CLINICAL STUDY PROTOCOL

Title: A Phase 2, Randomized, Placebo-controlled, Double-blind, Open-label Extension Multicenter Study to Evaluate the Efficacy and Safety of Belumosudil (KD025) in Subjects with Diffuse Cutaneous Systemic Sclerosis

Protocol Number:	KD025-209
Study Drug:	Belumosudil (KD025)
IND Number:	140383
Phase:	2
Sponsor:	Kadmon Corporation, LLC 450 East 29th Street New York, NY 10016
Date of Protocol:	Original, Final, 19 September 2018 Amendment #1, Final, 18 January 2019 Amendment #2, Final, 03 April 2019 Amendment #3, Final, 02 November 2020 Amendment #4, Final, 27 May 2021
Version:	5.0

Procedures in Case of Emergency

Serious Adverse Events

Any serious adverse event (SAE)* occurring in a subject while receiving study drug or within 28 days of receiving their last dose of study drug, even though the event may not appear to be study drug related, must be promptly reported (within 24 hours) by telephone, e-mail, or telefax to the sponsor (or designee).

Emergency Contact Information

For medical questions contact the Kadmon Medical Monitor:

E-mail: [redacted]

Phone: [redacted]

For SAE Reporting send the SAE form, pregnancy form or follow-up within 24 hours of becoming aware to:

Kadmon Pharmacovigilance

Email: [redacted]

or

Fax: [redacted]

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 9.3.1 Serious Adverse Events, for additional information): • Death • Life-threatening adverse drug event • Inpatient hospitalization or prolongation of existing hospitalization • A persistent or significant disability/incapacity • A congenital anomaly/birth defect • An important medical event that may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

SPONSOR APPROVAL SIGNATURE PAGE

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) R2, the Code of Federal Regulations (CFR), and the ethical principles that have their origins in the Declaration of Helsinki.

[redacted]
Kadmon Corporation, LLC

Date of Signature
(DD MMM YYYY)

INVESTIGATOR SIGNATURE PAGE

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) R2, the Code of Federal Regulations (CFR), and the ethical principles that have their origins in the Declaration of Helsinki.

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

Investigator Signature	Date of Signature (DD MMM YYYY)

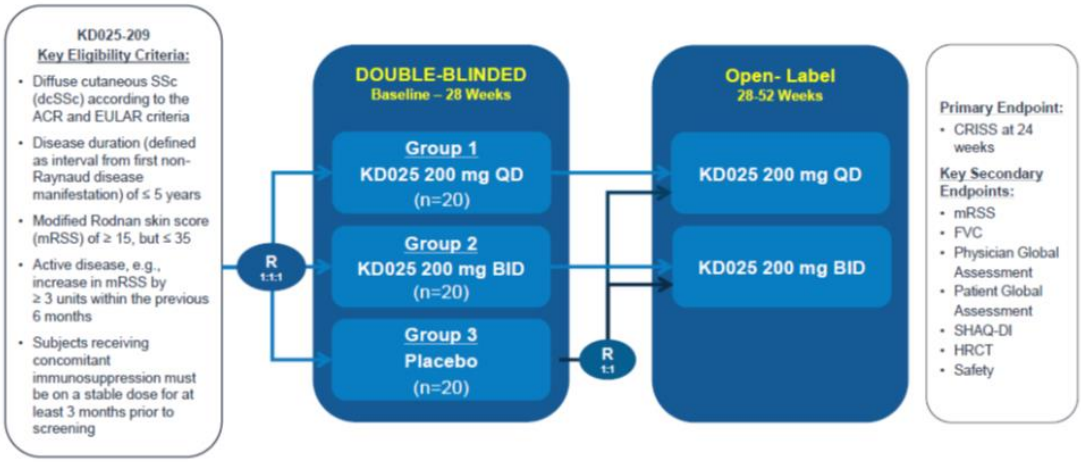
Name of Investigator (please print)

PROTOCOL SYNOPSIS

Study Title	A Phase 2, Randomized, Placebo-controlled, Double-blind, Open-label Extension Multicenter Study to Evaluate the Efficacy and Safety of Belumosudil (KD025) in Subjects with Diffuse Cutaneous Systemic Sclerosis
Clinical Phase	2
Number of Study Centers	Approximately 25
Study Background	Systemic sclerosis, also known as scleroderma, is a chronic autoimmune disease primarily affecting the skin, but with systemic manifestations. Diffuse cutaneous systemic sclerosis (dcSSc) is a more serious form of the disease and is often rapidly progressive, involving not only the skin, but also internal organs including kidney, heart, and lungs. The estimated yearly incidence of all types of systemic sclerosis in the United States is 20 cases per million with a prevalence of 240 cases per million population. Racial disparities exist and there is an increased incidence and severity in African-Americans. Women are far more likely to acquire the disease and make up 80%-90% of the systemic sclerosis population. It has been estimated that up to 60% of systemic sclerosis patients will develop interstitial lung disease (ILD). This interstitial disease begins with an inflammatory alveolitis suggesting that anti-inflammatory therapy be of benefit at early stages. Systemic sclerosis has the highest case-specific mortality among all systemic autoimmune diseases. Pulmonary hypertension, pulmonary fibrosis, and cardiac complications are among the most frequent causes of death. The single most common cause of mortality is pulmonary fibrosis from ILD. There remains a substantial unmet medical need for therapies with improved tolerability and effectiveness for patients with systematic sclerosis. The pathogenesis of dcSSc involves a variety of abnormalities, including immunological/inflammatory activation and vascular injury. The important role of T lymphocytes is well established and involves both IL-17-producing helper T cells (Th17) and regulatory T cell (Treg) subsets. Generally, Th17 cells upregulate inflammation and fibrosis while Treg cells provide an immunosuppressive opposing function. An imbalance of these immunomodulatory cell types may contribute to the pathogenesis of dcSSc. Several signaling pathways are activated and converge to create the pro-fibrotic state commonly seen in dcSSc. Importantly, extracellular mediators such as transforming growth factor-beta (TGF-β) and Wnt10b cause fibroblast activation and differentiation into myofibroblasts resulting in increased extracellular matrix deposition, collagen cross-linking, matrix remodeling, and tissue stiffness. Thus, fibrotic mechanisms appear to play a central role in the pathogenesis of systemic sclerosis.

Study Rationale	Rho-associated coiled-coil containing 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 ROCK isoforms have been identified: ROCK1 and ROCK2. While both are involved in Rho-mediated changes in the actin/myosin cytoskeletal network, ROCK1 and ROCK2 are not redundant signaling molecules and may serve different functions within cells. Recent research has uncovered additional roles for ROCK signaling, in conditions including autoimmune disease aggravated or caused by a Th17-polarized T cell response and pulmonary fibrosis. Rho GTPase-mediated signaling pathways play a central role in coordinating and balancing T cell mediated immune responses, including T cell receptor-mediated signaling, cytoskeletal reorganization, and the acquisition of the appropriate T cell effector program. Studies have demonstrated that aberrant activation of ROCK2 leads to induction of interleukin (IL)-17 and IL-21 via interferon regulatory factor 4-dependent mechanism. In addition, ROCK activity was found to be up-regulated in patients with rheumatoid arthritis and systemic lupus erythematosus and inhibition of ROCK2 effectively decreased IL-17 production in vivo and demonstrated efficacy in arthritis and lupus mouse models. Autoimmunity also involves alterations to regulatory T cells that suppress activation of the immune system and play a critical role in maintaining immunological tolerance to self-antigens and inhibiting autoimmune responses. ROCK2 inhibition may increase the suppressive function of regulatory T cells. ROCK is also downstream of several major pro-fibrotic mediators, including TGF-β, connective tissue growth factor (CTGF), and lysophosphatidic acid. A defining feature of pathologic fibrosis is the differentiation of fibroblasts to myofibroblasts, a process mediated by ROCK. In addition, ROCK mediates stress fiber formation and regulates the transcription of pro-fibrotic genes, including CTGF and alpha-smooth muscle actin (α-SMA). Further, ROCK inhibition has demonstrated anti-fibrotic activity in murine models.
Study Objective(s)	**Primary Objectives** The primary objective of this study is to evaluate the efficacy of belumosudil compared to placebo for the Combined Response Index in diffuse cutaneous Systemic Sclerosis (CRISS) at Week 24 **Secondary Objectives** • To assess the CRISS for each group at Week 52 • To evaluate the efficacy of belumosudil compared to placebo at Week 24 for: o Modified Rodnan Skin Score (mRSS) o Forced Vital Capacity (FVC) o Physician global assessment o Patient global assessment o Scleroderma Health Assessment Questionnaire–Disability Index (SHAQ-DI)

	• To evaluate the efficacy of belumosudil at Week 52 compared to baseline for subjects randomized to belumosudil for the parameters in the bullet above • To assess changes in lung fibrosis, via high resolution computerized tomography (HRCT), performed at baseline, Weeks 24 and Week 52 only in subjects with ILD at screening • To assess pharmacokinetics (PK) of belumosudil by sparse sampling of belumosudil on Weeks 4 and 8 (i.e., Days 29 and 57) immediately prior to belumosudil dosing and 3 hours post-dose • To assess the safety of belumosudil compared to placebo in subjects with dcSSc by examining the percentage of subjects with treatment-emergent adverse events (CTCAE v5.0) in subjects with diffuse cutaneous systemic sclerosis Exploratory Objectives • To evaluate changes in biomarkers of endothelial cell dysfunction, fibrosis, immune system function, and cytokine alterations from subjects receiving belumosudil or placebo • To assess histology and gene expression from skin biopsies taken from subjects at baseline, Week 24, and optionally at Week 52
Study Design	Phase 2, double-blind, placebo-controlled, randomized, multicenter trial in subjects with dcSSc with open-label extension.
Methodology	Subjects who have signed an IRB/IEC-approved informed consent form and met all of the inclusion/exclusion criteria will be enrolled. A total of 60 subjects will be randomized into 3 groups (1:1:1) to receive orally administered belumosudil 200 mg once daily (QD; n = 20), belumosudil 200 mg twice daily (BID; n = 20), or matched placebo (n = 20) for 28 weeks. The study will be double-blinded for the first 28 weeks followed by an open-label extension of 24 weeks. After unblinding, the subjects in Group 1 and 2 will continue on the same belumosudil dose whereas the subjects in the placebo group will be re-randomized to one of the belumosudil doses (200 mg QD or 200 mg BID) in 1:1 fashion. The primary endpoint will be analyzed using Week 24 data. Efficacy will be assessed at baseline and throughout the 52 weeks of dosing period using CRISS, mRSS, PFTs, Physician Global Assessment, and Patient Global Assessment. Safety will be assessed throughout the study. Subjects will undergo evaluations as outlined in the Study Assessment table. A 4-Week Follow-Up visit will occur 28 days (± 3 days) after the last dose of study drug.



Approximate Number of Subjects	Sixty male and female subjects will be enrolled (20 randomized to each of the 2 belumosudil dose groups and the placebo group).
Approximate Duration of Subject Participation	Approximately 14 months of study duration (4-week Screening Period, 52-week Dosing Period, and 4-week Follow-up). The study will be double-blinded for the first 28 weeks followed by an open-label extension of 24 weeks.
Diagnosis and Main Criteria for Inclusion and Exclusion	**Inclusion Criteria:** 1. Male and female subjects ≥ 18 years old with the diagnosis of dcSSc according to the 2013 American College of Rheumatology and European League Against Rheumatism criteria 2. Must have disease duration (defined as interval from first non-Raynaud disease manifestation) of ≤ 5 years 3. Must have mRSS of ≥ 15 but ≤ 35 4. Active disease defined as any of the following within the 6 months prior to screening: a. Increase in mRSS by ≥ 3 units b. Increase in mRSS by ≥ 2 units with involvement of 1 new body area c. Involvement of 2 new body areas d. Symptoms indicative of skin activity such as severe cutaneous itching or burning 5. Subjects receiving concomitant immunosuppression must be on a stable dose for at least 3 months prior to screening 6. Adequate organ and bone marrow functions evaluated during the 28 days prior to enrollment as follows: a. Absolute neutrophil count ≥ 1.5×10^9/L b. Platelet count ≥ 100×10^9/L

	c. Total bilirubin ≤ 1.0 × upper limit of normal (ULN) d. Alanine aminotransferase, (ALT), aspartate aminotransferase (AST), and serum creatinine ≤ 1.5 × ULN. 7. Female subjects of childbearing potential have a negative pregnancy test at screening. Females of childbearing potential are defined as sexually mature women without prior hysterectomy or who have had any evidence of menses in the past 12 months. However, women who have been amenorrheic for 12 or more months are still considered to be of childbearing potential if the amenorrhea is possibly due to prior chemotherapy, anti-estrogens, or ovarian suppression. a. Women of childbearing potential (i.e., menstruating women) must have a negative urine pregnancy test (positive urine tests are to be confirmed by serum test) documented within the 24-hour period prior to the first dose of study drug. b. Sexually active women of childbearing potential enrolled in the study must agree to use two forms of accepted methods of contraception during the course of the study and for 3 months after their last dose of study drug. Effective birth control includes (i) IUD plus one barrier method; (ii) on stable doses of hormonal contraception for at least 3 months (e.g., oral, injectable, implant, transdermal) plus one barrier method; or (iii) 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 a vasectomized partner. 8. For male patients who are sexually active and who are partners of premenopausal women: agreement to use 2 forms of contraception as in criterion number 7 above during the treatment period and for at least 3 months after the last dose of study drug. 9. Male subjects must not donate sperm for 3 months after last dose of study drug. 10. Able to provide written informed consent prior to the performance of any study-specific procedures. **Exclusion Criteria:** 1. Subject has corrected QT interval using Fredericia's formula (QTcF) > 450 ms

	2. Ongoing use or current use of concomitant medication known to have the potential for QTc prolongation 3. Female subject who is pregnant or breastfeeding 4. Participated in another study with an investigational drug within 28 days of study entry (for studies involving biologics, within three half-lives of the biologic) 5. History or other evidence of severe illness or any other conditions that would make the subject, in the opinion of the Investigator, unsuitable for the study 6. Chronic heart failure with New York Heart Association Classes II, III, or IV 7. Acute or chronic liver disease (e.g., cirrhosis) 8. Positive human immunodeficiency virus (HIV) test 9. Active hepatitis C virus (HCV), hepatitis B virus (HBV), or positive whole blood tuberculin test 10. Diagnosed with any malignancy within 3 years of enrollment, with the exception of basal cell or completely resected squamous cell carcinoma of the skin, resected in situ cervical malignancy, resected breast ductal carcinoma in situ, or low-risk prostate cancer after curative resection 11. Has had previous exposure to belumosudil or known allergy/sensitivity to belumosudil, or any other ROCK2 inhibitor 12. Scleroderma renal crisis within 4 months prior to enrollment 13. FVC ≤ 50% Predicted.
Test Article(s)	Belumosudil will be provided as 200 mg tablets. Matching placebo will be provided during the initial double-blind period as appropriate for subjects in Group 1 and Group 3.
Dosage and Administration	Subjects will be randomized to receive belumosudil 200 mg QD (Group 1), belumosudil 200 mg BID (Group 2), or matched placebo (Group 3) in the blinded 28 weeks as follows: **Group 1:** Belumosudil 200 mg QD (one 200 mg belumosudil tablet AM and one matched placebo PM) will be administered orally daily. **Group 2:** Belumosudil 200 mg BID (one 200 mg belumosudil tablet AM and one 200 mg belumosudil tablet PM) will be administered orally daily. **Group 3:** Matched placebo (one placebo tablet AM and one placebo tablet PM) will be administered orally daily. After unblinding, the subjects in Group 1 and 2 will continue on the same belumosudil dose whereas the subjects in the placebo group will be re-randomized to one of the belumosudil doses (200 mg QD or 200 mg BID) in 1:1 fashion.
Reference Therapy	Not applicable.

