NCT02841995

CLINICAL STUDY PROTOCOL

A Phase 2a, Dose-Escalation, Open-Label Study to Evaluate the Safety, Tolerability, and Activity of KD025 in Subjects with Chronic Graft Versus Host Disease

Protocol Number:	KD025-208
Study Drug:	KD025
IND Number:	IND 125890
Phase	2a
Sponsor:	Kadmon Corporation 450 East 29th Street New York, NY 10016
Medical Monitor:	[redacted]
Date of Protocol:	Original, Final, 22 December 2015 Amendment No. 1, Final, 22 February 2016 Amendment No. 2, Final 14 July 2016 Amendment No. 3, Final 06 June 2017 Amendment No. 4, Final 19 October 2017 Amendment No. 4.1, Final 26 October 2017 Amendment No. 5, Final 29 May 2018 Amendment No. 6, Final 15 October 2018 Amendment No. 7, Final 28 October 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 28 days of receiving their 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:
APCER Life Sciences, LLC. Fax: 646-430-9549 In the event of an issue with the fax line, forward the SAE/SUSAR via email to: ClinicalSAEReporting@kadmon.com	[redacted]

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 16.3.1, 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 one of the outcomes listed above. ** A suspected unexpected serious adverse reaction (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 16.3.2, Suspected Unexpected Serious Adverse Reactions). All suspected adverse reactions related to an investigational medicinal product which occur in the concerned trial 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 Harmonization (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.

[redacted]

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 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.

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 2a, Dose-Escalation, Open-Label Study to Evaluate the Safety, Tolerability, and Activity of KD025 in Subjects with Chronic Graft Versus Host Disease
Clinical Phase	2a
Number of Study Centers	Approximately 10
Study Objective(s)	**Primary Objectives** • To evaluate the activity of KD025 in subjects with steroid-dependent chronic Graft versus Host Disease (GVHD) and active disease in terms of partial response (PR) and complete response (CR), as defined by the 2014 National Institute of Health (NIH) Consensus Development Project on clinical trials in cGVHD • To evaluate the safety and tolerability of KD025 in subjects with cGVHD **Secondary Objectives** • To evaluate changes in cGVHD severity using the Physician-reported Global cGVHD Activity Assessment form (see Appendix A) • To assess changes in symptom activity using the cGVHD Activity Assessment Patient Self-Report • To evaluate Failure-free Survival (FFS) • To evaluate changes in corticosteroid and calcineurin inhibitor (CNI) dose • To evaluate Duration of Response (DOR) • To evaluate response by organ system • To assess the plasma pharmacokinetics (PK) of KD025 in subjects with cGVHD • To evaluate Overall Survival (OS) • To evaluate Time to Next Treatment (TTNT) • To evaluate the change in symptom burden/bother using the Lee cGVHD Symptom Scale **Exploratory Objectives** • To evaluate changes in the expression of several cytokines (including interleukin (IL)-17A, IL-21, and IL-2) in plasma after KD025 administration • To evaluate changes in percentage of immune-cell subtypes (including Th17 and regulatory T cells [Treg] cells) in whole blood after KD025 administration

<table>
<tr><td>Study Design</td><td>Phase 2a, open-label, dose-escalation, safety, tolerability, and activity study</td></tr>
<tr><td>Methodology</td><td>Subjects who have signed an Institutional Review Board (IRB)/Independent Ethics Committee- (IEC)-approved informed consent form (ICF) and who have met all of the inclusion/exclusion criteria will be enrolled. Approximately 48 subjects will be enrolled to receive orally administered KD025 200 mg once daily (QD), KD025 200 mg twice daily (BID_, or KD025 400 mg QD. Study drug will be administered in 28-day cycles until disease progression or unacceptable toxicity occurs. Subjects may receive study drug in the inpatient or outpatient setting.
<table>
<tr><td>Cohort 1</td><td>16 subjects</td><td>200 mg KD025 QD</td></tr>
<tr><td>Cohort 2</td><td>16 subjects</td><td>200 mg KD025 BID</td></tr>
<tr><td>Cohort 3</td><td>16 subjects</td><td>400 mg KD025 QD</td></tr>
</table>
BID = twice daily; QD = once daily

Prior to enrolling subsequent cohorts, the safety data in each previous cohort will be evaluated after 8 subjects have reached 2 months of treatment to assure there is no safety signal. If ≥ 25% of subjects in a cohort experience a Common Terminology Criteria for Adverse Events (CTCAE) v4.03 Grade 2 liver toxicity or a CTCAE v4.03 Grade 3 (or higher) adverse event (AE) in the same organ or body system, or if > 25% of subjects in a cohort are discontinued for toxicity that persists for 14 days, then dose escalation to the next cohort will not occur, and all subjects in that dose cohort will be dose reduced.

If ≥ 25% of subjects in the 200 mg QD cohort experience a CTCAE v4.03 Grade 2 liver toxicity or a CTCAE v4.03 Grade 3 (or higher) AE in the same organ or body system, or if > 25% of subjects in a cohort are discontinued for toxicity that persists for 14 days, then further dosing will not occur and the study will be terminated.

Response criteria will be assessed on Day 1 of each cycle, starting at Cycle 2 Day 1, as well as the end of treatment (EOT) visit using the criteria of 2014 NIH Consensus Development Project on Clinical Trials in cGVHD (CR, PR, or lack of response (unchanged, mixed, or progression); see Appendix B).

cGVHD severity (clinician-reported) and symptom (subject-reported) assessments will be performed on Day 1 of each cycle starting at Cycle 1 Day 1 as well as the EOT visit using the Physician-reported Global Chronic GVHD Activity Assessment form (Appendix A), cGVHD Activity Assessment: Patient Self Report, and Lee cGVHD Symptom Scale (see Appendices C and D).

At Cycle 25 Day 1 (C25D1) and all odd cycles thereafter (ie, C27D1, C29D1, C31D1, etc.), subjects will receive 2 cycles worth of study drug along with 2 diaries and will return to the clinic at the next odd cycle for</td></tr>
</table>

	assessments and investigational product (IP) accountability. Investigators and/or subjects have the option of coming into the clinic at one or more even cycles (ie, C26D1, C28D1, C30D1, etc.). On even cycles, when subjects do not come to clinic, the study staff will contact the patient via phone and document any new adverse events and concomitant medications. Subjects will also undergo pre-specified safety assessments throughout the study. **Follow-Up Period** Follow-Up visits will occur 28 days (± 7 days) after the last dose of study drug. Subjects will undergo physical examinations (PEs); vital sign measurements; blood sample collection for hematology, chemistry, and pharmacodynamic (PD) markers; urinalysis; ECGs; AE assessments; concomitant medication assessments; and pregnancy testing for females of childbearing potential. **Long-Term Follow-Up** Subjects will be contacted approximately every 8 weeks and can be contacted via telephone, email, or postal mail to confirm survival status and the initiation of any anti-cancer treatment or any changes in treatment of cGVHD. This can also be confirmed from electronic medical records.
Number of Subjects	Approximately 48 subjects (adult male and female) total will be enrolled (16 subjects in each KD025 dose cohort).
Approximate Duration of Subject Participation	After approximately 3 weeks for screening, study drug will be administered in 28-day cycles until disease progression or unacceptable toxicity occurs followed by 4 weeks of follow-up. Subjects will be contacted approximately every 8 weeks and can be contacted via telephone, email or postal mail to confirm survival status and the initiation of any anti-cancer treatment or any changes in treatment of cGVHD. This can also be confirmed from electronic medical records
Diagnosis and Main Criteria for Inclusion	**Inclusion Criteria:** 1) Adult male and female subjects at least 18 years of age who have had allogenic bone marrow transplant or hematopoietic stem cell transplantation. 2) Receiving glucocorticoid therapy and calcineurin therapy or glucocorticoid therapy alone for cGVHD at study entry. Subjects on calcineurin therapy only, without glucocorticoid therapy, are not eligible. Subjects also receiving other therapies thought not to be immunosuppressive (such as extracorporeal photopheresis [ECP]), will be considered for enrollment in this study on a case-by-case basis. 3) Have persistent active cGVHD manifestations, as defined by 2014 NIH Consensus Development Project on Criteria for Clinical Trials in cGVHD, after at least 2 months of steroid therapy. 4) No more than 3 prior lines of treatment for cGVHD. 5) Karnofsky Performance Scale of >40 (see Appendix E). 6) Adequate organ and bone marrow functions evaluated during the

	14 days prior to enrollment as follows: a. Absolute neutrophil count ≥ 1.5 × 10^9/L (without myeloid growth factors within 1 week of study entry) b. Platelet count ≥ 50 × 10^9/L (without transfusion or thrombopoietin or thrombopoietin analogues within 2 weeks of study entry) 7) Adequate safety laboratory values: a. Total bilirubin ≤ 1.5 × upper limit of normal (ULN) b. ALT and AST ≤ 3 × ULN c. Glomerular filtration rate (GFR) ≥ 30 mL/min/1.73 m^2 using the 4-Variable Modification of Diet in Renal Disease (MDRD-4) variable formula (see Appendix F) 8) 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 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. 9) Women of childbearing potential (ie, 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. 10) 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 1 barrier method; b. Stable doses of hormonal contraception for at least 3 months (eg, 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 11) For male subjects who are sexually active and who are partners of premenopausal women: agreement to use two forms of contraception as in criterion 10 above during the treatment period and for at least 3 months after the last dose of study drug. **12)** Able to provide written informed consent prior to the performance of any study-specific procedures. **Exclusion Criteria:** 1) Female subject who is pregnant or breastfeeding. 2) Receiving an investigational GVHD treatment within 28 days of study entry. 3) Has acute GVHD. 4) Taking any medication known to be a moderate or strong inhibitor of the CYP3A4 isozyme or any drugs that are moderate or strong

	CYP3A4 inducers (see Appendix H). 5) 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 (such as poorly controlled psychiatric disease or coronary artery disease). 6) Regular and excessive use of alcohol within the 6 months 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. 7) Known history of human immunodeficiency virus (HIV) or active hepatitis C virus (HCV) or hepatitis B virus (HBV). 8) Diagnosed with another malignancy (other than malignancy for which transplant was performed) within 3 years of enrollment, with the exception of completely resected basal cell or squamous cell carcinoma of the skin, resected in situ cervical malignancy, resected breast ductal carcinoma in situ, or low-risk prostate cancer after curative resection. 9) Relapse of the underlying cancer or post-transplant lymphoproliferative disease at the time of screening. 10) Has had previous exposure to KD025 or known allergy/sensitivity to KD025 or any other ROCK2 inhibitor. 11) Taking other immunosuppressant drugs for GVHD, including mTOR (mammalian target of rapamycin) inhibitors (Note: Only steroids, CNIs, and ECP are acceptable). 12) QTcF > 450 msec
Investigational Product/Study Drug	KD025 will be provided as 100 mg capsules or 200 mg tablets.
Dosage and Administration	Subjects will receive KD025 200 mg QD, KD025 200 mg BID, or KD025 400 mg QD. Subjects should take study drug with a meal or within 5 minutes of completing a meal.
Duration of Treatment	Study drug will be administered in 28-day cycles until disease progression or unacceptable toxicity occurs.
Concomitant Treatment	Subjects will be counseled to avoid non-prescribed medicines or complementary alternative medicines excluded by the study. Use of drugs that prolong QT/QTc should be used with caution in subjects who are receiving KD025. All medications a subject receives from the signing of informed consent through the 28-Day Follow-Up visit will be documented, including steroids and CNIs. **Prohibited Medications** The use of strong CYP3A4 inducers (see Appendix H for a listing of these drugs) is prohibited.
Safety Evaluation	Safety assessments include AEs, serious adverse events (SAEs), PEs, vital sign measurements, clinical laboratory evaluations (hematology, chemistry, and urinalysis), pulmonary function tests (PFTs), and ECGs.

	Prior to enrolling subsequent cohorts, the safety data in each previous cohort will be evaluated after 8 subjects have reached 2 months of treatment to assure there is no safety signal. Two months was selected as the time for the safety review because all of the clinically significant KD025-related AEs to date occurred within 36 days or less of starting KD025 treatment. The AE reporting period for a subject enrolled in the study begins when the subject provides informed consent and is continued through 28 days after their last dose of study drug. All AEs that occur in enrolled subjects during the AE reporting period must be recorded, 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 at least possibly related to study drug also should be reported to Kadmon. A Follow-Up Visit will occur 28 days after the last dose of study drug, but prior to starting on a new therapy if a new therapy is started earlier. This visit may be done within ± 7 days of the scheduled visit. Exacerbation of any of the signs or symptoms of the disease will constitute a potential rationale for cessation of therapy. Both laboratory and clinical data may constitute a reason to pause or cease therapy. Previous studies have indicated that reversible and modest liver toxicity may occur spontaneously after a few weeks of initiation of therapy. • When treatment-related Grade 3 toxicities occur, drug administration will be halted until recovery to at least Grade 1, and study drug may be resumed at a reduced dose. • When treatment-related Grade 2 toxicities other than liver toxicities that cannot definitively be attributed to a cause other than the study drug occur, drug administration will be halted until recovery to at least Grade 1 at which time study drug administration may resume at the same dose. • When greater than Grade 2 liver toxicities occur, drug administration will be halted until recovery to at least Grade 1 at which time study drug administration may resume at a reduced dose. Pauses in therapy may not last more than 14 days; subjects requiring pauses of more than 14 days will be discontinued from the study. If Grade 2 or 3 treatment-related toxicities persist for 14 days, subjects will be discontinued from the study. Other organ-based toxicity has not been observed in clinical studies with KD025, but as this is the first study in cGVHD, careful monitoring of all toxicities will be carried out. CTCAE v4.03 grading will be used for all AEs.
Activity Evaluation	The primary activity outcome will be the percentage of subjects who meet the overall response (OR) criteria (PR + CR). This will be assessed overall (ie, any subject meeting the PR or CR criteria at any time point). Response criteria and activity in terms of cGVHD severity will be evaluated on Day 1 of each cycle starting at Cycle 2 Day 1 using the Physician-reported Global Chronic GVHD Activity Assessment Form, while activity in terms of symptom burden will be evaluated using the

	cGVHD Activity Assessment—Patient Self-report. Failure-free survival, Overall Survival, TTNT, and changes in corticosteroid and CNI dose will be documented. Changes in symptom burden/bother will be documented using the Lee cGVHD Symptom Scale. Compliance with oral dosing will be confirmed using patient diaries.
Pharmacokinetics	Blood samples (approximately 5 mL) for determination of plasma concentrations of KD025 and its metabolites, will be collected on Day 1 of Cycles 1 and 2 at the following time points: Pre-dose (Time 0), and 1, 2, 3, 4, 5, and 6 hours after dosing (after first dose for subjects in the BID group). In addition, subjects will have samples collected pre-dose on Day 1 of Cycle 4 and pre-dose at the Cycle 7, Day 1 visit. Subjects should be instructed to withhold taking study drug on these days as dosing will be performed at the clinic. Subjects will have a total 16 samples drawn (80 mL). KD025 and metabolite concentrations will be used to calculate the following PK parameters: C_{max}, T_{max}, and $AUC_{0\text{-}6hr}$.
Pharmacodynamics	All subjects will have PD blood samples drawn 4 times over the course of the study: Pre-dose on Cycle 1 Day 1, Cycle 2 Day 1 (4 weeks), Cycle 4 Day 1 (12 weeks) and Cycle 7 Day 1 (24 weeks). The samples will be analyzed to evaluate changes in the expression of several cytokines in plasma (including IL-17A, IL-21, and IL-2), and changes in percentages of circulating Th17 and Treg cells in blood.
Statistical Analysis	Four populations will be included in the analysis of study data: • The modified intent-to-treat (mITT) population will consist of all subjects who are enrolled in the study and receive at least 1 dose of study medication. • The safety population will consist of all subjects who receive at least one dose of KD025 • The PK population will consist of all subjects who receive at least 1 dose of study drug and have at least 1 post-dose PK sample drawn All analyses of safety will be performed on the safety population while activity will be performed on the mITT population. The primary activity outcome will be the percentage of subjects who meet the OR criteria (PR + CR). This will be assessed overall (ie, any subject meeting the PR or CR criteria at any time point). Assuming an underlying 25% rate for subjects to meet the OR, each treatment group of 16 subjects has an approximately 80% chance of having at least 3 subjects meet the overall response criteria, and approximately 90% chance of at least 2 subjects meet the overall response criteria. The change in cGVHD severity will be evaluated using the Physician-reported Global cGVHD Activity Assessment form. The change in symptom burden will be evaluated using the cGVHD Activity Assessment - Patient Self-report. Changes in symptom burden/bother will be documented using the Lee cGVHD Symptom Scale and compared among KD025 treatment groups.

	The FFS will be defined as the time from first dose of study drug to either the start of another treatment, relapse of the underlying disease, or death. The time to FFS will be summarized for each treatment group. The OS will be defined as the time from first dose of KD025 to the date of death due to any cause. Kaplan-Meier plots, descriptive statistics of OS and landmark OS at 6, 12, 18 and 24 months will be provided. The TTNT will be defined as the time from the first dose of KD025 to the start of additional systemic cGVHD therapy. Changes in corticosteroid and CNI dose will be evaluated and results will be summarized by treatment group. Corticosteroids may be tapered at the discretion of the investigator after 4 weeks of KD025 administration. The DOR is defined as the time of initial response until documented progression. Responses by organ system (PR and CR) will be assessed based on the 2014 NIH Consensus Development Project on Clinical Trials in cGVHD. The exploratory outcome variables are expression of several cytokines (including IL-17A, IL-21, and IL-2), and changes in percentages of immune-cell subtypes (including Th17 and Treg cells). Results will be summarized by treatment group. Demographics, subject disposition, and screening and baseline characteristics will be summarized overall and by treatment group. Treatment-emergent AEs will be evaluated using the CTCAE v4.03. The secondary safety outcome will be the number (%) of subjects experiencing AEs overall. The total sample size of 16 subjects per KD025 dose group will provide > 90% probability of one or more KD025 subjects experiencing an AE that has an underlying rate of ≥ 14% and > 80% probability of one or more subjects in the study experiencing an AE that has an underlying rate of ≥ 10%. Treatment-emergent AEs (TEAEs) will be summarized by treatment group using Medical Dictionary for Regulatory Activities (MedDRA®) System Organ Class (SOC) and preferred term (PT), classified from verbatim terms. MedDRA® Version 20.0 or higher will be used. 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, treatment-related AEs, treatment-related SAEs, ≥ Grade 3 AEs, treatment-related ≥ Grade 3 AEs, and AEs leading to withdrawal or treatment discontinuation will be summarized overall and by treatment group according to SOC and PT. 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 CTCAE v4.03 and summarized by treatment group. Incidence of laboratory abnormalities will be summarized. The worst on-study grade after the first dose of study drug will be summarized. 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 and ECGs will be summarized by treatment group at each scheduled time point using descriptive statistics and included in data listings.

