NCT: NCT05305989

CLINICAL STUDY PROTOCOL

Extended Treatment and Follow-up of Subjects Treated with Belumosudil in Study KD025-208 or Study KD025-213

Protocol Number:	KD025-217
Study Drug:	Belumosudil (formerly KD025)
IND Number:	IND 125890
Phase:	2
Sponsor:	Kadmon Corporation, LLC 450 East 29th Street New York, NY 10016
Original Protocol:	26 July 2021
Amendment 1:	01 September 2021

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 medical monitor, [redacted]:

Email: [redacted]

Phone: [redacted]

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

Kadmon Pharmacovigilance

[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 7.3.1, 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) E6 (R2), and the ethical principles that have their origins in the Declaration of Helsinki.

[redacted]
Executive Medical Director, Clinical and Regulatory Development
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) E6 (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)

SYNOPSIS

Study Title	Extended Treatment and Follow-up of Subjects Treated with Belumosudil in Study KD025-208 or Study KD025-213
Clinical Phase	2
Study Background	Chronic graft-versus-host disease (cGVHD) remains a major complication of allogeneic hematopoietic cell transplantation (HCT) occurring in approximately 50% of transplant recipients and involving multiple organs. Patients with cGVHD require prolonged immunosuppressive treatment for an average of 2 to 3 years from the initial diagnosis, with 10% of those surviving for at least 7 years still requiring immunosuppressive treatment at that time and beyond. There remains substantial unmet medical need for therapies with improved tolerability and effectiveness for adults and adolescents with cGVHD. Belumosudil (previously known as KD025) is an orally available Rho-associated coiled-coil kinase 2 (ROCK2) selective inhibitor that has been shown to be active and well-tolerated in cGVHD. Study KD025-208 enrolled subjects with active cGVHD who had previously received no more than 3 prior lines of treatment. Study KD025-213 enrolled subjects who had previously received 2 to 5 prior lines of treatment. Over two-thirds of cGVHD patients treated with belumosudil in these 2 trials achieved clinical responses. In both Study KD025-208 and Study KD025-213, subjects were treated with belumosudil until cGVHD progression or unacceptable toxicity. Several subjects remain on active treatment. This study will provide extended treatment and follow-up for these subjects utilizing the same dose and treatment schedule of belumosudil that each subject was receiving in Study KD025-208 or Study KD025-213.
Study Objective	The objective of this study is to evaluate long-term safety and efficacy of belumosudil in subjects with cGVHD who have previously been treated with belumosudil.
Study Design	This will be a Phase 2, open-label, long-term treatment and follow-up study in subjects with cGVHD who have been previously treated with belumosudil in Study KD025-208 or in Study KD025-213. Subjects will not be screened. Subjects who have signed the informed consent form will be enrolled in Study KD025-217 if they have met 1 of the following conditions: • Actively receiving belumosudil or in long-term follow-up (LTFU) in Study KD025-208 or Study KD025-213 • Enrolled in the Companion Study as specified in Study KD025-213 Amendment 2 and received at least 6 months of treatment or is in LTFU After signing the ICF, at Baseline, subjects will undergo efficacy assessments by Clinician-reported Global cGVHD Activity Assessment, response assessment, pulmonary function tests, Lee Symptom Scale (LSS) score, and documentation of corticosteroid dosage and/or other therapies for cGVHD. Subjects will undergo safety assessments including symptom-directed physical examination (PE), vital signs, weight, height, Karnofsky Performance Status (KPS) score, hematology and clinical chemistry laboratory testing, pregnancy testing, 12-lead electrocardiogram (ECG), documenting concomitant medications, and monitoring for adverse events (AEs). Subjects will continue on their same

	dosing regimen as they received in Study KD025-208 or Study KD025-213: belumosudil 200 mg once daily (QD), 200 mg twice daily (BID), or 400 mg QD. If the Investigator reduced the dose, i.e., a subject received a reduced dose of belumosudil in either Study KD025-208 or Study KD025-213, the subject would continue to receive that same reduced dose treatment with belumosudil throughout Study KD025-217 or until the AE that led to the temporary dose reduction had resolved, in which the dose treatment can resume at the original dose at the discretion of the Investigator. Subjects will be given a study drug diary to record daily dosing. Subjects may be administered the first dose either in the clinic or self-administered at home. At 3 months after Baseline and every 3 months thereafter (± 14 days), subjects will report to the clinic for the same efficacy and safety assessments and dispensing of belumosudil as Baseline. The study drug diaries for the past 3 months will be collected, and new study drug diaries dispensed. Any remaining belumosudil will be collected. Subjects may receive belumosudil in Study KD025-217 for up to an additional 2 years, at the discretion of the Investigator (and with guidance from the medical monitor), beyond what they had received in Study KD025-208 or Study KD025-213. Subjects will be treated with belumosudil until cGVHD progression or unacceptable toxicity. Subjects will return to the clinic for a 28-day Follow-up Visit 28 (± 7 days) at 28 days after the last dose of study drug. After the 28-day Follow-Up Visit has been completed, subjects will have LTFU approximately every 3 months until a failure-free survival (FFS) event occurs. This LTFU assessment will occur by subjects being contacted by telephone, e-mail, or postal mail to confirm survival status, any initiation of new systemic cGVHD therapies, and relapse of underlying disease. Alternatively, this information may be obtained from the subject's medical records.
Number of Study Centers	Approximately 20
Number of Subjects	Approximately 70
Approximate Duration of Subject Participation	Subjects may receive belumosudil up to an additional 2 years beyond what they had received in Study KD025-208 or Study KD025-213, at the discretion of the Investigator and with guidance from the medical monitor. Subjects will be treated with belumosudil until cGVHD progression or unacceptable toxicity. Subjects will return to the clinic for a 28-day Follow-up Visit at 28 days (± 7 days) after the last dose of study drug. Subjects will have LTFU approximately every 3 months until a FFS event occurs. After the 28-day Follow-up Visit has been completed, subjects will be contacted approximately every 3 months by telephone, e-mail, or postal mail to confirm survival status, any initiation of new systemic cGVHD therapies, and relapse of underlying disease.
Study Treatment	Belumosudil will be administered orally at the same dose the subject received in Study KD025-208 or in Study KD025-213. Subjects will be provided with an adequate supply of belumosudil. Study drug accounting will be performed at each visit.
Criteria for Inclusion and Exclusion	**Inclusion Criteria:** 1. Subjects must have been treated with belumosudil for at least 1 of the following:

	a. Actively receiving belumosudil on Study KD025-208 or Study KD025-213 (excluding adults in the Companion Study and excluding adolescents enrolled under KD025-213 Amendment 2 [01 June 2020]). b. Is in Long-term Follow-up (LFTU) on Study KD025-208 or Study KD025-213. Long-term Follow-up will be defined as the period after ending treatment with belumosudil and until a FFS event occurs. c. Adult enrolled in the Companion Study under KD025-213 Amendment 2 (01 June 2020) and has received at least 6 months of treatment of belumosudil or is in LTFU 2. Female subjects of childbearing potential have a negative pregnancy test at enrollment. Females of childbearing potential are defined as sexually mature females without prior hysterectomy or who have had any evidence of menses in the past 12 months. However, females 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. 3. Sexually active females of childbearing potential enrolled in the study must agree to use 2 forms of accepted methods of contraception during the course of the study and for 3 months after their last dose of study drug. Effective birth control includes: a. Intrauterine device plus 1 barrier method b. Stable doses of hormonal contraception for at least 3 months (e.g., oral, injectable, implant, transdermal) plus 1 barrier method c. 2 barrier methods. Effective barrier methods are male or female condoms, diaphragms, and spermicides (creams or gels that contain a chemical to kill sperm) or d. A vasectomized partner 4. For male subjects who are sexually active and who are partners of females of childbearing potential: agreement to use 2 forms of contraception and to not donate sperm during the treatment period and for at least 3 months after the last dose of study drug. 5. Subject (or the subject's legally authorized representative) is able to provide written informed consent prior to the performance of any study-specific procedures. 6. It is in the best interest of the subject to participate in the study. **<u>Exclusion Criteria</u>** 1. Female subject who is pregnant or breastfeeding 2. Subject considered unlikely to adhere to treatment and/or follow protocol in the opinion of the Investigator
Efficacy Follow-up Variables	• Duration of Responses (DOR): Response is defined by the 2014 National Institutes of Health (NIH) Consensus Development Project on clinical trials in cGVHD and are assessed by investigators • Change in Lee Symptom Scale Score (LSS) • Time to Next Treatment (TTNT) • FFS • Overall Survival (OS)

	• Percentage of subjects who have a best response of PR and percentage of subjects who have a best response of CR • Response by individual organ • Change in corticosteroid dose • Change in cGVHD Global Severity Rating based on the Clinician-reported Global cGVHD Activity Assessment
Safety Follow-up Variables	Safety assessments will be performed at regular intervals and will include AEs, Grade ≥ 3 AEs, serious adverse events (SAEs), PEs, vital sign measurements, clinical laboratory evaluations, and ECGs. Reasons for treatment discontinuation will be documented. The AE reporting period for a subject enrolled in the study will begin when the subject signs the informed consent and is continued through the 28-day Follow-up Visit at 28 days (± 7 days) after their last dose study drug.
Statistical Analysis	An interim analysis will be performed when all patients have completed at least 3 years of treatment with belumosudil or withdrew earlier (not inclusive of the companion study subjects). **Study Subjects** Demographic (e.g., gender, age, and race) and Baseline characteristics will be summarized. **Efficacy Analyses:** The efficacy endpoint analyses include • DOR • Change in LSS • TTNT • FFS • OS • Proportion of subjects with a CR and proportion with a PR • Response by individual organ • Change in corticosteroid use • Change in cGVHD global severity rating based on the Clinician-reported Global cGVHD Activity Assessment. **Safety Analyses:** Safety analyses will be performed on all subjects who receive at least 1 dose of belumosudil. Adverse events will be coded using the Medical Dictionary of Regulatory Activities (MedDRA version 24.0 or greater). The number and percentages of subjects experiencing treatment-emergent AEs will be tabulated by System Organ Class and Preferred Term (PT). The number of events by PT will also be summarized. Tabulation by maximum severity and relationship to treatment will also be included by treatment group. Summary subject listing will be provided for SAEs, AEs resulting in study discontinuation, and deaths. The AEs, SAEs, related AEs, related SAEs, Grade ≥ 3 AEs, related Grade ≥ 3 AEs, deaths, and AEs leading to withdrawal and treatment discontinuation will be summarized.

	Laboratory results and incidence of laboratory abnormalities will be summarized by treatment group. The worst on-study grade during the treatment period will be summarized. The incidence of Grade ≥ 3 laboratory abnormalities under treatment and shifts in toxicity grading from Baseline to highest grade post-baseline will be displayed. Vital sign measurements and ECGs will be summarized by treatment group at each scheduled time point using descriptive statistics and included in data listings.