Duration of Treatment	Study drug dosing will be for 52 weeks: double-blinded for the first 28 weeks followed by an open-label extension of 24 weeks).
Concomitant Treatment	Ongoing immunosuppressive therapy with steroids ≤ 10 mg per day is permitted. All medications a subject receives from the signing of informed consent through the 28-Day Follow-Up visit will be documented. • CYP3A4 inhibitors/inducers should be used with caution. • Subjects on concomitant medication known to have potential for QTc prolongation will be excluded.
Safety Evaluation	Safety data will be collected from the time the subject signs the informed consent form until 28 days after their last dose of study drug (the adverse event [AE] reporting period). The primary safety outcome will be the percentage of subjects experiencing treatment-emergent AEs (TEAEs) in each group. Safety assessments will include AEs, serious adverse events (SAEs), PEs, vital sign measurements (blood pressure, pulse rate, respiratory rate, and temperature), clinical laboratory evaluations (hematology, chemistry and urinalysis), and electrocardiograms (ECGs). Reasons for treatment discontinuation because of toxicity will be documented. As this is the first study of belumosudil in subjects with dcSSc, careful monitoring of all toxicities will be carried out.
Efficacy/Activity Evaluation	**Primary Efficacy Endpoint** The primary efficacy endpoint is the effect of belumosudil compared to placebo for CRISS, an exponential algorithm determining the predicted probability of improvement from baseline, incorporating changes in mRSS, FVC % predicted, and physician and patient global assessments. The outcome is a continuous variable between 0.0 and 1.0 (0-100%). A higher score indicates greater probability of improvement. A CRISS score ≥ 20% is considered a clinically meaningful improvement. **Secondary Efficacy Endpoints** Secondary efficacy outcomes include the change from baseline in mRSS, FVC, SHAQ-DI, physician global assessment, and patient global assessment for belumosudil-treated and placebo-treated subjects. Onset/progression of ILD will be evaluated by the effect of belumosudil compared to placebo in the change in predicted FVC In addition, changes in lung fibrosis on HRCT performed at baseline, Week 24 and Week 52 will be assessed only in subjects who have SSc lung disease at screening. **Exploratory Endpoints** Exploratory outcome assessments include changes in PD parameters measured in plasma and/or skin biopsy sample (discussed below).
Pharmacokinetics	Sparse PK sampling will be performed on Weeks 4 and 8 (i.e., Days 29 and 57) immediately prior to belumosudil dosing and 3 hours post-dose
Pharmacodynamics	All subjects will have PD blood samples drawn at the following time points prior to dosing: Week 1 (Day 1, baseline), Week 8 (Day 57), Week 24 (Day 169), and Week 52 (Day 365). These samples will be

	analyzed to evaluate autoantibody levels at baseline and biomarkers of extracellular matrix turnover which could correlate with both SSc disease activity and disease modification by belumosudil. All subjects will be required to provide skin biopsies obtained from the dorsal mid-forearm at the Week 1 (Day 1) and Week 24 (Day 169) visits. An optional skin biopsy may be obtained at the Week 52 (Day 365) visit. Biopsy sections will be assessed for histology including fibrosis and inflammation. In addition, gene expression profiling will be performed on skin biopsies.
Statistical Analysis	This proof of concept study will inform future development of belumosudil in dcSSc. The sample size is not driven by hypothesis testing. Two populations will be employed in the analysis of study data: • The Modified Intent-to-Treat Population (mITT) will consist of all subjects who receive at least one dose of study drug. • The Evaluable for Efficacy/Activity population will consist of subjects who have received at least 80% of expected study drug and have post-baseline efficacy data. The primary endpoint will be analyzed on the mITT Population. Demographics, subject disposition, and baseline characteristics will be summarized in each population and by group. Efficacy will be evaluated by comparing Week 24 CRISS scores for subjects treated with belumosudil and placebo. Secondary endpoints will include changes in mRSS, FVC, SHAQ-DI, Physician Global Assessment, and Patient Global Assessment from baseline to Week 24 in subjects treated with belumosudil compared to placebo and the change from baseline for subjects with belumosudil at Week 52. No formal comparison will be conducted between the belumosudil QD and belumosudil BID dosing cohorts. Treatment-emergent AEs will be evaluated using the Common Terminology Criteria for Adverse Events (CTCAE) v 5.0. The total sample size of 20 subjects per belumosudil dose group will provide > 90% probability of one or more belumosudil subjects experiencing an AE that has an underlying rate of ≥ 14% and > 80% probability of one or more subjects in the study experiencing an AE that has an underlying rate of ≥ 10%. The TEAEs will be summarized overall and by group using MedDRA (Version 21.0 or higher) System Organ Class (SOC) and preferred term (PT), classified from verbatim terms. The incidence and percentage of subjects with at least one occurrence of a preferred term will be included, according to the most severe grade using a 5-point scale (mild, moderate, severe, life threatening, or death). The number of events per preferred term will also be summarized. Causality (relationship to study treatment) will be summarized separately. Adverse events, SAEs, related AEs, related SAEs, ≥ Grade 3 AEs, related Grade ≥ 3 AEs, and AEs leading to withdrawal, or treatment discontinuation will be summarized overall and by group according to SOC and PTs. Adverse events 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 graded using the CTCAE v5.0. Incidence of laboratory abnormalities will be summarized. The worst on-study grade after the first dose of study drug will be summarized. The incidence of Grade ≥ 3 laboratory abnormalities under treatment and shifts in toxicity grading from baseline to highest-grade post-baseline will be displayed. Vital sign measurements and ECGs will be summarized by group at each scheduled time point using descriptive statistics and included in data listings.

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List of Tables and Figures

List of Abbreviations

AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the curve
BID	Twice daily
BSC	Best supportive care
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
CPK	Creatinine phosphokinase
CRISS	Combined Response Index in Diffuse Cutaneous Systemic Sclerosis
cGVHD	Chronic graft versus host disease
CTCAE	Common Terminology Criteria for Adverse Events
CTGF	Connective tissue growth factor
dcSSc	Diffuse cutaneous systemic sclerosis
DL_{CO}	Diffusing capacity of the lungs for carbon monoxide
ECG	Electrocardiogram
ECM	Extracellular matrix
eCRF	Electronic case report form
EOT	End-of-Treatment
FDA	Food and Drug Administration
FEV_1	Forced expiratory volume (in the first second)
FVC	Forced vital capacity
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GGT	Gamma-glutamyl transferase
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HRCT	High-resolution computerized tomography
ICF	Informed consent form
IEC	Independent Ethics Committee
ILD	Interstitial lung disease
IND	Investigational New Drug
IP	Investigational Product
IPF	Idiopathic pulmonary fibrosis
IRB	Institutional review board

IUD	Intrauterine device
LFT	Liver function tests
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent-to-treat
mRSS	Modified Rodnan Skin Score
PASI	Psoriasis Area and Severity Index
PE	Physical examination
PFT	Pulmonary function test
PK	Pharmacokinetic
QD	Once daily
QOD	Once every other day
QTc(F)	Corrected QT interval using Fridericia's formula
ROCK	Rho-associated protein kinase
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SHAQ-DI	Scleroderma Health Assessment Questionnaire—Disability Index
SOC	System organ class
SSc	Systemic sclerosis
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
TGF-β	Transforming growth factor-beta
TLC	Total lung capacity
Treg	Regulatory T-cells
ULN	Upper limit of normal
VAS	Visual Analog Scale

1. INTRODUCTION

1.1 BACKGROUND

Systemic sclerosis, also known as scleroderma, is a chronic autoimmune disease primarily affecting the skin, but with systemic manifestations. Diffuse cutaneous systemic sclerosis is a more serious form of the disease and is often rapidly progressive, involving not only the skin but also internal organs including kidney, heart, and lungs.[1]

The estimated annual incidence of systemic sclerosis in the United States is 20 cases per million with a prevalence of 240 cases per million population.[2,3,4] Racial disparities exist and there is an increased incidence and severity in African-Americans. Women are far more likely to acquire the disease and make up 80%-90% of the systemic sclerosis population.[5]

It has been estimated that up to 60% of systemic sclerosis patients will develop interstitial lung disease. This interstitial disease begins with an inflammatory alveolitis suggesting that anti-inflammatory therapy may be of benefit at early stages.[6,7]

Systemic sclerosis has the highest case-specific mortality among all systemic autoimmune diseases. Pulmonary hypertension, pulmonary fibrosis, and cardiac complications are the most frequent causes of death. The single most common cause of mortality is pulmonary fibrosis from interstitial lung disease.[8]

There remains substantial unmet need for therapies with improved tolerability and effectiveness for patients with dcSSc.

1.2 RHO-ASSOCIATED PROTEIN KINASE

Rho-associated coiled-coil containing 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 ROCK isoforms have been identified, ROCK1 and ROCK2.[9,10,11,12] While both are involved in Rho-mediated changes in the actin/myosin cytoskeletal network, ROCK1 and ROCK2 are not redundant signaling molecules and may serve different functions within cells.[13,14,15] Recent research has uncovered additional roles for ROCK signaling, in conditions including autoimmune disease aggravated or caused by a T-cell helper 17- (Th17)-polarized T-cell response[16] and pulmonary fibrosis.[17] Rho GTPase-mediated signaling pathways play a central role in coordinating and balancing T cell-mediated immune responses, including T cell receptor-mediated signaling, cytoskeletal reorganization, and the acquisition of the appropriate T-cell effector program.[18]

Studies have demonstrated that aberrant activation of ROCK2 leads to induction of interleukin (IL)-17 and IL-21 via interferon regulatory factor 4-dependent mechanism.[19] In addition, ROCK activity was found to be up-regulated in patients with rheumatoid arthritis and systemic lupus erythematosus[20] (and inhibition of ROCK2 effectively decreased IL-17 production *in vivo*) and demonstrated efficacy in arthritis and lupus mouse models. Autoimmunity also involves alterations to regulatory T-cells (Tregs) that suppress activation of the immune system and play a critical role in maintaining immunological tolerance to self-antigens and inhibiting autoimmune responses.[21] ROCK2 inhibition may increase the suppressive function of Tregs.

ROCK is also downstream of several major pro-fibrotic mediators, including transforming growth factor beta (TGF-β), connective tissue growth factor (CTGF), and lysophosphatidic acid. A defining feature of pathologic fibrosis is the differentiation of fibroblasts to myofibroblasts, a process mediated by ROCK. In addition, ROCK mediates stress fiber formation and regulates the transcription of pro-fibrotic genes, including CTGF and alpha-smooth muscle actin. Further, ROCK inhibition has demonstrated anti-fibrotic activity in murine models.

1.3 BELUMOSUDIL NONCLINICAL EXPERIENCE

In vitro, belumosudil has demonstrated an impact on the T-helper 17 (Th17) and regulatory T cells (Treg)-immune responses as well as on the actin/myosin cytoskeletal network and collagen formation. In vivo, belumosudil has demonstrated efficacy in a variety of clinically relevant animal models of disease including chronic graft versus host disease (cGVHD), scleroderma, idiopathic pulmonary fibrosis (IPF), and other autoimmune diseases.

Good Laboratory Practice (GLP) compliant rat and dog general toxicology/toxicokinetic studies of acute, sub-chronic (1-and 3-month), and chronic (6-month rat and 9-month dog) duration have been completed. In addition, safety pharmacology (human ether-à-go go related gene [in vitro], central nervous system [rat], respiratory [rat], and cardiovascular [dog]), embryo-fetal toxicology [rat and rabbit], male/female fertility [rat]), genotoxicity, and phototoxicity studies have also been completed. The primary nonclinical toxicology finding at/near clinically relevant exposures were limited to changes in the cardiovascular (blood pressure lowering), hepatic (transaminitis, hypertrophy/increased organ weight, and cholestasis/inflammation), renal (increased blood urea nitrogen [BUN], tubular changes, pigmentation, intracellular protein droplets in the epithelium), gastrointestinal (decreased appetite), and hematopoietic/immunologic (anemia with regeneration and thymic/splenic lymphoid depletion) systems.