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3. LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
$AUC_{0\text{-}24hr}$	area under the curve from 0 to 24 hours
BID	twice daily
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
cGVHD	chronic graft versus host disease
C_{max}	maximum concentration observed
CNI	calcineurin inhibitor
CPK	creatinine phosphokinase
CR	complete response
CTCAE	Common Terminology Criteria for Adverse Events
DOR	Duration of Response
D_{LCO}	diffusing capacity of carbon monoxide
ECG	electrocardiogram
ECP	extracorporeal photopheresis
eCRF	electronic case report form
EOT	End of Treatment
FDA	Food and Drug Administration
FEV_1	forced expiratory volume (in the first second)
FFS	failure-free survival
FVC	forced vital capacity
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GFR	glomerular filtration rate
HBV	hepatitis B virus
HCT	hematopoietic cell transplantation
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HSCT	hematopoietic stem cell transplantation
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Committee on Harmonisation
IEC	Independent Ethics Committee

IL	interleukin
IND	Investigational New Drug
IP	investigational product
IRB	institutional review board
LFT	liver function tests
LOR	lack of response
MAD	multiple ascending dose
MDRD-4	4-Variable Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
mTOR	Mammalian target of rapamycin
NIH	National Institutes of Health
OR	Overall Response
ORR	Overall Response Rate
OS	Overall Survival
PD	pharmacodynamic
PE	physical examination
PFT	pulmonary function test
PK	pharmacokinetic
PR	partial response
QD	once daily
QTc(F)	corrected QT interval using Fridericia's formula
ROCK	Rho-associated protein kinase
RV	residual volume
SAD	single ascending dose
SAE	serious adverse event
SD	stable disease
SOC	system organ class
SUSAR	suspected unexpected serious adverse event
$t_{1/2}$	half-life
T_{max}	observed time to reach peak plasma concentration
TEAE	treatment-emergent adverse event
TLC	total lung capacity
Treg	regulatory T cells
TSH	thyroid stimulating hormone
TTNT	Time to Next Treatment
ULN	upper limit of normal
WHO	World Health Organization

WHO-DD	World Health Organization Drug Dictionary

4. BACKGROUND AND RATIONALE

Chronic graft versus host disease (cGVHD) remains a major complication of allogeneic hematopoietic cell transplantation (HCT) occurring in approximately 50% of transplant recipients and involving multiple organs. Patients with cGVHD require prolonged immunosuppressive treatment for an average of 2 to 3 years from the initial diagnosis, with 10% of those surviving for at least 7 years still requiring immunosuppressive treatment at that time and beyond. Glucocorticoids, with or without CNIs, remain the standard initial treatment, but significant side effects and unsatisfactory outcomes, particularly for patients with high-risk features of cGVHD, support the need for more effective and less toxic therapies.

4.1. Study Rationale

Recent studies have demonstrated that a pro-inflammatory interleukin (IL)-17-producing lineage of T cells termed Th17 is actively involved in the pathogenesis of cGVHD. The development and function of Th17 cells is dependent on activation of STAT3, and transcription factors RORγt and IRF4. Recent studies have demonstrated that aberrant activation of Rho-associated protein kinases 2 (ROCK2) leads to induction of IL-17 and IL-21 via the IRF4-dependent mechanism. Moreover, inhibition of ROCK effectively decreased IL-17 production in vivo and ameliorated the development of autoimmune models of arthritis, diabetes and lupus in mice. In addition, patients with cGVHD have a relative deficiency of regulatory T-cells (Treg). This deficiency appears to be a consequence of abnormalities in Treg homeostasis after HCT wherein increased proliferation of Tregs is not sufficient to compensate for reduced thymic output and increased susceptibility to apoptosis. Recent in vitro data indicate that KD025, a specific ROCK2 inhibitor, significantly reduced the production of IL-17 and IL-21 in CD4+ T cells in response to T cell receptor stimulation and positively regulated the suppressive function of Treg. Experiments in a mouse model of cGVHD show that KD025 can reverse lung pathology and improve pulmonary function tests (PFTs), decrease collagen deposited in the lungs, and decrease the number of germinal centers and frequency of T follicular helper cells in spleens. In a second rodent model, KD025 administration was effective in blocking the progression of chronic sclerodermatous GVHD. Thus, this study will evaluate the potential of KD025 to ameliorate the symptoms of cGVHD.

4.2. Selection of Doses in this Study

This study will evaluate KD025 at doses of 200 mg once daily (QD), KD025 200 mg twice daily (BID), and KD025 400 mg QD. Preliminary data from an ongoing study of KD025 in patients with psoriasis suggest that the dose of 400 mg QD for 12 weeks is associated with clinical efficacy in psoriasis and is well tolerated.

KD025 has a plasma elimination half-life of 5-6 hours, indicating BID dosing may be necessary for more consistent inhibition of ROCK2 in patients throughout a 24-hour period, but whether BID dosing is more effective than QD dosing is unknown. Thus, the optimal dosing frequency for KD025 will be examined in this study by enrolling subjects in the two cohorts 200 mg BID and 400 mg QD. Safety data from prior studies in healthy human volunteers evaluating doses of 500 mg BID for 28 days support the use of 400 mg QD in this study.

The Investigator's Brochure (IB) includes additional nonclinical and clinical information about KD025.

4.3. Previous Clinical Experience with KD025

To date, there have been 6 Phase 1 trials conducted with KD025 in normal healthy subjects: a single-ascending dose (SAD) trial (2119-09-01), a combined single- and multiple-ascending dose (SAD/MAD) trial (KD025-101), a MAD trial with QD and BID dosing (KD025-102), a placebo-controlled safety and pharmacokinetic (PK) study (KD025-103), a food effect study (KD025-105), and a PK study (KD025-106) which compared a tablet formation with capsule formulation of KD025 (final data showed that after a single dose of KD025 200 mg, KD025 was rapidly absorbed with no lag time observed under both fasted and fed states and no statistically significant differences were observed between tablet and capsule formulation under fed conditions). A Phase 2a, open-label study in 8 adult subjects with moderately severe psoriasis vulgaris who have failed first-line therapy was recently completed (KD025-205). Additionally, a Phase 2 open-label, safety, and tolerability study in subjects with psoriasis vulgaris who have disease progression after 1 systemic therapy is currently on-going (KD025-206).

The SAD trial (SLx-2119-09-01) assessed the safety, tolerability, and PK of KD025. The dose levels of KD025 tested were 20, 40, 80, and 160 mg. Thirty-two subjects were enrolled in 4 sequential cohorts of 8 subjects, randomized with 6 receiving drug and 2 receiving placebo in

each cohort. No treatment-emergent adverse events (TEAEs) leading to withdrawal, deaths, or serious adverse events (SAEs) were reported in this trial. There were 14 TEAEs reported, 9 of which were determined by the investigator to be related to study drug and were mild in severity. One subject at the 160-mg KD025 dose level experienced joint swelling and arthralgia occurring after the follow-up visit. No subject had laboratory abnormalities during the dosing period or within 1 week after dosing. There were no changes in blood pressure or heart rate and no clinically significant QTcB or corrected QT interval using Fridericia's formula (QTc[F]) parameters.

KD025 was readily absorbed and was measured out to 24 hours in plasma. KD025 was the main analyte (> 90% parent derived area under the curve [AUC]) and KD025m2 was present at about 5%, with KD025m1 < 1%. The half-life ($t_{1/2}$) of KD025 was approximately 5–6 hours, supporting once- or twice-daily dosing.

A combined SAD/MAD (KD025-101) trial assessed the safety, tolerability, and PK of KD025 in healthy males with single doses followed by 1 week of rest and then 7 consecutive days of dosing. There were 8 cohorts with 8 subjects in each cohort. For each dosing cohort, 6 subjects received KD025 and 2 subjects received placebo. The dose levels studied were 40, 80, 120, 160, 240, 320, 400, and 500 mg. Few TEAEs were reported and of those reported, the majority were determined by the investigator to be mild in severity. There were no SAEs reported during the study. One subject (No. 50008) was withdrawn because of a TEAE that was considered not related to KD025 (elevated blood creatinine phosphokinase [CPK] levels of moderate intensity).

No clinically relevant clinical chemistry (apart from elevated [CPK] discussed above), hematology, coagulation, or urinalysis abnormalities were reported for any of the subjects. No clinically significant abnormalities were reported for any vital signs (systolic or diastolic blood pressure, or heart rate) or 12-lead electrocardiogram (ECG) parameters and no subject had an abnormal physical examination (PE) finding of concern.

A MAD trial (KD025-102) was a single-center, placebo-controlled, double-blind, randomized (6:2) study to assess the safety, tolerability, and PK of KD025 administered for 7 days in up to 32 healthy male and postmenopausal female subjects. This study enrolled 4 cohorts with 8 subjects in each cohort (6 subjects received KD025 and 2 subjects received placebo). The dose regimens studied were 500, 800, and 1000 mg administered QD, and 500 mg administered BID.

All 32 subjects received at least 1 dose of study drug, and 31 subjects completed the study; all 24 subjects completed all doses of study drug at 500 and 800 mg QD, and 500 mg BID. Seven of 8 subjects completed all doses of study drug at 1000 mg QD. One subject randomized to active study drug 1000 mg QD received 6 days of study drug before being discontinued because of a positive urine drug test.

Multiple escalating doses of KD025 ranging from 500 mg to 800 mg to 1000 mg QD and 500 mg BID for 7 days were generally well tolerated and no dose-limiting toxicities were reported in this study. Five treatment-related adverse events (AEs) were reported in 4 subjects (16.7%) receiving KD025, including upper abdominal pain and diarrhea in 1 subject receiving 500 mg QD, nausea in 2 subjects receiving 500 mg BID, and diarrhea in 1 subject receiving 1000 mg QD. There was 1 treatment-related AE of diarrhea in 1 subject (12.5%) receiving placebo. There were no treatment-related AEs in subjects receiving KD025 800 mg QD. No subjects discontinued study participation because of AEs. 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. There were no SAEs or deaths.

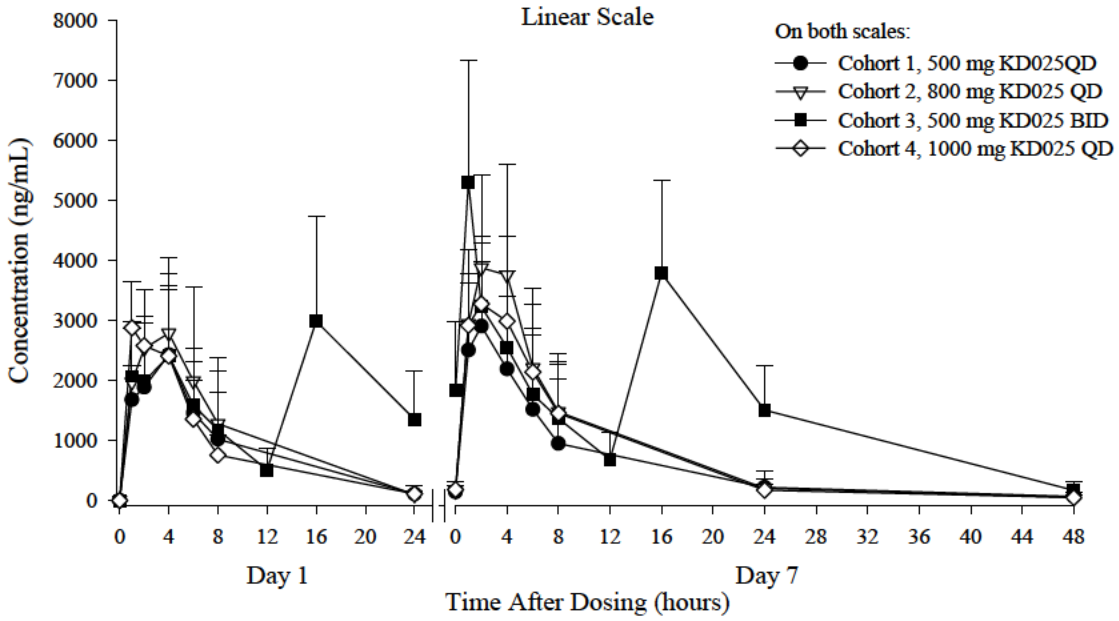
The following are PK conclusions from this study:

- KD025 was rapidly absorbed after QD oral dose administration with median observed time to reach peak plasma concentration (T_{max}) values ranging from 1.0 to 4.0 hours post-dose.
- Median T_{max} values after BID dosing were more variable and ranged from 4.0 hours after the first dose to 12.0 hours after the second dose.
- Mean $t_{1/2}$ values were similar across dose levels for each day, with values ranging from 4.55 to 5.76 hours for Day 1 and from 7.68 to 9.73 hours for Day 7.
- Mean KD025 maximum concentration observed (C_{max}) and area under the curve from 0 to 24 hours ($AUC_{0\text{-}24hr}$)values generally increased in a less than dose proportional manner with the increase in QD dose level from 500 to 1000 mg.
- Overall exposure ($AUC_{0\text{-}24hr}$) following BID dose administration of 500 mg of KD025 was 1.9- to 2-fold higher than the $AUC_{0\text{-}24hr}$ after QD dose administration of 1000 mg

KD025 and 2- to 2.3-fold higher than the $AUC_{0\text{-}24hr}$ following QD dose administration of 500 mg KD025.

- Possible accumulation of KD025 was observed after multiple doses.

Figure 1: Mean (±SD) Concentration-Time Profiles for KD025 following QD or BID Oral Dosing of KD025 for 7 Days (KD025-102)



BID = twice daily; QD = once daily

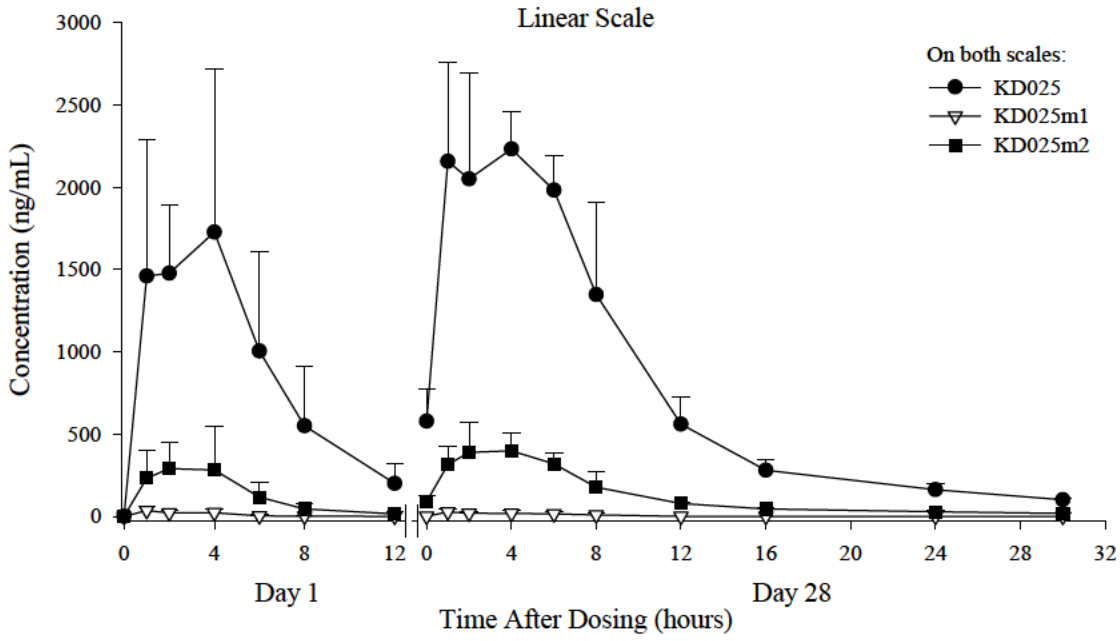
KD025-103 was a Phase 1, placebo-controlled study examining the safety, tolerability, and PK of 500 mg of KD025 administered BID for 28 days in healthy male and postmenopausal female subjects. KD025 500 mg, administered BID for up to 28 days was generally well tolerated. A total of 6 AEs were reported in 4 of the 6 subjects receiving KD025; there were no AEs reported in the 2 subjects receiving placebo. The most common TEAEs were hepatic enzyme elevation reported in 3 of 6 (50%) subjects receiving KD025 (of which 2 were determined to be possibly related to KD025). The AEs of increased liver enzymes were grades 1 or 2 in severity (1 was because of alcohol ingestion), and all resolved within 15 days of discontinuation with KD025. Other AEs reported in subjects receiving KD025 included nasopharyngitis in 1 subject and upper abdominal pain (stomach cramping) in 1 subject. All AEs, except nasopharyngitis, were considered at least possibly related to study drug. All AEs were mild in intensity, except for the

alanine aminotransferase (ALT) elevation in 1 subject, which was grade 2 in intensity. This subject was discontinued from the study due to the ALT elevation. There were no SAEs or deaths reported in this study.

The following are PK conclusions from this study:

- KD025 was rapidly absorbed after oral dose administration with median T_{max} values of 3.0 and 2.0 hours post-dose on Days 1 and 28, respectively.
- Possible accumulation of KD025 was observed after multiple doses.
- Two metabolites (KD025m1 and KD025m2) rapidly appeared in plasma and were readily eliminated. No accumulation of KD025m1 was observed after multiple doses, while potential accumulation of KD025m2 was observed after multiple dosing. KD025 was metabolized to KD025m2 more extensively than to KD025m1.

Figure 2: Arithmetic Mean (±SD) Concentration-Time Profiles for KD025, KD025m1, and KD025m2 following BID Oral Dosing of KD025 (500 mg) for 28 Days (KD025-103)



BID = twice daily; SD = standard deviation

The food effect study (KD025-105) was a single-dose, 2-period, crossover study to examine the safety and PK of KD025 in 12 healthy male subjects in the fed and fasted states. The dose level

was 500 mg. There were no TEAEs, no treatment-related AEs, SAEs, or deaths reported in this study.

The following are PK conclusions from this study:

- A high fat meal given 30 minutes prior to KD025 oral administration had a significant effect on the PK of KD025.
- Plasma systemic exposure (C_{max} and AUCs) of KD025 was approximately 3–fold higher under the fed state compared with the fasted state, and the median T_{max} value was delayed by 2 hours with food.
- Similar food effects were observed for metabolites KD025m1 and KD025m2 as for the parent drug.
- The high fat meal increased systemic exposure (mean C_{max} and AUC_{0-t} values) by approximately 1.7- to 2.3-fold for metabolite KD025m1 and approximately 3.1- to 4.4-fold for metabolite KD025m2 compared with the fasted treatment.

Recently completed, KD025-205 was a Phase 2a, open-label study in 8 adult subjects with moderately severe psoriasis vulgaris who had failed first-line therapy. The study evaluated the safety and tolerability of 200 mg KD025 daily for 28 days. Efficacy and activity measures included the evaluation of any decreases in Psoriasis Area and Severity Index in at least 50% of the subjects after 4 weeks of dosing with 200 mg of KD025 and improvement in the Physicians Global Assessment for psoriasis. Cytokine levels and expression associated with psoriasis were evaluated in pharmacodynamic (PD) whole blood samples and punch biopsies of selected lesions, respectively, collected at baseline and at the end of treatment. Eight subjects began treatment with KD025. Five SAEs were reported in this study and all 5 occurred in the same subject: Subject 001-008 experienced Grade 2 vomiting (2 events), Grade 2 nausea (2 events), Grade 3 anastomotic ulcer (related to the subject's previous gastric bypass surgery), and Grade 3 kidney stones, none of which were assessed to be related to study drug (she was subsequently discontinued after 20 days of dosing). Another subject experienced reversible grade 1 elevated ALT and aspartate aminotransferase (AST) on Day 22 with no known etiology and permanently discontinued treatment with KD025. The ALT/AST returned to normal levels 13 days after the last dose of KD025. No other TEAEs or SAEs were reported.

Follow-up for efficacy and activity measures in this study has completed. The following PK conclusions can be made for this study:

- KD025 was rapidly absorbed after oral dose administration with median T_{max} values of 2.0 hours and 4.0 hours post-dose on Days 1 and 28, respectively.
- Mean $t_{½}$ for KD025 was 6.08 hours and 5.27 hours on Days 1 and 28, respectively.
- Two metabolites (KD025m1 and KD025m2) rapidly appeared in plasma and were readily eliminated. No accumulation of either metabolite was apparent after multiple doses.

Exposure of daily dosing at 200 mg for 28 days was comparable to or slightly lower than that observed in study KD025-101 for daily dosing at similar dose levels.

KD025-206 is an ongoing Phase 2, open-label, safety and tolerability study of KD025 in subjects with psoriasis vulgaris who have disease progression after at least 1 systemic therapy. The primary objective is to evaluate the safety and tolerability of 3 daily dosing regimens (200 mg BID, 400 mg QD, and 400 mg BID) of KD025 in subjects with psoriasis vulgaris who have progressed despite first-line therapy. To date, preliminary safety data are available on 10 subjects who received KD025 at a dose of 200 mg BID, and 10 subjects who received KD025 at a dose of 400 mg QD. All subjects had normal ALT and AST values during screening. Four subjects (3 subjects receiving 200 mg BID and 1 subject receiving 400 mg QD) had TEAEs of elevation of ALT or AST. Bilirubin levels remained normal, and all ALT or AST increases were asymptomatic and reversible. The ALT and AST elevations first occurred from study Day 16 to study Day 36. The ALT/AST elevations were mild or moderate in intensity, except in 1 subject who had severe (grade 3) ALT elevation to a maximum of 377 U/L. KD025 administration was discontinued in 3 subjects, and ALT and AST levels decreased. One subject, who was receiving KD025 400 mg QD, had peak ALT of 121 U/L and AST of 127 U/L that then returned to the normal range despite continuing to receive KD025 400 mg QD. The data from these subjects suggest that increases in ALT and AST are modest and may be reversible despite the continuation of KD025.