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LIST OF ABBREVIATIONS

AE	Adverse events
BA/BE	Bioavailability/Bioequivalence
BID	Twice daily
CI	Confidence interval
C_{max}	Maximum concentration on concentration-time curve
CNI	Calcineurin inhibitor
CR	Complete response
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
cGVHD	Chronic graft-versus-host disease
DOR	Duration of response
ECG	Electrocardiogram
ECP	Extracorporeal photopheresis
eCRF	Electronic case report form
EOS	End-of-Study
EOT	End-of-Treatment
FDA	Food and Drug Administration
FFS	Failure-free survival
GCP	Good Clinical Practice
GI	Gastrointestinal
HCT	Hematopoietic cell transplantation
IB	Investigator's Brochure
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IL	Interleukin
IND	Investigational New Drug
IRB	Institutional Review Board
KPS	Karnofsky Performance Scale
LR	Lack of response
LSS	Lee cGVHD Symptom Scale
LTFU	Long-term Follow-up
MedDRA	Medical Dictionary of Regulatory Activities
MHC	Major Histocompatibility Complex
mITT	Modified Intent-to-Treat Population
NIH	National Institutes of Health

OS	Overall survival
PE	Physical examination
PK	Pharmacokinetic
PR	Partial response
PT	Preferred Term
PtR	Point reduction
QD	Once daily
ROCK	Rho-associated coiled-coil kinases
SAE	Serious adverse event
TEAE	Treatment-emergent adverse event
TFH	T follicular helper
TH17	T helper cell 17
TTNT	Time to next treatment

1 INTRODUCTION

1.1 Chronic Graft-versus-Host Disease

Chronic graft versus host disease (cGVHD) remains a major complication of allogeneic hematopoietic cell transplantation (HCT) involving multiple organs and occurring in up to 70% of transplant recipients depending upon donor and transplant characteristics.[1] Multicenter and registry data show a cumulative incidence of 30% to 50%.[2,3] Patients with cGVHD require prolonged immunosuppressive treatment for an average of 2 to 3 years from the initial diagnosis, with 10% of those surviving for at least 7 years still requiring immunosuppressive treatment at that time and beyond.[4]

Glucocorticoids, with or without calcineurin inhibitors (CNIs), remain the standard initial treatment, but are associated with significant side effects and unsatisfactory outcomes, particularly for patients with high-risk features of cGVHD.[5]

Based upon data from Study KD025-213, the Food and Drug Administration (FDA) approved REZUROCK (belumosudil) for the treatment of adult and pediatric patients 12 years and older with cGVHD after failure of at least 2 prior lines of systemic therapy (Section 1.4.2).[6] This is the second FDA approved drug indicated specifically for patients with cGVHD.

The first FDA approved cGVHD therapy is Ibrutinib (IMBRUVICA) for the treatment of adult patients with cGVHD after failure of one or more lines of systemic therapy based upon data from an open-label study (Study 1129; NCT02195869) of 42 subjects with cGVHD who had failed first-line corticosteroid therapy and required additional therapy.[7]

1.2 Rho-Associated Protein Kinases

Rho-associated coiled-coil kinases (ROCKs) play a central role in the control of actin cytoskeleton assembly and cellular functions, such as proliferation, adhesion, migration and phagocytosis.[8,9,10,11] Two isoforms of ROCK have been identified, ROCK1 and ROCK2, which are activated by Rho GTPases and promote actin-myosin mediated contractile force generation via serine-threonine phosphorylation of numerous downstream targets. During the immune response, ROCK signaling is critical in the coordination and balancing of T-cell-mediated immune responses, including cellular movement, T-cell receptor (TCR) signaling and the acquisition of the appropriate T-cell effector program.[12,13] However, only the ROCK2 isoform was shown to be physiologically activated in CD4+ T cells under T helper 17 (TH17) skewing, leading to increased secretion of interleukin- (IL-)17 and IL-21 in both mice and humans.[14,15]

Moreover, targeted ROCK2 inhibition effectively decreased IL-17 production in vivo and ameliorated the spontaneous development of arthritis, diabetes and lupus in mice.[15] Additionally, Rho-associated protein kinase (ROCK) activity was increased in patients with rheumatoid arthritis and systemic lupus erythematosus.[14,16,17] The specific inhibition of ROCK2 therefore has been examined for its potential as a therapy for autoimmune disorders.

1.3 Non-clinical Background of Belumosudil

Belumosudil is an orally available ROCK2 selective inhibitor. Data from a Phase 1 clinical trial demonstrated that oral administration of belumosudil to healthy human subjects down-regulates the ability of T cells to secrete IL-21 and IL-17, but not interferon-γ in response to TCR stimulation ex vivo. Treatment with belumosudil also promotes the suppressive function of regulatory T cells through up-regulation of STAT5 phosphorylation and positive regulation of Foxp3 expression.[18]

Chronic GVHD remains a major complication following allogeneic bone marrow transplantation.[19] The underlying pathogenesis of GVHD is similar to autoimmune attack in a number of respects, including a contributory role of pro-inflammatory TH17 and T follicular helper (TFH) cells and a protective role of T regulatory cells.[20] In addition, the aberrant activation of immune cells leads to increased secretion of transforming growth factor-β which promotes fibroblast activation, collagen production, and development of tissue fibrosis.[21] Belumosudil effectively ameliorates cGVHD in multiple models: a full major histocompatibility complex (MHC)-mismatch model of bronchiolitis obliterans syndrome that involved a wide spectrum of target organs including lung and liver[22] as well as a minor MHC-mismatch model of sclerodermatous GVHD.[23] Treatment with belumosudil resulted in normalization of pathogenic pulmonary function, which correlates with a marked reduction of antibody and collagen deposition in the lungs of treated mice to levels comparable to non-cGVHD controls.[24] Spleens of mice treated with belumosudil had decreased frequency of TFH and increased frequency of T follicular regulatory cells, accompanied by a reduction in STAT3 and concurrent increase in STAT5 phosphorylation. Together these data highlight the potential of targeted ROCK2 inhibition for cGVHD therapy.

Refer to the Belumosudil Investigator's Brochure (IB) for more detailed information.

1.4 Clinical Background of Belumosudil

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 twice daily (BID) for 28 days.

Administration of belumosudil 200 mg tablets in the fed state resulted in an approximate 2-fold increased exposure in terms of maximum concentration (C_{max}) and area under the concentration-time curve (AUC) when compared to the fasted state. Pharmacokinetic (PK) analyses showed that belumosudil administered as a 200 mg tablet in the fed state was rapidly absorbed with a median time of maximum concentration of approximately 3 hours. Elimination half-life is approximately 7 hours. Variability in exposure related parameters C_{max} and AUC was reduced when belumosudil was administered in the fed state when compared to the fasted state. Belumosudil should be taken with food.

Data from Study KD025-208 and Study KD025-213 in subjects with cGVHD are summarized in Section 1.4.1 and Section 1.4.2, respectively.

Refer to the Belumosudil IB for more detailed information.

1.4.1 Study KD025-208

Details of the objective, design, efficacy results, and safety results are available in the Study KD025-208 Clinical Study Report (CSR), 07 July 2020 and are summarized below.

Objectives:

The primary objectives of Study KD025-208 were to evaluate the activity of belumosudil in subjects with steroid-dependent cGVHD and active disease in terms of partial response (PR) and complete response (CR); and safety and tolerability of belumosudil in subjects with cGVHD.

Inclusion/Exclusion Criteria:

The major inclusion criteria were: (1) male and female subjects ≥ 18 years of age with allogeneic bone marrow transplant or HCT; (2) receiving glucocorticoid therapy and calcineurin therapy or glucocorticoid therapy along for cGVHD; (3) persistent active cGVHD manifestations; (4) ≤ 3 prior lines of treatment for cGVHD; and (5) Karnofsky Performance Scale (KPS) score > 40. Details of inclusion criteria are provided in the KD025-208 Protocol, Section 7.2.

The major exclusion criteria were: (1) receiving an investigational GVHD treatment within 28 days of study entry; (2) acute GVHD; (3) taking other immunosuppressant drugs for GVHD including mammalian target of rapamycin (mTOR) inhibitors; and (4) taking any medication known to be a moderate or strong inhibitor of the CYP3A4 isozyme or any drugs known to be moderate or strong CYP3A4 inhibitors. Details of exclusion criteria are provided in the KD025-208 Protocol, Section 7.2.

Study Design

Study KD025-208 was a Phase 2a, open-label, dose-escalation, safety, tolerability, and activity study of belumosudil in subjects with cGVHD. Approximately 48 subjects were to be enrolled to receive oral belumosudil in 3 cohorts, each cohort consisting of 16 subjects (1:1:1 fashion): belumosudil 200 mg QD (Cohort 1); belumosudil 200 mg BID (Cohort 2); and belumosudil 400 mg QD (Cohort 3). Belumosudil was to be administered in 28-day cycles until disease progression or unacceptable toxicity.

Efficacy assessments included using the criteria of 2014 NIH Consensus Development Project on Clinical Trials in cGVHD response (CR, PR, or lack of response [unchanged, mixed, or progression]), cGVHD severity (clinical-reported) and symptom (subject-reported), and Lee cGVHD Symptom Scale (LSS).

Safety assessments included physical examinations (PEs); vital sign measurements; blood sample collection for hematology and chemistry; urinalysis; electrocardiograms (ECGs); adverse event (AE) assessments; concomitant medication assessments; and pregnancy testing for females of childbearing potential.

A Follow-up Safety Visit occurred 28 days (± 7 days) after the last dose of study drug.

Subjects were contacted approximately every 8 weeks via telephone, email, or postal mail to confirm survival status and the initiation of any anti-cancer treatment or any changes in treatment of cGVHD.

Disposition of Subjects

Overall, 64 subjects were screened for the study of whom 54 were included in the modified Intent-to-Treat (mITT) Population: 17 subjects in Cohort 1, 16 subjects in Cohort 2, and 21 subjects in Cohort 3. As of the cut-off date for this analysis (19 February 2020), 47 (87.0%) subjects have discontinued treatment and 7 (13.0%) subjects remain on treatment with

belumosudil. The most frequent reason for treatment discontinuation was disease progression (22 [40.7%] subjects). A total of 37 (68.5%) subjects were participating in the study, either being actively treated with belumosudil or being followed for survival (in Long-term Follow-Up). Seventeen (31.5%) subjects have discontinued from the study for the following reasons: 11 (20.4%) subjects died, 5 (9.3%) subjects were lost to follow-up, and 1 (1.9%) subject discontinued for other reasons. The overall median follow-up duration was 28.8 months: 35.9 months for Cohort 1; 32.4 months for Cohort 2; and 24.0 months for Cohort 3.

Demographics and Baseline Characteristics

Overall, subjects had a median age of 51.5 years, were predominantly male (34 [63.0%]), and White (47 [87.0%]). Thirty-nine (72.2%) subjects had a KPS score ≥ 80. Most subjects had no previous autologous transplants (45 [83.3%] subjects); all had received a previous allogeneic transplant. The median time to cGVHD diagnosis from transplant was 7.9 months. The median time from cGVHD diagnosis to study enrollment was 20.0 months.

The overall median number of prior lines of systemic cGVHD therapy was 2.0. Thirty-five (72.9%) subjects were refractory to the last systemic cGVHD treatment prior to enrollment in the study. All subjects had received concomitant corticosteroid medication at study initiation; other common concomitant medications received at Baseline were CNI (23 subjects, 42.6%), and extracorporeal photopheresis (ECP; 12 subjects, 22.2%).

Efficacy

The primary efficacy endpoints are presented in Table 1.