Belumosudil demonstrated embryo-fetal toxicity/teratogenicity as well as reduced male fertility (reduced fertility index/sperm concentration/motility and increased abnormal sperm percentage), and changes in the testes/epididymis (decreased organ weights and degenerative histopathology). Male fertility findings were generally at higher than clinically relevant exposures.

All pivotal non-clinical safety studies (i.e., those studies identified in International Conference on Harmonization guidelines as needing to be conducted in accordance with GLP) were conducted in a country that is a member of the Organisation for Economic Cooperation and Development (OECD) Mutual Acceptance of Data program in accordance with the OECD Test Guidelines and Principles of GLP. Study details and potential clinically relevant findings from these studies are summarized in the Belumosudil Investigator's Brochure.

1.4 CLINICAL EXPERIENCE

1.4.1 Clinical Pharmacokinetics

Following a single oral dose of belumosudil 200 mg in the fed state, the mean absolute bioavailability (%F) was 64%. Systemic exposure of belumosudil was increased when administered in the fed state, and in ongoing and planned clinical studies, belumosudil should be taken with food or within 5 minutes of eating.

Across all clinical studies, observed time to reach maximum concentration for belumosudil, metabolites KD025m1 and KD025m2 has ranged from 2-4 hours, and the belumosudil terminal elimination half-life averages ~7 hours following single or multiple dose administration. Exposure of belumosudil (maximum concentration observed and area under concentration curve) in healthy subjects appears to be slightly greater than dose proportional over the 20 to 500 mg once daily (QD) dose range, but less than dose proportional for doses above 500 mg. Little to no accumulation of belumosudil or metabolites, KD025m1 or KD025m2, was observed following multiple dose administration. KD025m1 and KD025m2 exposures are < 5% and ≤ 20%, respectively, of belumosudil exposure.

A [^{14}C]-belumosudil human absorption, metabolism, and excretion study confirmed that the majority of radioactivity was recovered in feces (85%), with < 5% recovered in urine. This indicates minimal renal elimination and that the predominant route of clearance of belumosudil and associated metabolites is biliary and/or intestinal.

CYP34A likely plays a predominant role in the metabolism of belumosudil, and in a clinical drug-drug interaction study in healthy volunteers, co-administration with itraconazole (CYP3A4 inhibitor) resulted in a modest 20-25% increase in belumosudil exposure, while co-administration with rifampicin (CYP3A4 inducer) led to a 60-70% reduction in belumosudil exposure.

A delay in absorption and a reduction in belumosudil exposure were observed when belumosudil was co-administered with proton pump inhibitors (PPI) rabeprazole (80-90% decrease) or omeprazole (50-70% decrease), consistent with the finding that increased pH leads to decreased solubility of belumosudil. The clinical relevance of this interaction with PPIs is being evaluated in ongoing studies.

1.4.1.1 Chronic Graft Versus Host Disease

Study KD025-208 is an ongoing phase 2a, dose-escalation, open-label study to evaluate the safety, tolerability, and activity of belumosudil in subjects with cGVHD who have previously received 1-3 prior lines of treatment. The majority of subjects enrolled had cGVHD affecting at least 4 organs. Preliminary data from Cohort 1 (belumosudil 200 mg QD, n = 17), Cohort 2 (belumosudil 200 mg BID, n = 16) and Cohort 3 (belumosudil 400 mg QD, n = 18) show encouraging activity of belumosudil with response rates of 65%, 69% and 33% respectively. Responses have been durable. Among responders in Cohort 1, 8/11 (73%) subjects have sustained the response for ≥ 20 weeks. Data continue to mature in this ongoing study. Fifty-nine percent of subjects have achieved reductions in corticosteroid doses, with 10% discontinuing systemic corticosteroid therapy completely. Across the 3 cohorts, 61% of responders and 26% of non-responders have reported improvements in the Lee Symptom Scale score.

Study KD025-213 is another study in cGVHD which is currently ongoing at multiple sites in the U.S. Over 100 subjects have been enrolled and this study will be submitted as a potential registration study for cGVHD in 2020.

1.4.1.2 Idiopathic Pulmonary Fibrosis

Study KD025-207 is an ongoing, randomized, phase 2, open-label, multicenter study to evaluate the safety, tolerability, and activity of belumosudil in subjects with idiopathic pulmonary fibrosis (IPF) who have received pirfenidone and/or nintedanib or been offered both prior to enrollment. Subjects are randomized 2:1 to receive 400 mg belumosudil QD or best supportive care (BSC).

Forty subjects have been enrolled: 26 to the belumosudil arm and 14 subjects to the BSC arm. Nine BSC subjects have crossed over to the belumosudil arm. This study has been extended to enroll an additional 40 subjects.

Preliminary results demonstrate clinical activity of belumosudil in the treatment of IPF. In the modified Intent-to-Treat (mITT) population, there was an absolute median change in forced vital capacity (FVC) of 50 mL at Week 24 in subjects treated with belumosudil, compared to -175 mL in subjects treated with BSC. The decline in percentage predicted FVC was 1% with belumosudil versus 5% with BSC.

Overall, at Week 24, 29% of belumosudil patients had experienced an FVC decline ≥ 5% compared to 55% of BSC patients.

1.4.1.3 Psoriasis

In Study KD025-205, a study of 8 subjects with moderately severe psoriasis who had failed at least 1 line of systemic therapy, the mean Psoriasis Area and Severity Index (PASI) score decreased with 28 days of treatment by 1.1 (not statistically significant) from a mean baseline of 17.5. Some subjects experienced slight improvement in scaling and softening of plaques.

Study KD025-206 was a phase 2, open-label, safety and tolerability study of belumosudil dosing in 38 subjects with psoriasis vulgaris who had disease progression after at least 1 systemic therapy. The mean baseline PASI score was 19.8. The changes from baseline PASI scores were -8.8 (belumosudil 200 mg), -6.0 (belumosudil 400 mg QD) and -4.8 (belumosudil 400 mg BID) and were statistically significant for each treatment group and overall. Reductions of 50% in PASI scores were observed in 42% (belumosudil 200 mg BID), 50% (belumosudil 400 mg QD) and 18% (belumosudil 400 mg BID) of subjects.

Study KD025-211 was a Phase 2, two-period, dose-finding study of the safety, tolerability, and efficacy of belumosudil for the treatment of adult male and female subjects with moderate to severe chronic plaque psoriasis who were candidates for systemic therapy or phototherapy.

The first period (Week 1 through Week 16) was double-blind and placebo-controlled: the Double-blind Treatment Period. Approximately 110 subjects were randomly assigned to each of 5 dose cohorts in a 1:1:1:1:1 manner and were treated for up to 16 weeks (Table 1).

Table 1 Cohorts in Design of Study KD025-211

Cohort	Number of Subjects	Dose
1	22	200 mg belumosudil QD
2	22	200 mg belumosudil BID
3	22	400 mg belumosudil QD
4	22	600 mg belumosudil (400 mg in the morning; 200 mg in the evening)
5	22	Matching placebo BID

BID = twice daily; QD = once daily

Study drug was administered orally (PO), with a meal or within 5 minutes of finishing a meal, in a double-blind fashion.

The second period (Week 16 through Week 52) was an open-label study of belumosudil: the Open-label Treatment Period. All subjects were given the option to receive belumosudil for an additional 32 weeks. All subjects in the Open-label Period received belumosudil at 400 mg QD, regardless of initial randomization.

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

Subjects underwent medical history evaluations; physical examinations ([PEs] including weight, skeletal, and neurological measurements); vital sign measurements; adverse event (AE) assessments; concomitant medication assessments; blood sample collection for hematology, chemistry, coagulation, lipid panel, and thyroid-stimulating hormone; urinalysis; pregnancy testing for females of childbearing potential; photography (optional); punch biopsy (optional); and electrocardiogram (ECGs).

If a subject discontinued from the study prior to 16 weeks, an Early Termination Visit was performed, and procedures were conducted immediately upon discontinuation. For all subjects, including those who discontinued from the study prematurely, a Follow-Up visit occurred 30 days (± 3 days) after the last dose of study drug.

A placebo control was used in the Double-blind Period of this study. No control was used for the Open-label Continuation Period of the study.

A total of 110 subjects were randomized and included in the mITT Population: 23 subjects in the belumosudil 200 mg QD cohort, 22 in the belumosudil 200 mg BID cohort, 21 in the belumosudil 400 mg QD cohort, 26 in the belumosudil 600 mg/day cohort, and 18 in the placebo

cohort. The Safety Population had the same number of subjects as the mITT Population. Of the 110 subjects in the study, 27.3% (n = 30 subjects) completed treatment: 39.1% (n = 9) in the belumosudil 200 mg QD cohort; 27.3% (n = 6) in the 200 mg BID cohort; 42.9% (n = 9) in the 400 mg QD cohort; 15.4% (n = 4) in the 600 mg/day cohort; and 11.1% (n = 2) in the placebo cohort. Overall, the most frequent reasons for early study termination were withdrawal by subject (40.9%; n = 45 subjects), followed by loss to follow-up (12.7%; n = 14 subjects), and elevated liver enzymes (5.5%; n = 6 subjects).

The primary efficacy end point was the number (%) of subjects with a 75% decrease in PASI (PASI 75) by Week 16. When including subjects who completed 16 weeks of treatment and carrying forward the last results of subjects who did not complete 16 weeks of treatment, all belumosudil-treated subjects and all belumosudil cohorts had a proportion of subjects with PASI 75. Among all 92 belumosudil-treated subjects, 10.9% (95% confidence interval [CI]: 5.3%, 19.1%; n = 10 subjects) had a PASI 75 at Week 16. Of the 18 subjects in the placebo cohort, 16.7% (95% CI: 3.6%, 41.4%; n = 3 subjects) had a PASI 75. Each belumosudil cohort had a proportion of subjects with PASI 75: 8.7% (95% CI: 1.1%, 28.0%; 2/23 subjects) in the 200 mg QD cohort; 9.1% (95% CI: 1.1%, 29.2%; 2/22 subjects) in the 200 mg BID cohort; 19.0% (95% CI: 5.4%, 41.9%; 4/21 subjects) in the 400 mg QD cohort; and 7.7% (95% CI: 0.9%, 25.1%; 2/26 subjects) in the 600 mg/day cohort. The proportion of subjects who had a PASI 75 among all belumosudil-treated subjects was less than for placebo (-5.8% [95% CI: -24.2%, 12.6%]) but the difference was not statistically significantly different (p = 0.4435). None of the belumosudil-treated cohorts had a statistically significant difference compared to the placebo cohort: p = 0.6384 for the 200 mg QD cohort; p = 0.6419 for the 200 mg BID cohort; p > 0.9999 for the 400 mg QD cohort; and p = 0.3859 for the 600 mg/day cohort.

During the Entire Treatment Period, 92 subjects received belumosudil and 18 subjects received placebo. The proportions of TEAEs among all 92 belumosudil-treated subjects were comparable to or less than those occurring among the 18 subjects in the placebo cohort and were as follows:

- Severe TEAE: belumosudil = 8.7% (n = 8 subjects); placebo = 11.1% (n = 2 subjects)
- Grade ≥ 3 TEAEs: belumosudil = 10.9% (n = 10); placebo = 11.1% (n = 2)
- TEAEs related to study drug: belumosudil = 30.4% (n = 28) ; placebo = 33.3% (n = 6)
- Grade ≥ 3 TEAEs considered related to study drug: belumosudil = 5.4% (n = 5); placebo = 5.6% (n = 1)
- Grade 4: belumosudil = 1.1% (n = 1); placebo = 0

- SAEs: belumosudil = 4.3% (n = 4); placebo = 5.6% (n = 1)
- SAEs related to study drug: belumosudil = 0; placebo = 0
- TEAEs leading to discontinuation: belumosudil = 16.3% (n = 15; includes SAE); placebo = 16.7% (n = 3)
- Deaths: belumosudil = 1.1% (n = 1); placebo = 0
- Deaths related to study drug = 0

The conclusions of the study were that PO administration of belumosudil improves the clinical symptoms of subjects with psoriasis as demonstrated by:

- Improvement in PASI 75 score at 16 weeks, regardless of dosing regimen
- Improvement in PASI 75 score at 48 weeks
- Improvement in DLQI score at 16 weeks
- Improvement in DLQI score at 48 weeks
- Generally well-tolerated with no deaths or SAEs considered related to study drug

1.4.1.4 Other Potential Indicators

[redacted]

[redacted]

1.4.2 Clinical Summary

As of 19 February 2020, more than 600 individuals have been dosed with belumosudil as participants of Phase 1 and Phase 2 Kadmon-sponsored studies.

Single and multiple doses of belumosudil up to 1000 mg appear to be safe and well-tolerated in Phase 1 studies conducted in healthy volunteers. There were few SAEs, all unrelated to belumosudil. The most common AEs seen in Phase 1 studies were transient increases in transaminases which resolved after cessation of dosing.

Analysis of Phase 2 safety data from subjects with cGVHD, IPF, and psoriasis suggests an acceptable, manageable safety profile for belumosudil. Overall, TEAEs have generally been consistent with those expected in the populations enrolled in each of the studies.

Development of belumosudil is most advanced in the indication of cGVHD. Data from an early Phase 2 study, KD025-208, served as the basis for a Breakthrough Therapy Designation for belumosudil for the treatment of adult patients with cGVHD. These results were also the basis for a subsequent study, KD025-213 (the ROCKstar Study). Subjects who had received 2 to 5 prior lines of systemic therapy for cGVHD were enrolled into the ROCKstar study, a population with significant unmet medical need. Overall, 132 subjects were randomized to receive either belumosudil 200 mg QD (Arm A, n = 66) or belumosudil 200 mg BID (Arm B, n = 66). Subjects enrolled reflected a real-world population of complex, advanced cGVHD patients: median age 56 years; male 57%; 49% had received at least 4 prior lines of systemic therapy; median time from transplant to study 29 months; severe cGVHD at baseline 67%; prior treatment with ibrutinib 35%. The primary endpoint was met in both dosing arms at the primary analysis (6 months after last patient enrolled): overall response rate was 73.5% (95% CI: 65%, 81%).

