AMENDED CLINICAL TRIAL PROTOCOL 05

A Phase 2, Randomized, Multicenter Study to Evaluate the Efficacy and Safety of KD025 in Subjects with Chronic Graft Versus Host Disease (cGVHD) After At Least 2 Prior Lines of Systemic Therapy (The ROCKstar Study)

Protocol Number:	KD025-213 (DRI17633)
Study Drug:	KD025 (SAR445761)
INN:	Belumosudil
IND Number:	IND 125890
NCT Number:	NCT03640481
Phase:	2
Sponsor:	Kadmon Corporation, LLC 55 Corporate Drive Bridgewater, NJ 008807
Steering Committee:	
Chair	[redacted], [redacted]
Co-chair	[redacted], [redacted]

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Amended Clinical Trial Protocol 05	United States	14 March 2023, version 1 (electronic 6.0)
Clinical Study Protocol, Amendment 4	United States	11 April 2022
Clinical Study Protocol, Amendment 3	United States	30 August 2021
Clinical Study Protocol, Amendment 2	United States	01 June 2020
Clinical Study Protocol, Amendment 1	United States	26 June 2019
Clinical Study Protocol (Original)	United States	25 June 2018

a The name and numbering of the protocol is based on a new numbering system followed by the Sponsor

AMENDED PROTOCOL 05 (14 March 2023)

This amended protocol (amendment 05) is considered to be substantial.

OVERALL RATIONALE FOR THE AMENDMENT

The purpose of this amendment includes revising the eligibility criterion of AST/ALT increase, adjusting the frequency of clinical visits with the aim of reducing patient burden and updating the safety and contraception sections as per Sanofi standards. Other changes include clarifications or corrections of protocol inconsistencies.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Cover page	Modified logo, protocol information (ie, “CLINICAL TRIAL PROTOCOL” modified to “AMENDED CLINICAL TRIAL PROTOCOL 05”), protocol number, study drug, sponsor address, and document history text. Added INN.	Updated per Sanofi standards
Procedures in Case of Emergency	Removed contact information of Medpace medical monitor and modified SAE reporting contact information.	Updated per Sanofi standards

Section # and Name	Description of Change	Brief Rationale
Throughout the document	Modified header and footer	Updated per Sanofi standards
	Replaced “subject” and “patient” to “participant” as necessary	Updated per Sanofi standards
	Modified text on 12-lead ECG throughout the document, as applicable, such that it details that it is a “single” 12-lead ECG, and such that text on triplicate measurements are removed, and that from Cycle 19, ECG is only done if clinically indicated	Update
	Replaced “Kadmon” or “Kadmon Corporation” with “Sponsor”	Updated per Sanofi standards
	Added “assent” or “assent form” to be associated with informed consent or informed consent form wherever relevant	Updated per Sanofi standards
Sponsor Approval Signature Page	Removed entirely	Updated per Sanofi standards
Investigator Signature Page	Removed entirely	Updated per Sanofi standards
Synopsis	Modified text, including that ibrutinib is indicated for pediatric patients aged 1 year and older and added text on ruxolitinib and its indication for cGVHD.	Modified text to provide updated information on FDA approved drugs for treatment of cGVHD
	Modified text as follow: “20 adults into a site-specific Companion Study to collect biospecimens (~~Appendix O~~Section 21.13 Appendix M), these participants will ~~also~~ be randomized (1:1) to Arm A or Arm B”	Updated study design
Synopsis, 2.1 Primary objectives	Safety of belumosudil was changed from a primary objective to a secondary objective and sections were updated accordingly	Clarification to be aligned with the study endpoints
Synopsis, 3.1 Study design	Removed “Subjects who have not achieved a response after 12 cycles of belumosudil should be withdrawn if in the Investigator’s judgment there is no evidence of clinical benefit.” Also removed “(Section 4.7)” from section 3.1.	Clarification to be aligned with the United States Prescription Information (USPI)
	Schema was updated	Updated schema to reflect update made in the study design
Synopsis, 3.1 Study design, 5.2 Dosage and Administration	Text was updated with a modified version of removed Appendix N text	Clarification
Synopsis, 1.5 Study rationale, 3.1 Study design, 4.1 Number of participants, 5.2 Dosage and administration, 5.3 Treatment assignment, 22.1 Appendix A: Schedule of assessments, Appendix N	Removed appendix N (ie, Adolescent Cohort Addendum) and subsequent appendices were renumbered accordingly. Text referring to appendix N was removed throughout the document.	Removed to complement update in the study design, which took part of appendix N text in this update
Synopsis, 4.3 Inclusion criteria, 4.4 Exclusion criteria	Replaced inclusion criteria #3 with modified version of exclusion criteria #1 (ie, removed “not”). Added to exclusion criteria #1 “E01 is no longer applicable per amended protocol 05”	Updated inclusion and exclusion criteria as current standard of care may not include steroid therapy, which has been identified as a barrier to enrollment

Section # and Name	Description of Change	Brief Rationale
Synopsis, 4.3 Inclusion criteria	Added "(≤5 × ULN if due to cGVHD)" to inclusion criteria #8	Clarification
	For inclusion criteria 11-13, added a statement that they are no longer applicable per amended protocol 05 and added entire subsection on "Sex, contraceptive/barrier method and pregnancy testing requirements/breastfeeding"	Updated per Sanofi standards
Synopsis, 4.4 Exclusion criteria	Removed the following subheading "General Criteria"	Removed since this subheading is not necessary
Synopsis	Updated text on safety variables (ie, removed PEs and modified text on AE reporting period)	Physical exam was removed since it is not mandatory and updated text to improve clarity of language
Synopsis, 3.1 Study design	Updated text such that sparse PK sample is to be performed for the whole population, including the adolescent participants	Update
1.4 Belumosudil Background (Clinical)	Modified text to highlight that Phase 2 studies of belumosudil are now either ongoing or completed. Removed study numbers, added diffuse cutaneous systemic sclerosis, and updated the number of study participants from 300 to 750.	Updated text to align with the stage of, and the information based on, completed and ongoing belumosudil studies. Removed study numbers to improve clarity.
	Removed "Data from the KD025 208 study in subjects with cGVHD are summarized in Section 1.4.1."	Removed since extensive study details were removed from Section 1.4.1 per Sanofi standards
1.4.1 KD025-208	Replaced "an ongoing" with "a completed"	Updated text to align with the stage of KD025-208 study, which has been completed
	Replaced "Data from this ongoing study, with a data cut-off date of 19-Feb-2020, are presented below. This data was reported out in a Clinical Study Report (dated 07-Jul-2020)." with "Refer to the belumosudil IB for more detailed information."	Updated per Sanofi standards and removed extensive study details from the protocol
1.4.1.1 Demographics and Baseline Characteristics, 1.4.1.2 Subject Disposition, 1.4.1.3 Efficacy, 1.4.1.4 Safety	Removed entire sections	Removed extensive study details from the protocol per Sanofi standards
1.6 Summary of Known and Potential Risks and Benefits to Human Participants	Added text that details marketing authorization of belumosudil in Australia, Canada, and UK.	Update
2.1 Primary objectives	Removed "and safety"	Clarification to be aligned with the study endpoints
3.1 Study design	Added: "Following Protocol Amendment 5, in adolescent participants still to be enrolled, response criteria will be assessed after Cycles 1, 2, 4, and 6 and then after every third cycle (Day 1 of cycles 2, 3, 5, 7, 10, 13, etc.)."	Update

Section # and Name	Description of Change	Brief Rationale
4.7 Withdrawal Criteria	Added ", at the Investigator's discretion"	Update
	Removed "In addition, subjects should be withdrawn from the study if there has been no response after 12 cycles of treatment, if in the judgement of the Investigator there has been no clinical benefit for the subject, eg, in terms of organ score improvements, improvements in Lee symptom scores or reductions of corticosteroid / tacrolimus doses."	Update
4.8.1 Treatment Discontinuation	Added "pregnancy"	Correction
	Added "In case a participant wants to permanently discontinue the treatment (ie, withdrawal of consent for the intervention), the participant will be asked if a final assessment is possible to be performed using the procedure normally planned for the last dosing day (EOT and at 28-day follow up visit) with the IMP prior to consent of the withdrawal. See the SoA (Section 6.1) for the data to be collected at the time of the study treatment discontinuation, for information on the follow-up, and for any further evaluations that would need to be completed."	Update
5.2 Dosage and Administration	Updated dosage and administration text regarding the cycles for PK/PD sampling, and regarding when and where belumosudil should be taken (ie, home or clinic).	Updated PK/PD sampling schedule. Updated text to allow increased flexibility in terms of where doses can be taken to reduce participant burden.
5.2.1 Belumosudil Tapering Guidance	Replaced "Belumosudil will be tapered" with "Tapering of belumosudil is allowed" and added "at the Investigator's discretion"	Updated text to improve clarity of language and also to clarify that tapering of belumosudil and cessation of all other immunosuppressants should be determined at the discretion of the Investigator.
5.6 Missed Doses	Added "Participants should make every effort to take the study drug at the same time every day with their morning/evening meal."	Update
5.9 Treatment of Overdose	Updated first sentence as "Any dose of belumosudil >1000 mg within a 24-hour period will be considered an overdose."	Update in overdose definition
5.10 Dose Modification Guidelines	Modified Guidelines for Management of Treatment Emergent Toxicities table (ie, Table 2)	Update
	Removed Belumosudil Dose Decrements table (ie, Table 5 previously), the text below the table (ie, "If the reduced dose is tolerated for 1 complete cycle, the dose may be escalated to the previous dose."), and the statement referencing this table (ie, "When dose reduction is necessary, the dose should be decreased as shown in Table 5)	Update

Section # and Name	Description of Change	Brief Rationale
6.2.1 Screening, 6.2.2 Cycle 1, Day 1 (Baseline), 6.2.4 Cycle 2 and Beyond, Day 1 (±3 days), 6.2.5 End of Treatment (EOT), 6.2.6 28-Day Follow-Up Visit	Modified text on pregnancy test to state as follows: Highly sensitive urine or serum pregnancy test (for females of childbearing potential). Positive urine results are to be confirmed with serum testing.	Updated text to clarify the type of test required to assess pregnancy and to improve clarity of language
6.2.4 Cycle 2 and Beyond, Day 1 (±3 days)	Modified text, expanding upon the cycles beyond Cycle 2	Modified text to clarify the cycles that participants will need to be back at the clinics for
	Modified text such that single 12-lead ECG is to be done on C2D1, C3D1, C5D1, C7D1, and Day 1 of every 3rd cycle thereafter through C19D1, and only if clinically indicated from C19D1 and onward for pre-dose	Update
	Changed cycle number such that full PFT is required after Cycle 2 (ie, Day 1 of Cycle 3) instead of after Cycle 3 (ie, Day 1 of Cycle 4)	Update
	Replaced “These items must be completed on Day 1 of Cycles 2-5, then on Day 1 of every other Cycle thereafter, (i.e. Day 1 of Cycles 2, 3, 4, 5, 7, 9, 11 etc.)” with “These items must be completed on Day 1 of Cycles 2, 3, 5, 7, then on Day 1 of every 3 cycles thereafter, (Day 1 of Cycles 10, 13, 16, 19 etc.)”	
	Replaced “From Cycle 19, Day 1 (C19D1), subjects may receive 2 cycles worth of study drug along with 2 diaries and return to the clinic every other cycle for assessments and investigational product accountability.” with “On Cycle 2 Day 1 (C2D1) participants will receive study drug for 1 cycle along with 1 diary. On Cycle 3 and 5 Day 1 (C3D1 and C5D1), participants will receive the study drug for the next 2 cycles along with 2 diaries, and from cycle 7 onwards (C7D1, C10D1, C13D1 etc.) participants will receive the study drug for 3 cycles along with 3 diaries and return to the clinic every 3 cycles for assessments and investigational product accountability.”	Update
6.2.4 Cycle 2 and Beyond, Day 1 (±3 days), 7.2 Full PK, 21.1 Appendix A: Schedule of Assessments	Text on Sparse PK was updated to reflect change of sparse PK sampling from Cycle 4 to Cycle 7 and removal of sparse PK sampling 5 hours post dose.	Updated PK sampling
6.4.5 Pregnancy Testing	Modified text on pregnancy such that it details that pregnancy tests are to be done using highly sensitive urine or serum test at timepoints specified in the SoA, and that Sponsor will continue to collect pregnancy data until after the birth of the baby to assess pregnancy outcome and status of newborn, as well as, collecting data on the participant’s partner’s pregnancy, birth, and condition of newborn.	Updated per Sanofi standards
6.5 Use of Biological Samples and Data for future Research	Added entire section	Updated per Sanofi standards

Section # and Name	Description of Change	Brief Rationale
9.1 Safety Parameters	Removed urinalysis results from safety parameters, replaced "serum" chemistry with "clinical" chemistry, and added "Adverse events will be recorded after the ICF/assent form is signed until 28 days after the last dose of belumosudil."	Update
9.2 Adverse Event Definition	Modified entire section	Updated per Sanofi standards
9.3 Evaluating Adverse Events	Replaced "intensity" with "severity"	Updated text to improve clarity of language
9.3.1 Serious Adverse Events	Modified entire section	Updated per Sanofi standards
9.3.2 Recording and follow-up of AE and/or SAE	Replaced entire section with the following section: "Recording and follow-up of AE and/or SAE"	Updated per Sanofi standards
9.3.3 Reporting Requirements for SAEs	Replaced entire section with the following section: "Reporting Requirements for SAEs"	Updated per Sanofi standards
9.3.4 Relationship to cGVHD or Underlying Disease	Removed entire section	Updated per Sanofi standards
9.3.5 Recording Adverse Events	Removed entire section	Updated per Sanofi standards
9.3.6 Serious Adverse Event Reporting	Removed entire section	Updated per Sanofi standards
9.4.2 Follow-Up of Adverse Events	Removed entire section	Updated per Sanofi standards
14.4 Future Use of Subject Samples	Removed entire section	Updated per Sanofi standards
20 Publication of Data and Protection of Trade Secrets	Added "For those journals that request sharing of the analyzable data sets that are reported in the publication, interested researchers are directed to submit their request to vivli.org. Individual anonymized participant data and supporting clinical documents are available for request at vivli.org. While making information available we continue to protect the privacy of participants in our clinical trials. Details on data sharing criteria and process for requesting access can be found at this web address: vivli.org."	Updated per Sanofi standards
21.1 Appendix A: Schedule of Assessments	Replaced "Pregnancy test (urine)" with "Highly sensitive urine or serum pregnancy test"	Updated per Sanofi standards
	Removed footnote d and reorganized subsequent footnotes and updated annotations accordingly	Updated to clarify changes in assessment schedules
	Modified footnote e	Updated adolescent height measurement schedule
	Modified footnote j	Updated study drug administration schedule
	Modified footnote l	Updated text to clarify changes in assessment schedules

Section # and Name	Description of Change	Brief Rationale
	In table 10, added “3, 5” to “Cycle 2” and for Cycle 19 and onward, modified text such that From Cycle 19 and onward, ECG assessments are only to be performed if clinically indicated	Updated ECG assessment schedule
22.9 Appendix I: Determining Relationship of AEs to Study Drug	Removed entire appendix	Updated per Sanofi standards
22.10 Appendix J: PFT Assessments	Updated “response” timepoints and footnote (ie, footnote a)	Updated PFT assessment schedule
	Updated footnote b and moved ‘X’ from C4 to C3 for full PFT	Updated PFT assessment schedule
	Updated “Spirometry” timepoints	Updated PFT assessment schedule
21.14 Appendix N: Contraceptive and Barrier Guidance	Added entire appendix	Updated per Sanofi standards
21.15 Appendix O: Protocol Amendment History	Added entire appendix	Updated per Sanofi standards

In addition, other minor editorial changes (eg, grammatical, stylistic, references, minor typographical error corrections) were implemented throughout the protocol. Also, abbreviations, section/table/figure/appendix numbers or letters, and dates were updated as needed.

Procedures in Case of Emergency

Serious Adverse Events

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

Emergency Contact Information

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

Sanofi Pharmacovigilance

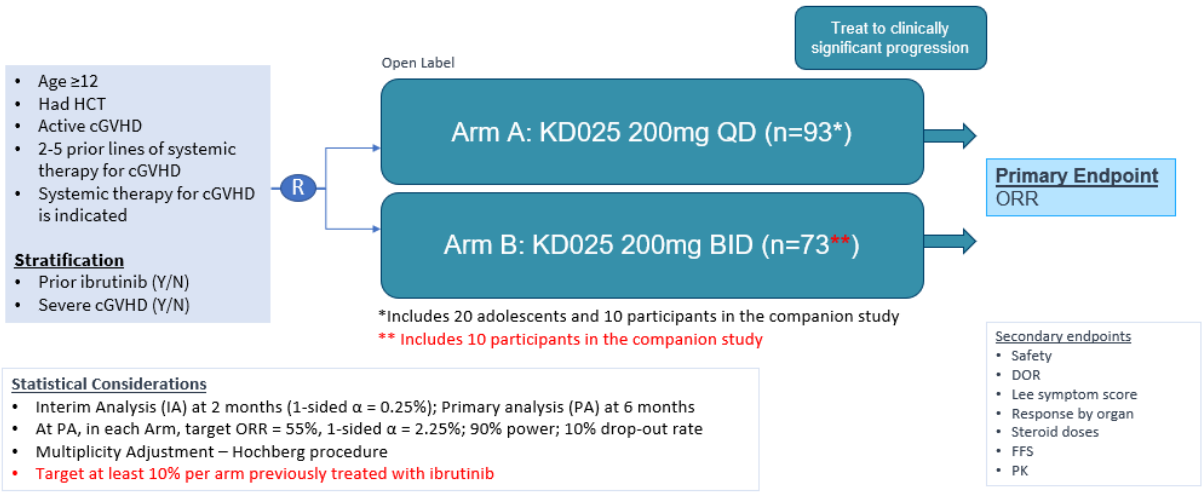
KDM-ClinicalSAEReporting@Sanofi.com

SAE CRITERIA
* A SAE is any untoward medical occurrence that at any dose results in any of the following outcomes, regardless of relationship to study drug (see Section 9.3.1, Serious Adverse Events, for additional information): • Death. • Life-threatening adverse drug event. • Inpatient hospitalization or prolongation of existing hospitalization. • A persistent or significant disability/incapacity. • A congenital anomaly/birth defect. • An important medical event that may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

SYNOPSIS

Study Title	A Phase 2, Randomized, Multicenter Study to Evaluate the Efficacy and Safety of KD025 in Subjects with Chronic Graft Versus Host Disease (cGVHD) After At Least 2 Prior Lines of Systemic Therapy
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. Glucocorticoids, with or without calcineurin inhibitors, remain the standard initial treatment, but are associated with significant side effects and unsatisfactory outcomes, particularly for patients with high-risk features of cGVHD. Based upon data from this 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. The other FDA approved drugs for the treatment of cGVHD are ibrutinib and ruxolitinib. Ibrutinib is indicated for the treatment of adults and pediatric patients aged 1 year and older with cGVHD after failure of one or more lines of systemic therapy. Ruxolitinib is indicated for the treatment of adults and pediatric patients aged 12 years and older with cGVHD after failure of one or two lines of systemic therapy. Belumosudil (formerly known as KD025) is an orally available Rho-associated coiled-coil kinase 2 (ROCK2) selective inhibitor. Belumosudil has been shown to downregulate pro-inflammatory T helper 17 cells and T follicular helper cells while upregulating anti-inflammatory regulatory T cells, which may potentially correct the immunological imbalance seen in cGVHD. Furthermore, belumosudil has been shown to be active and well-tolerated in cGVHD. Study KD025-208 enrolled participants with active cGVHD who had previously received no more than 3 prior lines of treatment. Approximately two-thirds of cGVHD patients treated with belumosudil 200 mg QD (Cohort 1) and 200 mg BID (Cohort 2) achieved clinical responses.

Study Objective(s) / Purpose	The objective of this study is to evaluate the efficacy of belumosudil at dose levels of 200 mg QD and 200 mg BID in participants with cGVHD who have previously been treated with at least 2 prior lines of systemic therapy.
Study Design	Phase 2, open label, randomized, multicenter study in participants aged ≥12 with cGVHD who have previously been treated with at least 2 prior lines of systemic therapy. Approximately 166 participants with active cGVHD will be randomized (1:1) to receive treatment with one of two belumosudil regimens: • Arm A: belumosudil 200 mg QD • Arm B: belumosudil 200 mg BID With Amendment 2, the sample size was increased from approximately 126 participants, with additional participants to be enrolled as follows: • 20 adolescents • 20 adults into a site-specific Companion Study to collect biospecimens (Section 21.13 Appendix M), these participants will be randomized (1:1) to Arm A or Arm B. With amendment 4, eligible adolescent participants were enrolled into the study at the belumosudil 200 mg QD dose. Since amendment 4, there are no more randomization and stratification factors applied for this group. The expected sample size in each Arm is therefore: Arm A, N = 93 with addition of 20 adolescents and 10 adults and Arm B, N = 73 with addition of 10 adults. Randomized participants withdrawn from the study before receiving any study drug will be replaced. Randomization will be stratified according to prior cGVHD treatment with ibrutinib (Yes / No) and severe cGVHD at baseline (Yes / No). Participants may receive treatment in 28-day treatment cycles until clinically significant progression of cGVHD. Participants will undergo evaluations as outlined in the Schedule of Assessments (APPENDICES). The primary endpoint is the overall response rate (ORR) with responses as defined by the 2014 National Institutes of Health (NIH) Consensus Development Project on clinical trials in cGVHD. Responses are assessed with respect to baseline.



Number of Study Centers	Approximately 30
Number of Participants	Approximately 166
Approximate Duration of Participant Participation	Up to 2 weeks for screening, treatment until clinically significant progression of disease, and 4 weeks of follow-up.
Study Treatment	Belumosudil will be provided as 200 mg tablets to be taken with food either QD (Arm A) or BID (Arm B).
Criteria for Inclusion and Exclusion	**Inclusion Criteria** 1. Male and female participants at least 12 years of age who have had allogeneic hematopoietic cell transplant (HCT). 2. Previously received at least 2 and not more than 5 lines of systemic therapy for cGVHD. 3. Participant has been on a stable dose/regimen of systemic cGVHD treatments for at least 2 weeks prior to screening. Note: Concomitant corticosteroids, calcineurin inhibitors, sirolimus, MMF, methotrexate, rituximab, and extracorporeal photopheresis (ECP) are acceptable. Systemic investigational GVHD treatments are not permitted. 4. Have persistent cGVHD manifestations and systemic therapy is indicated. 5. Karnofsky (if aged ≥16 years) / Lansky (if aged <16 years) Performance Score of ≥60. Laboratory Parameters 6. Absolute neutrophil count ≥1.5 × 10^9/L. 7. Platelet count ≥50 × 10^9/L with no transfusions within 72 hours. 8. ALT and AST ≤3 × ULN (≤5 × ULN if due to cGVHD).

