CLINICAL STUDY PROTOCOL

A Randomized, Phase 2, Open-Label, Multicenter Study to Evaluate the Safety, Tolerability, and Activity of KD025 in Subjects with Idiopathic Pulmonary Fibrosis (IPF)

Protocol Number:	KD025-207
Study Drug:	KD025
IND Number:	128024
Phase	2
Sponsor:	Kadmon Corporation 450 East 29th Street New York, NY 10016
Medical Monitor:	Sanjay Aggarwal, M.D.
Date of Protocol:	Original, Final, 22 September 2015 Amendment No. 1, Final, 17 November 2015 Amendment No. 2, Final, 04 December 2015 Amendment No. 3, Final, 04 January 2016 Amendment No. 4, Final, 01 February 2016 Amendment No. 5, Final 07 April 2017 Amendment No. 6, Final, 16 October 2017 Amendment No. 7, Final, 22 December 2017 Amendment No. 8, Final, 20 September 2019 **Amendment No. 9, Final, 03 March 2020**

PROCEDURES IN CASE OF EMERGENCY

Serious and Unexpected Adverse Events

Any serious adverse event (SAE)* or suspected unexpected serious adverse reaction (SUSAR)** occurring in a subject while receiving study drug or within 30 days of receiving 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 SAE/SUSAR via email to: ClinicalSAEReporting@kadmon.com	Sanjay Aggarwal, M.D. Kadmon Corporation, LLC 55 Cambridge Parkway, Suite 300E Cambridge, MA 02142 Telephone: 724-778-6129 Cell: 857-253-8642 E-mail: Sanjay.Aggarwal@kadmon.com

SAE CRITERIA

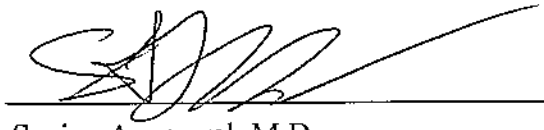
* A SAE is any untoward medical occurrence that at any dose results in any of the following outcomes, regardless of relationship to study drug (see Section 13.1, Serious Adverse Events, for additional information):

- 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 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 13.1 of this document; 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 Guideline for Good Clinical Practice (GCP) E6 (R2), and the ethical principles that have their origins in the Declaration of Helsinki.



Sanjay Aggarwal, M.D.
Medical Monitor

05-MAR-2020
Date of Signature
(DD MMM YYYY)

INVESTIGATOR SIGNATURE

I have read and approve this protocol. My signature, in conjunction with the signature of the sponsor, confirms the agreement of both parties that the clinical study will be conducted in accordance with the protocol and all applicable laws and regulations including, but not limited to, the International Conference on Harmonization Guideline for Good Clinical Practice (GCP) E6 (R2), 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 Randomized, Phase 2, Open-Label, Multicenter Study to Evaluate the Safety, Tolerability, and Activity of KD025 in Subjects with Idiopathic Pulmonary Fibrosis (IPF)
Clinical Phase	2
Number of Study Centers/Sites	Approximately 10-15
Study Background	Idiopathic pulmonary fibrosis is a chronic, progressive, irreversible, and often fatal lung disease of unknown cause. With a prevalence of 2 to 29 per 100,000 people and an incidence of approximately 10 per 100,000/per year, IPF meets the criteria for classification as an orphan disease. It affects older adults with peak prevalence around 65 years of age. The natural history for patients with IPF varies. While most patients progress slowly and gradually over many years, others have an accelerated decline often associated with episodes of acute respiratory worsening. The median survival time is 2 to 4 years from diagnosis and the 5-year survival rate ranges between 30% and 50%. Its mortality rate is higher than that of most cancers. The commonly accepted method of determining disease progression is to identify a decline in forced vital capacity (FVC). Functionally stable patients show a FVC decline of a maximum of 5% of the baseline value over 6 to 12 months. A decline in FVC of 5% to 10% indicates prognostically relevant progression, while a decline of ≥ 10% in 6 months is associated with a 4- to 8-fold increase in the risk of death in the subsequent 12 months. Regular lung function checks to measure FVC and diffusing capacity are recommended at intervals of 3 to 6 months. Acute exacerbations are an important aspect of clinical progression. These are defined by a subacute or acute increase in shortness of breath over a period of 30 days and a high-resolution computed tomography ([HRCT] slice thickness ≤ 2.0 mm, no contrast media) showing new infiltration of the lungs with no identifiable cause. Acute exacerbation frequency is 5% to 15% per year and acute exacerbations are associated with high mortality. After an acute exacerbation of IPF, approximately 50% of patients die within 3 months, and approximately 80% to 90% within 12 months. There is no cure for IPF and treatment options are limited. Historically, available pharmacological therapies have had limited efficacy/activity and potential serious side effects. However, recently both nintedanib and pirfenidone have been shown to slow decline in FVC in separate Phase 3

	clinical trials, and both received Food and Drug Administration approval in October 2014.
Study Rationale	This study is being conducted to evaluate the safety, tolerability, and activity of 400 mg of KD025 once-daily (QD) compared to best supportive care (BSC) in subjects with IPF. Rho-associated protein kinases (ROCK) are members of the serine/threonine kinase family, often studied for their role in cell morphology, motility, and shape through effects on the cytoskeleton. Two isoforms of ROCK have been identified, ROCK1 and ROCK2. Early work with nonspecific ROCK inhibitors (eg, fasudil) suggested that both ROCK1 and ROCK2 are involved in Rho-mediated changes in the actin/myosin cytoskeletal network. However more recent research has uncovered additional relevant roles for ROCK signaling, particularly ROCK2, in conditions including IPF. Matrix stiffening and myofibroblast resistance to apoptosis are cardinal features of chronic fibrosis. The ROCK pathway, which is necessary for contraction and force generation in fibroblasts and for downstream actin polymerization, may therefore be a molecular driver for the formation and progression of pulmonary fibrosis The possibility that pulmonary fibrosis could be directly treated by inhibitors of ROCK has been investigated in mouse models. In a bleomycin-induced model of lung fibrosis, intratracheal (IT) administration of bleomycin in mice induces changes similar to those of diffuse pulmonary fibrosis or fibrosing alveolitis in humans, making this a good model of pulmonary fibrosis for testing of new IPF therapies. In particular, bleomycin causes increased deposition and net synthesis of collagen in the lungs. A study conducted in bleomycin-treated mice, showed that fasudil reduced pulmonary fibrosis even when administered 14 days after IT bleomycin when fibrosis was presumably already present. Treatment with fasudil, an inhibitor of ROCK1 and ROCK2, significantly reduced the levels of alpha-smooth muscle actin and collagen content of the lungs. This study in bleomycin-treated mice also demonstrated that ROCK inhibitors may be effective for treating pulmonary fibrosis through more than 1 mechanism. Fasudil blocked actin cytoskeletal reorganization, fibroblast acquisition of contractile activity, and megakaryoblastic leukemia (translocation) 1 (MKL1) nuclear translocation, preventing the differentiation of fibroblasts into matrix/collagen depositing myofibroblasts in vitro. Kadmon Corporation has internally evaluated the efficacy/activity of 13 days of therapy with KD025 in a bleomycin-induced pulmonary fibrosis model in mice. C57Bl/6 mice were treated with KD025 or vehicle (0.4% carboxymethyl cellulose) beginning 8 days after IT

	treatment with 2.25 U/kg of bleomycin. At the initiation of treatment, pulmonary fibrosis was already established. Unlike vehicle control therapy, oral QD treatment with 100 mg/kg and 150 mg/kg of KD025 significantly reduced pulmonary fibrosis and inflammation. Matrix metalloproteinase (MMPs) have been found to be increased in the lung and bronchoalveolar lavage (BAL) fluid of patients with IPF. A matrix metalloproteinase-7 (MMP7) previously implicated in the pathogenesis of IPF, is significantly increased in plasma, serum, BAL fluid, and lung tissue of IPF patients, suggesting that MMP7 may be a biomarker for IPF disease progression or mortality. The MMP7 levels will therefore be studied in this clinical trial, in addition to other potential future biomarkers for patient selection and pharmacodynamic response; chemokine ligand 18 (CCL18) and surfactant protein-D (SPD).
Dose Rationale	This study will evaluate KD025 at a dose of 400 mg QD. Preliminary data from an ongoing study of KD025 in patients with moderate to severe psoriasis suggests that the dose of 400 mg QD for 12 weeks is associated with clinical efficacy/activity and is well tolerated. This study will examine the safety and clinical efficacy/activity of the 400 mg QD dose in subjects with IPF as compared to BSC. The administration of this dose to subjects with IPF who have disease progression after receiving both nintedanib and pirfenidone is supported by the data from a previous KD025 trial in subjects with psoriasis as well as by the clinical situation of subjects to be enrolled into this study. The safety data from KD025 psoriasis study indicate that the dose of 400 mg QD for 12 weeks was tolerable with an acceptable safety profile. Finally, subjects with IPF who have disease progression after receiving both nintedanib and pirfenidone have a poor clinical prognosis, as poor as some types of aggressive cancer. Thus the risk to benefit ratio in these subjects favors the use of the 400 mg QD dose level which has demonstrated tolerability and clinical activity in previous clinical studies.

Study Objective(s)/ Purpose	Primary objectives • To evaluate the change in FVC from baseline to 24 weeks after dosing with KD025 400 mg QD in subjects with IPF compared with BSC • To evaluate the safety and tolerability of KD025 400 mg QD when administered for 24 weeks to subjects with IPF compared to BSC Secondary objectives • To evaluate the change in 6-minute walk distance (6MWD) from baseline to 24 weeks • To evaluate the occurrence of acute exacerbation of IPF (frequency and severity) throughout treatment • To evaluate change in severity of lung fibrosis as measured by quantitative HRCT • To evaluate the percentage of subjects with disease progression before or at 24 weeks Exploratory Objective • To evaluate the change in MMP7, CCL18, and SPD serum levels
Trial Design	Phase 2, randomized (2:1), open-label, multicenter in subjects with IPF
Methodology	Approximately 81 eligible subjects will be enrolled and randomized to treatment with KD025 400 mg QD for 24 weeks (Treatment Group 1) or BSC for 24 weeks (Treatment Group 2) in a 2:1 ratio (KD025 to BSC). Subjects in Treatment Group 1 who complete 24 weeks of treatment with KD025 400 mg QD will have the option of continuing therapy with KD025 400 mg QD up to an additional 72 weeks if there are no safety signals and if clinical progress continues. No subject in Treatment Group 1 will be permitted to receive therapy with KD025 greater than a total of 96 weeks. Subjects in Treatment Group 2 who complete 24 weeks of BSC will have the option of crossing over to therapy with KD025 400 mg QD for up to 96 weeks if there are no safety signals and if clinical progress continues. No subject in Treatment Group 2 will be permitted to receive KD025 400 mg QD therapy greater than 96 weeks. For subjects from Treatment Group 2 who switch to KD025, prior to receiving their first dose of KD025, Investigators should perform the Week 1, Day 1 assessments (except for safety labs [hematology and chemistry] if performed within 1 week of this visit and PFTs if

	performed within 4 weeks) and all subsequent visits as outlined in Table 1, Study Assessments. All subjects will receive the same assessments. Subjects will undergo medical history evaluations, physical examinations (PEs), vital sign measurements, weight measurements, adverse event (AE) assessments, concomitant medication and procedures assessments, blood sample collection for hematology (including coagulation) and chemistry, urinalysis, thyroid function assessment (TSH), HRCT, and electrocardiogram (ECG), as outlined in the Study Assessments table (Table 1). Additionally, FVC, residual volume (RV), diffusing capacity of the lungs for carbon monoxide (DL_{CO}), 6MWD, and MMP7, CCL18, and SPD serum levels will be measured. The 6MWD, weight, heart rate, blood pressure, and pulse oximeter oxygen saturation (SpO_2) will be recorded before and after the walk. Occurrence of acute exacerbation (frequency and severity) of IPF will be assessed throughout the study. Follow-up visits will occur 30 days (± 3 days) after the last dose of KD025. (A Follow-up visit is not necessary for subjects receiving BSC.) Subjects will undergo the following safety assessments: Complete PEs, vital signs measurements, weight measurements, AE assessments, concomitant medication and procedures assessments, blood sample collection for hematology (including coagulation), chemistry and thyroid function (TSH), PFTs, and urinalysis. If another therapy is started within 30 days after the last dose of study drug, the Follow-up visit will be conducted before the start of the other therapy.
Number of Subjects	Approximately 81 subjects with IPF.
Approximate Duration of Subject Participation	Subjects in Treatment Group 1, KD025 400 mg QD for 24 weeks, will have the option of continuing therapy with KD025 400 mg QD. Subjects who do not continue KD025 400 mg QD after 24 weeks may remain on-study up to 32 weeks: 4 weeks for screening, 24 weeks of KD025 400 mg QD, and 4 weeks of Follow-up. Subjects who choose to continue therapy with KD025 400 mg QD after 24 weeks may remain on-study up to 104 weeks: 4 weeks for screening, a total of 96 weeks of KD025 400 mg QD (an initial 24 weeks of KD025 400 mg and an additional 72 weeks of KD025 400 mg QD), and 4 weeks of Follow-up. No subject will receive more than 96 weeks of treatment with KD025 400 mg QD. Subjects in Treatment Group 2, BSC for 24 weeks, will have the option of crossing over to treatment with KD025 after 24 weeks. Subjects who

	do not crossover will remain on-study up to 32 weeks: 4 weeks for screening, 24 weeks of BSC, and 4 weeks of Follow-up. Subjects who do crossover to KD025 therapy may remain on-study up to 128 weeks: 4 weeks for screening, 24 weeks of BSC, 96 weeks of KD025 400 mg QD, and 4 weeks of Follow-up. No subject will receive more than 96 weeks of treatment with KD025 400 mg QD.
Criteria for Inclusion and Exclusion	Inclusion Criteria 1. Adult male and postmenopausal/surgically sterilized female subjects at least 18 years of age (if female, is surgically sterilized [ie, total hysterectomy, or bilateral salpingo-oophorectomy]) 2. Able to provide written informed consent before the performance of any study specific procedures 3. IPF diagnosis within 5 years before study entry, proven according to the American Thoracic Society/European Respiratory Society consensus conference criteria, with surgical lung biopsy. In the absence of a surgical lung biopsy, HRCT must be consistent with usual interstitial pneumonitis. 4. Resting state $SpO_2 \geq 88\%$ with or without supplemental oxygen, FVC % $\geq$ 50% normal predicted value, and $DL_{CO} \geq 30\%$ normal predicted value at baseline 5. Men with partners of childbearing potential must be willing to use 2 medically acceptable methods of contraception during the trial and for 3 months after the last dose of study drug. Effective birth control includes (a) intrauterine device (IUD) plus 1 barrier method; (b) stable doses of hormonal contraception for at least 3 months (eg, oral, injectable, implant, transdermal) plus 1 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) vasectomy. 6. Have adequate bone marrow function: a. absolute neutrophil count > $1500/mm^3$ b. Hemoglobin > 9.0 g/L c. Platelets > $100,000/mm^3$ 7. Willing to complete all study measurements and assessments in compliance with the protocol 8. Has either received pirfenidone and/or nintedanib or has been offered both treatments (with last dose administered at least 1 month before the expected start of study drug dosing). If either or both pirfenidone and nintedanib treatment has not been given, then documentation that the subject was offered both treatments must be documented. Exclusion Criteria 1. Interstitial lung disease caused by conditions other than IPF

