addition, delays and all other alterations in KD025 administration will be presented.

12.6 Concomitant Medications

Concomitant medications will be coded using WHO Drug Dictionary and the data will be summarized by treatment and presented in tables and listings.

12.7 Efficacy Analysis

The primary efficacy endpoint for analyses will be the number (%) of subjects with a 75% decrease in PASI by Week 16.

The secondary efficacy endpoints for analysis will include the following:

1. A 50% reduction in Week 16 PASI score (PASI 50)
2. The mean Week 16 percent change from baseline in PASI
3. Improvements in PGA of "clear" or "almost clear" at Week 16
4. Improvements in DLQI at Week 16

The exploratory efficacy endpoints are:

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

Efficacy analyses will be divided into 2 periods: the double-blind treatment period through database lock at Week 16 and the open-label, 32-week continuation period.

Efficacy analyses will include the number (%) of subjects with a 75% decrease in PASI (number of subjects that reach PASI 75) at Week 16 in the KD025 treatment groups compared with the placebo group in a pairwise manner using a Fisher's Exact test. The number of subjects who reach PASI 50 at Week 16 will be analyzed similarly. Treatment group differences in DLQI and PGA changes from baseline to Week 16 will be assessed using an analysis of covariance (ANCOVA) model with treatment as a fixed effect and a subject's baseline value as a covariate.

No adjustments for multiplicity are being made for this Phase 2 study.

For further details, see the statistical analysis plan (SAP).

12.8 Safety Data

Safety assessments will include AEs, SAEs, PEs (including weight), vital sign measurements (including BP, pulse rate, respiratory rate, and temperature), clinical laboratory evaluations (hematology, chemistry, urinalysis, coagulation, lipid panel, TSH) ECGs, and reasons for treatment discontinuation due to toxicity.

The primary safety endpoint will be the percentage of subjects in each treatment group experiencing AEs.

TEAEs will be summarized by treatment group using MedDRA® SOC and preferred term, classified from verbatim terms (Version 18.1 or higher). The incidence and percentage of subjects with at least 1 occurrence of a preferred term will be included, according to the most

severe grade using a 5-point scale (mild, moderate, severe, life threatening, or death). The number of events per preferred term will also be summarized. Causality (relationship to study treatment) will be summarized separately.

AEs, SAEs, related AEs, related SAEs, ≥ Grade 3 AEs, related ≥ Grade 3 AEs, and AEs leading to withdrawal or treatment discontinuation will be summarized by treatment group according to SOC and preferred terms. AEs will also be presented in listings. Duration of AEs will be determined and included in listings, along with action taken and outcome.

Laboratory results will be classified using the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Studies (see Appendix A) and summarized. Incidence of laboratory abnormalities will be summarized by treatment group. The worst on-study grade after the first dose of study drug will be summarized by treatment group. The incidence of ≥ Grade 3 laboratory abnormalities under treatment and shifts in toxicity grading from baseline to highest grade post-baseline will be displayed.

Vital sign measurements will be summarized at each scheduled time point using descriptive statistics.

13 DATA QUALITY ASSURANCE

Accurate and reliable data collection will be ensured by verification and cross-check of the eCRFs against the investigator's records by the study monitor (source document verification) and by the maintenance of a drug-dispensing log by the investigator. Collected data will be entered into a computer database and subject to electronic and manual quality assurance procedures.

14 ETHICAL ASPECTS

14.1 Local Regulations

The study must fully adhere to the principles outlined in "Guideline for Good Clinical Practice" ICH E6 Tripartite Guideline (January 1997), and in general, be conducted in a manner consistent with the most recent version of the Declaration of Helsinki. The investigator will ensure that the conduct of the study complies with the basic principles of GCP as outlined in the current version of 21 CFR, subpart D, Part 312, "Responsibilities of Sponsors and Investigators", Part 50, "Protection of Human Subjects", and Part 56, "Institutional Review Boards".

14.2 Informed Consent Form

Sample ICFs will be supplied to each site. Kadmon or its designee must review any ICF prior to submission for review by the IRB. The final IRB-approved document must be provided to Kadmon for regulatory purposes.