The ORR was 64.8% (95% confidence interval [CI]: 50.6%, 77.3%) across all 3 cohorts: 64.7% (95% CI: 38.3%, 85.8%) in Cohort 1; 68.8% (95% CI: 41.3%, 89.0%) in Cohort 2; and 61.9% (95% CI: 38.4%, 81.9%) in Cohort 3. All responses were PRs. The lower bound of the 95% CI around the ORR exceeded 30% overall and for each cohort.

Table 1. Primary Efficacy Endpoint Results from Study KD025-208

Primary Efficacy Outcomes	Cohort 1 200 mg QD N = 17	Cohort 2 200 mg BID N = 16	Cohort 3 400 mg QD N = 21	Overall N = 54
ORR (CR or PR) - n (%)	11 (64.7)	11 (68.8)	13 (61.9)	35 (64.8)
95% CI of ORR	(38.3, 85.8)	(41.3, 89.0)	(38.4, 81.9)	(50.6, 77.3)
Best response				
CR	0 (0)	0 (0)	0 (0)	0 (0)
PR	11 (64.7)	11 (68.8)	13 (61.9)	35 (64.8)
LR				
LR-Unchanged	2 (11.8)	3 (18.8)	4 (19.0)	9 (16.7)
LR-Mixed	3 (17.6)	1 (6.3)	0 (0)	4 (7.4)
LR-Progression	1 (5.9)	0 (0)	1 (4.8)	2 (3.7)
No response assessment	0 (0)	1 (6.3)	3 (14.3)	4 (7.4)

BID = twice daily; CI = confidence interval; CR = complete response; LR = Lack of Response; mITT = modified Intent-to-Treat; NIH = National Institutes of Health; ORR = Overall Response Rate; PR = partial response; QD = once daily.
Note: mITT Population.
Note: The percentages were calculated based on the number of subjects in the mITT Population

Safety

The median duration of treatment overall was 8.4 months: 8.5 months for Cohort 1; 7.5 months for Cohort 2; and 9.0 months for Cohort 3. Overall, 42.6% of subjects received > 12 months of belumosudil treatment. The median relative dose intensity was 98.3%: 99.1% for Cohort 1; 96.6% for Cohort 2; and 99.1% for Cohort 3.

Safety results are presented in Table 2.

In total, 18 (33.3%) subjects experienced a treatment-emergent AE (TEAE) leading to discontinuation of treatment: 6 (35.3%) subjects in Cohort 1; 5 (31.3%) subjects in Cohort 2; and 7 (33.3%) subjects in Cohort 3. Two subjects discontinued belumosudil treatment for AEs considered probably related to belumosudil: 1 subject in Cohort 1 (headache and diarrhea) and 1 subject in Cohort 3 (fatigue). Overall, 11 subjects experienced a serious TEAE (SAE) that led to discontinuation of treatment: 3 subjects in Cohort 1; 2 subjects in Cohort 2; and 6 subjects in Cohort 3. None of these serious SAEs were considered related to belumosudil. In Cohort 3, 4 (19.0%) subjects experienced a SAE that led to death. However, none were considered related to belumosudil. No subjects died in Cohorts 1 or 2 due to a SAE.

Table 2. Safety Results from Study KD025-208

Safety Outcomes	Cohort 1 200 mg QD N = 17 n (%)	Cohort 2 200 mg BID N = 16 n (%)	Cohort 3 400 mg QD N = 21 n (%)	Overall N = 54 n (%)
Subjects with at least 1 TEAE	17 (100)	16 (100)	20 (95.2)	53 (98.1)
Subjects with TEAEs by maximum severity				
Grade 3: Severe	8 (47.1)	8 (50.0)	6 (28.6)	22 (40.7)
Grade 4: Life-threatening	1 (5.9)	2 (12.5)	4 (19.0)	7 (13.0)
Grade 5: Fatal	0 (0)	0 (0)	4 (19.0)	4 (7.4)
TEAEs by PT occurring in > 20% subjects overall				
Upper respiratory tract infection	9 (52.9)	9 (56.3)	7 (33.3)	25 (46.3)
Diarrhea	6 (35.3)	5 (31.3)	7 (33.3)	18 (33.3)
Nausea	6 (35.3)	4 (25.0)	8 (38.1)	18 (33.3)
Fatigue	6 (35.5)	3 (18.8)	9 (42.9)	18 (33.3)
Dyspnea	3 (17.6)	6 (37.5)	7 (33.3)	16 (29.6)
Headache	4 (23.5)	3 (18.8)	6 (28.6)	13 (24.1)
Edema peripheral	3 (17.6)	4 (25.0)	6 (28.6)	13 (24.1)
Cough	1 (5.9)	4 (25.0)	7 (33.3)	12 (22.2)
Hypertension	5 (29.4)	2 (12.5)	4 (19.0)	11 (20.4)
Subjects with ≥ 1 study drug-related TEAE	8 (47.1)	8 (50.0)	14 (66.7)	30 (55.6)
Study drug-related TEAEs by PT occurring in > 10% of subjects overall				
Fatigue	1 (5.9)	2 (12.5)	3 (14.3)	6 (11.1)
Nausea	2 (11.8)	1 (6.3)	3 (14.3)	6 (11.1)
Subjects with at least 1 Grade ≥ 3 TEAE	9 (52.9)	10 (62.5)	14 (66.7)	33 (61.1)
Grade ≥ 3 TEAEs by PT occurring in ≥ 5% of subjects overall				
Dyspnea	1 (5.9)	2 (12.5)	4 (19.0)	7 (13.0)
GGT increased	2 (11.8)	2 (12.5)	0 (0)	4 (7.4)
Hyperglycemia	2 (11.8)	0 (0)	2 (9.5)	4 (7.4)
Hypoxia	1 (5.9)	1 (6.3)	2 (9.5)	4 (7.4)
Anemia	2 (11.8)	1 (6.3)	0 (0)	3 (5.6)
Lung infection	0 (0)	1 (6.3)	2 (9.5)	3 (5.6)
Subjects with ≥ 1 study drug-related Grade ≥ 3 TEAE	1 (5.9)	3 (18.8)	2 (9.5)	6 (11.1)
Study drug-related Grade ≥ 3 TEAEs by PT occurring in > 3% if subjects overall				
ALT increased	1 (5.9)	1 (6.3)	0 (0)	2 (3.7)
AST increased	1 (5.9)	1 (6.3)	0 (0)	2 (3.7)
Subjects with at least 1 SAE	5 (29.4)	6 (37.5)	12 (57.1)	23 (42.6)
SAEs by PT occurring in > 2% subjects overall				
Dyspnea	0 (0)	1 (6.3)	3 (14.3)	4 (7.4)
Lung infection	0 (0)	1 (6.3)	2 (9.5)	3 (5.6)
Hypoxia	0 (0)	0 (0)	2 (9.5)	2 (3.7)
Influenza-like illness	0 (0)	0 (0)	2 (9.5)	2 (3.7)

Safety Outcomes	Cohort 1 200 mg QD N = 17 n (%)	Cohort 2 200 mg BID N = 16 n (%)	Cohort 3 400 mg QD N = 21 n (%)	Overall N = 54 n (%)
Subjects with TEAE leading to dose discontinuation	6 (35.3)	5 (31.3)	7 (33.3)	18 (33.3)
Subjects with a study drug-related TEAE leading to dose discontinuation	2 (11.8)	0	1 (4.8)	3 (5.6)
Subjects with TEAE leading to death	0	0	4 (19.0)	4 (7.4)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BID = twice daily; GGT = gamma glutamyl transferase; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; QD = once daily; SAE = serious (treatment-emergent adverse event); TEAE = treatment-emergent adverse event.
Note: Safety Population

Conclusions

In this heavily pre-treated population with active cGVHD, belumosudil demonstrated clinical activity and a treatment effect at all 3 dose levels with consistent response rates overall as well as in subgroup populations. Not only did belumosudil show high percentage of overall response, but the responses were clinically meaningful, durable, and associated with improvement in measures of symptom score and reduction in corticosteroid dose. With a median follow-up duration of 29 months, these results suggest a favorable benefit/risk profile with belumosudil for the treatment of subjects with cGVHD after 1 to 3 lines of prior therapy.

1.4.2 Study KD025-213

Details of the objective, design, efficacy results, and safety results are available in the Study KD025-213 CSR, 16 July 2020, and are summarized below.

Objectives

The objective of Study KD025-213 was to evaluate the efficacy and safety of belumosudil at dose levels of 200 mg QD and 200 mg BID in subjects with cGVHD who had previously been treated with at least 2 prior lines of systemic therapy.

Inclusion/Exclusion Criteria

The major inclusion criteria were: (1) ≥ 12 years of age who had allogeneic HCT; (2) previously received at least 2 and not more than 5 lines of systemic therapy for cGVHD; (3) received

glucocorticoid therapy with a stable dose of the 2 weeks prior to screening; and (4) had persistent cGVHD manifestations such that systemic therapy was indicated. Details of inclusion criteria are provided in the KD025-213 Protocol, Section 4.3.

The major exclusion criteria were: (1) not been on a stable dose/regimen of systemic cGVHD treatments for at least 2 weeks prior to screening; (2) histologic relapse of the underlying cancer or post-transplant lymphoproliferative disease at the time of screening; and (3) 30 current treatments with ibrutinib (prior treatment with ibrutinib was permitted with a washout of ≥ 28 days prior to randomization). Details of exclusion criteria are provided in the Study KD025-213 Protocol, Section 4.4.

Study Design

Study KD025-213 was an open-label, randomized, multicenter study in subjects ≥ 12 years of age with cGVHD who had previously been treated with ≥ 2 prior lines of systemic therapy.

In the original protocol, after a 2-week screening period, 126 subjects with active cGVHD were to be randomized in a 1:1 fashion to receive 1 of 2 treatment regimens with belumosudil:

- Arm A: Belumosudil 200 mg QD
- Arm B: Belumosudil 200 mg BID

However, with Amendment 2, the sample size was increased with 20 additional adolescent subjects and 20 adult subjects into a site-specific Companion Study to collect biospecimens. These additional 40 subjects were also be randomized in a 1:1 fashion to Arm A or Arm B. Randomization was stratified according to prior cGVHD treatment with ibrutinib (Yes/No) and severe cGVHD at Baseline (Yes/No).

Subjects received 28-day treatment cycles until clinically significant progression of cGVHD. Subjects who did not achieved a response after 12 cycles of belumosudil were withdrawn if, in the Investigator's judgment, there was no evidence of clinical benefit. After treatment was stopped, subjects had a 4-week Follow-up Visit.

The primary endpoint was the ORR, with responses as defined by the 2014 NIH Consensus Development Project on clinical trials in cGVHD.

Disposition of Subjects

Overall, 132 subjects received at least 1 dose of belumosudil: 66 subjects in Arm A and 66 subjects in Arm B.

As of the cutoff date, 19 February 2020, the median follow-up duration was 7.9 months: 8.0 months for Arm A and 7.9 months for Arm B. In total, 62 (47.0%) subjects had discontinued from treatment; 70 (53.0%) remain on treatment with belumosudil. The most frequent reasons for treatment discontinuation were progression of cGVHD (16 [12.1%] subjects) and withdrawal by subject (14 [10.6%]). A total of 119 (90.2%) subjects participated in the study, either actively treated with belumosudil or followed for survival. Thirteen (9.8%) subjects had discontinued from the study: 8 (6.1%) subjects died; 3 (2.3%) subjects withdrew; 1 (0.8%) subject lost to follow-up; and 1 (0.8%) subject for which data was missing.