	2. Severe concomitant illness limiting life expectancy (< 1 year) 3. DL_{CO} < 30% predicted 4. Residual volume ≥ 120% predicted 5. Obstructive lung disease: FEV_1/ FVC ratio < 0.70 6. Documented sustained improvement of the subject's IPF condition up to 12 months before study entry with or without IPF-specific therapy 7. Pulmonary or upper respiratory tract infection within 4 weeks before study entry 8. Acute or chronic impairment (other than dyspnea) limiting the ability to comply with study requirements (eg, pulmonary function tests) 9. Chronic heart failure with New York Heart Association Class III/IV or known left ventricular ejection fraction < 25% 10. Moderate to severe hepatic impairment (ie, Child-Pugh Class B or C) 11. Estimated creatinine clearance < 30 mL/min 12. Aspartate aminotransferase (AST) and/or alanine aminotransaminase (ALT) > 2.0 × upper limit of normal (ULN) 13. Hemoglobin < 75% of the lower limit of normal 14. Systolic blood pressure < 100 mmHg 15. Female subject who is pregnant or breastfeeding 16. Men whose partner is pregnant or breastfeeding 17. Current drug or alcohol dependence 18. Chronic treatment with the following drugs (within 4 weeks of study entry and during the study) a. Immunosuppressive or cytotoxic drugs including cyclophosphamide and azathioprine b. Antifibrotic drugs including pirfenidone, nintedanib, D penicillamine, colchicine, tumor necrosis factor α blockers, imatinib and interferon-γ c. Chronic use of N-acetylcysteine prescribed for IPF (> 600 mg/day) d. Oral anticoagulants prescribed for IPF 19. Treatment with endothelin receptor antagonists within 4 weeks before study entry

	20. Systemic treatment within 4 weeks before study entry with cyclosporine A or tacrolimus, everolimus, or sirolimus (calcineurin or mammalian target of rapamycin inhibitors) 21. Previous exposure to KD025 or known allergy/sensitivity to KD025 or any other ROCK2 inhibitor 22. Planned treatment, or treatment with another investigational drug within 4 weeks before study entry 23. Subject is taking a medication that has the potential for QTC prolongation 24. Subject is taking a drug that is a sensitive substrate of CYP enzymes 25. Subject is taking a strong inducer of CYP3A4 26. Subject has consumed an herbal medication (eg, St. John's Wort) or grapefruit/grapefruit juice within 14 days prior to the Week 1, Day 1 visit
Test Drug	Oral KD025. KD025 will be provided as 200-mg tablets.
Dosage and Administration	KD025 400 mg (two 200-mg tablets) will be administered orally QD. Subjects should take KD025 within 5 minutes of completing a meal.
Reference Therapy	Best supportive care (BSC) as deemed appropriate by the Investigator. Subjects randomized to BSC will undergo the same procedures and assessments as subjects on KD025.
Concomitant Treatment	Subjects will be counseled to avoid non-prescribed medicines or complementary alternative medicines excluded by the study. All medications and procedures a subject receives/undergoes from the date that the ICF is signed until 30 days after last dose of study drug will be documented. All subjects who receive KD025 therapy, that is, all subjects in Treatment Group 1 and subjects in Treatment Group 2 who crossover to KD025 therapy, are not to take drugs that are sensitive substrates of CYP enzymes from first dose until 14 days after last dose of study drug. Additionally, use of strong CYP3A4 inducers are prohibited. Other CYP3A4 inhibitors or inducers should be used with caution. Herbal medications (eg, St. John's Wort) or grapefruit/grapefruit juice should not be consumed 14 days prior to first dose of study drug until the end of study treatment.
Safety Evaluation	The primary safety outcome will be the percent of subjects in each treatment group experiencing AEs. Safety assessments include AEs, serious AEs (SAEs), PEs, vital sign measurements, clinical laboratory evaluations, and ECGs. Reasons for

	treatment discontinuation because of toxicity will be documented. Safety assessments will be performed at specified time points and before discharge from the clinic. The AE reporting period for a subject enrolled in the study begins when the subject signs the informed consent and is continued through 30 days after their last dose of study drug. All AEs that occur in enrolled subjects during the AE reporting period must be reported to the sponsor (Kadmon Corporation), 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 the sponsor. Subjects with ongoing AEs/SAEs will be followed until resolution or a new treatment for IPF is started. Vital sign measurements, including blood pressure, pulse rate, respiratory rate, and temperature will be monitored throughout the study.
Efficacy/Activity Evaluation	**Pulmonary function testing (PFT)** will be performed at screening, baseline, 12 weeks, 24 weeks, and at a 30-day Follow-up visit (for subjects continuing, PFTs will be performed every 12 weeks). Pulmonary function testing will include FVC, RV, and DL_{CO}. 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. The **6MWD** will be assessed at baseline and after 12 weeks and 24 weeks (for subjects continuing, 6MWD will be performed every 12 weeks). The distance traveled during 6 minutes (meters) will be measured in accordance with published guidelines. The total distance ambulated in meters during the 6-minute walk test and the number of rest stops is recorded. The 6MWD, weight, heart rate, blood pressure, and pulse oximeter oxygen saturation ($Sp0_2$) are recorded before and after the walk. **Occurrence of acute exacerbation** (frequency and severity) of IPF will be assessed throughout the study. The following clinical deterioration symptoms within a month that cannot be explained by other reasons will be assessed as acute exacerbation: 1. Aggravated dyspnea; 2. Newly discovered chest interstitial lung abnormality by radiograph/HRCT, without pneumothorax or pleural effusion;

	3. SpO_2 decreases to < 88% (heart failure or pulmonary embolism excluded). Acute exacerbation can be diagnosed if Items 1 and 2 are present or if Items 1 and 3 are present. Infection, pulmonary embolism, pneumothorax, or heart failure must be ruled out. The change in severity of lung fibrosis will be determined using measurements from quantitative HRCT. **Time to progression of IPF** is defined as time from the Week 1, Day 1 visit to any 1 of the following: 1. First respiratory-related hospitalization. 2. Respiratory-related death. 3. Absolute decline in FVC percent of predicted value of ≥ 10% versus FVC percent of predicted value recorded at baseline. 4. Absolute decline in DLCO, adjusted for hemoglobin, percent of predicted value of ≥ 15% versus DL_{CO} recorded at baseline.
Pharmacodynamics	Serum levels for MMP7, CCL18, and SPD will be assessed at baseline, 12 weeks, and 24 weeks (For subjects continuing, biomarkers will be assessed at End of Week 36, End of Week 48 and EOT). Serum MMP7 concentrations in peripheral blood are easily measureable and reflect changes in the alveolar microenvironment. Thus, mean serum MMP7 concentrations after 24 weeks of KD025 treatment will be studied as a potential surrogate biomarker of the effect of KD025 administration on disease progression.
Statistical Analysis	<u>Study Populations</u> Three populations will be employed in the analysis of study data: • The Safety Population will consist of all subjects who are randomized and receive at least 1 dose of KD025 (Treatment Group 1) or have week 1 assessment for BSC subjects. All safety analyses will be performed on the safety population • The Modified Intent-to-Treat (mITT) Population will consist of all subjects in the safety population who have evaluable baseline and at least 1 evaluable post baseline FVC assessment. Only evaluable FVC will be used in efficacy analyses. • The Per Protocol (PP) Population will consist of all subjects in the safety population who have evaluable baseline and evaluable Week 24 FVC assessment. For any analysis on the per-protocol population, for patients assigned to treatment and actually

	received treatment, re-calculated baseline value should be used for cross over patients. Primary Endpoints • The primary efficacy/activity endpoint is the change in FVC from baseline to 24 weeks. • The primary safety endpoint is a subject experiencing one or more AEs during the treatment period. Secondary Endpoints: • The change in 6MWD from baseline to 24 weeks • Acute exacerbation of IPF throughout treatment with KD025 • The change in severity of lung fibrosis as measured by quantitative HRCT at baseline and after 24 weeks of treatment • To evaluate the percentage of subjects with disease progression before or at 24 weeks Exploratory Endpoints: • The change in MMP7, CCL18, and SPD serum levels from baseline at 24 weeks. Data Presentations/Descriptive Statistics Demographics, subject disposition, and baseline characteristics will be summarized for the safety, mITT and PP, where appropriate. The primary analysis will be conducted with a data cutoff of approximately 24 weeks after last patient enrolled has received KD025 or when all subjects can be evaluated for primary endpoints. AEs will be coded using the MedDRA dictionary (Version 20.0 or greater.) The number and percentages of subjects experiencing treatment-emergent AEs will be tabulated by System Organ Class and preferred term and will be presented by treatment group. The number of events by preferred term will also be summarized. Tabulation by maximum severity and relationship to KD025/BSC treatment will also be included by treatment group. Summary subject listing will be provided for SAEs, AEs resulting in study discontinuation, and deaths. All AEs (including SAEs) will be graded using a 5-point scale (mild, moderate, severe, life threatening, or death; see Appendix B). Adverse events, SAEs, related AEs, related SAEs, ≥ Grade 3 AEs, related ≥ Grade 3 AEs, and AEs leading to withdrawal and treatment

	discontinuation will be summarized according to treatment group; SOC; and preferred terms. AEs will also be presented in Listings. Duration of AEs will be determined and included in listings, along with action taken and outcome. Laboratory results will be classified using the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (see Appendix A) and summarized by treatment group. Incidence of laboratory abnormalities will be summarized by treatment group. The worst on-study grade during the treatment period after the first dose of KD025 will be summarized (or after Week 1, Day 1 visit for BSC cohort). 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. Sample Size With 54 subjects in the KD025 Treatment Group and 27 in the BSC Treatment Group, the study has over 90% power at the 2-sided 0.05 significance level to detect a 20% difference between treatment groups at 24 weeks in percent change from baseline in FVC assuming a standard deviation (SD) in percent change from baseline in FVC of 17%. The sample size of 54 subjects receiving KD025 will provide over 90% probability of 1 or more subjects in the study experiencing an AE that has an underlying rate of ≥ 5%.