Taken together, the totality of the data support the continued development of belumosudil.

1.5 STUDY RATIONALE

Belumosudil is an inhibitor of the ROCK2 isoform. This family of kinases has been shown to have profound activity on cell morphology, motility, and shape through effects on the

cytoskeleton. Data show that ROCK2 inhibition has an anti-inflammatory effect predominantly through the down-regulation of signal transducer and activator of transcription 3 (STAT3) and the Th17 axis. Thus IL-17, IL-21, and IL-22 are downregulated.

Chronic fibrosis is characterized by myofibroblast resistance to apoptosis. Inhibition of the ROCK pathway has demonstrated a beneficial effect on bleomycin induced fibrosis acting through the inhibition of activation of myofibroblasts. Anti-inflammatory activity, coupled with anti-fibrotic activity, suggests that inhibiting the ROCK2 pathway may be an effective therapy for inflammatory fibrotic diseases such as lung disease, which is associated with the majority of subjects with systemic sclerosis (SSc). Belumosudil has been shown to increase STAT5, which leads to an increase in the Treg population of lymphocytes and helps balance the immune system during inflammation.

Nonclinical pharmacology studies have demonstrated the potential of belumosudil to have a therapeutic benefit in a number of indications, particularly in autoimmune and fibrotic diseases. In vitro, belumosudil has demonstrated an impact on the Th17-type immune responses as well as on the actin/myosin cytoskeletal network and collagen formation. In vivo, belumosudil has demonstrated efficacy in a variety of clinically relevant animal models of disease including cGVHD, scleroderma, IPF, and other autoimmune diseases at clinically relevant drug exposures. Belumosudil has also been shown to significantly decrease the GVHD score in the sclerodermatous GVHD mouse model.

In a 3-month study in patients with moderate-to-severe psoriasis, belumosudil demonstrated both clinical and pharmacodynamic activity. Similarly, in an open-label study of belumosudil in the treatment of IPF, belumosudil slowed the decrease in lung function in IPF patients over 24 weeks of treatment when compared to best supportive care. Finally, in a study of patients with steroid refractory or dependent cGVHD, approximately two-thirds of patients achieved a clinical response with belumosudil. In this study, patients were able to reduce doses of steroids and immunosuppressant drugs during treatment with belumosudil. It is noteworthy that cGVHD represents a paradigm for immune-inflammatory triggering of chronic fibrosis that shares important similarities with SSc.

1.6 DOSE RATIONALE

Belumosudil was well-tolerated in Phase 1 studies of healthy volunteers at single doses up to 1000 mg, and with repeat doses up to 500 mg BID for 28 days.

Phase 2 studies of belumosudil have been initiated, enrolling patients with IPF (Study KD025-207), cGVHD (Study KD025-208 and Study KD025-215) and psoriasis (Study KD025-205, Study KD025-206, and Study KD025-211). More than 600 subjects have been dosed with belumosudil for inflammatory or fibrotic diseases or as healthy volunteers at doses ranging from 20 mg to 1000 mg QD and 500 mg BID.

Preliminary data from Phase 2 studies of belumosudil indicate that the dose of 200 mg QD is associated with clinical efficacy and are well-tolerated in indications with immune and fibrotic manifestations (e.g., cGVHD and IPF).

This study will evaluate belumosudil at doses of 200 mg QD and belumosudil 200 mg BID (400 mg/day) for the treatment of dcSSc.

Refer to the Belumosudil IB for more detailed information.

2. STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVE

To evaluate the efficacy of belumosudil compared to placebo for the Combined Response Index in diffuse cutaneous Systemic Sclerosis (CRISS) at Week 24

2.2 SECONDARY OBJECTIVES

- To assess the CRISS for each group at Week 52
- To evaluate the efficacy of belumosudil compared to placebo at Week 24 for:
  - mRSS
  - FVC
  - Physician Global Assessment
  - Patient Global Assessment
  - Scleroderma Health Assessment Questionnaire–Disability Index (SHAQ-DI)
- To evaluate the efficacy of belumosudil at Week 52 compared to baseline for subjects randomized to belumosudil for the parameters in the bullet above
- To assess changes in lung fibrosis, via high resolution computerized tomography (HRCT), performed at baseline, Weeks 24 and Week 52 only in subjects with ILD at screening
- To assess pharmacokinetics (PK) of belumosudil by sparse sampling of belumosudil on of Weeks 4 and 8 (i.e., Days 29 and 57) immediately prior to belumosudil dosing and 3 hours post-dose
- To assess the safety of belumosudil compared to placebo in subjects with dcSSc by examining the percentage of subjects with TEAEs (CTCAE v5.0) in subjects with dcSSc

2.3 EXPLORATORY OBJECTIVES

- To evaluate changes in biomarkers of endothelial cell dysfunction, fibrosis, immune system function, and cytokine alterations from subjects receiving belumosudil or placebo
- To assess histology and gene expression from skin biopsies taken from subjects at baseline, Week 24 and optionally at Week 52

3. INVESTIGATIONAL PLAN

3.1 STUDY DESIGN

This is a phase 2, placebo-controlled, double-blinded, randomized, multicenter trial in subjects with dcSSc with an open-label extension.

The duration of the study will be approximately 14 months (4 weeks for screening, 52 weeks of dosing period, and 4 weeks of Follow-up). The study will be double-blinded for the first 28 weeks followed by an open-label extension of 24 weeks.

Subjects who have signed an IRB/IEC-approved informed consent form (ICF) and met all of the inclusion/exclusion criteria will be enrolled. A total of 60 subjects will be randomized into 3 groups (1:1:1) to receive orally administered belumosudil 200 mg QD (n = 20), belumosudil 200 mg BID (n = 20), or matched placebo (n = 20) for 28 weeks. The study will be double-blinded for the first 28 weeks followed by an open-label extension of 24 weeks. After unblinding, the subjects in Group 1 and 2 will continue on the same belumosudil dose whereas the subjects in the placebo group will be re-randomized to one of the belumosudil doses (200 mg QD or 200 BID) in 1:1 fashion.

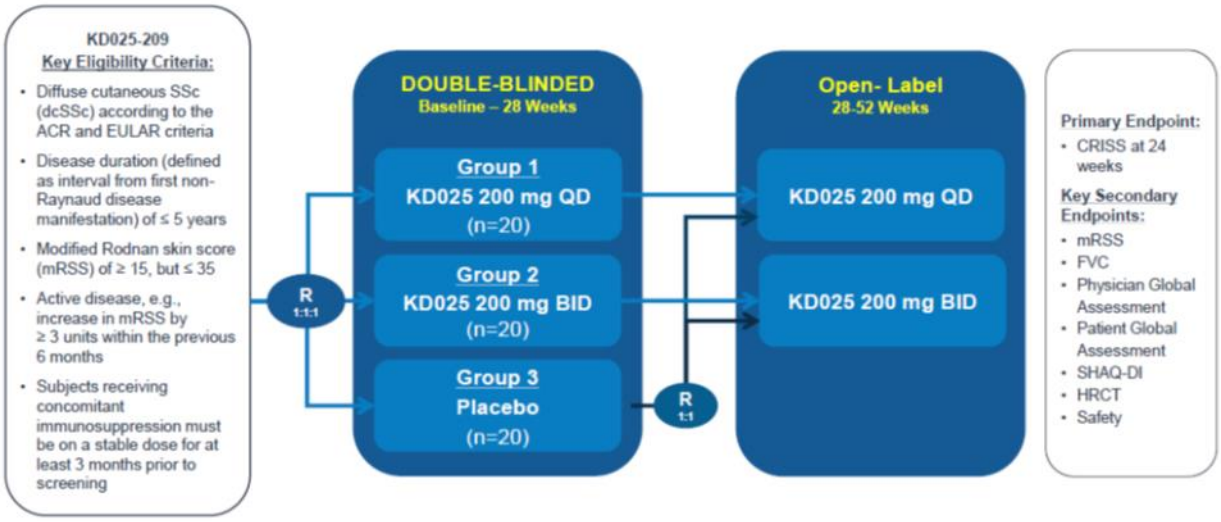
Subjects will undergo evaluations as outlined in the Study Assessment Tables in Appendix A.

Efficacy will be assessed throughout the 52-week dosing period using CRISS, mRSS, PFTs, physician global assessment, and patient global assessments.

Follow-up Period

A 4-Week Safety Follow-Up visit will occur 28 (± 3) days after the last dose of study drug. Subjects will undergo PEs; vital sign measurements; weight measurement; blood sample collection for hematology and chemistry; thyroid function: urinalysis; ECGs; AE assessments; concomitant medication assessments; and pregnancy testing for females of childbearing potential. In addition, patients will also have efficacy assessments done as per Appendix A.

Figure 1 Schematic of Study KD025-209



3.2 Number of Subjects

Sixty male and female subjects will be enrolled (20 randomized to each of the 2 belumosudil dose groups and the placebo group).

3.3 Study Centers

Approximately 25 centers will participate in this study.

3.4 Inclusion Criteria

1. Male and female subjects ≥ 18 years old with the diagnosis of dcSSc according to the 2013 American College of Rheumatology and European League Against Rheumatism criteria
2. Must have disease duration (defined as interval from first non-Raynaud disease manifestation) of ≤ 5 years
3. Must have mRSS of ≥ 15 but ≤ 35
4. Active disease defined as any of the following within the 6 months prior to screening:
    a. Increase in mRSS by ≥ 3 units
    b. Increase in mRSS by ≥ 2 units with involvement of 1 new body area
    c. Involvement of 2 new body areas

d. Symptoms indicative of skin activity such as severe cutaneous itching or burning

5. Subjects receiving concomitant immunosuppression must be on a stable dose for at least 3 months prior to screening
6. Adequate organ and bone marrow functions evaluated during the 28 days prior to enrollment as follows:
    a. Absolute neutrophil count $\geq 1.5 \times 10^9$/L
    b. Platelet count $\geq 100 \times 10^9$/L
    c. Total bilirubin $\leq 1.0 \times$ upper limit of normal (ULN)
    d. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and serum creatinine $\leq 1.5 \times$ ULN
7. Female subjects of childbearing potential have a negative pregnancy test at screening. Females of childbearing potential are defined as sexually mature women without prior hysterectomy or who have had any evidence of menses in the past 12 months. However, women who have been amenorrheic for 12 or more months are still considered to be of childbearing potential if the amenorrhea is possibly due to prior chemotherapy, anti-estrogens, or ovarian suppression.
    a. Women of childbearing potential (i.e., menstruating women) must have a negative urine pregnancy test (positive urine tests are to be confirmed by serum test) documented within the 24-hour period prior to the first dose of study drug.
    b. Sexually active women of childbearing potential enrolled in the study must agree to use 2 forms of accepted methods of contraception during the course of the study and for 3 months after their last dose of study drug. Effective birth control includes (i) IUD plus 1 barrier method; (ii) on stable doses of hormonal contraception for at least 3 months (e.g., oral, injectable, implant, transdermal) plus 1 barrier method; or (iii) two barrier methods. Effective barrier methods are male or female condoms, diaphragms, and spermicides (creams or gels that contain a chemical to kill sperm), or a vasectomized partner.
8. For male patients who are sexually active and who are partners of premenopausal women: agreement to use 2 forms of contraception as in Criterion Number 7 above during the treatment period and for at least 3 months after the last dose of study drug.
9. Male subjects must not donate sperm for 3 months after last dose of study drug.

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

3.5 EXCLUSION CRITERIA

1. Subject has corrected QT interval using Fredericia's formula (QTcF) > 450 ms
2. Ongoing use or current use of concomitant medication known to have the potential for QTc prolongation;
3. Female subject who is pregnant or breastfeeding
4. Participated in another study with an investigational drug within 28 days of study entry (for studies involving biologics, within 3 half-lives of the biologic)
5. History or other evidence of severe illness or any other conditions that would make the subject, in the opinion of the Investigator, unsuitable for the study
6. Chronic heart failure with New York Heart Association Classes II, III, and IV
7. Acute or chronic liver disease (e.g., cirrhosis)
8. Positive human immunodeficiency virus (HIV) test
9. Active hepatitis C virus (HCV), hepatitis B virus (HBV), or positive whole blood tuberculin test
10. Diagnosed with any malignancy within 3 years of enrollment, with the exception of basal cell or completely resected squamous cell carcinoma of the skin, resected in situ cervical malignancy, resected breast ductal carcinoma in situ, or low-risk prostate cancer after curative resection
11. Has had previous exposure to belumosudil or known allergy/sensitivity to belumosudil or any other ROCK2 inhibitor
12. Scleroderma renal crisis within 4 months prior to enrollment
13. FVC ≤ 50% Predicted

3.6 SCREENING

The screening period commences once the ICF is signed. Adequate time must be allowed for the subject to ask questions and make a voluntary decision. The ICF must be signed before any study-specific samples are taken or study -specific tests or evaluations are conducted.

Data regarding screen-failures will be captured in the electronic data capture (EDC) system.

Screening assessments as summarized in the Schedule of Assessments (Appendix A) will be performed 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.

Re-screening of subjects will be allowed only upon approval of the Medical Monitor.

3.7 WITHDRAWAL CRITERIA

Subjects may be withdrawn from study treatment at any time by the Investigator if it is considered detrimental for the subject to continue in the study. The reason for withdrawal must be captured in the eCRF.

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. Every effort should be made to have such subjects attend End-of-Treatment (EOT) and 28-day Follow-Up visits. In the instances where a reason for withdrawal of consent is given, this will be captured in the electronic case report form (eCRF). Subject data up to withdrawal of consent will be included in the analysis of the study, and where permitted, publicly available data can be included after withdrawal of consent.