	9. Total bilirubin ≤1.5 × ULN. 10. Glomerular filtration rate (GFR) ≥ 30 mL/min/1.73 m^2 using the MDRD-4 variable formula (if aged ≥18 years) or using the Bedside Schwartz formula (if aged <18 years). General Criteria 11. I11 is no longer applicable per amended protocol 05. 12. I12 is no longer applicable per amended protocol 05. 13. I13 is no longer applicable per amended protocol 05. 14. Participant (or the participant's legally authorized representative) is able to provide written informed consent / assent prior to the performance of any study-specific procedures. 15. Weight ≥40 kg. 16. It is in the best interest of the participant to participate in the study. Sex, contraceptive/barrier method and pregnancy testing requirements/breastfeeding 17. All Contraceptive use by men and women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. **a)** Male participants Male participants are eligible to participate if they agree to the following during the study intervention period and for at least 90 days after the last administration of study intervention: - Refrain from donating sperm or cryopreserving sperm; PLUS, either: - Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent; OR - Must agree to use contraception/barrier as detailed below - A male condom and an additional highly effective contraceptive method as described in Section 21.14 (Appendix N: Contraceptive and Barrier Guidance) when having sexual intercourse with a woman of childbearing potential (WOCBP) who is not currently pregnant.

b) Female participants

A female participant is eligible to participate if she is not pregnant or breastfeeding, and one of the following conditions applies:

- Is a woman of nonchildbearing potential (WONCBP) as defined in Section 21.14 Appendix N: Contraceptive and Barrier Guidance.

  OR

- Is a woman of childbearing potential (WOCBP) and agrees to use a contraceptive method that is highly effective (with a failure rate of <1% per year), preferably with low user dependency, as described in Section 21.14 (Appendix N: Contraceptive and Barrier Guidance) during the study intervention period (to be effective before starting the intervention) and for at least 90 days after the last administration of study intervention and agrees not to donate or cryopreserve eggs (ova, oocytes) for the purpose of reproduction during this period.
- A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within 28 days before the first administration of study intervention, see Section 6.4.5 Pregnancy testing. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

Exclusion Criteria

1. E01 is no longer applicable per amended protocol 05.
2. Histological relapse of the underlying cancer or post-transplant lymphoproliferative disease at the time of screening.
3. Current treatment with ibrutinib. Prior treatment with ibrutinib is allowed with a washout of at least 28 days prior to randomization.
4. Female participant who is pregnant or breastfeeding.
5. History or other evidence of severe illness or any other conditions that would make the participant, in the opinion of the Investigator, unsuitable for the study (such as malabsorption syndromes, poorly controlled psychiatric disease or coronary artery disease).
6. Known active hepatitis B virus (HBV) or hepatitis C virus (HCV) or history of human immunodeficiency virus (HIV).

	7. Diagnosed with another malignancy (other than malignancy for which transplant was performed) within 3 years of enrollment, with the exception of: • Completely resected basal cell or squamous cell carcinoma of the skin. • Carcinoma in situ of the cervix. • Resected breast ductal carcinoma in situ. • Prostate cancer with Gleason score <6 and stable PSA over 12 months. 8. Has had previous exposure to belumosudil. 9. Known allergy/sensitivity to belumosudil or any other ROCK2 inhibitor. 10. Participant has QTc(F) >480 ms. 11. Participant has FEV_1 ≤39% or has lung score of 3. 12. Participant considered unlikely to adhere to treatment and / or follow protocol in the opinion of the Investigator. 13. Treatment with any non-GVHD investigational agent, or any investigational device or procedure, within 28 days (or 5 half-lives, whichever is greater) of enrollment.
Efficacy Variables	**Primary Endpoint** The primary efficacy endpoint is the ORR [including Partial Response (PR) and Complete Response (CR)]. Responses are as defined by the 2014 National Institutes of Health (NIH) Consensus Development Project on clinical trials in cGVHD, and are assessed by Investigators. **Secondary Endpoints** • Duration of Response (DOR). • Change in Lee Symptom Scale Score. • Response rate by organ system. • Time to Response (TTR). • Time to Next Treatment (TTNT). • Percentage of participants who have a best response of PR and percentage of participants who have a best response of CR. • Change in corticosteroid dose. • Change in calcineurin inhibitor dose. • Failure-free survival (FFS). • Overall survival (OS).

	• Change in cGVHD global severity rating as based on the Clinician-Reported Global cGVHD Activity Assessment. • Change in symptom activity as based on cGVHD Activity Assessment Patient Self-Report. • Pharmacokinetics. **Exploratory Endpoints** • PROMIS Global Health subscores for physical and mental functioning. • ORR using Kadmon Algorithmic Response Assessment (KARA) for overall response. • Pharmacodynamics - Changes in the expression of relevant biomarkers after belumosudil administration.
Safety Variables	Safety is a secondary endpoint. The primary safety outcome will be the percent of participants in each arm experiencing AEs. Safety assessments include AEs, Grade ≥3 AEs, SAEs, vital sign measurements, clinical laboratory evaluations, and ECGs. Reasons for treatment discontinuation will be documented. Adverse events will be recorded after the ICF/assent form is signed and for 28 days after the last dose of belumosudil.
Pharmacokinetics	Full PK profiles will be collected for approximately 12 participants in each treatment arm at selected sites, and sparse PK sampling will be performed for the whole population, including adolescent participants.
Pharmacodynamics	Samples will be collected for exploratory PD analyses from all participants at sites with appropriate capabilities prior to dosing with belumosudil on Day 1 of Cycles 1, 2 and 7, and upon progression of cGVHD (or flare). PD samples will not be required from adolescents if the site has policies limiting the daily volume of blood allowed to be drawn as part of a clinical trial. Additional samples will be collected from participants enrolled in the site-specific Companion Study for PD analyses as described in Section 21.13 Appendix M.
Statistical Analysis	**Sample Size:** Sample size is based on the primary efficacy endpoint of ORR, with a target ORR of 55% and with one planned Interim Analysis (IA). With 63 participants, and a 10% dropout rate, each treatment arm is estimated to have 90% power to yield a 95% confidence interval of ORR that excludes 30%. The Hochberg procedure will be applied for multiplicity adjustment for the primary efficacy endpoint of ORR. **Analysis Population:** The modified Intent-to-Treat (mITT) population is defined as all participants who are randomized and receive at least one dose of study drug.

	The mITT population is the primary population for the analysis of the primary efficacy endpoint. **Data Presentations/Descriptive Statistics** Three analyses are planned: 1. An IA will be conducted approximately 2 months after 126 participants have been enrolled into the mITT population. A nominal 1-sided alpha of 0.0025 will be spent, but there will be no early study termination for efficacy. 2. The primary analysis (PA) will be conducted approximately 6 months after 126 participants have been enrolled into the mITT population, with 1-sided alpha 0.0225 (or 0.025 if the ORRs of both arms are significant at interim). 3. A follow-up analysis will be conducted approximately 12 months after 126 participants have been enrolled into the mITT population. 4. Additional analyses will be conducted to include adolescent participants and Companion Study participants, approximately 6 months after completion of enrollment of the respective participants. Alpha will only be allocated to the primary endpoint, ORR. Demographics, participant disposition, and screening and baseline characteristics will be summarized for the ITT population. AEs will be coded using the MedDRA dictionary (Version 20.0 or greater). The number and percentages of participants experiencing treatment-emergent AEs will be tabulated by system-organ-class (SOC) and preferred term (PT) and will be presented by treatment group. The number of events by preferred term will also be summarized. Tabulation by maximum severity and relationship to treatment will also be included by treatment group. Summary participant listing will be provided for SAEs, AEs resulting in study discontinuation, and deaths. AEs, SAEs, related AEs, related SAEs, Grade ≥3 AEs, related Grade ≥3 AEs, and AEs leading to withdrawal and treatment discontinuation will be summarized according to treatment group. Laboratory results will be summarized by treatment group. 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 event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
BA/BE	Bioavailability/Bioequivalence
BID	twice daily
BMT	bone marrow transplant
BUN	blood urea nitrogen
C1D1	cycle 1 day 1
C2D1	cycle 2 day 1
CFR	Code of Federal Regulations
cGVHD	chronic graft versus host disease
CI	confidence interval
C_{max}	maximum concentration observed
CNI	calcineurin inhibitor
CPK	creatinine phosphokinase
CR	complete response
CRO	contract research organization
CTCAE	common terminology criteria for adverse events
DOR	duration of response
DL_{CO}	diffusing capacity of carbon monoxide
ECG	electrocardiogram
ECP	extracorporeal photopheresis
eCRF	electronic case report form
EOT	end of treatment
FDA	Food and Drug Administration
FEV_1	forced expiratory volume (in the first second)
FFS	failure-free survival
FVC	forced vital capacity
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase
GI	gastrointestinal
Hb	hemoglobin
HBV	hepatitis B virus
HCT	hematopoietic cell transplantation
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IA	interim analysis
IB	investigator’s brochure
ICF	informed consent form
IEC	Independent Ethics Committee

IND	Investigational New Drug
IRB	Institutional Review Board
ITT	intent-to-treat
IUD	intrauterine device
IXRS	Interactive voice / web response system
KARA	Kadmon Algorithmic Response Assessment
LFT	liver function tests
LR	lack of Response
LR-M	lack of Response - mixed
LR-P	lack of Response - progression
LR-U	lack of Response - unchanged
MCV	mean corpuscular volume
MAD	multiple ascending dose
MDRD-4	4-Variable Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MMF	mycophenolate Mofetil
NIH	National Institutes of Health
ORR	overall response rate
OS	overall survival
PA	primary analysis
PD	pharmacodynamic
PE	physical examination
PFT	pulmonary function test
PK	pharmacokinetic
PPI	proton pump inhibitor
PR	partial response
PT	preferred term
QD	once daily
QOD	once every other day
QTc(F)	corrected QT interval using Fridericia's formula
ROCK	rho-associated protein kinase
RV	residual volume
SAD	single ascending dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	stable disease
SOC	system organ class
SUSAR	suspected unexpected serious adverse event
$T_{1/2}$	half-life
TCR	T cell receptor
T_{max}	observed time to reach peak plasma concentration
TEAE	treatment-emergent adverse event
TLC	total lung capacity
TTNT	time to next treatment

TTR	time to response
ULN	upper limit of normal

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, 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 this Study, KD025-213 (NCT03640481), 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 (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 participants with cGVHD who had failed first line corticosteroid therapy and required additional therapy (7). Of note, participants were required “to have either >25% body surface area erythematous rash or a National Institutes of Health (NIH) mouth score >4” (8). The ORR in this selected population was 67%. Twenty-four percent of participants receiving IMBRUVICA in the cGVHD trial discontinued treatment due to adverse reactions (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 (9, 10, 11, 12). 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 (13, 14). 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 IL-17 and IL-21 in both mice and humans (15, 16). Moreover, targeted ROCK2 inhibition effectively decreased IL-17 production in vivo and

ameliorated the spontaneous development of arthritis, diabetes and lupus in mice (16). Additionally, ROCK activity was increased in participants with RA and SLE (15, 17, 18). The specific inhibition of ROCK2 therefore has been examined for its potential as a therapy for autoimmune disorders.

1.3 BELUMOSUDIL BACKGROUND (NON-CLINICAL)

Belumosudil is an orally available Rho-associated protein kinase-2 (ROCK2) selective inhibitor. Data from a Phase 1 clinical trial demonstrate that oral administration of belumosudil to healthy human participants down-regulates the ability of T cells to secrete IL-21 and IL-17, but not interferon (IFN)-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 (19).

Chronic GVHD remains a major complication following allogeneic bone marrow transplantation (20). 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 Tregs (21). In addition, the aberrant activation of immune cells leads to increased secretion of transforming growth factor (TGF)-β which promotes fibroblast activation, collagen production and development of tissue fibrosis (22). Belumosudil effectively ameliorates cGVHD in multiple models: a full MHC-mismatch model of bronchiolitis obliterans syndrome that involved a wide spectrum of target organs including lung and liver(23) as well as a minor MHC-mismatch model of sclerodermatous GVHD (24). 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 (25). 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.

Also refer to the belumosudil Investigator's Brochure (IB) for more detailed information.

1.4 BELUMOSUDIL BACKGROUND (CLINICAL)

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

Administration of belumosudil 200 mg tablets in the fed state resulted in a ~2-fold increased exposure in terms of Cmax and AUC when compared to the fasted state. Pharmacokinetic analyses showed that belumosudil administered as a 200 mg tablet in the fed state was rapidly absorbed with a median Tmax of approximately 3 hours. Elimination half-life is approximately 7 hours. Variability in exposure related parameters Cmax and AUC was reduced when belumosudil was administered in the fed state when compared to the fasted state. Belumosudil should be taken with food.

Phase 2 studies of belumosudil are ongoing or have been completed, enrolling participants with idiopathic pulmonary fibrosis, cGVHD and psoriasis, diffuse cutaneous systemic sclerosis (dcSSc). More than 750 participants have been dosed with belumosudil for inflammatory or fibrotic diseases or as healthy volunteers at doses ranging from 20 mg to 1000 mg QD and 500 mg BID.

Also refer to the belumosudil IB for more detailed information.

1.4.1 KD025-208

KD025-208 is a completed Phase 2a, dose-escalation, open-label study to evaluate the safety, tolerability, and activity of belumosudil in participants with cGVHD. Eligible participants with persistent, active cGVHD manifestations after at least 2 months of steroid therapy and no more than 3 prior lines of treatment for cGVHD are enrolled into 3 sequential cohorts:

- Cohort 1: 200 mg belumosudil QD
- Cohort 2: 200 mg belumosudil BID
- Cohort 3: 400 mg belumosudil QD

The primary endpoint is the overall response rate (ORR), as defined by the 2014 National Institutes of Health (NIH) Consensus Development Project on clinical trials in cGVHD. Secondary endpoints include Duration of Response (DOR), patient reported outcomes (Lee Symptom Scale Score), changes in corticosteroid dose and response by organ system.

Refer to the belumosudil IB for more detailed information.

1.5 STUDY RATIONALE

Building upon data from the KD025-208 study, this current study, KD025-213, is designed to further demonstrate the efficacy and safety of belumosudil in participants with cGVHD, who may or may not have been treated with ibrutinib. In particular, given the similar response rates and tolerability demonstrated in Cohorts 1 and 2 of study KD025-208, with belumosudil treatment at 200 mg QD and 200 mg BID respectively, this study will further evaluate the efficacy and safety of these 2 regimens of belumosudil.

Eligible participants are required to have active cGVHD despite treatment with corticosteroids and after failure of at least 2 prior lines of systemic therapy. A target of ≥10% of the enrolled population will have previously received ibrutinib as a therapy for cGVHD.

Participants will be randomized (1:1) to two treatment arms:

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

This study is intended to demonstrate clinically meaningful, durable responses in this population of participants with significant unmet medical need, with an ORR in excess of 30%.

1.6 SUMMARY OF KNOWN AND POTENTIAL RISKS AND BENEFITS TO HUMAN PARTICIPANTS

All the side effects related to belumosudil are not known; the belumosudil IB contains data on risks associated with belumosudil. Other risks to participants involve side effects from study procedures. There are also other risks associated with taking part in this study, such as the risks associated with a loss of privacy or confidentiality because of improper disclosure.

There may be no direct benefit to participants enrolled into this study. Participants may receive a clinical benefit from belumosudil, and some participants may progress. The information from this study may help other participants with cGVHD and more may be learned about the study drug to further inform the prescribing information of REZUROCK.

In July 2021 FDA granted approval of belumosudil (REZUROCK) 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. In November 2021, belumosudil received marketing authorization approval in Australia. The approved indication was treatment of patients with cGVHD aged 12 years and older who have an inadequate response to corticosteroids. In March 2022, belumosudil received marketing authorization approval in Canada, and in July 2022 in the United Kingdom (UK). The indication is the same as in the US in both countries.

The Sponsor will maintain clinical trial insurance to cover injury associated with clinical study participation. Pursuant to site-specific clinical trial agreements, the Sponsor will pay for all reasonable costs associated with the study.

2 STUDY OBJECTIVES / PURPOSE

2.1 PRIMARY OBJECTIVE

The objective of this study is to evaluate the efficacy of belumosudil, at dose levels of 200 mg QD and 200 mg BID, in participants with cGVHD who have previously been treated with at least 2 prior lines of systemic therapy.

2.2 SECONDARY OBJECTIVES

The secondary objectives of the study are to evaluate:

- Duration of response (DOR).
- Changes in the Lee Symptom Scale Score.
- Response by organ system.
- Time to response (TTR).
- Time to next treatment (TTNT).
- Percentage of participants who have a best response of PR and percentage of participants who have a best response of CR.
- Change in corticosteroid dose.
- Change in calcineurin inhibitor dose.
- Failure-free-survival (FFS).
- Overall survival (OS).
- Change in cGVHD global severity rating using the Clinician-Reported Global cGVHD Activity Assessment.
- Change in symptom activity using the cGVHD Activity Assessment Patient Self-Report.
- PK of belumosudil in participants with Cgvhd.
- Safety.

2.3 EXPLORATORY OBJECTIVES

The exploratory objectives of the study are:

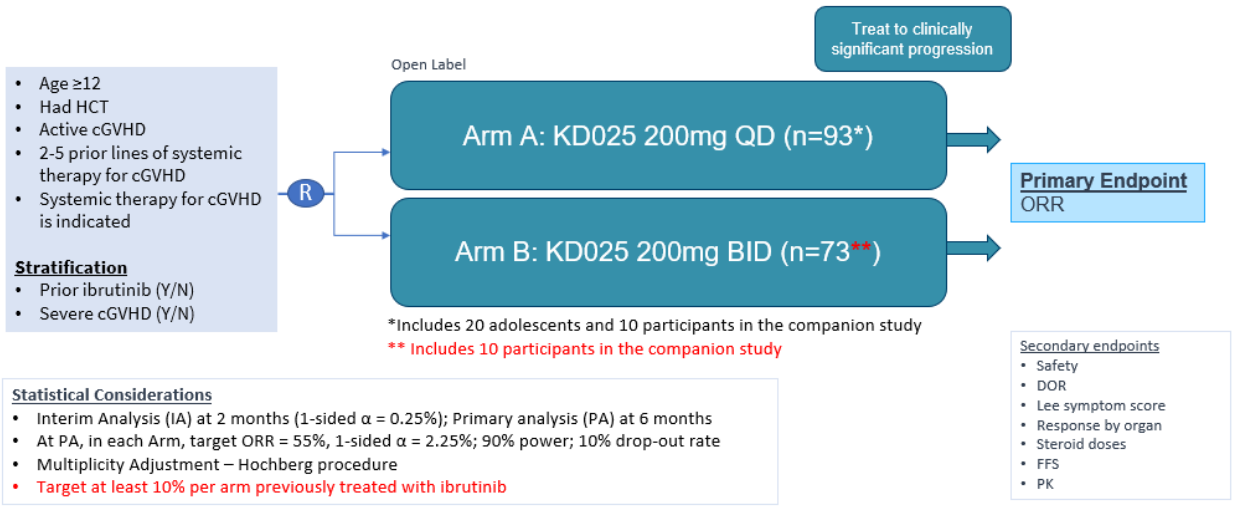
- To evaluate changes in the PROMIS Global Health subscores for physical and mental functioning.
- To evaluate ORR using Kadmon Algorithmic Response Assessment (KARA) for overall response.
- To evaluate changes in relevant biomarkers after belumosudil administration.

3 INVESTIGATIONAL PLAN

3.1 STUDY DESIGN

This is a Phase 2, randomized, multi-center, open-label, study designed to evaluate the efficacy and safety of belumosudil in participants with active cGVHD after at least 2 prior lines of systemic therapy. The study design is illustrated in Figure 1.

Figure 1 - KD025-213 Study Schema



Participants who consented and/or provided assent documented with a signed an IRB/IEC-approved informed consent/assent form as applicable, and meet all of the eligibility criteria will be enrolled. The study population will be adults and adolescents who:

- Have undergone allogeneic hematopoietic cell transplantation (HCT).
- Have previously received at least 2 lines of systemic therapy for cGVHD.
- Have persistent cGVHD manifestations and systemic therapy for cGVHD is indicated.

A target of ≥10% of the enrolled population will have previously received ibrutinib as a therapy for cGVHD.

After confirmation of eligibility during a 14-day screening period, eligible participants will be randomized (1:1) to one of two treatment arms:

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

These doses are selected based upon the data from study KD025-208 (Section 1.4.1).

Randomization will be stratified according to prior cGVHD treatment with ibrutinib (Yes / No) and severe cGVHD (Yes / No).

With amendment 4, eligible adolescent participants were enrolled into the study at the belumosudil 200 mg QD dose. Since amendment 4, there are no more randomization and stratification factors applied for this group. The additional 20 adults in the companion study will be randomized (1:1) to Arm A or Arm B. The expected sample size in each Arm is therefore: Arm A, N = 93 with addition of 20 adolescents and 10 adults and Arm B, N = 73 with addition of 10 adults. Any adolescent taking a PPI or a strong CYP3A4 inducer will begin C1D1 at the following escalated dose: belumosudil 200 mg BID.

Concomitant treatment with standard of care systemic cGVHD therapies such as calcineurin inhibitors (tacrolimus, cyclosporine), sirolimus, MMF, methotrexate, rituximab or extracorporeal photopheresis (ECP), are permitted as long as the participant has been on a stable dose / regimen of these per the eligibility criteria. Initiation of new systemic cGVHD therapy while on study is not permitted.

Participants will receive belumosudil treatment in 28-day cycles 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, participant preference / withdrawal of consent, lost to follow-up, sponsor decision, or death (whichever occurs first).

Participants 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 cycle. If progression per NIH criteria is not confirmed or no new systemic therapy is planned, participants may continue on belumosudil per investigator discretion until they fulfill one of the criteria requiring discontinuation of study drug.