Table 1: Study Assessments

Assessments	Screening Period	Treatment Period									30-Day Follow-Up[i] (±3 days)	UNS[m]
								EOPT Visit	Continuation Visits: (Every 4 Weeks)[k]	EOT		
	Screening Visit	Week 1 Baseline	End of Week 4	End of Week 8	End of Week 12	End of Week 16	End of Week 20	End of Week 24				
Study Day	-29 to -1	1[j]	28 (±3 days)	56 (±3 days)	84 (±3 days)	112 (±3 days)	140 (±3 days)	168 (±3 days)				
Informed consent	X											
St. George's Respiratory Questionnaire		X			X			X	X[o]			X
Medical history[a]	X											
Physical examination[b]	X	X			X			X	X[o]	X	X	X
Vital signs[c]	X	X	X	X	X	X	X	X	X	X	X	X
Hematology and chemistry[d]	X	X	X	X	X	X	X	X	X	X	X	X
TSH		X	X	X	X	X	X	X	X	X	X	X
PT, PTT, INR		X	X	X	X	X	X	X	X	X	X	X
Urinalysis		X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG[e, q]	X	X	X					X		X	X	X
Pulmonary function tests (including FVC, RV, and DL_{CO})[q]	X	X			X			X	X[o]	X[o]	X	X
HRCT		X						X	X[p]	X[p]		X
MMP7, CCL18, and SPD biomarkers		X			X			X	X[n]	X[n]		X

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Assessments	Screening Period	Treatment Period									30-Day Follow-Up[j] (±3 days)	UNS[m]
								EOPT Visit	Continuation Visits: (Every 4 Weeks)[k]	EOT		
	Screening Visit	Week 1 Baseline	End of Week 4	End of Week 8	End of Week 12	End of Week 16	End of Week 20	End of Week 24				
Study Day	-29 to -1	1[j]	28 (±3 days)	56 (±3 days)	84 (±3 days)	112 (±3 days)	140 (±3 days)	168 (±3 days)				
6MWD[f]		X			X			X	X[o]	X		X
Occurrence of exacerbation of IPF (frequency and severity)		X	X	X	X	X	X	X	X	X	X	X
Randomization		X										
Study diary (dispense/collect)[g]		X	X	X	X	X	X	X	X	X	X	X
Study drug administration[h]		X	X									X
Dispense/Collect study drug		X	X	X	X	X	X	X	X	X		X
Best supportive care[i]		*To be determined by Investigator*										X
Concomitant medications and procedures		*To be collected from the date that the ICF is signed until 30 days after last dose of KD025. For BSC subjects, to be collected through the End-of-Week 24 visit.*										
Adverse events												

6MWD = 6-minute walk distance;BSC = best supportive care; ECG = electrocardiogram; EOPT = End-of-Primary-Treatment; HRCT = High Resolution Computerized Tomography; ICF = informed consent form; INR = international normalized ratio; IPF = idiopathic pulmonary fibrosis; PE = physical examination; PT = prothrombin time; PTT = partial thromboplastin time; TSH = thyroid stimulating hormone; UNS = unscheduled.

a. Medical history to include exacerbation of IPF (such as presence of dyspnea, chest interstitial lung abnormalities, or SpO_2 < 88%) for 6 months prior.
b. A complete PE is to include documentation of height (screening only), weight, body temperature, and vital signs (blood pressure [sitting], pulse rate [sitting], 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).

All PEs will include assessment of cardiac (including heart rate, vital sign, and CPK measurements), musculoskeletal (ie, muscle aches), and neurological (ie, gait) systems.

c. Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, and temperature) will be collected after a 5 minute of rest. See Section 8.2 for appropriate blood pressure measuring technique.
d. See Section 8.9 for a complete list of laboratory safety assessments. If increases in liver enzymes are observed at any time in a subject, refer to Section 12.4.
e. Supine 12-Lead ECG (repeat 3 times consecutively within 30 minutes [must have an interval of at least 1-2 minutes between ECGs]; perform ECG immediately before blood sample collection; see Section 8.10 for additional information). At the Week 1 Day 1 and End-of-Week 4 visits, ECG to be performed predose and 4 hours post-dose (T_{max}) for subjects in Treatment Group 1.
f. The 6MWD, weight, heart rate, blood pressure, and SpO_2 will be recorded before and after the walk.
g. Subjects receiving KD025 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, reviewed, and/or collected at each visit.
h. Subjects in Treatment Group 1 will receive their first dose of KD025 in the clinic at Week 1 and at the End of Week 4 visits. KD025 will then be dispensed for home administration. Treatment Group 1: Subjects should take all 2 KD025 tablets within 5 minutes of finishing a meal.
i. Best supportive care (BSC; Treatment Group 2); as deemed appropriate by the Investigator. Subjects randomized to BSC will be treated the same as subjects on KD025 and undergo all tests in similar fashion.
j. If screening assessments are done within 7 days of the baseline visit, only the PE and vital sign measurements need to be redone.
k. Subjects may continue to receive therapy with KD025 as long as there is no safety signal and clinical progress continues. (Subjects receiving BSC have the option of switching to therapy with KD025 after Week 24; see Section 12.1.2). All continuing subjects will return to the clinic every 4 weeks thereafter.
l. Subjects dosed with KD025 will return to the clinic 30 days (± 3 days) after their last dose of study drug. A Follow-up visit is not required for BSC subjects.
m. These assessments should be performed if a subject discontinues early from the study and are suggested for any UNS.
n. For those subjects continuing, biomarker sample collection to be performed only at Weeks 36 and 48, and EOT.
o. For those subjects continuing, tests to be completed every 12 weeks. If PFTs were performed within 1 month of the EOT visit, PFTs do not need to be performed again.
p. For those subjects continuing HRCT to be performed every 24 weeks. If the HRCT is performed within 1 month of the EOT visit, it does not need to be done again at the EOT visit.
q. Every effort should be made to utilize the same ECG and PFT machines and technician to collect data.

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3. LIST OF ABBREVIATIONS

6MWD	6-minute walk distance
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
BAL	bronchoalveolar lavage
BID	twice daily
BSC	best supportive care
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CCL18	chemokine ligand 18
C_{max}	maximum concentration observed
CPK	creatinine phosphokinase
DL_{CO}	diffusing capacity of carbon monoxide
ECG	electrocardiogram
eCRF	electronic case report form
EOPT	End-of-Primary-Treatment
ET	Early Termination
FDA	Food and Drug Administration
FVC	forced vital capacity
GCP	Good Clinical Practice
HRCT	high-resolution computed tomography
IB	Investigator's Brochure
ICF	informed consent form
IEC	Independent Ethics Committee
IND	Investigational New Drug
INR	international normalized ratio
IP	intraperitoneal
IPF	idiopathic pulmonary fibrosis
IRB	institutional review board
ITT	intent-to-treat
KD025m1	KD025 Metabolite 1
KD025m2	KD025 Metabolite 2
LFT	liver function tests
MAD	multiple ascending dose
MCV	mean corpuscular volume

MedDRA	Medical Dictionary for Regulatory Activities
MMP7	matrix metalloproteinase-7
mITT	modified Intent-to-Treat
MMP	matrix metalloproteinase
PE	physical examination
PK	pharmacokinetic
PT	prothrombin time
PTT	partial thromboplastin time
QD	once daily
QTc(F)	corrected QT interval using Fridericia's formula
ROCK	Rho-associated protein kinase
RPE	Rating of Perceived Exertion
RV	residual volume
SAD	single ascending dose
SAE	serious adverse event
SGRQ	St George's Respiratory Questionnaire
SOC	System Organ Class
SPD	surfactant protein-D
SpO_2	pulse oximeter oxygen saturation
SUSAR	suspected unexpected serious adverse event
$t_{1/2}$	half-life
T_{max}	observed time to reach peak plasma concentration
TSH	thyroid stimulating hormone
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary

4. BACKGROUND AND RATIONALE

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, irreversible, and often fatal lung disease of unknown cause. With a prevalence of 2 to 29 per 100,000 and an incidence of approximately 10 per 100,000/year, IPF meets the criteria for classification as an orphan disease.[1] It affects older adults with peak prevalence around 65 years-of-age.[1]

The natural history for patients with IPF varies. While most patients progress slowly and gradually over many years, others have an accelerated decline often associated with episodes of acute respiratory worsening.[2,3,4,5] The median survival time is 2 to 4 years from diagnosis and the 5-year survival rate ranges between 30% and 50%.[1,4,6,7] Its mortality rate is higher than that of most cancers.

The commonly accepted method of determining disease progression is to identify a decline in forced vital capacity (FVC). Functionally stable patients show a FVC decline of a maximum of 5% of the baseline value over 6 to 12 months.[1,7,8] A decline in FVC of 5% to 10% in any subject indicates prognostically relevant progression, while a decline of ≥ 10% in 6 months is associated with a 4-to 8-fold increase in the risk of death in the subsequent 12 months.[8,9,10] Regular lung function checks to measure FVC and diffusing capacity are recommended at intervals of at least 3 to 6 months.[1,3]

Acute exacerbations are an important aspect of clinical progression. These are defined by a subacute or acute increase in shortness of breath over a period of 30 days and a high-resolution computed tomography ([HRCT] slice thickness ≤ 2.0 mm, no contrast media) showing new infiltration of the lungs with no identifiable cause. Acute exacerbation frequency is 5% to 15% per year and acute exacerbations are associated with high mortality. After an acute exacerbation of IPF, approximately 50% of patients die within 3 months, and approximately 80% to 90% within 12 months.[1,3,4,6,7]

There is no cure for IPF and treatment options are limited. Historically, available pharmacological therapies have had limited efficacy/activity and potential serious side effects. However, recently both nintedanib and pirfenidone have been shown to slow decline in FVC in separate Phase 3 clinical trials[9,10] and both received Food and Drug Administration (FDA) approval in October 2014.

4.1. Study Rationale

This study is being conducted to evaluate the safety, tolerability, and activity of 400 mg of KD025 orally administered once-daily (QD) compared to best supportive care (BSC) in subjects with IPF.

Rho-associated protein kinases (ROCK) are members of the serine/threonine kinase family, often studied for their role in cell morphology, motility, and shape through effects on the cytoskeleton.[11,12] Two isoforms of ROCK have been identified, ROCK1 and ROCK2. Early work with nonspecific

ROCK inhibitors (eg, fasudil) suggested that both ROCK1 and ROCK2 are involved in Rho-mediated changes in the actin/myosin cytoskeletal network. However, more recent research has uncovered additional relevant roles for ROCK signaling, particularly ROCK2, in conditions including IPF. Matrix stiffening and myofibroblast resistance to apoptosis are cardinal features of chronic fibrosis. The ROCK pathway, which is necessary for contraction and force generation in fibroblasts and for downstream actin polymerization, may therefore be a molecular driver for in the formation and progression of pulmonary fibrosis.

The possibility that pulmonary fibrosis could be directly treated by inhibitors of ROCK has been investigated in mouse models. In a bleomycin-induced model of lung fibrosis, intratracheal (IT) administration of bleomycin in mice induces changes similar to those of diffuse pulmonary fibrosis or fibrosing alveolitis in humans, making this a good model of pulmonary fibrosis for testing of new IPF therapies. In particular, bleomycin causes increased deposition and net synthesis of collagen in the lungs. A study conducted in bleomycin-treated mice, showed that fasudil reduced pulmonary fibrosis even when administered 14 days after IT bleomycin when fibrosis was presumably already present.[13] Treatment with fasudil, an inhibitor of ROCK1 and ROCK2, significantly reduced the levels of alpha-smooth muscle actin and collagen content of the lungs. This study in bleomycin-treated mice also demonstrated that ROCK inhibitors may be effective for treating pulmonary fibrosis through more than 1 mechanism. Fasudil blocked actin cytoskeletal reorganization, fibroblast acquisition of contractile activity, and megakaryoblastic leukemia (translocation) 1 MKL1 nuclear translocation, preventing the differentiation of fibroblasts into matrix/collagen depositing myofibroblasts in vitro.

Kadmon Corporation has internally evaluated the efficacy/activity of 13 days of therapy with KD025 in a bleomycin-induced pulmonary fibrosis model in mice. C57Bl/6 mice were treated with KD025 or vehicle (0.4% carboxymethyl cellulose) beginning 8 days after IT treatment with 2.25 U/kg of bleomycin. At the initiation of treatment, pulmonary fibrosis was already established. Unlike vehicle control therapy, oral QD treatment with 100 mg/kg and 150 mg/kg of KD025 significantly reduced pulmonary fibrosis and inflammation.

Matrix metalloproteinase (MMPs) have been found to be increased in the lung and bronchoalveolar lavage (BAL) fluid of patients with IPF. A matrix metalloproteinase-7 (MMP7) previously implicated in the pathogenesis of IPF,[14,15] is significantly increased in plasma, serum, BAL fluid, and lung tissue of IPF patients, suggesting that MMP7 may be a biomarker for IPF disease progression or mortality. The MMP7 levels will therefore be studied in this clinical trial, in addition to other

potential future biomarkers for patient selection and pharmacodynamic response; chemokine ligand 18 (CCL18) and surfactant protein-D (SPD).[16]

4.2. Summary of Known and Potential Risks and Benefits to Human Subjects

All the possible side effects related to KD025 are not known. The KD025 Investigator's Brochure (IB) contains data on risks associated with KD025. Other risks to subjects involve side effects from study procedures. There are also other risks associated with taking part in this study, such as the risks associated with a loss of privacy or confidentiality because of improper disclosure.

There may be no direct benefit to subjects enrolled into this study. Subjects may receive a clinical benefit from KD025, and some subjects may progress. The information from this study may help other subjects with IPF and more may be learned about the study drug as a possible new treatment for IPF.

4.3. Selection of Doses in this Study

This study will evaluate KD025 at a dose of 400 mg QD. Preliminary data from an ongoing study of KD025 in patients with moderate to severe psoriasis suggests that the dose of 400 mg QD for 12 weeks is associated with clinical efficacy/activity and is well-tolerated. This study will examine the safety and clinical efficacy/activity of the 400 mg QD dose compared to BSC in patients with IPF.

The administration of KD025 400 mg QD to subjects with IPF who have disease progression after receiving both nintedanib and pirfenidone is supported by the data from a previous KD025 trial in subjects with psoriasis as well as by the clinical situation of subjects to be enrolled into this study. The safety data from KD025 psoriasis study indicate that the dose of 400 mg daily for 12 weeks was tolerable with an acceptable safety. Finally, subjects with IPF who have disease progression after receiving both nintedanib and pirfenidone have a poor clinical prognosis, as poor as some types of aggressive cancer. Thus the risk to benefit ratio in these subjects favors the use of the 400 mg QD dose level which has demonstrated tolerability and clinical activity in previous clinical studies.

The IB includes additional nonclinical and clinical information about KD025.

