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Belumosudil for Treating Chronic Lung Allograft Dysfunction

Abstract

The present disclosure relates generally to the treatment of patients with chronic lung allograft dysfunction (CLAD) following lung transplantation, with bronchiolitis obliterans syndrome (BOS) following lung transplantation, or with bronchiolitis obliterans syndrome (BOS) following allogeneic hematopoietic stem cell transplantation, by administering belumosudil.

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Background/Summary

TECHNICAL FIELD

[0001] The present disclosure relates generally to the treatment of patients with lung disorders, including chronic lung allograft dysfunction (CLAD), restrictive allograft syndrome (RAS), bronchiolitis obliterans syndrome (BOS), following lung transplantation or allogeneic hematopoietic stem cell transplantation by administering belumosudil.

BACKGROUND

[0002] Chronic lung allograft dysfunction (CLAD) has two subtypes, bronchiolitis obliterans syndrome (BOS) and restrictive allograft syndrome (RAS). CLAD is a major cause of morbidity and mortality following lung transplantation. CLAD results from inflammatory and fibrotic changes either in the airways (BOS) or in the lung parenchyma (RAS). The pathogenesis of CLAD is driven by a combination of immune dysfunction and pro-fibrotic pathway activation leading to tissue injury and fibrosis.

[0003] Standard of care in the treatment of post-lung transplant recipients include a calcineurin inhibitor (CNI) (such as tacrolimus or cyclosporin), an anti-proliferation agent (cell cycle inhibitor such as mycophenolate or azathioprine), and low dose steroids (such as prednisolone). The management of CLAD has been center-specific and disappointing with no currently approved therapies. Lung transplant centers typically increase or modify baseline immunosuppressive protocols, introduce an mTOR inhibitor (mTORi), in lieu of a CNI or an anti-proliferation agent, increase steroid doses, introduce anti-thymocyte globulin and in some cases extracorporeal photopheresis (ECP) or less commonly, alemtuzumab (anti-CD52). The macrolide antibiotic, azithromycin, is frequently used based on studies showing that it can stabilize lung function in a subset of patients with CLAD, usually those with broncho-alveolar lavage (BAL) neutrophilia. However, in most patients, CLAD is unresponsive with progressive decline in graft function. Taken together this evidence highlights the critical unmet need and the urgency to investigate novel therapies that could stabilize lung function in patients with CLAD, potentially leading to better overall survival.

[0004] Bronchiolitis obliterans syndrome (BOS) is one of the most severe complications after lung or allogeneic hematopoietic stem cell transplantation (allo-HSCT); however, it is also observed in systemic autoimmune diseases and after exposure to environmental contaminants. BOS after lung transplantation is characterized by inflammation of subepithelial structures and dysregulated repair of the small airways of transplanted lungs; this causes fibroproliferation and abnormal regeneration of epithelium and leads to scarring which results in narrowing of the airways, limited airflow and, finally, loss of lung function (K. C. Meyer, et al., An international ISHLT/ATS/ERS clinical practice guideline: diagnosis and management of bronchiolitis obliterans syndrome, Eur. Respir. J. 44 (6) (2014) 1479-1503; Krishna, Rachana, and Tony I. Oliver. “Bronchiolitis Obliterans (Obliterative Bronchiolitis, Constrictive Bronchiolitis).” (2017); Mini-Series, Lung Transplantation. “Bronchiolitis Obliterans Syndrome (BOS) following lung transplant.” Am J Respir Crit Care Med 193 (2016): P19-P20). BOS is the leading cause of late mortality and morbidity after lung transplantation or allo-HSCT. Approximately 40%-50% of patients undergoing lung transplantation are diagnosed with BOS within 5 years following their transplant and have a median survival of 3-5 years following this diagnosis (K. C. Meyer, et al., An international ISHLT/ATS/ERS clinical practice guideline: diagnosis and management of bronchiolitis obliterans syndrome, Eur. Respir. J. 44 (6) (2014) 1479-1503; R. D. Yusen, et al., The registry of the International Society for Heart and Lung Transplantation: thirty-first adult lung and heart-lung transplant report-2014; focus theme: retransplantation, J. Heart Lung Transplant. 33 (10) (2014) 1009-1024).

[0005] BOS after HSCT results from an immunological attack of the small airways by the donor immune system, leading to fibrotic narrowing of the respiratory bronchioles and subsequent obliteration. (Williams K M. How I treat bronchiolitis obliterans syndrome after hematopoietic stem cell transplantation. Blood 2017; 129 (4): 448-455). Historically, treatment options for BOS after hematopoietic stem cell transplantation have consisted of standard cGVHD therapies, including systemic corticosteroids and immunosuppressive agents with a hope to intervene of disease before irreversible damage has occurred. In a small randomized, double-blind study, inhaled budesonide/formoterol led to a significant improvement in FEV1 as compared to placebo in patients with mild/severe BOS following hematopoietic stem cell transplantation. (Bergeron A, et al. Budesonide/Formoterol for bronchiolitis obliterans after hematopoietic stem cell transplantation. Am J Respir Crit Care Med 2015; 191 (11): 1242-1249). A phase II trial evaluating the combination of inhaled fluticasone, azithromycin, and montelukast (FAM) and a brief steroid pulse suggested that this therapeutic approach may limit pulmonary decline in new-onset BOS. (Williams K M, et al. Fluticasone, Azithromycin, and Montelukast Treatment for New-Onset Bronchiolitis Obliterans Syndrome after Hematopoietic Cell Transplantation. Biol Blood Marrow Transplant 2016; 22 (4): 710-716). Similarly, other immunosuppressive or immunomodulatory therapeutics can halt disease progression, but rarely improve either pulmonary function or symptoms. (Brownback K R et al. Effect of extracorporeal photopheresis on lung function decline for severe bronchiolitis obliterans syndrome following allogeneic stem cell transplantation. J Clin Apher 2016; 31 (4): 347-352; Brownback K R, et al. Effect of Rituximab on Pulmonary Function in Bronchiolitis Obliterans Syndrome due to Graft-Versus-Host-Disease. Lung 2017; 195 (6): 781-788). Therefore, novel therapeutic approaches for BOS after HSCT remain an unmet need.

SUMMARY

[0006] The present disclosure provides methods of treating a subject diagnosed with bronchiolitis obliterans syndrome following lung transplantation, by administering to a subject in need thereof a therapeutically effective amount of 2-{3-[4-(1H-indazol-5-ylamino)-2-quinazolinyl]phenoxy}-N-(propan-2-yl) acetamide, or a pharmaceutically acceptable salt thereof (belumosudil).

[0007] The present disclosure provides methods of treating a subject diagnosed with chronic lung allograft dysfunction (CLAD) following lung transplantation, by administering to a subject in need thereof a therapeutically effective amount of 2-{3-[4-(1H-indazol-5-ylamino)-2-quinazolinyl]phenoxy}-N-(propan-2-yl) acetamide, or a pharmaceutically acceptable salt thereof (belumosudil).

[0008] The present disclosure also provides methods of treating a subject diagnosed with bronchiolitis obliterans syndrome following allogeneic hematopoietic stem cell transplantation by administering to a subject in need thereof a therapeutically effective amount of 2-{3-[4-(1H-indazol-5-ylamino)-2-quinazolinyl]phenoxy}-N-(propan-2-yl) acetamide, or a pharmaceutically acceptable salt thereof (belumosudil), wherein the subject has mild to moderate bronchiolitis obliterans syndrome or early bronchiolitis obliterans syndrome.

[0009] The present disclosure additionally provides methods of treating a subject diagnosed with chronic lung allograft dysfunction following lung transplantation, the method comprising administering a therapeutically effective amount of 2-{3-[4-(1H-indazol-5-ylamino)-2-quinazolinyl]phenoxy}-N-(propan-2-yl) acetamide, or a pharmaceutically acceptable salt thereof (belumosudil) to the subject in need thereof.

[0010] In some embodiments, the chronic lung allograft dysfunction comprises bronchiolitis obliterans syndrome. In some embodiments, the chronic lung allograft dysfunction comprises restrictive allograft syndrome. In some embodiments, the subject has mild bronchiolitis obliterans syndrome. In some embodiments, the subject has moderate bronchiolitis obliterans syndrome.

[0011] In some embodiments, belumosudil can be administered to the subject at a dose selected from the group consisting of 200 mg daily, 200 mg twice daily, and 400 mg daily. In some embodiments, belumosudil can be administered to the subject at a dose selected from the group

consisting of 200 mg daily, 200 mg twice daily, and 400 mg daily, wherein the belumosudil is administered as a 28-day cycle, wherein the number of cycles ranges from 3-15. In some embodiments, the number of cycles is greater than 3, 4, 5, 10, 15, 20, 25, or 30, or until a desired response is achieved.
[0012] The present embodiments can be understood more fully by reference to the detailed description and examples, which are intended to exemplify non-limiting embodiments.