Demographic and Baseline Characteristics

Overall, subjects had a median age of 55.5 years and were predominantly male (75 [56.8%] subjects), White (112 [84.8%] subjects), and not Hispanic or Latino (110 [83.3%] subjects). In total, 103 (78.0%) subjects had a KPS $\geq$ 80.

All subjects had received a previous allogeneic transplant. The most frequent indications for the most recent transplant received by subjects included acute myelogenous leukemia (53 [40.2%] subjects), acute lymphoblastic leukemia (19 [14.4%] subjects), other (18 [13.6%] subjects), and myelodysplastic syndrome (13 [9.8%] subjects). The majority of subjects had prior acute GVHD (93 [70.5%] subjects): 42 (63.6%) subjects in Arm A and 51 (77.3%) subjects in Arm B. The median time to cGVHD diagnosis from the most recent transplant was 6.8 months. The median time from cGVHD diagnosis to study enrollment was 28.9 months: 25.2 months in Arm A and 30.2 months in Arm B. The overall median number of prior lines of systemic cGVHD therapy was 3.0 for Arm A and 4.0 for Arm B. Overall, 79 (72.5%) subjects with known status were refractory to the last systemic cGVHD treatment prior to enrollment in the study (stable disease or progressive disease): 45 (80.4%) subjects in Arm A and 34 (64.2%) subjects in Arm B. All subjects were taking a concomitant cGVHD medication, most frequently prednisone (128 [97.0%] subjects), tacrolimus (48 [36.4%] subjects), ECP (41 [31.1%] subjects), and sirolimus (36 [27.3%] subjects).

Efficacy

The primary efficacy endpoint, ORR, is presented in Table 3.

At the cutoff date, 6 months after the last subject first visit, the ORR with belumosudil was 73.5% (95% CI: 65.1%, 80.8%): 72.7% (95% CI: 60.4%, 83.0%) in Arm A and 74.2% (95% CI: 62.0%, 84.2%) in Arm B. Across both arms, 4 (3.0%) subjects achieved CR and 93 (70.5%) subjects achieved PR. Response rates between the 2 arms were not noticeably different.

Table 3. Primary Efficacy Endpoint Results from Study KD025-213

Response Rate	Arm A 200 mg QD N = 66	Arm B 200 mg BID N = 66	Overall N = 132
ORR (CR or PR) - n (%)	48 (72.7)	49 (74.2)	97 (73.5)
CR	3 (4.5)	1 (1.5)	4 (3.0)
PR	45 (68.2)	48 (72.7)	93 (70.5)
Exact method			
95% CI of ORR	(60.4, 83.0)	(62.0, 84.2)	(65.1, 80.8)

BID = twice daily; CI = confidence interval; CR = complete response; mITT = modified Intent-to-Treat; ORR = Overall Response Rate; PR = partial response; QD = once daily
Note: mITT Population
Note: 2-sided, exact CI was calculated using the Clopper-Pearson method.
Note: Results based on cutoff data date 19 February 2020.

Safety

The median duration of treatment in each arm was 6.7 months. Overall, 6.1% of subjects received > 12 months of belumosudil treatment. The median relative dose intensity (RDI) was 99.7%. Overall, 110 (83.3%) subjects had an RDI > 95%: 54 (81.8%) subjects in Arm A and 56 (84.8%) subjects in Arm B.

Safety results are presented in Table 4.

In total, 130 (98.5%) subjects experienced ≥ 1 TEAE: 65 (98.5%) subjects in Arm A and 65 (98.5%) subjects in Arm B. Thirty-five (26.5%) subjects experienced ≥ 1 TEAE that led to dose interruption: 19 (28.8%) subjects in Arm A and 16 (24.2%) subjects in Arm B. The most frequent TEAE that led to dose interruption by PT was pneumonia (7 [5.3%] subjects): 4 (6.1%) subjects in Arm A and 3 (4.5%) subjects in Arm B. Five (3.8%) subjects experienced ≥ 1 TEAE that led to dose reduction: 2 (3.0%) subjects in Arm A and 3 (4.5%) subjects in Arm B.

Five subjects experienced a SAE that led to treatment discontinuation: 4 subjects in Arm A (cellulitis; aspiration; septic shock; multiple organ dysfunction syndrome) and 1 subject in Arm B (sepsis and microangiopathic hemolytic anemia).

Five subjects died within 28 days of study treatment. Four subjects died in Arm A due to hemothorax; aspiration and respiratory failure; septic shock, multiple organ dysfunction syndrome; and recurrent acute myeloid leukemia. One subject died in Arm B due to cardiac arrest. The AE of multiple organ dysfunction syndrome was considered related to belumosudil. All other AEs that led to death were not considered related to belumosudil.

Table 4. Safety Results from Study KD025-213

Safety Outcomes	Arm A 200 mg QD N = 66 n (%)	Arm B 200 mg BID N = 66 n (%)	Overall N = 132 n (%)
Subjects with at least 1 TEAE	65 (98.5)	65 (98.5)	130 (98.5)
Subjects with TEAEs by maximum severity			
Grade 1: Mild	5 (7.6)	4 (6.1)	9 (6.8)
Grade 2: Moderate	25 (37.9)	31 (47.0)	56 (42.4)
Grade 3: Severe	29 (43.9)	26 (39.4)	55 (41.7)
Grade 4: Life-threatening	2 (3.0)	3 (4.5)	5 (3.8)
Grade 5: Fatal	4 (6.1)	1 (1.5)	5 (3.8)
TEAEs by PT occurring in > 20% subjects overall			
Fatigue	26 (39.4)	16 (24.2)	42 (31.8)
Diarrhea	20 (30.3)	18 (27.3)	38 (28.8)
Nausea	17 (25.8)	17 (25.8)	34 (25.8)
Cough	19 (28.8)	13 (19.7)	32 (24.2)
Dyspnea	20 (30.3)	11 (16.7)	31 (23.5)
Upper respiratory tract infection	14 (21.2)	16 (24.2)	30 (22.7)
Edema peripheral	17 (25.8)	11 (16.7)	28 (21.2)
Subjects with at least 1 study drug-related TEAE	47 (71.2)	36 (54.5)	83 (62.9)
Study drug-related TEAEs by PT occurring in > 10% of subjects overall			
Fatigue	14 (21.2)	11 (16.7)	25 (18.9)
Nausea	8 (12.1)	7 (10.6)	15 (11.4)
Subjects with at least 1 Grade ≥ 3 TEAE	35 (53.0)	30 (45.5)	65 (49.2)
Grade ≥ 3 TEAEs by PT occurring in ≥ 5% of subjects overall			
Pneumonia	5 (7.6)	5 (7.6)	10 (7.6)
Hypertension	3 (4.5)	4 (6.1)	7 (5.3)
Subjects with at least 1 study drug-related Grade ≥ 3 TEAE	11 (16.7)	9 (13.6)	20 (15.2)
Study drug-related Grade ≥3 TEAEs by PT occurring in > 1% of subjects overall			
Fatigue	0 (0)	2 (3.0)	2 (1.5)
GGT increased	2 (3.0)	0 (0)	2 (1.5)
Headache	0 (0)	2 (3.0)	2 (1.5)
Hypertension	0 (0)	2 (3.0)	2 (1.5)
Nausea	1 (1.5)	1 (1.5)	2 (1.5)
Subjects with at least 1 SAE	27 (40.9)	18 (27.3)	45 (34.1)
SAEs by PT occurring in > 2% subjects overall			
Pneumonia	6 (9.1)	4 (6.1)	10 (7.6)

Safety Outcomes	Arm A 200 mg QD N = 66 n (%)	Arm B 200 mg BID N = 66 n (%)	Overall N = 132 n (%)
Pyrexia	4 (6.1)	0 (0)	4 (3.0)
Dyspnea	1 (1.5)	2 (3.0)	3 (2.3)
Lung infection	1 (1.5)	2 (3.0)	3 (2.3)
Sepsis	2 (3.0)	1 (1.5)	3 (2.3)
Subjects with at least 1 study drug-related serious SAE	6 (9.1)	1 (1.5)	7 (5.3)
Subjects with TEAE leading to dose discontinuation	14 (21.2)	9 (13.6)	23 (17.4)
Subjects with study drug-related TEAE leading to dose discontinuation	8 (12.1)	5 (7.6)	13 (9.8)
Subjects with TEAE leading to death	4 (6.1)	1 (1.5)	5 (3.8)

BID = twice daily; cGVHD = graft versus host disease; GGT = gamma glutamyl transferase; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; QD = once daily; SAE = serious (treatment-emergent) adverse event; TEAE = treatment-emergent adverse event.
Notes:
1. Safety Population
2. MedDRA version 20.0.
3. Definitely related, probably related, and possibly related were all considered as related to belumosudil.
4. A subject with multiple events within a category was counted only once in that category.
5. A subject with multiple conditions within a PT was counted only once for that PT.
6. The results presented are based on the data cut-off date of 19 February 2020.

Conclusions

Belumosudil at 200 mg QD and 200 mg BID demonstrated clinically meaningful responses in a population of subjects with advanced, heavily pre-treated cGVHD. The ORR for the mITT Population was 73.5% (95% CI: 65.1, 80.8): 72.7% (95% CI: 60.4, 83.0) in Arm A (QD) and 74.2% (95% CI: 62.0, 84.2) in Arm B (BID). The point estimates and 95% CIs all exceeded 80.8%. Responses were durable. These findings were supported by subgroup analyses, and by secondary and exploratory endpoints. While the ORR was similar with both dose levels, there was a greater response with BID dosing in organs such as the skin and eye, and a trend towards a longer DOR with BID dosing. These results suggest a favorable benefit/risk profile for both dose levels.

1.5 Study Rationale

Study KD025-217 is an extension study of subjects enrolled and treated in Study KD025-208 and Study KD025-213.

Most subjects in both Study KD025-208 and Study KD025-213 were treated with belumosudil at 200 mg QD or 200 mg BID and had similar inclusion/exclusion criteria.

Study KD025-217 will be an extension study to assess the long-term safety and efficacy of these subjects treated with belumosudil, the bulk of whom were treated with 200 mg QD or 200 mg BID, but also some treated with 400 mg QD.

1.6 Summary of Known and Potential Risks and Benefits to Human Subjects

All possible side effects related to belumosudil are not known; the Belumosudil IB contains data on risks associated with this study drug.

Subjects may receive a clinical benefit from belumosudil while some subjects may progress.

This study is intended to assess the long-term clinical benefits and risks of belumosudil for the treatment of cGVHD.

2 STUDY OBJECTIVES

The objective of this study is to evaluate long-term safety and efficacy of belumosudil in subjects with cGVHD who have previously been treated with belumosudil in Study KD025-208 or Study KD025-213.

3 INVESTIGATIONAL PLAN

3.1 Study Design

This will be a Phase 2, open-label, extended treatment and follow-up study in subjects with cGVHD who have been previously treated with belumosudil in Study KD025-208 (see Section 1.4.1) or in Study KD025-213 (see Section 1.4.2).

Subjects will not be screened.