4.4. Previous Clinical Experience with KD025

To date, there have been 5 Phase 1 trials conducted with KD025 in normal healthy subjects: a single-ascending dose (SAD) trial (Study 2119-09-01), a combined single- and multiple-ascending dose (SAD/MAD) trial (Study KD025-101), a MAD trial with QD and BID dosing

(Study KD025-102), a placebo-controlled safety and pharmacokinetic (PK) study (Study KD025-103), and a food effect study (Study KD025-105). A Phase 2a, open-label study in 8 adult subjects with moderately severe psoriasis vulgaris who have failed first-line therapy was recently completed (Study 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 (Study KD025-206).

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

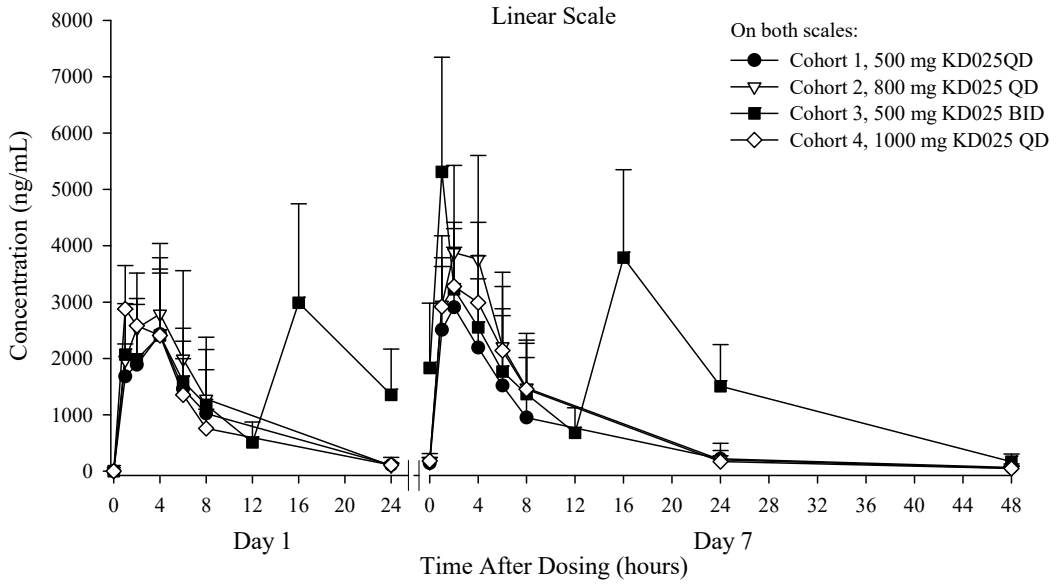
Multiple escalating doses of KD025 ranging from 500 mg to 800 mg to 1000 mg QD and 500 mg BID for 7 days were generally well tolerated and no dose-limiting toxicities were reported in this study. Five TEAEs were reported in 4 subjects (16.7%) receiving KD025, including upper abdominal pain and diarrhea 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 TEAEs 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 half-life ($t_{1/2}$) 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 $AUC_{0\text{-}24hr}$ 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 (Study KD025-102)



BID = twice daily; QD = once daily

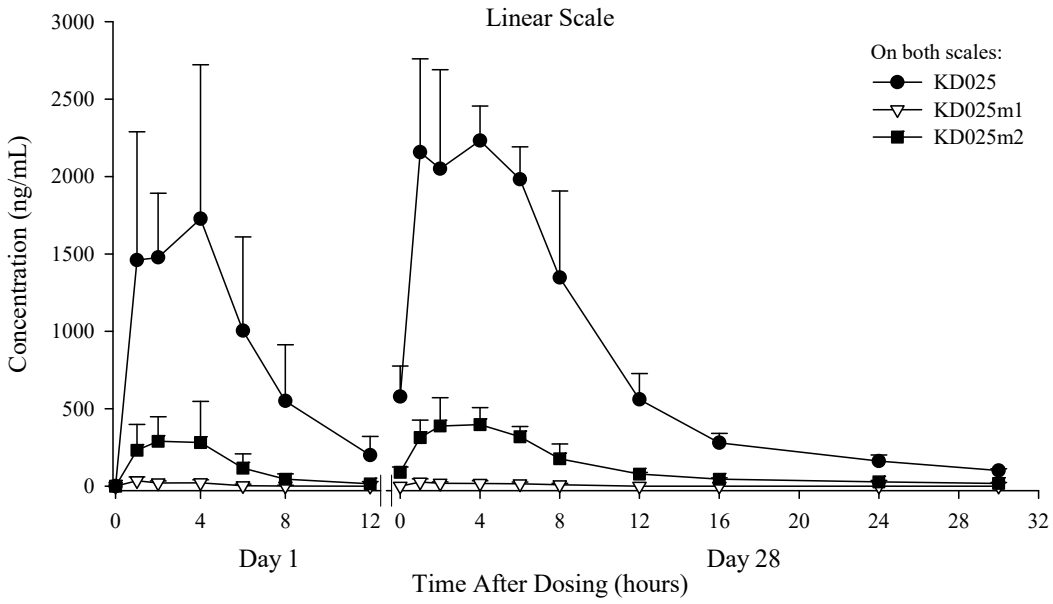
Study KD025-103 was a Phase 1, placebo-controlled study examining the safety, tolerability, and PK of 500 mg of KD025 administered BID for 28 days in healthy male and postmenopausal female subjects. KD025 500 mg, administered BID for up to 28 days was generally well-tolerated. A total of 6 AEs were reported 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 [KD025 Metabolite 1] and KD025m2 [KD025 Metabolite 2]) 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 (Study KD025-103)



BID = twice daily; SD = standard deviation

The food effect study (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, no 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, Study 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 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 $t_{1/2}$ 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 of KD025 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.

Study 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 which 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.

4.5. 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 (rat), respiratory (rat), and cardiovascular (dog) function. Furthermore, KD025 is not considered genotoxic or mutagenic based on a panel of studies. Fertility (rat [segment 1] and Reproductive toxicology studies (rat and rabbit embryo-fetal [segment 2]) are completed.

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

4.6. Compliance Statement

This study will be conducted in compliance with Good Clinical Practice (GCP) E6 (R2), including International Conference on Harmonisation 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 as follows:

- To evaluate the change in FVC from baseline to 24 weeks after dosing with KD025 400 mg QD in subjects with IPF compared with BSC
- To evaluate the safety and tolerability of KD025 400 mg QD when administered for 24 weeks to subjects with IPF compared with BSC

5.2. Secondary Objectives

The following are the secondary objectives of the study:

- To evaluate the change in 6-minute walk distance (6MWD) from baseline to 24 weeks
- To evaluate the occurrence of acute exacerbation of IPF (frequency and severity) throughout treatment
- To evaluate change in severity of lung fibrosis as measured by quantitative HRCT
- To evaluate the percentage of subjects with disease progression before or at 24 weeks

5.3. Exploratory Objective

The following is the exploratory objective of the study:

- To evaluate the change in MMP7, CCL18, and SPD serum levels

6. STUDY DESIGN

6.1. Study Sites

This study will be conducted at approximately 10-15 sites in the United States.

6.2. Study Endpoints

For Study Endpoints, refer to Section 5. Further details on the statistical and analytical plan for these endpoints are available in Section 14, Statistical Considerations.

6.3. Overview of Study Design

Approximately 81 eligible subjects will be enrolled and randomized to treatment with KD025 400 mg QD for 24 weeks (Treatment Group 1) or BSC for 24 weeks (Treatment Group 2) in a 2:1 ratio (KD025 to BSC).

Subjects in Treatment Group 1 who complete 24 weeks of treatment with KD025 400 mg QD will have the option of continuing therapy with KD025 400 mg QD up to an additional 72 weeks if there are no safety signals and if clinical progress continues. No subject in Treatment Group 1 will be permitted to receive therapy with KD025 greater than a total of 96 weeks.

Subjects in Treatment Group 2 who complete 24 weeks of BSC will have the option of crossing over to therapy with KD025 400 mg QD for up to 96 weeks if there are no safety signals and if clinical progress continues. No subject in Treatment Group 2 will be permitted to receive KD025 400 mg QD therapy greater than 96 weeks.

All subjects will receive the same assessments.

Subjects will undergo medical history evaluations, physical examinations (PEs); vital sign measurements; collection of weight; adverse event (AE) assessments; concomitant medication and procedures assessments; blood sample collection for hematology (including coagulation), chemistry, and thyroid function (TSH); urinalysis; HRCT; and ECG as outlined in the Study Events (Table 1).

Additionally, FVC, residual volume (RV), diffusing capacity of the lungs for carbon monoxide (DL_{CO}), and MMP7, CCL18, and SPD serum levels will be measured as outlined in the Study Events (Table 1). For the 6MWD, weight, heart rate, blood pressure, and pulse oximeter oxygen saturation (SPO_2) will be recorded before and after the walk.

The occurrence of acute exacerbation (frequency and severity) of IPF will be assessed throughout the study.

Note: If increases in liver enzymes are observed at any time, refer to Section 12.4 for risk management of liver function tests (LFTs) changes observed during the study.

Follow-up visits will occur 30 days (± 3 days) after the last dose of KD025 (Follow-up visit not required for BSC subjects). Subjects will undergo complete PEs, vital signs measurements, collection of weight, AE assessments, concomitant medication and procedures assessments, blood sample collection for hematology (including coagulation), and chemistry, thyroid function (TSH), PFTs, and urinalysis. If another therapy is started within 30 days after the last dose of study drug, the Follow-up visit will be conducted before the start of the other therapy.

6.4. Randomization and Blinding

This is an open-label study. Subjects who are eligible will be enrolled and randomized into Treatment Group 1 or Treatment Group 2 in a 2:1 ratio (KD025 to BSC) and receive KD025 400 mg QD orally or BSC for at least 24 weeks. Study treatment is not blinded. Approximately 81 subjects will be randomized in a 2:1 ratio.

7. STUDY POPULATION

7.1. Target Population

Approximately 81 adult subjects with IPF will be enrolled and randomized into Treatment Group 1 or Treatment Group 2 in a 2:1 ratio (KD025 to BSC). 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 postmenopausal/surgically sterilized female subjects at least 18 years of age (if female, is surgically sterilized [ie, total hysterectomy, or bilateral salpingo-oophorectomy])
2. Able to provide written informed consent before the performance of any study specific procedures
3. IPF diagnosis within 5 years before study entry, proven according to the American Thoracic Society/European Respiratory Society consensus conference criteria, with surgical lung biopsy. In the absence of a surgical lung biopsy, HRCT must be consistent with usual interstitial pneumonitis.
4. Resting state $SpO_2 \geq 88\%$ with or without supplemental oxygen, FVC % $\geq 50\%$ normal predicted value, and $DL_{CO} \geq 30\%$ normal predicted value at baseline
5. Men with partners of childbearing potential must be willing to use 2 medically acceptable methods of contraception during the trial and for 1 month after the last dose of study drug. Effective birth control includes (a) intrauterine device (IUD) plus 1 barrier method; (b) stable doses of hormonal contraception for at least 3 months (eg, oral, injectable, implant, transdermal) plus 1 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) vasectomy.
6. Have adequate bone marrow function:
    a. Absolute neutrophil count > $1500/mm^3$
    b. Hemoglobin > 9.0 g/L
    c. Platelets > $100,000/mm^3$
7. Willing to complete all study measurements and assessments in compliance with the protocol

8. Has either received pirfenidone and/or nintedanib or has been offered both treatments (with last dose administered at least 1 month before the expected start of study drug dosing). If either or both pirfenidone and nintedanib treatment has not been given, then documentation that the patient was offered both treatments must be documented.

7.3. Exclusion Criteria

The exclusion criteria are detailed below:

1. Interstitial lung disease caused by conditions other than IPF
2. Severe concomitant illness limiting life expectancy (< 1 year)
3. Diffusing capacity of the lung for carbon monoxide (DL_{CO}) < 30% predicted
4. RV ≥ 120% predicted
5. Obstructive lung disease: FEV_1/ FVC ratio < 0.70
6. Documented sustained improvement of the subject's IPF condition up to 12 months before study entry with or without IPF-specific therapy
7. Pulmonary or upper respiratory tract infection within 4 weeks before study entry
8. Acute or chronic impairment (other than dyspnea) limiting the ability to comply with study requirements (eg, PFTs)
9. Chronic heart failure with New York Heart Association Class III/IV or known left ventricular ejection fraction < 25%
10. Moderate to severe hepatic impairment (ie, Child-Pugh Class B or C)
11. Estimated creatinine clearance < 30 mL/min
12. AST and/or ALT > 2.0 × upper limit of normal (ULN)
13. Hemoglobin < 75% of the lower limit of normal
14. Systolic blood pressure < 100 mmHg
15. Female subject who is pregnant or breastfeeding
16. Men whose partner or female subject who is pregnant or breastfeeding
17. Current drug or alcohol dependence
18. Chronic treatment with the following drugs (within 4 weeks of study entry and during the study):

a. Immunosuppressive or cytotoxic drugs including cyclophosphamide and azathioprine

b. Antifibrotic drugs including pirfenidone, nintedanib, D penicillamine, colchicine, tumor necrosis factor α blockers, imatinib and interferon-γ

c. Chronic use of N-acetylcysteine prescribed for IPF (> 600 mg/day)

d. Oral anticoagulants prescribed for IPF

19. Treatment with endothelin receptor antagonists within 4 weeks before study entry
20. Systemic treatment within 4 weeks before study entry with cyclosporine A or tacrolimus, everolimus, or sirolimus (calcineurin or mammalian target of rapamycin inhibitors)
21. Previous exposure to KD025 or known allergy/sensitivity to KD025 or any other ROCK2 inhibitor
22. Planned treatment, or treatment with another investigational drug within 4 weeks before study entry
23. Subject is taking a medication that has the potential for QTc prolongation
24. Subject is taking a drug that is a sensitive substrate of CYP enzymes
25. Subject is taking a strong inducer of CYP3A4 (see Appendix F).
26. Subject has consumed an herbal medication (eg, St. John's Wort) or grapefruit/grapefruit juice within 14 days prior to the Week 1, Day 1 visit (see Appendix G).