Under Protocol Amendment 3, all participants (excluding the 20 adolescent participants) that have received at least 6 months of belumosudil treatment or are in long-term follow-up without having a failure-free survival event are expected to end participation in study KD025-213. Participants may continue to participate in study KD025-213 if the Investigative Site is awaiting IRB approval of the KD025-217 rollover study titled: “Extended Treatment and Follow-up of Participants Treated with Belumosudil in Study KD025-208 or Study KD025-213”.

The primary endpoint is the overall response rate (ORR), defined as the proportion of participants achieving a partial response (PR) or a complete response (CR) as defined by the 2014 NIH Consensus Development Project on Clinical Trials in cGVHD (Appendix B). Response criteria will be assessed after Cycles 1, 2, 3 and 4 and then after every other Cycle thereafter (Day 1 of Cycles 2, 3, 4, 5, 7, 9, 11, etc.) (Table 6). Following Protocol Amendment 5, in adolescent participants still to be enrolled, response criteria will be assessed after Cycles 1, 2, 4, and 6 and then after every third cycle (Day 1 of cycles 2, 3, 5, 7, 10, 13, etc.). Responses are assessed with respect to baseline.

Analyses of the primary endpoint will be participant to multiplicity adjustment per a Hochberg procedure (Section 11.2.1).

Secondary endpoints will include assessments to evaluate the clinical meaningfulness of responses. These include duration of response, changes in Lee Symptom Scale Scores, response by organ system and changes in corticosteroid dosage.

This study uses the Clinician-Reported Global cGVHD Activity Assessment to evaluate cGVHD global severity rating along with other organ severities; the cGVHD Activity Assessment Patient Self Report to assess symptom activity (Appendix F) and evaluates failure-free survival (FFS).

Full PK profiles will be collected for a subset of approximately 12 participants per arm, and sparse PK sampling will be conducted for the entire study population including adolescent participants.

As exploratory endpoints, changes in the PROMIS Global Health score and changes in relevant biomarkers after belumosudil administration will be explored.

All AEs will be followed for 28 additional days after discontinuation of belumosudil treatment. All SAEs and treatment-related AEs will be followed until either resolution of the event or determination by the Investigator that the event has become stable or irreversible.

In addition, after discontinuation of belumosudil treatment, participants will be contacted every 12 weeks until a failure-free survival event occurs or until study close-out (whichever occurs first) to allow follow up for FFS and survival status.

3.2 STUDY STEERING COMMITTEE

A study Steering Committee (SC) will advise on study conduct, and study stopping rules (Section 10).

The chair is [redacted].

The co-chair is [redacted].

The SC charter will serve to describe membership and responsibilities.

3.3 ESTIMATED STUDY DURATION

The study enrollment period is expected to be approximately 24 months.

Individual participant duration on study will consist of up to 2 weeks for screening, treatment until progression of disease (Section 4.7), and 4 weeks of post treatment follow-up.

In addition, after discontinuation of belumosudil treatment, participants will be contacted every 12 weeks until a failure-free survival event occurs or until study close-out (whichever occurs first) to allow follow up for FFS and survival status.

Study close out is anticipated to occur within approximately 4 years after the first participant is enrolled.

4 STUDY POPULATION

4.1 NUMBER OF PARTICIPANTS

Approximately 166 adult and adolescent participants with cGVHD treated with at least 2, but no more than 5, prior lines of systemic therapy will be enrolled, approximately 83 participants in each treatment arm. With KD025-213 Protocol Amendment 2, the sample size was increased from approximately 126 participants, with additional participants to be enrolled as follows:

- 20 adolescents.
- 20 adults into a site-specific Companion Study to be conducted at selected sites to collect biospecimens (Section 21.13 Appendix M).

A target of ≥10% of the enrolled population will have previously received ibrutinib as a therapy for cGVHD.

4.2 STUDY CENTERS

This study will be conducted at approximately 30 sites.

4.3 INCLUSION CRITERIA

GVHD Criteria

1. Male and female participants at least 12 years of age who have had allogeneic hematopoietic cell transplant (HCT).
2. Previously received at least 2 and not more than 5 lines of systemic therapy for cGVHD.
3. Participant has been on a stable dose / regimen of systemic cGVHD treatments for at least 2 weeks prior to screening. Note: Concomitant corticosteroids, calcineurin inhibitors, sirolimus, MMF, methotrexate, rituximab, and extracorporeal photopheresis (ECP) are acceptable. Systemic investigational GVHD treatments are not permitted.
4. Have persistent cGVHD manifestations and systemic therapy is indicated.
5. Karnofsky (if aged ≥16 years) / Lansky (if aged <16 years) Performance Score of ≥60.

Laboratory Parameters

6. Absolute neutrophil count ≥1.5 × 109/L.
7. Platelet count ≥50 × 109/L with no transfusions within 72 hours.
8. ALT and AST ≤3 × ULN (≤5 × ULN if due to cGVHD).
9. Total bilirubin ≤1.5 × ULN.

10. Glomerular filtration rate (GFR) ≥30 mL/min/1.73 m2 using the MDRD-4 variable formula (if aged ≥18 years) or using the Bedside Schwartz formula (if aged <18 years).

General Criteria

11. I11 is no longer applicable per amended protocol 05.
12. I12 is no longer applicable per amended protocol 05.
13. I13 is no longer applicable per amended protocol 05.
14. Participant (or the participant's legally authorized representative) is able to provide written informed consent / assent prior to the performance of any study-specific procedures.
15. Weight ≥40 kg.
16. It is in the best interest of the participant to participate in the study.

Sex, contraceptive/barrier method and pregnancy testing requirements/breastfeeding

17. All

Contraceptive use by men and women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

- Male participants

  Male participants are eligible to participate if they agree to the following during the study intervention period and for at least 90 days after the last administration of study intervention:

  - Refrain from donating sperm or cryopreserving sperm;

    PLUS, either:

  - Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent;

    OR

  - Must agree to use contraception/barrier as detailed below:
  - A male condom and an additional highly effective contraceptive method as described in Section 21.14 (Section 21.14: Contraceptive and Barrier Guidance) when having sexual intercourse with a woman of childbearing potential (WOCBP) who is not currently pregnant.

- Female participants

  A female participant is eligible to participate if she is not pregnant or breastfeeding, and one of the following conditions applies:

  - Is a woman of nonchildbearing potential (WONCBP) as defined in Section 21.14 Appendix N: Contraceptive and Barrier Guidance.

OR

- Is a woman of childbearing potential (WOCBP) and agrees to use a contraceptive method that is highly effective (with a failure rate of <1% per year), preferably with low user dependency, as described in Section 21.14 (Appendix N: Contraceptive and Barrier Guidance) during the study intervention period (to be effective before starting the intervention) and for at least 90 days after the last administration of study intervention and agrees not to donate or cryopreserve eggs (ova, oocytes) for the purpose of reproduction during this period.
- A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within 28 days before the first administration of study intervention, see Section 6.4.5 Pregnancy testing. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

4.4 EXCLUSION CRITERIA

1. E01 is no longer applicable per amended protocol 05.
2. Histological relapse of the underlying cancer or post-transplant lymphoproliferative disease at the time of screening.
3. Current treatment with ibrutinib. Prior treatment with ibrutinib is allowed with a washout of at least 28 days prior to randomization.
4. Female participant who is pregnant or breastfeeding.
5. History or other evidence of severe illness or any other conditions that would make the participant, in the opinion of the Investigator, unsuitable for the study (such as malabsorption syndromes, poorly controlled psychiatric disease or coronary artery disease).
6. Known active hepatitis B virus (HBV) or hepatitis C virus (HCV) or history of human immunodeficiency virus (HIV).
7. Diagnosed with another malignancy (other than malignancy for which transplant was performed) within 3 years of enrollment, with the exception of:

- Completely resected basal cell or squamous cell carcinoma of the skin.
- Carcinoma in situ of the cervix.
- Resected breast ductal carcinoma in situ.
- Prostate cancer with Gleason score <6 and stable PSA over 12 months.

8. Has had previous exposure to belumosudil.
9. Known allergy/sensitivity to belumosudil or any other ROCK2 inhibitor.
10. Participant has QTc(F) >480 ms.

11. Participant has FEV1 ≤39% or has lung score of 3.
12. Participant considered unlikely to adhere to treatment and / or follow protocol in the opinion of the Investigator.
13. Treatment with any non-GVHD investigational agent, or any investigational device or procedure, within 28 days (or 5 half- lives, whichever is greater) of enrollment.

4.5 PRIOR LINES OF THERAPY

Participants must have previously received at least 2 lines of systemic therapy, and no more than 5 lines of systemic therapy for cGVHD. When documenting prior lines of therapy for cGVHD, the following guidelines should be employed:

- Initiation of one or more new systemic therapies for cGVHD is considered a new line of therapy:
  - If the intention is to initiate more than one agent at the same time, start dates may differ by up to 4 weeks in view of eg, scheduling delays, insurance approval, or obtaining drug.
- Topical agents are not considered a line of therapy.

4.6 SCREENING

The screening period commences once the informed consent form (ICF) or assent form is signed. Adequate time must be allowed for the participant to ask questions and make a voluntary decision. The ICF or assent form must be signed before any study-specific samples are taken or study-specific tests or evaluations are conducted. Documented standard of care assessments performed within 14 days of Cycle 1 Day 1 (C1D1) can be used as screening assessments even if done prior to signing of ICF or assent form.

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

Screening assessments as summarized in the Schedule of Assessments (Table 6) will be performed within 14 days of Cycle 1 Day 1.

Study eligibility will be based on satisfying all of the study inclusion and exclusion criteria. Participant eligibility must be confirmed by the Medical Monitor or designee prior to randomization.

Re-screening of participants will be allowed only upon approval of the Medical Monitor. A new consent/assent form must be signed to allow re-screening.

4.7 WITHDRAWAL CRITERIA

Participants will receive belumosudil treatment in 28-day cycles 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, participant preference / withdrawal of consent, loss to follow-up, sponsor decision, or death (whichever occurs first). Belumosudil treatment failures require discontinuation of study drug.

Participants 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 cycle. If progression per NIH criteria is not confirmed or no new systemic therapy is planned, participants may continue on belumosudil per investigator discretion until they fulfill one of the criteria requiring discontinuation of study drug.

Taper belumosudil after a sustained response for 6 months and cessation of all other immunosuppressants for at least 3 months, at the Investigator's discretion. The tapering schedule for belumosudil is described in Section 5.2.1.

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

Participants 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 participant wishes to voluntarily withdraw from the study, the physician will consult with the participant regarding procedures for safe withdrawal. Every effort should be made to have such participants attend EOT and 28-day follow up visits. In the instances where a reason for withdrawal of consent/assent is given, this will be captured in the eCRF. Participant data up to withdrawal of consent/assent will be included in the analysis of the study, and where permitted, publicly available data can be included after withdrawal of consent/assent.

If a participant becomes pregnant while on study, belumosudil will be discontinued (Section 6.4.5).

Under Protocol Amendment 3, all participants (excluding the 20 adolescent participants) that have received at least 6 months of belumosudil treatment or are in long-term follow-up without having a failure-free survival event are expected to end participation in study KD025-213. Participants may continue to participate in study KD025-213 if the Investigative Site is awaiting IRB approval of the KD025-217 rollover study titled: "Extended Treatment and Follow-up of Participants Treated with Belumosudil in Study KD025-208 or Study KD025-213".

4.8 REPLACEMENTS

Randomized participants withdrawn from the study before receiving any study drug will be replaced.

4.8.1 Treatment Discontinuation

Treatment discontinuation reasons include the following:

- Clinically significant cGVHD progression requiring addition of systemic therapy for cGVHD. Of note, clinically significant progression does not necessarily require cGVHD progression as defined by NIH Consensus Criteria. For example, a participant with a score of 3 in a given organ may present with clinically significant progression that warrants urgent intervention even though the NIH score remains unchanged.
- Progression of underlying disease as defined by established disease specific criteria.
- An AE that requires permanent discontinuation of study drug.
- Pregnancy.
- Investigator decision.
- Voluntary discontinuation/ withdrawal from the study treatment by the participant (participant may remain eligible for follow up).
- In case a participant wants to permanently discontinue the treatment (ie, withdrawal of consent for the intervention), the participant will be asked if a final assessment is possible to be performed using the procedure normally planned for the last dosing day (EOT and at 28-day follow up visit) with the IMP prior to consent of the withdrawal. See the SoA (Section 6.1) for the data to be collected at the time of the study treatment discontinuation, for information on the follow-up, and for any further evaluations that would need to be completed.
- Noncompliance to protocol.
- Participant lost to follow-up.
- Termination of the study by sponsor.
- Participant death.
- Received more than 6 months of belumosudil (this does not apply to the 20 adolescents). Of note, participants may continue to participate in KD025-213 if the Investigative Site is awaiting IRB approval of the KD025-217 rollover study titled: “Extended Treatment and Follow-up of Participants Treated with Belumosudil in Study KD025-208 or Study KD025-213”.

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), formerly also known as KD025, is an orally available Rho-associated protein kinase-2 (ROCK2) selective inhibitor. Belumosudil will be provided as 200 mg tablets.

In July 2021, FDA granted approval of belumosudil (REZUROCK) 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 and subsequently is commercially available for this indication.

5.2 DOSAGE AND ADMINISTRATION

Eligible participants in this study will be randomized (1:1) to one of two treatment arms:

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

Any adolescent taking a PPI or a strong CYP3A4 inducer will begin C1D1 at the following escalated dose: belumosudil 200 mg BID. On Day 1 of cycles 1, 2, 3, 5, 7 and then every 3 cycles (C10D1, C13D1, etc.), and on scheduled PK and PD sampling days, participants must take their dose of belumosudil at the clinic. On Day 1 of other cycles, belumosudil may be taken at home or in the clinic. Other daily doses will be taken at home and the study drug will be dispensed for home administration (see Section 6.2.2 and Section 6.2.4).

Participants will be instructed to start a meal within 30 minutes prior to taking their belumosudil treatment.

Additional information on dosage and administration of belumosudil can be found in the KD025-213 Pharmacy Manual.

5.2.1 Belumosudil Tapering Guidance

Tapering of belumosudil is allowed after a sustained response for 6 months and cessation of all other immunosuppressants for at least 3 months, at the Investigator's discretion. The tapering schedule for belumosudil is as follows:

- Arm A (QD): 200 mg QD → 200 mg QOD for 2 cycles→ Discontinue
- Arm B (BID): 200 mg BID → 200 mg QD for 2 cycles → 200 mg QOD for 2 cycles → Discontinue

Similarly, participants whose cGVHD has not progressed at the time of discontinuation of belumosudil treatment (Section 4.7) and who come off study for reasons other than AEs should be tapered off belumosudil by reducing the dose every 2 cycles as described above.

5.3 TREATMENT ASSIGNMENT

Eligible participants will be randomized and assigned to a treatment arm (A or B) in this open label, randomized study in accordance with the randomization schedule.

Randomization will be stratified according to:

- Prior ibrutinib therapy (yes/no).
- Severe cGVHD (yes/no) where severe cGVHD is defined as at least one organ with a score of 3, or a lung score of 2 or 3 (Table 1) (26).

The randomization will be a block randomization with a block size of 4.

Table 1 - cGVHD Severity Definitions

cGVHD Severity	Definition
Mild cGVHD	1 or 2 organs involved with no more than score 1 plus Lung score 0
Moderate cGVHD	3 or more organs involved with no more than score 1 OR At least 1 organ (not lung) with a score of 2 OR Lung score 1
Severe cGVHD	At least 1 organ with a score of 3 OR Lung score of 2 or 3

Key points:
1. In skin: higher of the two scores to be used for calculating global severity.
2. In lung: FEV_1 is used instead of clinical score for calculating global severity.
3. If the entire abnormality in an organ is noted to be unequivocally explained by a non-GVHD documented cause, that organ is not included for calculation of the global severity.
4. If the abnormality in an organ is attributed to multifactorial causes (GVHD plus other causes) the scored organ will be used for calculation of the global severity regardless of the contributing causes (no downgrading of organ severity score).

Reference: Jagasia et al. (26)

5.4 BLINDING

This is an open-label study.

5.5 TREATMENT COMPLIANCE

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

5.6 MISSED DOSES

Participants should make every effort to take the study drug at the same time every day with their morning/evening meal. Participants will be instructed to start a meal within 30 minutes prior to taking their belumosudil treatment. In the event that the participant misses the planned dose of study drug, the following protocol should be followed:

For participants in Arm A, 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 participant 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 participant should then resume the regular planned dosing schedule the following day.

For participants in Arm B, 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 participant 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 participant should resume dosing with the next the regular planned dose.

If the participant skips more than 7 consecutive days of drug, the participant should be discontinued from the study unless approved by the Medical Monitor and Investigator.

In the event of vomiting, the participant 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 investigational product received from and returned to the sponsor, and the amounts of investigational product dispensed to study participants, and the amount returned by study participants. 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; this necessitates discontinuing from study drug.

5.8.1 Corticosteroids

Corticosteroid dose data will be collected throughout the study. Corticosteroids may be tapered at the discretion of the Investigator after ≥2 weeks of belumosudil administration.

Transient increases in corticosteroid dosing (not exceeding 1mg/kg/day prednisone equivalent, Appendix K) are permitted for the treatment of cGVHD flare, but dose must be reduced back to the pre-randomization dose within 6 weeks. If the dose remains elevated for more than 6 weeks, this will be considered a belumosudil treatment failure. More than 2 episodes of cGVHD flare requiring increased corticosteroid therapy in the first 6 months of belumosudil treatment will also be considered a belumosudil treatment failure; this necessitates discontinuing from study drug.

Response assessments scheduled to occur during treatment of a cGVHD flare will be conducted as planned but will not be included in the primary efficacy analysis.

PD samples should be collected at time corticosteroid dose is increased. Refer to the Laboratory Manual for detailed instructions.

5.8.2 Systemic cGVHD Therapies

Per the eligibility criteria, participants receiving standard of care systemic cGVHD therapies such as calcineurin inhibitors (tacrolimus, cyclosporine), sirolimus, MMF, methotrexate, rituximab or ECP, may be enrolled if they have been on a stable dose / schedule. Changes in doses of drugs to maintain therapeutic levels are not considered as a change in dose/schedule.

Doses and schedules of these therapies will be collected throughout the study and changes will be documented.

Doses may be tapered at the discretion of the Investigator after ≥4 weeks of belumosudil administration.

Increases in dosage to above the baseline dose are not permitted. An exception is for dose adjustments to maintain therapeutic drug levels.

5.8.3 Topical / Organ Specific Therapies for cGVHD

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

5.8.4 CYP3A4 Inducers and Proton Pump Inhibitor

Use of strong CYP3A4 inducers decreases belumosudil exposure (Section 21.9 Appendix I). Use of PPIs (eg, omeprazole [Prilosec], esomeprazole [Nexium], lansoprazole [Prevacid], rabeprazole [AcipHex], pantoprazole [Protonix]) decreases belumosudil exposure. Participants on strong CYP3A4 inducers or PPIs can dose modify to 200 mg BID if they are dosing at 200 mg QD at the Investigator's discretion.

5.8.5 Prohibited Concomitant Medications

Treatment with investigational systemic immunosuppressant drugs for cGVHD is prohibited. Concomitant use of Ruxolitinib is prohibited.

5.9 TREATMENT OF OVERDOSE

Any dose of belumosudil >1000 mg within a 24-hour period will be considered an overdose. In clinical studies of belumosudil, repeat dosing of 500 mg BID for 28 days was generally well tolerated in healthy volunteers. There are no known antidotes to belumosudil, and no specific treatment is recommended in the event of a suspected overdose. The treating Investigator should employ clinical judgment in managing participants with suspected overdose. Overdose should be reported as an AE (Section 9.2).

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 participants receiving belumosudil are outlined in Table 2 below.

Table 2 - Guidelines for Management of Treatment-Emergent Toxicities

Toxicity	Recommended Action
ALT or AST increased (more than 20x ULN), blood bilirubin increased (more than 3x ULN) considered at least possibly related to belumosudil	Discontinue belumosudil
Other Grade 4 organ toxicities considered at least possibly related to belumosudil	• Discontinue belumosudil
AST or ALT increased (5x to 20x ULN) or total bilirubin increased (1.5x to 3x ULN) considered at least possibly related to belumosudil	• Hold belumosudil dosing until recovery of total bilirubin (≤1.5x ULN), AST and ALT (≤3x ULN), then consider resuming belumosudil at the recommended dose • Complete the "Treatment Emergent LFT Elevations" eCRF • Consider resuming belumosudil. If resuming, then resume at the recommended dose • 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 the recommended dose • If toxicity recurs, hold dose as above then consider resuming belumosudil at the recommended dose

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; eCRF=electronic case report form; LFT=liver function enzymes.

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

6 STUDY ASSESSMENTS AND PROCEDURES

6.1 SCHEDULE OF ASSESSMENTS

The schedule of assessments is outlined in Section 21.1

- Table 6: Schedule of Assessments.
- Table 7: Pharmacokinetics Sampling.
- Table 9: Pharmacodynamic Sampling.

Further details of pulmonary function testing are provided in Appendix J.

In addition to the assessments detailed below, Investigators may, with appropriate consenting of participants, take serial photographs to further document changes in cGVHD (eg, skin, range of motion).

6.2 STUDY VISITS

6.2.1 Screening

During screening, participants will have the following completed:

- Provide informed consent / assent.
- Demographic information including gender, age (date of birth), ethnic origin and race.
- Medical history.
- Transplant history including indication for and type of prior transplant(s).
- GVHD history (acute and chronic).
- cGVHD treatment history, including prior therapies and lines of treatment for cGVHD (Section 4.5).
- Physical examination. All clinically significant findings, either new of worsening throughout the study will be documented as AEs or SAEs.
- Height, weight and body mass index (BMI).
- Seated vital sign measurements (sitting blood pressure, pulse, respiratory rate, temperature).
- Karnofsky (if aged ≥16 years) / Lansky (if aged <16 years) Performance Scale score (Appendix G).
- Hematology (Table 4).

- Clinical chemistry (Table 4).
- Virology.
- Spirometry (FEV1 and FVC) (Appendix J).
- Supine 12 Lead ECG, single.
- Highly sensitive urine or serum pregnancy test (for females of childbearing potential). Positive urine results are to be confirmed with serum testing.
- Concomitant medications / procedures assessment

Baseline cGVHD severity must be assessed (a stratification factor for randomization). Chronic GVHD severity is defined in Section 5.3 (26).