Subjects who have signed the ICF will be enrolled in Study KD025-217 if they have met any of the following conditions:

- Actively receiving belumosudil in Study KD025-208 or in Study KD025-213 (excluding adults in the Companion Study and excluding adolescents enrolled under KD025-213 Amendment 2 [01June 2020])
- Is in long-term follow-up (LFTU) on Study KD025-208 or Study KD025-213. Long-term follow-up will be defined as the period after ending treatment with belumosudil and until an FFS event occurs.
- Adult enrolled in the Companion Study as specified in Study KD025-213 Amendment 2 (01 June 2020) and received at least 6 months of treatment or is in LTFU

After signing the ICF, at Baseline, subjects will undergo efficacy assessments by Clinician-reported Global cGVHD Activity Assessment, response assessment, pulmonary function tests (PFTs), Lee Symptom Scale (LSS) score, and documentation of corticosteroid dosage and/or other therapies for cGVHD.

Subjects will undergo safety assessments including symptom-directed PE, vital signs, weight, height, KPS, hematology and clinical chemistry laboratory testing, pregnancy testing, 12lead ECG, documenting concomitant medications, and monitoring for AEs. Subjects will continue on their same dosing regimen they received in Study KD025-208 or Study KD025-213: belumosudil 200 mg QD, 200 mg BID, or 400 mg QD. If the Investigator reduced the subject's dose of belumosudil in either Study KD025-208 or Study KD025-213, the subject will continue to receive that same reduced dose treatment with belumosudil throughout Study KD025-217 or until the AE that led to the temporary dose reduction has resolved, in which case the dose treatment can resume at the original dose at the discretion of the Investigator. Subjects will be

given a study drug diary to record daily dosing. Subjects may be administered the first dose either in the clinic or self-administered at home.

At 3 months after Baseline and every 3 months thereafter (± 14 days), subjects will report to the clinic for the same efficacy and safety assessments and dispensing of belumosudil at Baseline. (Height is only required at Baseline.) The study drug diaries for the past 3 months will be collected, and new study drug diaries dispensed. Any remaining belumosudil will be collected.

Subjects may receive belumosudil on Study KD025-217 for up to an additional 2 years, at the discretion of the Investigator (and with guidance from the medical monitor), beyond what they had received in Study KD025-208 or Study KD025-213, cGVHD progression, or unacceptable toxicity.

Efficacy and safety endpoints are described in Section 6.3 and Section 6.4, respectively.

Subjects will return to the clinic for a 28-day Follow-up Visit at 28 days (± 7 days) after the last dose of study drug. Subjects will have LFTU approximately every 3 months until an FFS event occurs. After the 28-day Follow-up Visit has been completed, subjects will be contacted approximately every 3 months by telephone, e-mail, or postal mail to confirm survival status, any initiation of new systemic cGVHD therapies, and relapse of underlying disease. Alternatively, this information may be obtained from the subject's medical records. The Schedule of Assessments is presented in Appendix A: Schedule of Assessments.

3.2 Estimated Study Duration

Subjects may receive belumosudil for 2 years at the discretion of the Investigator and with guidance from the medical monitor.

Subjects will be treated with belumosudil until cGVHD progression or unacceptable toxicity.

Subjects will return to the clinic for a 28-day Follow-up Visit (± 7 days) after the last dose of study drug. Subjects will have long-term follow-up approximately every 3 months until an FFS event occurs. After the 28-day Follow-up Visit has been completed, subjects will be contacted approximately every 3 months by telephone, e-mail, or postal mail to confirm survival status, any initiation of new systemic cGVHD therapies, and relapse of underlying disease (see Section 3.1). Alternatively, this information may be obtained from the subject's medical records.

4 STUDY POPULATION

4.1 Number of Subjects

Approximately 70 subjects may be enrolled.

4.2 Study Centers

This study will be conducted at approximately 20 sites.

4.3 Inclusion Criteria

1. Subjects must have been treated with belumosudil for at least 1 of the following criteria:
    a. Actively receiving belumosudil on Study KD025-208 or on Study KD025-213 (excluding adults in the Companion Study and excluding adolescents enrolled under KD025-213 Amendment 2 [01 June 2020])
    b. Is in LTFU on Study KD025-208 or on KD025-213. Long-term Follow-up will be defined as the period after ending treatment with belumosudil and until an FFS event occurs.
    c. Adult enrolled in the Companion Study under KD025-213 Amendment 2 (01 June 2020) who has received at least 6 months of treatment of belumosudil or is in long-term follow-up
2. Female subjects of childbearing potential have a negative pregnancy test at enrollment. Females of childbearing potential are defined as sexually mature females without prior hysterectomy or who have had any evidence of menses in the past 12 months. However, females 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.
3. Sexually active females of childbearing potential enrolled in the study must agree to use 2 forms of accepted methods of contraception during the course of the study and for 3 months after their last dose of study drug. Effective birth control includes:
    a. Intrauterine device plus 1 barrier method
    b. Stable doses of hormonal contraception for at least 3 months (e.g., oral, injectable, implant, transdermal) plus 1 barrier method

c. 2 barrier methods. Effective barrier methods are male or female condoms, diaphragms, and spermicides (creams or gels that contain a chemical to kill sperm) or

d. A vasectomized partner

4. For male subjects who are sexually active and who are partners of females of childbearing potential: agreement to use 2 forms of contraception and to not donate sperm during the treatment period and for at least 3 months after the last dose of study drug.
5. Subject (or the subject's legally authorized representative) is able to provide written informed consent prior to the performance of any study-specific procedures.
6. It is in the best interest of the subject to participate in the study.

4.4 Exclusion Criteria

1. Female subject who is pregnant or breastfeeding
2. Subject considered unlikely to adhere to treatment and/or follow protocol in the opinion of the Investigator

4.5 Screening

No screening will be performed in this study. Subjects who meet the inclusion/exclusion criteria will be included once the ICF is signed.

4.6 Withdrawal Criteria

Subjects will receive belumosudil treatment until clinically significant progression of cGVHD (defined as progression requiring addition of new systemic therapy for cGVHD), histologic recurrence of underlying malignancy, unacceptable toxicity, Investigator decision, subject preference/withdrawal of consent, loss to follow-up, Sponsor decision, or death (whichever occurs first).

Subjects who experience cGVHD progression as defined by NIH criteria but for whom no new systemic therapy is planned may continue to receive belumosudil and be assessed again at their next visit. If progression per NIH criteria is not confirmed or no new systemic therapy is planned, subjects may continue on belumosudil at the Investigator's discretion until subjects fulfill at least 1 criterion requiring discontinuation of study drug.

Belumosudil may be tapered after a sustained response for 6 months and cessation of all other immunosuppressants for at least 3 months. The tapering schedule for belumosudil is described in Dosage and Administration 5.2.

Subjects may be withdrawn from study treatment at any time by the Investigator or the Sponsor if it is considered detrimental for the subject to continue in the study. The reason for withdrawal will 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. If the subject wishes to voluntarily withdraw from the study, the physician will consult with the subject regarding procedures for safe withdrawal. Every effort should be made to have such subjects attend protocol visits including the 28-day Follow-up Visit. Reasons for withdrawal of consent will be captured in the 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.

4.7 Replacements

No subjects will be replaced in this study.

4.8 Treatment Discontinuation

Reasons for discontinuation of treatment with belumosudil include:

- Clinically significant cGVHD progression requiring addition of systemic therapy
- Progression of underlying disease as defined by established disease specific criteria
- An AE that requires permanent discontinuation of study drug
- Investigator decision
- Voluntary discontinuation/withdrawal from study by subject (subject may remain eligible for follow-up)
- Noncompliance to protocol
- Subject lost to follow-up
- Termination of the study by Sponsor
- Subject death

5 STUDY TREATMENT

5.1 Investigational Product

Belumosudil (2-(3-(4-(1H-indazol-5-ylamino) quinazolin-2-yl) phenoxy)-N-isopropylacetamide-methane sulfonic acid salt), previously known as KD025, is an orally available ROCK2 selective inhibitor. Belumosudil will be provided as 200 mg tablets.

5.2 Dosage and Administration

Subjects will be treated with the same dosage of belumosudil as they were assigned in Study KD025-208 or Study KD025-213:

- Study KD025-208: belumosudil 200 mg QD, belumosudil 200 mg BID, or belumosudil 400 mg QD
- Study KD025-213: belumosudil 200 mg QD or belumosudil 200 mg BID

Belumosudil will be tapered after a sustained response for 6 months and cessation of all other immunosuppressants for at least 3 months. Tapering is also expected if subjects withdraw for reasons other than cGVHD progression or adverse events. The tapering schedule for belumosudil is as follows:

- 200 mg QD → 200 mg QOD for 1 month→ Discontinue
- 200 mg BID → 200 mg QD for 1 month →200 mg QOD for 1 month→ Discontinue
- 400 mg QD → 200 mg QD for 1 month →200 mg QOD for 1 month→ Discontinue

5.3 Treatment Assignment

Subjects will continue to receive the same dosage of belumosudil (200 mg QD, 200 mg BID, or 400 mg QD) as they were assigned in Study KD025-208 or Study KD025-213. If the Investigator reduced the dose of belumosudil in either Study KD025-208 or Study KD025-213, the subject will continue to receive that same reduced dose treatment with belumosudil through Study KD025-217 or until the AE that led to the temporary dose reduction has resolved, in which the dose treatment can resume at the original dose at the discretion of the Investigator.

5.4 Blinding

This will be an open-label study. No subjects will be blinded.

5.5 Treatment Compliance

Subjects will be given a study drug diary to record the details of each dose of study drug.

5.6 Missed Doses

Subjects should make every effort to take the study drug at the same scheduled time daily with their morning/evening meal or within 5 minutes of completing the meal. In the event that the subject misses the planned dose of study drug, the protocol below should be followed:

For subjects receiving study drug on a QD dosing schedule:

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

For subjects receiving study drug on a BID dosing schedule:

- If less than 6 hours of time have elapsed after the scheduled dose, the drug should be taken. The subject should then resume the regular planned dosing schedule.
- If more than 6 hours of time have elapsed after the scheduled dose, the dose should be skipped and the subject should resume dosing with the next the regular planned dose.

If the subject skips more than 7 consecutive days of drug, the subject should be discontinued from the study unless approved by the medical monitor and Investigator.

In the event of vomiting, the subject should report the AE and should not take additional doses of study drug to compensate.

5.7 Product Accountability

In accordance with regulatory requirements, study sites must document the amount of belumosudil received from and returned to the Sponsor, the amounts of belumosudil dispensed to study subjects, and the amount returned by study subjects. Product accountability records must be maintained throughout the course of the study.

5.8 Concomitant Medications and Procedures

All concomitant medications including dietary/herbal/over the counter supplements taken during the study and relevant procedures will be recorded. Initiation of new systemic cGVHD therapy will be considered a new line of treatment and a belumosudil treatment failure.

5.8.1 Corticosteroids

Corticosteroid dose data will be collected throughout the study. Corticosteroids may be tapered at the discretion of the Investigator.

Transient increases in corticosteroid dosing (not exceeding 1 mg/kg/day prednisone equivalent, see Appendix K: Prednisone Dose Equivalents) are permitted for the treatment of cGVHD flare, but the dose must be reduced within 6 weeks. If the dose remains elevated for more than 6 weeks, this will be considered a belumosudil treatment failure.

5.8.2 Systemic cGVHD Therapies

Subjects may be receiving the standard of care systemic cGVHD therapies such as CNIs (tacrolimus, cyclosporine), sirolimus, mycophenolate mofetil, methotrexate, rituximab, or ECP. Changes in doses of drugs to maintain therapeutic levels are not considered as a change in dose/schedule.