4.4. KD025 Nonclinical Toxicology

To date, Good Laboratory Practice compliant general toxicology/toxicokinetic studies of acute, subchronic (1 and 3 month), and chronic (6-month rat and 9-month dog) duration have been

completed in rats and dogs. In addition, safety pharmacology studies have been completed evaluating central nervous system and respiratory (rat), and cardiovascular (dog) function. Furthermore, KD025 is not considered genotoxic or mutagenic based on a panel of studies. Developmental and reproductive toxicology studies (rat and rabbit embryo-fetal [segment 2] and rat fertility) have also been completed.

Study details and potential clinically-relevant findings from these studies are summarized in the IB.

4.5. Compliance Statement

This study will be conducted in compliance with Good Clinical Practice (GCP), including ICH of Technical Requirements for Registration of Pharmaceuticals for Human Use, 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) before implementation.

Freely given written informed consent must be obtained from every subject before participation in this clinical trial. 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 trial will be qualified by education, training, and experience to perform their respective task(s). This trial will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct of fraud (eg, loss of medical licensure, debarment).

5. STUDY OBJECTIVES

5.1. Primary Objectives

The primary objectives of the study are:

- To evaluate the activity of KD025 in subjects with steroid-dependent cGVHD and active disease in terms of partial response (PR) and complete response (CR) as defined by the 2014 National Institute of Health (NIH) Consensus Development Project on clinical trials in cGVHD
- To evaluate the safety and tolerability of KD025 in subjects with cGVHD

5.2. Secondary Objectives

The secondary objectives of the study are:

- To evaluate changes in cGVHD severity using the Physician-reported global cGVHD Activity Assessment form (see Appendix A)
- To assess changes in symptom activity using the cGVHD Activity Assessment Patient Self-Report
- To evaluate Failure-free Survival (FFS)
- To evaluate changes in corticosteroid and CNI dose
- To evaluate Duration of Response (DOR)
- To evaluate response by organ system
- To assess the plasma PK of KD025 in subjects with cGVHD
- To evaluate Overall Survival (OS)
- To evaluate Time to Next Treatment (TTNT)
- To evaluate the change in symptom burden/bother using the Lee cGVHD Symptom Scale

5.3. Exploratory Objective

The exploratory objectives of the study are:

- To evaluate changes in the expression of several cytokines (including IL-17A, IL-21, and IL-2) in plasma after KD025 administration

- To evaluate changes in percentage of immune-cell subtypes (including Th17 and Treg cells) in whole blood after KD025 administration

6. STUDY DESIGN

6.1. Study Sites

This study will be conducted at approximately 10 sites in the United States.

6.2. Study Endpoints

Primary Endpoint

The primary activity outcome will be the percentage of subjects who meet the Overall Response Rate criteria (PR + CR). This will be assessed overall (ie, any subject meeting the PR or CR criteria at any time point).

Secondary Endpoints

- Number and percentage of KD025 in subjects with steroid-dependent cGVHD who have a best response of PR or CR
- Change in cGVHD severity as based on the Physician-reported global cGVHD Activity Assessment
- Change in symptom activity as based on cGVHD Activity Assessment Patient Self-Report
- Median FFS
- Changes in corticosteroid and CNI dose
- DOR
- Response rate by organ system
- Analyses of plasma PK of KD025 in subjects with cGVHD
- OS
- TTNT
- Change in symptom burden/bother using the Lee cGVHD Symptom Scale

Exploratory Endpoints

- Changes in the expression of several cytokines (including IL-17A, IL-21, and IL-2) in plasma after KD025 administration to subjects with cGVHD
- Changes in percentage of immune-cell subtypes (including Th17 and Treg cells) in whole blood after KD025 administration to subjects with cGVHD

Further details on the statistical and analytical plan for these endpoints are available in Section 17.

6.3. Overview of Study Design

This is a Phase 2a, dose-escalation, open-label study designed to evaluate the safety, tolerability, and activity of KD025 in subjects with steroid-dependent cGVHD and active disease in terms of PR and CR as defined by the 2014 NIH Consensus Development Project on clinical trials in cGVHD (see Appendix B). This study also is designed to use the Physician-reported global cGVHD Activity Assessment to evaluate cGVHD severity; use the cGVHD Activity Assessment Patient Self-Report to assess symptom activity (see Appendix C); evaluate FFS; evaluate OS; assess changes in corticosteroid and calcineurin inhibitor (CNI) dose; evaluate TTNT; and assess the PK of KD025 in subjects with cGVHD. Changes in symptom burden/bother will be documented using the Lee cGVHD Symptom Scale (see Appendix D). Changes in the expression of several cytokines (including IL-17A, IL-21, and IL-2) in plasma and percentages of immune-cell subtypes (including Th17 and Treg cells) in whole blood after KD025 administration to subjects with cGVHD.

Subjects who have signed an IRB/IEC-approved informed consent form, and met all of the inclusion/exclusion criteria (Section 7.2 and 7.3), will be enrolled. Approximately 48 subjects will receive orally administered KD025 200 mg QD (n = 16), KD025 200 mg BID (n = 16), or KD025 400 mg QD (n = 16). Study drug will be administered in 28-day cycles until disease progression or unacceptable toxicity occurs. For disease progression, subjects with a "Lack of Response (LOR) – Mixed" response assessment (Appendix B) may continue treatment with KD025 and remain on study if the investigator considers continued treatment to be in the subject's best interest, only after approval from the medical monitor and documentation of the subject's willingness to continue. Subjects may receive study drug treatment either in the inpatient or outpatient setting.

Prior to enrolling subsequent cohorts, the safety data in each previous cohort will be evaluated after 8 subjects have reached 2 months of treatment to assure there is no safety signal. As this is an open-label study, safety data will be continuously monitered. If ≥ 25% of subjects in a cohort experience a Common Terminology Criteria for Adverse Events (CTCAE) v4.03 Grade 2 liver toxicity or a CTCAE v4.03 Grade 3 (or higher) AE in the same organ or body system, or if

> 25% of subjects in a cohort are discontinued for toxicity that persists for 14 days, then dose escalation to the next cohort will not occur, and all subjects in that dose cohort will be dose reduced.

If ≥ 25% of subjects in the 200 mg QD cohort experience a CTCAE v4.03 Grade 2 liver toxicity or a CTCAE v4.03 Grade 3 (or higher) AE in the same organ or body system, or if > 25% of subjects in a cohort are discontinued for toxicity that persists for 14 days, then further dosing will not occur and the study will be terminated. See Section 14.4 for additional information.

Response criteria will be assessed on Day 1 of each cycle starting at Cycle 2 Day 1 visit as well as the end of treatment (EOT) visit using the criteria of 2014 NIH Consensus Development Project on Clinical Trials in cGVHD (CR, PR, and Lack of Response (unchanged, mixed, or progression); Lee et al., 2015). cGVHD severity (clinician reported) and symptom (subject reported) assessments will be performed on Day 1 of each cycle starting on Cycle 1 Day 1 as well as the EOT visit using the Physician-reported global cGVHD Activity Assessment form (Appendix A), cGVHD Activity Assessment: Patient Self Report, and Lee cGVHD Symptom Scale (see Appendices C and D).

At Cycle 25, Day 1 (C25D1), and all odd cycles thereafter (ie, C27D1, C29D1, C31D1, etc.), subjects will receive 2 cycles worth of study drug along with 2 diaries and will return to the clinic at the next odd cycle for assessments and IP accountability. Investigators and/or subjects have the option of coming into the clinic at one or more even cycles (i.e., C26D1, C28D1, C30D1, etc). On even cycles, when patients do not come to clinic, the study staff will contact the patient via phone and document any new adverse events and concomitant medications.

Subjects will also undergo assessments as described in Table 1.

Table 1: Study Assessments

Assessments	Screen[n]	Treatment Period (Each Cycle is 4 Weeks)							EOT[q,t]	28-Day Follow-Up (±7 days)[r]	UNS[s]	Long-Term Follow-Up
		Cycle 1					Cycle 2 and Beyond[o,p]					
Cycle Day	-29 to -1	1	2	8 (±3 days)	15 (±3 days)	22 (±3 days)	1 (±3 days)	2				
Informed consent	X											
Medical history/Demographics	X											
Physical examination[a]	X	X		X	X	X	X		X	X	X	
Vital signs[b]	X	X		X	X	X	X		X	X	X	
Karnofsky Performance Scale score	X	X		X	X	X	X		X	X	X	
Hematology and chemistry	X	X		X	X	X	X		X	X	X	
TSH	X						X		X	X	X	
Urinalysis	X						X			X	X	
Virology[c]	X											
12-Lead ECG[d]	X	X[d]					X[d]			X	X	
Pregnancy test (urine)[e]	X	X[e]					X			X	X	
Pulmonary Function Tests[f]		X					X[f]		X		X	
Pharmacokinetic sampling[g]		X[g]	X				X[g]	X				
Pharmacodynamic sample[h]		X					X[h]					
Study drug administration[i]		X[i]		X	X	X	X					
Dispense/Collect Study Drug & Study Drug Diary		X		X	X	X	X				X	
Response Criteria Assessment[j]							X[j]		X			
Physician-reported global cGVHD activity assessment[k]		X					X[k]		X		X	
cGVHD Activity Assessment - Patient Self Report & Lee cGVHD Symptom Scale[k]		X					X[k]		X		X	

Assessments	Screen[n]	Treatment Period (Each Cycle is 4 Weeks)							EOT[q,t]	28-Day Follow-Up (±7 days)[r]	UNS[s]	Long-Term Follow-Up
		Cycle 1					Cycle 2 and Beyond[o,p]					
Cycle Day	-29 to -1	1	2	8 (±3 days)	15 (±3 days)	22 (±3 days)	1 (±3 days)	2				
Concomitant medications[l]	*Concomitant medications and AEs to be collected from the date that the ICF is signed until 28 days after last dose of study drug.*											
Adverse events												
Follow-up contact[m]												X

BID = twice daily; cGHVD = chronic graft versus host disease; CNI = calcineurin inhibitor; CR = complete response; DL_{CO} = diffusing capacity of carbon monoxide; ECG = electrocardiogram; EOT = end of treatment; FEV_1 = forced expiratory volume in the first second; FVC = forced vital capacity; ICF = informed consent form; IP = investigational product; NIH = National Institutes of Health; PD = pharmacodynamic; PE = physical examination; PFTs = pulmonary function tests; PR = partial response; RV = residual volume; SD = stable disease; TLC = total lung capacity; TSH = thyroid stimulation hormone; UNS = unscheduled
All visits (Cycle 2 and beyond) will have a ±3 day visit window.

a. All PEs to include weight; PE at screening to include height and weight. All PEs to include Karnofsky Performance Scale evaluation.
b. Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, and temperature) to be obtained (after 5 minutes of rest).
c. Virology to include testing for Hepatitis B, Hepatitis C, and HIV.
d. ECG to be obtained after 5 minutes of resting in the supine position at the following time points: Screening; 4 hours post-morning dose on Day 1 of Cycle 1; at the 28-Day Follow-Up visit, and, if appropriate, will be requested if a subject discontinues treatment prematurely. At each time point, repeat ECG 3 times consecutively within 30 minutes (must have an interval of at least 1–2 minutes between ECGs). ECGs also will be obtained pre-dose on Day 1 of Cycle 4 and pre-dose at the Cycle 7 Day 1 visit.
e. Urine pregnancy test for 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. Positive results are to be confirmed with serum testing.
f. PFTs will be performed only if lung involvement is suspected. If no lung involvement is suspected, subjects will undergo PFTs every other cycle, starting with Cycle 3. PFTs (to include FEV_1, FVC, DL_{CO}, TLC, and RV) are to be performed on Day 1 of each cycle starting at Cycle 2 Day 1 visit (only if lung involvement is suspected), as well as at the EOT visit.
g. Blood samples (approximately 5 mL) for determination of plasma concentrations of KD025 and its metabolites will be collected on Day 1 of Cycles 1 and 2 at the following timepoints: Pre-dose (Time 0), and 1, 2, 3, 4, 5, 6 hours after dosing (after first dose for subjects in the BID group). In addition, subjects will have samples collected pre-dose on Day 1 of Cycle 4, pre-dose at the Cycle 7 Day 1 visit.
h. All subjects will have pre-dose PD blood samples drawn up to 4 times over the course of the study.
i. Subjects will receive their first dose of study drug in the clinic on Cycle 1, Day 1, then will be dispensed study drug for home administration. On scheduled visit days, subjects will take their dose at the clinic.
j. Response criteria assessment will be assessed on Day 1 of each cycle starting at Cycle 2 Day 1 visit; as well as at the EOT visit using the 2014 NIH Consensus Development Project for Clinical Trials in cGVHD criteria.
k. Physician-reported global cGVHD activity assessment (see Appendix A), cGVHD Activity Assessment - Patient Self Report (see Appendix C) & Lee cGVHD Symptom Scale (see Appendix D) to be assessed on Day 1 of each cycle starting at Cycle 1 Day 1 visit; as well as the EOT visit.
l. To include systemic steroids and CNI.
m. Subjects will be contacted approximately every 8 weeks and can be contacted via telephone, email or postal mail to confirm survival status and the initiation of any anti-cancer treatment or any changes in treatment of cGVHD. This can also be confirmed from electronic medical records.

n. If screening assessments are done within 14 days of Cycle 1, Day 1, they do not need to be repeated on Cycle 1 Day 1.
o. Subjects who achieve SD, PR, or CR will continue dosing with study drug until disease progression or unacceptable toxicity occurs. For LOR –Mixed subjects please refer to Section 9.1 of protocol.
p. At Cycle 25 Day 1 (C25D1) and all odd cycles thereafter (i.e., C27D1, C29D1, C31D1, etc.), subjects will receive 2 cycles worth of study drug along with 2 diaries and will return to the clinic at the next odd cycle for assessments and IP accountability. Investigators and/or subjects have the option of coming into clinic at one or more even cycles (i.e., C26D1, C28D1, C30D1, etc.). On even cycles, when patients do not come to clinic, the study staff will contact the patient via phone and document any new adverse events and concomitant medications.
q. Subjects who discontinue treatment prematurely also will be asked to come to the clinic for EOT assessments.
r. The Follow-Up visit will occur 28 days after the last dose of study drug, but prior to starting on a new therapy, if a new therapy is started earlier. This visit may be done within ± 7 days of the scheduled visit.
s. These assessments are suggested for any unscheduled visits (UNS).
t. Subjects are to return to the study site within 3 days after the subject's last dose of study drug to complete all EOT assessments. This may occur at the visit at which disease progression is diagnosed.

Table 2: Timing Allowance Windows for Pharmacokinetic and ECG Measurements

Pharmacokinetic Sampling	
Time point	**Tolerance Window**
0 hour	-240 min to 0 hour
>0 hour – 2 hours	-5 minutes/+ 5 minutes
4 hour – 6 hours	-10 minutes/+ 10 minutes
24 hours	-60 minutes /+ 60 minutes
ECG	
Time point	**Tolerance Window**
0 hour	-240 min to 0 hour
4 hours	-30 minutes/+ 30 minutes

ECG = electrocardiogram

As shown in the table of study assessments (Table 1), subjects will undergo PEs; vital sign measurements; Karnofsky Performance Scale assessments, blood sample collection for hematology, chemistry, PK, and PD markers; urinalysis; PFTs, ECGs; AE assessments; concomitant medication assessments; activity assessments, and pregnancy testing for females of childbearing potential.

Follow-Up Period

Follow-Up visits will occur 28 days (± 7 days) after the last dose of study drug. Subjects will undergo PEs; vital sign measurements; blood sample collection for hematology, chemistry, and PD markers; urinalysis; ECGs; AE assessments; and concomitant medication assessments; and pregnancy testing for females of childbearing potential.

Long-Term Follow-Up

Subjects will be contacted approximately every 8 weeks and can be contacted via telephone, email or postal mail to confirm survival status and the initiation of any anti-cancer treatment or any changes in treatment of cGVHD. This can also be confirmed from electronic medical records.

6.4. Randomization and Blinding

This is an open-label study.

7. STUDY POPULATION

7.1. Target Population

Approximately 48 adult male and female subjects with cGVHD will be enrolled. Subjects will be eligible for enrollment as defined by the following inclusion and exclusion criteria.

7.2. Inclusion Criteria

The inclusion criteria are detailed below:

1. Adult male and female subjects at least 18 years of age who have had allogenic bone marrow transplant or hematopoietic stem cell transplantation.
2. Receiving glucocorticoid therapy and calcineurin therapy or glucocorticoid therapy alone for cGVHD at study entry. Subjects on calcineurin therapy only, without glucocorticoid therapy, are not eligible. Subjects also receiving other therapies thought not to be immunosuppressive (such as extracorporeal photopheresis [ECP]), will be considered for enrollment in this study on a case-by-case basis.
3. Have persistent active cGVHD manifestations, as defined by 2014 NIH Consensus Development Project on Criteria for Clinical trials in cGVHD, after at least 2 months of steroid therapy.
4. No more than 3 prior lines of treatment for cGVHD.
5. Karnofsky Performance Scale of > 40 (see Appendix E).
6. Adequate organ and bone marrow functions evaluated during the 14 days prior to enrollment as follows:
    a. Absolute neutrophil count $\geq 1.5 \times 10^9$/L (without myeloid growth factors within 1 week of study entry)
    b. Platelet count $\geq 50 \times 10^9$/L (without transfusion or thrombopoietin or thrombopoietin analogues within 2 weeks of study entry)
7. Adequate safety laboratory values:
    a. Total bilirubin $\leq 1.5 \times$ upper limit of normal (ULN)

b. ALT and AST ≤ 3 × ULN

c. Glomerular filtration rate (GFR) ≥ 30 mL/min/1.73 m^2 using the 4-Variable Modification of Diet in Renal Disease (MDRD-4) variable formula (see Appendix F)

8. 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 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.

9. Women of childbearing potential (ie, 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.

10. 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 1 barrier method;

    b. Stable doses of hormonal contraception for at least 3 months (eg, oral, injectable, implant, transdermal) plus one barrier method;

    c. Two 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

11. For male subjects who are sexually active and who are partners of premenopausal women: agreement to use 2 forms of contraception as in Criterion #10 above during the treatment period and for at least 3 months after the last dose of study drug.

12. Able to provide written informed consent prior to the performance of any study-specific procedures.

7.3. Exclusion Criteria

The exclusion criteria are detailed below:

1. Female subject who is pregnant or breastfeeding.
2. Receiving an investigational GVHD treatment within 28 days of study entry.
3. Has acute GVHD.
4. Taking any medication known to be a moderate or strong inhibitor of the CYP3A4 isozyme or any drugs that are moderate or strong CYP3A4 inducers (see Appendix H).
5. 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 (such as poorly controlled psychiatric disease or coronary artery disease).
6. Regular and excessive use of alcohol within the 6 months 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.
7. Known history of human immunodeficiency virus (HIV) or active hepatitis C virus (HCV) or hepatitis B virus (HBV).
8. Diagnosed with another malignancy (other than malignancy for which transplant was performed) within 3 years of enrollment, with the exception of completely resected basal cell or squamous cell carcinoma of the skin, resected in situ cervical malignancy, resected breast ductal carcinoma in situ, or low-risk prostate cancer after curative resection.
9. Relapse of the underlying cancer or post-transplant lymphoproliferative disease at the time of screening.
10. Has had previous exposure to KD025 or known allergy/sensitivity to KD025 or any other ROCK2 inhibitor.
11. Taking other immunosuppressant drugs for GVHD, including mammalian target of rapamycin (mTOR) inhibitors (Note: Only steroids, CNIs, and ECP are acceptable).
12. QTcF > 450 msec

8. STUDY ASSESSMENTS

8.1. Overview

The timing for these study assessments is presented in Table 1, while a listing of clinical laboratory parameters to be measured in presented in Section 8.8.