Description

BRIEF DESCRIPTION OF THE DRAWINGS
[0013] FIG. **1** is the CONSORT flow diagram describing the phase IIa, open-label, dose-finding study of belumosudil of Example 1.
[0014] FIG. **2** is a forest plot for subgroup analyses of ORR in the safety population.
[0015] Subgroups were defined based on baseline assessment.
[0016] FIG. **3**A describes the best individual response by organ system among responders. n=number of responder population for global severity rating and number of specific organs involved at baseline. The percentages are calculated based on the corresponding n.
[0017] FIG. **3**B is a response and progression heat map for all patients in the safety population. Of 11 patients with progression in joints, seven had a reduction in P-ROM of just one unit.
[0018] FIG. **4** describes time to response among belumosudil responders. Percentages are calculated based on the number of responder population.
[0019] FIG. **5** describes time to response by selected organs among responders.
[0020] Percentages are calculated based on the number of responder population.
[0021] FIG. **6**A describes changes in percentage of CD41 Tregs following treatment with belumosudil compared with baseline for Tregs (regulatory T cells all). Predose peripheral blood samples were collected on C1D1 (cycle 1 day 1), C2D1 (cycle 2 day 1), C4D1 (cycle 4 day 1), C7D1 (cycle 7 day 1), and end-of-treatment visits.
[0022] FIG. **6**B describes changes in percentage of CD41 Tregs following treatment with belumosudil compared with baseline for Tregs (regulatory T cells responders). Predose peripheral blood samples were collected on C1D1 (cycle 1 day 1), C2D1 (cycle 2 day 1), C4D1 (cycle 4 day 1), C7D1 (cycle 7 day 1), and end-of-treatment visits.
[0023] FIG. **6**C describes changes in percentage of CD41 Tregs following treatment with belumosudil compared with baseline for Tregs (regulatory T cells nonresponders). Predose peripheral blood samples were collected on C1D1 (cycle 1 day 1), C2D1 (cycle 2 day 1), C4D1 (cycle 4 day 1), C7D1 (cycle 7 day 1), and end-of-treatment visits.
[0024] FIG. **7** is the CONSORT flow diagram describing the phase II randomized study of belumosudil of Example 2.
[0025] FIG. **8** is a forest plot of subgroup analyses of ORR (mITT). High ORRs were observed in all subgroups analyzed in the mITT population, and efficacy was maintained irrespective of prior treatments. The 50th percentile for duration of cGVHD before enrollment was 29 months. Response assessments performed on or after the initiation of a new systemic therapy for cGVHD were excluded from the analysis.
[0026] FIG. **9** describes ORR by organ system in the mITT population. Organ-specific analyses in the mITT population demonstrated ORRs in the skin, eyes, mouth, liver, lungs, joints/fascia, upper GI tract, lower GI tract, and esophagus. CR was seen across all affected organs.
[0027] FIG. **10**A describes durability of response to belumosudil by dose. Kaplan-Meier plot of DOR in the responder population. DOR was defined as the time from response until documented progression or start of another cGVHD systemic treatment; durability data continue to mature.
[0028] FIG. **10**B describes durability of response to belumosudil by dose. Kaplan-Meier curves of

estimated FFS in the mITT population, including reasons for failure. FFS was defined as the absence of cGVHD treatment change, NRM, and recurrent malignancy.

[0029] FIG. **10**C describes durability of response to belumosudil by dose. Kaplan-Meier curves of estimated OS in the mITT population.

[0030] FIG. **11** describes the clinical study design of Example 2.

[0031] FIG. **12** describes the best change in percent predicted FEV1 from baseline in 59 subjects of Example 3. Dotted lines mark absolute improvement by 5% and 10%, respectively. Baseline NIH lung scores are 1, 2, or 3. Each bar represents an individual subject.

[0032] FIG. **13** describes the best change in Lee Symptom Scale (LSS) for lung from baseline in 59 subjects of Example 3. LSS lung scores (white) are grouped according to baseline NIH lung score. A 10 point change (half a standard deviation from baseline scores) was considered clinically meaningful. The corresponding best change in % FEV1 from baseline for the individual subject is shown in black.

[0033] FIG. **14** is a heatmap of best response metrics of disease and symptoms in BOS. Baseline characteristics for all 59 subjects and best improvement in multiple metrics of lung response are shown. Detailed definitions of metrics are provided in Table 35. Abbreviations used in FIG. **14** are as follows cGVHD: chronic graft-versus-host disease; F: female; FEV1: forced expiratory volume in 1 second; M: male; mod: moderate; NIH: National Institutes of Health; NR: no response; PD: progressive disease; PFT: pulmonary function tests; PR: partial response; SD: stable disease; Sev: severe; Unk: unknown.

[0034] FIGS. **15**A to **15**G describe the correlation among multiple metrics of disease and symptoms in BOS. Analysis of 583 paired time points found a lack of significant association between PFT evaluations (% FEV1 or FEV1 in L) and symptom metrics (LSS lung subscore or the NIH lung symptom score).

[0035] FIG. **16** describes the trajectory of all % predicted FEV1 measurements collected while on belumosudil therapy. Graphical representation demonstrates the % predicted FEV1 measurements for subjects of Example 3 who were responders (PR or CR by NIH criteria, n=19) in black and non-responders (n=40) in white. Fitted lines for responders and non-responders generated using locally weighted smoothing (LOESS technique) to visually present the relationship between % predicted FEV1 and response over time.

[0036] FIG. **17** shows the best ORR for pulmonary cGVHD according to NIH response criteria for subjects of Example 3.

DETAILED DESCRIPTION

Definitions

[0037] “Bronchiolitis obliterans syndrome (BOS)” can result after lung transplantation or hematopoietic stem cell transplantation (HSCT). BOS after HSCT is also known as lung cGVHD, pulmonary cGVHD or cGVHD with lung involvement. The pathophysiology of cGVHD can be separated into three phases: early inflammation because of tissue injury, a dysregulated adaptive immune system, and chronic inflammation and aberrant tissue repair with fibrosis. The diagnosis of BOS is based on the occurrence of obstruction (measured as a decrease in forced expiratory volume in 1 s [FEV1]), the absence of restriction (decrease in forced vital capacity [FVC] or total lung capacity), as well as an absence of opacities observed in computed tomography scans ((K. C. Meyer, G. Raghu, G. M. Verleden, et al., An international ISHLT/ATS/ERS clinical practice guideline: diagnosis and management of bronchiolitis obliterans syndrome, *Eur. Respir. J.* 44 (6) (2014) 1479-1503; G. M. Verleden, A. R. Glanville, E. D. Lease, et al., Chronic lung allograft dysfunction: definition, diagnostic criteria, and approaches to treatment-A consensus report from the Pulmonary Council of the ISHLT, *J. Heart Lung Transplant.* 38 (5) (2019) 493-503). In particular, FEV1 has been identified as a prognostic marker in BOS after allo-HSCT or lung transplant (J. H. Ahn, K. W. Jo, J. W. Song, et al., Prognostic role of FEV1 for survival in bronchiolitis obliterans syndrome after allogeneic hematopoietic stem cell transplantation, *Clin.*

Transplant. 29 (12) (2015) 1133-1139).

[0038] BOS arising after lung transplantation or HSCT may be diagnosed at various stages of progression. The NIH lung symptom scoring system, which has been used to score BOS associated with cGVHD after HSCT, may be used to identify and/or monitor BOS status and progression including as mild BOS, moderate BOS, and severe BOS. The term "NIH lung symptom score" or "NIH cGVHD lung score" is a clinical symptom-based score ranging from 0 to 3. A Score 0 is used for no symptoms, Score 1 is used for symptoms of shortness of breath with stairs, Score 2 is used for symptoms of shortness of breath on flat ground, and Score 3 is used for shortness of breath at rest or requiring oxygen. As used herein, the term "mild BOS" refers to a subject that has a NIH lung symptom score of 1 and the term "moderate BOS" refers to a subject that has a NIH lung symptom score of 2. The term "severe BOS" refers to a subject that has a NIH symptom score of 3.

[0039] "Early stage" BOS includes both mild and moderate BOS, and may also be referred to as "early BOS." In some embodiments, the term "early BOS" refers to a subject that has a NIH lung symptom score of 1 or 2. In some embodiments, "severe BOS" or "late stage BOS" refers to a subject that has a NIH lung symptom score of 3.