5.8.3 Topical / Organ Specific Therapies for cGVHD

Use of topical/organ specific therapies for cGVHD is permitted but must be documented.

5.8.4 CYP 3A4 Inducers

Use of strong CYP3A4 inducers decreases belumosudil exposure (Appendix H: Drugs that Induce CYP3A4).

5.8.5 Drugs Prolonging the QTc Interval

Drugs that prolong QT/QTc should be used with caution (Appendix J: Drugs That Prolong QTc).

5.8.6 Prohibited Concomitant Medications

Treatment with investigational systemic immunosuppressant drugs for cGVHD (including ruxolitinib) is prohibited.

5.9 Treatment of Overdose

Doses of belumosudil considered to represent an overdose have not been defined. In clinical studies of belumosudil in healthy volunteers, repeat dosing of 500 mg BID for 28 days was generally well-tolerated. There are no known antidotes to belumosudil; 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 (Section 7.2) regardless of whether there are any other associated AEs.

5.10 Dose Modification Guidelines

Any clinically significant toxicity will necessitate consideration of either a pause or cessation of therapy. Guidelines for management of treatment-emergent toxicities in subjects receiving belumosudil are outlined in Table 5. When dose reduction is necessary, the dose should be decreased as shown in Table 6.

Table 5. Guidelines for the Management of TEAEs with Belumosudil Treatment

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

ALT = alanine aminotransferase; AST = aspartate aminotransferase; eCRF = electronic case report form; LFT = liver function test; TEAE = treatment-emergent adverse event

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

Table 6. Belumosudil Dose Decrements

Belumosudil Dose	Dose Reduction
400 mg QD	200 mg QD
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 of belumosudil is tolerated for 1 month, the dose may be escalated to the previous dose.

6 STUDY ASSESSMENTS AND PROCEDURES

6.1 Schedule of Assessments

The efficacy and safety assessments for this study are presented in Appendix A: Schedule of Assessments.

6.2 Study Visits

6.2.1 Screening

This study will have no formal screening.

Subjects who meet all inclusion/exclusion criteria and sign the ICF will be enrolled in the study.

6.2.2 Baseline Visit

Subjects will be evaluated to determine if they meet all inclusion/exclusion criteria. Those signing the ICF will be enrolled in the study.

Note: If the subject was in LTFU in Study KD025-208 or in Study KD025-213, the subject will only have LTFU assessments performed once approximately every 3 months (Section 6.2.5).

Belumosudil will be administered as follows:

- Subject receives same dose of belumosudil as assigned in Study KD025-208 or in Study KD025-213, as appropriate. The first dose may be taken at home or in the clinic.
- Dispense a study drug diary to the subject

The following data will need to be captured from Study KD025-208 or Study KD025-213:

- The dosing group to which the subject was assigned or randomized
- Clinician-reported Global cGVHD Activity Assessment from Day 1
- Any ongoing AEs

The following efficacy assessments will be performed:

- Clinician-reported Global cGVHD Activity Assessment

- Response assessment. (Note: all responses will be assessed with respect to Cycle 1 Day 1 of Study KD025-208 or Study KD025-213.)
- PFT (for subjects with lung cGVHD or when lung cGVHD is suspected)
- LSS
- Use of corticosteroid dosage
- Use of other cGVHD therapies

The following safety assessments will be performed:

- Symptom-directed PE
- Vital signs
- Weight and height
- KPS
- Hematology lab testing
- Clinical chemistry lab testing
- 12-lead ECG
- Urine pregnancy test (any positive results will be confirmed with serum testing)
- Use of concomitant medications
- AEs

6.2.3 Month 3 Visit and Every 3 Month Visits Thereafter (± 14 days)

Three months (± 14 days) after Baseline, subjects will have the following procedures/assessments:

- Collection of any remaining belumosudil from subject
- Dispensing belumosudil medication at the same dose. Doses may be taken at home or in the clinic.
- Collection of study drug diary
- Dispensing new study drug diary
- Clinician-reported Global cGVHD Activity assessment

- Response assessment
- PFT*
- LSS
- Use of corticosteroid dosage
- Use of other cGVHD therapies
- Symptom-directed PE
- Vital signs
- Weight
- KPS
- Hematology lab testing
- Clinical chemistry lab testing
- 12-lead ECG
- Urine pregnancy test (any positive results will be confirmed with serum testing)
- Use of concomitant medications
- AEs

* When performing PFT, the same equipment and tester should be used during the course of the study when possible. The PFTs should be conducted in accordance with study guidelines and the American Thoracic Society/European Respiratory Society standardization of lung function testing.

6.2.4 28 Day Follow-Up Visit

This 28-day Follow-up Visit (± 7 days) will be 28 days after the last dose of belumosudil.

Subjects will have the following assessments and procedures:

- Collection of any remaining belumosudil from subject
- Collection of study drug diary
- Use of corticosteroid dosage
- Use of other cGVHD therapies

- Symptom-directed PE
- Vital signs
- Weight
- KPS
- Hematology lab testing
- Clinical chemistry lab testing
- 12-lead ECG
- Urine pregnancy test (any positive results will be confirmed with serum testing)
- Use of concomitant medications
- AEs

6.2.5 Long-term Follow-up

Long-term Follow-up will start at Baseline for enrolled subjects who have been permanently discontinued from belumosudil in Study KD025-208 or in Study KD025-213 where they have not yet had an FFS event. The LTFU will occur after the 28-day Follow-up Visit has been completed for enrolled subjects who were actively dosed with belumosudil at Baseline.

Subjects will have LTFU approximately every 3 months until an FFS event occurs. This LTFU assessment will occur by subjects being contacted by telephone, e-mail, or postal mail to confirm survival status, any initiation of new systemic cGVHD therapies, and relapse of underlying disease. Alternatively, this information may be obtained from the subject's medical records.

6.2.6 Unscheduled Visit

The assessments and procedures performed at any unscheduled visit will depend on the clinical judgment of the Investigator.

6.3 Efficacy Endpoints

The efficacy endpoints of this study will be:

- Duration of Response (DOR)
- Change in LSS (Appendix D: Lee cGVHD Symptom Score)

- Time to Next Treatment (TTNT): defined as the time from the first dose of belumosudil to the start of additional systemic cGVHD therapy
- FFS: defined as the absence of cGVHD treatment change, non-relapse mortality, and recurrent malignancy
- Overall Survival (OS): defined as the time from first dose of belumosudil to the date of death due to any cause
- Percentage of subjects who have a best response of CR and percentage of subjects who have a best response of PR
- Response by individual organ
- Change in corticosteroid dose: the change in prednisone equivalent dose of corticosteroids (mg/kg/day) during the study
- Change in cGVHD Global Severity Rating using the Clinician-reported Global cGVHD Activity Assessment (Appendix B: Clinician-reported Global cGVHD Activity Assessment)

6.4 Safety Endpoints

The follow-up safety endpoints of this study will be obtained at regular intervals and will include:

- AEs
- Grade ≥ 3 AEs
- SAEs
- Deaths
- PEs
- Vital signs
- Clinical laboratory evaluations
    - Hematologic: white blood cell count with differential, red blood cell count, hemoglobin, hematocrit, platelet count, and mean corpuscular volume
    - Serum chemistry: albumin, alkaline phosphatase, ALT, AST, blood urea nitrogen, Ca, Cl, CO_2, creatinine/glomerular filtration rate (Appendix F:

Equations to Predict Glomerular Filtration Rate (MDRD-4), creatinine phosphokinase, total and direct bilirubin, gamma glutamyl transferase, globulin, glucose, lactate dehydrogenase, Mg, P, K, Na, total protein, and uric acid

- Pregnancy testing: urine pregnancy tests will be done in females of childbearing potential. Positive urine results will be confirmed with serum testing. If pregnancy is confirmed with serum testing, belumosudil will be discontinued.

- ECGs

The AE reporting period for a subject enrolled in the study will begin when the subject signs the ICF and continues through the 28-day Follow-up Visit, i.e., 28 days after the last dose of belumosudil.

7 SAFETY

7.1 Safety Parameters

The Common Terminology Criteria for Adverse Events version 4.03 (CTCAE v4.03) will be used for classifying laboratory results and grading AEs. Subjects will be monitored throughout the treatment and follow-up period for occurrence of AEs (acute, delayed, and/or cumulative) as well as for changes in clinical status, vital sign measurements, and laboratory data. Safety parameters to be measured/assessed include vital sign measurements; PE; hematology and serum chemistry results; and ECG recordings.

7.2 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 product 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 the 28-day Follow-up Visit are to be recorded on eCRFs by the investigational site.

7.3 Evaluating Adverse Events

The Investigator will determine the seriousness, intensity, and causality of AEs based on the definitions that follow.

7.3.1 Serious Adverse Events

The Sponsor or designee must be notified within 24 hours.

The SAE definition and reporting requirements will be 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 (BA/BE).

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, not an AE in itself. The event(s) that caused death (e.g., illness, accident) is the SAE. Death due to any other cause(s) must also be reported as an outcome of the reportable SAE.
- Life-threatening AE: An AE or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization: The Investigator should not report hospitalization or prolongation of hospitalization in the following situations: (1) hospitalization or prolongation of hospitalization is needed for a procedure required by the protocol; (2) hospitalization or prolongation of hospitalization is part of routine procedure followed by study center; or (3) hospitalization for survey visits or annual physicals. Note: 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.

7.3.2 Protocol-Related Adverse Events

Adverse events 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, i.e., 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.

7.3.3 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; (Appendix G: Determining Relationship of AEs to Study Drug).

7.3.4 Recording Adverse Events

All AEs and 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 v4.03 scale. The date of onset as well as the end date of the event also should be recorded or the event should be entered as "ongoing". In addition, the method used to treat the AE and the outcome of the AE also will be noted. In the event that the grade of an AE worsens, an end date should be entered to the initial AE and a new AE entered with the updated grade and date of onset. The Investigator will assess the relationship of the event to study drug.

Note: All SAEs also are to be entered onto an SAE form and sent to the Sponsor or designee within 24 hours.

7.3.5 Serious Adverse Event Reporting

7.3.5.1 Timeframe for Reporting

Any death, SAE, or 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, including follow-up information, or any SAE 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).

SAE Form or Pregnancy Form (initial report or follow-up report) must be sent within 24 hours of becoming aware to: clinicalSAEreporting@Kadmon.com.

Additionally, the Investigator will be able to contact the medical monitor at all times. Refer to sponsor and CRO contact list for up to date contact information.

7.3.5.2 SAE 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 the 28-day Follow-up Visit at 28 days after last dose of study drug. In addition, any SAEs that are assessed as at least 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 Pharmacovigilance (or designee) as described below:

Report SAEs on an SAE form within 24 hours of becoming aware to:

clinicalSAEreporting@Kadmon.com.

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

A.Woolfrey@medpace.com.

The minimum information required for SAE reporting includes identity of Investigator, site number, subject number, an event description, SAE term(s), onset date, 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.