8.2. Screening Period (Day -29 to -1)

Informed consent must be obtained before any study-specific samples are taken or study-specific tests or evaluations are conducted. The following assessments at the screening visit are to occur within 28 days of first dose of study drug. Study eligibility will be based on satisfying all of the study inclusion and exclusion criteria.

At the screening visit, information will be collected and subjects will have clinical evaluations as follows:

- Informed consent
- Medical history and demographic data
- Complete PE, including height and weight
- Seated vital sign measurements (sitting blood pressure, pulse, respiratory rate, temperature)
- Karnofsky Performance Scale score
- Clinical laboratory tests (hematology and serum chemistry panel)
- Thyroid stimulating hormone (TSH)
- Urinalysis
- Virology (HBV, HCV, and HIV)
- Supine 12-Lead ECG; to be performed 3 times consecutively within 30 minutes (must have an interval of at least 1–2 minutes between ECGs); perform ECG immediately prior to blood sample collection, if possible
- Urine pregnancy test (for women of childbearing potential. Positive results are to be confirmed with serum testing.)
- Concomitant medications assessment
- AE assessment

8.3. Enrollment

After completion of screening procedures and confirmation of subject eligibility, the subject will be enrolled into the study. Subjects who are enrolled into the study are to undergo all subsequent evaluations required by the protocol.

8.4. Treatment Period

8.4.1 Cycle 1, Day 1 (Baseline)

At the Cycle 1 Day 1 visit, subjects will come to the clinic to have the following procedures completed. (Note that if screening assessments are done within 14 days prior to Cycle 1 Day 1, they do not need to be repeated on Day 1).

- Complete PE, including weight
- Seated vital sign measurements (sitting blood pressure, pulse, respiratory rate, temperature)
- Karnofsky Performance Scale score
- Clinical laboratory tests (hematology and serum chemistry panel)
- Supine 12-Lead ECG (to be obtained 4 hours post-morning dose; to be performed 3 times consecutively within 30 minutes [must have an interval of at least 1–2 minutes between ECGs]; perform ECG immediately prior to blood sample collection, if possible)
- Urine pregnancy test (for women of childbearing potential. Positive results are to be confirmed with serum testing.)
- Pulmonary function tests (including forced expiratory volume in 1 second [FEV_1], forced vital capacity [FVC], diffusing capacity of carbon monoxide [DL_{CO}], total lung capacity [TLC], and residual volume [RV])
- PK sample collection (pre-dose [Time 0], and 1, 2, 3, 4, 5, and 6 hours after dosing [after first dose for subjects in the BID group])
- PD blood sample collection (pre-dose)
- Study drug administration
- Dispense study drug
- Dispense study drug diary
- Physician-Reported Global cGVHD Activity Assessment
- cGVHD Activity Assessment - Patient Self Report

- Lee cGVHD Symptom Scale
- Concomitant medications assessment
- AE assessment

8.4.2 Cycle 1, Days 8, 15, and 22 (±3 days)

On Days 8, 15, and 22 of Cycle 1, subjects will come to the clinic to have the following procedures completed:

- Complete PE, including weight
- Seated vital sign measurements (sitting blood pressure, pulse, respiratory rate, temperature)
- Karnofsky Performance Scale score
- Clinical laboratory tests (hematology and serum chemistry panel)
- Study drug administration
- Collect study drug diary
- Concomitant medications assessment
- AE assessment

8.4.3 Cycles 2 and Beyond, Day 1 (±3 days)

On Day 1 of Cycles 2 and beyond, subjects will come to the clinic to have the following procedures completed:

- Complete PE, including weight
- Seated vital sign measurements (sitting blood pressure, pulse, respiratory rate, temperature)
- Karnofsky Performance Scale score
- Clinical laboratory tests (hematology and serum chemistry panel)
- TSH
- Urinalysis
- Supine 12-Lead ECG; pre-dose on Day 1 of Cycle 4 and Cycle 7 only; to be performed 3 times consecutively within 30 minutes (must have an interval of at least 1–2 minutes between ECGs)
- Urine pregnancy test (for women of childbearing potential. Positive results are to be confirmed with serum testing.)

- Pulmonary function tests (including FEV_1, FVC, DL_{CO}, TLC, and RV; to be performed every other cycle, starting with Cycle 3 for subjects without lung involvement
- PK sample collection (Cycle 2 only at the following time points: pre-dose [Time 0], and 1, 2, 3, 4, 5, and 6 hours after dosing [after first dose for subjects in the BID group]); a pre-dose sample is to be collected at the Cycle 4 and Cycle 7 visit
- PD blood sample collection (Cycles 2, 4, and 7 only: pre-dose)
- Study drug administration
- Dispense/Collect study drug
- Collect study drug diary
- Response assessment.
- Physician-Reported Global cGVHD Activity Assessment
- cGVHD Activity Assessment - Patient Self Report
- Lee cGVHD Symptom Scale
- Concomitant medications assessment
- AE assessment

At Cycle 25, Day 1 (C25D1), and all odd cycles thereafter (i.e., C27D1, C29D1, C31D1, etc.), subjects will receive 2 cycles worth of study drug along with 2 diaries and will return to the clinic at the next odd cycle for assessments and IP accountability. Investigators and/or subjects have the option of coming into clinic at one or more even cycles (i.e., C26D1, C28D1, C30D1, etc). On even cycles, when patients do not come to clinic, the study staff will contact the patient via phone and document any new adverse events and concomitant medications.

8.5. End of Treatment (EOT)

Subjects are to return to the study site within 3 days after the subject's last dose of study drug to complete all EOT assessments. This may occur at the visit at which disease progression is diagnosed. The following procedures will be completed:

- Complete PE, including weight
- Seated vital sign measurements (sitting blood pressure, pulse, respiratory rate, temperature)
- Karnofsky Performance Scale score
- Clinical laboratory tests (hematology and serum chemistry panel)

- TSH
- Pulmonary function tests (including FEV1, FVC, DLCO, TLC, and RV)
- Response criteria assessment
- Physician-Reported Global cGVHD Activity Assessment
- cGVHD Activity Assessment - Patient Self Report
- Lee cGVHD Symptom Scale
- Concomitant medications assessment
- AE assessment

8.6. 28-Day Follow-Up Visit

The Follow-Up visit will occur 28 (± 7) days after the last dose of study drug, but prior to starting on a new therapy (if a new therapy is started earlier). Subjects will return to the clinic and the following procedures will be completed:

- Complete PE, including weight
- Seated vital sign measurements (sitting blood pressure, pulse, respiratory rate, temperature)
- Karnofsky Performance Scale score
- Clinical laboratory tests (hematology and serum chemistry panel)
- TSH
- Urinalysis
- Supine 12-lead ECG; to be performed 3 times consecutively within 30 minutes (must have an interval of at least 1–2 minutes between ECGs); perform ECG immediately prior to blood sample collection, if possible
- Urine pregnancy test (for women of childbearing potential. Positive results are to be confirmed with serum testing.)
- Concomitant medications assessment
- AE assessment

8.7. Unscheduled Visits

For subjects requiring an unscheduled visit, the following assessments may be performed at the investigator's discretion:

- Complete PE, including weight
- Seated vital sign measurements (sitting blood pressure, pulse, respiratory rate, temperature)
- Karnofsky Performance Scale score
- Clinical laboratory tests (hematology and serum chemistry panel)
- TSH
- Urinalysis
- Supine 12-Lead ECG; to be performed 3 times consecutively within 30 minutes (must have an interval of at least 1–2 minutes between ECGs); perform ECG immediately prior to blood sample collection, if possible
- Urine pregnancy test (for women of childbearing potential. Positive results are to be confirmed with serum testing.)
- Pulmonary function tests (including FEV_1, FVC, DL_{CO}, TLC, and RV)
- Collect study drug (if appropriate)
- Collect study drug diary (if appropriate)
- Physician-Reported Global cGVHD Activity Assessment
- cGVHD Activity Assessment - Patient Self Report
- Lee cGVHD Symptom Scale
- Concomitant medications assessment
- AE assessment

8.8. Long-Term Follow-Up

Subjects will be contacted approximately every 8 weeks and can be contacted via telephone, email or postal mail to confirm survival status and the initiation of any anti-cancer treatment or any changes in treatment of cGVHD. This can also be confirmed from electronic medical records.

9. STUDY PROCEDURES

9.1. Procedures to be Performed

*All screening assessments are to be performed within **28 days** before first study drug dose, unless otherwise specified.*

Study Day 1 is defined as the date the subject takes the first dose of study drug, with subsequent study days numbered sequentially thereafter.

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).

Informed Consent

All subjects must take part in the informed consent 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.

Demographics and Medical History

A complete medical history will be taken. Information to be documented includes demographic information, prior medical illnesses and conditions, and surgical procedures.

Physical Examination

Complete PEs will be performed. All PEs will include assessment of cardiac (including heart rate, and vital sign measurements), musculoskeletal (eg, muscle aches) and neurological (eg, gait) body systems. A complete PE is to include documentation of height (screening only), weight, body temperature, and vital signs (blood pressure [sitting], pulse rate [sitting], Karnofsky Performance Scale, and respiratory rate) and will be performed by a physician or staff member who is qualified to perform such examinations (eg, physician's assistant, nurse practitioner).

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

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 sitting blood pressure (mm Hg), heart rate (beats per minute), respiration rate (breaths per minute), and temperature (Celsius).

Please note that blood pressure measurements are to be performed using appropriate technique (per guidelines of the American Heart Association). Specifically, subjects should be seated quietly for at least 5 minutes in a chair with their backs supported, their feet flat on floor (legs uncrossed), and their 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 mm Hg, an additional 2 readings should be obtained and averaged. Record cuff size, arm used, and subject's position (if not seated).

Karnofsky Performance Scale

Subject's performance status will be assessed using the Karnofsky Performance Scale tool (see Appendix E).

Laboratory Assessments

Laboratory samples (hematology, serum chemistry, TSH, urinalysis, and virology) are to be collected as outlined in Table 1and Section 8.8. Safety laboratory analyses will be performed by the central laboratory. Laboratory results will be graded using the CTCAE v4.03.

12-Lead Electrocardiogram

Electrocardiograms will be performed with the subject in a supine position having rested in this position for at least 5 minutes before each reading. ECGs are to be performed 3 times consecutively within 30 minutes (must have an interval of at least 1–2 minutes between ECGs). ECG is to be performed immediately prior to any blood sample collections, if possible. See Section 9.3 for additional ECG procedure information and Table 2 for timing allowances.

Pregnancy Testing

Pregnancy tests (urine) will be done in women of childbearing potential. Positive urine results are to be confirmed with serum testing.

Pulmonary Function Testing

Pulmonary function tests (to include FEV_1, FVC, DL_{CO}, TLC, and RV) will be performed according to the guidelines published by the American Thoracic Society or European Respiratory Society for standardization of spirometry (ATC 1995; Quanjer et al., 1993). Diffusion capacity (DL_{CO}) determinations will be performed at the same time as spirometric testing; FEV_1, FVC, DL_{CO}, TLC, and RV will also be expressed as absolute values and % predicted of normal based on published reference values for adults (Hankinson et al., 1999). See Section 9.4 for additional information.

Pharmacokinetics (PK) Sampling

Blood samples (approximately 5 mL) for determination of plasma concentrations of KD025 and its metabolites, will be collected on Day 1 of Cycles 1 and 2 at the following time points: Pre-dose (Time 0), and 1, 2, 3, 4, 5, and 6 hours after dosing (after first dose for subjects in the BID group). In addition, subjects will have samples collected pre-dose on Day 1 of Cycle 4 and pre-dose at the Cycle 7 Day 1 visit. See Section 11 for additional information.

Blood Sampling for Pharmacodynamics (PD)

All subjects will have PD blood samples drawn up to 4 times over the course of the study: Pre-dose on Cycle 1 Day 1, Cycle 2 Day 1 (4 weeks), Cycle 4 Day 1 (12 weeks) and Cycle 7 Day 1 (24 weeks). Samples will be analyzed to evaluate changes in the expression of several cytokines in plasma (including IL-17A, IL-21, and IL-2), and changes in percentages of circulating Th17 and Treg cells in blood. See Section 12 for additional information.

KD025 Administration and Treatment Duration

Subjects will receive their first dose of study drug in the clinic on Day 1 of Cycle 1, and then study drug will be dispensed for home administration. On scheduled visit days, subjects will take their dose at the clinic.

Subjects will receive KD025 200 mg QD, KD025 200 mg BID, or KD025 400 mg QD. Subjects will be treated until disease progression or unacceptable toxicity. Subjects with a "LOR - Mixed" response assessment may continue treatment with KD025 and remain on study if the investigator considers continued treatment to be in the subject's best interest only after approval from the medical monitor and documentation of the subject's willingness to continue.

Subjects who have SD, PR, or CR at the time of decision to discontinue treatment and who come off study for reasons other than AEs will be tapered off of KD025 by lowering the dose by 50% every 2 weeks (see Section 14.1 for additional details) until they reach a dose of 100 mg QD or equivalent. Further instructions will be listed in the pharmacy manual.

Study Drug Diary

Subjects will be given a study drug diary to record the details of each dose of study drug. Diaries will be dispensed/collected on Day 1 of each cycle. Compliance with oral dosing will be confirmed using patient diaries, which will be examined at each visit.

Response and Activity Assessments

Response criteria will be assessed using the 2014 NIH Consensus Development Project for Clinical Trials in cGVHD criteria (CR, PR, or LOR [unchanged, mixed, or progression; see (Lee et al., 2015).

Activity in terms of cGVHD severity will be evaluated using the Physician-reported Global cGVHD Activity Assessment form (see Appendix A), while activity in terms of symptom burden will be evaluated using the cGVHD Activity Assessment - Patient Self Report (see Appendix C). Failure-free survival, OS and TTNT will be evaluated at the same time points. Changes in corticosteroid and CNI dose will be documented as they occur on the appropriate eCRF. Changes in symptom burden/bother will be documented using the Lee cGVHD Symptom Scale (see Appendix D).

See Section 10 for additional information on response assessment.

Prior and Concomitant Medications

All concomitant medications, including systemic steroids and CNIs, are to be collected from time the subject signs the ICF throughout the subject's participation in the study. See Section 15 for additional information.

Adverse Event Assessments

Information regarding the occurrence of AEs will be collected from the time the subject signs the ICF throughout their participation in the study, including a period of 28 days after last dose of

study drug. AE severity will be determined using the CTCAE v4.03 grading scale. Also, see Appendix G for criteria for determining relationship of AE to study drug.

> **Note**: Adverse events 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 13.2 for stopping rules for this study.

9.2. Laboratory Assessments

The central laboratory will perform hematology, serum chemistry, and urinalysis tests and results will be provided to the investigator (Table 3). Blood and urine samples for hematology, serum chemistry, and urinalysis will be prepared using standard procedures.

Table 3: 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)
Biomarkers[a]		**Thyroid Function**
• IL-17A • IL-21 • IL-2 • Th17 • Treg cells		• TSH

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CPK = creatinine phosphokinase; GGT = gamma glutamyl transferase; IL = interleukin; INR = international normalized ratio; MCV = mean corpuscular volume; TSH = thyroid stimulating hormone
a: Other markers may be added

Abnormalities in clinical laboratory tests that lead to a change in subject management (eg, dose delay, 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. Laboratory results will be classified using the CTCAE v4.03. 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 16.3.1).

9.3. Electrocardiogram Assessments

A digital 12-lead ECG will be obtained during the study (see Table 1 for timing of ECG assessments and Table 2 for timing allowances).

Digital 12-lead ECG recordings are to be made with the subject in a supine position having rested in this position for at least 5 minutes before each reading. ECGs are to be performed 3 times consecutively within 30 minutes (must have an interval of at least 1–2 minutes between ECGs). At each visit, the ECG is to be performed immediately before any blood sample collection, if possible.

The following ECG parameters will be collected: PR interval, QRS interval, and QTc[F]. 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 (eg, dose reduction 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 in the AE eCRF. If ECG abnormalities meet criteria defining them as serious, they must be reported as an SAE (see Section 16.3.1).

9.4. Pulmonary Function Tests

Pulmonary function testing will include FEV_1, FVC, DL_{CO}, TLC, and RV. The same equipment and tester should be used during the course of the study to the extent possible. The person responsible for conducting the pulmonary function tests will be required to comply with the study guidelines and the American Thoracic Society/European Respiratory Society joint criteria on lung function testing.

10. ACTIVITY

The primary activity endpoint of this study is subject response based on the 2014 NIH Consensus Development Project on Clinical Trials in cGVHD. Secondary endpoints include evaluation of cGVHD severity using the Physician-reported global cGVHD Activity Assessment; evaluation of symptom burden using the cGVHD Activity Assessment - Patient Self Report; FFS; OS; TTNT; changes in corticosteroid and CNI dose; and changes in symptom burden/bother using the Lee cGVHD Symptom Scale.

10.1. 2014 NIH Consensus Development Project on Clinical Trials in cGVHD

Subject response (CR, PR, or LOR [unchanged, mixed response, progression]) based on the 2014 NIH Consensus Development Project on Clinical Trials in cGVHD is the primary activity endpoint for this study (see Appendix B). Response criteria will be assessed on Day 1 of each cycle starting on Cycle 2 Day 1 as well as the EOT visit.

10.2. Physician-Reported Global cGVHD Activity Assessment

Activity in terms of cGVHD severity also will be evaluated using the Physician-reported Global cGVHD Activity Assessment (see Appendix A for form). cGVHD severity will be performed on Day 1 of each cycle starting on Cycle 1 Day 1 as well as the EOT visit.

10.3. cGVHD Activity Assessment - Patient Self Report

Activity in terms of symptom burden also will be evaluated using the cGVHD Activity Assessment - Patient Self Report (see Appendix C for report). Symptom burden will be assessed on Day 1 of each cycle starting on Cycle 1 Day 1 as well as the EOT visit.

10.4. Failure-Free Survival

Failure-free survival data will be collected throughout the study.

10.5. Overall Survival

Overall Survival data will be collected throughout the study.

10.6. Corticosteroid and Calcineurin Inhibitor Use

Corticosteroid and CNI dose will be collected throughout the study and changes in requirements will be documented. Corticosteroids may be tapered at the discretion of the investigator after 4 weeks of KD025 administration. In addition, data on use of non-immunosuppressive therapy, such as ECP, will be collected as well.

10.7. Time to Next Treatment (TTNT)

Time to Next Treatment data will be collected throughout the study.

10.8. Lee cGVHD Symptom Scale

Changes in symptom burden/bother will be documented using the Lee cGVHD Symptom Scale (see Appendix D). Symptom burden will be assessed on Day 1 of each cycle starting on Cycle 1 Day 1; as well as at the EOT visit. Lee et al., 2002 developed a symptom scale designed for individuals with chronic GVHD. The questionnaire asks subject to indicate the degree of bother that they experienced due to symptoms in seven domains potentially affected by chronic GVHD (skin, eyes, mouth, breathing, eating and digestion, energy, and emotional distress).

The degree to which subjects report that they are bothered by a symptom represents a global assessment incorporating not only the intensity of the symptom and its frequency, but also the degree to which it causes emotional disturbance or interferes with functioning.

11. PHARMACOKINETICS

Blood samples (approximately 5 mL) for determination of plasma concentrations of KD025 and its metabolites, will be collected on Day 1 of Cycles 1 and 2 at the following time points: Pre-dose (Time 0), and 1, 2, 3, 4, 5, and 6 hours after dosing (after first dose for subjects in the BID group). In addition, subjects will have samples collected pre-dose on Day 1 of Cycle 4 and Day 1 of Cycle 7. Subjects should be instructed to withhold taking study drug on these days as dosing will be performed at the clinic.

The pre-dose and all post-dose PK collection time points are to be documented on the appropriate eCRF. Additionally, the time of a subject's dose of study drug is to be documented (for subjects receiving study drug BID, the time of the previous evening's dose administration also is to be noted).