[0040] The terms "allogeneic hematopoietic stem cell transplantation (allo-HSCT)" also called bone marrow transplantation or stem cell transplantation, or "allogeneic hematopoietic cell transplantation (allo-HCT)" refer to cell transplants in which the hematopoietic cells from a donor are grafted into a recipient who is not an identical twin. The source of hematopoietic stem cells for allogeneic transplantation may be peripheral blood stem cells (PBSC) or bone marrow (BM). In some circumstances umbilical cord blood may be used. The donor and recipient may be matched at the human leukocyte antigen (HLA) genes, such as siblings. The donor and recipient may be a parent and a child who are only half-matched (haploidentical). A myeloablative transplant uses very high doses of chemotherapy or radiation prior to transplantation with autologous or allogeneic hematopoietic stem cells. A non-myeloablative transplant, or reduced intensity transplant, allows the patient to have less intensive chemotherapy before transplantation with allogeneic hematopoietic stem cells.

[0041] Belumosudil is an oral selective rho-associated coiled-coil-containing protein kinase-2 (ROCK2) inhibitor. ROCK2 inhibition acts on the dysregulated adaptive immune system and the fibrosis that occurs as a result of aberrant tissue repair. (Zanin-Zhorov A, Weiss J M, Nyuydzefe M S, Chen W, Scher J U, Mo R et al. Selective oral ROCK2 inhibitor down-regulates IL-21 and IL-17 secretion in human T cells via STAT3-dependent mechanism. *Proceedings of the National Academy of Sciences of the United States of America* 2014; 111 (47): 16814-16819. Flynn R, Paz K, Du J, Reichenbach D K, Taylor P A, Panoskaltsis-Mortari A et al. Targeted Rho-associated kinase 2 inhibition suppresses murine and human chronic GVHD through a Stat3-dependent mechanism. *Blood* 2016; 127 (17): 2144-2154.)

[0042] The term "belumosudil" as used herein is intended to include 2-{3-[4-(1H-indazol-5-ylamino)-2-quinazolinyl]phenoxy}-N-(propan-2-yl) acetamide, and any pharmaceutically acceptable salt thereof. Belumosudil, also known as KD025, is marketed as REZUROCK™ in the United States for the treatment of patients with chronic GVHD after failure of at least two prior lines of systemic therapy. The active pharmaceutical ingredient of REZUROCK™ is belumosudil mesylate with the molecular formula C.sub.27H.sub.28N.sub.6O.sub.5S and the molecular weight is 548.62 g/mol. The chemical name for belumosudil mesylate is 2-{3-[4-(1H-indazol-5-ylamino)-2-quinazolinyl]phenoxy}-N-(propan-2-yl) acetamide methanesulfonate (1:1). The chemical structure of belumosudil mesylate is as follows:

##STR00001##

[0043] Belumosudil mesylate is a yellow powder that is practically insoluble in water, slightly soluble in methanol and DMF and soluble in DMSO. Belumosudil tablets are for oral administration. Each tablet contains 200 mg of the free base equivalent to 242.5 mg of belumosudil mesylate. The tablet also contains the following inactive ingredients: microcrystalline cellulose,

hypromellose, croscarmellose sodium, colloidal silicon dioxide, and magnesium stearate. The tablet film consists of polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide and yellow iron oxide.

[0044] Belumosudil is described in the following US patents: U.S. Pat. Nos. 8,357,693, 9,815,820, 10,183,931, and 10,696,660.

[0045] First-line therapy for National Institutes of Health (NIH)-defined moderate to severe chronic graft-versus-host disease (cGVHD) is corticosteroids alone or in combination with sirolimus or a calcineurin inhibitor. (Carpenter P A, Logan B R, Lee S J, et al: A phase II/III randomized, multicenter trial of prednisone/sirolimus versus prednisone/sirolimus/calcineurin inhibitor for the treatment of chronic graft-versus-host disease: BMT CTN 0801. Haematologica 103:1915-1924, 2018). However, up to 70% of patients require additional lines of therapy. (Bachier C R, Aggarwal S K, Hennegan K, et al: Epidemiology and real-world treatment of chronic graft-versus-host disease post allogeneic hematopoietic cell transplantation: A US claims analysis. Presented at ASH 2019, Orlando, FL, Dec. 7-10, 2019; Lee S J, Nguyen T D, Onstad L, et al: Success of immunosuppressive treatments in patients with chronic graft-versus-host disease. Biol Blood Marrow Transpl 24:555-562, 2018: Flowers M E D, Martin P J: How we treat chronic graft-versus-host disease. Blood 125:606-615, 2015). Furthermore, the long-term use of corticosteroids is associated with significant side effects. (Biol Blood Marrow Transpl 24:555-562, 2018: Flowers MED, Martin P J: How we treat chronic graft-versus-host disease. Blood 125:606-615, 2015); MacDonald KPA, Hill G R, Blazar B R: Chronic graft-versus-host disease: Biological insights from preclinical and clinical studies. Blood 129:13-21, 2017). Examples of corticosteroid therapies for treatment of cGVHD include, but are not limited to, prednisone, prednisolone, methylprednisolone, budesonide.

[0046] Pulmonary function tests (PFTs) measure lung volume, capacity, rates of flow, and gas exchange. Spirometry or plethysmography may be used to obtain the measurements. Spirometry is a physiological test which measures the ability to inhale and exhale air in relation to time. The main results of spirometry are forced vital capacity (FVC) and forced expiratory volume (FEV). The procedure of spirometry has 3 phases: 1) maximal inspiration; 2) a “blast” of exhalation; 3) continued complete exhalation to the end of the test. Vital capacity (VC) is the volume of gas expelled from full inspiration to residual volume. FVC involves a patient exhaling at maximal speed and effort. Forced expiratory volume in 1 second (FEV1) is the volume of air in liters that is exhaled in the first second during forced exhalation after maximal inspiration. Normally, at least 80% of the forced vital capacity (FVC) is exhaled in the first second. Lung plethysmography may be used to measure total lung capacity; the amount of air left in your lungs when you breathe out normally, which is called functional residual capacity (FRC); and how much air is left when you breathe out as much as possible, or residual capacity (RC). Radiology may also be used to measure lung function, such as inspiratory and expiratory chest CT scans, 18-fluorodeoxyglucose positron emission tomography imaging, or MRI.

[0047] Lee Symptom Scale (LSS) summary score measures the effect on patients' functioning and well-being. The Lee Symptom Scale is a 30-item scale developed to measure the symptoms of cGVHD and is described in Lee S J, Cook E F, Soiffer R, Antin J H. Development and validation of a scale to measure symptoms of chronic graft-versus-host disease. Biol Blood Marrow Transplant 2002; 8:444-452.

[0048] As used herein, the term “line of treatment” or “line of therapy” describes the sequence or order in which different therapies are given to a patient as the patient's disease progresses. Initial treatment (first-line therapy) may not work or may stop working after a period of time. After such first-line therapy is discontinued, a second different treatment (second-line therapy) may be given. Subsequent lines of therapy may be given when a second-line therapy does not work or stops working. Some patients may be administered multiple lines of therapy over the course of a disease. Examples of prior systemic therapies for treating cGVHD include, but are not limited to,

prednisone, tacrolimus, ECP, sirolimus, ibruitinib, ruxolitinib, MMF, rituximab, MTX, cyclosporine, imatinib, ixazomib, and ofatumumab.

[0049] The term “subject” or “patient” as used herein includes an animal or a human.

[0050] Examples of clinical endpoints include the following. Overall response rate (ORR) is the percentage of people in a study or treatment group who have a partial response (PR) or complete response (CR) to the treatment within a certain period of time. Failure-free survival (FFS) means the time from the first dose of belumosudil to a failure event, or the interval between the start of belumosudil and the addition of a new cGVHD therapy, relapse of the underlying disease, or nonrelapse mortality (NRM). Overall survival (OS) means the length of time from either the date of diagnosis or the start of treatment for a disease. Duration of response (DOR) means from the time of initial response (e.g., PR or CR) until documented progression from best response of cGVHD, time from initial response to start of additional systemic cGVHD therapy, or death. Time to next treatment (TTNT) means time to initiation of a subsequent systemic cGVHD therapy.

[0051] Steroid-refractory (SR) cGVHD is defined as cGVHD progression while on prednisone at ≥1 mg/kg/day for 1-2 weeks, or stable cGVHD while on ≥0.5 mg/kg/day for 1-2 months.

[0052] Immunosuppressive therapy (IST) is typically administered for at least six months after allo-HSCT in order to prevent GVHD. Examples of IST's include sirolimus, prednisone and calcineurin inhibitors such as tacrolimus and cyclosporine. In some embodiments, standard-of-care immunosuppressants may comprise at least one of the following: calcineurin inhibitor, a cell cycle inhibitor and an mTOR inhibitor.

[0053] BOS can occur after allogenic HSCT and after lung transplantation. Bronchiolitis obliterans syndrome after lung transplantation and after allogeneic HSCT are different diseases, but clinical, imaging, and functional features are similar in both settings and include progressive dyspnea, eventually associated with chronic cough, sputum production, nasal congestion, and progressive airflow limitation that may result in respiratory failure.