8. STUDY ASSESSMENTS AND PROCEDURES

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 Table 2.

8.2. Procedures to be Performed

*All screening assessments are to be performed within **29 days** before the Week 1, Day visit, unless otherwise specified.*

Study Day 1 is defined as the date the subject takes the first dose of study drug (or the Week 1, Day 1 visit for the BSC treatment group), 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, surgical procedures, and smoking history. Medical history should include exacerbation of IPF, such as presence of dyspnea, chest interstitial lung abnormalities, or SpO_2 <88%), within 6 months prior to screening visit.

IPF history should include:

- When diagnosis was made
- Previous treatments with dates and reasons for discontinuation
- History of PFTs for at least 1 year prior to enrollment

Physical Examination

Complete PEs will be performed. All PEs will include assessment of cardiac (including heart rate, vital sign, and CPK measurements), musculoskeletal (ie, muscle aches) and neurological (ie, 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], 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).

Laboratory Assessments

Laboratory samples (hematology, chemistry, and urinalysis) are to be collected as outlined in Section 8.9. Coagulation parameter assessments are to include measurements of PT, PTT, and INR. Thyroid function assessments are to include measurements of TSH

Safety laboratory analyses will be performed.

Laboratory results will be classified using the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (see Appendix C).

If significant increases in liver enzymes (ALT, AST, and bilirubin) are observed at any time, study drug may be held for that subject at the discretion of the Investigator. Refer to Section 12.4 additional information and recommended procedures.

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. See Section 8.10 for additional ECG procedure information and Table 1 for timing allowances. At the Week 1 Day 1 and End of Week 4 visits, an ECG is to be performed predose and 4 hours post-dose (T_{max}) in subjects receiving KD025.

Blood Sampling for Pharmacodynamics

All subjects will have serum blood samples drawn for MMP7, CCL18, and SPD at baseline, end of Week 12, and end of Week 24.

St. George's Respiratory Questionnaire

The St George's Respiratory Questionnaire (SGRQ) is a standardized self-completed questionnaire to measure and quantify health-related health status in subjects with impaired health and perceived well-being ('quality of life'); see Appendix E. The SGRQ will be administered prior to all other scheduled procedures. Subjects will complete the SGRQ at Weeks 1, 12, 24, and continuation visits end of Week 28 and end of Week 48 (and every 12 weeks thereafter).

The St George's Respiratory Questionnaire is a standardized self-completed questionnaire for measuring impaired health and perceived well-being ('quality of life') in airways disease.[21] It has been designed to allow comparative measurements of health between patient populations and quantify changes in health following therapy.

KD025 Administration

Subjects in Treatment Group 1 will receive their first dose of study drug in the clinic on Week 1, Day 1, and then study drug will be dispensed for home administration. These subjects also will take their dose of study drug at the clinic at the End of Week 4 visit.

Subjects in Treatment Group 1 will receive 400 mg KD025 QD for 24 weeks. Subjects should take two 200-mg tablets within 5 minutes of completing a meal.

Subjects may continue to receive therapy with KD025 as long as there is no safety signal and clinical progress continues.

See Section 12.1 for dosing schedule and Section 12.2 for missed doses.

Best Supportive Care

Subjects in Treatment Group 2 will receive BSC (as deemed appropriate by the Investigator). Subjects receiving BSC will have the option of switching to therapy with KD025 after Week 24.

Subjects who switch to KD025 may receive 24 weeks of dosing with KD025, with the potential to continue as long as there is no safety signal and clinical progress continues. For subjects who switch, prior to their first dose of KD025, Investigators should perform the Week 1, Day 1 assessments (except for safety labs [hematology and chemistry] if performed within 1 week of this visit and PFTs if performed within 4 weeks) and all subsequent visits as outlined Table 1.

Study Drug Diary

Subjects will be supplied study drug diaries in which they are to record the amount, date and time of each dose of study drug. In addition, subjects are to bring their diary to each study visit.

Prior and Concomitant Medications and Procedures

All concomitant medications and procedures will be collected from time the subject signs the ICF until 30 days after last dose of KD025. For BSC subjects, concomitant medications and procedures will be recorded through the end of Week 24 visit.

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 30 days after last dose of KD025. For BSC subjects, AE information will be recorded through the end of Week 24 visit. Subjects with ongoing AE/SAE(s) will be followed until resolution of the AE/SAE(s) or until a new treatment for IPF is started.

> **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 11.2 for stopping rules for this study. Also, if significant increases in liver enzymes are observed at any time, the Investigator should refer to Section 12.4 for additional information.

8.3. 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 29 days of first dose of study drug (Week 1, Day 1 visit). 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, including documentation of previous exacerbations of IPF (such as presence of dyspnea, chest interstitial lung abnormalities, or SpO_2 <88%) during past 6 months and demographic data
- Complete PE, including height and weight
- Seated vital sign measurements (sitting blood pressure, pulse, respiratory rate, temperature)
- Clinical laboratory tests (hematology and serum chemistry panel)
- Supine 12-Lead ECG (repeat 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)
- Pulmonary function tests (including FVC, RV, and DL_{CO})
- Screening concomitant medications and procedures assessment
- Urine pregnancy test (for females of childbearing potential. Positive results are to be confirmed with serum testing.)
- Screening AE assessment

8.4. Enrollment

After completion of screening procedures and confirmation of subject eligibility, the subject will be enrolled and randomized into Treatment Group 1 or Treatment Group 2 in a 2:1 ratio (KD025 to BSC). Subjects who are enrolled and randomized into the study are to undergo all subsequent evaluations required by the protocol.

8.5. Treatment Period

8.5.1 Week 1, Day 1 Visit (Baseline)

At the Week 1, Day 1 visit, subjects will come to the clinic to have the following procedures completed (if screening was completed within 7 days of baseline, only the complete PE and vital sign measurements need to be repeated):

- St. George's Respiratory Questionnaire
- Complete PE, including weight
- Seated vital sign measurements (sitting blood pressure, pulse, respiratory rate, temperature)

- Clinical laboratory tests (hematology and serum chemistry panel)
- PT, PTT, and INR
- TSH
- Urinalysis
- Supine 12-Lead ECG; perform predose and 4 hours post-dose (for subjects receiving KD025) (repeat 3 times consecutively within 30 minutes [must have an interval of at least 1-2 minutes between ECGs]; perform ECG immediately before blood sample collection)
- MMP7, CCL18, and SPD serum biomarkers
- Occurrence of exacerbation of IPF (frequency and severity)
- Study diary (dispense/collect) (for subjects receiving KD025)
- Pulmonary function tests (including FVC, RV, and DL_{CO})
- HRCT
- 6MWD
- Randomization
- Study drug administration (for subjects receiving KD025), only to be performed at Week 4.
- Dispense/collect study drug (for subjects receiving KD025)
- Concomitant medications and procedures assessment
- Urine pregnancy test (for females of childbearing potential. Positive results are to be confirmed with serum testing.)
- Adverse event assessment

8.5.2 End of Week 4, Day 28 (±3 days) and End of Week 8, Day 56 (±3 days) Visits

Subjects will come to the clinic to have the following procedures completed:

- Seated vital sign measurements (sitting blood pressure, pulse, respiratory rate, temperature)
- Clinical laboratory tests (hematology and serum chemistry panel)
- PT, PTT, INR
- TSH
- Urinalysis
- Supine 12-Lead ECG; End of Week 4 visit only; perform predose and 4 hours post-dose (for subjects receiving KD025) (repeat 3 times consecutively within 30 minutes [must have an interval of at least 1-2 minutes between ECGs]; perform ECG immediately before blood sample collection)

- Occurrence of exacerbation of IPF (frequency and severity)
- Study drug administration (for subjects receiving KD025)
- Study diary (dispense/collect) (for subjects receiving KD025)
- Dispense/collect study drug (for subjects receiving KD025)
- Concomitant medications assessment
- Urine pregnancy test (for females of childbearing potential. Positive results are to be confirmed with serum testing.)
- Adverse event assessment

8.5.3 End of Week 12, Day 84 (± 3 days) Visit

Subjects will come to the clinic to have the following procedures completed:

- St. George's Respiratory Questionnaire
- Seated vital sign measurements (sitting blood pressure, pulse, respiratory rate, temperature)
- Complete PE, including weight
- Clinical laboratory tests (hematology and serum chemistry panel)
- PT, PTT, INR
- TSH
- Urinalysis
- Pulmonary function tests (including FVC, RV, and DL_{CO})
- MMP7, CCL18, and SPD biomarkers
- Occurrence of exacerbation of IPF (frequency and severity)
- 6MWD
- Study diary (dispense/collect) (for subjects receiving KD025)
- Dispense/collect study drug (for subjects receiving KD025)
- Concomitant medications assessment
- Urine pregnancy test (for females of childbearing potential. Positive results are to be confirmed with serum testing.)
- Adverse event assessment

8.5.4 End of Week 16, Day 112 (± 3 days) and End of Week 20, Day 140 (± 3 days) Visits

Subjects will come to the clinic to have the following procedures completed:

- Seated vital sign measurements (sitting blood pressure, pulse, respiratory rate, temperature)
- Clinical laboratory tests (hematology and serum chemistry panel)
- PT, PTT, INR
- TSH
- Urinalysis
- Occurrence of exacerbation of IPF (frequency and severity)
- Study diary (dispense/collect) (for subjects receiving KD025)
- Dispense/collect study drug (for subjects receiving KD025)
- Concomitant medications assessment
- Urine pregnancy test (for females of childbearing potential. Positive results are to be confirmed with serum testing.)
- Adverse event assessment

8.5.5 End-of-Primary-Treatment Visit (End of Week 24, Day 168 [± 3 days])

Subjects will come to the clinic to have the following procedures completed: St. George's Respiratory Questionnaire

- Complete PE, including weight
- Seated vital sign measurements (sitting blood pressure, pulse, respiratory rate, temperature)
- Clinical laboratory tests (hematology and serum chemistry panel)
- PT, PTT, and INR
- TSH
- Urinalysis
- Supine 12-Lead ECG (repeat 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)
- Pulmonary function tests (including FVC, RV, and DL_{CO})
- HRCT
- MMP7, CCL18, and SPD biomarkers
- 6MWD
- Study diary (dispense/collect) (for subjects receiving KD025)
- Occurrence of exacerbation of IPF (frequency and severity)

- Collect/Dispense study drug (for subjects receiving KD025; if continuing)
- Concomitant medications assessment
- Urine pregnancy test (for females of childbearing potential. Positive results are to be confirmed with serum testing.)
- Adverse event assessment

8.6. Monthly Follow-Up Treatment Period for Those Subjects Continuing Study Drug

8.6.1 Continuation Visits (Every 4 Weeks [± 3 days])

After 24 weeks, subjects in Treatment Group 1 with a stable FVC from baseline may continue to receive therapy with KD025 as long as there is no safety signal and clinical progress continues. Subjects receiving BSC have the option of switching to therapy with KD025 after Week 24. Subjects who switch may receive 24 weeks of dosing with KD025, with the potential to continue on the trial as long as there is no safety signal and clinical progress continues. These subjects will start over at Week 1 and follow the same schedule as outlined in Section 8.5. All subjects will return to the clinic every 4 weeks to have the following procedures completed as per below:

- Seated vital sign measurements (sitting blood pressure, pulse, respiratory rate, temperature), to be completed every 4 weeks.
- Clinical laboratory tests (hematology and serum chemistry panel), to be completed every 4 weeks.
- PT, PTT, and INR, to be completed every 4 weeks.
- TSH, to be completed every 4 weeks.
- Urinalysis, to be completed every 4 weeks.
- Occurrence of exacerbation of IPF (frequency and severity), to be completed every 4 weeks.
- Collect/dispense study drug (for subjects receiving KD025), to be completed every 4 weeks.
- Concomitant medications and procedures assessment, to be completed every 4 weeks.
- Urine pregnancy test (for females of childbearing potential. Positive results are to be confirmed with serum testing.)
- Adverse event assessment, to be completed every 4 weeks.
- St. George's Respiratory Questionnaire, to be completed every 12 weeks.
- Complete PE, including weight, to be completed every 12 weeks.

- Pulmonary function tests (including FVC, RV, and DL_{CO}), to be completed every 12 weeks.
- MMP7, CCL18, and SPD biomarkers (at End of Week 36 and End of Week 48 visits only), to be completed every 12 weeks.
- 6MWD (at End of Week 36 and End of Week 48 visits only), to be completed every 12 weeks.
- HRCT, to be completed every 24 weeks.