Eligible participants may be randomized after Medical Monitor approval during the screening window or on C1D1 prior to dosing with belumosudil.

6.2.2 Cycle 1, Day 1 (Baseline)

At the Cycle 1, Day 1 visit, participants will come to the clinic to have the following procedures completed. (Note that if screening assessments, apart from hematology, clinical chemistry and urine pregnancy are done within 7 days prior to Cycle 1, Day 1, they do not need to be repeated on Cycle 1 Day 1).

Pre-dose

- Concomitant medications / procedures assessment.
- AE assessment.
- Symptom directed PE.
- Highly sensitive urine or serum pregnancy test (for females of childbearing potential). Positive urine results are to be confirmed with serum testing. Refer to Section 6.4.5 for positive serum tests.
- Seated vital sign measurements (sitting blood pressure, pulse, respiratory rate, temperature).
- Weight measurement.
- Height and BMI if aged <18 years.
- Karnofsky (if aged ≥16 years) / Lansky (if aged <16 years) Performance Scale score (Appendix G).
- Hematology (Table 4).
- Clinical chemistry (Table 4).
- Single 12-lead ECG (Table 10).

- Clinician-Reported Global cGVHD Activity Assessment.
- Full pulmonary function tests (including FEV1, FVC, diffusing capacity of lung for carbon monoxide [DLCO, corrected for Hb], total lung capacity [TLC], and residual volume [RV]) (Appendix J). Baseline PFTs may also be performed post dose on C1D1 or at any time in the 7 days prior to C1D1.
- cGVHD Activity Assessment - Patient Self Report.
- Lee cGVHD Symptom Scale (Appendix D).
- Document dosing of corticosteroids, and other cGVHD therapies.
- For full PK participants, PK sampling (Table 7).
- Pharmacodynamic sampling (Table 9).
- PROMIS Global Health score (Appendix E).

Dosing / Post-dose

- Study drug administration.
- Dispense study drug.
- Dispense study drug diary.
- Single 12-lead ECG 3 hours post dose (Table 10).
- For full PK participants, PK sampling 1, 2, 3, 4, 5, 6, 7 and 8 hours post dose with optional sample at 12 hours post dose (prior to belumosudil PM dosing for Arm B participants) (Table 7).
  - Full PK participants should also have C1D2 PK sample drawn prior to dosing with belumosudil.

6.2.3 Cycles 1, Day 15 (±3 days)

On Day 15 of Cycle 1 only, participants will come to the clinic to have the following procedures completed:

- Concomitant medications / procedures assessment.
- AE assessment.
- Symptom directed PE.
- Weight measurement.
- Seated vital sign measurements (sitting blood pressure, pulse, respiratory rate, temperature).
- Hematology (Table 4).
- Clinical chemistry (Table 4).

6.2.4 Cycle 2 and Beyond, Day 1 (±3 days)

On Day 1 of Cycles 2, 3, 5, 7 and then every other 3 treatment cycles (C10D1, C13D1, etc.), participants will come to the clinic to have the following procedures completed:

Pre-dose

- Concomitant medications / procedures assessment.
- AE assessment.
- Symptom directed PE.
- Highly sensitive urine or serum pregnancy test (for females of childbearing potential). Positive urine results are to be confirmed with serum testing. Refer to Section 6.4.5 for positive serum tests.
- Weight measurement.
- Height and BMI if aged <18 years.
- Seated vital sign measurements (sitting blood pressure, pulse, respiratory rate, temperature).
- Karnofsky (if aged ≥16 years) / Lansky (if aged <16 years) Performance Scale score (Appendix G).
- Hematology (Table 4).
- Clinical Chemistry (Table 4).
- Single 12-lead ECG (Table 10).
  - Single ECG on C2D1, C3D1, C5D1, C7D1 and Day 1 of every 3rd cycle thereafter through C19D1.
  - Starting on C19D1 only if clinically indicated.
- Document corticosteroid dosage.
- Document other cGVHD therapies.
- * Pulmonary function tests (Appendix J).
  - Can be post-dose.
  - Full PFTs (including FEV1, FVC, DLCO (corrected for Hb), TLC, and RV) are required after Cycle 2, 6, 12 and every 6th Cycle thereafter (Day 1 of Cycles 3, 7, 13, 19 etc.). At other cycles, spirometry (FEV_1 and FVC) is sufficient.
- * Clinician-Reported Global cGVHD Activity Assessment.
- * Response assessment.
- * cGVHD Activity Assessment - Patient Self Report.
- * Lee cGVHD Symptom Scale (Appendix D).

- * PROMIS Global Health score (Appendix E).
- Sparse PK sampling on C2D1 and C7D1 only for all participants (Table 7).
- Pharmacodynamic sampling on C2D1 and C7D1 only (Table 9).

Dosing / Post dose

- Study drug administration.
- Dispense / collect study drug.
- Dispense / collect study drug diary.
- Sparse PK sampling on C2D1 and C7D1 only for all participants at 3 hours post-dose (Table 7).
- For full PK participants, PK sampling 1, 2, 3, 4, 5, 6, 7 and 8 hours post dose with an optional sample at 12 hours post dose on C2D1 only (prior to belumosudil PM dosing for Arm B participants) (Table 7).
    - Full PK participants should also have C2D2 PK sample drawn prior to dosing.

*** These items must be completed on Day 1 of Cycles 2, 3, 5, 7, then on Day 1 of every 3 cycles thereafter, (Day 1 of Cycles 10, 13, 16, 19, etc.). These items may be completed on Day 1 of other cycles if deemed appropriate by the Investigator.**

Note: On Day 1 of Cycles 8 and beyond, participants will come to the clinic to have the same procedures as described above, except belumosudil may be administered at home or in the clinic (procedures can then be pre- or post-dose).

On Cycle 2 Day 1 (C2D1) participants will receive study drug for 1 cycle along with 1 diary. On Cycle 3 and 5 Day 1 (C3D1 and C5D1), participants will receive the study drug for the next 2 cycles along with 2 diaries, and from cycle 7 onwards (C7D1, C10D1, C13D1, etc.) participants will receive the study drug for 3 cycles along with 3 diaries and return to the clinic every 3 cycles for assessments and investigational product accountability. On cycles when participants do not come to clinic, the study staff will contact the participant, eg, via phone and document any new AEs and concomitant medications. Also, from C19D1 onwards, ECGs will be done only if clinically indicated.

6.2.5 End of Treatment (EOT)

Participants are to return to the study site within 7 days after the participant's last dose of study drug to complete all EOT assessments. This may occur at the visit at which disease progression is diagnosed. The following procedures will be completed:

- Concomitant medications assessment.
- AE assessment.
- Symptom directed PE.

- Highly sensitive urine or serum pregnancy test (for females of childbearing potential). Positive results are to be confirmed with serum testing.
- Weight measurement.
- Height and BMI if aged <18 years.
- Seated vital sign measurements (sitting blood pressure, pulse, respiratory rate, temperature).
- Karnofsky (if aged ≥16 years) / Lansky (if aged <16 years) Performance Scale score (Appendix G).
- Hematology (Table 4).
- Clinical Chemistry (Table 4).
- Single 12-lead ECG (Table 10).
- Full PFTs (including FEV_1, FVC, DLCO (corrected for Hb), TLC, and RV) or spirometry (FEV_1, FVC) if full PFTs have been taken in the previous month.
- Clinician-Reported Global cGVHD Activity Assessment.
- Response assessment.
- Pharmacodynamic sampling in event of progression of cGVHD.
- cGVHD Activity Assessment - Patient Self Report.
- Lee cGVHD Symptom Scale.
- PROMIS Global Health score (Appendix E).
- Document corticosteroid dosage.
- Document other cGVHD therapies.
- Collect study drug.
- Collect study drug diary.

If the participant is discontinuing study due to enrolling in the KD025-217 study, the EOT visit is expected to be the same day as C1D1 of KD025-217. The EOT visit for these participants rolling into the extension study includes minimal assessments: collect study drug and collect study drug diary.

If the participant is discontinuing and not participating in KD025-217, all the EOT visit assessments are to be performed.

6.2.6 28-Day Follow-Up Visit

The follow-up visit should occur 28 (±7) days after the last dose of study drug. However, when possible, this visit should occur prior to starting on a new cGVHD therapy (if a new therapy is started earlier). Participants will return to the clinic and the following procedures will be completed:

- Concomitant medications assessment.
- AE assessment.
- Symptom directed PE.
- Highly sensitive urine or serum pregnancy test (for females of childbearing potential). Positive urine results are to be confirmed with serum testing.
- Weight measurement.
- Seated vital sign measurements (sitting blood pressure, pulse, respiratory rate, temperature).
- Karnofsky (if aged ≥16 years) / Lansky (if aged <16 years) Performance Scale score (Appendix G).
- Hematology (Table 4).
- Clinical chemistry (Table 4).
- Single 12-lead ECG (Table 10).

6.2.7 Unscheduled Visits

For participants requiring an unscheduled visit, assessments described in Section 6 may be performed at the Investigator's discretion.

6.2.8 Long-Term Follow-Up

After the follow-up visit is completed, participants will be contacted approximately every 12 weeks eg, by telephone, e-mail, or postal mail until a failure-free survival event occurs or until the study close-out (whichever occurs first) to confirm survival status, any changes in treatment for cGVHD and the initiation of treatment for the underlying disease. Alternatively, this information may be derived from medical records.

With Protocol Amendment 3, all participants that have not yet had a failure free survival event will end participation with KD025-213. Participants may continue to participate in KD025-213 if the Investigative Site is awaiting IRB approval of the KD025-217 rollover study titled: "Extended Treatment and Follow-up of Participants Treated with Belumosudil in Study KD025-208 or Study KD025-213".

6.3 EFFICACY

6.3.1 Efficacy Endpoints

6.3.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the overall response rate (ORR). Responders include participants that achieve a [PR+CR]. Responses are defined by the 2014 National Institutes of Health (NIH) Consensus Development Project on Clinical Trials in cGVHD.

6.3.1.2 Secondary Endpoints

- Duration of Response (DOR).
- Change in Lee Symptom Scale Score.
- Response rate by organ system.
- Time to response (TTR).
- Time to next treatment (TTNT).
- Percentage of participants who have a best response of PR or CR.
- Change in corticosteroid dose.
- Change in calcineurin inhibitor dose.
- Failure-free survival (FFS).
- Overall Survival (OS).
- Change in cGVHD global severity rating as based on the Clinician-Reported global cGVHD Activity Assessment.
- Change in symptom activity as based on cGVHD Activity Assessment Patient Self-Report.
- Pharmacokinetics.

6.3.1.3 Exploratory Endpoints

- PROMIS Global Health subscores for physical and mental functioning.
- ORR per Kadmon Algorithmic Response Assessment (KARA).
- Pharmacodynamics - Changes in relevant biomarkers after belumosudil administration.

6.3.2 Overall Response Rate

The overall response determination is based on the cGVHD response assessment performed by Investigators (see Appendix B) per the Schedule of Assessments. Where possible, the same assessor at the site should perform response assessments for a given participant.

The overall response is assessed using the global scores from ten systems (Skin, Eyes, Mouth, Esophagus, Upper GI, Lower GI, Liver, Lungs, Joints and Fascia and Global Severity Rating). The overall response at each assessment time point will be categorized as Complete Response (CR), Partial Response (PR), or Lack of Response (LR), where LR includes the response status of unchanged, mixed, or progression as defined in Table 3. For clarity, Lack of Response - Mixed will be considered a progression event for analysis purposes. These response categories are based on the 2014 NIH Consensus Development Project on Clinical Trials in cGVHD (Appendix C).

Table 3 - cGVHD Response Definitions

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

* Considered progression for purposes of analysis

Pulmonary function testing is required (FEV_1) for this assessment. The same equipment and tester should be used during the course of the study to the extent possible. Pulmonary function tests should be conducted in accordance with study guidelines and the American Thoracic Society/European Respiratory Society standardization of lung function testing (27).

6.3.3 Patient Reported Outcomes

6.3.3.1 Lee Symptom Scale Score

Changes in symptom burden/bother will be explored using the Lee cGVHD Symptom Scale (Appendix D). Symptom burden will be assessed on Day 1 of each cycle starting on Cycle 1 Day 1, as well as at the EOT visit. Lee et al developed a symptom scale designed for individuals with chronic GVHD (28). The questionnaire asks participants to indicate the degree of bother that they experienced due to symptoms in seven domains potentially affected by chronic GVHD (skin, eyes, mouth, breathing, eating and digestion, energy, and emotional distress).

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

6.3.3.2 cGVHD Activity Assessment – Patient Self Report

Changes in the cGVHD Activity Assessment – Patient Self Report will be evaluated (Appendix F).

6.3.3.3 PROMIS Global Health Score

As an exploratory endpoint, changes in the PROMIS Global Health subscores for physical and mental functioning will be evaluated (Appendix E) (29).

6.3.4 Change in Corticosteroid Dose

The change in systemic corticosteroid dose over time will be determined. If participants are not using prednisone as the corticosteroid therapy, then the prednisone dose equivalent will be determined (Appendix K). Dose equivalency tables are provided in the Statistical Analysis Plan.

6.3.5 Failure Free Survival

Descriptive statistics of Failure Free Survival (FFS) will be reported. FFS is defined as the absence of cGVHD treatment change, non-relapse mortality and recurrent malignancy (30).

6.4 SAFETY

6.4.1 Safety Endpoints

Safety is a secondary endpoint. The primary safety outcome will be the percent of participants in each arm experiencing AEs. See below and Section 9 for additional details.

- Adverse Events and SAEs.
- Hematological and clinical chemistry parameters.
- Vital signs.
  - Change from baseline in systolic blood pressure, diastolic blood pressure and heart rate.
- 12-Lead ECG
  - Mean and maximum change from baseline in QTc(F).

6.4.2 Vital Signs

Seated pulse rate and blood pressure measurements will be performed as outlined in the schedule of assessments (Table 6). Measurements will be taken with the participant sitting, having rested in this position for at least 5 minutes. Vital signs should be taken before ECGs and other scheduled assessments. Respiratory rate and temperature will also be measured.

6.4.3 Twelve-lead ECG

Twelve-lead ECGs will be performed as outlined in the schedule of assessments (and Table 10). ECGs will be recorded after the participant has rested in the supine position for at least 5 minutes. ECGs should be performed prior to any blood sample collections.

Abnormalities in the ECG that lead to a change in participant management or result in clinical signs and symptoms are considered clinically significant for the purposes of this study and will be recorded in the AE eCRF. If ECG abnormalities meet criteria defining them as serious, they must be reported as an SAE (Section 9.3.1).

6.4.4 Clinical Laboratory Parameters

Clinical laboratory tests will be performed as outlined in the schedule of assessments (Table 6). Samples should be taken predose and will be sent to a central laboratory for analysis. Screening laboratory tests will include HBsAg and hepatitis C antibodies. Full details for collection and shipping of samples are provided in the Laboratory Manual.

Table 4 - Clinical Laboratory Panels

Hematology	Serum Chemistry
• White blood cell count with differential (including at minimum: neutrophils, basophils, eosinophils, lymphocytes, monocytes) • Red blood cell count • Hemoglobin • Hematocrit • Platelet count • MCV	• Albumin • Alkaline phosphatase • ALT • AST • BUN • Calcium • Chloride • CO_2 • Creatinine / GFR • CPK • Total and direct bilirubin • GGT • Globulin • Glucose • Lactate dehydrogenase • Magnesium • Phosphorus • Potassium • Sodium • Total protein • Uric acid

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CPK = creatine phosphokinase; GFR = Glomerular Filtration Rate; GGT = gamma glutamyl transferase; MCV = mean corpuscular volume

Abnormalities in clinical laboratory tests that lead to a change in participant management (eg, dose delay, requirement for additional medication or monitoring) are considered clinically significant for the purposes of this study and will be recorded on the AE eCRF page. Laboratory results will be classified using the CTCAE v5.0. If laboratory values constitute part of an event that meets criteria defining it as serious, the event (and associated laboratory values) must be reported as an SAE (see Section 9.3.1).

6.4.5 Pregnancy Testing

Pregnancy tests (highly sensitive urine or serum test) will be done at the timepoints specified in the SoA (Section 21) in females of childbearing potential. Positive urine results are to be confirmed with serum testing. If pregnancy is confirmed with serum testing, belumosudil will be discontinued. The Sponsor will continue to collect data on the pregnancy and the participant will be followed until after the birth of the baby to assess outcome of the pregnancy and the status of the newborn.

In the event that a participant's partner becomes pregnant during the study, the Sponsor will also collect data on the pregnancy, birth and the condition of the newborn.

6.5 USE OF BIOLOGICAL SAMPLES AND DATA FOR FUTURE RESEARCH

Future research may help to further increase the understanding of the disease and the development of new medicines. Reuse of coded data and biological samples (leftover and additional) will be limited to future scientific research conducted under a research plan for the purpose of diagnosing, preventing or treating diseases. The future research projects will be conducted under the responsibility of the Sponsor's and/or its affiliates' and/or, if applicable, the partner of the Sponsor which has licensed the study drug to the Sponsor or which is co-developing the study drug with the Sponsor's control, acting alone or in collaboration with research partners such as universities, research institutions or industrial partners with whom the coded data may be shared.

Data and biological samples will be stored and used for future research only when consented to by participants (see Section 14.1) and, when applicable, further information on the future research has been provided to the study participant, unless prohibited by local laws or IRBs/IECs (in such case, consent for future use of sample will not be included in the local ICF). The conditions for reuse will be adapted locally with the appropriate language in the ICF.

In any case, a specific consent will be collected for the performance of genetic analyses on leftover and/or additional samples.

Data protection - Processing of coded clinical data

The study participant will be provided with all mandatory details of the data processing in the ICF.

The Sponsor adopts safeguards for protecting participant confidentiality and personal data (see Section 19).

Use of leftover samples and additional samples for future research

Remaining leftover samples will be used only after the study ends, ie, end of study as defined in the study protocol. Additional/extra samples can be collected and used during the study conduct at a given timepoint (eg, at randomization visit) as defined in the study protocol.

The study participant will be provided with all mandatory details of the use of the human biological samples (leftover and additional) in the ICF.

Relating data will be stored for up to 25 years for regulatory purposes and future research. Biological samples for future use will be stored for up to 25 years after the end of the study. Any samples remaining at the end of the retention period will be destroyed. If a participant requests destruction of his/her samples before the end of the retention period, the Investigator must notify the Sponsor (or its contract organization) in writing. In such case, samples will be destroyed, and related coded data will be anonymized unless otherwise required by applicable laws.

7 PHARMACOKINETICS

On PK sampling days, participants will take their belumosudil morning dose in the clinic. The time at which the prior dose was taken will be documented. Participants should be instructed accordingly.

The pre-dose and all post-dose PK collection time points are to be documented on the appropriate eCRF. Additionally, the time of a participant's dose of study drug is to be documented.

7.1 SPARSE PK

For sparse PK analyses, blood samples (approximately 6 mL) will be collected for all participants, as outlined in Pharmacokinetics Sampling Table 7.

7.2 FULL PK

Blood samples (approximately 6 mL) for determination of plasma concentrations of belumosudil and its metabolites will be collected for a subset of participants, approximately 12 in each arm, at selected sites as outlined in Pharmacokinetics Sampling Table 7. Sites are selected based on the capabilities and agreement of the site to conduct Full PK sampling. Full PK profiles will be collected only for participants that have consented to the optional Full PK sampling.

A total of up to 23-25 samples will be collected from full PK participants (including C7D1 sparse PK). Note that the 12-hour post dose PK samples are optional.

Belumosudil and metabolite concentrations will be used to calculate the following PK parameters: C_{max}, T_{max}, $T_{1/2}$ and AUC.

Detailed instructions for sample collection and preparation will be provided in the Central Laboratory Manual.

8 PHARMACODYNAMICS

Pharmacodynamic samples will be collected for all participants as outlined in Pharmacodynamic sampling Table 9. Samples will be collected at sites with appropriate capabilities. PD samples will not be required from adolescents if the site has policies limiting the daily volume of blood allowed to be drawn as part of a clinical trial (less than the FDA guidelines).

Detailed instructions for sample collection and preparation will be provided in the Laboratory Manual.

Changes in the relevant biomarkers after belumosudil administration will be explored.

Additional samples will be collected from participants enrolled in the site-specific Companion Study for PD analyses as described in Section 21.13 Appendix M.

9 SAFETY

9.1 SAFETY PARAMETERS

The CTCAE v5.0 will be used for grading toxicities. Laboratory results also will be classified using the CTCAE v5.0. Participants will be monitored throughout the treatment and follow-up period for occurrence of AEs (acute, delayed, and/or cumulative), as well as for changes in clinical status, vital sign measurements, and laboratory data. Safety parameters to be measured/assessed include vital sign measurements, PE findings, hematology, clinical chemistry, and ECG recordings. Adverse events will be recorded after the ICF/assent form is signed until 28 days after the last dose of belumosudil.

9.2 ADVERSE EVENT DEFINITION

AE definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Definition of unsolicited and solicited AE

- An unsolicited AE is an AE that was not solicited using a participant diary and that is communicated by a participant/participant's parent(s)/legally authorized representative (LAR)(s) who has signed the informed consent. Unsolicited AEs include serious and nonserious AEs.
- Potential unsolicited AEs may be medically attended (ie, symptoms or illnesses requiring a hospitalization, emergency room visit, or visit to/by a health care provider). The participants/ participant's parent(s)/LAR(s) will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of participant/participant's parent(s)/LAR(s) concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records.
- Unsolicited AEs that are not medically attended nor perceived as a concern by the participant/participant's parent(s)/LAR(s) will be collected during an interview with the participants/participant's parent(s)/LAR(s) and by review of available medical records at the next visit.
- Solicited AEs are predefined local and systemic events for which the participant is specifically questioned, and which are noted by the participants in their diary.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease, or more severe than expected for the participant's condition), eg:
  - Leading to belumosudil discontinuation or modification of dosing, and/or,
  - Fulfilling a seriousness criterion, and/or,
  - Defined as an AESI.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or severity of the condition.
- New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- Signs, symptoms, or the clinical sequelae of any medication errors, misuse and abuse with belumosudil
- Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT meeting the AE definition

- Any abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

9.3 EVALUATING ADVERSE EVENTS

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

9.3.1 Serious Adverse Events

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:

a) Results in death

b) Is life-threatening

The term *life-threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c) Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d) Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e) Is a congenital anomaly/birth defect

f) Other situations:

- Medical or scientific judgment should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

- The following list of medically important events is intended to serve as a guideline for determining which condition has to be considered as a medically important event. The list is not intended to be exhaustive:
  - Intensive treatment in an emergency room or at home for:
    - Allergic bronchospasm.
    - Blood dyscrasias (ie, agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc).
    - Convulsions (seizures, epilepsy, epileptic fit, absence, etc).
  - Development of drug dependence or drug abuse.
  - ALT >3 × ULN + total bilirubin >2 × ULN or asymptomatic ALT increase >10 × ULN.
  - Suicide attempt or any event suggestive of suicidality.
  - Syncope, loss of consciousness (except if documented as a consequence of blood sampling).
  - Bullous cutaneous eruptions.