3.8 REPLACEMENTS

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

3.9 TREATMENT DISCONTINUATION

Treatment discontinuation reasons include the following:

- An AE requiring permanent discontinuation of study drug
- Investigator decision
- Clinically significant disease progression. For example:
  - mRSS increase ≥ 5 units
  - Absolute decrease in FVC (% predicted) ≥10% or absolute decrease in diffuse capacity of the lungs for carbon monoxide (DLco) (corrected for Hb) of ≥ 15%
  - Renal crisis
- Study stopping rules for the sponsor (Section 9.6.1)
- Subjects meeting criteria for discontinuation from the study (Section 9.6.2)

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

4. STUDY TREATMENT

4.1 INVESTIGATIONAL PRODUCT

Belumosudil (2-(3-(4-(1H-indazol-5-ylamino) quinazolin-2-yl) phenoxy)-N-isopropylacetamide-methane sulfonic acid salt) is an orally available ROCK2 selective inhibitor. Belumosudil will be provided as 200 mg tablets. Placebo oral medication will match belumosudil oral medication.

4.2 DOSAGE AND ADMINISTRATION

Subjects will be randomized to receive belumosudil 200 mg QD (Group 1), belumosudil 200 mg BID (Group 2), or matched placebo (Group 3) in the double-blinded 28 weeks as follows:

Table 2 Dosing of Treatment Groups for Double-blind Period of Study

Belumosudil Group	AM	PM
Group 1 (200 mg QD)	One 200 mg belumosudil tablet	One matched placebo
Group 2 (200 mg BID)	One 200 mg belumosudil tablet	One 200 mg belumosudil tablet
Group 3 (Placebo)	One matched placebo	One matched placebo

BID = twice daily; QD = once daily

After unblinding, the subjects in Group 1 and 2 will continue on the same belumosudil dose whereas the subjects in the placebo group will be re-randomized to one of the belumosudil doses (200 mg QD or 200 mg BID) in 1:1 fashion.

4.3 TREATMENT ASSIGNMENT

All subjects in the study will be double-blinded for the first 28 weeks and open-label for another 24 weeks.

Subjects will be randomized 1:1:1 to receive belumosudil 200 mg QD (Group 1), belumosudil 200 mg BID (Group 2), and matched placebo (Group 3) for the first 28 weeks. After unblinding, the subjects in Group 1 and 2 will continue on the same belumosudil dose whereas the subjects in the placebo group will be re-randomized to one of the belumosudil doses (200 mg QD or 200 mg BID) in 1:1 fashion. This unblinding will be done as each subject reaches 28 weeks.

4.4 BLINDING

Study will be double-blinded for the first 28 weeks and open-label for another 24 weeks.

4.5 TREATMENT COMPLIANCE

Subjects will be given a study drug diary to record the details of each dose of study drug. Diaries will be dispensed/collected on each visit. Compliance with oral dosing will be confirmed using patient diaries, which will be examined at each visit by site staff to determine if dosing is as instructed per protocol and follow-up with the subject accordingly. If the subject skips more than 7 consecutive days of drug dosing (other than those specified in the Dose Modification Guideline for Toxicity), the subject should be discontinued from the study unless approved by the Medical Monitor and Investigator.

4.6 MISSED DOSES

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

For subjects during the 28 weeks of double-blinding:

- If less than 6 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 ≥ 6 hours of time have elapsed after the scheduled dose, the drug should be skipped for that day. The subject should then resume the regular planned dosing schedule the following day.

For subjects during the 24 weeks of open-label:

For subjects receiving study drug on a QD dosing schedule:

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

For subjects receiving study drug on a BID dosing schedule:

- If < 6 hours of time have elapsed after the scheduled dose, the drug should be taken. The subject should then resume the regular planned dosing schedule.

- If ≥ 6 hours of time have elapsed after the scheduled dose, the dose should be skipped and the subject should resume dosing with the next regular planned dose.

4.7 PRODUCT ACCOUNTABILITY

In accordance with regulatory requirements, study sites must document the amount of investigational product (IP) received from and returned to the sponsor, and the amounts of IP dispensed to study subjects, and the amount returned by study subjects. Product accountability records must be maintained throughout the course of the study.

4.8 CONCOMITANT MEDICATION AND THERAPIES

All concomitant medications taken during the study and relevant procedures will be recorded on the eCRF.

Ongoing immunosuppressive therapy with steroids ≤ 10 mg/day is permitted and must be documented in the source documentation and eCRFs.

Subjects will be counseled to avoid non-prescribed medicines or complementary alternative medicines excluded by the study. All medications a subject receives from the signing of the ICF through the 28-Day Follow-Up visit will be documented.

After discontinuation of study drug, any medication used in response to an AE is to be recorded on the appropriate eCRF.

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

4.9 CYP3A4 INHIBITORS/INDUCERS

CYP3A4 inhibitors/inducers should be used with caution.

4.10 DRUGS PROLONGING THE QTC INTERVAL

Subjects on concomitant medications known to have the potential for QTc prolongation will be excluded.

4.11 OVERDOSE

Doses of belumosudil considered to represent an overdose have not been defined. In clinical studies of belumosudil, repeat dosing of 500 mg BID for 28 days was generally well tolerated in healthy volunteers. There are no known antidotes to belumosudil, and no specific treatment is recommended in the event of a suspected overdose. The treating Investigator should employ clinical judgment in managing subjects with suspected overdose. Overdose should be reported as an AE.

4.12 DOSE MODIFICATION GUIDELINES

Any clinically significant toxicity will necessitate consideration of either a pause or cessation of therapy. Dose modification of therapy is permitted in the open label phase as outlined in Table 5.Guidelines for management of treatment-emergent toxicities in subjects receiving belumosudil are outlined in Table 3**Error! Reference source not found.**.

Table 3 Guidelines for Management of Treatment-emergent Toxicities (Double-blinded Phase)

Toxicity	Recommended Action
Grade ≥ 3 LFTs (AST, ALT or total bilirubin)	• Complete the "Treatment-emergent LFT elevations" eCRF • Discontinue belumosudil
Other Grade ≥ 3 clinically significant toxicities considered related to belumosudil	• Discontinue belumosudil
Grade 2 clinically significant toxicities	• Consider pause or cessation of therapy • Dose interruption for toxicity will be permitted up to 14 days. • If toxicity does not resolve to Grade 1 or below for 14 days, subjects will be discontinued from treatment

ALT = alanine aminotransaminase; AST = aspartate aminotransaminase; eCRF = electronic case report form; LFT = liver function tests

Table 4 Guidelines for Management of Treatment-emergent Toxicities (Open-Label Phase)

Toxicity	Recommended Action
Grade ≥ 3 LFTs (AST, ALT or total bilirubin)	• Complete the "Treatment-emergent LFT elevations" eCRF • Discontinue belumosudil
Other Grade ≥ 3 clinically significant toxicities considered related to belumosudil	• Discontinue belumosudil
Grade 2 clinically significant toxicities	• Consider pause or dose modification(table 5) of therapy • Dose interruption for toxicity will be permitted up to 14 days. If toxicity resolves to grade 1 or below then consider resuming belumosudil at current dose or one dose decrement as outlined in Table 5 below • If toxicity recurs, hold dose as above then consider resuming belumosudil at one dose decrement • If toxicity does not resolve to Grade 1 or below for 14 days, subjects will be discontinued from treatment

ALT = alanine aminotransaminase; AST = aspartate aminotransaminase; eCRF = electronic case report form; LFT = liver function tests

Dose interruption for toxicity management for 14 days is permitted. Subjects requiring pauses of more than 14 days will be discontinued from the study unless approved by the Medical Monitor.

Table 5. Belumosudil Dose Decrements

Belumosudil Dose	Dose Reduction
200 mg BID	200 mg QD
200 mg QD	200 mg QOD

BID = twice daily; QD = once daily; QOD = once every other day

If the reduced dose is tolerated for 1 complete cycle, the dose may be escalated to the previous dose.

5. STUDY ASSESSMENTS AND PROCEDURES

The schedule of assessments is outlined in **Error! Reference source not found.**

CRISS assessments will not be performed on site in either the Double-blind or Open-label Periods, but rather will be calculated outside of EDC.

5.1 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 the study inclusion and exclusion criteria.

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

- Informed consent
- Subject demography
- Medical history
- Inclusion/exclusion criteria
- mRSS
- FVC
- Complete PE
- Vital signs
- Weight
- Hematology and chemistry
- 12-lead ECG
- Pregnancy test
- Concomitant medication assessment
- AE assessment

5.2 DOUBLE-BLINDED TREATMENT PERIOD

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

5.2.1 Week 1, Day 1 Visit (Baseline)

At the Week 1 Day 1 visit, subjects will come to the clinic to have the following procedures:

- Confirmation of inclusion/exclusion criteria
- Randomization
- mRSS
- SHAQ-DI
- Physician Global Assessment
- Patient Global Assessment
- Pulmonary function test (PFT)*
- HRCT (± 7 days; for subjects with ILD at screening only)
- Skin biopsies
- Sampling for PD
- Complete PE
- Vital signs
- Weight
- Hematology and chemistry*
- Urinalysis*
- 12-lead ECG
- Pregnancy test
- Dispense study diary
- Study drug administration - review with patient
- Dispense study drug
- Concomitant medication assessment
- AE assessment

  **If these assessments were conducted within seven (7) days of baseline, they do not need to be repeated.*

5.2.2 Day 15 (± 3 Days) Visit

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

- Symptom-directed PE
- Vital signs
- Weight

- Hematology and chemistry
- Urinalysis
- 12-lead ECG
- Pregnancy test
- Study drug administration
- Concomitant medication assessment
- AE assessment

5.2.3 End of Week 4, Day 29 (± 3 Days) Visit

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

- Sampling for PK
- Symptom-directed PE
- Vital signs
- Weight
- Hematology and chemistry
- Urinalysis
- 12-lead ECG
- Pregnancy test
- Dispense and collect study diary
- Study drug administration
- Dispense & collect study drug
- Concomitant medication assessment
- AE assessment

5.2.4 End of Week 8, Day 57 (± 3 Days) Visit

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

- CRISS
- mRSS
- FVC
- SHAQ-DI
- Physician Global Assessment
- Patient Global Assessment
- Sampling for PK
- Sampling for PD

- Symptom-directed PE
- Vital signs
- Weight
- Hematology and chemistry
- Urinalysis
- 12-lead ECG
- Pregnancy test
- Dispense and collect study diary
- Study drug administration
- Dispense and collect study drug
- Concomitant medication assessment
- AE assessment

5.2.5 End of Week 12, Day 85 (± 3 Days) Visit

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

- Symptom-directed PE
- Vital signs
- Weight
- Hematology and chemistry
- Urinalysis
- 12-lead ECG
- Pregnancy test
- Collect and dispense study diary
- Study drug administration
- Collect and dispense study drug
- Concomitant medication assessment
- AE assessment

5.2.6 End of Week 16, Day 113 (± 3 Days)

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

- CRISS
- mRSS
- FVC
- SHAQ-DI

- Physician Global Assessment
- Patient Global Assessment
- Symptom-directed PE
- Vital signs
- Weight
- Hematology and chemistry
- Urinalysis
- 12-lead ECG
- Pregnancy test
- Collect and dispense study diary
- Study drug administration
- Collect and dispense study drug
- Concomitant medication assessment
- AE assessment

5.2.7 End of Week 20, Day 141 (± 3 Days)

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

- Symptom-directed PE
- Vital signs
- Weight
- Hematology and chemistry
- Urinalysis
- 12-lead ECG
- Pregnancy test
- Collect and dispense study diary
- Study drug administration
- Collect and dispense study drug
- Concomitant medication assessment
- AE assessment

5.2.8 End of Week 24, Day 169 (± 3 Days)

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

- CRISS

- mRSS
- FVC (if PFT not performed at visit)
- SHAQ-DI
- Physician Global Assessment
- Patient Global Assessment
- PFTs (± 7 days)
- HRCTs (± 7 days)
- Skin biopsies
- Sampling for PD
- Complete PE
- Vital signs
- Weight
- Hematology and chemistry
- Urinalysis
- 12-lead ECG
- Pregnancy test
- Collect and dispense study diary
- Study drug administration
- Collection and dispense study drug
- Concomitant medication assessment
- AE assessment

5.2.9 End of Double-Blinded Treatment Visit (End of Week 28, Day 197 [± 3 Days])

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

- Randomization (for subjects who had been receiving placebo [Group 3] to 1 of 2 treatments with belumosudil)
- CRISS
- mRSS
- FVC
- SHAQ-DI
- Physician Global Assessment
- Patient Global Assessment

- Complete PE
- Vital signs
- Weight
- Hematology and chemistry
- Urinalysis
- 12-lead ECG
- Pregnancy test
- Dispense and collect study diary
- Study drug administration
- Collect and dispense study drug
- Concomitant medication assessment
- AE assessment

5.3 OPEN-LABEL VISITS EVERY 4 WEEKS (± 3 DAYS) UNTIL WEEK 52

After 28 weeks of blinded treatment, subjects will continue on open-label treatment for 24 weeks. All subjects will return to the clinic every 4 weeks. Until Week 52, subjects will have safety assessments every 4 weeks and efficacy assessments every (8 weeks) as follows:

Every 4 weeks, subjects will have the following safety assessments, i.e., End of Week 32, Week 36, Week 40, Week 44, and Week 48.

- Symptom-directed PE (at Week 32, Week 36, Week 40, Week 44, and Week 48 visits)
- Vital signs
- Weight
- Hematology and chemistry
- Urinalysis
- 12-lead ECG
- Pregnancy test
- Collect and dispense study diary
- Study drug administration
- Collect and dispense study drug
- Concomitant medication assessment
- AE assessment

Every 8 weeks, subjects will have the following efficacy assessments, i.e., End of Week 36 (Day 253 ± 3 days) and Week 44 (Day 309 ± 3 days):

- CRISS
- mRSS
- FVC
- SHAQ-DI
- Physician Global Assessment
- Patient Global Assessment

5.4 END OF TREATMENT OR WEEK 52, (DAY 365 [± 3 DAYS])

Subjects who complete Week 52 the study will have the following procedures:

- CRISS
- mRSS
- FVC (if PFT not performed at visit)
- SHAQ-DI
- Physician Global Assessment
- Patient Global Assessment
- PFTs (± 7 days)
- HRCT (± 7 days)
- Skin biopsies (optional)
- Sampling for PD
- Complete PE
- Vital signs
- Weight
- Hematology and chemistry
- Urinalysis
- 12-lead ECG
- Pregnancy test
- Collect study diary
- Collect study drug
- Concomitant medication assessment
- AE assessment

Subjects who discontinue from the study prior to Week 52 will have the same assessments performed as subjects who complete Week 52.