[0054] Chronic lung allograft dysfunction (CLAD) has two subtypes, bronchiolitis obliterans syndrome (BOS) and restrictive allograft syndrome (RAS). CLAD is a major cause of morbidity and mortality following lung transplantation. CLAD results from inflammatory and fibrotic changes either in the airways (BOS) or in the lung parenchyma (RAS). The pathogenesis of CLAD is driven by immune dysregulation leading to tissue injury and the subsequent secretion of pro-fibrotic mediators. The underlying mechanisms of CLAD appear to be similar to those seen in chronic graft-versus-host disease (cGVHD) of the lung following allogeneic hematopoietic stem cell transplantation.

[0055] The nomenclature of CLAD is typically described as follows:

TABLE-US-00001 CLAD Stage Criteria CLAD 0 Current FEV.sub.1 >80% FEV.sub.1 PTBL CLAD 1 Current FEV.sub.1 >65-80% FEV.sub.1 PTBL CLAD 2 Current FEV.sub.1 >50-65% FEV.sub.1 PTBL CLAD 3 Current FEV.sub.1 >35-50% FEV.sub.1 PTBL CLAD 4 Current FEV.sub.1 ≤35% FEV.sub.1 PTBL Abbreviations: CLAD = chronic lung allograft dysfunction; FEV1 = forced expiratory volume at 1 second; PTBL = post-transplant baseline. See Verleden et al. Chronic lung allograft dysfunction: definition, diagnostic criteria, and approaches to treatment-A consensus report from the Pulmonary Council of the ISHLT. J Heart Lung Transplant. 2019; 38(5): 493-503.

[0056] In some embodiments, provided herein are methods of treating a subject diagnosed with chronic lung allograft dysfunction (CLAD) following lung transplantation, the methods comprising administering a therapeutically effective amount of 2-{3-[4-(1H-indazol-5-ylamino)-2-quinazolinyl]phenoxy}-N-(propan-2-yl) acetamide, or a pharmaceutically acceptable salt thereof (belumosudil) to the subject in need thereof. In some embodiments, the subject is human. In some embodiments, the CLAD comprises bronchiolitis obliterans syndrome (BOS). In some embodiments, the CLAD comprises restrictive allograft syndrome (RAS). In some embodiments, the CLAD is stage 1 or stage 2. In some embodiments, the CLAD is stage 1, stage 2, or stage 3. In

some embodiments, the CLAD is stage 1, stage 2, stage 3 or stage 4. In some embodiments, the CLAD is stage 1. In some embodiments, the CLAD is stage 2. In some embodiments, the subject has mild BOS. In some embodiments, the subject has moderate BOS. In some embodiments, the subject has early BOS. In some embodiments, the subject does not have severe BOS.

[0057] In some embodiments, provided herein are methods of treating a subject diagnosed with chronic lung allograft dysfunction (CLAD), wherein the CLAD is BOS following lung transplantation, the methods comprising administering a therapeutically effective amount of 2-{3-[4-(1H-indazol-5-ylamino)-2-quinazolinyl]phenoxy}-N-(propan-2-yl) acetamide, or a pharmaceutically acceptable salt thereof (belumosudil) to the subject in need thereof.

[0058] In some embodiments, provided herein are methods of treating a subject diagnosed with chronic lung allograft dysfunction (CLAD), wherein the CLAD is RAS following lung transplantation, the methods comprising administering a therapeutically effective amount of 2-{3-[4-(1H-indazol-5-ylamino)-2-quinazolinyl]phenoxy}-N-(propan-2-yl) acetamide, or a pharmaceutically acceptable salt thereof (belumosudil) to the subject in need thereof.

[0059] In some embodiments, provided herein are methods of treating a subject diagnosed with bronchiolitis obliterans syndrome (BOS) following lung transplantation, the methods comprising administering a therapeutically effective amount of 2-{3-[4-(1H-indazol-5-ylamino)-2-quinazolinyl]phenoxy}-N-(propan-2-yl) acetamide, or a pharmaceutically acceptable salt thereof (belumosudil) to the subject in need thereof. In some embodiments, the subject is human.

[0060] In some embodiments, provided herein are methods of treating a subject diagnosed with bronchiolitis obliterans syndrome (BOS) following allogeneic hematopoietic stem cell transplantation, the methods comprising administering a therapeutically effective amount of 2-{3-[4-(1H-indazol-5-ylamino)-2-quinazolinyl]phenoxy}-N-(propan-2-yl) acetamide, or a pharmaceutically acceptable salt thereof (belumosudil) to a subject in need thereof. In some embodiments, the subject is human.

[0061] In some embodiments, provided herein are methods of treating a subject diagnosed with bronchiolitis obliterans syndrome (BOS) following allogeneic hematopoietic stem cell transplantation, the methods comprising administering a therapeutically effective amount of 2-{3-[4-(1H-indazol-5-ylamino)-2-quinazolinyl]phenoxy}-N-(propan-2-yl) acetamide, or a pharmaceutically acceptable salt thereof (belumosudil) to a subject in need thereof, wherein the subject has mild BOS or moderate BOS. In some embodiments, the subject is human. In some embodiments, the subject has mild BOS. In some embodiments, the subject has moderate BOS. In some embodiments, the subject does not have severe BOS.

[0062] In some embodiments, use of a therapeutically effective amount of 2-{3-[4-(1H-indazol-5-ylamino)-2-quinazolinyl]phenoxy}-N-(propan-2-yl) acetamide, or a pharmaceutically acceptable salt thereof for preparing a medicament for the treatment of a subject diagnosed with chronic lung allograft dysfunction (CLAD) following lung transplantation is provided. In some embodiments, a compound comprising a therapeutically effective amount of 2-{3-[4-(1H-indazol-5-ylamino)-2-quinazolinyl]phenoxy}-N-(propan-2-yl) acetamide, or a pharmaceutically acceptable salt thereof for use in the treatment of a subject diagnosed with chronic lung allograft dysfunction (CLAD) following lung transplantation is provided.

[0063] In some embodiments, use of a therapeutically effective amount of 2-{3-[4-(1H-indazol-5-ylamino)-2-quinazolinyl]phenoxy}-N-(propan-2-yl) acetamide, or a pharmaceutically acceptable salt thereof for preparing a medicament for the treatment of a subject diagnosed with bronchiolitis obliterans syndrome following lung transplantation is provided. In some embodiments, a compound comprising a therapeutically effective amount of 2-{3-[4-(1H-indazol-5-ylamino)-2-quinazolinyl]phenoxy}-N-(propan-2-yl) acetamide, or a pharmaceutically acceptable salt thereof for use in the treatment of a subject diagnosed with bronchiolitis obliterans syndrome following lung transplantation is provided.

[0064] In some embodiments, use of a therapeutically effective amount of 2-{3-[4-(1H-indazol-5-

ylamino)-2-quinazolinyl]phenoxy}-N-(propan-2-yl) acetamide, or a pharmaceutically acceptable salt thereof for preparing a medicament for the treatment of a subject diagnosed with bronchiolitis obliterans syndrome (BOS) following allogeneic hematopoietic stem cell transplantation is provided, optionally wherein the subject has mild BOS or moderate BOS.

[0065] In some embodiments, a compound comprising a therapeutically effective amount of 2-{3-[4-(1H-indazol-5-ylamino)-2-quinazolinyl]phenoxy}-N-(propan-2-yl) acetamide, or a pharmaceutically acceptable salt thereof for use in the treatment of a subject diagnosed with bronchiolitis obliterans syndrome (BOS) following allogeneic hematopoietic stem cell transplantation is provided, optionally wherein the subject has mild BOS or moderate BOS.

[0066] In some embodiments, provided herein are methods of treating a subject diagnosed with chronic lung allograft dysfunction (CLAD) following lung transplantation, the method comprising administering 2-{3-[4-(1H-indazol-5-ylamino)-2-quinazolinyl]phenoxy}-N-(propan-2-yl) acetamide, or a pharmaceutically acceptable salt thereof (belumosudil) at a dose selected from 200 mg daily and 200 mg twice daily, to the subject in need thereof. In some embodiments, the subject is human.

[0067] In some embodiments, provided herein are methods of treating a subject diagnosed with bronchiolitis obliterans syndrome (BOS) following lung transplantation or allogeneic hematopoietic stem cell transplantation, the method comprising administering 2-{3-[4-(1H-indazol-5-ylamino)-2-quinazolinyl]phenoxy}-N-(propan-2-yl) acetamide, or a pharmaceutically acceptable salt thereof (belumosudil) at a dose selected from 200 mg daily, 200 mg twice daily, and 400 mg daily to the subject in need thereof. In some embodiments, the subject is human.

[0068] In some embodiments, provided herein are methods of treating a subject diagnosed with chronic lung allograft dysfunction (CLAD) following lung transplantation, the method comprising administering belumosudil at a dose selected from 200 mg daily and 200 mg twice daily. In some embodiments, the subject is human.