9.3.2 Recording and follow-up of AE and/or SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information.
- It is not acceptable for the Investigator to send photocopies of the participant's medical records to the Sponsor's representative in lieu of completion of the required form.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor's representative. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor's representative.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of severity

The Investigator will make an assessment of severity for each AE and SAE reported during the study and assign it to one of the following categories as per NCI CTCAE V5.0 definitions:

- Grade 1 Mild: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

- Grade 2 Moderate: Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL). Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- Grade 3 Severe: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, limiting self-care ADL. Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.
- Grade 4 Life-threatening consequences; urgent intervention indicated.
- Grade 5 Death related to AE.

An event is defined as serious when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The Investigator will use clinical judgment to determine the relationship.
- A reasonable possibility of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than that a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), cGVHD, concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- For causality assessment, the Investigator will also consult the IB and/or product information, for marketed products.
- The Investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes. There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report to the Sponsor's representative. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor's representative.
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor's representative to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the originally submitted documents.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

9.3.2.1 Time period and frequency for collecting AE and SAE information

All AEs (serious or nonserious) will be collected from the signing of the informed consent form (ICF) and for 28 days after the last dose of belumosudil at the timepoints specified in the SoA (Section 21.1), and any SAEs and study drug related nonserious AEs that occur more than 28 days after the last dose of belumosudil.

All SAEs and AESI will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and the Investigator considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor.

9.3.2.2 Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

9.3.2.3 Follow-up of AEs and SAEs

After the initial AE/AESI/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. At the pre-specified study end-date, all SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 4.8.1).

9.3.3 Reporting Requirements for SAEs

9.3.3.1 Regulatory reporting requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.
- Serious adverse events that are considered expected will be specified in the reference safety information (IB).
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.
- An Investigator who receives an Investigator safety report describing an SAE, SUSAR or any other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements. It is the responsibility of the Sponsor to assess whether an event meets the criteria for a SUSAR, and therefore, is expedited to regulatory authorities.

9.3.3.2 Reporting of SAEs

SAE reporting to the Sponsor via an electronic data collection tool

- The primary mechanism for reporting an SAE to the Sponsor's representative will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form or to the Sponsor's representative by telephone.
- Contacts for SAE reporting can be found in Emergency Contact Information.

SAE reporting to the Sponsor via paper data collection tool

- Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the Sponsor's representative.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE data collection tool within the designated reporting timeframes.
- Contacts for SAE reporting can be found in Emergency Contact Information.

9.3.3.3 Pregnancy

- Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study intervention and until determination of the outcome of the pregnancy.
- If a pregnancy is reported, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the female participant or female partner of male participant (after obtaining the necessary signed informed consent from the female partner) pregnancy.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant/pregnant female partner will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant/pregnant female partner and the neonate and the information will be forwarded to the Sponsor. Beyond the estimated delivery date follow-up should last up to 8 weeks.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 9.3.3. While the Investigator is not obligated to actively seek this information in former study participants/pregnant female partner, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention.

9.4 OTHER SAFETY CONSIDERATIONS

9.4.1 Laboratory Data

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

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

10 STUDY STOPPING RULES

In the event of any of the following safety findings occurring in either treatment arm, after at least 10 participants have been enrolled into the mITT population (Section 11.2.1) in that arm, enrollment will be paused for assessment of safety:

1. Secondary graft failure in >10% of participants.
2. Histological recurrence of underlying malignancy within 6 months of randomization in >20% of participants.
3. Withdrawal due to related AEs in >20% of participants.

Note: The rates of these events observed in the ongoing KD025-208 study as of 7-Mar-2018, with 51 participants enrolled, were 0%, 4% and 4% respectively.

These stopping criteria will be assessed on an on-going basis by the Medical Monitor and shared with the study Steering Committee (Section 3.2).

The Sponsor has the right to terminate or to stop the study at any time (Section 16).

11 STATISTICAL CONSIDERATIONS

Three analyses are planned:

1. An interim analysis (IA) will be conducted approximately 2 months after 126 participants have been enrolled into the mITT population. A nominal 1-sided alpha of 0.0025 will be spent, but there will be no early study termination for efficacy.
2. The primary analysis (PA) will be conducted approximately 6 months after 126 participants have been enrolled into the mITT population, with 1-sided alpha 0.0225 (or 0.025 if the ORRs of both arms are significant at interim).
3. A follow-up analysis will be conducted approximately 12 months after 126 participants have been enrolled into the mITT population.

Additional analyses will be conducted to include adolescent participants and Companion Study participants, approximately 6 months after completion of enrollment of the respective participants.

Alpha will only be allocated to the primary endpoint, ORR.

11.1 HYPOTHESIS

This study is designed to show an ORR of at least 30% in participants with cGVHD, treated with belumosudil after at least 2 prior lines of systemic therapy.

11.2 SAMPLE SIZE AND POWER CALCULATION

Sample size is based on the primary efficacy endpoint of ORR, with one planned interim analysis (0.0025 1-sided alpha spending) and a target ORR of 55%. With 63 participants, and a 10% dropout rate, each treatment arm is estimated to have approximately 90% power to yield a 95% confidence interval of ORR that excludes 30% (equivalently, 90% power to reject the null hypothesis of ORR ≤30% at 1-sided alpha level 0.0225).

The Hochberg procedure will be used for multiplicity adjustment for the primary endpoint of ORR as described below (Section 11.2.1).

Table 5 provides powers for interim analysis (Table 5a) under various hypothetic ORRs to exclude 30%, and provides study powers under various hypothetic ORRs for at least one arm to exclude 30% at primary analysis (Table 5b).

Table 5 - Power for Various Hypothetic ORRs

Table 5a: IA Power (1-sided alpha 0.0025)*						
For both arms to be statistically significant						
		Arm 1 ORR (%)				
		40	**45**	**50**	**55**	**60**
Arm 2 ORR (%)	**40**	<1	<1	<1	<1	<1
	45	-	<1	1	2	3
	50	-	-	2	6	9
	55	-	-	-	12	22
	60	-	-	-	-	37
For at least one arm to be statistically significant						
		Arm 1 ORR (%)				
		40	**45**	**50**	**55**	**60**
Arm 2 ORR (%)	**40**	1	3	10	28	51
	45	-	5	12	29	53
	50	-	-	20	35	57
	55	-	-	-	65	65
	60	-	-	-	-	77
Table 5b: PA Power (1-sided alpha 0.0225)*						
		Arm 1 ORR (%)				
		40	**45**	**50**	**55**	**60**
Arm 2 ORR (%)	**40**	20	39	64	84	95
	45	-	52	72	89	97
	50	-	-	83	93	98
	55	-	-	-	97	99
	60	-	-	-	-	100

IA = Interim Analysis; PA = Primary Analysis
* Power estimated based upon 10,000 simulations for each cell

A 10% dropout rate (non-efficacy and non-safety related) is assumed based upon preliminary data from the ongoing KD025-208 study. If during the course of the current study the dropout rate is observed to exceed 10%, the sample size may be adjusted eg, to approximately 85 participants per arm if the dropout rate reaches 15%.

11.2.1 Efficacy Decision Rules with Multiplicity Adjustment

The Hochberg procedure is the primary multiplicity adjustment method for inferential purposes for the primary endpoint ORR.

The inferential decision for primary endpoint of ORR is described below and shown in Figure 2.

1. Calculate two-sided 99.5% confidence interval of ORR by using Clopper-Pearson (exact) method for both arms at interim analysis.
2. If the lower bounds of their 2-sided 99.5% confidence interval both are above 30%, then claim both arms are efficacious, and stop. Otherwise, go to Step 3.
3. If the lower bounds of their 2-sided 99.5% confidence interval both are below 30%, then cannot determine efficacy for either arm, and go to Step 5. Otherwise, go to Step 4.

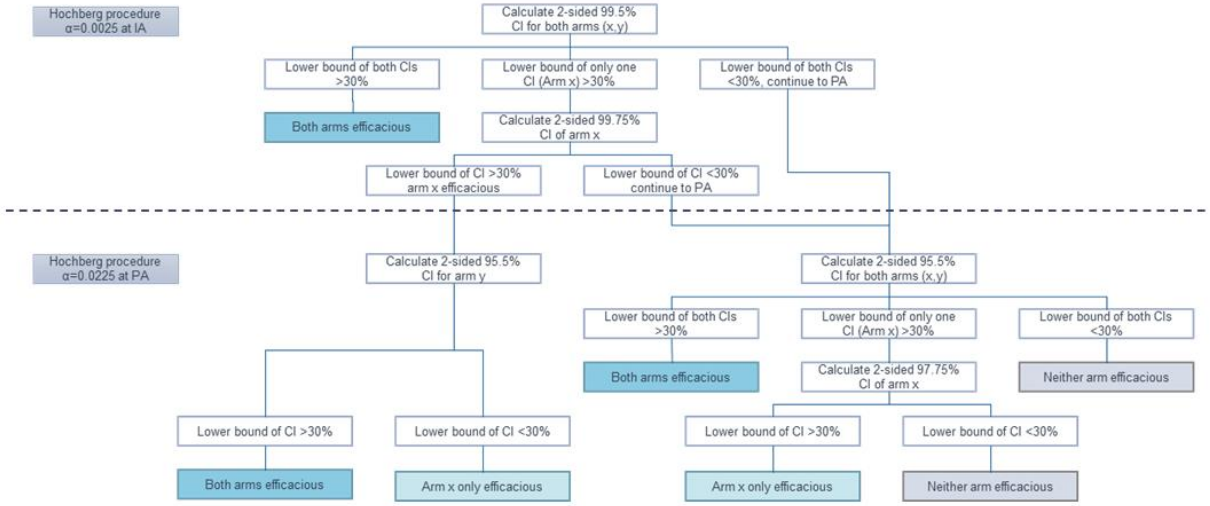
4. Calculate 2-sided 99.75% confidence interval of ORR by using Clopper-Pearson (exact) method for treatment group with higher response rate. If its lower bound is above 30%, then claim this arm is efficacious, and go to step 6. Otherwise, cannot decide efficacy for both arms, and go to Step 5.
5. Use following Hochberg procedure for the 6-month primary efficacy analysis of ORR
   a) Calculate 2-sided 95.5% confidence interval of ORR by using Clopper-Pearson (exact) method for both arms.
   b) If the lower bounds of their 2-sided 95.5% confidence interval both are above 30%, then claim both arms are efficacious, and stop. Otherwise, go to Step 5c.
   c) If the lower bounds of their 2-sided 95.5% confidence interval both are below 30%, then claim both arm are non-efficacious, and stop. Otherwise, go to Step 5d.
   d) Calculate 2-sided 97.75% confidence interval of ORR by using Clopper-Pearson (exact) method for treatment group with higher response rate. If its lower bound is above 30%, then claim this arm is efficacious, and stop. Otherwise, claim both arms are non-efficacious, and stop.
6. At the 6-month primary analysis, calculate 2-sided 95.5% confidence interval (CI) of ORR by using Clopper-Pearson (exact) method for the treatment group with lower response rate at interim analysis. If its lower bound is above 30%, then claim this arm is efficacious, and stop. Otherwise, claim this arm is non-efficacious, and stop.

If one arm is discontinued in view of the prescribed stopping rules (Section 10), efficacy will only be assessed for the remaining arm without multiplicity adjustment.

The 12-month follow up analyses is an extension of the primary analysis with more mature data for DOR and other endpoints.

In addition to inferential analysis results, nominal 95% CIs will be provided for ORR and other efficacy endpoints without multiplicity adjustment.

Figure 2 - ORR Multiplicity Adjustment



11.3 ANALYSIS POPULATIONS

Modified Intent-to-Treat Population

The modified Intent-to-Treat (mITT) population will consist of all randomized participants who receive at least one dose of study drug. This is the primary population for the analysis of the primary endpoint.

The mITT population will be used for tables of demography, baseline characteristics, efficacy and safety.

11.4 SUBGROUP ANALYSES

Subgroup analyses will be conducted for the following subgroups:

- Prior ibrutinib (Yes / No).
- Severe cGVHD (Yes / No).
- Number of organs involved (<4 / ≥4).
- Number of prior lines of therapy (≤3 / >3).
- Duration of cGVHD before enrollment.
- Lung involvement (Yes / No).
- Concomitant treatment with a proton pump inhibitor (Yes / No).
- Age (12-17, 18-64, ≥65).

11.5 DATA ANALYSIS

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

11.6 INTERIM ANALYSIS

Interim, primary, and follow-up analyses are described above.

Ongoing monitoring of safety data will be conducted in accordance with study stopping rules (Section 10).

11.7 EFFICACY ANALYSES

11.7.1 Primary Efficacy Endpoint

The ORR is defined as the proportion of participants (from the mITT population) meeting the overall response criteria assessment of complete or partial responses at any post-baseline response assessment (Section 6.3.2).

11.7.2 Secondary Efficacy Endpoints

Secondary endpoints are as follows:

- Duration of response (DOR): Assessments of DOR will include:
  - The time from initial response of PR or CR until documented progression from best response of cGVHD, new cGVHD therapy, or death.
  - Time from initial response to start of additional systemic cGVHD therapy or death.
- Changes in the Lee Symptom Scale Score: Analyses will include:
  - Number of participants with a ≥7 point reduction.
  - Number of participants with a ≥7 point reduction on 2 consecutive assessments.
  - Duration of a ≥7 point reduction.
- Response by organ system: The response assessment for the nine individual organs (Skin, Eyes, Mouth, Esophagus, Upper GI, Lower GI, Liver, Lungs, and Joints and fascia).
- Time to response (TTR): defined as the time from the first dose of belumosudil to the first documented cGVHD response.
- Time to next therapy (TTNT): defined as the time from the first dose of belumosudil to the start of additional systemic cGVHD therapy.
- Number and percentage of participants who have a best response of PR and number and percentage of participants who have a best response of CR.
- Change in corticosteroid dose:
  - The prednisone equivalent dose of corticosteroids (mg/kg/day) during the study will be analyzed (Appendix K).
- Change in calcineurin inhibitor dose.
- Failure-free-survival (FFS): FFS is defined as the absence of cGVHD treatment change, non-relapse mortality and recurrent malignancy (Section 6.3.5). Median FFS (from first dose of belumosudil) and landmark FFS at 1 year will be analyzed.
- Overall survival (OS): Defined as time from first dose of belumosudil to the date of death due to any cause.
- Changes in cGVHD global severity rating using the Clinician-Reported Global cGVHD Activity Assessment.

- Changes in symptom activity using the cGVHD Activity Assessment Patient Self-Report.

Descriptive statistics will be provided for all secondary endpoints.

11.8 EXPLORATORY ANALYSES

- Changes in the PROMIS Global Health subscores for physical and mental functioning.
- ORR using Kadmon Algorithmic Response Assessment (KARA) for overall response.
- Changes in the expression of relevant biomarkers after belumosudil administration (Section 11.11).

11.9 SAFETY ANALYSES

Safety is a secondary endpoint.

Treatment exposure will be summarized.

Safety analyses include:

- Adverse Events and SAEs
  - Treatment-emergent AEs will be summarized by treatment group using MedDRA® (Version 20.0 or greater) System Organ Class (SOC) and preferred term, classified from verbatim terms. The incidence and percentage of participants with at least 1 occurrence of a preferred term will be included. Causality (relationship to study treatment) will be summarized separately.
  - AEs, SAEs, related AEs, related SAEs, ≥Grade 3 AEs, related ≥ Grade 3 AEs, and AEs leading to withdrawal, or treatment discontinuation will be summarized overall and by treatment arm. AEs will also be presented in listings. Duration of AEs will be determined and included in listings, along with action taken and outcome.
- Hematological and clinical chemistry parameters using central laboratory
  - Laboratory results will be classified using CTCAE v5.0 and summarized by treatment arm. Incidence of laboratory abnormalities will be summarized. The worst on-study grade after the first dose of study drug will be summarized. The incidence of ≥Grade 3 laboratory abnormalities under treatment and shifts in toxicity grading from baseline to highest grade post-baseline will be displayed.
- Vital signs
  - Change from baseline in systolic blood pressure, diastolic blood pressure and heart rate will be presented.
- 12-Lead ECG
  - Mean and maximum change from baseline in QTc(F) will be derived.

11.10 PHARMACOKINETIC ANALYSES

The pharmacokinetic profile of belumosudil and major metabolites will be evaluated. Further details will be described in the Pharmacokinetic Analysis Plan.

11.11 PHARMACODYNAMIC ANALYSES

Further details will be described in the Pharmacodynamics Analysis Plan.

12 DATA QUALITY ASSURANCE

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

13 REGULATORY OBLIGATIONS

13.1 COMPLIANCE STATEMENT

This study will be conducted in compliance with Good Clinical Practice (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 agrees to adhere to all applicable local laws and regulatory requirements relevant to the use of new therapeutic agents in the countries involved.

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

Freely given written informed consent must be obtained from every participant before participation in this clinical trial. The rights, safety, and well-being of participating participants are the most important considerations and should prevail over interests of science and society.

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

14 ETHICAL ASPECTS

14.1 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 Participants", and Part 56, "Institutional Review Boards", or applicable local equivalent.

14.2 INFORMED CONSENT

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

It is the responsibility of the Investigator, or a person designated by the Investigator, to obtain written informed consent and/ or assent from each participant (or the participant'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 (eg, federal and state) regulations. In the case where the participant is unable to read, an impartial witness should be present during the entire informed consent/ assent discussion. After the participant has orally consented/ assented to participation in the trial, the witness' signature on the form will attest that the information in the consent/ assent form was accurately explained and understood. A copy of the ICF/ assent form must be provided to the participant or to the participant'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 participant consent/ assent, and this must be completed appropriately. Signed ICFs/ assent forms must remain in each participant's study file and must be available for verification by study monitors at any time. If new safety information results in changes in the risk/benefit assessment, the consent and assent form should be reviewed and updated as necessary. All participants (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/ assent to continue in the study.

14.3 RESEARCH ETHICS COMMITTEES

Prior to the initiation of the study, the protocol and associated documentation must be given a favourable 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.

15 CONDITIONS FOR MODIFYING THE PROTOCOL

Protocol modifications will be reviewed, and approved by the Sponsor 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 participants, or when the change involves only logistical or administrative aspects of the trial (eg, change in monitor, change of telephone number).

16 CONDITIONS FOR TERMINATING THE STUDY

The Sponsor has the right to terminate the study at any time. In terminating the study, the Sponsor and the Investigator will ensure that adequate consideration is given to the protection of the participants' interests.

17 STUDY DOCUMENTATION, CRFS, AND RECORD KEEPING

17.1 INVESTIGATOR'S FILES AND RETENTION OF DOCUMENTS

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

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

Participant clinical source documents (usually predefined by the project to record key efficacy and safety parameters independent of the eCRFs) may include participant 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 participant screening and enrollment logs. The Investigator must keep these 2 categories of documents on file for at least 2 years following the marketing application approval date for the study drug and for the indication being investigated or for 2 years after the investigation is discontinued and the FDA is notified. After that period of time, the documents may be destroyed participant to local regulations with prior written permission from the Sponsor. If the Investigator wants to assign the study records to another party or move them to another location, the Sponsor 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 the Sponsor 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 participant, appropriate copies should be made for storing outside of the study site.

17.2 SOURCE DOCUMENTS AND BACKGROUND DATA

Upon request, the Investigator will supply the Sponsor 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 participant confidentiality is protected.

17.3 AUDITS AND INSPECTIONS

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

17.4 ELECTRONIC CASE REPORT FORMS

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

An eCRF is required to be submitted for every participant who provides informed consent/assent. This includes submission of retrievable data on participants who withdraw before completion of the study. eCRFs must be reviewed for completeness and accuracy, and electronically signed where indicated, by the Principal Investigator or authorized delegate from the study staff. If a participant stops treatment or terminates from the study, the dates and reasons must be noted on the eCRF.

18 MONITORING OF THE STUDY

It is understood that the responsible the Sponsor 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 participant confidentiality is maintained in accordance with local requirements.

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

19 CONFIDENTIALITY OF TRIAL DOCUMENTS AND PARTICIPANT RECORDS

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

20 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

The results of this study may be published or presented at scientific meetings. The Investigator agrees to submit all manuscripts or abstracts to the Sponsor for review at least 30 days before submission. This allows the Sponsor 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 the Sponsor 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 the Sponsor's policy and generally accepted standards for authorship.

For those journals that request sharing of the analyzable data sets that are reported in the publication, interested researchers are directed to submit their request to vivli.org.

Individual anonymized participant data and supporting clinical documents are available for request at vivli.org. While making information available we continue to protect the privacy of participants in our clinical trials. Details on data sharing criteria and process for requesting access can be found at this web address: vivli.org.