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

- When the diagnosis of an SAE is known or suspected, the Investigator should report the diagnosis or syndrome as the primary SAE term, rather than as signs or symptoms. Signs and symptoms may then be described in the event description. For example, dyspnea should not be used as an SAE term if the diagnosis which caused the dyspnea is known to be malignant pleural effusion.
- Death should not be reported as an SAE but as an outcome of a specific SAE, unless the event preceding the death is unknown. In the exceptional case where the events leading

to death are unknown, then death may be used as an event term. If an autopsy was performed, the autopsy report should be provided.

While most hospitalizations necessitate reporting an SAE, some hospitalizations do not require SAE reporting: (1) elective or previously scheduled surgery (e.g., a previously scheduled ventral hernia repair); (2) procedures for pre-existing conditions that have not worsened after initiation of treatment; (3) pre-specified study hospitalizations for observation; and (4) events that result in emergency room stays of less than 24 hours and that do not require admission.

However, SAEs must be reported for any surgical or procedural complication resulting in prolongation of the hospitalization.

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 as a follow-up in the same timeframe and manner as the initial SAE report. Furthermore, the Investigator may be required to provide supplementary information as requested by the Kadmon Pharmacovigilance or designee.

Report follow-up SAE information within 24 hours of becoming aware to:

clinicalSAEreporting@Kadmon.com.

7.3.5.3 Pregnancy

Pregnancies occurring in subjects enrolled in a study or in a female partner of a male study participant must be reported and followed to outcome. If a female subject inadvertently becomes pregnant while on study treatment, the subject will immediately be removed from the study. Any pregnancies of female study subjects and partners of male study subject that occur within 120 days following the last dose of study treatment must be captured in the eCRF.

The Investigator should complete the initial Pregnancy Report Form and forward it to the Sponsor (or designee) within 24 hours of becoming aware of the pregnancy as described in Section 7.3.5.1 of the protocol. If there is an associated serious outcome, then both the initial Pregnancy Report Form and SAE Report Form should be completed.

The site will follow-up with the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The Investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. The Pregnancy Report Form should be updated and submitted to the

Sponsor within 24 hours of becoming aware of the pregnancy outcome. If an SAE occurred, then the SAE Report Form must be completed and submitted as well.

In the event the pregnancy outcome occurs following the end of the study and database lock, the Investigator will report the pregnancy outcome to the Sponsor (or designee) within 24 hours after the outcome of the pregnancy is known to the Investigator in accordance with the procedure for reporting SAEs (Section 7.3.5.1).

Pregnancy alone is not regarded as an AE unless there is a possibility that the study drug may have interfered with the effectiveness of a contraceptive medication. Elective abortions without complications should not be considered AEs unless they were therapeutic abortions but should be reported to the Sponsor. Hospitalization for normal delivery of a healthy newborn should not be considered an SAE. Pregnancy is not considered an SAE unless there is an associated serious outcome. Spontaneous abortions should always be reported as SAEs.

Any SAE that occurs during pregnancy must be recorded on the SAE Report Form (e.g., maternal serious complications, therapeutic abortion, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, birth defect) and reported within 24 hours in accordance with the procedure for reporting SAEs.

The Pregnancy Report Form and any related SAE Report Forms must be reported to the Sponsor as outlined for SAEs in Section 7.3.5.2.

7.3.5.4 Regulatory Reporting

Kadmon Pharmacovigilance (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.

7.4 Other Safety Considerations

7.4.1 Laboratory Data

All laboratory data obtained during the course of the study should be reviewed. Any abnormal value that leads to a change in subject management (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 v4.03.

7.4.2 Follow-Up of Adverse Events

All SAEs and TEAEs (including clinically significant abnormal laboratory values that meet these criteria) will be followed until either resolution of the event or determination by the Investigator that the event has become stable or irreversible. The status of all other continuing AEs will be documented as of 28 days after last dose of study drug.

8 STUDY STOPPING RULES

There are no stopping rules for this study.

9 STATISTICAL CONSIDERATIONS

9.1 Hypothesis

This will be a long-term follow-up study of the efficacy and safety of subjects treated with belumosudil in Study KD025-208 and Study KD025-213. No formal hypothesis will be used.

9.2 Sample Size and Power Calculation

No formal power calculation will be performed to determine the study sample size.

9.3 Analysis Populations

The populations for efficacy and safety analyses will be the Full Analysis Set consisting of all subjects enrolled in the study.

There are 3 treatment groups for this study: belumosudil 200 mg QD, 200 mg BID, and 400 mg QD. Each subject's treatment group is determined by their originally assigned dosing cohort (Study KD025-208) or randomized arm (Study KD025-213).

9.4 Subgroup Analyses

No subgroup analysis will be conducted.

9.5 Data Analysis

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

9.6 Interim Analysis

An interim analysis will be performed when all subjects have completed at least 3 years of treatment with belumosudil or withdrew earlier (not inclusive of the companion study subjects).

9.7 Efficacy Analyses

The follow-up efficacy endpoints in this study are described in Section 6.3.

9.8 Exploratory Analyses

No exploratory analyses will be conducted.

9.9 Safety Analyses

Safety analyses will be performed on all subjects who receive at least one dose of belumosudil.

Adverse events will be coded using the Medical Dictionary of Regulatory Activities (MedDRA) (Version 24.0 or greater). The number and percentages of subjects experiencing TEAEs will be tabulated by System Organ Class and Preferred Term (PT). The number of events by PT will also be summarized. Tabulation by maximum severity and relationship to treatment will also be included by treatment group.

Summary subject listing will be provided for SAEs, AEs resulting in study discontinuation, and deaths.

Adverse events, SAEs, related AEs, related SAEs, Grade ≥ 3 AEs, related Grade ≥ 3 AEs, and AEs leading to withdrawal and treatment discontinuation, and deaths will be summarized.

Laboratory results will be summarized by treatment group, incidence of laboratory abnormalities, and worst on-study grade during the treatment period will be summarized. The incidence of Grade ≥ 3 laboratory abnormalities under treatment and shifts in toxicity grading from Baseline to highest grade post-baseline will be displayed.

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

9.10 Pharmacokinetic Analyses

No PK assessments for analysis will be performed in this study.

9.11 Pharmacodynamic Analyses

No pharmacodynamic assessments for analysis will be performed in this study.

10 DATA QUALITY ASSURANCE

Accurate and reliable data collection will be ensured by verification and cross-checking 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.

11 REGULATORY OBLIGATIONS & COMPLIANCE STATEMENT

This study will be conducted in compliance with GCP, including International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, and in general, consistent with the most recent version of the Declaration of Helsinki. In addition, the Investigator will agree to adhere to all applicable local laws and regulatory requirements relevant to the use of new therapeutic agents in the countries involved.

The study will be conducted in compliance with the protocol.

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).

12 ETHICAL ASPECTS

12.1 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", or applicable local equivalent.

12.2 Informed Consent

Sample ICFs will be supplied to each site.

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 applicable federal and state regulations. In the case where the subject is unable to read, an impartial witness should be present during the entire informed consent discussion. After the subject has orally consented to participation in the trial, the witness' signature on the form will attest that the information in the consent form was accurately explained and understood. A copy of the ICF must be provided to the subject or to the subject's legally authorized representative. If applicable, it will be provided in a certified translation of the local language.

The eCRF for this study contains a section for documenting informed subject consent, and this must be completed appropriately. Signed ICFs must remain in each subject's study file and be available for verification by study monitors at any time. If new safety information results in changes in the risk/benefit assessment, the ICF 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.

12.3 Research Ethics Committees

Prior to the initiation of the study, the protocol and associated documentation must be given a favorable opinion and/or approval by an Ethic Committee and/or an Institutional Review Board. A copy of this written approval and any correspondence with the EC/IRB will be provided to the Sponsor.

12.4 Future Use of Subject Samples

All of the blood components obtained during this study may be required for the tests that are part of the clinical trial.

13 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).

14 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.

15 STUDY DOCUMENTATION, CRFS, AND RECORD KEEPING

15.1 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: Investigator's Study Files and 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, 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 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 is 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.

15.2 Source Documents and Background Data

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

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

15.3 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.

15.4 Electronic Case Report Forms

Clinical trial data for this study will be captured on eCRFs. The Investigator will agree 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 provides informed consent. 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.

16 MONITORING OF THE STUDY

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

It will be the study 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 study 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.

17 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.

18 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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Appendix A: Schedule of Assessments

Table 7. Schedule of Assessments

Assessment	Treatment Period		Follow-Up Period
Assessment	**Baseline[a]**	**Month 3 and Every 3 Months Thereafter**	**28-day Follow-up Visit (28 Days from Last Dose)**
Window		**± 14 days**	**± 7 days**
Evaluate I/E Criteria	X		
Sign ICF	X		
Study KD025-208 or Study KD025-213 History[b]	X		
EFFICACY ASSESSMENTS			
Clinician-reported Global cGVHD Activity Assessment	X	X	
Response Assessment	X	X	
PFT[c]	X	X	
LSS	X	X	
Document Corticosteroid Dosage	Data to be collected from the date the ICF is signed until 28 days after the last dose of study drug		
Document Other cGVHD Therapies	Data to be collected from the date the ICF is signed until 28 days after the last dose of study drug		
SAFETY ASSESSMENTS			
Symptom-directed PE	X	X	X
Vital Signs[d]	X	X	X
Weight	X	X	X
Height	X		
KPS	X	X	X
Hematology	X	X	X
Clinical Chemistry	X	X	X
12-lead ECG	X	X	X
Pregnancy Test (Urine)[e]	X	X	X
Concomitant Medications and Procedures	Data to be collected from the date the ICF is signed until 28 days after the last dose of study drug		
AEs	AEs to be collected from the date the ICF is signed until 28 days after the last dose of study drug		
BELUMOSUDIL			
Study Drug Administration[f]	X	X	
Dispense Study Drug Diary	X	X	
Collect Study Drug Diary		X	X

AE = adverse event; BID = twice daily; cGVHD = chronic graft-versus-host disease; DL_{CO} = diffuse capacity of carbon monoxide; ECG = electrocardiograph; FEV1 = forced expiratory volume in 1 second; FVC = forced vital capacity; Hb = hemoglobin; ICF = informed consent form; I/E = inclusion/exclusion criteria; KPS = Karnofsky Performance Status; LSS = Lee Symptom Scale score; LTFU = long-term follow-up; PE = physical examination; PFT = pulmonary function test; QD = once daily; RV = residual volume; TLC = total lung capacity

a. Evaluation of inclusion/exclusion criteria and signing of ICF do not necessarily have to occur on the same day as efficacy and safety assessments. However, the ICF must be signed before any study procedures begin.

b. At Baseline, the following assessments need to be documented from the KD025-208 or KD025-213 studies: dosing group to which the subject was assigned or randomized, Clinician-reported Global cGVHD Activity Assessment from Cycle 1 Day 1, and ongoing AEs.

c. Pulmonary function tests are to be conducted for subjects with lung cGVHD or when cGVHD is suspected and include: FEV1, FVC, DL_{CO} (corrected for Hb), RV, and TLC.

d. Vital sign measurements include sitting blood pressure and heart rate (after 5 minutes of rest); respiratory rate; and temperature.
e. Females of childbearing potential must have a negative urine pregnancy test. Positive results are to be confirmed with serum testing.
f. Subjects will receive the same dose of belumosudil as they were assigned and received during Study KD025-208 or Study KD025-213 (i.e., belumosudil 200 mg QD, 200 mg BID, or 400 mg QD). First dose may be taken at home or in the clinic.