[0069] In some embodiments, provided herein are methods of treating a subject diagnosed with chronic lung allograft dysfunction (CLAD), wherein the CLAD is BOS following lung transplantation, the method comprising administering belumosudil at a dose selected from 200 mg daily and 200 mg twice daily. In some embodiments, the subject is human.

[0070] In some embodiments, provided herein are methods of treating a subject diagnosed with chronic lung allograft dysfunction (CLAD), wherein the CLAD is RAS following lung transplantation, the method comprising administering belumosudil at a dose selected from 200 mg daily and 200 mg twice daily. In some embodiments, the subject is human.

[0071] In some embodiments, provided herein are methods of treating a subject diagnosed with bronchiolitis obliterans syndrome (BOS) following lung transplantation or allogeneic hematopoietic stem cell transplantation, wherein belumosudil is administrated to the subject in need thereof until a desired response is achieved. In some embodiments, provided herein are methods of treating a subject diagnosed with bronchiolitis obliterans syndrome (BOS) following lung transplantation or allogeneic hematopoietic stem cell transplantation, the method comprising administering belumosudil at a dose selected from the group consisting of 200 mg daily, 200 mg twice daily, and 400 mg daily, wherein the belumosudil is administered to the subject in need thereof until a desired response is achieved. In some embodiments, provided herein are methods of treating a subject diagnosed with bronchiolitis obliterans syndrome (BOS) following lung transplantation or allogeneic hematopoietic stem cell transplantation, the method comprising administering belumosudil at a dose selected from the group consisting of 200 mg daily, 200 mg twice daily, and 400 mg daily, wherein the belumosudil is administered as a 28-day cycle, wherein the number of cycles ranges from 3 to 15 to the subject in need thereof. In some embodiments, the number of cycles is greater than 3, 4, 5, 10, 15, 20, 25, or 30, or until a desired response is achieved. In some embodiments, a desired response comprises no further disease progression. In some embodiments, a desired response comprises slowing the disease progression. In some

embodiments, a desired response comprises no further decline in lung function. In some embodiments, a desired response comprises slowing the lung function decline. In some embodiments, the belumosudil is administered until there is no disease progression. In some embodiments, the belumosudil is administered until there is no decline in lung function. In some embodiments, the administration of the belumosudil is maintained to preserve the achieved desired response. In some embodiments, the subject is human.

[0072] In some embodiments, provided herein are methods of treating a subject diagnosed with bronchiolitis obliterans syndrome (BOS) following lung transplantation, the method comprising administering belumosudil at a dose selected from the group consisting of 200 mg daily and 200 mg twice daily, to the subject in need thereof.

[0073] In some embodiments, the number of cycles ranges from 3 cycles to loss of response. In some embodiments, the number of cycles ranges from 4 cycles to loss of response. In some embodiments, the number of cycles ranges from 5 cycles to loss of response. In some embodiments, the number of cycles ranges from 6 cycles to loss of response. In some embodiments, the number of cycles ranges from 7 cycles to loss of response. In some embodiments, the number of cycles ranges from 8 cycles to loss of response.

[0074] In some embodiments, the allogeneic hematopoietic stem cell transplantation is a matched-HSCT. In some embodiments, the allogeneic hematopoietic stem cell transplantation is a haploidentical-HSCT.

[0075] In some embodiments, the belumosudil is administered in a 28-day cycle.

[0076] In some embodiments, the number of cycles ranges from 3 to 15. In some embodiments, the number of cycles ranges from 3 to 14, from 3 to 13, from 3 to 12, from 3 to 11, from 3 to 10, from 3 to 9, from 3 to 8, from 3 to 7, from 3 to 6, from 3 to 5, or from 3 to 4. In some embodiments, the number of cycles ranges from 5 to 11. In some embodiments, the number of cycles ranges from 6 to 12. In some embodiments, the number of cycles ranges from 5 to 10, from 5 to 9, or from 5 to 8. In some embodiments, the number of cycles ranges from 5 to 7. In some embodiments, the number of cycles ranges from 5 to 6. In some embodiments, the number of cycles is 5. In some embodiments, the number of cycles is 6. In some embodiments, the number of cycles is 7. In some embodiments, the number of cycles is 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15.

[0077] In some embodiments, the belumosudil is administered to the subject at a dose selected from the group consisting of 200 mg daily, 200 mg twice daily, and 400 mg daily. In some embodiments, the dose is 200 mg daily. In some embodiments, the dose is 200 mg twice daily. In some embodiments, the dose is 400 mg daily.

[0078] In some embodiments, a treatment response in the lung is defined by at least one of the NIH lung symptom score and pulmonary function tests. In some embodiments, a treatment response in the lung is defined solely by pulmonary function tests. In some embodiments, a treatment response in the lung is defined solely by NIH lung symptom score. In some embodiments, pulmonary function test measurements are obtained by spirometry. In some embodiments, pulmonary function test measurements are obtained by plethysmography.

[0079] In some embodiments, the treatment response in the lung is defined by measurement of % FEV1. In some embodiments, the subject experiences an improvement in % FEV1 from baseline during treatment with belumosudil. In some embodiments, the subject experiences ≥5% absolute improvement in % FEV1 from baseline during treatment with belumosudil. In some embodiments, the subject experiences ≥10% absolute improvement in % FEV1 from baseline during treatment with belumosudil. In some embodiments, the subject experiences ≥20% absolute improvement in % FEV1 from baseline during treatment with belumosudil. In some embodiments, the subject experiences ≥1%, ≥2%, ≥3%, ≥4%, ≥5%, ≥6%, ≥7%, ≥8%, ≥9%, ≥10%, ≥11%, ≥12%, ≥13%, ≥14%, ≥15%, ≥16%, ≥17%, ≥18%, ≥19%, ≥20%, ≥ 21%, ≥22%, ≥23%, ≥24%, ≥25%, ≥26%, ≥27%, ≥28%, ≥29%, or ≥30% absolute improvement in % FEV1 from baseline during treatment with belumosudil. In some embodiments, the subject experiences from about 5% to about 30%

absolute improvement in % FEV1 from baseline during treatment with belumosudil. In some embodiments, the subject experiences from about 10% to about 30% absolute improvement in % FEV1 from baseline during treatment with belumosudil. In some embodiments, the subject experiences from about 20% to about 30% absolute improvement in % FEV1 from baseline during treatment with belumosudil.

[0080] In some embodiments, the treatment response in the lung is defined by measurement of FEV1 in mL. In some embodiments, the subject experiences at least a 200 mL improvement in FEV1 from baseline during treatment with belumosudil. In some embodiments, the subject experiences at least a 100 mL improvement in FEV1 from baseline during treatment with belumosudil. In some embodiments, the subject experiences at least a 50 mL, at least a 100 mL, at least a 150 mL, at least a 200 mL, at least a 250 mL, at least a 300 mL improvement in FEV1 from baseline during treatment with belumosudil.

[0081] In some embodiments, FEV1 is evaluated at baseline and on day 1 of cycle 2-5. In some embodiments, FEV1 is evaluated at baseline and on day 1 of each cycle starting at cycle 2 day 1.

[0082] In some embodiments, the improvement is maintained over at least two consecutive FEV1 evaluations. In some embodiments, the improvement is maintained over at least three consecutive FEV1 evaluations. In some embodiments, the improvement is maintained over at least two, three, four, five, six, seven, eight, nine or ten consecutive FEV1 evaluations.

[0083] In some embodiments, the treatment response in the lung is a complete response. In some embodiments, the treatment response in the lung is a partial response. In some embodiments, the treatment response in the lung is stable disease. In some embodiments, the treatment response in the lung is upgraded from a partial response according to measurement of the % FEV1 alone to a complete response according to measurement of the NIH lung symptom score.

[0084] In some embodiments, the subject has a baseline NIH lung symptom score of 1 prior to treatment with belumosudil. In some embodiments, the subject has a baseline NIH lung symptom score of 2 prior to treatment with belumosudil. In some embodiments, the subject has a baseline NIH lung symptom score of 3 prior to treatment with belumosudil.

[0085] In some embodiments, the subject experiences an improvement in NIH lung symptom score during treatment with belumosudil. In some embodiments, the subject experiences NIH lung symptom score of 0 during treatment with belumosudil. In some embodiments, the subject has a baseline NIH lung symptom score of 1 prior to treatment with belumosudil and the subject experiences an improved NIH lung symptom score of 0 during treatment with belumosudil. In some embodiments, the subject has a baseline NIH lung symptom score of 2 prior to treatment with belumosudil and the subject experiences an improved NIH lung symptom score of 0 during treatment with belumosudil. In some embodiments, the subject has a baseline NIH lung symptom score of 3 prior to treatment with belumosudil and the subject experiences an improved NIH lung symptom score of 0 during treatment with belumosudil.