21 APPENDICES

21.1 APPENDIX A: SCHEDULE OF ASSESSMENTS

Table 6 - Schedule of Assessments

Assessment	Screening	Baseline[k]	Cycle 1 Day 15	28-Day Treatment Cycles[l]	End of Treatment (EOT)	28-Day Follow-Up (±7 days)	Long Term Follow-Up (LTFU)
Cycle Day	**-14 to -1**	**C1D1**	**C1D15 (±3 days)**	**CxD1 (±3 days)**			
Written Informed Consent/Assent	X[a]						
Participant Demography	X						
Medical History	X						
Transplant History	X						
GVHD History	X						
cGVHD Prior Treatments	X						
Inclusion/Exclusion Criteria	X						
cGVHD severity assessment	X						
Randomization[b]	X						
Efficacy Assessments							
Clinician-reported global cGVHD activity assessment		X		X	X		
Response Assessment				X	X		
Pulmonary Function Tests[c]	X	X		X	X		
cGVHD Activity Assessment - Patient Self Report		X		X	X		
Lee Symptom Scale Score		X		X	X		
PROMIS Global Health Score		X		X	X		
Document Corticosteroid Dosage	*Corticosteroid dosage to be collected from the date the ICF/assent form is signed until 28 days after last dose of study drug*						
Document other cGVHD therapies	*Other cGVHD therapies to be collected from the date the ICF/assent form is signed until 28 days after last dose of study drug*						

Assessment	Screening	Baseline[k]	Cycle 1 Day 15	28-Day Treatment Cycles[l]	End of Treatment (EOT)	28-Day Follow-Up (±7 days)	Long Term Follow-Up (LTFU)
Cycle Day	**-14 to -1**	**C1D1**	**C1D15 (±3 days)**	**CxD1 (±3 days)**			
Follow-Up Contact[d]							X
New Treatment for cGVHD or underlying disease							X
Safety Assessments							
Complete PE[e]	X						
Symptom directed PE		X	X	X	X	X	
Vital signs[f]	X	X	X	X	X	X	
Weight	X	X	X	X	X		
Karnofsky / Lansky Performance Scale score	X	X		X	X	X	
Hematology	X	X	X	X	X	X	
Clinical Chemistry	X	X	X	X	X	X	
Virology[g]	X						
12-Lead ECG[h] (Table 10)	X[h]	X[h]		X[h]	X[h]	X[h]	
Highly sensitive urine or serum pregnancy test[i]	X	X		X	X	X	
Concomitant medications / procedures	*Concomitant medications / procedures to be collected from the date the ICF/assent form is signed until 28 days after last dose of study drug.*						
Adverse events	*AEs to be collected from the date the ICF/assent form is signed until 28 days after last dose of study drug.*						
Investigational Product							
Study drug administration		X[j]	X[j]	X[j]			
Dispense/Collect Study Drug & Study Drug Diary		X		X	X		
Pharmacokinetics	See Table 7 Table 7and Table 8						
Pharmacodynamics	See Table 9						

cGVHD = chronic graft versus host disease; ECG = electrocardiogram; ICF = informed consent form; ECP = Extracorporeal Photopheresis; PE = Physical Examination

a The informed consent/assent form must be signed before any study procedures begin. Documented standard of care assessments performed within 14 days of C1D1 can be used as screening assessments even if done prior to signing of ICF/assent form.

b Randomization after eligibility for the study is confirmed by the Medical Monitor or designee. Randomization may occur during screening or pre-dose on C1D1.

Assessment	Screening	Baseline[k]	Cycle 1 Day 15	28-Day Treatment Cycles[l]	End of Treatment (EOT)	28-Day Follow-Up (±7 days)	Long Term Follow-Up (LTFU)
Cycle Day	**-14 to -1**	**C1D1**	**C1D15 (±3 days)**	**CxD1 (±3 days)**			

c Lung function assessment to be conducted at time of response assessments (see item d below). Pulmonary Function Tests (PFTs), to include FEV_1, FVC, DL_{CO} (corrected for Hb), TLC, and RV, will be performed at baseline (within 7 days of C1D1 or on C1D1) and Day 1 of Cycles 3, 7, 13 and every 6th Cycle thereafter. During screening, and on Day 1 of other cycles with response assessments, spirometry (FEV_1 and FVC) is sufficient (Appendix J)

d Participants are to be contacted eg. by telephone, e-mail, or postal mail approximately every 12 weeks until a failure-free survival event occurs or until study close-out (whichever comes first) to confirm survival status, any changes in treatment for cGVHD, and the initiation of any anti-cancer treatment.

e Including height. Note that for adolescents (12 – 17 years old) height is also to be assessed at Day 1 of Cycles 1 (ie, baseline), 2, 3, 5, 7, and then at every other 3 treatment cycles.

f Vital sign measurements (sitting blood pressure and heart rate to be obtained after 5 minutes of rest), and respiratory rate and temperature

g Virology to include testing for Hepatitis B and Hepatitis C

h ECGs – see Table 10

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

j On Day 1 of Cycles 1, 2, 3, 5, 7, and then every 3 cycles (C10D1, C13D1, etc.) and on scheduled PK and PD sampling days, participants must take their dose of belumosudil at the clinic. From Cycle 8 onwards, the Day 1 dose may be taken at home or in the clinic

k If screening assessments, apart from hematology, clinical chemistry, and urine pregnancy are done within 7 days prior to C1D1, they do not need to be repeated on C1D1

l Participants will come to the clinic for visit on Day 1 of Cycles 2, 3, 5, 7. Next visit after Cycle 7 Day 1 is Cycle 10 Day 1. From C10D1 onwards, participants may return to clinic after every other 3 treatment cycles (ie, C13D1, C16D1, then every 12 weeks) ±3 days from the most recent visit. The exceptions are for 12-lead ECG, which should be performed only if clinically indicated starting from C19D1 and full PFT tests, which should be completed every 6 cycles starting from C13D1.

Table 7 - Pharmacokinetics Sampling

PK Sample Collection		
Sample		Blood (approximately 6 mL)
Full PK Profile: Subset of participants at selected sites		
Cycle 1	Day 1	Immediately prior to belumosudil dosing, and at 1, 2, 3, 4, 5, 6, 7, 8 and 12 hours post dose. Note: 12 hour sample is optional (For Arm B participants the optional 12 hour post dose sample should be drawn immediately prior to belumosudil PM dosing)
	Day 2	Immediately prior to belumosudil dosing
Cycle 2	Day 1	Immediately prior to belumosudil dosing, and at 1, 2, 3, 4, 5, 6, 7, 8 and 12 hours post dose. Note: 12 hour sample is optional (For Arm B participants the optional 12 hour post dose sample should be drawn immediately prior to belumosudil PM dosing)
	Day 2	Immediately prior to belumosudil dosing
Sparse PK: All Participants		
Cycle 2	Day 1	Immediately prior to belumosudil dosing 3 hours post dose
Cycle 7	Day 1	Immediately prior to belumosudil dosing 3 hours post dose

Timing allowances for PK sampling are as described in Table 8.

Table 8 - Pharmacokinetics Sampling Timing Allowance

PK Time point	**Tolerance Window**	
	Full PK Profile	**Sparse PK**
Prior to belumosudil dose	-60 mins to belumosudil dosing	-60 mins to belumosudil dosing
1, 2, 3 hours	±10 minutes	±10 minutes
4, 5, 6, 7, 8 hours	±15 minutes	+60 minutes
12 hours	±60 minutes	NA

Table 9 - Pharmacodynamic Sampling

PD Sample Collection		
Sample		Blood (approximately 20 mL)
All Participants		
Cycle 1	Day 1	Within 60 minutes prior to belumosudil dosing
Cycle 2	Day 1	Within 60 minutes prior to belumosudil dosing
Cycle 7	Day 1	Within 60 minutes prior to belumosudil dosing
Conditional		
cGVHD Flare		At time of increase of corticosteroid dosing
EOT		If progression of cGVHD

Table 10 - ECG Assessments

ECG Assessments		
Screening	Screening window	Single ECG
Cycle 1	Day 1	Single ECG within 60 minutes prior to belumosudil dosing and at 3 hours post dose (± 20 minutes)
Cycle 2, 3, 5	Day 1	Single ECG
Cycle 7 and every 3rd cycle thereafter through C19	Day 1	Single ECG
From C19 onward only if clinically indicated	Day 1	Single ECG
EOT		Single ECG
28-Day Follow Up		Single ECG

21.2 APPENDIX B: CGVHD ACTIVITY ASSESSMENT FOR CLINICIAN

	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	FEV_1 (% Predicted):	FEV_1 (L):	FVC (% Predicted):	FVC (L):
Not done ☐	_____	_____	_____	_____

☐ *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

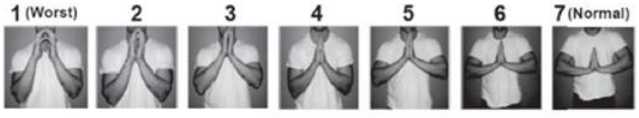
Shoulder

Score _____
Not done ☐

Elbow

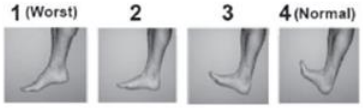
Score _____
Not done ☐

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

Additional cGVHD details per organ *

LUNGS	**Pulmonary Function Tests (PFTs)**	**DL_{CO} (single breath, adjusted for hemoglobin)** _____	**RV (L)** _____	**TLC (L)** _____

OTHER SKIN GVHD FEATURES (NOT scored by BSA)

Check all that apply:

□ Hyperpigmentation	□ Poikiloderma	□ Hair Involvement
□ Hypopigmentation	□ Severe or generalized pruritus	□ Nail Involvement

EYES	*Keratoconjunctivitis sicca (KCS) confirmed by ophthalmologist:*	□ **Yes**	□ **No**	□ **Not examined**

OTHER cGVHD FEATURES

Other indicators, clinical features or complications related to chronic GVHD [check all that apply and assign a score to severity (0-3) based on functional impact where applicable; none: 0; mild: 1; moderate: 2; severe: 3]

□ Ascites (serositis) ___	□ Myasthenia Gravis ___
□ Pericardial Effusion ___	□ Peripheral Neuropathy ___
□ Pleural Effusion ___	□ Polymyositis ___
□ Nephrotic syndrome ___	□ Others (specify): _____

cGVHD STATUS

Since starting belumosudil, would you say that this patient's cGvHD is:

-3	-2	-1	0	+1	+2	+3	**Score:**
Very much worse	Moderately worse	A little worse	About the same	A little better	Moderately better	Very much better	__

* Additional cGVHD details which do not contribute to response assessments will be collected when available.

Abstracted from: Lee SJ et al. (*Biol Blood Marrow Transplant* 2015; 21:984 – 999) and Jagasia, et al (Biol Blood Marrow Transplant. 2015;21:389–401)

21.3 APPENDIX C: CGVHD RESPONSE ASSESSMENT

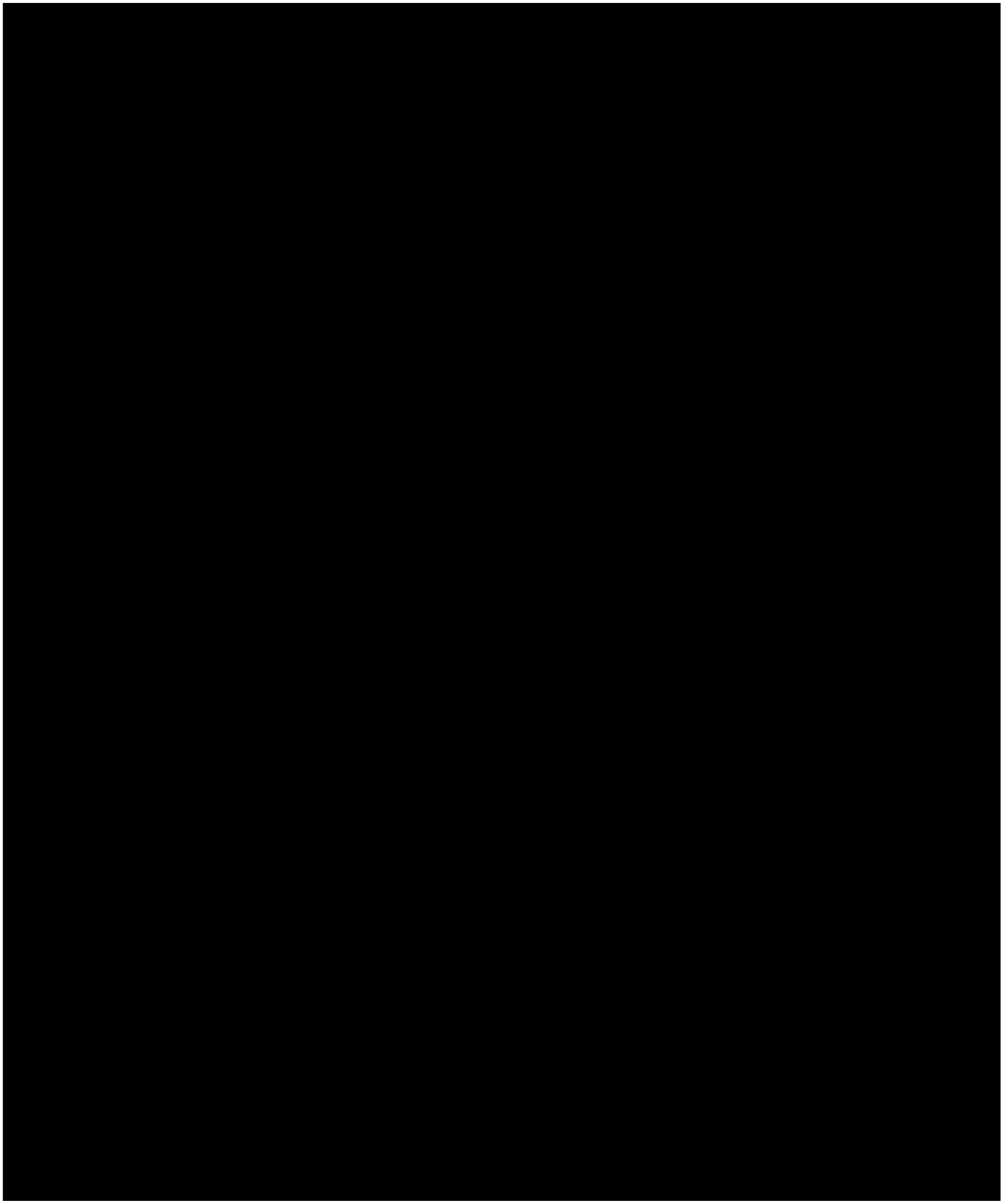
Response Determination for Chronic GVHD Clinical Trials based on Clinician Assessments

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.

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

21.4 APPENDIX D: LEE CGVHD SYMPTOM SCORE



21.5 APPENDIX E: PROMIS GLOBAL HEALTH SCORE

	Please respond to each item by marking one box per row	Excellent	Very Good	Good	Fair	Poor
Global 01	In general, would you say your health is:	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global 02	In general, would you say your quality of life is:	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global 03	In general, how would you rate your physical health?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global 04	In general, how would you rate your mental health, including your mood and your ability to think?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global 05	In general, how would you rate your satisfaction with your social activities and relationships?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global 09	In general, please rate how well you carry out your usual social activities and roles. (This includes activities at home, at work and in your community, and responsibilities as a parent, child, spouse, employee, friend, etc.)	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		Completely	**Mostly**	**Moderately**	**A Little**	**Not At All**
Global 06	To what extent are you able to carry out your everyday physical activities such as walking, climbing stairs, carrying groceries, or moving a chair?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		Never	**Rarely**	**Sometimes**	**Often**	**Always**
Global 10	How often have you been bothered by emotional problems such as feeling anxious, depressed or irritable?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		None	**Mild**	**Moderate**	**Severe**	**Very Severe**
Global 08	How would you rate your fatigue on average?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global 07	How would you rate your pain on average?	☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 No Pain … Worst Imaginable Pain				

Adapted from
http://www.healthmeasures.net/administrator/components/com_instruments/uploads/Global%20Health%20Scale%20v1.2%2008.22.2016.pdf (Accessed 30-May, 2018)

21.6 APPENDIX F: CGVHD ACTIVITY ASSESSMENT-PATIENT SELF REPORT

FORM B

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

CHRONIC GVHD ACTIVITY ASSESSMENT-PATIENT SELF REPORT

Symptoms **Please rate how severe the following symptoms have been in the last seven days. Please fill in the circle below from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.**	**Not Present** 0	1	2	3	4	5	6	7	8	9	**As Bad As You Can Imagine** 10
Your **skin itching** at its WORST?	O	O	O	O	O	O	O	O	O	O	O
Your **skin and/or joint tightening** at their WORST?	O	O	O	O	O	O	O	O	O	O	O
Your **mouth sensitivity** at its WORST?	O	O	O	O	O	O	O	O	O	O	O
Your **genital discomfort** at its WORST? (Women – vagina, vulva, or labia) (Men – penis)	O	O	O	O	O	O	O	O	O	O	O

Eyes	What is your main complaint with regard to your eyes?	
	Please rate how severe this symptom is, from 0 (not at all severe) to 10 (most severe):	0 1 2 3 4 5 6 7 8 9 10

Patient Global Ratings:

1. Overall, do you think that your chronic graft versus host disease is mild, moderate or severe?
1= mild
2=moderate
3=severe

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

0 1 2 3 4 5 6 7 8 9 10

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

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

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

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

21.7 APPENDIX G: KARNOFSKY PERFORMANCE SCALE

Karnofsky Scale (recipient age ≥16 years)		Lansky Scale (recipient age <16 years)	
Able to carry on normal activity; no special care is needed.		**Able to carry on normal activity; no special care is needed.**	
100	Normal, no complaints, no evidence of disease.	100	Fully active
90	Able to carry on normal activity	90	Minor restriction in physically strenuous play
80	Normal activity with effort	80	Restricted in strenuous play, tires more easily, otherwise active
Unable to work, able to live at home and care for most personal needs, a varying degree of assistance is needed.		**Mild to moderate restriction**	
70	Cares for self, unable to carry on normal activity or to do active work.	70	Both greater restrictions of, and less time spent in active play
60	Requires occasional assistance, but is able to care for most needs.	60	Ambulatory up to 50% of time, limited active play with assistance / supervision
50	Requires considerable assistance and frequent medical care.	50	Considerable assistance required for any active play, fully able to engage in quiet play
Unable to care for self, requires equivalent of institutional or hospice care, disease may be progressing rapidly.		**Moderate to severe restriction**	
40	Disabled, requires special care and assistance.	40	Able to initiate quiet activities
30	Severely disabled, hospitalization indicated. Death not imminent.	30	Needs considerable assistance for quiet activity
20	Very sick, hospitalization indicated. Death not imminent.	20	Limited to very passive activity initiated by others (eg, TV)
10	Moribund, fatal processes progressing rapidly.	10	Completely disabled, not even passive play

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

Lansky SB, List MA, Lansky LL, Ritter-Sterr C, Miller DR. The measurement of performance in childhood cancer patients. Cancer. 1987 Oct 1;60(7):1651-6.

21.8 APPENDIX H: EQUATIONS TO PREDICT GLOMERULAR FILTRATION RATE

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

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

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

Creatinine-Based Bedside Schwartz Equation

eGFR = 0.413 x (height/Creatinine), where height is expressed in centimeters, creatinine in mg/dL

eGFR = 41.3 x (height/Creatinine), where height is expressed in meters, creatinine in mg/dL

Source: National Kidney Foundation https://www.kidney.org/content/creatinine-based-%E2%80%9Cbedside-schwartz%E2%80%9D-equation-2009

Accessed: 19 Aug 2021

21.9 APPENDIX I: DRUGS THAT INDUCE CYP3A4

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

Table 11 - 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 28 Jul 2021

21.10 APPENDIX J: PFT ASSESSMENTS

PFTs are required with each response assessment. Full PFTs (FEV1, FVC, DL_{CO} [corrected for Hb], and TLC) are required at baseline, C4D1, C7D1, and every 6 cycles thereafter (C13D1, C19D1, C25D1, etc.). At other PFT timepoints, spirometry alone (FEV1 and FVC) is sufficient. Where possible, all PFTs should be performed consistently in the same setting.

Schedule of PFT Assessments

			Day 1 of Cycle																
	Screening	**Baseline**	**C2**	**C3**	**C4**	**C5**	**C6**	**C7**	**C8**	**C9**	**C10**	**C11**	**C12**	**C13**	**C14**	**C15**	**C16**	**C17**	**C18**	**C19**
Response[a]			X	X		X		X			X			X			X			X
Full PFT[b]		X		X				X						X						X
Spirometry[c]	X		X			X					X						X			

C[number] = Cycle[number]; DL_{CO} = diffusing capacity of carbon monoxide; EOT = end of treatment; FEV1 = forced expiratory volume (in the first second); FVC = forced vital capacity; Hb = hemoglobin; PFT = pulmonary function test; RV = residual volume; TLC = total lung capacity

a Response assessments are on Day 1 of Cycles 2, 3, 5, 7 then on Day 1 of every 3 cycle thereafter.

b Full PFT tests include FEV1, FVC, DLCO (corrected for Hb), and TLC. Full PFTs are performed at baseline, C3D1, C7D1, and every 6 cycles thereafter (C13D1, C19D1, C25D1, etc.). At EOT, a Full PFT will be performed unless a Full PFT was conducted the previous month, in which case only a FEV1 and FVC is required.

c Spirometry tests include FEV1 and FVC.

21.11 APPENDIX K: PREDNISONE DOSE EQUIVALENTS

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

1 mg 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, Ahmet A, Ward L, et al. A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy. Allergy Asthma Clin Immunol. 2013;9(1):30. Published 2013 Aug 15. doi:10.1186/1710-1492-9-30

21.12 APPENDIX L: CENTRAL LAB AND CRO CONTACT INFORMATION

The CRO for this study is Medpace. Medpace has the following contact information:

Medpace
5375 Medpace Way
Cincinnati, Ohio 45227

Clinical laboratory testing will be performed by Medpace Reference Laboratories (MRL). Clinical laboratory parameters include those described in Table 4, reflexive serum pregnancy testing (human chorionic gonadotropin), and HBsAg and hepatitis C antibodies. MRL has the following contact information:

Medpace Reference Laboratories
5365 Medpace Way
Cincinnati, Ohio 45227

Pharmacokinetic testing will be performed by Labcorp. Labcorp has the following contact information:

Labcorp Bioanalytical Services LLC
3301 Kinsman Boulevard
Madison, Wisconsin 53704

Pharmacodynamic testing will be performed by Vanderbilt University Medical Center Innovative Translational Research Shared Resource (ITR). Vanderbilt has the following contact information:

Vanderbilt University Medical Center
Innovative Translational Research Shared Resource (ITR)
c/o KD025-213
2220 Pierce Avenue South
722 Preston Research Building
Nashville, Tennessee 37232

21.13 APPENDIX M: COMPANION STUDY FOR BIOSPECIMEN COLLECTION

Biospecimen Collection in a Phase 2, Randomized, Multicenter Study to Evaluate the Efficacy and Safety of KD025 in Subjects with Chronic Graft Versus Host Disease (cGVHD) After At Least 2 Prior Lines of Systemic Therapy (The ROCKstar Study)

21.13.1 Purpose

This addendum contains a detailed description of biospecimen collection at the following sites: National Institutes of Health (NIH), Dana Farber Cancer Institute, the University of Texas MD Anderson Cancer Center, and Washington University in St. Louis.