It is the responsibility of the investigator, or a person designated by the investigator, to obtain a written ICF from each subject (or the subject's legally authorized representative) agreeing to participate in this study after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study in accordance with federal and state regulations is provided. In the case where the subject is unable to read, an impartial witness should be present during the entire ICF discussion. After the subject has orally consented to participation in the study, the witness' signature on the form will attest that the information in the consent form was accurately explained and understood. A copy of the ICF must be provided to the subject or to the subject's legally authorized representative. If applicable, it will be provided in a certified translation of the local language.

The eCRF for this study contains a section for documenting informed subject consent, and this must be completed appropriately. Signed ICFs must remain in each subject's study file and must be available for verification by study monitors at any time. If new safety information results in changes in the risk/benefit assessment, the consent form should be reviewed and updated as necessary. All subjects (including those already being treated) should be informed of the new

information, should be given a copy of the revised form, and should give their consent to continue in the study.

14.3 Institutional Review Board

This study is being conducted under a US IND application. This protocol (and any modifications) and appropriate consent procedures must be reviewed and approved by an IRB. This board must operate in accordance with the current federal or local regulations. The investigator will send a letter or certificate of IRB approval to Kadmon (or designee) before subject enrollment and whenever subsequent modifications to the protocol are made.

14.4 Future Use of Subject Samples

Not all of the tissue and blood components obtained during this study may be required for the tests that are part of the clinical study. Following the conclusion of the study, the samples may be used for additional research. This research will help to understand disease subtypes, drug response and toxicity, and possibly identify new drug targets or biomarkers that predict subject response to treatment. The use of the samples for internal research will be done according to the guidelines defined by the FDA guidance for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individual Identifiable (issued 25 April 25 2006) and the European Medicines Agency (EMEA) Reflection Paper on Pharmacogenetic Samples, Testing and Data Handling (EMEA/CHMP/PGxWP/201914/2006). If a subject requests destruction of their blood samples and the samples have not yet been de-identified, Kadmon will destroy the samples as described in this FDA guidance. Kadmon will notify the investigator in writing that the samples have been destroyed.

15 CONDITIONS FOR MODIFYING THE PROTOCOL

Protocol modifications to ongoing studies must be made only after consultation between a Kadmon representative and the investigator. Protocol modifications will be reviewed and approved by Kadmon representatives.

All protocol modifications must be submitted to the IRB for information and approval in accordance with local requirements, and to regulatory agencies if required. Approval must be obtained before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to study subjects, or when the change involves only logistical or administrative aspects of the study (e.g., change in monitor, change of telephone number).

16 CONDITIONS FOR TERMINATING THE STUDY

Kadmon has the right to terminate the study at any time. In terminating the study, Kadmon and the investigator will ensure that adequate consideration is given to the protection of the subjects' interests.

17 STUDY DOCUMENTATION, CRFS, AND RECORD KEEPING

17.1 Investigator's Files and Retention of Documents

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into 2 separate categories as follows: (1) investigator's study files; and (2) subject clinical source documents.

The investigator's study file will contain the protocol and protocol amendments, eCRFs, IRB, and governmental approval with correspondence, sample ICF, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

Subject clinical source documents (usually predefined by the project to record key efficacy and safety parameters independent of the eCRFs) may include subject hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, electroencephalogram, X-ray, pathology, and special assessment reports, signed ICFs, consultant letters, and subject screening and enrollment logs. The investigator must keep these 2 categories of documents on file for at least 2 years following the marketing application approval date for the study treatment and for the indication being investigated or for 2 years after the investigation is discontinued and the FDA notified. After that period of time, the documents may be destroyed subject to local regulations with prior written permission from Kadmon. If the investigator wants to assign the study records to another party or move them to another location, Kadmon must be notified in advance.

If the investigator cannot guarantee the archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and Kadmon to store these in a sealed container outside of the study site so that they can be returned sealed to the investigator in case of a regulatory audit. When source documents are required for the continued care of the subject, appropriate copies should be made for storing outside of the study site.

17.2 Source Documents and Background Data

Upon request, the investigator will supply Kadmon with any required background data from the study documentation or clinic records. In case of special problems or governmental queries or

requests for audit inspections, it is also necessary to have access to the complete study records, provided that subject confidentiality is protected.

17.3 Audits and Inspections

The investigator should understand that source documents for this study should be made available to appropriately qualified personnel from the Kadmon Quality Assurance Unit (or designee), or to health authority inspectors after appropriate notification. The verification of the eCRF data must be by direct inspection of source documents.