5.5 28-DAY FOLLOW-UP VISIT

Subjects will return to the clinic twenty-eight (28) days (± 3 days) after their last dose of study drug. At this visit, the following procedures will be completed:

- CRISS
- mRSS
- SHAQ-DI
- Physician Global Assessment
- Patient Global Assessment
- PFT
- Complete PE
- Vital signs
- Weight
- Hematology and chemistry
- Urinalysis
- 12-lead ECG
- Pregnancy test
- Concomitant medication assessment
- AE assessment

5.6 UNSCHEDULED VISIT

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

- CRISS
- mRSS
- FVC (if PFT not performed at visit)
- SHAQ-DI
- Physician Global Assessment
- Patient Global Assessment
- PFTs
- Complete PE

- Vital signs
- Weight
- Hematology and chemistry
- Urinalysis
- 12-lead ECG
- Pregnancy test
- Collect and dispense study diary
- Study drug administration
- Collect study drug
- Concomitant medication assessment
- AE assessment

6. EFFICACY AND SAFETY ASSESSMENTS

6.1 EFFICACY ENDPOINTS

Efficacy measurements will be performed as outlined in Appendix A.

The primary efficacy endpoint is the effect of belumosudil compared to placebo for the CRISS at the end of Week 24 in the mITT Population. The CRISS exponential algorithm determines the predicted probability of improvement from baseline, incorporating changes in mRSS, FVC% predicted, and Physician and Patient Global Assessments. The outcome is a continuous variable between 0.0 and 1.0 (0-100%). A higher score indicates greater probability of improvement. A CRISS score ≥ 20% is considered a clinically meaningful improvement.

Other efficacy outcomes include the change from baseline in mRSS for belumosudil-treated and placebo-treated subjects. The mRSS is a measure of skin thickness rated with scores ranging from 0 (normal) to 3 (severe skin thickening) across 17 different sites. The total score is the sum of the individual skin scores in the 17 body areas (i.e., face, hands, fingers; proximal area of the arms, distal area of the arms, thorax, abdomen; proximal area of the legs, and distal area of the legs, feet), giving a range of 0-51 units. The mRSS has been validated for patients with SSc. A negative change from baseline demonstrates improvement.

The effect of belumosudil compared to placebo will be explored for the change in baseline for SHAQ-DI, which assesses 5 scleroderma-specific Visual Analog Scale (VAS) items to explore the impact of participant's disease. Each VAS item will be rated separately in scale of a 0−100 mm, with higher scores indicating more severe disease. The 5 items are: (1) intestinal disease, (2) breathing problem, (3) Raynaud syndrome, (4) finger ulcers, and (5) overall disease.

Onset/progression of ILD will be evaluated by the effect of belumosudil compared to placebo in the change in predicted FVC, which is based on institutional standards and will be measured as part of PFTs, including FEV_1, FVC, DL_{CO}, and total lung capacity (TLC). The same equipment and tester should be used during the course of the study to the extent possible. The person responsible for conducting the PFTs will be required to comply with the study guidelines and the American Thoracic Society/European Respiratory Society joint criteria on lung function testing.

6.1.1 Primary Endpoint

The primary endpoint of this study is to evaluate the efficacy of belumosudil compared to placebo for the CRISS at Week 24

6.1.2 Secondary Endpoints

- To assess the CRISS for each group at Week 52
- To evaluate the efficacy of belumosudil compared to placebo at Week 24 for:
    - mRSS
    - FVC
    - Physician Global Assessment
    - Patient Global Assessment
    - SHAQ-DI
- To evaluate the efficacy of belumosudil at Week 52 compared to baseline for subjects randomized to belumosudil for the parameters in the bullet above
- To assess changes in lung fibrosis, via HRCT, performed at baseline, Week 24, and Week 52 only in subjects with ILD at screening
- To assess PK of belumosudil by sparse sampling of belumosudil on Weeks 4 and 8 (i.e., Days 29 and 57) immediately prior to belumosudil dosing and 3 hours post-dose
- To assess the safety of belumosudil compared to placebo in subjects with dcSSc by examining the percentage of subjects with TEAEs (CTCAE v5.0) in subjects with dcSSc

6.1.3 Exploratory Endpoints

- To evaluate changes in biomarkers of endothelial cell dysfunction, fibrosis, immune system function, and cytokine alterations from subjects receiving belumosudil or placebo
- To assess histology and gene expression from skin biopsies taken from subjects at baseline, Week 24, and optionally at Week 52

6.2 SAFETY

6.2.1 Safety Endpoints

Also see Section 9 for additional detail on AEs.

- AEs and SAEs

- Hematological and clinical chemistry parameters
- Vital signs: change from baseline in systolic blood pressure, diastolic blood pressure and heart rate
- 12-lead ECG: mean and maximum change from baseline in QTcF

6.2.2 Vital Signs

Seated pulse rate and blood pressure measurements will be performed as outlined in the Schedule of Assessments (Appendix A). Measurements will be taken with the subject sitting, having rested in this position for at least 5 minutes. Vital signs should be taken before ECGs and other scheduled assessments.

6.2.3 12-Lead ECG

Twelve-lead ECGs will be performed as outlined in the Schedule of Assessments (Appendix A). ECGs will be recorded after the subject has rested in the supine position for at least 5 minutes and should be performed prior to any blood sample collections.

The following ECG parameters will be collected: PR interval, QRS interval, and QTc or QTcF. 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 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 (Section **Error! Reference source not found.**).

6.2.4 Clinical Laboratory Parameters

Clinical laboratory tests will be performed as outlined in the Schedule of Assessments (Appendix A). Samples should be taken pre-dose and will be sent to a central laboratory for analysis (Table 4). Full details for collection and shipping of samples are provided in the Laboratory Manual.

Table 4 Clinical Laboratory Panels

Hematology	Serum Chemistry	Other
• 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 • Chloride • CO_2 • Creatinine • CPK • Total and direct bilirubin • GGT • Globulin • Glucose • HBV (screening only) • HCV (screening only) • HIV (screening only) • Lactate dehydrogenase • Magnesium • Phosphorus • Potassium • Sodium • Total protein • Uric acid	• Whole blood tuberculin test (screening only)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; GGT = gamma-glutamyl transferase; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; MCV = mean corpuscular volume

Abnormalities in clinical laboratory tests that lead to a change in subject management (e.g., dose delay, requirement for additional medication or monitoring) are considered clinically significant for the purposes of this study and will be recorded on the AE eCRF page. Laboratory results will be classified using the CTCAE v5.0. 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 **Error! Reference source not found.**).

6.2.5 Pregnancy Testing

Pregnancy tests (urine) will be done in women of childbearing potential. Positive urine results are to be confirmed with serum testing. In the event of a positive urine test at baseline, serum testing results should be acquired within 48 hours prior to study start.

In the event that a subject or subject's partner becomes pregnant while on study, they will be monitored until the outcome of the pregnancy is known. The baby will continue to be monitored to 30 days after delivery. The data are reported on a pregnancy form within 24 hours of becoming aware.

7. PHARMACOKINETICS

Evaluation of the PK of belumosudil is a secondary objective of this study.

Sparse PK sampling will be performed at Week 4 and Week 8 (i.e., Day 29 and Day 57) immediately prior to dosing and 3 hours post-dose. Each PK blood sample should be approximately 6 mL. A total of up to 4 samples will be collected from each subject. Subjects should be instructed to withhold taking study drug on PK sampling days as dosing will be performed at the clinic. The pre-dose and all post-dose PK collection time points are to be precisely documented on the appropriate eCRF. Additionally, the time of a subject's dose of study drug is to be documented. Detailed instructions for sample collection and preparation will be provided in the Central Laboratory Manual.

8. PHARMACODYNAMICS

All subjects will have PD blood samples, up to 20 mL, drawn within 60 minutes prior to dosing at the following time points: Day 1, Week 8 (Day 57), Week 24 (Day 169), and EOT/Week 52 (Day 365). Study medication should be taken in the clinic after PD samples are taken. These samples will be analyzed to evaluate autoantibody levels at baseline and biomarkers of extracellular matrix turnover which could correlate with both SSc disease activity and disease modification by belumosudil.

All subjects will provide mandatory skin biopsies obtained from the dorsal mid-forearm at the baseline (Week 1 Day 1), Week 24 (Day 169), and optional at End of Treatment/Week 52 (Day 365). Biopsy sections will be assessed for histology including myofibroblast (fibrosis) and hyalinized collagen (inflammation) content. In addition, gene expression profiling will also be performed on skin biopsies.

9. SAFETY

9.1 SAFETY PARAMETERS

Safety data will be collected from the time the subject signs the ICF form until 28 days after their last dose of study drug (the AE reporting period). The primary safety outcome will be the percentage of subjects experiencing AEs in each group.

Safety assessments will include AEs, SAEs, PEs, vital sign measurements, clinical laboratory evaluations (hematology, chemistry, and urinalysis), and ECGs. Reasons for treatment discontinuation because of toxicity will be documented.

All AEs that occur in enrolled subjects during the AE reporting period must be recorded, regardless of the relationship of the AE to study drug. Any known untoward event that occurs beyond the AE reporting period that the Investigator assesses as possibly related to study drug also should be reported to Kadmon.

As this is the first study in subjects with dcSSc, careful monitoring of all toxicities will be carried out. Vital sign measurements, including blood pressure, pulse rate, respiratory rate, and temperature will be monitored throughout the study.

9.2 ADVERSE EVENT DEFINITION

An AE is defined as any untoward medical occurrence in a clinical trial subject associated with the use of a drug, whether or not considered drug related. An AE can be an unfavorable and unintended sign (e.g., 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 (e.g., use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose. An AE also includes, but is not limited to, any clinically significant worsening of a pre-existing condition. Examples include:

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

- Exacerbation of a pre-existing condition

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

9.3 EVALUATING ADVERSE EVENTS

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

9.3.1 Serious Adverse Events

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

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

Death: This includes any death that occurs while the subject is “on study” as well as any death that occurs within 28 days after study drug discontinuation.

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

Life-threatening 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 one of the outcomes listed in this definition.

All SAEs will be collected from the time of ICF.

9.3.2 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.

9.3.3 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).

9.3.4 Recording Adverse Events

All AEs (including SAEs) are to be accurately recorded on the Adverse Event page of the subject's eCRF during the subject's participation in the study. The severity of each AE will be graded using the CTCAE v5.0 scale. The date of onset as well as the end date of the event also should be recorded, or the event should be entered as "ongoing". In

addition, the method used to treat the AE and the outcome of the AE also will be noted. In the event that the grade of an AE worsens, an end date should be entered to the initial AE and a new AE entered with the updated grade and date of onset. The Investigator will assess the relationship of the event to study drug. Note: All SAEs also are to be entered onto an SAE form and sent to sponsor or designee.

9.3.5 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 for elective procedures planned before or after the start of the study for a pre-existing condition that has not worsened does not count as an SAE.

9.3.6 Serious Adverse Event Reporting

9.3.6.1 Governing Regulatory Requirements

Compliance with this request for prompt reporting is essential in that the sponsor is responsible for informing the US Food and Drug Administration (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 Bioavailability/Bioequivalence studies, the sponsor is required to submit written documentation, in the form of an IND safety report, detailing:

- Any event associated with the use of the drug, that is both serious and unexpected, or

- Any findings from clinical, epidemiological, or pooled analysis of multiple studies or any findings from animal or *in vitro* testing that suggest a significant risk in humans exposed to the drug.

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

Time Frame for Reporting

Any death, SAE, pregnancy (including pregnancy of a partner), experienced by a subject while receiving or within 28 days of receiving study drug, regardless of relationship to study drug, or any death that occurs more than 28 days after receiving study drug, and is believed to be study drug-related, must be promptly reported (within 24 hours of the Investigator becoming aware of the event) by e-mail to the sponsor (or designee). The contact information for SAE reporting:

For medical questions contact the Kadmon Medical Monitor:

E-mail: [redacted]

Phone: [redacted]

For SAE reporting send the SAE form, pregnancy form, or follow-up within 24 hours of becoming aware:

Kadmon Pharmacovigilance

Email: [redacted]

or

Fax: [redacted]

In the event of a subject, or a subject's partner, becomes pregnant while on study, they will be monitored until the outcome of the pregnancy is known. The baby will continue to be monitored to 30 days after delivery. The data are reported on a pregnancy form within 24 hours of becoming aware.

9.3.6.2 Information to be Provided by the Investigator

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

The minimum information required for SAE reporting includes identity of Investigator, site number, subject number, an event description, SAE term(s), onset date, the reason why the event is considered to be serious (i.e., 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 SAEs, the following additional points should be noted:

- When the diagnosis of an SAE is known or suspected, the Investigator should report the diagnosis or syndrome as the primary SAE term, rather than as signs or symptoms. Signs and symptoms may then be described in the event description. For example, dyspnea should not be used as an SAE term if the diagnosis which caused the dyspnea is known to be malignant pleural effusion.

- Death should not be reported as an SAE, but as an outcome of a specific SAE, unless the event preceding the death is unknown. In the exceptional case where the events leading to death are unknown, then death may be used as an event term. If an autopsy was performed, the autopsy report should be provided.

- While most hospitalizations necessitate reporting of an SAE, some hospitalizations do not require SAE reporting, as follows:

- Elective or previously scheduled surgery (e.g., a previously scheduled ventral hernia repair)
- Procedures for pre-existing conditions that have not worsened after initiation of treatment
- Pre-specified study hospitalizations for observation
- Events that result in hospital stays of less than 24 hours and that do not require admission (e.g., an emergency room visit for hematuria that results in a diagnosis of cystitis and discharge to home on oral antibiotics)
- SAEs must, however, be reported for any surgical or procedural complication resulting in prolongation of the hospitalization.