[0086] In some embodiments, the subject experiences an improvement in NIH lung symptom score during treatment with belumosudil. In some embodiments, the subject experiences NIH lung symptom score of 1 during treatment with belumosudil. In some embodiments, the subject has a baseline NIH lung symptom score of 2 prior to treatment with belumosudil and the subject experiences an improved NIH lung symptom score of 1 during treatment with belumosudil. In some embodiments, the subject has a baseline NIH lung symptom score of 3 prior to treatment with belumosudil and the subject experiences an improved NIH lung symptom score of 1 during treatment with belumosudil.

[0087] In some embodiments, the subject experiences an improvement in NIH lung symptom score during treatment with belumosudil. In some embodiments, the subject experiences NIH lung symptom score of 2 during treatment with belumosudil. In some embodiments, the subject has a baseline NIH lung symptom score of 3 prior to treatment with belumosudil and the subject experiences an improved NIH lung symptom score of 2 during treatment with belumosudil.

[0088] In some embodiments, a treatment response in the lung is measured according to the Lee Symptom Scale lung score. In some embodiments, the subject experiences at least a 10-point reduction in the Lee Symptom Scale lung subscore from baseline during treatment with belumosudil. In some embodiments, the subject experiences at least a 5-point reduction in the Lee Symptom Scale lung subscore from baseline during treatment with belumosudil. In some embodiments, the subject experiences at least a 1-point, 2-point, 3-point, 4-point, 5-point, 6-point, 7-point, 8-point, 9-point, 10-point, 11-point, 12-point, 13-point, 14-point, 15-point reduction in the Lee Symptom Scale lung subscore from baseline during treatment with belumosudil.
[0089] In some embodiments, the subject has chronic graft-versus-host disease and has failed one to three prior lines of systemic therapy for the chronic graft-versus-host disease. In some embodiments, the subject has chronic graft-versus-host disease and has failed at least two prior lines of systemic therapy for the chronic graft-versus-host disease. In some embodiments, the subject has chronic graft-versus-host disease and has failed two to five prior lines of systemic therapy for the chronic graft-versus-host disease. In some embodiments, the subject has failed at least one, at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine or at least ten prior lines of systemic therapy for the chronic graft-versus-host disease.
[0090] In some embodiments, the subject experienced a complete response to last treatment for the graft-versus-host disease prior to belumosudil. In some embodiments, the subject experienced a partial response to last treatment for the graft-versus-host disease prior to belumosudil. In some embodiments, the subject experienced stable disease during the last treatment for the graft-versus-host disease prior to belumosudil.
[0091] In some embodiments, the prior lines of systemic therapy for the chronic graft-versus-host disease have been discontinued.
[0092] In some embodiments, the prior lines of systemic therapy are selected from the group consisting of prednisone, tacrolimus, ECP, sirolimus, ibruitinib, ruxolitinib, MMF, rituximab, MTX, cyclosporine, imatinib, ixazomib, and ofatumumab.
[0093] In some embodiments, the cGVHD is steroid-refractory (SR) cGVHD.
[0094] In some embodiments, the subject is receiving concomitant corticosteroid therapy. In some embodiments, the concomitant corticosteroid therapy is selected from the group consisting of prednisone, prednisolone, methylprednisolone, and budesonide. In some embodiments, the concomitant corticosteroid therapy is prednisone. In some embodiments, the dose of the concomitant corticosteroid therapy is reduced after at least 1 cycle of the belumosudil treatment. In some embodiments, the dose of the concomitant corticosteroid therapy is reduced by at least about 10%, by at least about 20%, by at least about 30%, by at least about 40%, by at least about 50%, by at least about 60%, or by at least about 70% after at least 1 cycle of the belumosudil treatment. In some embodiments, the dose of the concomitant corticosteroid therapy is reduced by from about 10% to about 70%, from about 15% to about 65%, from about 20% to about 60%, from about 30% to about 60%, from about 35% to about 60%, from about 40% to about 60%, or from about 45% to about 55% after at least 1 cycle of the belumosudil treatment. In some embodiments, the concomitant corticosteroid therapy is discontinued after at least 1 cycle of the belumosudil treatment.
[0095] In some embodiments, the subject is receiving concomitant calcineurin inhibitor therapy.
[0096] In some embodiments, the subject has received an allogenic bone marrow transplant or hematopoietic stem cell transplantation. In some embodiments, the subject is receiving glucocorticoid therapy and calcineurin therapy. In some embodiments, the subject is receiving glucocorticoid therapy. In some embodiments, the subject is receiving one or more concomitant therapies that are not generally considered to be immunosuppressive. In some embodiments, the subject is receiving concomitant extracorporeal photopheresis (ECP). In some embodiments, the subject has persistent active cGVHD manifestations, as defined by the 2014 NIH Consensus

Development Project on Criteria for Clinical Trials in cGVHD, after at least 2 months of corticosteroid therapy. In some embodiments, the subject has received no more than 3 prior lines of treatment for cGVHD. In some embodiments, the subject has a Karnofsky Performance Scale of >40. In some embodiments, the subject has an absolute neutrophil count ≥1.5×10.sup.9/L (without myeloid growth factors in the previous week) and a platelet count ≥50×10.sup.9/L (without transfusion or thrombopoietin or thrombopoietin analogues within the previous 2 weeks). In some embodiments, the subject has total bilirubin≤1.5×upper limit of normal (ULN), ALT and AST≤3×ULN, and a glomerular filtration rate (GFR) ≥30 mL/min/1.73 m.sup.2 using the 4-Variable Modification of Diet in Renal Disease (MDRD-4) variable formula. In some embodiments, the subject is at least 18 years old In some embodiments, the subject is not pregnant.

[0097] In some embodiments, the subject has at least one of the following characteristics: has received an allogenic bone marrow transplant; has received a hematopoietic stem cell transplantation; is receiving glucocorticoid therapy and calcineurin therapy; is receiving glucocorticoid therapy; is receiving one or more concomitant therapies that are not generally considered to be immunosuppressive; is receiving concomitant extracorporeal photopheresis [ECP]; has persistent active cGVHD manifestations as defined by the 2014 NIH Consensus Development Project on Criteria for Clinical Trials in cGVHD, after at least 2 months of corticosteroid therapy; has received no more than 3 prior lines of treatment for cGVHD; has a Karnofsky Performance Scale of >40; has an absolute neutrophil count ≥1.5×10.sup.9/L (without myeloid growth factors within the previous week) and a platelet count ≥50×10.sup.9/L (without transfusion or thrombopoietin or thrombopoietin analogues within the previous 2 weeks); has total bilirubin≤1.5×upper limit of normal (ULN), ALT and AST≤3×ULN, and a glomerular filtration rate (GFR) ≥30 mL/min/1.73 m.sup.2 using the 4-Variable Modification of Diet in Renal Disease (MDRD-4) variable formula; is at least 18 years old; is not pregnant.

[0098] In some embodiments, the subject is not concomitantly receiving an investigational GVHD treatment. In some embodiments, the subject does not have acute GVHD. In some embodiments, the subject is not pregnant or breastfeeding. In some embodiments, the subject is not taking any medication generally known to be a moderate or strong inhibitor of the CYP3A4 isozyme or any drugs that are moderate or strong CYP3A4 inducers. In some embodiments, the subject does not have a history of poorly controlled psychiatric disease. In some embodiments, the subject does not have a history of coronary artery disease. In some embodiments, the subject does not have regular and excessive use of alcohol in the previous 6 months, defined as alcohol intake >14 drinks per week in a male or >7 drinks per week in a female (where approximately 10 g of alcohol equals one “drink” unit, and one unit equals 1 ounce of distilled spirits, one 12-ounce beer, or one 4-ounce glass of wine). In some embodiments, the subject does not have a history of human immunodeficiency virus (HIV) or active hepatitis C virus (HCV) or hepatitis B virus (HBV). In some embodiments, the subject is not diagnosed with another malignancy (other than malignancy for which transplant was performed) within the previous 3 years, with the exception of completely resected basal cell or squamous cell carcinoma of the skin, resected in situ cervical malignancy, resected breast ductal carcinoma in situ, or low-risk prostate cancer after curative resection. In some embodiments, the subject does not have relapse of the underlying cancer or post-transplant lymphoproliferative disease. In some embodiments, the subject does not have previous exposure to belumosudil or known allergy/sensitivity to belumosudil or any other ROCK2 inhibitor. In some embodiments, the subject is not taking other immunosuppressant drugs for GVHD, including mTOR (mammalian target of rapamycin) inhibitors. In some embodiments, the subject does not have a QTcF >450 msec.