17.4 Electronic Case Report Forms

Clinical study data for this study will be captured on eCRF. The investigator agrees to provide all information requested on the eCRF in an accurate manner according to instructions provided. eCRFs are designed for computer processing and analysis. The investigator should ensure the accuracy, completeness, and timeliness of the data reported to Kadmon in the eCRF and in all required reports.

An eCRF is required to be submitted for every subject who receives any amount of study drug. This includes submission of retrievable data on subjects who withdraw before completion of the study. If a subject stops treatment or terminates from the study, the dates and reasons must be noted on the eCRF.

18 MONITORING THE STUDY

It is understood that the responsible Kadmon monitor (or designee) will contact and visit the investigator regularly and will be allowed on request to inspect the various records of the study (eCRFs and other pertinent data), provided that subject confidentiality is maintained in accordance with local requirements.

It will be the monitor's responsibility to inspect the eCRFs at regular intervals throughout the study, to verify the adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to laboratory test reports and other subject records needed to verify the entries on the eCRF. The investigator (or designee) must agree to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

19 CONFIDENTIALITY OF STUDY DOCUMENTS AND SUBJECT RECORDS

The investigator must ensure that subjects' anonymity will be maintained and that their identities are protected from unauthorized parties. On eCRFs or other documents submitted to Kadmon, subjects should be identified by an identification code and not by their names. The investigator should keep a subject enrollment log showing codes, names, and addresses. The investigator should maintain documents not for submission to Kadmon (e.g., subjects' written consent forms) in strict confidence.

20 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

The results of this study may be published or presented at scientific meetings. The investigator agrees to submit all manuscripts or abstracts to Kadmon for review at least 30 days before submission. This allows Kadmon to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In the event that Kadmon coordinates a publication or presentation of study results from all study sites, the participation of investigator or other representatives of study site as a named author shall be determined in accordance with Kadmon policy and generally accepted standards for authorship.

21 REFERENCES

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http://www.fda.gov/downloads/Drugs/ScienceResearch/ResearchAreas/ucm091457.pdf.

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Appendix A: Tables for Grading Laboratory Abnormalities

The laboratory values provided in the tables below serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

Note: For LFT and bilirubin abnormalities, see Table 9-2 in Section 9.4.

Chemistry*	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)**
Sodium – Hyponatremia mEq/L	132 – 134	130 – 131	125 – 129	< 125
Sodium – Hypernatremia mEq/L	144 – 145	146 – 147	148 – 150	> 150
Potassium – Hyperkalemia mEq/L	5.1 – 5.2	5.3 – 5.4	5.5 – 5.6	> 5.6
Potassium – Hypokalemia mEq/L	3.5 – 3.6	3.3 – 3.4	3.1 – 3.2	< 3.1
Glucose – Hypoglycemia mg/dL	65 – 69	55 – 64	45 – 54	< 45
Glucose – Hyperglycemia Fasting – mg/dL Random – mg/dL	 100 – 110 110 – 125	 111 – 125 126 – 200	 >125 >200	Insulin requirements or hyperosmolar coma
Blood Urea Nitrogen BUN mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Calcium – hypocalcemia mg/dL	8.0 – 8.4	7.5 – 7.9	7.0 – 7.4	< 7.0
Calcium – hypercalcemia mg/dL	10.5 – 11.0	11.1 – 11.5	11.6 – 12.0	> 12.0
Magnesium – hypomagnesemia mg/dL	1.3 – 1.5	1.1 – 1.2	0.9 – 1.0	< 0.9
Phosphorous – hypophosphatemia mg/dL	2.3 – 2.5	2.0 – 2.2	1.6 – 1.9	< 1.6
CPK – mg/dL	1.25 – 1.5 × ULN***	1.6 – 3.0 × ULN	3.1 –10 × ULN	> 10 × ULN
Albumin – Hypoalbuminemia g/dL	2.8 – 3.1	2.5 – 2.7	< 2.5	--
Total Protein – Hypoproteinemia g/dL	5.5 – 6.0	5.0 – 5.4	< 5.0	--

Chemistry*	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)**
Cholesterol	201 – 210	211 – 225	> 226	---
Pancreatic enzymes – amylase, lipase	1.1 – 1.5 × ULN	1.6 – 2.0 × ULN	2.1 – 5.0 × ULN	> 5.0 × ULN

*The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

** The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as Potentially Life Threatening (Grade 4). For example, a low sodium value that falls within a grade 3 parameter (125-129 mEq/L) should be recorded as a grade 4 hyponatremia event if the subject had a new seizure associated with the low sodium value.