9.3.6.3 Regulatory Reporting

Kadmon Corporation Pharmacovigilance Department (or designee) will process and evaluate all SAEs as soon as the reports are received. For each SAE received, Kadmon Corporation will determine whether the criteria for expedited reporting have been met.

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

9.4 FOLLOW-UP FOR ADVERSE EVENTS

Any SAE or AE assessed as at least possibly related that led to treatment discontinuation (including clinically significant abnormal laboratory values that meet these criteria) and is ongoing 28 days after last dose of study drug must be followed until either resolution of the event or determination by the Investigator that the event has become stable or irreversible. This follow-up guidance also applies to possibly related SAEs that occur more than 28 days after last dose of study drug. The status of all other continuing AEs will be documented as of 28 days after last dose of study drug.

9.5 OTHER SAFETY CONSIDERATIONS

9.5.1 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 (e.g., dose reduction or delay, requirement for additional medication or monitoring) or is considered to be of clinical significance by the Investigator should be reported as an AE and/or SAE as appropriate, unless this value is consistent with the subject's present disease state or is consistent with values obtained before entry into the study.

Laboratory results will be classified using the CTCAE v5.0.

9.5.2 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.

9.6 STUDY STOPPING RULES

9.6.1 Stopping Rules for Study

Kadmon reserves the right to discontinue the trial at any time for the following reasons:

1. Failure to meet expected enrollment goals
2. Emergence of any safety information that could significantly affect continuation of the trial
3. Violation of GCP (R2), the Clinical Trial Program, or the contract by a trial site or Investigator, or any other administrative reasons, disturbing the appropriate conduct of the trial
4. Results from other competing clinical trials make this trial not worthy to continue

9.6.2 Stopping Criteria for Subjects

Subjects will be discontinued from the study at any time for the following reasons:

1. Grade ≥ 3 LFT increase (AST, ALT, or total bilirubin)
2. Grade ≥ 3 clinically significant toxicity considered related to belumosudil

3. QTc > 500 ms or AE of *Torsade de Pointe*

9.7 STATISTICAL CONSIDERATIONS

9.7.1 Hypothesis

This study will explore the efficacy of belumosudil (200 mg QD, 200 mg BID) compared to placebo on proposed primary, secondary, and exploratory endpoints. The main focus is to provide guidance for the follow up studies.

9.7.2 Sample Size

This is an exploratory study; sample size and power are not driven by hypothesis testing. A total of 60 subjects will be randomized (1:1:1) to receive orally administered belumosudil 200 mg QD (n = 20), belumosudil 200 mg BID (n = 20), or matched placebo (n = 20).

9.7.3 Analysis Populations

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

- The mITT Population will consist of all subjects who receive at least 1 dose of study drug.
- The Evaluable for Efficacy/Activity Population will consist of subjects who have received at least 80% of expected study drug and have post-baseline efficacy data.

The primary analysis will be performed on the mITT Population.

9.7.4 Data Analysis

All pre-specified analyses will be described in a Statistical Analysis Plan (SAP).

Demographics, subject disposition, and screening and baseline characteristics will be summarized in each population and by group.

9.7.5 Interim Analysis

There is no interim analysis planned.

9.8 EFFICACY ANALYSIS

9.8.1 Primary Efficacy Endpoint

The primary efficacy endpoint of this study is to evaluate the efficacy of belumosudil compared to placebo for the CRISS score at Week 24

9.8.2 Secondary Efficacy Endpoints

Secondary endpoints are as follows:

- To assess the CRISS for each group at Week 52
- To evaluate the efficacy of belumosudil compared to placebo at Week 24 for:
    - mRSS
    - FVC
    - Physician global assessment
    - Patient global assessment
    - SHAQ-DI
- To evaluate the efficacy of belumosudil at Week 52 compared to baseline for subjects randomized to belumosudil for the parameters in the bullet above
- To assess changes in lung fibrosis via HRCT performed at baseline, Weeks 24, and Week 52 only in subjects with ILD at screening
- To assess the PK of belumosudil by sparse sampling of belumosudil on Weeks 4 and 8 (i.e., Days 29 and 57) immediately prior to belumosudil dosing and 3 hours post-dose
- To assess the safety of belumosudil compared to placebo in subjects with dcSSc by examining the percentage of subjects with TEAEs by CTCAE v5.0 in subjects with diffuse cutaneous systemic sclerosis

9.8.3 Exploratory Efficacy Endpoints

Exploratory endpoints are as follows:

- To evaluate changes in biomarkers of endothelial cell dysfunction, fibrosis, immune system function, and cytokine alterations from subjects receiving belumosudil or placebo
- To assess histology and gene expression from skin biopsies taken from subjects at baseline, Week 24, and optionally at Week 52

9.8.4 Analysis Method

- Mixed models with treatment and week as fixed effects, and subject as random effect will be used to analyze all longitudinal efficacy endpoints.

- Descriptive statistics will be provided for all endpoints by treatment groups and visits.

9.9 SAFETY ANALYSES

Treatment exposure will be summarized.

The TEAEs will be evaluated using the CTCAE v5.0. The total sample size of 20 subjects per belumosudil dose group will provide > 90% probability of one or more belumosudil subjects experiencing an AE that has an underlying rate of ≥ 14% and > 80% probability of one or more subjects in the study experiencing an AE that has an underlying rate of ≥ 10%.

The TEAEs will be summarized overall and by group using Medical Dictionary of Regulatory Activities Version 21.0 (MedDRA v21.0) or higher, System Organ Class (SOC) and preferred term (PT), classified from verbatim terms. The incidence and percentage of subjects with at least one occurrence of a preferred term will be included, according to the most severe grade using a 5-point scale (mild, moderate, severe, life threatening, or death). The number of events per preferred term will also be summarized. Causality (relationship to study treatment) will be summarized separately.

AEs, SAEs, related AEs, related SAEs, Grade ≥ 3 AEs, related Grade ≥ 3 AEs, and AEs leading to withdrawal or treatment discontinuation will be summarized overall and by group according to SOC and PT. Adverse events 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 graded; Incidence of laboratory abnormalities will be summarized. The worst on-study grade after the first dose of study drug will be summarized. The incidence of Grade ≥ 3 laboratory abnormalities under treatment and shifts in toxicity grading from baseline to highest-grade post-baseline will be displayed.

Vital sign measurements and ECGs will be summarized by group at each scheduled time point using descriptive statistics and included in data listings.

9.10 PHARMACOKINETIC ANALYSES

Further details will be described in the SAP.

9.11 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.

10. REGULATORY OBLIGATIONS

This study will be conducted in compliance with GCP, including International Conference on Harmonization 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 IRBs/IECs must approve the protocol and any amendments, and the subject 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 (e.g., loss of medical licensure, debarment).

11. ETHICAL ASPECTS

11.1 LOCAL REGULATIONS

The study must fully adhere to the principles outlined in Guideline for Good Clinical Practice ICH E6(R2) Integrated Addendum to ICH E6(R1) (March 2018), 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".

11.2 INFORMED CONSENT

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

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

11.3 INSTITUTIONAL REVIEW BOARD

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

11.4 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 April 25, 2006) and/or 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. Once all samples have been analyzed for additional research, the samples will be discarded and will not be stored for future research.

12. CONDITIONS FOR MODIFYING THE PROTOCOL

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

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

13. 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.

14. STUDY DOCUMENTATION, CRFS AND RECORD KEEPING

14.1 INVESTIGATOR'S FILES AND RETENTION OF DOCUMENTS

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

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

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

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

14.2 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 if subject confidentiality is protected.

14.3 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.

14.4 ELECTRONIC CASE REPORT FORMS

Clinical trial data for this study will be captured on electronic eCRF. The Investigator agrees to provide all information requested on the eCRF in an accurate manner according to instructions provided. Electronic CRFs are designed for computer processing and analysis. The Investigator should ensure the accuracy, completeness, and timeliness of the data reported to Kadmon Corporation (or designee) in the eCRF and in all required reports.

An eCRF is required to be submitted for every subject who receives any amount of study drug. This includes submission of retrievable data on subjects who withdraw before completion of the study. The 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.

15. MONITORING OF THE STUDY

It is understood that the responsible 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 if 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.

16. CONFIDENTIALITY OF TRIAL DOCUMENTS AND SUBJECT RECORDS

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

17. 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.

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19. APPENDIX A: SCHEDULE OF ASSESSMENTS

Schedule of Assessments *(continued on next page)*

		Double-Blind Treatment Period (28 Weeks)									Open-Label Treatment Period (24 Weeks)							
Assessment	Screening Visit	Week 1 (Baseline)	Day 15	End of Week 4	End of Week 8	End of Week 12	End of Week 16	End of Week 20	End of Week 24	End of Week 28[e]	End of Week 32	End of Week 36	End of Week 40	End of Week 44	End of Week 48	End of Week 52/ EOT	28-Day Safety Follow-Up (±3 days)	Unscheduled Visit
Study Day	-29 to -1	1	15 (±3 days)	29 (±3 days)	57 (±3 days)	85 (±3 days)	113 (±3 days)	141 (±3 days)	169 (±3 days)	197 (±3 days)	225 (±3 days)	253 (±3 days)	281 (±3 days)	309 (±3 days)	337 (±3 days)	365 (±3 days)		
Informed consent[a]	X																	
Subject Demography	X																	
Medical history	X																	
Inclusion/Exclusion Criteria	X	X																
Randomization[b]		X								X								
EFFICACY ASSESSMENTS																		
CRISS[c]					X		X		X	X		X		X		X	X	X
mRSS[d]	X	X			X		X		X	X		X		X		X	X	X
FVC[d]	X				X		X		X	X		X		X		X		
SHAQ-DI[d]		X			X		X		X	X		X		X		X	X	X
Physician global assessment[d]		X			X		X		X	X		X		X		X	X	X
Patient global assessment[d]		X			X		X		X	X		X		X		X	X	X
PFTs[e]		X							X							X	X	X
HRCT[f]		X							X							X[f]		

Schedule of Assessments *(continued)*

	Double-Blind Treatment Period (28 Weeks)	Open-Label Treatment Period (24 Weeks)	

	Screening Visit	Week 1 (Baseline)	Day 15	End of Week 4	End of Week 8	End of Week 12	End of Week 16	End of Week 20	End of Week 24	End of Week 28[o]	End of Week 32	End of Week 36	End of Week 40	End of Week 44	End of Week 48	End of Week 52 / End of Treatment	28-Day Safety Follow-Up (±3 days)	Unscheduled Visit
Study Day	**-29 to -1**	**1**	**15 (±3 days)**	**29 (±3 days)**	**57 (±3 days)**	**85 (±3 days)**	**113 (±3 days)**	**141 (±3 days)**	**169 (±3 days)**	**197 (±3 days)**	**225 (±3 days)**	**253 (±3 days)**	**281 (±3 days)**	**309 (±3 days)**	**337 (±3 days)**	**365 (±3 days)**		
Skin Biopsies[g]		X							X							X		
Pharmacokinetics[n]				X	X													
Pharmacodynamics[m]		X			X				X							X		
SAFETY ASSESSMENTS																		
Complete PE[h]	X	X							X	X						X	X	X
Symptom-directed PE[h]			X	X	X	X	X	X			X	X	X	X	X			
Vital signs[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology and chemistry[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study diary (dispense/collect)		X		X	X	X	X	X	X	X	X	X	X	X	X	X		X
Study drug administration[l]		X	X	X	X	X	X	X	X	X	X	X	X	X	X			X
Dispense/Collect study drug[l]		X		X	X	X	X	X	X	X	X	X	X	X	X	X		X
Concomitant Medications	*To be collected from the date that the ICF is signed until 28 days after last dose of Belumosudil.*																	
Adverse Events																		

Abbreviations: CRISS = Combined Response Index in Diffuse Cutaneous Systemic Sclerosis; ECG = electrocardiogram; EDC = electronic data capture; EOT = End-of-Treatment; FVC = forced vital capacity; HRCT = high-resolution computerized tomography; ICF = informed consent form; ILD = interstitial lung disease; mRSS = modified Rodnan Skin Score; PE = physical examination; PFT = pulmonary function test; SHAQ—DI = Scleroderma Health Assessment Questionnaire—Disability Index

a. The ICF must be signed before any study procedure begins.

b. Re-randomization of the placebo group to one of two arms will take place after the un-blinding procedures take place.

c. CRISS will not be performed on site, but rather will be calculated outside of EDC.

d. mRSS, SHAQ-DI, FVC, physician global assessment and patient global assessment will be performed at baseline Day 1, Day 57, Day 113, Day 169, Day 197, and then every 8 weeks thereafter until Week 52. In addition, after their last dose of study drug (4-Week Follow-Up Visit). mRSS and FVC will also be performed at screening as one of the inclusion criteria. FVCs should be performed if PFT is not performed at the same visit. FVCs need not be performed if PFT is performed at the same visit.

e. HRCT and PFTs, to include FEV_1, FVC, DL_{CO} (corrected for Hb), TLC, and RV, will be performed at baseline, Day 169, and Day 365 (each ± 7 days). In addition, PFTs will be performed after their last dose of study drug (4-Week Follow-Up Visit). If the HRCT or PFTs is performed within one month of the EOT visit, it does not need to be done again at the EOT visit.

f. HRCT will be done only in subjects at Day 1, Day 169, and Day 365 (each ± 7 days) if they have confirmed ILD at baseline. This is not required at the End of Treatment visit.

g. Double punch Skin biopsies are MANDATORY for all subjects on Day 1 and Day 169 and Optional on Day 365 and will be obtained from the dorsal mid-forearm for Gene Profiling. This assessment is not required for End of Treatment.

h. 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 (e.g., physician assistant, nurse practitioner). All PEs, whether complete or symptom-directed, will include assessment of cardiac (including heart rate and vital signs), musculoskeletal (i.e., muscle aches), and neurological (i.e., gait) systems. A complete PE include will include evaluation of primary endpoints. A symptom-directed PE will be focused on symptoms and not include evaluations of primary endpoints.

i. Sitting blood pressure, heart rate to be obtained (after 5 minutes of rest)

j. See Section 6.2.4 for a complete list of laboratory safety assessments. If increases in liver enzymes are observed at any time in a subject, refer to Section 4.13.

k. Women of childbearing potential must have a negative urine pregnancy test. Positive results are to be confirmed with serum testing.

l. Subjects will take their morning dose at the clinic and then will be dispensed study drug for home administration.

m. Pharmacodynamics will be collected as follows: within 60 minutes pre-dose at baseline, Week 8, week 24, and Week 52. ELFT collected at Baseline, Week 8, Week 24 and Week 52.