Note: Following the 28-day Follow-up Visit, subjects will have LTFU by being contacted by telephone, e-mail, or postal mail to confirm survival status, any initiation of new systemic cGVHD therapies, and relapse of underlying disease. If the subject was in LTFU in Study KD025-208 or in Study KD025-213, the subject will only have LTFU assessments performed once approximately every 3 months (Section 6.2.5).

Note: At Unscheduled Visit, subject should not receive have any remaining belumosudil collected, or have study diaries dispensed or collected unless treatment is stopped.

Note: The assessments and procedures performed at any unscheduled visit depend on the clinical judgment of the Investigator.

Appendix B: Clinician-reported Global cGVHD Activity Assessment

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
ESOPHAGUS	No esophageal symptoms	Occasional dysphagia or odynophagia with solid food or pills during the past week	Intermittent dysphagia or odynophagia with solid foods or pills, but not for liquids or soft foods, during the past week	Dysphagia or odynophagia for almost all oral intake, on almost every day of the past week
	☐	☐	☐	☐
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				
☐ *Abnormality thought to represent GVHD PLUS other causes (specify):*				

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
UPPER GI	No symptoms	Mild, occasional symptoms, with little reduction in oral intake during the past week	Moderate, intermittent symptoms, with some reduction in oral intake during the past week	More severe or persistent symptoms throughout the day, with marked reduction in oral intake, on almost every day of the past week
	☐	☐	☐	☐
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				
☐ *Abnormality thought to represent GVHD PLUS other causes (specify):*				

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
LOWER GI	No loose or liquid stools during the past week	Occasional loose or liquid stools, on some days during the past week	Intermittent loose or liquid stools throughout the day, on almost every day of the past week, **without requiring** intervention to prevent or correct volume depletion	Voluminous diarrhea a on almost every day of the past week, **requiring** intervention to prevent or correct volume depletion
	☐	☐	☐	☐
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				
☐ *Abnormality thought to represent GVHD PLUS other causes (specify):*				

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
LUNGS	No symptoms	Mild symptoms (shortness of breath after climbing one flight of steps)	Moderate symptoms (shortness of breath after walking on flat ground)	Severe symptoms (shortness of breath at rest; requiring O_2)
	☐	☐	☐	☐
	Spirometry **Not done** ☐	**FEV_1 (% Predicted):** _____	**FEV_1 (L):** _____	**FVC (% Predicted):** _____	**FVC (L):** _____
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				
☐ *Abnormality thought to represent GVHD PLUS other causes (specify):*				

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
EYES	No symptoms	Mild dry eye symptoms not affecting ADL (requirement of lubricant eye drops ≤ 3 x per day)	Moderate dry eye symptoms partially affecting ADL (requiring lubricant eye drops > 3 x per day or punctal plugs). **WITHOUT** new vision impairment due to KCS	Severe dry eye symptoms significantly affecting ADL (special eyewear to relieve pain) **OR** unable to work because of ocular symptoms **OR** loss of vision due to KCS
	☐	☐	☐	☐

☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*

☐ *Abnormality thought to represent GVHD PLUS other causes (specify):*

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
JOINTS AND FASCIA	No symptoms	Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) AND not affecting ADL	Tightness of arms or legs OR joint contractures, erythema thought due to fasciitis, moderate decrease ROM AND mild to moderate limitation of ADL	Contractures WITH significant decrease of ROM AND significant limitation of ADL (unable to tie shoes, button shirts, dress self etc.)
	☐	☐	☐	☐

☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*

☐ *Abnormality thought to represent GVHD PLUS other causes (specify):*

P-ROM Score

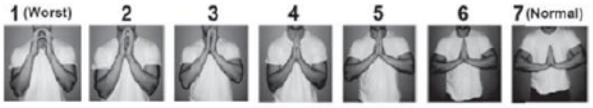
Shoulder

Score _____
Not done ☐

Elbow

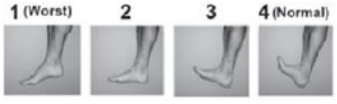
Score _____
Not done ☐

Wrist/finger



Score _____
Not done ☐

Ankle



Score _____
Not done ☐

☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*

☐ *Abnormality thought to represent GVHD PLUS other causes (specify):*

	SCORE 0 No BSA involved	SCORE 1 1-18% BSA	SCORE 2 19-50% BSA	SCORE 3 > 50% BSA
SKIN	☐	☐	☐	☐

☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*

☐ *Abnormality thought to represent GVHD PLUS other causes (specify):*

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
SKIN FEATURES SCORE	No sclerotic features		Superficial sclerotic features "not hidebound" (able to pinch)	**Check all that apply:** ☐ Deep sclerotic features ☐ "Hidebound" (unable to pinch) ☐ Impaired mobility ☐ Ulceration
	☐		☐	☐

If skin features score = 3, BSA% of non-moveable sclerosis/fasciitis: _____

Other skin GVHD features (scored by BSA)
Check all that apply:

☐ Maculopapular rash / erythema	☐ Sclerotic features	☐ Keratosis pilaris-like
☐ Lichen planus-like features	☐ Papulosquamous lesions or ichthyosis	

How would you rate the severity of this patient's skin and/or joint tightening on the following scale, where 0 is not at all severe and 10 is the most severe symptoms possible:

0	1	2	3	4	5	6	7	8	9	10
Symptoms not at all severe										Most severe symptoms possible

MOUTH

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

☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*

☐ *Abnormality thought to represent GVHD PLUS other causes (specify):*

LIVER Central Labs	Total serum bilirubin (mg/dL):	ALT (U/L)	ALP (U/L)
	_____	_____	_____

☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*

☐ *Abnormality thought to represent GVHD PLUS other causes (specify):*

GLOBAL SEVERITY RATING

Where would you rate the severity of this patient's chronic GvHD symptoms on the following scale, where 0 is cGVHD symptoms that are not at all severe and 10 is the most severe cGVHD symptoms possible:

0	1	2	3	4	5	6	7	8	9	10
cGvHD symptoms not at all severe										Most severe cGvHD symptoms possible

Sources: Lee et al. 2015[25] and Jagasia et al. 2015[26]

Appendix C: cGVHD Response Assessment

Response Determination for Chronic GVHD Clinical Trials based on Clinician Assessments

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

ULN indicates upper limit of normal.

Source: Lee et al. 2015[25]

Appendix D: Lee cGVHD Symptom Score

By circling one number per line, please indicate how much you have been bothered by the following problems in the past 7 days: (Lee et al. 2002[27])

Skin		Not at all	Slightly	Moderately	Quite a bit	Extremely
1.	Abnormal skin color	0	1	2	3	4
2.	Rashes	0	1	2	3	4
3.	Thickened skin	0	1	2	3	4
4.	Sores on skin	0	1	2	3	4
5.	Itchy skin	0	1	2	3	4
Eyes and Mouth		**Not at all**	**Slightly**	**Moderately**	**Quite a bit**	**Extremely**
6.	Dry eyes	0	1	2	3	4
7.	Need to use eye drops frequently	0	1	2	3	4
8.	Difficulty seeing clearly	0	1	2	3	4
9.	Need to avoid certain foods due to mouth pain	0	1	2	3	4
10.	Ulcers in mouth	0	1	2	3	4
11.	Receiving nutrition from and intravenous line or feeding tube	0	1	2	3	4
Breathing		**Not at all**	**Slightly**	**Moderately**	**Quite a bit**	**Extremely**
12.	Frequent cough	0	1	2	3	4
13.	Colored sputum	0	1	2	3	4
14.	Shortness of breath with exercise	0	1	2	3	4
15.	Shortness of breath at rest	0	1	2	3	4
16.	Need to use oxygen	0	1	2	3	4
Eating and Digestion		**Not at all**	**Slightly**	**Moderately**	**Quite a bit**	**Extremely**
17.	Difficulty swallowing solid foods	0	1	2	3	4
18.	Difficulty swallowing liquids	0	1	2	3	4
19.	Vomiting	0	1	2	3	4
20.	Weight loss	0	1	2	3	4
Muscles and Joints		**Not at all**	**Slightly**	**Moderately**	**Quite a bit**	**Extremely**
21.	Joint and muscle aches	0	1	2	3	4
22.	Limited joint movement	0	1	2	3	4
23.	Muscle cramps	0	1	2	3	4
24.	Weak muscled	0	1	2	3	4
Energy		**Not at all**	**Slightly**	**Moderately**	**Quite a bit**	**Extremely**
25.	Loss of energy	0	1	2	3	4
26.	Need to sleep more/take naps	0	1	2	3	4
27.	Fevers	0	1	2	3	4
Mental and Emotional		**Not at all**	**Slightly**	**Moderately**	**Quite a bit**	**Extremely**
28.	Depression	0	1	2	3	4
29.	Anxiety	0	1	2	3	4
30.	Difficulty sleeping	0	1	2	3	4

Appendix E: Karnofsky Performance Scale

Score	Description
100	Normal, no complaints, no evidence of disease
90	Able to carry on normal activity
80	Normal activity with effort
70	Cares for self; unable to carry on normal activity or to do active work
60	Requires occasional assistance but is able to care for most needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization indicated; death not imminent
20	Very sick; hospitalization indicated; death not imminent
10	Moribund; fatal processes progressing rapidly

Scores 80 to 100: able to carry on normal activity; no special care is needed
Scores 50 to 70: unable to work; able to live at home and care for most personal needs; a varying degree of assistance needed
Scores 10 to 40: unable to care for self; requires equivalent of institutional or hospice care; disease may be progressing rapidly
Source: Karnofsky et al. 1949[28]

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

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

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

Levey et al. 2006[29]

Appendix G: Determining Relationship of AEs to Study Drug

1 NOT RELATED

This category applies to those AEs which, after careful medical consideration, are clearly felt to be due to extraneous causes (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.

Source: Adapted from Cobert B 2012[30]

Appendix H: Drugs that Induce CYP3A4

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

Table 8. Examples of Clinical Inducers of CYP3A4

Strong Inducer	Moderate Inducer	Weak Inducer
Apalutamide	Bosentan	Armodafinil
Carbamazepine	Efavirenz	Modafinil
Enzalutamide	Etravirine	Rufinamide
Mitotane	Phenobarbital	
Phenytoin	Primidone	
Rifampin		
St. John's wort		

Source: FDA. Drug Development and Drug Interactions.
https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm
Accessed 25 Jun 2021[31]

Appendix I: Drugs That Induce and Inhibit CYP1A2

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

Table 9. Examples of Clinical Inducers/Inhibitors of CYP1A2

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

Source: FDA. Drug Development and Drug Interactions.
https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm
Accessed 25 Jun 2021[31]

Appendix J: Drugs That Prolong QTc

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

Table 10. Examples of Drugs that Prolong QTc

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

Source: https://crediblemeds.org/pdftemp/pdf/CombinedList.pdf Accessed 11 May 2020[32]

Appendix K: Prednisone Dose Equivalents

Change in corticosteroid doses will be analyzed by using prednisone dose equivalents. If subjects are not using prednisone as the systemic corticosteroid, then the prednisone dose equivalent will be determined according to following conversion ratios.

One mg of prednisone is equivalent to:

- 4.0 mg hydrocortisone
- 0.8 mg Methylprednisolone
- 0.15 mg Dexamethasone
- 1.0 mg Prednisolone
- 0.8 mg Triamcinolone

Source: Liu D et al. 2013[33]