A total of 16 samples will be collected (80 mL) from subjects in the dose escalation portion of the study. KD025 and metabolite concentrations will be used to calculate the following PK parameters: C_{max}, T_{max}, and $AUC_{0\text{-}6hr}$.

Detailed instructions for sample collection and preparation will be provided in a separate manual.

12. PHARMACODYNAMICS

All subjects will have PD blood samples drawn 4 times over the course of the study: Pre-dose on Cycle 1 Day 1, Cycle 2 Day 1 (4 weeks), Cycle 4 Day 1 (12 weeks) and Cycle 7 Day 1 (24 weeks). Samples will be analyzed to evaluate changes in the expression of several cytokines in plasma (including IL-17A, IL-21, and IL-2), and changes in percentages of circulating Th17 and Treg cells in blood.

Detailed instructions for sample collection and preparation will be provided in a separate manual.

13. REMOVING SUBECTS 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 page must be completed for any subject who is enrolled in the study.

13.1. Subjects' Decision to Withdraw

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

Subjects can decline to continue receiving study drug and/or other protocol-required therapies or procedures at any time during the study. If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation from study drug or other protocol-required therapies and must discuss with the subject the options for continuation of the Schedule of Assessments (Table 1) and collection of data, including endpoints and adverse events.

Withdrawal of consent for a study means that the subject does not wish to receive further protocol-required therapies or procedures, and the subject does not wish to or is unable to continue further study participation. Subject data up to withdrawal of consent will be included in the analysis of the study, and where permitted, publically available data can be included after withdrawal of consent. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study.

13.1.1 Treatment Discontinuation

Treatment discontinuation reasons include any of the following:

- Disease Progression
- An AE requires permanent discontinuation of study drug (refer to Section 14.4)
- Investigator decision
- Voluntary withdrawal by subject
- Noncompliance to protocol

- Subject lost to follow-up
- Termination of the study by sponsor
- Subject death

13.1.2 Study Termination

Reasons for study termination include:

- Completion of follow-up period
- Voluntary withdrawal by subject
- Subject lost to follow-up
- Termination of the study by sponsor
- Subject death

In the event of premature discontinuation of treatment, subjects must return to the clinic to complete the EOT Visit and 28-Day Follow-Up assessments. Refer to Section 8.5 for a complete list of procedures to be performed at these visits. If a subject dies, Kadmon Corporation will actively seek to know the date of death.

If there is an ongoing toxicity because of 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 survival information.

13.2. Stopping Rules

Stopping criteria will be assessed using the CTCAE scale v.4.03.

13.2.1 Adverse Events Stopping Criteria

AEs that require consideration of study drug discontinuation or dose reduction (see Section 14.4) include the following:

- AEs of clinical concern
- Treatment-related Grade 3 TEAEs that cannot definitively be attributed to a cause other than the study drug

- Treatment-related Grade 2 (moderate) TEAEs that cannot definitively be attributed to a cause other than the study drug and last at least 5 days.

13.2.2 Liver-Related Abnormalities

The liver-specific AE grading scale (CTCAE v4.03) shown in Table 4 will be used for liver-related laboratory abnormalities. Refer to Sections 14.3 and 14.4.

Table 4: Grading of Liver-Related Laboratory Abnormalities (CTCAE v4.03)

FEATURE	Grade 1	Grade 2	Grade 3	Grade 4
ALT	> ULN-3.0 × ULN	> 3.0-5.0 × ULN	> 5.0-20.0 × ULN	> 20.0 × ULN
AST	> ULN-3.0 × ULN	> 3.0-5.0 × ULN	> 5.0-20.0 × ULN	> 20.0 × ULN
Alkaline Phosphatase	> ULN - 2.5 × ULN	> 2.5 - 5.0 × ULN	> 5.0 - 20.0 × ULN	> 20.0 × ULN
GGT	> ULN - 2.5 × ULN	> 2.5 - 5.0 × ULN	> 5.0 - 20.0 × ULN	> 20.0 × ULN
Bilirubin	> ULN - 1.5 × ULN	> 1.5 - 3.0 × ULN	> 3.0 - 10.0 × ULN	> 10.0 × ULN

ALT = Alanine aminotransferase; AST = aspartate aminotransferase; GGT = Gamma-glutamyl transferase; ULN = upper limit of normal

13.3. Study Discontinuation

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:

- If ≥ 25% of subjects in the 200 mg QD cohort experience a CTCAE v4.03 Grade 2 liver toxicity or a CTCAE v4.03 Grade 3 (or higher) AE in the same organ or body system, or if > 25% of subjects in a cohort are discontinued for toxicity that persists for 14 days, then further dosing will not occur and the study will be terminated.
- Subject enrollment is unsatisfactory
- Drug supply issues
- Excessive subject self-withdrawal
- Significant protocol violations (eg, violation of eligibility criteria, dosing errors, missing data for study endpoint analysis)

13.4. Replacements

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

14. STUDY DRUG

14.1. Dose and Schedule of Study Drug

Kadmon will provide each investigator with adequate supplies of KD025.

Eligible subjects will receive KD025 200 mg QD, KD025 200 mg BID, or KD025 400 mg QD. Study drug will be dispensed by the site pharmacist. After the completion and review of all screening and baseline procedures, qualified subjects will receive study drug.

Cohort	No. of Subjects	Dosage	Number of 100 mg capsules to be administered per dose	Number of 200 mg tablets to be administered per dose
Cohort 1	16 subjects	200 mg KD025 QD	2	1
Cohort 2	16 subjects	200 mg KD025 BID	2	1
Cohort 3	16 subjects	400 mg KD025 QD	4	2

KD025 will be supplied as 100 mg capsules or 200 mg tablets.

Product	Strength	Dosage Form	Route
KD025	100 mg	Yellow opaque capsule (size 00)	Oral
KD025	200 mg	Oblong yellow-coated tablet	Oral

Cohort 1: Subjects should take 2 capsules/1 tablet with their morning meal or within 5 minutes of finishing the meal.

Cohort 2: Subjects should take 2 capsules/1 tablet with their morning meal or within 5 minutes of completing the meal and 2 capsules with their evening meal or within 5 minutes of finishing the meal.

Cohort 3: Subjects should take 4 capsules/2 tablets with their morning meal or within 5 minutes of finishing the meal.

Subjects who have SD, PR, or CR at the time of decision to discontinue treatment and who come off study for reasons other than AEs will be tapered off KD025 by lowering the dose by 50% every 2 weeks until they reach a dose of 100 mg QD or equivalent. Further instructions will be listed in the pharmacy manual.

Subjects will be dispensed study drug to self-administer while on an outpatient basis and subjects will be provided a study drug diary in which to record the day and time of dosing. Subjects will return to the clinic as outlined in the Study Assessments table (Table 1), and will receive that day's dose of study drug (first dose for BID subjects) while at the clinic.

14.2. Dose Escalation

Prior to enrolling subsequent cohorts, the safety data in each prior cohort will be evaluated after 8 subjects have reached 2 months of treatment to assure there is no safety signal. Two months was selected as the time for the safety review because all of the clinically significant KD025-related AEs to date occurred within 36 days or less of starting dosing with KD025. As this is an open-label study, safety results will be continuously monitered. If ≥ 25% of subjects in a cohort experience a CTCAE v4.03 Grade 2 liver toxicity or a CTCAE v4.03 Grade 3 (or higher) AE in the same organ or body system, or if > 25% of subjects in a cohort are discontinued for toxicity that persists for 14 days, then dose escalation to the next cohort will not occur, and all patients in that dose cohort will be dose reduced.

14.3. Missed Doses

Subjects should make every effort to take the study drug at the same scheduled time daily. In the event that the subject misses the planned dose of study drug, the following protocol should be followed:

For subjects receiving study drug on a QD dosing schedule:

- If less than 12 hours of time have elapsed after the scheduled dose, the drug should be taken. The subject should then resume the regular planned daily dosing schedule the following day.
- If more than 12 hours of time have elapsed after the scheduled dose, the drug should be skipped for that day. The subject should then resume the regular planned dosing schedule the following day.

For subjects receiving study drug on a BID dosing schedule:

- If less than 6 hours of time have elapsed after the morning scheduled dose, the drug should be taken. The subject should then resume the regular planned dosing that evening. If less than 6 hours of time have elapsed after the evening scheduled dose, the drug should be taken. The subject should then resume the regular planned dosing the following morning.

- If more than 6 hours of time have elapsed after the morning scheduled dose, the drug should be skipped and the subject should resume the regular planned dosing schedule that evening. If more than 6 hours of time have elapsed after the evening scheduled dose, the drug should be skipped and the subject should resume the regular planned dosing the following morning.

If the subject skips more than 7 consecutive days of drug, the subject should be discontinued from the study.

14.4. Dose Pause or Reduction of KD025

Exacerbation of any of the signs or symptoms of the disease will constitute a potential rationale for cessation of therapy. Any clinically significant toxicity will necessitate consideration of either a pause or cessation of therapy. Both laboratory and clinical data may constitute a reason to pause or cease therapy. Previous studies have indicated that reversible and modest liver toxicity may occur spontaneously after a few weeks of initiation of therapy.

- When treatment-related Grade 3 toxicities occur, drug administration will be halted until recovery to at least Grade 1, at which time study drug may be resumed at a reduced dose.
- When treatment-related Grade 2 toxicities, other than liver toxicities, occur, drug administration will be halted until recovery to at least Grade 1 at which time study drug administration may resume at the same dose.
- When greater then Grade 2 liver toxicities occur, drug administration will be halted until recovery to at least Grade 1 at which time study drug administration may resume at a reduced dose.

Pauses in therapy may not last more than 14 days; subjects requiring pauses of more than 14 days will be discontinued from the study. If treatment-related Grade 2 or treatment-related Grade 3 toxicities persist for 14 days, subjects will be discontinued from the study.

14.4.1 Dose Reduction Steps

Every effort should be made to keep the subject on the full dose of drug. When dose reduction is necessary (see Section 14.4), the drug should be decreased as shown in Table 5 (for subjects on 100 mg capsules) and Table 6 (for subjects on 200 mg tablets), until the event has resolved. Once a subject has the dose decreased, an increase is not allowed.

Table 5: Dose Reductions for Toxicity Related to Study Drug – 100 mg Capsule

Study Drug	Cohort	Starting Dose	Dose Reduction
KD025	Cohort 1	200 mg KD025 QD	100 mg KD025 QD
KD025	Cohort 2	200 mg KD025 BID	200 mg KD025 QD
KD025	Cohort 3	400 mg KD025 QD	200 mg KD025 QD

BID = twice daily; QD = once daily
No more than 1 dose reduction is permitted. Subjects who require more than 1 dose reduction will have study drug discontinued and enter the Follow-Up Period.

Table 6: Dose Reductions for Toxicity Related to Study Drug – 200 mg Tablet

Study Drug	Cohort	Starting Dose	Dose Reduction
KD025	Cohort 1	200 mg KD025 QD	200 mg KD025 QOD
KD025	Cohort 2	200 mg KD025 BID	200 mg KD025 QD
KD025	Cohort 3	400 mg KD025 QD	200 mg KD025 QD

BID = twice daily; QD = once daily; QOD = every other day
No more than 1 dose reduction is permitted. Subjects who require more than 1 dose reduction will have study drug discontinued and enter the Follow-Up Period.

14.5. Identity of Investigational Products

KD025 will be supplied by Kadmon Corporation.

14.6. Study Drug Packaging and Labeling

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

- Description of contents (number and strength of capsules) 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.”

14.7. Dispensing of Study Drug and Dosing Compliance

Subjects will be dispensed study drug to self-administer while on an outpatient basis. Subjects will return to the clinic as outlined in the Study Assessments (Table 1), and will receive that day's dose of study drug while at the clinic.

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 with KD025.

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 trial 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 capsule/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 date and time of study drug administrations. These diaries will be dispensed and/or reviewed/collected at each visit.

14.8. Study Drug Storage

All supplies of study drug are to be stored at USP controlled room temperature of 20−25°C (66−77°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.

14.9. Study Drug Accountability

The US Food and Drug Administration (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.

14.10. Study Drug Handling and Disposal

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.

14.10.1 Disposition of Used Supplies

At the completion of a subject's participation in the trial, all partially used and empty study drug containers 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.

14.10.2 Inventory of Unused Supplies

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

15. CONCOMITANT MEDICATION AND TREATMENT

If the subject must use a concomitant medication during the study, it is the responsibility of the principal investigator to ensure that details regarding the medication are recorded on the eCRF.

A reasonable effort is to be made to document any medications the subject received at the time of signing the ICF through the end of the study (follow-up visit). After discontinuation of study drug, any concomitant medication used during the study in response to an AE is to be recorded on the appropriate eCRF.

Subjects must be receiving glucocorticoid therapy for cGVHD at study entry (subjects also may be receiving CNI therapy). Any changes in corticosteroid, CNI, or ECP doses will be documented.

Use of drugs that prolong QT/QTc should be used with caution in subjects who are receiving KD025. Discuss with medical monitor the appropriate monitoring of subjects while receiving any of these drugs in conjunction with KD025.

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

The use of medications that are strong CYP3A4 inducers is prohibited. Other CYP3A4 inhibitors / inducers should be used with caution. (See Appendix H for a listing of these drugs.) CYP1A2 inhibitors/ inducers should be used with caution.

16. SAFETY

16.1. Safety Parameters

The CTCAE v.4.03 will be used for grading toxicities. Laboratory results also will be classified using the CTCAE v4.03. Subjects will be monitored throughout the treatment and follow-up period for occurrence of AEs (acute, delayed, and/or cumulative), as well as for changes in clinical status, vital sign measurements, and laboratory data. Safety parameters to be measured/assessed include vital sign measurements, PE findings, hematology, serum chemistries, and urinalysis results, and ECG recordings.

16.2. Adverse Event Definition

An AE is defined as any untoward medical occurrence in a clinical trial subject associated with the use of a drug, whether or not considered drug related. An AE can be an unfavorable and unintended sign (eg, an abnormal laboratory value finding), a symptom, or a disease temporally associated with the use of a drug, without judgment as to causality. An AE can arise from use of the drug (eg, use in combination with another drug) and from any route of administration, formulation or dose, including an overdose. An AE also includes, but is not limited to, any clinically significant worsening of a pre-existing condition. Examples include:

- Any sign, symptom, physical finding, or laboratory result that has worsened in nature, severity or frequency compared to baseline;
- Reactions from an investigational drug, including those occurring as a result of an overdose, abuse of the study drug, withdrawal phenomena, sensitivity or toxicity;
- Concurrent illness that was not present or worsens in nature, severity, or frequency compared to baseline;
- Injury or accident; and/or
- Exacerbation of a pre-existing condition

For the purpose of data collection, all untoward events that occur after informed consent through 28 days after last dose of study drug are to be recorded on eCRFs by the investigational site.

16.3. Evaluating Adverse Events

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

16.3.1 Serious Adverse Events

(Notify sponsor or designee within 24 hours)

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 (INDs) and Bioavailability/Bioequivalence 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 28 days after study drug discontinuation.

  Note: Death is an outcome of an AE, and not an AE in itself. The event(s) that caused death (eg, 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 patient or 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 one of the outcomes listed in this definition.

16.3.2 Suspected Unexpected Serious Adverse Reaction (SUSAR)

(Notify sponsor or designee within 24 hours of first awareness)

A suspected unexpected serious adverse reaction 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 (eg, included in the IB), rather than from the perspective of such an event not being anticipated from the pharmacological properties of the product.

16.3.3 Unexpected Adverse Events

(Notify sponsor or designee by the next business day)

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. 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.

16.3.4 Non-Serious Adverse Events

All other AEs, not fulfilling the previous definitions, are classified as nonserious.

16.3.5 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.

16.3.6 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 G).

16.3.7 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 the CTCAE v 4.03 scale. 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. In the event that the grade of an AE worsens, an end date should be entered to the initial AE and a new AE entered with the updated grade and date of onset. The investigator will assess the relationship of the event to study drug. Note: All SAEs also are to be entered onto an SAE form and sent to sponsor or designee.

16.3.8 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.

16.3.9 Serious Adverse Event Reporting

16.3.9.1. 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 (US Code of Federal Regulations, 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 IRB/IECs as soon as possible and in no event later than 15 calendar days after the sponsor's initial notification of the event. Any unexpected death or life-threatening suspected adverse drug 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.

16.3.9.2. Time-Frame for Reporting

Any death, SAE, pregnancy (including pregnancy of a partner), or unexpected (and severe) AE experienced by a subject while receiving or within 28 days of receiving study drug, regardless of relationship to study drug, or any death that occurs more than 28 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 designee).

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

APCER Life Sciences, Inc.
Fax Number: 1-646-430-9549
Email: clinicalsaereporting@kadmon.com

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

16.3.9.3. Information to be Provided by the Investigator

SAEs for all enrolled subjects must be recorded on the SAE form (during study participation). This requirement includes all SAEs that occur after informed consent and through 28 days after last dose of study drug, and in addition, any SAEs that are assessed as possibly related to study drug by the investigator, even if the SAE occurs more than 28 days after the last dose of study drug must be reported to the Kadmon Corporation Pharmacovigilance Department (or designee).

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 (ie, the seriousness criteria) and the investigator's assessment of the relationship of the event to study drug. Additional SAE information including medications or other therapeutic measures used to treat the event, action taken with the study drug due to the event, and the outcome/resolution of the event will be recorded on the SAE form. Forms for reporting SAE 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 Corporation Drug Safety personnel or designee.

When reporting 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 (eg, 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 (eg, 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.

16.3.9.4. Regulatory Reporting

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

Kadmon Corporation (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/IEC will be done in accordance with the standard operating procedures and policies of the IRB/IEC. Adequate documentation must be maintained showing that the IRB/IEC was properly notified.

16.4. Other Safety Considerations

16.4.1 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 (eg, dose reduction or 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 before entry into the study.

Laboratory results will be classified using the CTCAE v4.03.

16.4.2 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.

16.4.3 Follow-Up of Adverse Events

Any SAE or AE assessed as at least possibly related that led to treatment discontinuation (including clinically significant abnormal laboratory values that meet these criteria) and is ongoing 28 days after last dose of study drug 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 28 days after last dose* of study drug. The status of all other continuing AEs will be documented as of 28 days after last dose of study drug.

17. STATISTICAL CONSIDERATIONS

All descriptive and inferential statistical analyses will be performed using SAS® (SAS Institute, Cary, North Carolina) statistical software, 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, 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. All clinical data captured will be provided in data listings.

17.1. 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, standard deviation, median, minimum and maximum. Frequencies and percentages will be used for summarizing discrete (categorical) data. When categorical data are presented, the percent will be suppressed when the count is zero in order to draw attention to the nonzero counts. The denominator for all percentages, unless otherwise specified, will be the number of subjects in the specified analysis population. Two-sided 95% confidence interval employing the exact binomial method will be provided for activity outcomes.

Hypothesis testing, if appropriate, will be carried out at the 5% (2-sided) significance level. Because of the exploratory nature of the study, no adjustments will be made for the multiplicity of endpoints. Nonparametric tests may be used in preference to parametric tests if parametric assumptions are notably violated. Missing values will not be imputed. If a subject does not have sufficient data for a particular analysis, they will be excluded from that analysis. Endpoints defined as an average of multiple measurements will be used those data points that are non-missing, and the denominator was adjusted accordingly.

17.2. Sample Size Justification

The total sample size of 16 subjects per KD025 dose group will provide > 90% probability of one or more KD025 subjects experiencing an AE that has an underlying rate of ≥ 14% and > 80% probability of one or more subjects in the study experiencing an AE that has an underlying rate of ≥ 10%.

Assuming an underlying 25% rate for subjects to meet the ORR, each treatment group of 16 subjects has an approximately 80% chance of having at least 3 subjects meet the overall response criteria, and approximately 90% chance of at least 2 subjects meet the overall response criteria.

17.3. Statistical Considerations

The statistical methodology will be further described in a Statistical Analysis Plan, which will be finalized prior to database lock.