8.6.2 End of Treatment Visit [± 3 days])

Subjects who discontinue from the study will have the following tests completed:

- Complete PE, including weight
- Seated vital sign measurements (sitting blood pressure, pulse, respiratory rate, temperature)
- Clinical laboratory tests (hematology and serum chemistry panel)
- PT, PTT, and INR
- TSH
- Urinalysis
- 12 Lead ECG
- Pulmonary function tests. Not to be performed if PFTs were done within 1 month of the EOT visit.
- HRCT. Not to be performed if HRCT was done within 1 month of the EOT visit.
- MMP7, CCL18, and SPD biomarkers 6MWD (to be performed at End of Week 48 and every 12 weeks thereafter)
- Study diary (dispense/collect) (for subjects receiving KD025)
- Occurrence of exacerbation of IPF (frequency and severity)
- Collect/dispense study drug (for subjects receiving KD025)
- Concomitant medications and procedures assessment
- Urine pregnancy test (for females of childbearing potential. Positive results are to be confirmed with serum testing.)
- Adverse event assessment

8.7. 30-Day Follow-Up Visit

Subjects will return to the clinic 30 days (± 3) after their last dose of KD025 (Follow-up visit not required for BSC subjects). At this visit, the following procedures will be completed:

- Complete PE, including weight
- Seated vital sign measurements (sitting blood pressure, pulse, respiratory rate, temperature)
- Clinical laboratory tests (hematology and serum chemistry panel)
- PT, PTT, and INR
- TSH
- Urinalysis
- Supine 12-Lead ECG (repeat 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)
- Pulmonary function tests (including FVC, RV, and DL_{CO})
- Occurrence of exacerbation of IPF (frequency and severity)
- Collect study diary (for subjects receiving KD025)
- Concomitant medications and procedures assessment
- Urine pregnancy test (for females of childbearing potential. Positive results are to be confirmed with serum testing.)
- Adverse event assessment

8.8. Unscheduled Visits

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

- St. George's Respiratory Questionnaire
- Complete PE, including weight
- Seated vital sign measurements (sitting blood pressure, pulse, respiratory rate, temperature)
- Clinical laboratory tests (hematology and serum chemistry panel)
- PT, PTT, INR
- TSH
- Urinalysis

- Supine 12-Lead ECG (repeat 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)
- MMP7, CCL18, and SPD biomarkers
- Pulmonary function tests (including FVC, RV, and DL_{CO})
- 6MWD
- Occurrence of exacerbation of IPF (frequency and severity)
- Dispense /collect study drug (for subjects receiving KD025)
- Dispense /collect study drug diary (for subjects receiving KD025)
- Concomitant medications and procedures assessment
- Urine pregnancy test (for females of childbearing potential. Positive results are to be confirmed with serum testing.)
- Adverse event assessment

8.9. Laboratory Assessments

A Central laboratory will perform hematology, serum chemistry, coagulation, thyroid, and urinalysis tests and results will be provided to the Investigator (Table 2). Blood and urine samples for hematology, serum chemistry, coagulation, TSH, and urinalysis will be prepared using standard procedures.

Table 2: Clinical Laboratory Panels

Hematology	Serum Chemistry	Urinalysis
• white blood cell count with differential (including at minimum: neutrophils, basophils, eosinophils, lymphocytes, monocytes) • red blood cell count • hemoglobin • hematocrit • platelet count • MCV	• albumin • alkaline phosphatase • ALT • AST • BUN • calcium • carbon dioxide • chloride • cholesterol • creatinine • CPK • direct bilirubin • GGT • globulin • glucose • lactate dehydrogenase • magnesium • phosphorus • potassium • sodium • total bilirubin • total protein • uric acid	• appearance • color • pH • specific gravity • ketones • protein • glucose • bilirubin • nitrite • urobilinogen • occult blood (microscopic examination of sediment will be performed only if the results of the urinalysis dipstick evaluation are positive)
Coagulation	**Thyroid**	
• INR • PT • PTT	• TSH	
Biomarkers		
• MMP7 • CCL18 • Serum SPD		

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CCL18 = chemokine ligand 18; CPK = creatine phosphokinase; GGT = gamma glutamyl transferase; INR = international normalized ratio; MCV = mean corpuscular volume; MMP7 = matrix metalloproteinase; PT = prothrombin time; PTT = partial thromboplastin time; SPD = surfactant protein-D; TSH = thyroid stimulating hormone

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 Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (see Appendix C). 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 13.1).

8.10. Electrocardiogram Assessments

Digital 12-lead ECGs will be obtained during the study (see Table 1 for timing of ECG assessments). Note that at the Week 1 Day 1 and End of Week 4 visits, an ECG is to be performed predose and 4 hours post-dose (T_{max}) for subjects in Treatment Group 1.

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. The ECG is to be repeated 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.

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

Abnormalities in the ECG that lead to a change in subject management (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 13.1).

8.11. Pulmonary Function Tests (including FVC, RV, and DLCO)

Pulmonary function testing will be performed during the study (see Table 1 for timing of assessments). Pulmonary function testing will include FVC, RV, and DL_{CO}. The same equipment and tester should be used during the course of the study. For each subject, PFT should be done at approximately the same time of the day. The test will be conducted while the subject is in a seated position and will be done in triplicate.

8.12. 6-Minute Walking Distance

The 6MWD will be measured during the study (see Table 1 for timing of assessment). The distance travelled during 6 minutes (meters) will be measured in accordance with published guidelines. The total distance ambulated in meters during the 6MWD test and the number of rest stops is recorded. The 6MWD, weight, heart rate, blood pressure, and Sp02 will be recorded before and after the walk.

8.13. High Resolution Computed Tomography

The change in severity of lung fibrosis as measured by Quantitative HRCT during the study (see Table 1 for timing of assessment) will be read via a central reader. Optimal HRCT technique for evaluation is listed in Table 3 below.

Table 3: Clinical Optimal HRCT Technique for Evaluation of Interstitial Lung Disease[17]

The scans should be without contrast and include at a minimum:
1. Scans obtained on full inspiration without respiratory motion
2. Contiguous or noncontiguous axial scans with thin sections, reconstructed at ≤ 2 cm intervals
3. Reconstructed slice collimation ≤ 2 mm
4. High-resolution reconstruction algorithm
5. Field of view to include lungs only
6. Expiratory scans are helpful to exclude lobular air trapping suggestive of hypersensitivity pneumonitis
7. Prone scans if dependent density obscures detail on supine images
8. Optional coronal and sagittal reconstructions if volumetric images are obtained

8.14. Occurrence of Acute Exacerbation

Occurrence of acute exacerbation (frequency and severity) of IPF will be assessed throughout treatment (see Table 1 for timing of assessment). The following clinical deterioration symptoms within a month that cannot be explained by other reasons will be assessed as acute exacerbation.

1. Aggravated dyspnea;
2. Newly discovered chest interstitial lung abnormality by radiograph/HRCT, without pneumothorax or pleural effusion;
3. SpO_2 decreases to < 88% (heart failure or pulmonary embolism excluded).

Acute exacerbation can be diagnosed if items 1 and 2 are present or if items 1 and 3 are present. Per the 2011 IPF Diagnosis Management and Guidelines,[1] criteria for acute exacerbations should include an absence of an alternative explanation such as infection, pulmonary embolism, pneumothorax, or heart failure.

8.15. Time to Progression of IPF

Time to progression of IPF will be determined and is defined as time from Week 1, Day 1 to any 1 of the following:

1. First respiratory-related hospitalization.
2. Respiratory-related death.
3. Absolute decline in FVC percent of predicted value of ≥ 10% versus FVC percent of predicted value recorded at baseline.
4. Absolute decline in DL_{CO}, adjusted for hemoglobin, percent of predicted value of ≥ 15% versus DL_{CO} recorded at baseline.

9. PHARMACOKINETICS

Not applicable.

10. PHARMACODYNAMICS

The MMP7, CCL18, and SPD serum levels will be assessed during the study (see Table 1 for sampling times). Serum MMP7 concentrations in peripheral blood are easily measurable and reflect changes in the alveolar microenvironment. Thus, mean serum MMP7 concentrations after 24 weeks of KD025 treatment will be studied as a potential surrogate biomarker of the effect of KD025 administration on disease progression.

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

11. REMOVING SUBJECTS FROM STUDY

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

11.1. 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 AEs.

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.

11.1.1 Treatment Discontinuation

Treatment discontinuation reasons include any of the following:

- An AE requires permanent discontinuation of study drug or BSC
- Investigator decision
- Voluntary withdrawal by subject
- Noncompliance to protocol
- Subject lost to follow-up
- Termination of the study by sponsor
- Subject death
- Disease progression

11.1.2 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, every effort should be made to have the subject come to the clinic for an End of Treatment visit in order for the Investigator to perform study follow-up procedures. Refer to Table 1, Study Assessments for a complete list of procedures to be performed at the End of Treatment visit.

Subjects who are withdrawn from this study because of toxicity are to be followed until there is either:

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

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.

Once a subject discontinues from the study for any reason, every effort will be made to collect all clinical and laboratory data as scheduled for the follow-up.

11.2. Stopping Rules

Stopping criteria will be assessed using the Clinical Symptom Adverse Event Grading scale (see Appendix B) and will include clinically significant changes with respect to blood pressure, dyspepsia, nausea or vomiting, or other TEAEs that are Grade 2 (moderate) or higher.

11.2.1 Adverse Events Stopping Criteria

AEs that require consideration of study drug discontinuation include the following:

- AEs of clinical concern
- Grade 2 (moderate) or higher TEAEs that are determined by the Investigator to be possibly, probably or definitely related to study drug and last at least 5 days.
- Clinically significant elevation of ALT or AST. See Section 12.4 for risk management of LFT changes observed during the study.

11.2.2 Blood Pressure Stopping Criteria

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

Clinically significant blood pressure decreases will be defined as follows:

- An absolute systolic blood pressure < 85 mm Hg at any time point, or a decrease > 30 mm Hg in systolic blood pressure from baseline with accompanying symptoms of hypotension at any time point, or an asymptomatic decrease > 30 mm Hg from baseline on any 2 consecutive time points; or
- An absolute diastolic blood pressure < 45 mm Hg at any time point, or a decrease > 20 mm Hg in diastolic blood pressure from baseline with accompanying symptoms of hypotension at any time point, or an asymptomatic decrease > 20 mm Hg in diastolic blood pressure from baseline on 2 consecutive time points.

Clinically significant blood pressure increases are defined as:

- An absolute systolic blood pressure > 180 mm Hg at any time point, or an increase > 30 mm Hg in systolic blood pressure from baseline with accompanying symptoms of hypertension at any time point, or an asymptomatic increase > 30 mm Hg from baseline on any 2 consecutive time points; or
- An absolute diastolic blood pressure > 110 mm Hg at any time point, or an increase > 20 mm Hg in diastolic blood pressure from baseline with accompanying symptoms of hypertension at any time point or an asymptomatic increase > 20 mm Hg in diastolic blood pressure from baseline on 2 consecutive time points.

11.3. 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:

- The incidence or severity of AEs in this or other related studies indicates a potential health hazard to subjects
- Subject enrollment is unsatisfactory

- Drug supply issues
- Excessive subject self-withdrawal
- Significant protocol violations (eg, violation of eligibility criteria, dosing errors, missing data for study endpoint analysis)

11.4. Replacements

Subjects withdrawn from the study before receiving any study drug or BSC drugs/treatment will be replaced by enrolling additional subjects into the study.

12. STUDY DRUG

12.1. Dose and Schedule of Study Drug and Comparator

12.1.1 Primary 24-Week Treatment Period

Eligible subjects will be treated with 400 mg KD025 QD orally administered for 24 weeks or BSC (as determined by the Investigator).

Treatment Group 1	400 mg KD025 QD
Treatment Group 2	BSC

Treatment Group 1: Subjects should take 2 tablets within 5 minutes of finishing a meal. Subjects will be dispensed study drug to self-administer while on an outpatient basis. Subjects will take their first dose of study drug at the clinic on Day 1 and also take their dose of study drug at the clinic at the End of Week 4 visit. Additionally, subjects will be asked to bring their study drug diary to each visit.

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. KD025 will be supplied as 200-mg tablets.

Product	Strength	Dosage Form	Route
KD025	200 mg	Pale yellow tablet	Oral

Product	Dose	Number of 200-mg tablets to be administered per dose
KD025	400 mg QD	2

Treatment Group 2: Subjects will receive BSC (as deemed appropriate by the Investigator). Subjects randomized to BSC will be treated exactly the same as subjects on KD025 and undergo all tests in a similar fashion.

12.1.2 Switching from BSC to KD025

Subjects receiving BSC have the option of switching to therapy with KD025 after Week 24. Subjects who switch may receive 24 weeks of dosing with KD025, with the potential to continue on the trial as long as there is no safety signal and clinical progress continues. For subjects who switch to KD025, prior to their first dose of KD025, Investigators should perform the Week 1, Day 1 assessments (except for safety labs [hematology and chemistry] if performed within 1 week of this

visit and PFTs if performed within 4 weeks) and all subsequent visits as outlined in Table 1, Study Assessments.

12.1.3 Continuation of KD025 Dosing

Subjects in Treatment Group 1 may receive additional therapy with KD025 as long as there is no safety signal and clinical progress continues.

No subject will receive more than 96 weeks of study drug treatment in this study.

12.2. 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:

- 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.

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

12.3. Dose Reduction for KD025

Every effort should be made to keep the subject on the full dose of drug. However, in the event that the Investigator feels that an AE requires dose modification, the drug may be decreased as shown in Table 4 and Table 5. Once a subject has their dose decreased, an increase back to 400 mg QD is not allowed.

Table 4: Dose Reductions for Toxicity Related to Study Drug

Study Drug	Starting Dose	Dose Reduction
KD025	400 mg KD025 QD	200 mg QD

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. Liver function test risk management is treated separately; see Section 12.4, below.