21.13.2 Summary

Background:

Preclinical and clinical data support a role of IL-17 in cGVHD pathogenesis due to increased activity of proinflammatory T helper (Th)17 cells and diminished regulatory T cell activity (21). Increased levels of IL-17 mRNA transcripts were demonstrated in skin, and oral mucosa showed infiltration of Th17 cells, a CD4+T cell subset that secretes IL-17 (31). IL-17 can be secreted by innate and adaptive (CD4+ and CD8+) immune cells, epithelial cells and may be induced by local inflammation (32). Elevated IL-17 supports tissue sequestration of profibrogenic macrophages via unclear mechanisms, leading to inflammation and fibrosis (MacDonald, Betts, & Couriel, 2018). Thus, understanding IL-17 secretion by various cells and its distribution in tissues is critical to elucidate the pathogenesis of cGVHD.

ROCK (Rho-associated coiled-coil kinase) is an enzyme required for multiple intracellular processes including actin cytoskeleton assembly and cellular functions, such as proliferation, adhesion, migration, and phagocytosis and is critical for T cell responses (12). The ROCK2 isoform only is physiologically activated in CD4+ T cells under Th17-skewing, leading to increased secretion of IL-17 and IL-21 in mice and humans (16, 15). Belumosudil is an orally available ROCK2 selective inhibitor which has been shown to downregulate Th17 and follicular Th cells and upregulate regulatory T cells.

This appendix details additional assays that will be included for select participants enrolled in the ROCKstar trial. Four (4) centers will participate in this companion biologic sample protocol: National Institutes of Health (NIH), Dana Farber Cancer Institute, University of Texas MD Anderson Cancer Center, and Washington University in St. Louis.

Biologic samples will include oral and skin biopsies, microbiome swabs, saliva, and peripheral blood. These samples will be assayed to better understand the pathophysiology and immunopathology of cGVHD, with specific focus on differential IL-17 expression in cell types and tissues.

All analyses described in this site-specific addendum are planned to take place at the NIH.

21.13.3 Objective

To characterize changes in the immune cellular profile before and after treatment with belumosudil with a focus on IL-17 production in the oral cavity.

21.13.4 Eligibility

Be able to complete written informed consent.

For belumosudil treated participants:

Must be enrolled in the KD025-213 study, and

Must have oral mucosal cGVHD defined as lichenoid changes with or without clinical symptoms. Alternatively, distinctive features including mucoceles, mucosal atrophy, ulcers, or pseudomembranes are sufficient with or without clinical symptoms provided there is no suspicion for alternative causes. There is no restriction regarding oral cGVHD NIH severity.

Must be at least 18 years of age.

No contraindication(s) for biopsy collection.

21.13.5 Design

This site-specific addendum will enroll participants (approximately 20 evaluable participants) with cGVHD undergoing belumosudil treatment.

Biopsies will be taken at baseline and after 6-months of belumosudil therapy (C7D1 timepoint) or at the time of discontinuation of belumosudil therapy (whichever comes earlier) from the oral buccal mucosa, labial minor salivary gland and cutaneous skin. At the same time points, unstimulated 5-minute whole saliva, oral microbiome swabs and a research blood sample will be collected. Whole biopsies will be sent to the NIH for histologic review (formalin-fixation and paraffin embedding [FFPE]) and fluorescent immunohistochemistry (IHC) to identify changes in location and distribution of IL-17-producing cells at effector sites after belumosudil treatment.

Plasma and saliva will be used for multiplex ELISA analysis of IL-17-pathway chemokines and cytokines. Flow cytometric analysis may be done on peripheral blood cells to identify phenotype, transcription factor expression, and cytokine production.

All data and samples will be de-identified (ie, coded) prior to transfer to the NIH.

21.13.6 Introduction

21.13.6.1 Study objectives

21.13.6.1.1 Primary Objective

To characterize changes in the immune cellular profile before and after treatment with belumosudil with a focus on IL-17 production in the oral cavity

21.13.6.1.2 Secondary Objective

To determine feasibility of conducting a multi-center cGVHD study that includes analyses of tissue biopsies, saliva and peripheral blood.

21.13.6.1.3 Exploratory Objectives

To characterize changes in the skin immune cellular profile before and after treatment with belumosudil with a focus on IL-17 production.

To analyze and compare the effector cell profile of different sites (peripheral blood, skin, oral mucosa, minor salivary gland) during the pathogenesis of cGVHD.

To analyze changes in the local (saliva) and peripheral (blood) cytokine and chemokine profile after belumosudil treatment.

To compare changes in the oral microbiome before and after belumosudil treatment.

To analyze changes in the immune cell profile in peripheral blood before and after belumosudil treatment.

To compare gene expression profiles in immune cells before and after treatment with belumosudil in GVHD-affected tissues.

21.13.6.2 Background and rationale

Chronic graft versus host disease (cGVHD) remains a major multi-system complication of allogeneic hematopoietic cell transplantation (HCT) and occurs in about 50% of transplant recipients depending upon donor and transplant characteristics (33). Chronic GVHD occurs when immune cells transplanted from a non-identical donor (the graft) recognize the transplant recipient (the host) as non-self, thus leading to an immune reaction that causes disease in the transplant recipient.

Participants 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). There remains substantial unmet need for new targeted therapies with better tolerability and effectiveness.

Manifestations of cGVHD in the oral cavity are observed in 45-85% of cGVHD participants. Clinically, the first line of topical therapy for oral cGVHD is oral rinses with a dexamethasone (0.1 mg/mL) suspension. However, this topical agent is only effective or partially effective in approximately 29-58% of participants (34, 35). This necessitates more specific treatment modalities.

However, despite extensive research and progress over the last decade, there is still a profound unmet need to fully deciphering and understand cGVHD biology (36, 21, 37). The development of biomarkers for cGVHD has been similarly challenging (38, 39).

Preclinical and clinical data support a role of IL-17 in cGVHD pathogenesis due to increased activity of proinflammatory T helper (Th)17 cells and diminished regulatory T cell activity (21). Increased levels of IL-17 mRNA transcripts were demonstrated in skin, and oral mucosa showed infiltration of Th17 cells, a CD4+T cell subset that secretes IL-17 (31). IL-17 can be secreted by innate and adaptive (CD4+ and CD8+) immune cells, epithelial cells and may be induced by local inflammation (32). Elevated IL-17 supports tissue sequestration of profibrogenic macrophages via unclear mechanisms, leading to inflammation and fibrosis (21). Thus, understanding IL-17 secretion by various cells and its distribution in tissues is critical to elucidate the pathogenesis of cGVHD.

ROCK (Rho-associated coiled-coil kinase) is an enzyme required for multiple intracellular processes including actin cytoskeleton assembly and cellular functions, such as proliferation, adhesion, migration and phagocytosis and is critical for T cell responses (12). The ROCK2 isoform only is physiologically activated in CD4+ T cells under Th17-skewing, leading to increased secretion of IL-17 and IL-21 in mice and humans (16, 15). Belumosudil is an orally available (ROCK2) selective inhibitor which has been shown to downregulate Th17 and follicular Th cells and upregulate regulatory T cells.

It has been well established that the interplay between the oral microbiome and the mucosal immune cells is critical for the maintenance of health at the barrier sites. IL-17 plays a significant role in maintaining mucosal homeostasis by promoting the production of several antimicrobial peptides and by recruiting innate immune cells. Dysregulation in IL-17 has been associated with dysbiotic microbiome and exaggerated disease process.

It is not known how inhibition of ROCK2 will affect the IL-17-secreting cellular profile or oral microbiome at peripheral cGVHD effector sites including skin and oral mucosa.

There is already an ongoing Phase 2a, randomized, open-label study to evaluate the safety, tolerability, and activity of belumosudil in participants with cGVHD (ROCKstar trial, NCT03640481). In this ongoing study, participants receive belumosudil at dose levels of 200mg QD or 200mg BID and must have previously received at least 2 lines and more than 5 lines of systemic therapy for cGVHD.

The ROCKstar trial is multi-center, and 4 centers will participate in this companion biologic sample protocol: NIH, Dana Farber Cancer Institute, University of Texas MD Anderson Cancer Center, and Washington University in St. Louis.

Biologic samples will include oral and skin biopsies, microbiome swabs, saliva and peripheral blood. These samples will be assayed to better understand the pathophysiology and immunopathology of cGVHD after ROCK2 inhibition, with specific focus on differential IL-17 expression in cell types and tissues

21.13.7 Eligibility assessment and enrollment

This study is optional for participants.

21.13.7.1 Eligibility criteria

21.13.7.1.1 Inclusion Criteria

Must be able to complete informed consent.

Must be enrolled in ROCKstar trial (NCT03640481).

Participants must have oral mucosal cGVHD defined as lichenoid changes with or without clinical symptoms. Alternatively, distinctive features including mucoceles, mucosal atrophy, ulcers, or pseudomembranes are sufficient with or without clinical symptoms provided there is no suspicion for alternative causes. There is no restriction regarding oral cGVHD severity.

Must be at least 18 years of age.

No contraindication(s) for biopsy collection.

21.13.7.1.2 Exclusion Criteria

None applicable.

21.13.7.2 Screening evaluation

The PI or designee will obtain written informed consent from participants for participation in the biologic study.

21.13.7.2.1 Baseline evaluation [c1d1, pre-dose]

Prior to starting therapy with belumosudil on the ROCKstar trial, eligible participants will have samples collected:

- Unstimulated 5-minute whole saliva.

- Oral microbiome swabs from dorsal tongue and buccal mucosa.
- Peripheral blood collection (CPT tube, 10 mL).
- Biopsy of oral buccal mucosa (4mm punch).
- Biopsy of labial minor salivary gland.
- Biopsy of cutaneous skin (4mm punch).

21.13.7.2.2 6-month or off-treatment evaluation [c7d1 or end-of-treatment]

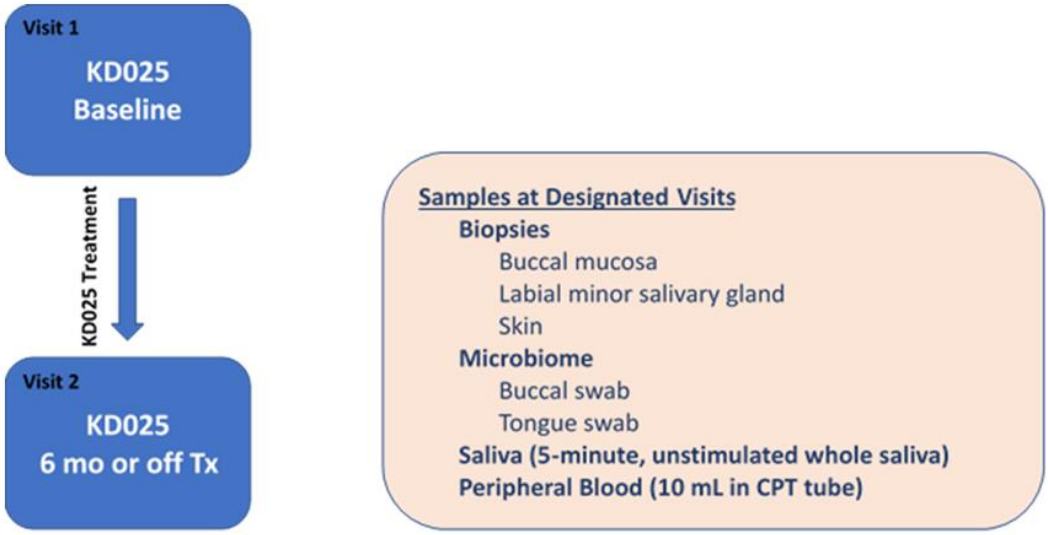
After 6-months of therapy with belumosudil on the ROCKstar trial or when study drug is stopped if this occurs prior to 6-months, eligible participants will have samples collected:

- Unstimulated 5-minute whole saliva.
- Oral microbiome swabs from dorsal tongue and buccal mucosa.
- Peripheral blood collection (CPT tube, 10 mL).
- Biopsy of oral buccal mucosa (4 mm punch).
- Biopsy of labial minor salivary gland.
- Biopsy of cutaneous skin (4 mm punch).

21.13.8 Study implementation

21.13.8.1 Study design

Figure 8-1 - Design of Site-specific Addendum



Participants with cGVHD undergoing belumosudil treatment. Samples will be collected at 4 selected study centers sites (n = 20 evaluable participants).

Biopsies from the oral buccal mucosa, labial minor salivary gland and cutaneous skin will be taken at baseline and after 6-months of belumosudil therapy or at the time going off treatment (whichever comes earlier) for belumosudil treated participants. At the same time points, unstimulated 5-minute whole saliva, oral microbiome swabs and a research blood sample (in a CPT tube to allow for separation of cells for flow and plasma for ELISA) will be collected.

The whole biopsy will be deposited into formalin and shipped to the NIH for processing and histologic review (formalin-fixation and paraffin embedding [FFPE]) prior to planned analyses. FFPE blocks will be used for fluorescent immunohistochemistry (IHC) to identify change in location and distribution of IL-17-producing cells at effector sites after belumosudil treatment.

Plasma and saliva will be used for multiplex ELISA analysis of IL-17-pathway chemokines and cytokines. Flow cytometric analysis may be done on fresh blood cells to identify phenotype, transcription factor expression and cytokine production. All samples will be de-identified prior to transfer to the NIH.

21.13.8.2 Study calendar

The study calendar of assessments is presented in Table 8-1.

Table 8-1 - Calendar of Assessments

Assessments	ROCKstar Participants		Laboratory/ Sample Details	
	[2]Baseline	[3]Post-Belumosudil *(6 months or off-treatment)*	Processing	Shipping
[1]Biologic sample collection				
Saliva collection (5-minute unstimulated whole saliva, collect in tared-tube on ice)	X	X	Keep cold and process ASAP. Weight tube and record. Pipette into cryovials. Centrifuge at 2800g for 5 minutes. Transfer supernatant into storage set of cryovials, discard pellet, and freeze saliva at -80°C.	Batch ship when collections are complete. Ship overnight on dry ice.
Microbiome swab collection (30-second swab on tongue and buccal mucosa, separate swab for each site)	X	X	Clip head of polysterene swab off into cryovial with RNAlater using sterile scissors. Close vial.	Ship overnight at room temperature with swabs, blood and biopsies.
Blood collection (10 mL in CPT tube)	X	X	Store upright and process within 2 hrs of collection. Centrifuge at room temperature (18-25° C) in a horizontal rotor (swing-out head) for a minimum of 20 minutes (max 30 minutes) at 1500 to 1800 RCF.	Pack carefully around tubes with absorbent material. Ship overnight at room temperature with swabs, blood and biopsies.

Assessments	ROCKstar Participants		Laboratory/ Sample Details	
	[2]Baseline	[3]Post-Belumosudil *(6 months or off-treatment)*	Processing	Shipping
[1]***Biologic sample collection***				
Oral buccal mucosa biopsy (4mm)	X	X	Deposit biopsy tissue into labelled cryovial filled with formalin.	Ship overnight at room temperature with swabs, blood and biopsies
Labial minor salivary gland biopsy	X	X	Deposit biopsy tissue into labelled cryovial filled with formalin.	Ship overnight at room temperature with swabs, blood and biopsies.
Skin biopsy (4mm)	X	X	Deposit biopsy tissue into labelled cryovial filled with formalin.	Ship overnight at room temperature with swabs, blood and biopsies.

[1] PI or designee will clear participant for sampling per site's policies.
[2] The baseline assessments can be collected from time of consent through pre-dose on C1D1.
[3] The C7D1 assessments have a ± 7-day window. If participant discontinues prior to the C7D1 time point, every effort should be made to collect the samples as close to the treatment discontinuation date as possible.

21.13.9 Biospecimen collection

21.13.9.1 Collection and shipping

21.13.9.1.1 Collection

All samples will be collected and processed as outlined below (also see lab manual)

Unstimulated 5-minute whole saliva collection: Each participant will split into a previously tared 50 mL conical tube, held on ice, every 30 seconds for 5 minutes; total saliva tube weight will be measured, and the sample will be processed immediately (centrifuged at 2800g for 5 mins at 4°C). Supernatant only will be aliquoted in 500-800 µl increments and frozen at -80oC prior to shipping.

Oral microbiome swabs from dorsal tongue and buccal mucosa: a polyester swab will be rubbed on either the oral buccal mucosa (bilateral) or dorsal tongue for 30 seconds. The head of the swab will be cut off into a cryovial containing RNA later and will be held at room temperature until storage at -20oC prior to DNA extraction for analysis.

10 mL peripheral blood collection (CPT tube): Peripheral blood will be drawn into 2 CPT tubes. After collection, store tube upright at room temperature until centrifugation. Centrifuge at room temperature (18-25° C) in a horizontal rotor (swing-out head) for a minimum of 20 minutes (max 30 minutes) at 1500 to 1800 RCF (Relative Centrifugal Force) then prepare tubes for shipping. Blood samples should be centrifuged within 2 hours of blood collection for best results.

Biopsy of oral buccal mucosa, 4 mm punch: A 4 mm punch biopsy should be taken from affected area of oral buccal mucosal lining of cheek, ideally from an area with erythema and lichenoid lesion. Do not biopsy an ulcer, but tissue adjacent to an ulcer is fine. Deposit biopsy tissue into formalin and prepare for shipping.

Biopsy of labial minor salivary gland: An approximate 0.5 cm incision should be made in the labial mucosa, and 4-6 salivary glands lobules should be clipped out, deposited into formalin or saline, and then the site should be sutured closed. Deposit biopsy tissue into formalin if not already completed and prepare for shipping.

Biopsy of cutaneous skin, 4 mm punch: A 4 mm punch biopsy should be taken from affected area of cutaneous skin—generally from the most active area that will heal reasonably well. If skin is unaffected, biopsy should generally be taken from medial upper arm or torso. Face, hands, feet, and lower extremities should be avoided. If possible, the post-treatment biopsy should be done adjacent to the site of the pre-treatment biopsy. Deposit biopsy tissue into formalin and prepare for shipping.

21.13.9.2 Sample Shipping

Biospecimens will be shipped to the NIH for further processing, storage and analysis. Samples should be shipped overnight via FedEx on Monday through Wednesday. Please notify lab below at time of shipping. Please make arrangements with lab if sample needs to be shipped Thursday or Friday and may arrive on the weekend.

Saliva aliquots may be stored at -80oC and shipped as a batch on dry ice.

All other samples: biopsies, blood and microbiome samples should be shipped at room temperature (not frozen) to the address below as soon as possible after collection
NIH, NIDCR, Oral Immunobiology Unit
ATTN: [redacted]
[redacted]
[redacted]
[redacted]
Office: [redacted]
Cell: [redacted]

Email: [redacted]

Note: CPT tubes containing separated blood cells must be placed in a red biohazard bag containing an absorbent material, such as a clinical pad. All glass has the potential for breakage; therefore, precautionary measures should be taken during handling. Please follow the instructions listed under “General Packaging Requirements” in the associated SOP document. Tubes for sample processing including cryovials with formalin for biopsies will be sent by the NIH lab to the collecting sites.

21.13.9.3 Correlative research studies

The following biospecimens will be collected and analyzed:

Saliva: Saliva will be processed and stored at -80oC until batched analyses are done using ELISA technology. Specific protein biomarkers of interest include IL-17A, IL-22, IL-21, IL-23, CCL20, IL-6, IL-17F, IL-1b, TNF, IL-26, CXCL10 and Zymogen Granule Protein 16B.

Microbiome swabs: Compositional and functional shifts in the oral microbiome will be assessed using targeted 16s sequencing or open-ended shotgun metagenomic sequencing approaches of non-human material only. Correlative laboratory assays may be done to corroborate initial findings.

Oral and skin biopsies: The oral tissue sections will be examined by a pathologist to assess oral cGVHD status. Fluorescent immunohistochemistry (IHC, 5+color) will be used to identify change in location and distribution of IL-17-producing cells at effector sites after belumosudil treatment. Correlative analysis of gene expression may be done using NanoString analysis on paraffin sections for interferon- and IL-17-related molecules.

Blood: Plasma will be used for multiplex ELISA analysis of IL-17-pathway chemokines and cytokines. Flow cytometric analysis may be done on fresh blood cells to identify phenotype, transcription factor expression and cytokine production.

21.13.9.3.1 Sample storage, tracking and disposition

The saliva, tissue and blood samples, collected for research will be stored by the Oral Immunobiology Unit (OIU), National Institute of Dental and Craniofacial Research (NIDCR), NIH. All data associated with archived clinical research samples is entered into a secure database. Access to this system is limited to OIU clinical staff, requiring individual login and password. All staff in the OIU laboratory complete training and maintain standards of computer security, as required locally.

The data recorded for each sample includes the deidentified (i.e., coded) participant ID number (as assigned by the ROCKstar study), trial name/protocol number, and date collected, as well as box and freezer location. All samples currently receive a unique bar code number, which is included in the OIU Stored Sample database. Only this bar code will be recorded on the sample vial and the vials will not be traceable back to the participants without authorized access to the Kadmon database.

Samples are stored in locked, monitored freezers at -80°C (saliva and blood) or -20oC (oral swabs) according to stability requirements. These freezers are located on site at the OIU Unit in Bethesda, MD.

Samples will not be sent outside NIH for analysis without appropriate Institutional Review Board (IRB) notification and an executed Material Transfer Agreement (MTA) if required.

All specimens obtained in the protocol will be used as defined in the protocol. Any specimens that are remaining at the completion of the protocol will be stored in the conditions described below. The study will remain open so long as sample or data analysis continues. Samples from consenting participants will be stored until they are no longer of scientific value or if a participant withdraws consent for their continued use, at which time they will be destroyed. The responsible site PI will report any loss or destruction of samples to the sponsor as soon as made aware of such loss.

If a participant withdraws consent, the associated data will be excluded from future sample distributions and analyses, but data already distributed for approved research use are not retrievable.

21.13.9.3.2 Data sharing plans

Participant's data will be deidentified and will be kept confidential. Participants will be identified by participant ID numbers in the clinical database. The link between the participants and their ID numbers will be securely maintained by the enrolling sites per local practices.

This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

The microbiome genomic data will be shared according to the NIH Genomic Data Sharing Policy: https://osp.od.nih.gov/wp-content/uploads/NIH_GDS_Policy.pdf.

This non-human data will be shared no later than the time of initial publication, per NIH policy: https://osp.od.nih.gov/wp-content/uploads/Supplemental_Info_GDS_Policy.pdf.