17.3.1 Study Populations

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

- The modified intent-to-treat (mITT) population will consist of all subjects who are enrolled in the study and receive at least 1 dose of study medication.
- The safety population will consist of all subjects who receive at least one dose of KD025
- The PK population which will consist of all subjects who receive at least one dose of study drug and have at least 1 post-dose PK sample drawn

17.3.2 Subject Accountability, Demographics, and Baseline Characteristics

Demographics, subject disposition, and screening and baseline characteristics will be summarized for the mITT population.

17.3.3 KD025 Exposure

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

17.3.4 Concomitant Medications

Concomitant medications will be coded using WHO-DD and the data will be summarized by treatment group and presented in tables and listings.

17.4. Activity Analysis

The primary activity outcome will be the percentage of subjects who meet the OR criteria (PR + CR). This will be assessed overall (ie, any subject meeting the PR or CR criteria at any time point). For clarity, addition of new systemic therapy for cGVHD will be considered a KD025 treatment failure and will be considered progression of cGVHD for analysis purposes.

Secondary Endpoints

- Number and percentage of KD025 in subjects with steroid-dependent cGVHD who have a best response of PR or CR
- Change in cGVHD severity as based on the Physician-reported Global cGVHD Activity Assessment
- Change in symptom activity as based on cGVHD Activity Assessment Patient Self-Report
- Median FFS will be defined as the time from first dose of study drug to either the start of another treatment, relapse of the underlying disease, or death.
- Changes in corticosteroid and calcineurin inhibitor dose
- To evaluate DOR, which will be defined as the time of initial response until documented progression.
- To evaluate response by organ system. The response by organ system (PR and CR) will be assessed based on the 2014 NIH Consensus Development Project on Clinical Trials in cGVHD.
- Analyses of plasma PK of KD025 in subjects with cGVHD
- OS will be defined as the time from first dose of KD025 to the date of death due to any cause. Kaplan-Meier plots, descriptive statistics of OS and landmark OS at 6, 12, 18 and 24 months will be provided.
- TTNT will be defined as the defined as the time from the first dose of KD025 to the start of additional systemic cGVHD therapy Change in symptom burden/bother using the Lee cGVHD Symptom Scale.

Exploratory Endpoints

- Changes in the expression of several cytokines (including IL-17A, IL-21, and IL-2) in plasma after KD025 administration to subjects with cGVHD
- Changes in percentage of immune-cell subtypes (including Th17 and Treg cells) in whole blood after KD025 administration to subjects with cGVHD

17.5. Safety Data

The primary safety endpoint is the percent of subjects experiencing AEs in Cohort 1 (200 mg QD), Cohort 2, (200 mg BID), and Cohort 3 (400 mg QD).

Safety assessments include AEs, SAEs, PEs, vital sign measurements, clinical laboratory evaluations (including TSH measurements), ECGs, PFTs, and reasons for treatment discontinuation due to toxicity.

Treatment-emergent AEs will be evaluated using the CTCAE v4.03. The secondary safety outcome will be the number and percent of subjects experiencing AEs overall. The total sample size of 16 subjects per KD025 dose group will provide > 90% probability of one or more KD025 subjects experiencing an AE that has an underlying rate of ≥ 14% and > 80% probability of one or more subjects in the study experiencing an AE that has an underlying rate of ≥ 10%.

Treatment-emergent AEs will be summarized by treatment group using Medical Dictionary for Regulatory Activities (MedDRA®) System Organ Class (SOC) and preferred term, classified from verbatim terms. MedDRA® Version 20.0 or higher will be used. The incidence and percentage of subjects with at least 1 occurrence of a preferred term will be included. The number of events per preferred term will also be summarized. Causality (relationship to study treatment) will be summarized separately.

All AEs, SAEs, treatment-related AEs, treatment-related SAEs, ≥ Grade 3 AEs, treatment-related ≥ Grade 3 AEs, and AEs leading to withdrawal, or treatment discontinuation will be summarized overall and 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 CTCAE v4.03 and summarized by treatment group. Incidence of laboratory abnormalities will be summarized. The worst on-study grade after

the first dose of study drug will be summarized. 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 by treatment group at each scheduled time point using descriptive statistics.

18. 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.

19. ETHICAL ASPECTS

19.1. 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".

19.2. Informed Consent

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

It is the responsibility of the investigator, or a person designated by the investigator, to obtain written informed consent from each subject (or the subject's legally authorized representative) participating 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. In the case where the subject is unable to read, an impartial witness should be present during the entire informed consent discussion. After the subject has orally consented to participation in the trial, 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.

19.3. Institutional Review Board

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

19.4. 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 trial. 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 Reflection Paper on Pharmacogenetic Samples, Testing and Data Handling (EMEA/CHMP/PGxWP/201914/2006). If a subject requests destruction of their tissue and blood samples and the samples have not yet been de-identified, Kadmon Corporation will destroy the samples as described in this FDA guidance. Kadmon Corporation will notify the investigator in writing that the samples have been destroyed.

20. CONDITIONS FOR MODIFYING THE PROTOCOL

Protocol modifications will be reviewed, and approved by Kadmon Corporation representatives.

All protocol modifications must be submitted to the IRB/IEC 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 trial (eg, change in monitor, change of telephone number).

21. CONDITIONS FOR TERMINATING THE STUDY

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

22. STUDY DOCUMENTATION, CRFS, AND RECORD KEEPING

22.1. 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, query forms, IRB/IEC, and governmental approval with correspondence, sample informed consent, 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 drug 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 Corporation. If the investigator wants to assign the study records to another party or move them to another location, Kadmon Corporation 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 Corporation 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.

22.2. Source Documents and Background Data

Upon request, the investigator will supply Kadmon Corporation 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.

22.3. Audits and Inspections

The investigator should understand that source documents for this study should be made available to appropriately qualified personnel from the Kadmon Corporation 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.

22.4. Electronic Case Report Forms

Clinical trial data for this study will be captured on electronic eCRF. The investigator agrees to provide all information requested on the eCRF in an accurate manner according to instructions provided. Electronic CRFs are designed for computer processing and analysis. The investigator should ensure the accuracy, completeness, and timeliness of the data reported to Kadmon Corporation (or designee) 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. eCRFs must be reviewed for completeness and accuracy, and electronically signed where indicated, by the principal investigator or authorized delegate from the study staff. If a subject stops treatment or terminates from the study, the dates and reasons must be noted on the eCRF.

23. MONITORING THE STUDY

It is understood that the responsible Kadmon Corporation monitor (or designee) will contact and visit the investigator regularly and will be allowed on request to inspect the various records of the trial (eCRFs and other pertinent data) provided 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.

24. CONFIDENTIALITY OF TRIAL 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 Corporation, subjects should be identified by an identification code and not by their names. The subjects' personal information should be redacted on all source documents prior to submission to Kadmon Corporation (or designee). The investigator should keep a Subject Enrollment Log showing codes, names, and addresses. The investigator should maintain documents not for submission to Kadmon Corporation (eg, subjects' written consent forms) in strict confidence.

25. 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 Corporation for review at least 30 days before submission. This allows Kadmon Corporation 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 Corporation 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 Corporation policy and generally accepted standards for authorship.

26. REFERENCES

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27. APPENDICES

Appendix A: Physician-Reported Global cGVHD Activity Assessment Form A

FORM A

Current Patient Weight: _____ Today's Date: _____ MR#/Name: _____

CHRONIC GVHD ACTIVITY ASSESSMENT- CLINICIAN

Health Care Provider Global Ratings:	Where would you rate the severity of this patient's chronic GvHD symptoms on the following scale, where 0 is cGVHD symptoms that are not at all severe and 10 is the most severe cGVHD symptoms possible:	Over the <<time>> would you say that this patient's cGvHD is
0=none 1= mild 2=moderate 3=severe	0 1 2 3 4 5 6 7 8 9 10 cGvHD symptoms not at all severe — Most severe cGvHD symptoms possible	+3= Very much better +2= Moderately better +1= A little better 0= About the same -1=A little worse -2=Moderately worse -3=Very much worse

Mouth	**Erythema**	None	0	Mild erythema or moderate erythema (<25%)	1	Moderate (≥25%) or Severe erythema (<25%)	2	Severe erythema (≥25%)	3
	Lichenoid	None	0	Lichen-like changes (<25%)	1	Lichen-like changes (25-50%)	2	Lichen-like changes (>50%)	3
	Ulcers	None	0			Ulcers involving (≤20%)	3	Severe ulcerations (>20%)	6
								Total score for all mucosal changes	

Gastrointestinal-Esophageal • Dysphagia OR Odynophagia	*0= no esophageal symptoms* *1=Occasional dysphagia or odynophagia with solid food or pills during the past week* *2=Intermittent dysphagia or odynophagia with solid foods or pills, but not for liquids or soft foods, during the past week* *3=Dysphagia or odynophagia for almost all oral intake, on almost every day of the past week*
Gastrointestinal-Upper GI • Early satiety OR • Anorexia OR • Nausea & Vomiting	*0= no symptoms* *1=mild, occasional symptoms, with little reduction in oral intake during the past week* *2=moderate, intermittent symptoms, with some reduction in oral intake during the past week* *3=more severe or persistent symptoms throughout the day, with marked reduction in oral intake, on almost every day of the past week*
Gastrointestinal-Lower GI • Diarrhea	*0= no loose or liquid stools during the past week* *1= occasional loose or liquid stools, on some days during the past week* *2=intermittent loose or liquid stools throughout the day, on almost every day of the past week, **without requiring** intervention to prevent or correct volume depletion* *3=voluminous diarrhea on almost every day of the past week, **requiring** intervention to prevent or correct volume depletion*

Lungs (Liters and % predicted) • Bronchiolitis Obliterans	FEV1	FVC	Single Breath DLCO (adjusted for hemoglobin)	TLC	RV
Liver Values	Total serum bilirubin mg/dL	ULN mg/dL	ALT U/L	ULN U/L	Alkaline Phosphatase U/L	ULN U/L
Baseline Values	Total Distance Walked in 2 or 6 Mins: ❑ 2 min ❑ 6 min	Karnofsky or Lansky	Platelet Count K/uL	Total WBC K/uL	Eosinophils %

☐ Abnormality present but explained entirely by non-GVHD documented cause (specify site/alternate cause):_____
☐ Abnormality present but explained entirely by non-GVHD documented cause (specify site/alternate cause):_____
☐ Abnormality present but explained entirely by non-GVHD documented cause (specify site/alternate cause):_____

Figure 1. Chronic GVHD Activity Assessment- Clinician Report.

Appendix A: Physician-Reported Global cGVHD Activity Assessment Form A (cont.)

CHRONIC GVHD ACTIVITY ASSESSMENT- CLINICIAN (FORM A)

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
SKIN *GVHD features to be scored by BSA:* **Check all that apply:** ☐ Maculopapular rash / erythema ☐ Lichen planus-like features ☐ Sclerotic features ☐ Papulosquamous lesions or ichthyosis ☐ Keratosis pilaris-like	☐ No BSA involved	☐ 1-18% BSA	☐ 19-50% BSA	☐ >50% BSA
☐ Abnormality present but explained entirely by non-GVHD documented cause (specify):_____				
SKIN FEATURES SCORE:	☐ No sclerotic features		☐ Superficial sclerotic features "not hidebound" (able to pinch)	**Check all that apply:** ☐ Deep sclerotic features ☐ "Hidebound" (unable to pinch) ☐ Impaired mobility ☐ Ulceration
If skin features score = 3, BSA% of non-moveable sclerosis/fasciitis _____ How would you rate the severity of this patient's skin and/or joint tightening on the following scale, where 0 is not at all severe and 10 is the most severe symptoms possible: 0 1 2 3 4 5 6 7 8 9 10 Symptoms not at all severe … Most severe symptoms possible				
EYES	☐ No symptoms symptoms	☐ Mild dry eye symptoms not affecting ADL (requirement of lubricant eye drops ≤ 3 x per day)	☐ Moderate dry eye symptoms partially affecting ADL (requiring lubricant eye drops > 3 x per day or punctal plugs), **WITHOUT** new vision impairment due to KCS	☐ Severe dry eye symptoms significantly affecting ADL (special eyeware to relieve pain) **OR** unable to work because of ocular symptoms **OR** loss of vision due to KCS
☐ Abnormality present but explained entirely by non-GVHD documented cause (specify):_____				
LUNGS	☐ No symptoms	☐ Mild symptoms (shortness of breath after climbing one flight of steps)	☐ Moderate symptoms (shortness of breath after walking on flat ground)	☐ Severe symptoms (shortness of breath at rest; requiring 0_2)
☐ Abnormality present but explained entirely by non-GVHD documented cause (specify):_____				

Figure 1. (continued).

Abstracted from: Lee SJ, et al. *Biol Blood Marrow Transplant*. 2015; 21:984-999.

Appendix B: cGVHD Response Assessment

Response Determination for Chronic GVHD Clinical Trials based on Clinician Assessments

Organ	Complete Response	Partial Response	Progression
Skin	NIH Skin Score 0 after previous involvement	Decrease in NIH Skin Score by 1 or more points	Increase in NIH Skin Score by 1 or more points, except 0 to 1
Eyes	NIH Eye Score 0 after previous involvement	Decrease in NIH Eye Score by 1 or more points	Increase in NIH Eye Score by 1 or more points, except 0 to 1
Mouth	NIH Modified OMRS 0 after previous involvement	Decrease in NIH Modified OMRS of 2 or more points	Increase in NIH Modified OMRS of 2 or more points
Esophagus	NIH Esophagus Score 0 after previous involvement	Decrease in NIH Esophagus Score by 1 or more points	Increase in NIH Esophagus Score by 1 or more points, except 0 to 1
Upper GI	NIH Upper GI Score 0 after previous involvement	Decrease in NIH Upper GI Score by 1 or more points	Increase in NIH Upper GI Score by 1 or more points, except 0 to 1
Lower GI	NIH Lower GI Score 0 after previous involvement	Decrease in NIH Lower GI Score by 1 or more points	Increase in NIH Lower GI Score by 1 or more points, except from 0 to 1
Liver	Normal ALT, alkaline phosphatase, and Total bilirubin after previous elevation of 1 or more	Decrease by 50%	Increase by 2 × ULN
Lungs	- Normal %FEV1 after previous involvement - If PFTs not available, NIH Lung Symptom Score 0 after previous involvement	- Increase by 10% predicted absolute value of %FEV1 - If PFTs not available, decrease in NIH Lung Symptom Score by 1 or more points	- Decrease by 10% predicted absolute value of %FEV1 - If PFTs not available, increase in NIH Lung Symptom Score by 1 or more points, except 0 to 1
Joints and fascia	Both NIH Joint and Fascia Score 0 and P-ROM score 25 after previous involvement by at least 1 measure	Decrease in NIH Joint and Fascia Score by 1 or more points or increase in P-ROM score by 1 point for any site	Increase in NIH Joint and Fascia Score by 1 or more points or decrease in P-ROM score by 1 point for any site
Global	Clinician overall severity score 0	Clinician overall severity score decreases by 2 or more points on a 0-10 scale	Clinician overall severity score increases by 2 or more points on a 0-10 scale

ULN indicates upper limit of normal.

Abstracted from: Lee SJ, Wolff D, Kitko C, et al. *Biol Blood Marrow Transplant* 2015; 21:984 – 999.

Definition of Response

Response	Definition
Complete Response (CR)	Resolution of all manifestations of cGVHD in each organ or site
Partial Response (PR)	Improvement in at least one organ or site without progression in any other organ or site
Lack of Response	
Mixed (LOR-M)	Complete or partial response in at least one organ accompanied by progression in another organ*
Unchanged (LOR-U)	Outcomes that do not meet the criteria for complete response, partial response, progression or mixed response
Progression (LOR-P)	Progression in at least one organ or site without a response in any other organ or site

* Considered progression for purposes of analysis

Appendix C: Chronic GVHD Activity Assessment-Patient Self Report

FORM B

Today's Date: _____ MR#/Name: _____

CHRONIC GVHD ACTIVITY ASSESSMENT-PATIENT SELF REPORT

Symptoms **Please rate how severe the following symptoms have been in the last seven days. Please fill in the circle below from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.**	**Not Present** 0	1	2	3	4	5	6	7	8	9	**As Bad As You Can Imagine** 10
Your **skin itching** at its WORST?	O	O	O	O	O	O	O	O	O	O	O
Your **mouth dryness** at its WORST?	O	O	O	O	O	O	O	O	O	O	O
Your **mouth pain** at its WORST?	O	O	O	O	O	O	O	O	O	O	O
Your **mouth sensitivity** at its WORST?	O	O	O	O	O	O	O	O	O	O	O

Eyes	What is your main complaint with regard to your eyes?	
	Please rate how severe is this eye symptom, between 0 (not at all severe) and 10 (most severe):	0 1 2 3 4 5 6 7 8 9 10
Vulvovaginal Symptoms (females only)	Do you have any burning, pain or discomfort in the area of your vagina, vulva or labia? **OR** Do you have any discomfort or pain with sexual intercourse?	o Yes o No o Not applicable

Patient Global Ratings:

1. Overall, do you think that your chronic graft versus host disease is mild, moderate or severe?
0= none
1= mild
2=moderate
3=severe

2. Please circle the number indicating how severe your chronic graft versus host disease symptoms are, where 0 is cGVHD symptoms that are not at all severe and 10 is the most severe chronic GVHD symptoms possible.

0 1 2 3 4 5 6 7 8 9 10

cGVHD symptoms not at all severe — Most severe cGVHD symptoms possible

3. Compared to a month ago, overall would you say that your cGVHD symptoms are:

+3= Very much better
+2= Moderately better
+1=A little better
0= About the same
-1=A little worse
-2=Moderately worse
-3=Very much worse

Attach copies of:

Adults (persons 18 years or older):
-Lee cGvHD Symptom Scale
-Human Activity Profile
-SF-36 v.2
-FACT-BMT

Children/Adolescents (persons 17 years or younger):
-Lee cGVHD Symptom Scale (persons 8-12 years old may complete with help of the health care professional)
-ASK - Activities Scale for Kids
-CHRIs-Generic and Disease Specific Inventory

Abstracted from: Lee SJ, Wolff D, Kitko C, et al. Measuring Therapeutic Response in Chronic Graft-versus-Host Disease. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: IV. The 2014 Response Criteria Working Group Report. *Biol Blood Marrow Transplant* 2015; 21:984 – 999.

Appendix D: Lee cGVHD Symptom Scale

	Not at all	Slightly	Moderately	Quite a bit	Extremely
SKIN:					
a. Abnormal skin color	0	1	2	3	4
b. Rashes	0	1	2	3	4
c. Thickened skin	0	1	2	3	4
d. Sores on skin	0	1	2	3	4
e. Itchy skin	0	1	2	3	4
EYES AND MOUTH:					
f. Dry eyes	0	1	2	3	4
g. Need to use eyedrops frequently	0	1	2	3	4
h. Difficulty seeing clearly	0	1	2	3	4
i. Need to avoid certain foods due to mouth pain	0	1	2	3	4
j. Ulcers in mouth	0	1	2	3	4
k. Receiving nutrition from an intravenous line or feeding tube	0	1	2	3	4
BREATHING:					
l. Frequent cough	0	1	2	3	4
m. Colored sputum	0	1	2	3	4
n. Shortness of breath with exercise	0	1	2	3	4
o. Shortness of breath at rest	0	1	2	3	4
p. Need to use oxygen	0	1	2	3	4
EATING AND DIGESTION:					
q. Difficulty swallowing solid foods	0	1	2	3	4
r. Difficulty swallowing liquids	0	1	2	3	4
s. Vomiting	0	1	2	3	4
t. Weight loss	0	1	2	3	4
MUSCLES AND JOINTS:					
u. Joint and muscle aches	0	1	2	3	4
v. Limited joint movement	0	1	2	3	4
w. Muscle cramps	0	1	2	3	4
x. Weak muscles	0	1	2	3	4
ENERGY:					
y. Loss of energy	0	1	2	3	4
z. Need to sleep more/take naps	0	1	2	3	4
aa. Fevers	0	1	2	3	4
MENTAL AND EMOTIONAL:					
bb. Depression	0	1	2	3	4
cc. Anxiety	0	1	2	3	4
dd. Difficulty sleeping	0	1	2	3	4

Abstracted from: Lee S, Cook EF, Soiffer R, et al. Development and validation of a scale to measure symptoms of chronic graft-versus-host disease. *Biol Blood Marrow Transplant.* 2002; 8:444-452.