***ULN" is the upper limit of the normal range.

Hematology *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Hemoglobin (Female) - gm/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	< 8.0
Hemoglobin (Female) change from baseline value - gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (Male) - gm/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Hemoglobin (Male) change from baseline value – gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
WBC Increase - cell/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	> 25,000
WBC Decrease - cell/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	< 1,000
Lymphocytes Decrease - cell/mm^3	750 – 1,000	500 – 749	250 – 499	< 250
Neutrophils Decrease - cell/mm^3	1,500 – 2,000	1,000 – 1,499	500 – 999	< 500
Eosinophils - cell/mm^3	650 – 1500	1501 - 5000	> 5000	Hypereosinophilic
Platelets Decreased - cell/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	< 25,000
PT – increase by factor (prothrombin time)	1.0 – 1.10 × ULN**	1.11 – 1.20 × ULN	1.21 – 1.25 × ULN	> 1.25 ULN
PTT – increase by factor (partial thromboplastin time)	1.0 – 1.2 × ULN	1.21 – 1.4 × ULN	1.41 – 1.5 × ULN	> 1.5 × ULN
Fibrinogen increase - mg/dL	400 – 500	501 – 600	> 600	--

Hematology *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Fibrinogen decrease - mg/dL	150 – 200	125 – 149	100 – 124	< 100 or associated with gross bleeding or disseminated intravascular coagulation (DIC)

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

** "ULN" is the upper limit of the normal range.

Urine *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Protein	Trace	1+	2+	Hospitalization or dialysis
Glucose	Trace	1+	2+	Hospitalization for hyperglycemia
Blood (microscopic) – red blood cells	1 - 10	11 – 50	> 50 and/or gross blood	Hospitalization or packed red blood cells (PRBC) transfusion

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

Food and Drug Administration (FDA). Guidance for Industry. Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials. US Department of Health and Human Services, Center for Biologics Evaluation and Research. September 2007.

Appendix B: Correction for Heart Rate (Fridericia)*

The following formula will be used to correct to QT interval:

$$QT_F = \frac{QT}{RR^{1/3}}$$

Where **QT_F** is the QT interval corrected for heart rate, and RR is the cube root of the interval from the onset of 1 QRS complex to the onset of the next QRS complex.

*Fridericia LS (1920). "The duration of systole in the electrocardiogram of normal subjects and of patients with heart disease." Acta Medica Scandinavica. (53): 469–486.

Appendix C: Relative Physician's Global Assessment

The relative PGA documents the physician's assessment of the subject's psoriasis status. Consideration should be given to the percent of body involvement as well as overall induration, scaling, and erythema. The PGA is assessed relative to baseline condition and is defined as: (1) = clear, (2) = excellent, (3) = good, (4) = fair, (5) = poor, and (6) = worse. The following table further defines the rating.

Rating	% Clearing	Definition of Response
1 = Clear	100% clear	Some residual pinkness or pigmentation: Woronoff's ring may be present.
2 = Excellent	75 to 99% clearing	Marked improvement: nearly normal skin texture; some erythema may be present.
3 = Good	50 to 74% clearing	Moderate improvement: plaque has cleared to point of small scattered papules with normal intervening epidermis.
4 = Fair	25 to 49% clearing	Slight improvement: decrease in scaling and softening of plaque.
5 = Poor	0 to 24% clearing	Little or no change in scaling, erythema, or plaque elevation.
6 = Worse		Worse

Appendix D: Dermatology Life Quality Index

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick ☑ one box for each question.

1.	Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	
2.	Over the last week, how **embarrassed** or **self-conscious** have you been because of your skin?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**? relevant ❒	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not
4.	Over the last week, how much has your skin influenced the **clothes** you wear? relevant ❒	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities? relevant ❒	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**? relevant ❒	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not
7.	Over the last week, has your skin prevented you from **working** or **studying**? relevant ❒	Yes No	❒ ❒	Not
	If "No", over the last week how much has your skin been a problem at **work** or **studying**?	A lot A little Not at all	❒ ❒ ❒	

8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒

Please check you have answered EVERY question. Thank you.

Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI): A simple practical measure for routine clinical use. Clinical and Experimental Dermatology 1994; 19: 210-216.

Appendix E: Clinical Symptom and Adverse Event Grading Scale

CLINICAL ADVERSE EVENT GRADING		
Severity	**Grade**	**Definition**
Mild	1	Awareness of symptom, but easily tolerated. Usually transient requiring no special treatment; does not interfere with usual status or activities
Moderate	2	May be ameliorated by simple therapeutic measures; may interfere with usual activities
Severe	3	Incapacitating; unable to perform usual activities
Life-threatening	4	Requires immediate intervention; need for emergency treatment
Death	5	Resulting in the subsequent death of the subject

Appendix F: Clinical Adverse Events: Determining Relationship to Study Drug

1 NOT RELATED

This category applies to those AEs which, after careful medical consideration, are clearly felt to be due to extraneous causes (disease, environment, etc.) that are unrelated to the administration of study drug.

2 UNLIKELY RELATED (must have first 2)

This category applies to those AEs which, after careful medical consideration, are felt unlikely to be related to the administration of the study drug. The relationship of an AE to the study drug can be considered unlikely if:

- It does not follow a reasonable temporal sequence from administration of the drug.
- It could readily have been a result of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject.
- It does not follow a known response pattern to the suspected drug.
- It does not reappear or worsen when the drug is re-administered.

3 POSSIBLY RELATED (must have first 2)

This category applies to those AEs which, after careful medical consideration, are felt unlikely to be related to the administration of the study drug, but the possibility cannot be ruled out with certainty. The relationship of an AE to the study drug can be considered possible if:

- It follows a reasonable temporal sequence from administration of the drug.
- It could readily have been a result of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject.
- It follows a known response pattern to the suspected drug.

4 PROBABLY RELATED (must have first 3)

This category applies to those AEs which, after careful medical consideration, are felt with a high degree of certainty to be related to the administration of the study drug. The relationship of an AE to the study drug can be considered probable if:

- It follows a reasonable temporal sequence from administration of the drug.
- It could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors or other modes of therapy administered to the subject.
- It disappears or decreases upon cessation of drug or reduction in dose.*
- It follows a known response pattern to the suspected drug.

5 **DEFINITELY RELATED** (must have first 3)

This category applies to those AEs, which, after careful medical consideration, are felt to be related to the administration of the study drug. The relationship of an AE to the study drug can be considered related if:

- It follows a reasonable temporal sequence from administration of the drug or drug levels have been established in body fluids or tissues.
- It could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors or other modes of therapy administered to the subject.
- It disappears or decreases upon cessation of drug or reduction on dose and appears upon rechallenge.*
- It follows a known response pattern to the suspected drug.

*There are exceptions when an AE does not disappear upon discontinuation of the drug, yet drug relatedness clearly exists.

Cobert, B. (2012). Cobert's Manual of Drug Safety and Pharmacovigilance (2nd ed.). Massachusetts: Jones & Bartlett Learning, LLC.

Appendix G: CYP3A4Inducersand inhibitors

Use of these drugs should be avoided in subjects who are receiving KD025 unless deemed clinically necessary (Flockhart 2007):

Inhibitor/Inducer	Drug Name
Inhibitors	indinavir[a] nelfinavir[a] ritonavir[a] clarithromycin[a] itraconazole[a] ketoconazole[a] nefazodone[a] erythromycin[b] grapefruit juice[b] verapamil[b] suboxone[b] diltiazem[b] cimetidine[c] amiodarone fluvoxamine troleandomycin voriconazole
Inducers	carbamazepine efavirenz nevirapine phenobarbital phenytoin pioglitazone rifabutin rifampin St. John's Wort troglitazone

a. A Strong inhibitor is one that causes a > 5-fold increase in the plasma AUC values or more than 80% decrease in clearance.
b. A Moderate inhibitor is one that causes a > 2-fold increase in the plasma AUC values or 50-80% decrease in clearance.
A Weak inhibitor is one that causes a > 1.25-fold but < 2-fold increase in the plasma AUC values or 20-50% decrease in clearance.