21.13.10 Statistical section

To facilitate evaluation of the primary and other objectives, a control group will be included in the sample analyses. These control samples will be acquired only at the NIH from existing open protocols. The primary analysis group (i.e., Group 1, as described herein) will be the pre- and post-treatment samples from 20 evaluable participants treated with belumosudil on the ROCKstar study. Group 2 will be post-transplant (post-HSCT) control participants without cGVHD (PT cohort, n=10, single timepoint, must be 1-4 years out of transplant, with matched samples will be taken at a single visit). Group 3 will be healthy volunteers (HV Cohort, n = 5, age 30-65 years, collected only at the NIH under protocol NCT03602599 with matched samples, will be taken at a single visit).

The primary objective of this Companion Study is to characterize changes in the immune cellular profile before and after treatment with belumosudil with a focus on IL-17 production in the oral cavity. A total of 20 evaluable participants will have oral samples obtained both at pre-treatment and post-treatment; with 20 complete paired samples, a paired t-test will have 88.9% power to detect a difference in values between the two time points equal to 0.75 standard deviation of the

change (effect size = 0.75), based on a 0.05 two-sided significance level test. In practice, if the paired differences are not normally distributed ($p<0.05$ by a Shapiro-Wilks test), a Wilcoxon signed rank test will be used.

The secondary objective of this study, to determine feasibility of conducting a multi-center cGVHD study that includes analyses of tissue biopsies, saliva and peripheral blood, will be assessed by the estimate of the percentage of usable specimens which are obtained from the procedure. There is no fixed target, but the percentage of specimens which are usable will be reported along with a 95% confidence interval (CI). In addition, the fraction of participants in which both pre- and post-treatment oral samples are usable will be reported along with a 95% CI.

Although they are considered exploratory objectives, the sample sizes for the comparisons with controls will be assessed as follows:

> The baseline IL-17-producing cells from the oral cavity identified at pre-treatment for participants who are to receive belumosudil will be compared to the number of cells obtained at a single time point from participants who do not have cGVHD.
> 20 participants and 10 non-GVHD controls would have 87.6% power to detect an effect size of 1.25 (difference between the two groups equal to 1.25 SD of the values within each group) using a two-sample t-test with a 0.05 two-sided significance level. In practice, if the values within both groups are not normally distributed ($p<0.05$ by a Shapiro-Wilks test), a Wilcoxon rank sum test will be used.
>
> The baseline IL-17-producing cells from the oral cavity identified at pre-treatment for participants who are to receive belumosudil will be compared to the number of cells obtained at a single time point from healthy volunteers; 20 participants with cGVHD and 5 healthy controls would have 81.9% power to detect an effect size of 1.5 (difference between the two groups equal to 1.5 SD of the values within each group) using a two-sample t-test with a 0.05 two-sided significance level. In practice, if the values within both groups are not normally distributed ($p<0.05$ by a Shapiro-Wilks test), a Wilcoxon rank sum test will be used.

All other evaluations will be considered completely exploratory and will be based on the available participants and usable data.

To allow for a small number of participants and controls which may not yield usable results for the primary analysis (or the main exploratory analyses involving the control participants), up to 24 participants with cGVHD, and 6 healthy volunteers may be enrolled.

21.14 APPENDIX N: CONTRACEPTIVE AND BARRIER GUIDANCE

21.14.1 Definitions

- A woman is considered WOCBP (fertile) from the time of menarche until becoming postmenopausal (see below) unless permanently sterile (see below).

- A postmenopausal state is defined as the period of time after a woman has experienced no menses for 12 consecutive months without an alternative medical cause.
- A high follicle-stimulating hormone (FSH) level in the postmenopausal range should be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT).
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Permanent sterilization methods include:

- Documented hysterectomy.
- Documented bilateral salpingectomy.
- Documented bilateral oophorectomy.
- For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry eligibility.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first administration of study intervention, additional evaluation should be considered.

21.14.2 Contraception Guidance

Participants should be given advice about donation and cryopreservation of germ cells prior to the start of the study intervention, in line with the fact that study intervention may affect ova and sperm up to 90 days (see Section 4.3).

If locally required, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

21.15 APPENDIX O: PROTOCOL AMENDMENT HISTORY

The Protocol Amendment Summary of Changes Table for the current amendment is located after the title page.

21.15.1 Amended Protocol 01 (26 June 2019)

SUMMARY

KD025-213 Protocol Amendment 1 has been amended from the KD025-213 Original Protocol dated 25 June 2018. General changes are detailed below:

- INTRODUCTION:
  - Clarification that ibrutinib is approved for the treatment of *adults* with cGVHD and that there is no currently FDA-approved treatment for *adolescents* with cGVHD (1.1)
  - Addition: a Section 1.6, Summary of Known and Potential Risks and Benefits to Human Subjects, clearly stating the possible side effects, possibility of no direct benefit to subjects, and that the study may help others or provide more information on the drug as a possible new treatment for cGVHD

- STUDY OBJECTIVES / PURPOSE:
  - Addition of Secondary Objectives: time to response (TTR) and time to next treatment (TTNT) (2.2)

- INVESTIGATIONAL PLAN:
  - Change: a new figure of study design replaces the previous figure of study design including the changes aged ≥ 12 years; treat to clinically significant progression; safety as secondary endpoint; and statistics that include interim analysis and change in alpha testing used (Figure 1)
  - Addition: text elaborating consent (Section 3.1)
  - Addition: statement that study population will include *adolescents* as well as adults (Section 3.1)
  - Modification: other allowable concomitant cGVHD therapies was replaced with standard of care systemic cGVHD therapies which included rituximab (3.1)
  - Modification: 28-day treatment cycles are to continue until *clinically significant* disease progression, and not limited to disease progression as defined by NIH criteria. (3.1)
  - Addition: guidance was provided for when patients may meet NIH defined progression but not clinically significant disease progression. If a subject experiences NIH defined progression but for whom no new systemic therapy is planned, they may continue on study and be assessed again at their next cycle. If patient does not have confirmed progression per NIH criteria or if no new systemic therapy is planned, subjects may continue on KD025 per investigator's discretion. (3.1)
  - Addition: statement regarding definition of responses, which will be assessed compared to baseline (3.1)
  - Deletion: subjects will no longer be limited to be contacted *by telephone* every 12 weeks until study close-out (3.1)
  - Modification: the Steering Committee will advise on study conduct and study stopping rules (3.2)

- STUDY POPULATION:
  - Number of Study Centers: Modified from approximately 25 centers to 30 centers (4.2)
  - Inclusion Criteria (4.3)
    - Substitution (Inclusion Criteria #1) subjects must now be at least 12 years of age replaces at least 18 years of age
    - Addition (Inclusion Criteria #5): Karnofsky (if aged ≥ 16 years) / Lansky (if aged < 16 years)
    - Addition (Inclusion Criteria #13): male subjects will not be permitted to donate sperm
    - Addition of Inclusion Criterion #15: subjects must weight ≥ 40 kg
    - Addition of Inclusion Criterion #16: "It is in the best interest of the subject to participate in the study"
  - Exclusion Criteria (4.4)
    - Substitution (Exclusion Criterion #1): subjects being excluded from the study if they received a systematic investigational treatment within 28 days of study entry was replaced with subjects being excluded if they were not on a stable dose / regimen of systemic cGVHD treatments for at least 2 weeks prior to screening.
    - Substitution (Exclusion Criterion #10): exclusion of subjects with a QTc(F) > 480 ms replaces exclusion of subjects with QTc(F) > 450 ms at baseline
    - Substitution (Exclusion Criterion #13): "treatment with any investigational agent, device, or procedure" was replaced with "treatment with any non-GVHD investigational agent, device, procedure" within 28 days of enrollment
  - Screening (4.6)
    - Addition of documented standard of care assessments performed within 14 days of Cycle 1 Day 1 permitted for screening if performed prior to subject signing the ICF
  - Withdrawal Criteria (4.7)
    - Addition: clarification of subjects with disease progression, whether NIH-defined or not, for continuing on study
    - Addition: tapering schedule after sustained response for 6 months and cessation of all other immunosuppressants for at least 3 months
    - Addition: pregnant subjects will be discontinued from the study
  - Replacements (4.8)
    - Revision: revised how cGVHD progression would meet the criteria for treatment discontinuation

- STUDY TREATMENT
  - Dosage and Administration (5.2)
    - Addition: At C19D1 and onwards, subjects may return to clinic after every other treatment cycle.
    - Addition: referenced where additional information can be found regarding dosage and administration of KD025
    - Addition of Section 5.2.1 Tapering Guidelines, describing tapering by cohort after sustained response for 6 months and cessation of immunosuppressants at

least 3 months
    - Substitution: changed the tapering guidance to reduce the dose every 2 cycles instead of every 2 weeks
  - Missed Doses (5.6)
    - Addition: Gave guidance on how to dose and to report an AE in the event of vomiting
  - Concomitant Medications and Procedures (5.8)
    - Addition: All concomitant medications include dietary / herbal / over the counter supplements
    - Addition: referenced a new Appendix on prednisone dose equivalents
    - Addition: standard of care systemic cGVHD therapies are permitted and include rituximab
    - Addition: Doses of systemic therapies listed in 5.8.2 may be tapered at the discretion of the Investigator after ≥ 4 weeks of KD025.
    - Substitution: strong CYP3A4 inducers are prohibited replaces the general guidance that CYP3A4 inducers should be used with caution
    - Addition: Strong CYP3A4 inducers are prohibited per Section 5.87
    - Addition: Table 7 Guidelines for Management of Treatment-Emergent Toxicities was revised. Grade 4 organ toxicities considered at least possibly related to KD025 has recommended action of KD025 discontinuation; Grade ≥ 3 LFTs require action regardless of attribution to KD025; other Grade ≥ 3 toxicities considered at least possibly related to KD025 require action

- STUDY ASSESSMENTS AND PROCEDURES
  - Addition: Further details of pulmonary function testing are provided in a new Appendix M (6.1)
  - Study Visits (6.2)
    - Addition: Provide informed assent at screening
    - Addition: (if aged ≥16 years) / Lansky (if aged <16 years) Performance Scale score for all time points where KPS is to be assessed
    - Addition: Eligible subjects may be randomized after Medical Monitor approval during the screening window or on C1D1 prior to dosing with KD025.
    - Addition: 5 and 7 hour post dose PK samples for full PK subjects
    - Addition: weight measurement to visit C1D15
    - Addition: defined sampling of sparse PK (Table 13)
    - Addition: reasons for exception of not using Full PFTs at End of Treatment
    - Addition: at C19D1 and after, subjects may return to clinic every other treatment cycle
    - Substitution: the 28-Day Follow-Up visit should occur 28 (± 7) days after the last dose of study drug; however, when possible, the visit should occur prior to starting on a new cGVHD therapy. This replaced the previous wording on when the 28-Day Follow-Up visit was to occur.
  - Efficacy (6.3)
    - Addition: Additional Secondary Endpoints: Time to Response (TTR) and Time to Next Treatment (TTNT)

- Safety (6.4)
  - Addition: safety is a secondary endpoint. The primary safety outcome will be the percent of subjects in each arm experience AEs.
  - Addition: Respiratory rate and temperature are vitals that will be measured.
  - Addition: tests to include HBsAg and hepatitis C antibodies
  - Addition: If pregnancy is confirmed with serum testing, KD025 will be discontinued. The sponsor will continue to collect data on the pregnancy and the subject will continue to be followed. In the event that a subject or a subject's partner becomes pregnant during the study, the sponsor will collect data on the pregnancy.

- PHARMACOKINETICS:
  - Addition: new Section 7.1, Sparse PK, describes sparse PK
  - Addition: new Section 7.2, Full PK. Added clarification that samples are collected from subjects that have consented to the optional Full PK sampling and will be performed at sites that have the capability and agree to conduct Full PK sampling.
  - Addition: Sparse PK: additional samples taken at 5 hours post-dose on C2D1 and C4D1 (Table 13)
  - Addition: Full PK: additional samples taken at 5 and 7 hours post-dose on C1D1 and C2D1 (Table 13)

- PHARMACODYNAMICS:
  - Clarification: samples collected from all subjects for PD analyses at only those sites with appropriate capabilities instead of not specifying sites where PD samples collected (8)

- STUDY STOPPING RULES
  - Substitution: that study arm will be terminated early was replaced with enrollment will be paused for assessment of safety (10)
  - Substitution: Withdrawal due to related AEs within 3 months of randomizing in > 20% of subjects was replaced with withdrawal due to related AEs in > 20% of subjects (10)

- STATISTICAL CONSIDERATIONS
  - Substitution: Figure 2 was revised
  - Substitution: Table 11 was revised
  - Addition: three analyses are planned; alpha will only be allocated to the primary endpoint, ORR
    - Interim analysis will be conducted approximately 2 months after 126 subjects have been enrolled in the mITT population.
    - Primary analysis will be conducted approximately 6 months after 126 subjects have been enrolled in the mITT population.
    - Follow-up analysis will be conducted approximately 12 months after 126 subjects have been enrolled in the mITT population.
  - Sample Size (11.2)
    - Addition: Power Calculation added to Section 11.2 header of Sample Size

        - Addition: explanation that the Hochberg procedure will be used for multiplicity adjustment for the overall response rate (ORR), the primary efficacy endpoint
        - Addition: description of power calculation for planned analysis
        - Substitution: analysis of power for various hypothetical ORRs replaced by power table for interim analysis and power table for primary analysis
        - Addition: "Efficacy Decision Rules with" was added to Section 11.2.1 header of "Multiplicity Adjustment"
        - Addition: (Section 11.2.1) described the inferential decision for primary endpoint of ORR and updated Figure 2
    - Analysis Populations (11.3)
        - New Designation: all randomized subjects who receive at least 1 dose of study medication will now be considered as a *modified* Intent-to-Treat (mITT) Population instead of an Intent-to-Treat (ITT) Population
    - Subgroup Analysis (11.4)
        - Addition: concomitant treatment with a PPI added to subgroup analyses (Section 11.4)
        - Addition: age (categorical) added to subgroup analyses (Section 11.4)
    - Interim Analysis (11.6)
        - Addition to Secondary Efficacy Endpoints: Duration of Response assessments include The time from initial response of PR or CR until documented progression from best response of cGVHD, new cGVHD therapy, or death and Time from initial response to start of additional systemic cGVHD therapy or death
        - Addition to Secondary Efficacy Endpoints: TTR and TTNT are defined

- ETHICAL ASPECTS
    - Addition: Samples will be held no longer than 10 years from time of collection. No genomic research will be conducted. (14.4)

- REFERENCES, APPENDICES, AND OTHER GENERAL CHANGES
    - Schedule of Assessments (Appendix A)
        - Merged randomization for screening and baseline (C1D1)
    - Addition: Appendix M on PFT Assessments providing schedule of PFT Assessments based on Response, Full PFT, or Spirometry
    - Addition: Appendix N on Prednisone Dose Equivalents for 1 mg prednisone
    - Addition: Appendix O on Central Lab and Contact Information
    - Administrative
    - Regulatory text (ICH instead of CFR)
    - Changes in List of Abbreviations to accommodate modifications in text
    - Changes in nomenclature
        - "Female" term replaces "woman"
        - "Consent/assent" replaces "consent"
        - "cGVHD global severity rating based on *Clinician*-Reported Global cGVHD Activity Assessment" replaces "cGVHD severity rating based on *Physician*-Reported Global cGVHD Activity Assessment"

- "Modified Intent-to-Treat (mITT)" Population replaces "Intent-to-Treat (ITT) Population"
- "Study Objectives/*Purpose*" replaces "Study Objectives"

- Grammar, format, and spelling where applicable

21.15.2 Amended Protocol 02 (01 June 2020)

SUMMARY

KD025-213 Protocol Amendment 2 has been amended from the KD025-213 Protocol Amendment 1 dated 26 June 2019. General changes are detailed below:

- STUDY OBJECTIVES / PURPOSE:
  - Exploratory Objectives (2.3)
    - Substitution: Kadmon Algorithmic Response Assessment (KARA) replaces sponsor assessments

- INVESTIGATIONAL PLAN:
  - Study Design (3.1)
    - Revision: Figure 1 KD025-213 Study Schema was revised with the new Arm A and Arm B expected accruals.
  - Estimated Study Duration (3.3)
    - Revision: The study enrollment period was revised from 12 to 24 months.
    - Revision: The anticipated study close out was revised to occur approximately 4 years after the first subject is enrolled.

- STUDY POPULATION:
  - Number of Subjects (4.1)
    - Revision: Revised the number of subjects from 126 to 166 to be enrolled; revised the number of subjects in each treatment arm from 63 to 83.
    - Addition: Sample size has increased from approximately 126 subjects with additional subjects to be enrolled (20 adolescents, 20 adults into a site-specific Companion Study)
  - Withdrawal Criteria (4.7)
    - Revision: Subjects with a Lack of Response – Mixed response assessment no longer need approval from the Medical Monitor and documentation of the subject's willingness to continue.

- STUDY TREATMENT
  - Investigational Product (5.1)
    - Addition: KD025 is also known as belumosudil
  - KD025 Tapering Guidance (5.2)
    - Revision: Subjects whose cGVHD has not progressed at the time of discontinuation of KD025 treatment should be tapered off KD025.
  - Concomitant Medications and Procedures (5.8)
    - Revision: Treatment with investigational systemic immunosuppressant drugs for cGVHD was revised; these drugs include ruxolitinib (rituximab is not considered an invitational systemic immunosuppressant drug for cGVHD).

- STUDY ASSESSMENTS AND PROCEDURES
  - Study Visits (6.2)

        - Revision: Single ECG on C7D1 and beyond was revised from occurring every 3rd Cycle thereafter to occurring every 4th Cycle thereafter
        - Revision: Examples of when full PFTs are to be conducted was revised to include an additional example of Day 1 of Cycles 19.
    - Efficacy (6.3)
        - Substitution: Kadmon Algorithmic Response Assessment (KARA) replaces sponsor assessments
        - Revision: The cGVHD response assessments performed by Investigators was clarified to be performed per the Schedule of Assessments.

- PHARMACODYNAMICS:
    - Addition: Additional samples will be collected from subjects enrolled in the site-specific Companion Study.
    - Addition: Appendix P is referenced; this describes the PD analyses for these additional samples

- STATISTICAL CONSIDERATIONS
    - Addition: Additional analyses will be conducted to include adolescent subjects and Companion Study subjects approximately 6 months after completion of enrollment of the respective subjects.
    - Subgroup Analysis (11.4)
        - Revision: age (categorical) was revised from 12-18 and 19-64 to 12-17 and 18-64.
    - Exploratory Analysis (11.8)
        - Substitution: Kadmon Algorithmic Response Assessment (KARA) replaces sponsor assessments
    - Safety Analyses (11.9)
        - Revision: MedDRA version was revised from Version 20.1 or greater to Version 20.0 or greater.

- ETHICAL ASPECTS
    - Local Regulations (14.1)
        - Revision: ICH E6 Tripartite Guidelines (January 1997) was revised to ICH E6(R2) Integrated Addendum to ICH E6(R1) (March 2018)

- REFERENCES, APPENDICES, AND OTHER GENERAL CHANGES
    - Schedule of Assessments (Appendix A)
        - Revision: Included superscript "d" for the Clinician –reported global cGVHD activity assessment for cycles CxD1 to align with the schedule of assessments outlined in Section 6: Study Assessments and Procedures
        - Revision: Table 16 was revised to have ECGs occur Cycle 7 and every 4th cycle thereafter
    - Drugs that Induce and Inhibit CYP3A4 (Appendix J)
        - Revision: Source site was accessed May 11, 2020 and Table 17 was revised accordingly.

- Drugs that Induce and Inhibit CYP1A2 (Appendix K)
  - Revision: Source site was accessed May 11, 2020 and Table 18 was revised accordingly.
- Drugs that Prolong QTc (Appendix L)
  - Revision: Source site was accessed May 11, 2020
- Addition: Appendix P, Companion Study for Biospecimen Collection. An addendum describing biospecimen collection for the following sites: National Institutes of Health (NIH), Dana Farber Cancer Institute, the University of Texas MD Anderson Cancer Center, and Washington University in St. Louis.
- Grammar, format, and spelling where applicable

21.15.3 Amended Protocol 03 (30 August 2021)

SUMMARY

KD025-213 Protocol Amendment 3 has been amended from the KD025-213 Protocol Amendment 2 dated 01 June 2020 to include all administrative letter updates as well as to include the following major updates:

1. FDA approval of REZUROCK (belumosudil)
2. Withdrawal criteria: Adult participation in KD025-213 will end if subject has incurred a failure-free survival event or has received belumosudil for more than 6 months. A new study: "Extended Treatment and Follow-up of Subjects Treated with Belumosudil in Study KD025-208 or Study KD025-213" will allow for adult patients to still receive belumosudil as an investigational product; else, subjects can receive commercial product once off KD025-213.
3. Use with CYP3A4 and CYP1A2 inducers/inhibitors: CYP3A4 inducers decrease exposure to belumosudil and all CYP3A4 and CYP1A2 inhibitors and inducers no longer need to be used with caution or are prohibited
4. Schedule of assessments: added in height assessment at additional timepoints for adolescent population to calculate BMI

Additional minor updates include:

1. Removing the safety vendor's name
2. Replacing the signatory of the Sponsor Approval page to [redacted].
3. Replacing the medical monitor to [redacted]
4. Clarified that PD samples are not required if an institute's policies limit the daily volume of blood allowed to be drawn as part of research.
5. Updated KD025-208 data in Introduction.
6. Clarified that at the End of Treatment visit, if subject is discontinuing study due to enrolling in the KD025-217 study, then less assessments are to be performed as this is expected to be the same day as C1D1 of the new rollover study.
7. Section 9 was revised to eliminate superfluous language and sections; a unique section on pregnancy was added.
8. Appendix on CRO information: revised Covance to Labcorp

21.15.4 Amended Protocol 04 (11 April 2022)

SUMMARY

KD025-213 Protocol Amendment 4 has been amended from the KD025-213 Protocol Amendment 3 dated 30 August 2021 to include the following major updates:

1. Appendix N: Remaining eligible adolescent subjects will enroll into the study at belumosudil 200 mg QD dose. There will be no more randomization and stratification factors applied. Any adolescent taking a PPI or a strong CYP3A4 inducer will begin C1D1 at the following escalated dose: belumosudil 200 mg BID
2. Removal of section "Drugs Prolonging the QTc interval" and corresponding appendix

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