Appendix E: Karnofsky Performance Scale

Condition	Percent	Description
Able to carry on normal activity and to work. No special care needed.	100	Normal, no complaints, no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work. Able to live at home and care for most personal needs. A varying degree of assistance is needed.	70	Cares for self, unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his/her needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self. Requires equivalent of institutional or hospice care. Disease may be progressing rapidly.	40	Disabled, requires special care and assistance.
	30	Severely disabled, hospitalization indicated. Death not imminent.
	20	Very sick, hospitalization indicated. Death not imminent.
	10	Moribund, fatal processes progressing rapidly.
	0	Dead

Reference: Karnofsky, D.A., and Burchenal, J.H. (1949). The Clinical Evaluation of Chemotherapeutic Agents in Cancer. In Evaluation of Chemotherapeutic Agents: Symposium Held at the New York Academy of Medicine, C.M. MacLeod, ed. (New York, Columbia University Press), pp. 191-205.

Appendix F: Equations to Predict Glomerular Filtration Rate (MDRD-4)

4-Variable Modification of Diet in Renal Disease (MDRD-4) Equation

High Level Formula for Black or African-American Males: Estimated GFR = 175 × (Creatinine $^{-1.154}$) × (Age $^{-0.203}$) × 1.212
High Level Formula for Males NOT Black or African-American (any other option): Estimated GFR = 175 × (Creatinine $^{-1.154}$) × (Age $^{-0.203}$)
High Level Formula for Black or African-American Females: Estimated GFR = 175 × (Creatinine $^{-1.154}$) × (Age $^{-0.203}$) × 1.212 × 0.742
High Level Formula for Females NOT Black or African-American (any other option): Estimated GFR = 175 × (Creatinine $^{-1.154}$) × (Age $^{-0.203}$) × 0.742

Adapted from: Levey AS, Coresh J, Greene T et al. . Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann Intern Med.* 2006; 145 (4): 247–54. PMID 16908915.

Appendix G: 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 (eg, 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.

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

Appendix H: Drugs that Induce and Inhibit CYP3A4

Use of drugs that are strong inducers of the CYP3A4 family of enzymes is prohibited in subjects who are receiving KD025. Other CYP3A4 inhibitors/ inducers should be used with caution.

This is not a comprehensive list, and all concomitant medications should be evaluated for possible interactions with KD025.

Drug Type		Drug Name
Moderate or Strong Inhibitors	Human immunodeficiency virus antivirals	amprenavir atazanavir atazanavir fosamprenavir indinavir
		nelfinavir
		ritonavir
		saquinavir
	Antifungals	itraconazole
		fluconazole
		ketoconazole
	Antibiotics	clarithromycin
		erythromycin
		telithromycin
	Antidepressants	nefazodone
	Calcium-channel blockers	diltiazem
		verapamil
	Others	aprepitant
		grapefruit juice

Source: http://medicine.iupui.edu/flockhart/table htm,

https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664 htm

Use of drugs that are strong inducers of the CYP3A4 family of enzymes (refer to source below) is prohibited in subjects who are receiving KD025.

Source:

https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm

28. SUMMARY OF CHANGES TO PROTOCOL

DOCUMENT HISTORY	
Document	**Date**
Amendment 7	23 Oct 2019
Amendment 6	15 Oct 2018
Amendment 5	24 May 2018
Amendment 4.1	26 Oct 2017
Amendment 4	19 Oct 2017
Amendment 3	06 Jun 2017
Amendment 2	14 July 2016
Amendment 1	22 Feb 2016
Original Protocol	22 Dec 2015

Amendment 7, 23 October 2019

This protocol was amended to include the following secondary endpoints:

- Overall Survival (OS)
- Time to Next Treatment (TTNT)
- Change in symptom burden/bother using the Lee cGVHD Symptom Scale

Also, clarification regarding Long Term Follow Up of subjects and mode of contact was made. Pharmacokinetic samples and Pharmacodynamic samples are not required to be collected at the End of Treatment visit. Also, CYP3A4 strong inducers are prohibited and other CYP3A4 inducers/ inhibitors are to be used with caution.

Minor grammatical and typographical corrections were also made.

Note that the changes made within the text of the protocol were also made within the synopsis of the protocol.

Original Text with Changes Shown (deleted text in ~~strikethrough~~ and added text in bold)	**New wording**	**Brief Rationale/ Justification for Change**
Synopsis-Study Objectives		

Original Text with Changes Shown (deleted text in ~~strikethrough~~ and added text in bold)	**New wording**	**Brief Rationale/ Justification for Change**
Secondary objectives • To evaluate changes in cGVHD severity using the Physician-reported global cGVHD Activity Assessment form (see Appendix A) • To assess changes in symptom activity using the cGVHD Activity Assessment Patient Self-Report • To evaluate failure-free survival (FFS) • To evaluate changes in corticosteroid and calcineurin inhibitor (CNI) dose • To evaluate duration of response (DOR) • To evaluate response by organ system • To assess the plasma pharmacokinetics (PK) of KD025 in subjects with cGVHD **• To evaluate Overall Survival (OS)** **• To evaluate Time to Next Treatment (TTNT)** **• To evaluate the change in symptom burden/bother using the Lee cGVHD Symptom Scale** Exploratory objectives • To evaluate changes in the expression of several cytokines (including IL-17A, IL-21, and IL-2) in plasma after KD025 administration • To evaluate changes in percentage of immune-cell subtypes (including Th17 and Treg cells) in whole blood after KD025 administration ~~• To evaluate the change in symptom burden/bother using the Lee cGVHD Symptom Scale~~	Secondary objectives • To evaluate Overall Survival (OS) • To evaluate Time to Next Treatment (TTNT) • To evaluate the change in symptom burden/bother using the Lee cGVHD Symptom Scale Exploratory objectives • To evaluate changes in the expression of several cytokines (including IL-17A, IL-21, and IL-2) in plasma after KD025 administration • To evaluate changes in percentage of immune-cell subtypes (including Th17 and Treg cells) in whole blood after KD025 administration	Statistical Analysis Plan is being updated to reflect these endpoints that will be analyzed.
Synopsis- Methodology		
Subjects will be contacted	Subjects will be contacted	Long-Term Follow-Up

Original Text with Changes Shown (deleted text in ~~strikethrough~~ and added text in bold)	**New wording**	**Brief Rationale/ Justification for Change**
approximately every 8 weeks and can be contacted via telephone, email or postal mail to confirm survival status and the initiation of any anti-cancer treatment or any changes in treatment of cGVHD. This can also be confirmed from electronic medical records. ~~After the follow-up visit is completed, subjects will be contacted by telephone every 8 weeks until study closeout to confirm survival status and the initiation of any anti-cancer treatment or any changes in treatment for cGVHD~~	approximately every 8 weeks and can be contacted via telephone, email or postal mail to confirm survival status and the initiation of any anti-cancer treatment or any changes in treatment of cGVHD. This can also be confirmed from electronic medical records.	clarification provided.
Synopsis—Approximate Duration of Subject Participation		
Subjects will be contacted approximately every 8 weeks and can be contacted via telephone, email or postal mail to confirm survival status and the initiation of any anti-cancer treatment or any changes in treatment of cGVHD. This can also be confirmed from electronic medical records. ~~In addition, subjects will be contacted by telephone every 8 weeks until study closeout to confirm survival status and the initiation of any anti-cancer treatment or any changes in treatment for cGVHD~~	Subjects will be contacted approximately every 8 weeks and can be contacted via telephone, email or postal mail to confirm survival status and the initiation of any anti-cancer treatment or any changes in treatment of cGVHD. This can also be confirmed from electronic medical records	Long-Term Follow-Up clarification provided.
Synopsis—Concomitant Treatment		
The use of **strong** CYP3A4 ~~inhibitor~~/inducers (see Appendix H for a listing of these drugs) is prohibited.	The use of strong CYP3A4 inducers (see Appendix H for a listing of these drugs) is prohibited.	Based upon data from KD025-107 (KD025 Drug-Drug-Interaction study).
Synopsis- Activity Evaluation		
Failure-free survival, **Overall**	Failure-free survival, Overall Survival,	Statistical Analysis Plan

Original Text with Changes Shown (deleted text in ~~strikethrough~~ and added text in bold)	**New wording**	**Brief Rationale/ Justification for Change**
Survival, Time to Next Treatment and changes in corticosteroid and calcineurin inhibitor dose will be documented. Changes in symptom burden/bother will be **documetned** ~~explored~~ using the Lee cGVHD Symptom Scale.	Time to Next Treatment and changes in corticosteroid and calcineurin inhibitor dose will be documented. Changes in symptom burden/bother will be documented using the Lee cGVHD Symptom Scale.	is being updated to reflect these endpoints that will be analyzed.
Synopsis- Pharmacokinetics		
Blood samples (approximately 5 mL) for determination of plasma concentrations of KD025 and its metabolites, will be collected on Day 1 of Cycles 1 and 2 at the following time points: Pre-dose (Time 0), and 1, 2, 3, 4, 5, and 6 hours after dosing (after first dose for subjects in the BID group). In addition, subjects will have samples collected pre-dose on Day 1 of Cycle 4, **and** pre-dose at the Cycle 7, Day 1 visit**.**~~, and at the EOT visit. Also, if appropriate, a sample will be requested if a subject discontinues treatment prematurely.~~ Subjects should be instructed to withhold taking study drug on these days as dosing will be performed at the clinic. Subjects will have a total ~~17~~ **16** samples drawn (~~85~~ **80** mL).	Blood samples (approximately 5 mL) for determination of plasma concentrations of KD025 and its metabolites, will be collected on Day 1 of Cycles 1 and 2 at the following time points: Pre-dose (Time 0), and 1, 2, 3, 4, 5, and 6 hours after dosing (after first dose for subjects in the BID group). In addition, subjects will have samples collected pre-dose on Day 1 of Cycle 4, and pre-dose at the Cycle 7, Day 1 visit. Subjects should be instructed to withhold taking study drug on these days as dosing will be performed at the clinic. Subjects will have a total 16 samples drawn (80 mL).	Last subjects enrolled into study more than one year ago and no more Pharmacokinetics samples will be analyzed.
Synopsis- Pharmacodynamics		
All subjects will have PD blood samples drawn **4** ~~6~~ times over the course of the study: Pre-dose on Cycle 1 Day 1, Cycle 2 Day 1 (4 weeks), ~~and~~ Cycle 4 Day 1 (12 weeks) **and** ~~at the~~ Cycle 7 Day 1 **(24 weeks)**~~visit; at the EOT visit, and at the 28 Day Follow-Up visit. Samples~~ will be analyzed to evaluate changes in the expression of several cytokines in plasma (including IL-17A, IL-21, and IL-2), and changes	All subjects will have PD blood samples drawn 4 times over the course of the study: Pre-dose on Cycle 1 Day 1, Cycle 2 Day 1 (4 weeks), Cycle 4 Day 1 (12 weeks) and Cycle 7 Day 1 (24 weeks) will be analyzed to evaluate changes in the expression of several cytokines in plasma (including IL-17A, IL-21, and IL-2), and changes in percentages of circulating Th17 and Treg cells in blood.	Pharmacodynamic samples do not have to be collected at the End of Treatment visit. Since it is not possible to predict the End of Treatment visits for the remaining subjects in the study, EOT samples for each subject would have to be analyzed on an as-

Original Text with Changes Shown (deleted text in ~~strikethrough~~ and added text in bold)	**New wording**	**Brief Rationale/ Justification for Change**
in percentages of circulating Th17 and Treg cells in blood. ~~PD blood samples also will be requested for any subject who discontinues treatment prematurely~~		collected basis.
Synopsis- Statistical Analysis		
Four populations will be included in the analysis of study data: • The **modified** intent-to-treat (**m**ITT) population will consist of all subjects who are enrolled in the study **and receive at least 1 dose of study medication** ~~who are not screen failures~~. • The safety population will consist of all subjects who receive at least one dose of KD025 • ~~The per protocol population will consist of subjects who have received at least 50% of study drug and have at least one evaluable response assessment~~ • The PK population will consist of all subjects who receive at least one dose of study drug and have at least 1 post-dose PK sample drawn All analyses of safety will be performed on the safety population while activity will be performed on the **m**ITT ~~and Per Protocol~~ populations~~.~~ **Overall survival (OS) will be defined as the time from first dose of KD025 to the date of death due to any cause. Kaplan-Meier plots, descriptive statistics of OS and landmark OS at**	Four populations will be included in the analysis of study data: • The modified intent-to-treat (mITT) population will consist of all subjects who are enrolled in the study and receive at least 1 dose of study medication. • The safety population will consist of all subjects who receive at least one dose of KD025 • The PK population will consist of all subjects who receive at least one dose of study drug and have at least 1 post-dose PK sample drawn All analyses of safety will be performed on the safety population while activity will be performed on the mITT population. Overall survival (OS) will be defined as the time from first dose of KD025 to the date of death due to any cause. Kaplan-Meier plots, descriptive statistics of OS and landmark OS at 6,	Statistical Analysis Plan is being updated to reflect these endpoints that will be analyzed.

Original Text with Changes Shown (deleted text in ~~strikethrough~~ and added text in bold)	**New wording**	**Brief Rationale/ Justification for Change**
6, 12, 18 and 24 months will be provided. **Time to Next Treatment (TTNT) will be defined as the time from the first dose of KD025 to the start of additional systemic cGVHD therapy.**	12, 18 and 24 months will be provided. Time to Next Treatment (TTNT) will be defined as the time from the first dose of KD025 to the start of additional systemic cGVHD therapy.	
Section 5.2 Secondary Objectives		
The secondary objectives of the study are: • To evaluate changes in cGVHD severity using the Physician-reported global cGVHD Activity Assessment form (see Appendix A) • To assess changes in symptom activity using the cGVHD Activity Assessment Patient Self-Report • To evaluate failure-free survival (FFS) • To evaluate changes in corticosteroid and calcineurin inhibitor (CNI) dose • To evaluate duration of response (DOR) • To evaluate response by organ system • To assess the plasma PK of KD025 in subjects with cGVHD **• To evaluate Overall Survival (OS)** **• To evaluate Time to Next Treatment (TTNT)** **• To evaluate the change in symptom burden/bother using the Lee cGVHD Symptom Scale**	The secondary objectives of the study are: • To evaluate changes in cGVHD severity using the Physician-reported global cGVHD Activity Assessment form (see Appendix A) • To assess changes in symptom activity using the cGVHD Activity Assessment Patient Self-Report • To evaluate failure-free survival (FFS) • To evaluate changes in corticosteroid and calcineurin inhibitor (CNI) dose • To evaluate duration of response (DOR) • To evaluate response by organ system • To assess the plasma PK of KD025 in subjects with cGVHD • To evaluate Overall Survival (OS) • To evaluate Time to Next Treatment (TTNT) • To evaluate the change in symptom burden/bother using the Lee cGVHD Symptom Scale	Statistical Analysis Plan is being updated to reflect these endpoints that will be analyzed.
Section 5.3 Exploratory Objective		
To evaluate changes in the expression of several cytokines (including IL-17A, IL-21, and IL-2) in plasma after KD025 administration To evaluate changes in percentage of immune-cell subtypes (including Th17 and Treg cells) in whole blood after	To evaluate changes in the expression of several cytokines (including IL-17A, IL-21, and IL-2) in plasma after KD025 administration To evaluate changes in percentage of immune-cell subtypes (including Th17 and Treg cells) in whole blood after	Statistical Analysis Plan is being updated to reflect these endpoints that will be analyzed.

Original Text with Changes Shown (deleted text in ~~strikethrough~~ and added text in bold)	**New wording**	**Brief Rationale/ Justification for Change**
KD025 administration ~~To evaluate the change in symptom burden/bother using the Lee cGVHD Symptom Scale~~	KD025 administration	
Section 6.2 Study Endpoints		
Secondary Endpoints • Number and percentage of KD025 in subjects with steroid-dependent cGVHD who have a best response of PR or CR • Change in cGVHD severity as based on the Physician-reported global cGVHD Activity Assessment • Change in symptom activity as based on cGVHD Activity Assessment Patient Self-Report • Median failure-free survival (FFS) • Changes in corticosteroid and calcineurin inhibitor dose • DOR • Response rate by organ system • Analyses of plasma PK of KD025 in subjects with cGVHD **• Overall Survival** **• Time to Next Treatment** **• Change in symptom burden/bother using the Lee cGVHD Symptom Scale** Exploratory Endpoints • Changes in the expression of several cytokines (including IL-17A, IL-21, and IL-2) in plasma after KD025 administration to subjects with cGVHD • Changes in percentage of immune-cell subtypes (including Th17 and Treg cells) in whole blood after KD025 administration to subjects with	Secondary Endpoints • Number and percentage of KD025 in subjects with steroid-dependent cGVHD who have a best response of PR or CR • Change in cGVHD severity as based on the Physician-reported global cGVHD Activity Assessment • Change in symptom activity as based on cGVHD Activity Assessment Patient Self Report • Median failure-free survival (FFS) • Changes in corticosteroid and calcineurin inhibitor dose • DOR • Response rate by organ system •Analyses of plasma PK of KD025 in subjects with cGVHD • Overall Survival • Time to Next Treatment • Change in symptom burden/bother using the Lee cGVHD Symptom Scale Exploratory Endpoints •Changes in the expression of several cytokines (including IL-17A, IL-21, and IL-2) in plasma after KD025 administration to subjects with cGVHD • Changes in percentage of immune-cell subtypes (including Th17 and Treg cells) in whole blood after KD025 administration to subjects with cGVHD	Statistical Analysis Plan is being updated to reflect these endpoints that will be analyzed.

Original Text with Changes Shown (deleted text in ~~strikethrough~~ and added text in bold)	**New wording**	**Brief Rationale/ Justification for Change**
cGVHD ~~• Change in symptom burden/bother using the Lee cGVHD Symptom Scale~~		
Section 6.3 Overview of Study Design		
This is a Phase 2a, dose-escalation, open-label study designed to evaluate the safety, tolerability, and activity of KD025 in subjects with steroid-dependent cGVHD and active disease in terms of partial response (PR) and complete response (CR) as defined by the 2014 NIH Consensus Development Project on clinical trials in cGVHD (see Appendix B). This study also is designed to use the Physician-reported global cGVHD Activity Assessment to evaluate cGVHD severity; use the cGVHD Activity Assessment Patient Self-Report to assess symptom activity (see Appendix C); evaluate failure-free survival (FFS); **evaluate Overall Survival (OS);** assess changes in corticosteroid and calcineurin inhibitor dose; **evaluate Time to Next Treatment (TTNT);** and assess the PK of KD025 in subjects with cGVHD. **Changes in symptom burden/bother will be documented using the Lee cGVHD Symptom Scale (see Appendix D).** Changes in the expression of several cytokines (including IL-17A, IL-21, and IL-2) in plasma and percentages of immune-cell subtypes (including Th17 and Treg cells) in whole blood after KD025 administration to subjects with cGVHD, ~~as well as changes in symptom burden/bother using the Lee cGVHD Symptom Scale, will be explored (see Appendix D)~~. Long-Term Follow-Up	This is a Phase 2a, dose-escalation, open-label study designed to evaluate the safety, tolerability, and activity of KD025 in subjects with steroid-dependent cGVHD and active disease in terms of partial response (PR) and complete response (CR) as defined by the 2014 NIH Consensus Development Project on clinical trials in cGVHD (see Appendix B). This study also is designed to use the Physician-reported global cGVHD Activity Assessment to evaluate cGVHD severity; use the cGVHD Activity Assessment Patient Self-Report to assess symptom activity (see Appendix C); evaluate failure-free survival (FFS); evaluate Overall Survival (OS); assess changes in corticosteroid and calcineurin inhibitor dose; evaluate Time to Next Treatment (TTNT); and assess the PK of KD025 in subjects with cGVHD. Changes in symptom burden/bother will be documented using the Lee cGVHD Symptom Scale (see Appendix D). Changes in the expression of several cytokines (including IL-17A, IL-21, and IL-2) in plasma and percentages of immune-cell subtypes (including Th17 and Treg cells) in whole blood after KD025 administration to subjects with cGVHD. Long-Term Follow-Up Subjects will be contacted approximately every 8 weeks and can	Statistical Analysis Plan is being updated to reflect these endpoints that will be analyzed. Long-Term Follow-Up is clarified.