[0099] In some embodiments, the subject has at least one of the following characteristics: is not concomitantly receiving an investigational GVHD treatment; does not have acute GVHD; is not pregnant or breastfeeding; is not taking any medication generally known to be a moderate or strong inhibitor of the CYP3A4 isozyme or any drugs that are moderate or strong CYP3A4 inducers; does

not have a history of poorly controlled psychiatric disease; does not have a history of coronary artery disease; does not have regular and excessive use of alcohol in the previous 6 months, defined as alcohol intake >14 drinks per week in a male or >7 drinks per week in a female (where approximately 10 g of alcohol equals one “drink” unit, and one unit equals 1 ounce of distilled spirits, one 12-ounce beer, or one 4-ounce glass of wine); does not have a history of human immunodeficiency virus (HIV); does not have a history of active hepatitis C virus (HCV); does not have a history of hepatitis B virus (HBV); is not diagnosed with another malignancy (other than malignancy for which transplant was performed) within the previous 3 years, with the exception of completely resected basal cell or squamous cell carcinoma of the skin, resected in situ cervical malignancy, resected breast ductal carcinoma in situ, or low-risk prostate cancer after curative resection; does not have relapse of the underlying cancer or post-transplant lymphoproliferative disease; does not have previous exposure to belumosudil; does not have a known allergy/sensitivity to belumosudil or any other ROCK2 inhibitor; is not taking other immunosuppressant drugs for GVHD, including mTOR (mammalian target of rapamycin) inhibitors; and does not have a QTcF >450 msec.

[0100] In some embodiments, the subject has at least one of the following characteristics: has received an allogenic bone marrow transplant; has received a hematopoietic stem cell transplantation; is receiving glucocorticoid therapy and calcineurin therapy; is receiving glucocorticoid therapy; is receiving one or more concomitant therapies that are not generally considered to be immunosuppressive; is receiving concomitant extracorporeal photopheresis [ECP]; has persistent active cGVHD manifestations as defined by the 2014 NIH Consensus Development Project on Criteria for Clinical Trials in cGVHD, after at least 2 months of corticosteroid therapy; has received no more than 3 prior lines of treatment for cGVHD; has a Karnofsky Performance Scale of >40; has an absolute neutrophil count ≥1.5×10.sup.9/L (without myeloid growth factors within the previous week) and a platelet count ≥50×10.sup.9/L (without transfusion or thrombopoietin or thrombopoietin analogues within the previous 2 weeks); has total bilirubin ≤1.5×upper limit of normal (ULN), ALT and AST ≤3×ULN, and a glomerular filtration rate (GFR) ≥30 mL/min/1.73 m.sup.2 using the 4-Variable Modification of Diet in Renal Disease (MDRD-4) variable formula; is at least 18 years old; is not pregnant or breastfeeding; is not concomitantly receiving an investigational GVHD treatment; does not have acute GVHD; is not taking any medication generally known to be a moderate or strong inhibitor of the CYP3A4 isozyme or any drugs that are moderate or strong CYP3A4 inducers; does not have a history of poorly controlled psychiatric disease; does not have a history of coronary artery disease; does not have regular and excessive use of alcohol in the previous 6 months, defined as alcohol intake >14 drinks per week in a male or >7 drinks per week in a female (where approximately 10 g of alcohol equals one “drink” unit, and one unit equals 1 ounce of distilled spirits, one 12-ounce beer, or one 4-ounce glass of wine); does not have a history of human immunodeficiency virus (HIV); does not have a history of active hepatitis C virus (HCV); does not have a history of hepatitis B virus (HBV); is not diagnosed with another malignancy (other than malignancy for which transplant was performed) within the previous 3 years, with the exception of completely resected basal cell or squamous cell carcinoma of the skin, resected in situ cervical malignancy, resected breast ductal carcinoma in situ, or low-risk prostate cancer after curative resection; does not have relapse of the underlying cancer or post-transplant lymphoproliferative disease; does not have previous exposure to belumosudil; does not have a known allergy/sensitivity to belumosudil or any other ROCK2 inhibitor; is not taking other immunosuppressant drugs for GVHD, including mTOR (mammalian target of rapamycin) inhibitors; and does not have a QTcF >450 msec.

[0101] In some embodiments, the subject has received an allogeneic hematopoietic cell transplant. In some embodiments, the subject has previously received at least 2 and not more than 5 lines of systemic therapy for cGVHD. In some embodiments, the subject has received glucocorticoid therapy with a stable dose over the previous 2 weeks. In some embodiments, the subject has

persistent cGVHD manifestations. In some embodiments, the subject has a Karnofsky (if aged ≥16 years)/Lansky (if aged <16 years) Performance Score of ≥60. In some embodiments, the subject has an absolute neutrophil count ≥1.5×10.sup.9/L and a platelet count ≥50×10.sup.9/L. In some embodiments, the subject has ALT and AST≤3×ULN, total bilirubin≤1.5×ULN, and a glomerular filtration rate (GFR) ≥30 mL/min/1.73 m.sup.2 using the MDRD-4 variable formula. In some embodiments, the subject has a weight ≥40 kg. In some embodiments, the subject is receiving concomitant corticosteroid therapy. In some embodiments, the subject is receiving concomitant calcineurin inhibitor therapy. In some embodiments, the subject is concomitantly receiving one or more of sirolimus, MMF, methotrexate, rituximab, and extracorporeal photopheresis (ECP) therapies.

[0102] In some embodiments, the subject has at least one of the following characteristics: has received an allogeneic hematopoietic cell transplant; has previously received at least 2 and not more than 5 lines of systemic therapy for cGVHD; has received glucocorticoid therapy with a stable dose over the previous 2 weeks; has persistent cGVHD manifestations; has a Karnofsky (if aged ≥16 years)/Lansky (if aged <16 years) Performance Score of ≥60; has an absolute neutrophil count ≥1.5×10.sup.9/L and a platelet count ≥50×10.sup.9/L; has ALT and AST≤3×ULN, total bilirubin≤1.5×ULN, and a glomerular filtration rate (GFR)≥30 mL/min/1.73 m.sup.2 using the MDRD-4 variable formula; has a weight ≥40 kg; is at least 18 years old; is receiving concomitant corticosteroid therapy; is receiving concomitant calcineurin inhibitor therapy; and is concomitantly receiving one or more of sirolimus, MMF, methotrexate, rituximab, and extracorporeal photopheresis (ECP) therapies.

[0103] In some embodiments, the subject is not receiving systemic cGVHD treatments. In some embodiments, the subject does not have histological relapse of the underlying cancer or post-transplant lymphoproliferative disease. In some embodiments, the subject is not receiving concomitant treatment with ibrutinib. In some embodiments, the subject does not have a history of human immunodeficiency virus (HIV) or hepatitis C virus (HCV) or a history of hepatitis B virus (HBV). In some embodiments, the subject is not diagnosed with another malignancy (other than malignancy for which transplant was performed) within the previous 3 years, 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, or prostate cancer with Gleason score<6 and stable PSA over 12 months. In some embodiments, the subject does not have previous exposure to belumosudil. In some embodiments, the subject does not have a known allergy/sensitivity to belumosudil or any other ROCK2 inhibitor. In some embodiments, the subject does not have a QTc (F)>480 msec. In some embodiments, the subject does not have a FEV1≤39% or a lung score of 3.

[0104] In some embodiments, the subject has at least one of the following characteristics: is not receiving systemic cGVHD treatments; does not have histological relapse of the underlying cancer or post-transplant lymphoproliferative disease; is not receiving concomitant treatment with ibrutinib; does not have a history of human immunodeficiency virus (HIV); does not have hepatitis C virus (HCV); does not have a history of hepatitis B virus (HBV); is not diagnosed with another malignancy (other than malignancy for which transplant was performed) within the previous 3 years, 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, or prostate cancer with Gleason score<6 and stable PSA over 12 months; does not have previous exposure to belumosudil; does not have a known allergy/sensitivity to belumosudil or any other ROCK2 inhibitor; does not have a QTc (F)>480 msec; and does not have a FEV1≤ 39% or a lung score of 3.

[0105] In some embodiments, the subject has at least one of the following characteristics: has received an allogeneic hematopoietic cell transplant; has previously received at least 2 and not more than 5 lines of systemic therapy for cGVHD; has received glucocorticoid therapy with a stable dose over the previous 2 weeks; has persistent cGVHD manifestations; has a Karnofsky (if aged ≥16 years)/Lansky (if aged <16 years) Performance Score of ≥60; has an absolute neutrophil

count ≥1.5×10.sup.9/L and a platelet count ≥50×10.sup.9/L; has ALT and AST≤3×ULN, total bilirubin≤1.5×ULN, and a glomerular filtration rate (GFR) ≥30 mL/min/1.73 m.sup.2 using the MDRD-4 variable formula; has a weight ≥40 kg; is at least 18 years old; is receiving concomitant corticosteroid therapy; is receiving concomitant calcineurin inhibitor therapy; is concomitantly receiving one or more of sirolimus, MMF, methotrexate, rituximab, and extracorporeal photopheresis (ECP) therapies; is not receiving systemic cGVHD treatments; does not have histological relapse of the underlying cancer or post-transplant lymphoproliferative disease; is not receiving concomitant treatment with ibrutinib; does not have a history of human immunodeficiency virus (HIV); does not have hepatitis C virus (HCV); does not have a history of hepatitis B virus (HBV); is not diagnosed with another malignancy (other than malignancy for which transplant was performed) within the previous 3 years, 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, or prostate cancer with Gleason score<6 and stable PSA over 12 months; does not have previous exposure to belumosudil; does not have a known allergy/sensitivity to belumosudil or any other ROCK2 inhibitor; does not have a QTc (F)>480 msec; and does not have a FEV1≤39% or a lung score of 3.