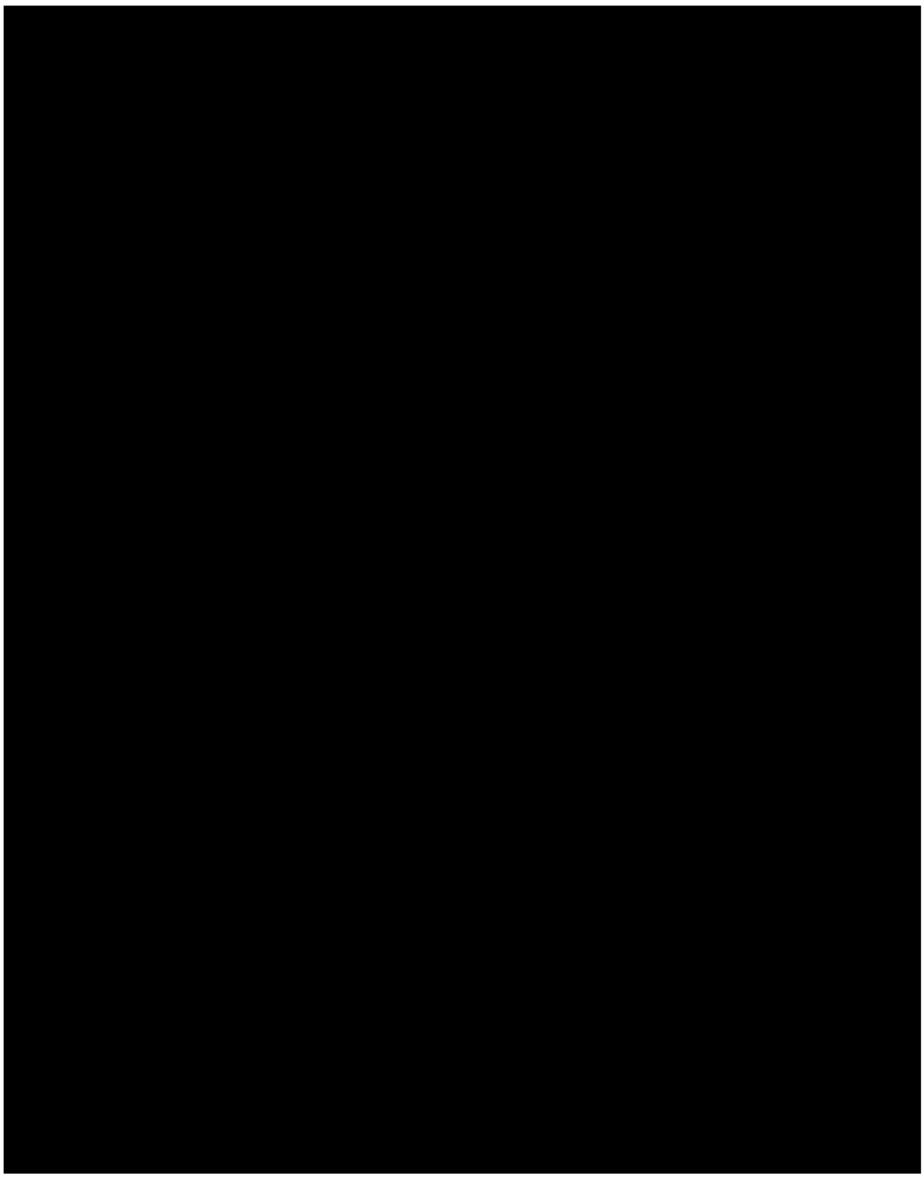
n. Pharmacokinetics will be collected within 60 minutes pre-dose of dosing and 3 hours post-dose with a window of 10 minutes at Week 4 and Week 8.

o. All subjects will be un-blinded at this visit.

Note: At Week 1, Day 1 visit, if screening was completed within 7 days of baseline, only the complete PE and vital sign measurements need to be repeated.
Note: The term EOT refers to early withdrawal or Week 52, as appropriate.

20. APPENDIX B: CALCULATION OF MODIFIED RODNAN SKIN SCORE

The mRSS is displayed below.[redacted]

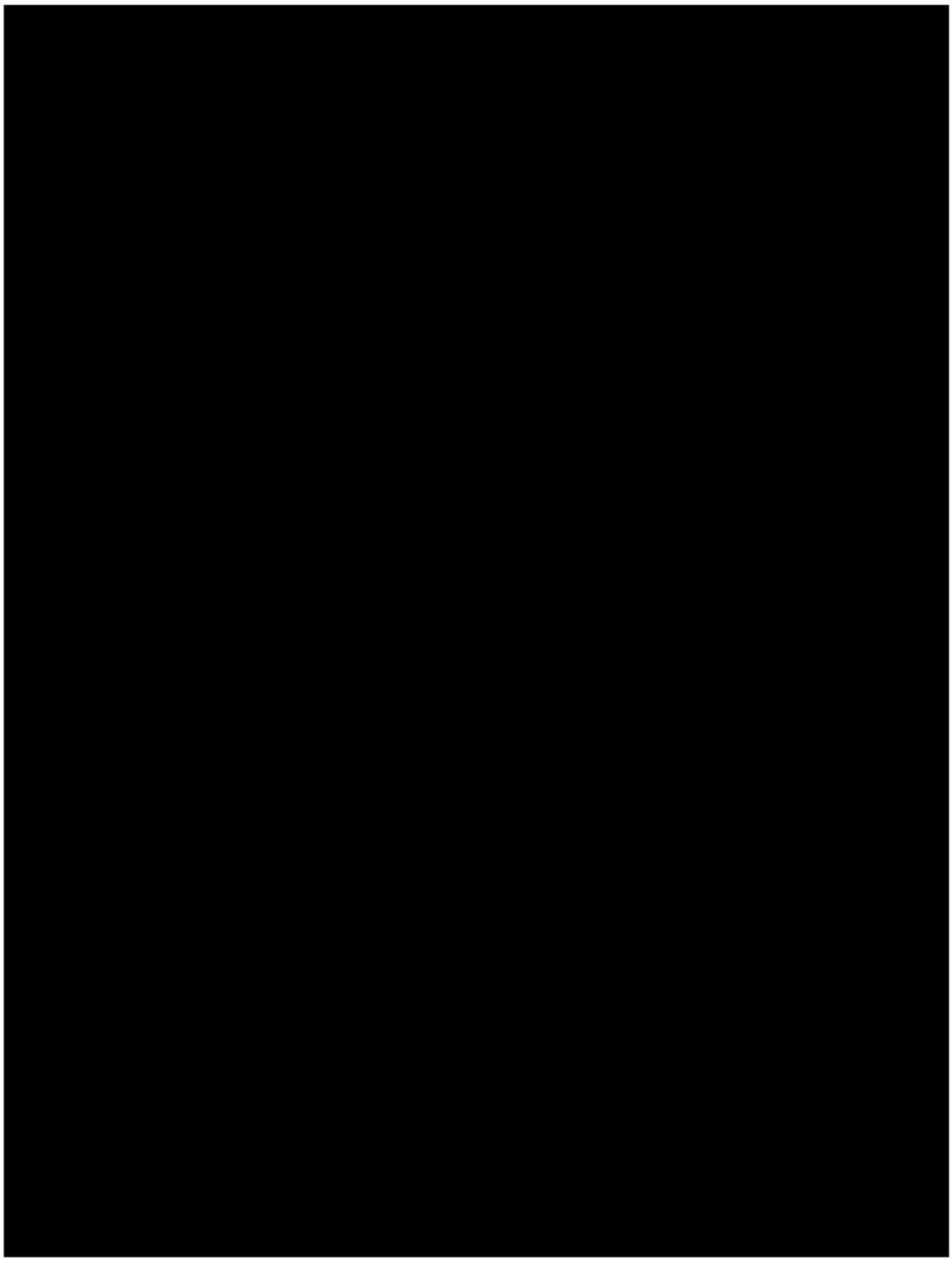


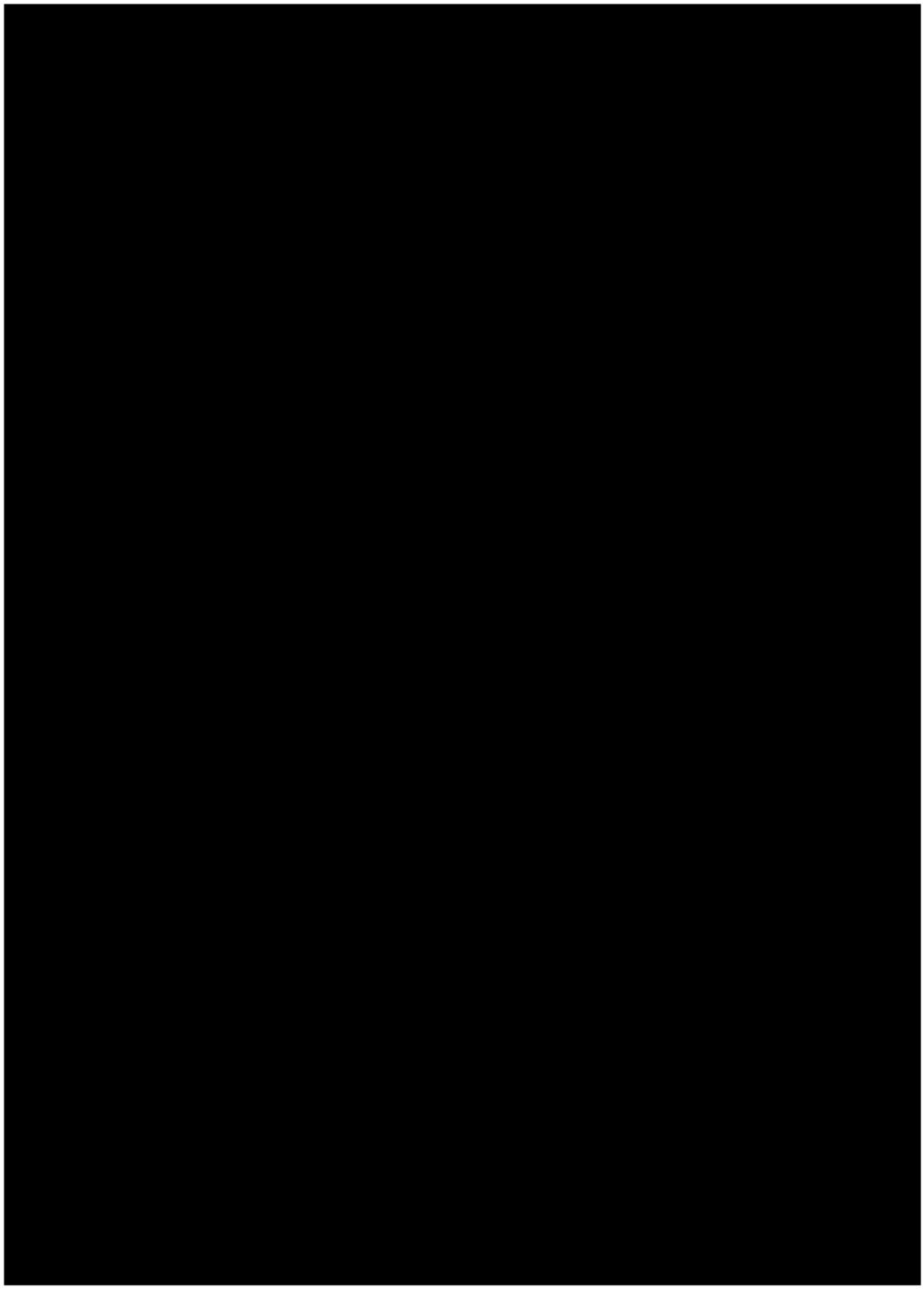
21. APPENDIX C: SCLERODERMA HEALTH ASSESSMENT QUESTIONNAIRE

The SHAQ-DI is displayed below:[redacted]

[redacted]

SHAQ – USA/English (original)
SHAQ_AU2.0_eng-USori





Source: https://eprovide.mapi-trust.org/instruments/scleroderma-health-assessment-questionnaire

22. APPENDIX D: PHYSICIAN GLOBAL ASSESSMENT

23. APPENDIX E: PATIENT GLOBAL ASSESSMENT

24. APPENDIX F: DETERMINING RELATIONSHIP OF ADVERSE EVENTS TO STUDY DRUG

Determination the relationship of AEs to study drug is displayed below.[27]

1 NOT RELATED

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

2 UNLIKELY RELATED (must have first 2)

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

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

3 POSSIBLY RELATED (must have first 2)

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

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

4 PROBABLY RELATED (must have first 3)

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

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

5 DEFINITELY RELATED (must have first 3)

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

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

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

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

25. APPENDIX G: DRUGS THAT INDUCE AND INHIBIT CYP3A4

This is not a comprehensive list, and all concomitant medications should be evaluated for possible interactions with belumosudil.[28]

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 05 Apr 2018

26. APPENDIX H: DRUGS KNOWN TO HAVE THE POTENTIAL FOR QTC PROLONGATION

Drugs known to have the potential for prolonging of QTc are prohibited. The list below is not comprehensive. All concomitant medications should be evaluated for possible interactions with belumosudil.[29]

Drugs Known to 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 04 Jun 2018