Original Text with Changes Shown (deleted text in ~~strikethrough~~ and added text in bold)	**New wording**	**Brief Rationale/ Justification for Change**
Subjects will be contacted approximately every 8 weeks and can be contacted via telephone, email or postal mail to confirm survival status and the initiation of any anti-cancer treatment or any changes in treatment of cGVHD. This can also be confirmed from electronic medical records. ~~Once subjects complete the 28 Day Follow-Up visit, subjects will be contacted by telephone every 8 weeks until study closeout to confirm survival status and the initiation of any anti-cancer treatment or any changes in treatment for cGVHD.~~	be contacted via telephone, email or postal mail to confirm survival status and the initiation of any anti-cancer treatment or any changes in treatment of cGVHD. This can also be confirmed from electronic medical records.	
Table 1		
g. All Blood samples (approximately 5 mL) for determination of plasma concentrations of KD025 and its metabolites will be collected on Day 1 o Cycles 1 and 2 at the following timepoints: Pre-dose (Time 0), and 1, 2, 3, 4, 5, 6 hours after dosing (after first dose for subjects in the BID group). In addition, subjects will have samples collected pre-dose on Day 1 of Cycle 4, pre-dose at the Cycle 7 Day 1 visit~~, and at the EOT visit. Also, if appropriate, a sample will be requested if a subject discontinues treatment prematurely.~~	g. All Blood samples (approximately 5 mL) for determination of plasma concentrations of KD025 and its metabolites will be collected on Day 1 of Cycles 1 and 2 at the following timepoints: Pre-dose (Time 0), and 1, 2, 3, 4, 5, 6 hours after dosing (after first dose for subjects in the BID group). In addition, subjects will have samples collected pre-dose on Day 1 of Cycle 4, pre-dose at the Cycle 7 Day 1 visit	Last subjects enrolled into study more than one year ago and no more Pharmacokinetics samples will be analyzed.
h. All subjects will have pre-dose PD blood samples drawn up to ~~6~~ **4** times over the course of the study. ~~Also, if appropriate, a sample will be requested if a subject discontinues treatment prematurely.~~	h. All subjects will have pre-dose PD blood samples drawn up to 4 times over the course of the study.	Pharmacodynamics samples are not required to be collected.
m. **Subjects will be contacted approximately every 8 weeks and can be contacted via telephone, email or postal mail to confirm**	m. Subjects will be contacted approximately every 8 weeks and can be contacted via telephone, email or postal mail to confirm survival status and the initiation of any anti-cancer	Long-Term Follow-Up clarification provided.

Original Text with Changes Shown (deleted text in ~~strikethrough~~ and added text in bold)	**New wording**	**Brief Rationale/ Justification for Change**
survival status and the initiation of any anti-cancer treatment or any changes in treatment of cGVHD. This can also be confirmed from electronic medical records ~~Subjects are to be contacted by telephone every 8 weeks until study close out to confirm survival status and the initiation of any anti-cancer treatment or any changes in treatment for cGVHD.~~	treatment or any changes in treatment of cGVHD. This can also be confirmed from electronic medical records	
Section 8.5 End of Treatment		
~~• PK sample collection~~ ~~• PD sample collection~~		Last subjects enrolled into study more than one year ago and no more Pharmacokinetics samples will be analyzed. Pharmacodynamics samples are not required to be collected.
Section 8.6 28 Day Follow Up		
~~• PD sample collection~~		Pharmacodynamics samples are not required to be collected.
Section 8.7 Unscheduled Visits		
~~• PK sample collection (if appropriate)~~ ~~• PD sample collection~~		Last subjects enrolled into study more than one year ago and no more Pharmacokinetics samples will be analyzed. Pharmacodynamics samples are not required to be collected.
Section 8.8 Long-Term Follow-Up		

Original Text with Changes Shown (deleted text in ~~strikethrough~~ and added text in bold)	**New wording**	**Brief Rationale/ Justification for Change**
~~After the follow-up visit is completed, subjects will be contacted by telephone every 8 weeks until study closeout to confirm survival status and the initiation of any anti-cancer treatment or any changes in treatment for cGVHD.~~ **Subjects will be contacted approximately every 8 weeks and can be contacted via telephone, email or postal mail to confirm survival status and the initiation of any anti-cancer treatment or any changes in treatment of cGVHD. This can also be confirmed from electronic medical records**	Subjects will be contacted approximately every 8 weeks and can be contacted via telephone, email or postal mail to confirm survival status and the initiation of any anti-cancer treatment or any changes in treatment of cGVHD. This can also be confirmed from electronic medical records	Long-Term Follow-Up clarification provided.
Section 9.1 Procedures to be Performed		

Original Text with Changes Shown (deleted text in ~~strikethrough~~ and added text in bold)	**New wording**	**Brief Rationale/ Justification for Change**
Pharmacokinetics (PK) Sampling Blood samples (approximately 5 mL) for determination of plasma concentrations of KD025 and its metabolites, will be collected on Day 1 of Cycles 1 and 2 at the following time points: Pre-dose (Time 0), and 1, 2, 3, 4, 5, and 6 hours after dosing (after first dose for subjects in the BID group). In addition, subjects will have samples collected pre-dose on Day 1 of Cycle 4 and pre-dose at the Cycle 7 Day 1 visit ~~as well as the EOT visit. Also, if appropriate, a sample will be requested if a subject discontinues treatment prematurely.~~. See Section 11 for additional information.	Pharmacokinetics (PK) Sampling Blood samples (approximately 5 mL) for determination of plasma concentrations of KD025 and its metabolites, will be collected on Day 1 of Cycles 1 and 2 at the following time points: Pre-dose (Time 0), and 1, 2, 3, 4, 5, and 6 hours after dosing (after first dose for subjects in the BID group). In addition, subjects will have samples collected pre-dose on Day 1 of Cycle 4 and pre-dose at the Cycle 7 Day 1 visit. See Section 11 for additional information.	Last subjects enrolled into study more than one year ago and no more Pharmacokinetics samples will be analyzed. Pharmacodynamics samples are not required to be collected Statistical Analysis Plan is being updated to reflect these endpoints that will be analyzed.
Blood Sampling for Pharmacodynamics (PD) ~~All subjects will have samples drawn to evaluate changes in the expression of several cytokines (including IL-17A, IL-21and IL-21) in plasma, and changes in percentages of immune cell subtypes (including Th17 and Treg cells) in blood.~~ ~~All subjects will have PD blood samples drawn up to 6 times over the course of the study: Pre-dose on Cycle 1 Day 1, Cycle 2 Day 1 (4 weeks), and Cycle 4 Day 1 (12 weeks); at the Cycle 7 Day 1 visit; and at the EOT visit and 28 Day Follow Up visit. Also, if appropriate, a sample will be requested if a subject discontinues treatment prematurely. See Section 12 for additional information.~~ **All subjects will have PD blood samples drawn up to 4 times over the course of the study: Pre-dose on Cycle 1 Day 1, Cycle 2 Day 1 (4 weeks), Cycle 4 Day 1 (12 weeks) and Cycle 7 Day 1 (24 weeks).**	Blood Sampling for Pharmacodynamics (PD) All subjects will have PD blood samples drawn 4 times over the course of the study: Pre-dose on Cycle 1 Day 1, Cycle 2 Day 1 (4 weeks), and Cycle 4 Day 1 (12 weeks) and Cycle 7 Day 1 (24 weeks) will be analyzed to evaluate changes in the expression of several cytokines in plasma (including IL-17A, IL-21, and IL-2), and changes in percentages of circulating Th17 and Treg cells in blood. See Section 12 for additional information.	

Original Text with Changes Shown (deleted text in ~~strikethrough~~ and added text in bold)	**New wording**	**Brief Rationale/ Justification for Change**
Samples will be analyzed to evaluate changes in the expression of several cytokines in plasma (including IL-17A, IL-21, and IL-2), and changes in percentages of circulating Th17 and Treg cells in blood. See Section 12 for additional information Response Activity and Assessments Activity in terms of cGVHD severity will be evaluated using the Physician-reported global cGVHD Activity Assessment form (see Appendix A), while activity in terms of symptom burden will be evaluated using the cGVHD Activity Assessment - Patient Self Report (see Appendix C). Failure-free survival (FFS), **Overall Survival (OS) and Time to Next Treatment (TTNT),** will be evaluated at the same time points. Changes in corticosteroid and calcineurin inhibitor dose will be documented as they occur on the appropriate eCRF. Changes in symptom burden/bother will be ~~explored~~ documented using the Lee cGVHD Symptom Scale (see Appendix D).	Response Activity and Assessments Activity in terms of cGVHD severity will be evaluated using the Physician-reported global cGVHD Activity Assessment form (see Appendix A), while activity in terms of symptom burden will be evaluated using the cGVHD Activity Assessment - Patient Self Report (see Appendix C). Failure-free survival (FFS), Overall Survival (OS) and Time to Next Treatment (TTNT) will be evaluated at the same time points. Changes in corticosteroid and calcineurin inhibitor dose will be documented as they occur on the appropriate eCRF. Changes in symptom burden/bother will be documented using the Lee cGVHD Symptom Scale (see Appendix D).	
Section 10 Activity		
Secondary endpoints include evaluation of cGVHD severity using the Physician-reported global cGVHD Activity Assessment; evaluation of symptom burden using the cGVHD Activity Assessment - Patient Self Report; failure-free survival (FFS); **Overall Survival (OS); Time to Next Treatment (TTNT);** ~~and~~ changes in corticosteroid and calcineurin inhibitor dose; **and** ~~C~~changes in symptom burden/bother using the Lee cGVHD Symptom Scale. ~~will be an exploratory endpoint.~~	Secondary endpoints include evaluation of cGVHD severity using the Physician-reported global cGVHD Activity Assessment; evaluation of symptom burden using the cGVHD Activity Assessment - Patient Self Report; failure-free survival (FFS); Overall Survival (OS); Time to Next Treatment (TTNT); changes in corticosteroid and calcineurin inhibitor dose; and changes in symptom burden/bother using the Lee cGVHD Symptom Scale.	Statistical Analysis Plan is being updated to reflect these endpoints that will be analyzed.

Original Text with Changes Shown (deleted text in ~~strikethrough~~ and added text in bold)	**New wording**	**Brief Rationale/ Justification for Change**
Section 10.5 Overall Survival		
	Overall Survival (OS) data will be collected throughout the study	Overall Survival has been included as a secondary endpoint in this protocol amendment
Section 10.7 Time to Next Treatment		
	Time to Next Treatment (TTNT) data will be collected throughout the study	Time to Next Treatment has been included as a secondary endpoint in this protocol amendment
Section 10.8 Lee cGVHD Symptom Scale		
Changes in symptom burden/bother will be **documented** ~~explored~~ using the Lee cGVHD Symptom Scale (see Appendix D).	Changes in symptom burden/bother will be documented using the Lee cGVHD Symptom Scale (see Appendix D).	Change in symptom burden/bother using the Lee cGVHD Symptom Scale has been included as a secondary endpoint in this protocol amendment
Section 11 Pharmacokinetics		
In addition, subjects will have samples collected pre-dose on Day 1 of Cycle 4, **and** Cycle 7 Day 1 visit~~, and at the EOT visit. Subjects should be instructed to withhold taking study drug on these days as dosing will be performed at the clinic.~~ A total of **16** ~~17~~ samples will be collected (**80** ~~85~~ mL) from subjects in the dose escalation portion of the study.	In addition, subjects will have samples collected pre-dose on Day 1 of Cycle 4, and Cycle 7 Day 1 visit. A total of 16 samples will be collected (80 mL) from subjects in the dose escalation portion of the study.	Last subjects enrolled into study more than one year ago and no more Pharmacokinetics samples will be analyzed.
Section 12 Pharmacodynamics		
~~All subjects will have PD blood samples drawn 6 times over the course of the study: Pre-dose on Cycle 1 Day 1, Cycle 2 Day 1 (4 weeks), and Cycle 4 Day 1 (12 weeks); at the Cycle 7 Day 1 (24 weeks); at the EOT visit, and at the 28 Day Follow Up visit. Samples will be analyzed to evaluate changes in the expression of several cytokines (including IL 17A, IL 21,~~	All subjects will have PD blood samples drawn 4 times over the course of the study: Pre-dose on Cycle 1 Day 1, Cycle 2 Day 1 (4 weeks), and Cycle 4 Day 1 (12 weeks) and Cycle 7 Day 1 (24 weeks) will be analyzed to evaluate changes in the expression of several cytokines in plasma (including IL-17A, IL-21, and IL-2), and changes in percentages of circulating Th17 and	Pharmacodynamics samples are not required to be collected

Original Text with Changes Shown (deleted text in ~~strikethrough~~ and added text in bold)	**New wording**	**Brief Rationale/ Justification for Change**
~~and IL-2) in plasma, and changes in percentages of immune cell subtypes (including Th17 and Treg cells) in blood.~~ ~~PD blood samples also will be requested for any subject who discontinues treatment prematurely.~~ **All subjects will have PD blood samples drawn 4 times over the course of the study: Pre-dose on Cycle 1 Day 1, Cycle 2 Day 1 (4 weeks), and Cycle 4 Day 1 (12 weeks) and Cycle 7 Day 1 (24 weeks) will be analyzed to evaluate changes in the expression of several cytokines in plasma (including IL-17A, IL-21, and IL-2), and changes in percentages of circulating Th17 and Treg cells in blood.**	Treg cells in blood.	
Section 14.4 Dose Pause or Reduction of KD025		
If **treatment-related** Grade 2 or treatment-related Grade 3 toxicities persist for 14 days, subjects will be discontinued from the study.	If treatment-related Grade 2 or treatment-related Grade 3 toxicities persist for 14 days, subjects will be discontinued from the study.	Guidance for this discontinuation reason was always intended for G2 and G3 treatment-related toxicities; now clarified with revised wording.
Section 15 Concomitant Medication and Treatment		
The use of medications that are **strong** CYP3A4 ~~inhibitor/~~inducers ~~(see Appendix H for a listing of these drugs)~~ is prohibited. **Other CYP3A4 inhibitors / inducers should be used with caution. (See Appendix H for a listing of these drugs)**	The use of medications that are strong CYP3A4 inducers is prohibited. Other CYP3A4 inhibitors / inducers should be used with caution. (See Appendix H for a listing of these drugs.)	Based upon data from KD025-107 (KD025 Drug-Drug-Interaction study).
Section 17.3 Statistical Considerations		
Four populations will be employed in the analysis of study data: • The **modified** intent-to-treat	Four populations will be employed in the analysis of study data: • The modified intent-to-treat	Statistical Analysis Plan is being updated to reflect these endpoints that will be analyzed.

Original Text with Changes Shown (deleted text in ~~strikethrough~~ and added text in bold)	**New wording**	**Brief Rationale/ Justification for Change**
(**m**ITT) population will consist of all subjects who are enrolled in the study and **receive at least 1 dose of study medication.** ~~who are not screen failures.~~ ~~The safety population which will consist of all subjects who receive at least one dose of KD025.~~ • The safety population will consist of all subjects who receive at least one dose of KD025. ~~The per protocol population will consist of subjects who have received at least 50% of study drug and have at least one evaluable response assessment.~~ • The PK population which will consist of all subjects who receive at least one dose of study drug and have at least 1 post-dose PK sample drawn Demographics, subject disposition, and screening and baseline characteristics will be summarized for the **m**ITT **population** ~~and Per Protocol popualtions,~~ ~~where appropriate.~~	(mITT) population will consist of all subjects who are enrolled in the study and receive at least 1 dose of study medication. • The safety population will consist of all subjects who receive at least one dose of KD025. • The PK population which will consist of all subjects who receive at least one dose of study drug and have at least 1 post-dose PK sample drawn Demographics, subject disposition, and screening and baseline characteristics will be summarized for the mITT population.	
Section 17.4 Activity Analysis		

Original Text with Changes Shown (deleted text in ~~strikethrough~~ and added text in bold)	**New wording**	**Brief Rationale/ Justification for Change**
Secondary Endpoints • Number and percentage of KD025 in subjects with steroid-dependent cGVHD who have a best response of PR or CR • Change in cGVHD severity as based on the Physician-reported global cGVHD Activity Assessment • Change in symptom activity as based on cGVHD Activity Assessment Patient Self Report • Median FFS will be defined as the time from first dose of study drug to either the start of another treatment, relapse of the underlying disease, or death • Changes in corticosteroid and calcineurin inhibitor dose • To evaluate DOR. The DOR is defined as the time of initial response until documented progression. • To evaluate response by organ system. The response by organ system (PR and CR) will be assessed based on the 2014 NIH Consensus Development Project on Clinical Trials in cGVHD. **• Overall Survival (OS) will be defined as the time from first dose of KD025 to the date of death due to any cause. Kaplan-Meier plots, descriptive statistics of OS and landmark OS at 6, 12, 18 and 24 months will be provided** **• Time to Next Treatment (TTNT) will be defined as the defined as the time from the first dose of KD025 to the start of additional systemic cGVHD therapy** **• Change in symptom burden/bother using the Lee cGVHD Symptom Scale**	Secondary Endpoints • Number and percentage of KD025 in subjects with steroid-dependent cGVHD who have a best response of PR or CR • Change in cGVHD severity as based on the Physician-reported global cGVHD Activity Assessment • Change in symptom activity as based on cGVHD Activity Assessment Patient Self Report • Median FFS will be defined as the time from first dose of study drug to either the start of another treatment, relapse of the underlying disease, or death • Changes in corticosteroid and calcineurin inhibitor dose • To evaluate DOR. The DOR is defined as the time of initial response until documented progression. • To evaluate response by organ system. The response by organ system (PR and CR) will be assessed based on the 2014 NIH Consensus Development Project on Clinical Trials in cGVHD. • Overall Survival (OS) will be defined as the time from first dose of KD025 to the date of death due to any cause. Kaplan-Meier plots, descriptive statistics of OS and landmark OS at 6, 12, 18 and 24 months will be provided • Time to Next Treatment (TTNT) will be defined as the defined as the time from the first dose of KD025 to the start of additional systemic cGVHD therapy • Change in symptom burden/bother using the Lee cGVHD Symptom Scale	Statistical Analysis Plan is being updated to reflect these endpoints that will be analyzed.

Original Text with Changes Shown (deleted text in ~~strikethrough~~ and added text in bold)	**New wording**	**Brief Rationale/ Justification for Change**
Exploratory Endpoints • Changes in the expression of several cytokines (including IL-17A, IL-21, and IL-2) in plasma after KD025 administration to subjects with cGVHD • Changes in percentage of immune-cell subtypes (including Th17 and Treg cells) in whole blood after KD025 administration to subjects with cGVHD ~~• Change in symptom burden/bother using the Lee cGVHD Symptom Scale~~	Exploratory Endpoints • Changes in the expression of several cytokines (including IL-17A, IL-21, and IL-2) in plasma after KD025 administration to subjects with cGVHD • Changes in percentage of immune-cell subtypes (including Th17 and Treg cells) in whole blood after KD025 administration to subjects with cGVHD	
Appendix H: Drugs that Induce and Inhibit CYP3A4		
Use of drugs that are ~~moderate or~~ strong ~~inhibitors~~ **inducers** of the CYP3A4 family of enzymes is prohibited in subjects who are receiving KD025. **Other CYP3A4 inhibitors/ inducers should be used with caution.** Use of drugs that are ~~moderate or~~ strong inducers of the CYP3A4 family of enzymes (refer to source below) is prohibited in subjects who are receiving KD025.	Use of drugs that are strong inducers of the CYP3A4 family of enzymes is prohibited in subjects who are receiving KD025. Other CYP3A4 inhibitors/ inducers should be used with caution. Use of drugs that are strong inducers of the CYP3A4 family of enzymes (refer to source below) is prohibited in subjects who are receiving KD025.	Based upon data from KD025-107 (KD025 Drug-Drug-Interaction study).