Table 5 Guidelines for Management of Treatment-emergent Toxicities

Toxicity	Recommended Action
Grade 4 organ toxicities considered at least possibly related to KD025	• Discontinue KD025
Grade ≥3 LFTs (AST, ALT or total bilirubin) regardless of attribution to KD025	• Hold KD025 dosing until resolution to Grade 1 or below levels • Consider resuming KD025. If resuming, then resume at one dose decrement • If toxicity recurs, discontinue KD025 permanently
Other Grade ≥3 clinically significant toxicities considered at least possibly related to KD025	• Hold KD025 dosing until toxicity has resolved to Grade 1 or below then consider resuming KD025. If resuming, then resume at one dose decrement • If toxicity recurs, hold dose as above then consider resuming KD025 at one dose decrement

ALT = alanine aminotransaminase; AST = aspartate aminotransaminase; LFT = liver function test

12.4. Evaluation of Liver-Related Blood Tests

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

1. Immediately contacting the medical monitor.
2. Repeating liver enzyme, serum bilirubin, and PT/INR once a week.

   (Frequency of retesting can decrease if abnormalities stabilize or the trial drug has been discontinued and the subject is asymptomatic.)
3. Obtaining a more detailed history of symptoms and prior or concurrent diseases.
4. Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
5. Ruling out acute viral hepatitis types A, B, C; autoimmune or alcoholic hepatitis; nonalcoholic steatohepatitis; hypoxic/ischemic hepatopathy; and biliary tract disease.
6. Obtaining a history of exposure to environmental chemical agents.

If close observation is not possible, the subject should be discontinued from the study at the Investigators discretion.

Subjects with ALT or AST > 3 × ULN, who do not have clinically significant elevations of liver-related blood tests as described below, should have KD025 administration halted for 2 to 3 weeks with weekly evaluation of ALT and AST. If ALT and AST return to normal within 3 weeks, then KD025 can be restarted at a lower dose. If ALT and AST do not return to normal within 3 weeks, then KD025 administration should be terminated (Table 6).

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

1. ALT or AST > 5 × ULN
2. ALT or AST > 3 × ULN and total bilirubin > 2 ×ULN or INR > 1.5
3. ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
4. If the total bilirubin is > 2 × ULN then discontinue KD025 and obtain direct bilirubin

Table 6: Grading of Liver-Related Laboratory Abnormalities[18,19,20]

Feature	Grade 1	Grade 2	Grade 3	Grade 4
ALT	> ULN-3.0 × ULN	> 3.0-5.0 × ULN	> 5.0-20 × ULN	> 20 × ULN
AST	> ULN-3.0 × ULN	> 3.0-5.0 × ULN	> 5.0-20 × ULN	> 20 × ULN
Alkaline Phosphatase	> ULN-2.5 × ULN	> 2.5-5.0 × ULN	> 5.0-20.0 × ULN	> 20 × ULN
GGT	> ULN-2.5 × ULN	> 2.5-5.0 × ULN	> 5.0-20.0 × ULN	> 20 × 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

12.5. Identity of Investigational Products

KD025 will be supplied by Kadmon Corporation.

12.6. 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 tablet) 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.”

12.7. 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 (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 or 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 amount, date and time of study drug administrations. These diaries will be dispensed and/or reviewed/collected at each visit.

12.8. Study Drug Storage

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

12.9. Study Drug Accountability

The US FDA and other regulatory agencies require accounting for the disposition of all investigational drugs received by each clinical site. Information on drug disposition required by law consists of the date received, date administered, quantity administered, and the subject to whom the drug was administered. The principal Investigator is responsible for the accounting for all unused

study drugs and all used study drug containers. The Investigator must maintain a complete and current dispensing and inventory record that has been supplied by the sponsor.

12.10. 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.

12.10.1 Disposition of Used Supplies

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

12.10.2 Inventory of Unused Supplies

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

13. CONCOMITANT MEDICATION AND PROCEDURES

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

A reasonable effort is to be made to document any medications or procedures the subject receives from the date that the ICF is signed until 30 days after last dose of KD025. For BSC subjects, concomitant medications and procedures will be recorded through the End-of-Week 24 visit.

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.

13.1. Prohibited Medications for Subjects Receiving KD025

All subjects who receive KD025 therapy, that is, all subjects in Treatment Group 1 and subjects in Treatment Group 2 who crossover to KD025 therapy are not to take drugs that are sensitive substrates of CYP enzymes from first dose until 14 days after last dose of study drug. Additionally, use of strong CYP3A4 inducers are prohibited. Other CYP3A4 inhibitors or inducers should be used with caution. Herbal medications (eg, St. John's Wort) or grapefruit/grapefruit juice should not be consumed 14 days prior to first dose of study drug until the end of treatment. Please refer to Appendix F for drugs that induce and inhibit CYP3A4 and Appendix G for drug that induce and inhibit CYP1A2.

SAFETY

Safety Parameters

The Clinical Symptom and Adverse Event Grading Scale will be used for grading toxicities (see Appendix B). Laboratory results will be classified using the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (see Appendix A). 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, coagulation, and urinalysis results, and ECG recordings.

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 30 days after last dose of KD025 are to be recorded on eCRFs by the investigational site. For BSC subjects, AEs will be recorded through the End-of-Week 24 visit.

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.

Serious Adverse Events

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

The SAE definition and reporting requirements are in accordance with Title 21 Part Code of Federal Regulations (CFR) 312.32 and the Guidance for Industry and Investigators Safety Reporting Requirements for Investigational New Drug (INDs) and Bioavailability /Bioequivalence Studies.

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

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

Note: Death is an outcome of an AE, and not an AE in itself. The event(s) that caused death (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 adverse event: 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 1 of the outcomes listed in this definition.

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 Investigator Brochure), rather than from the perspective of such an event not being anticipated from the pharmacological properties of the product.

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.

Non-Serious Adverse Events

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

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.

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 C).

Recording Adverse Events

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

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.

Serious Adverse Event Reporting

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 IRBs 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.

13.1.1.1. 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 30 days of receiving study drug, regardless of relationship to study drug, or any death that occurs more than 30 days after receiving study drug, and is believed to be study drug-related, must be promptly reported (within 24 hours of the Investigator becoming aware of the event) by e-mail to the sponsor (or designee).

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

APCER Life Sciences, LLC
Fax: 646-430-9549

In the event of an issue with the fax line, forward
SAE/SUSAR via email to:
ClinicalSAEReporting@kadmon.com

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

Sanjay Aggarwal, M.D. Kadmon Corporation
55 Cambridge Parkway, Suite 300E
New York, NY 10016
Telephone:
Direct: 724-778-6129
Cell: 857-253-8642
E-mail: Sanjay.Aggarwal@kadmon.com

13.1.1.2. Information to be Provided by the Investigator

SAEs for all enrolled subjects must be recorded on both the SAE form and the AE eCRF page (during study participation). This requirement includes all SAEs that occur after informed consent and through 30 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 30 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.

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

13.2. Other Safety Considerations

13.2.1 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 Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (see Appendix A).

13.2.2 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.

13.2.3 Follow-Up of Adverse Events

Any SAE or AE assessed as possibly related that led to treatment discontinuation (including clinically significant abnormal laboratory values that meet these criteria) and is ongoing 30 days after last dose of study 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 30 days after last dose* of study drug. The status of all other continuing AEs will be documented as of 30 days after last dose of study drug.

14. STATISTICAL CONSIDERATIONS

All statistical analyses will be performed using SAS® (SAS Institute, Cary, North Carolina) statistical software Version 9.3 or higher, unless otherwise noted.

The primary analysis will be conducted with a data cutoff of approximately 24 weeks after last patient enrolled has received KD025 or when all subjects can be evaluated for primary endpoints. Ongoing monitoring of safety data will be conducted in accordance with study stopping rules.

14.1. General Design

All data for randomized 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.

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.

14.2. Sample Size Justification

With 54 subjects in the KD025 Treatment Group and 27 in the BSC Treatment Group, the study has over 90% power at the two-sided 0.05 significance level to detect a 20% difference between treatment groups at 24 weeks in percent change from baseline in FVC assuming a standard deviation in percent change from baseline in FVC of 17%.

The sample size of 54 subjects receiving KD025 will provide over 90% probability of 1 or more subjects in the study experiencing an AE that has an underlying rate of ≥ 5%.

14.3. Statistical Considerations

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

14.3.1 Study Populations

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

- The Safety Population will consist of all subjects who are randomized and receive at least 1 dose of KD025 (Treatment Group 1) or have Week 1 assessment for BSC subjects. All safety analyses will be performed on the safety population
- The Modified Intent-to-Treat (mITT) Population will consist of all subjects in the Safety Population who have evaluable baseline and at least one evaluable post baseline FVC assessment. Only evaluable FVC will be used in efficacy.
- The Per Protocol (PP) Population will consist of all subjects in the safety population who have evaluable baseline and evaluable Week 24 FVC assessment. For any analysis on the PP Population, for subjects assigned to treatment and actually received treatment, re-calculated baseline value should be used for cross over patients.

The primary and secondary efficacy/activity endpoints will be analyzed using both the mITT and PP Populations.

14.3.2 Subject Accountability, Demographics, and Baseline Characteristics

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

14.3.3 KD025 Exposure

For the KD025 Treatment Group, 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.

14.3.4 Concomitant Medications and Procedures

Concomitant medications will be coded using WHO Drug Dictionary and the data will be summarized by treatment group and presented in tables and listings. Concomitant procedures performed during the study will also be collected and presented in listings.

14.4. Activity/Efficacy Analysis

The primary efficacy/activity endpoint is the change in FVC from baseline to 24 weeks. A mixed model (if numeric stable) or analysis of covariance (ANCOVA) model will be used for the between treatment groups comparison of the Week 24 change from baseline in FVC with treatment group as a fixed effect and baseline FVC as a covariate.

The primary safety endpoint is a subject experiencing one or more AEs during the treatment period. The percentage of subjects experiencing an AE will be summarized for the KD025 and BSC treatment groups (descriptive statistics only). Primary safety analyses will be performed on the safety population.

Secondary Endpoints

- The change in 6MWD from baseline to 24 weeks
- Acute exacerbation of IPF throughout the treatment period
- The change in occurrence, frequency and severity of lung fibrosis as measured by quantitative HRCT at baseline and after 24 weeks of treatment
- To evaluate the percentage of subjects with disease progression before or at 24 weeks

Treatment group differences in the Week 24 change from baseline to 24 weeks in 6MWD and Week 24 change from baseline in severity of lung fibrosis as measured by quantitative HRCT will be analyzed by a mixed or ANCOVA model with treatment group as a fixed effect and the corresponding baseline value as a covariate.

The percentage of subjects in each treatment group who experience acute exacerbation of IPF throughout the treatment period will be compared by a Fisher's Exact test.

Exploratory Endpoints

- The change in MMP7, CCL18 and SPD serum levels from baseline to 24 weeks

For each of these exploratory endpoints, a mixed or ANCOVA model will be used to assess treatment differences with treatment as a fixed effect and the corresponding baseline value as a covariate.

14.5. Safety Data

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

AEs will be coded using the MedDRA dictionary (Version 20.0 or greater.) The number and percentages of subjects experiencing treatment-emergent AEs will be tabulated by SOC and preferred term and will be presented by treatment group. The number of events by preferred term will also be

summarized. Tabulation by maximum severity and relationship to KD025 will also be included by treatment group. Summary subject listing will be provided for SAEs, AEs resulting in study discontinuation and deaths. All AEs (including SAEs will be graded using a 5-point scale (mild, moderate, severe, life threatening, or death; see Appendix B).

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

Laboratory results will be classified using the Toxicity Grading Scale for Healthy Adult and summarized by treatment group. Incidence of laboratory abnormalities will be summarized by treatment group. The worst on-study grade after the first dose of study drug will be summarized (or after Week 1, Day 1 visit for BSC cohort). 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.

15. 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.

16. ETHICAL ASPECTS

16.1. 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" or applicable local equivalent.

16.2. 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. The final IRB-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.

16.3. 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. This board must operate in accordance with the current federal or local regulations. The Investigator will

send a letter or certificate of IRB approval to Kadmon Corporation (or designee) before subject enrollment and whenever subsequent modifications to the protocol are made.

16.4. 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. Samples will be held no longer than 10 years from time of collection. No genomic research will be conducted.

17. CONDITIONS FOR MODIFYING THE PROTOCOL

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

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

18. 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.

19. STUDY DOCUMENTATION, CRFS, AND RECORD KEEPING

19.1. 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, 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/activity 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. When source documents are required for the continued care of the subject, appropriate copies should be made for storing outside of the study site.

19.2. 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.

19.3. 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.

19.4. Electronic Case Report Forms

Clinical trial data for this study will be captured on eCRF. The Investigator agrees to provide all information requested on the eCRF in an accurate manner according to instructions provided. 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.

20. 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 that subject confidentiality is maintained in accordance with local requirements.

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

21. 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 number and not by their names. The subjects' personal information should be redacted on all source documents prior to submission to Kadmon Corporation. The Investigator should keep a subject enrollment log showing subject numbers, names, and addresses. The Investigator should maintain documents not for submission to Kadmon Corporation (eg, subjects' written consent forms) in strict confidence.

22. 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.

23. REFERENCES

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24. APPENDICES

APPENDIX A: TABLES FOR GRADING LABORATORY ABNORMALITIES

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

Note: For LFT and bilirubin abnormalities, see Section 12.4.

Chemistry*	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening**
Sodium – Hyponatremia mEq/L	132 – 134	130 – 131	125 – 129	< 125
Sodium – Hypernatremia mEq/L	144 – 145	146 – 147	148 – 150	> 150
Potassium – Hyperkalemia mEq/L	5.1 – 5.2	5.3 – 5.4	5.5 – 5.6	> 5.6
Potassium – Hypokalemia mEq/L	3.5 – 3.6	3.3 – 3.4	3.1 – 3.2	< 3.1
Glucose – Hypoglycemia mg/dL	65 – 69	55 – 64	45 – 54	< 45
Glucose – Hyperglycemia Fasting – mg/dL Random – mg/dL	100 – 110 110 – 125	111 – 125 126 – 200	>125 >200	Insulin requirements or hyperosmolar coma
Blood Urea Nitrogen BUN mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Calcium – hypocalcemia mg/dL	8.0 – 8.4	7.5 – 7.9	7.0 – 7.4	< 7.0
Calcium – hypercalcemia mg/dL	10.5 – 11.0	11.1 – 11.5	11.6 – 12.0	> 12.0
Magnesium – hypomagnesemia mg/dL	1.3 – 1.5	1.1 – 1.2	0.9 – 1.0	< 0.9
Phosphorous – hypophosphatemia mg/dL	2.3 – 2.5	2.0 – 2.2	1.6 – 1.9	< 1.6
CPK – mg/dL	1.25 – 1.5 × ULN***	1.6 – 3.0 × ULN	3.1 –10 × ULN	> 10 × ULN
Albumin – Hypoalbuminemia g/dL	2.8 – 3.1	2.5 – 2.7	< 2.5	--
Total Protein – Hypoproteinemia g/dL	5.5 – 6.0	5.0 – 5.4	< 5.0	--
Cholesterol	201 – 210	211 – 225	> 226	---
Pancreatic enzymes – amylase, lipase	1.1 – 1.5 × ULN	1.6 – 2.0 × ULN	2.1 – 5.0 × ULN	> 5.0 × ULN

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

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

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

Hematology *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening**
Hemoglobin (Female) - gm/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	< 8.0
Hemoglobin (Female) change from Baseline value - gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (Male) - gm/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Hemoglobin (Male) change from Baseline value – gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
WBC Increase - cell/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	> 25,000
WBC Decrease - cell/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	< 1,000
Lymphocytes Decrease - cell/mm^3	750 – 1,000	500 – 749	250 – 499	< 250
Neutrophils Decrease - cell/mm^3	1,500 – 2,000	1,000 – 1,499	500 – 999	< 500
Eosinophils - cell/mm^3	650 – 1500	1501 - 5000	> 5000	Hypereosinophilic
Platelets Decreased - cell/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	< 25,000
PT – increase by factor (prothrombin time)	1.0 – 1.10 × ULN**	1.11 – 1.20 × ULN	1.21 – 1.25 × ULN	> 1.25 ULN
PTT – increase by factor (partial thromboplastin time)	1.0 – 1.2 × ULN	1.21 – 1.4 × ULN	1.41 – 1.5 × ULN	> 1.5 × ULN
Fibrinogen increase - mg/dL	400 – 500	501 – 600	> 600	--
Fibrinogen decrease - mg/dL	150 – 200	125 – 149	100 – 124	< 100 or associated with gross bleeding or disseminated intravascular coagulation (DIC)

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

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

Urine *	**Mild (Grade 1)**	**Modera te (Grade**	**Severe (Grade 3)**	**Potentially Life Threatening**
Protein	Trace	1+	2+	Hospitalization or dialysis
Glucose	Trace	1+	2+	Hospitalization for

Blood (microscopic) – red blood cells per high power field (rbc/hpf)	1 - 10	11 – 50	> 50 and/or gross blood	Hospitalization or packed red blood cells (PRBC) transfusion

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

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

APPENDIX B: CLINICAL SYMPTOM AND ADVERSE EVENT GRADING SCALE

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

APPENDIX C: 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.

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

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

APPENDIX D: CORRECTION FOR HEART RATE (FRIDERICIA)*

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

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

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

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

APPENDIX E: ST. GEORGE'S RESPIRATORY QUESTIONNAIRE (SGRQ) ENGLISH FOR THE U.S.A.[22]

This questionnaire is designed to help us learn much more about how your breathing is troubling you and how it affects your life. We are using it to find out which aspects of your illness cause you most problems, rather than what the doctors and nurses think your problems are.

Please read the instructions carefully and ask if you do not understand anything. Do not spend too long deciding about your answers.

Before completing the rest of the questionnaire:

Please tick in one box to show how you describe your current health:

Very good	Good	Fair	Poor	Very poor
☐	☐	☐	☐	☐

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Continued……

UK/ English (original) version
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St. George's Respiratory Questionnaire
PART 1

Questions about how much chest trouble you have had over the past 3 months.

Please tick (✓) *one box for each question*:

	most days a week	several days a week	a few days a month	only with chest infections	not at all
1. Over the past 3 months, I have coughed:	☐	☐	☐	☐	☐
2. Over the past 3 months, I have brought up phlegm (sputum):	☐	☐	☐	☐	☐
3. Over the past 3 months, I have had shortness of breath:	☐	☐	☐	☐	☐
4. Over the past 3 months, I have had attacks of wheezing:	☐	☐	☐	☐	☐

5. During the past 3 months how many severe or very unpleasant attacks of chest trouble have you had?

Please tick (✓) *one*:

- more than 3 attacks ☐
- 3 attacks ☐
- 2 attacks ☐
- 1 attack ☐
- no attacks ☐

6. How long did the worst attack of chest trouble last?
(Go to question 7 if you had no severe attacks)

Please tick (✓) *one*:

- a week or more ☐
- 3 or more days ☐
- 1 or 2 days ☐
- less than a day ☐

7. Over the past 3 months, in an average week, how many good days (with little chest trouble) have you had?

Please tick (✓) *one*:

- No good days ☐
- 1 or 2 good days ☐
- 3 or 4 good days ☐
- nearly every day is good ☐
- every day is good ☐

8. If you have a wheeze, is it worse in the morning?

Please tick (✓) *one*:

- No ☐
- Yes ☐

Continued……

St. George's Respiratory Questionnaire
PART 2

Section 1

How would you describe your chest condition?

Please tick (✓) *one*:

- The most important problem I have ☐
- Causes me quite a lot of problems ☐
- Causes me a few problems ☐
- Causes no problem ☐

If you have ever had paid employment.

Please tick (✓) *one*:

- My chest trouble made me stop work altogether ☐
- My chest trouble interferes with my work or made me change my work ☐
- My chest trouble does not affect my work ☐

Section 2

Questions about what activities usually make you feel breathless <u>these days</u>.

Please tick (✓) in ***each box*** that applies to you ***these days***:

	True	False
Sitting or lying still	☐	☐
Getting washed or dressed	☐	☐
Walking around the home	☐	☐
Walking outside on the level	☐	☐
Walking up a flight of stairs	☐	☐
Walking up hills	☐	☐
Playing sports or games	☐	☐

Continued……

St. George's Respiratory Questionnaire
PART 2

Section 3

Some more questions about your cough and breathlessness <u>these days</u>.

	Please tick (✓) in *each box* that applies to you *these days*: True	False
My cough hurts	☐	☐
My cough makes me tired	☐	☐
I am breathless when I talk	☐	☐
I am breathless when I bend over	☐	☐
My cough or breathing disturbs my sleep	☐	☐
I get exhausted easily	☐	☐

Section 4

Questions about other effects that your chest trouble may have on you <u>these days</u>.

	Please tick (✓) in *each box* that applies to you *these days*: True	False
My cough or breathing is embarrassing in public	☐	☐
My chest trouble is a nuisance to my family, friends or neighbours	☐	☐
I get afraid or panic when I cannot get my breath	☐	☐
I feel that I am not in control of my chest problem	☐	☐
I do not expect my chest to get any better	☐	☐
I have become frail or an invalid because of my chest	☐	☐
Exercise is not safe for me	☐	☐
Everything seems too much of an effort	☐	☐

Section 5

Questions about your medication, if you are receiving no medication go straight to section 6.

	Please tick (✓) in *each box* that applies to you *these days*: True	False
My medication does not help me very much	☐	☐
I get embarrassed using my medication in public	☐	☐
I have unpleasant side effects from my medication	☐	☐
My medication interferes with my life a lot	☐	☐

Continued……

St. George's Respiratory Questionnaire
PART 2

Section 6

These are questions about how your activities might be affected by your breathing.

	Please tick (✓) in *each box* that applies to you *because of your breathing*: True	False
I take a long time to get washed or dressed	☐	☐
I cannot take a bath or shower, or I take a long time	☐	☐
I walk slower than other people, or I stop for rests	☐	☐
Jobs such as housework take a long time, or I have to stop for rests	☐	☐
If I walk up one flight of stairs, I have to go slowly or stop	☐	☐
If I hurry or walk fast, I have to stop or slow down	☐	☐
My breathing makes it difficult to do things such as walk up hills, carrying things up stairs, light gardening such as weeding, dance, play bowls or play golf	☐	☐
My breathing makes it difficult to do things such as carry heavy loads, dig the garden or shovel snow, jog or walk at 5 miles per hour, play tennis or swim	☐	☐
My breathing makes it difficult to do things such as very heavy manual work, run, cycle, swim fast or play competitive sports	☐	☐

Section 7

We would like to know how your chest <u>usually</u> affects your daily life.

	Please tick (✓) in *each box* that applies to you *because of your chest trouble*: True	False
I cannot play sports or games	☐	☐
I cannot go out for entertainment or recreation	☐	☐
I cannot go out of the house to do the shopping	☐	☐
I cannot do housework	☐	☐
I cannot move far from my bed or chair	☐	☐

Continued…

St. George's Respiratory Questionnaire

Here is a list of other activities that your chest trouble may prevent you doing. (You do not have to tick these, they are just to remind you of ways in which your breathlessness may affect you):

Going for walks or walking the dog

Doing things at home or in the garden

Sexual intercourse

Going out to church, pub, club or place of entertainment

Going out in bad weather or into smoky rooms

Visiting family or friends or playing with children

Please write in any other important activities that your chest trouble may stop you doing:

.....

.....

.....

.....

Now would you tick in the box (one only) which you think best describes how your chest affects you:

It does not stop me doing anything I would like to do ☐

It stops me doing one or two things I would like to do ☐

It stops me doing most of the things I would like to do ☐

It stops me doing everything I would like to do ☐

Thank you for filling in this questionnaire. Before you finish would you please check to see that you have answered all the questions.

UK/ English (original) version
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APPENDIX F: DRUGS THAT INDUCE AND INHIBIT CYP3A4

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

Table 7: Examples of Clinical Inducers / Inhibitors of CYP3A4

	Strong	Moderate	Weak
Inducers	Carbamazepine Enzalutamide Mitotane Phenytoin Rifampin St. John's wort	Bosentan Efavirenz Etravirine Modafinil	Armodafinil Rufinamide
Inhibitors	Boceprevir Cobicistat Conivaptan Danoprevir Dasabuvir Elvitegravir Grapefruit juice Indinavir Itraconazole Ketoconazole Lopinavir Paritaprevir Ombitasvir Posaconazole Ritonavir Saquinavir Telaprevir Tipranavir Troleandomycin Voriconazole	Aprepitant Cimetidine Ciprofloxacin Clotrimazole Crizotinib Cyclosporine Dronedarone Erythromycin Fluconazole Fluvoxamine Imatinib Tofisopam Verapamil	Chlorzoxazone Cilostazol Fosaprepitant Istradefylline Ivacaftor Lomitapide Ranitidine Ranolazine Tacrolimus Ticagrelor

Source:

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

Accessed 5-Apr-18

APPENDIX G: DRUGS THAT INDUCE AND INHIBIT CYP1A2

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

Table 8: Examples of Clinical Inducers / Inhibitors of CYP1A2

	Strong	Moderate	Weak
Inducers	-	Phenytoin Rifampin Ritonavir Smoking Teriflunomide	-
Inhibitors	Ciprofloxacin Enoxacin Fluvoxamine Zafirlukast	Methoxsalen Mexiletine Oral contraceptives	Acyclovir Allopurinol Cimetidine Peginterferon α-2a Piperine Zileuton

Source:
https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm
Accessed 5-Apr-18

APPENDIX H: DRUGS THAT PROLONG QTC

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

Table 8: Examples of Drugs that Prolong QTc

Generic Name	
• Aclarubicin	• Iloperidone
• Amiodarone	• Levofloxacin
• Anagrelide	• Levomepromazine
• Arsenic trioxide	• Levomethadyl acetate
• Astemizole	• Levosulpiride
• Azithromycin	• Mesoridazine
• Bepridil	• Methadone
• Chloroquine	• Moxifloxacin
• Chlorpromazine	• Ondansetron
• Cilostazol	• Oxaliplatin
• Ciprofloxacin	• Papaverine HCl
• Cisapride	• Pentamidine
• Citalopram	• Pimozide
• Clarithromycin	• Probucol
• Disopyramide	• Procainamide
• Dofetilide	• Propofol
• Domperidone	• Quinidine
• Donepezil	• Roxithromycin
• Dronedarone	• Sevoflurane
• Droperidol	• Sotalol
• Erythromycin	• Sparfloxacin
• Escitalopram	• Sulpiride
• Flecainide	• Sultopride
• Fluconazole	• Terfenadine
• Gatifloxacin	• Terlipressin
• Grepafloxacin	• Terodiline
• Halofantrine	• Thioridazine
• Haloperidol	• Vandetanib
• Ibogaine	
• Ibutilide	

Source: https://crediblemeds.org/pdftemp/pdf/CombinedList.pdf Accessed 4-Jun-18