[0106] In some embodiments, the subject is at least 18 years old. In some embodiments, the subject received a bilateral lung transplantation at least one year previously. In some embodiments, the subject received a diagnosis of CLAD within the previous 9 months. In some embodiments, the subject has CLAD Stage 1 or 2, and has a FEV1 from >50% to 80% of PTBL. In some embodiments, the subject has progressive CLAD. In some embodiments, the subject is receiving concomitant corticosteroid therapy. In some embodiments, the subject is receiving concomitant therapy with one or more of a calcineurin inhibitor, a cell cycle inhibitor, and an mTORi. In some embodiments, the subject received concomitant azithromycin therapy for at least 6 weeks previously. In some embodiments, the subject has a body mass index ≥18 kg/m.sup.2.

[0107] In some embodiments, the subject has at least one of the following characteristics: is at least 18 years old; received a bilateral lung transplantation at least one year previously; received a diagnosis of CLAD within the previous 9 months; has CLAD Stage 1 or 2, and has a FEV1 from >50% to 80% of PTBL; has progressive CLAD; is receiving concomitant corticosteroid therapy; is receiving concomitant therapy with one or more of a calcineurin inhibitor, a cell cycle inhibitor, and an mTORi; has received concomitant azithromycin therapy for at least 6 weeks previously; and has a body mass index ≥18 kg/m.sup.2.

[0108] In some embodiments, the subject does not have a FEV1≤50% of their post-transplant baseline value (CLAD 3 and 4). In some embodiments, the subject is not intolerant to belumosudil or any of its components. In some embodiments, the subject does not have any condition that can affect the ability to perform pulmonary function testing. In some embodiments, the subject does not have lung function decline that can be explained by non-CLAD causes. In some embodiments, the subject has not been diagnosed or treated for malignancy within the previous 3 years prior except for complete resection of basal cell carcinoma or squamous cell carcinoma of the skin, an in-situ malignancy, or low risk prostate cancer after curative therapy. In some embodiments, the subject does not have untreated symptomatic gastroesophageal reflux disease (GERD). In some embodiments, the subject does not have a baseline resting oxygen saturation of <88% on room air or use of supplemental oxygen at rest. In some embodiments, the subject does not have known prolongation of the QT interval (>480 msec). In some embodiments, the subject has not received prior therapy for CLAD other than azithromycin and standard-of-care immunosuppressants. In some embodiments, the subject has not previously received belumosudil. In some embodiments, the subject does not have a known hypersensitivity to azithromycin, erythromycin, any macrolide, or any ketolide drug. In some embodiments, standard-of-care immunosuppressants may comprise at least one of the following: calcineurin inhibitor, a cell cycle inhibitor and an mTOR inhibitor.

[0109] In some embodiments, the subject has at least one of the following characteristics: does not

have a FEV1≤50% of their post-transplant baseline value (CLAD 3 and 4); is not intolerant to belumosudil or any of its components; does not have any condition that can affect the ability to perform pulmonary function testing; does not have lung function decline that can be explained by non-CLAD causes; has not been diagnosed or treated for malignancy within the previous 3 years prior except for complete resection of basal cell carcinoma or squamous cell carcinoma of the skin, an in-situ malignancy, or low risk prostate cancer after curative therapy; does not have untreated symptomatic gastroesophageal reflux disease (GERD); does not have a baseline resting oxygen saturation of <88% on room air or use of supplemental oxygen at rest; does not have known prolongation of the QT interval (>480 msec); has not received prior therapy for CLAD other than azithromycin and standard-of-care immunosuppressants; has not previously received belumosudil; and does not have a known hypersensitivity to azithromycin, erythromycin, any macrolide, or any ketolide drug. In some embodiments, standard-of-care immunosuppressants may comprise at least one of the following: calcineurin inhibitor, a cell cycle inhibitor and an mTOR inhibitor.

[0110] In some embodiments, the subject has at least one of the following characteristics: is at least 18 years old; received a bilateral lung transplantation at least one year previously; received a diagnosis of CLAD within the previous 9 months; has CLAD Stage 1 or 2, and has a FEV1 from >50% to 80% of PTBL; has progressive CLAD; is receiving concomitant corticosteroid therapy; is receiving concomitant therapy with one or more of a calcineurin inhibitor, a cell cycle inhibitor, and an mTORi; has received concomitant azithromycin therapy for at least 6 weeks previously; has a body mass index ≥18 kg/m.sup.2; does not have a FEV1≤ 50% of their post-transplant baseline value (CLAD 3 and 4); is not intolerant to belumosudil or any of its components; does not have any condition that can affect the ability to perform pulmonary function testing; does not have lung function decline that can be explained by non-CLAD causes; has not been diagnosed or treated for malignancy within the previous 3 years prior except for complete resection of basal cell carcinoma or squamous cell carcinoma of the skin, an in-situ malignancy, or low risk prostate cancer after curative therapy; does not have untreated symptomatic gastroesophageal reflux disease (GERD); does not have a baseline resting oxygen saturation of <88% on room air or use of supplemental oxygen at rest; does not have known prolongation of the QT interval (>480 msec); has not received prior therapy for CLAD other than azithromycin and standard-of-care immunosuppressants; has not previously received belumosudil; and does not have a known hypersensitivity to azithromycin, erythromycin, any macrolide, or any ketolide drug. In some embodiments, standard-of-care immunosuppressants may comprise at least one of the following: calcineurin inhibitor, a cell cycle inhibitor and an mTOR inhibitor.

EXAMPLES

Example 1: A Phase IIa, Open-Label, Dose-Finding Study of Belumosudil

Subject Eligibility

[0111] Eligible patients were allogeneic bone marrow transplant or allogeneic hematopoietic cell transplant (alloHCT) recipients of age ≥18 years with persistent cGVHD manifestations after having received one to three prior systemic lines of therapy and who were receiving corticosteroid treatment with or without a calcineurin inhibitor and/or concurrent extracorporeal photopheresis. Belumosudil was continued until cGVHD progression or unacceptable toxicity.

[0112] Inclusion criteria. Adult male and female subjects at least 18 years of age who had allogenic bone marrow transplant or hematopoietic stem cell transplantation. Received glucocorticoid therapy and calcineurin therapy or glucocorticoid therapy alone for cGVHD at study entry. Participants on calcineurin therapy only, without glucocorticoid therapy, were not eligible. Participants also received other therapies thought not to be immunosuppressive (such as extracorporeal photopheresis; ECP), were considered for enrollment in this study on a case-by-case basis. Had persistent active cGVHD manifestations, as defined by 2014 National Institute of Health Consensus Development Project on Criteria for Clinical trials in cGVHD, after at least 2 months of steroid therapy. No more than 3 prior lines of treatment for cGVHD. Karnofsky Performance Scale

of greater than (>) 40. Adequate organ and bone marrow functions evaluated during the 14 days prior to enrollment as follows: Absolute neutrophil count greater than or equal to (>=) 1.5×10.sup.9/L (without myeloid growth factors within 1 week of study entry); Platelet count >=50×10.sup.9/L (without transfusion or thrombopoietin or thrombopoietin analogues within 2 weeks of study entry); Adequate safety laboratory values: Total bilirubin less than or equal to (<=) 1.5×upper limit of normal (ULN); ALT and AST <=3*ULN; Glomerular filtration rate >=30 milliliter per minute per 1.73 square meter (mL/min/1.73 m.sup.2) using the 4-Variable Modification of Diet in Renal Disease variable formula.

[0113] Exclusion Criteria. Female participant who was pregnant or breastfeeding. Received an investigational GVHD treatment within 28 days of study entry. Had acute GVHD. Taken any medication known to be a moderate or strong inhibitor of the cytochrome (CY) P3A4 isozyme or any drugs that are moderate or strong CYP3A4 inducers. 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 poorly controlled psychiatric disease or coronary artery disease). Regular and excessive use of alcohol within the 6 months prior to study entry defined as alcohol intake >14 drinks per week in a man or >7 drinks per week in a woman. Approximately 10 grams of alcohol equals one “drink” unit. One unit equals 1 ounce of distilled spirits, one 12-ounce beer, or one 4-ounce glass of wine. Known history of human immunodeficiency virus or active hepatitis C virus or hepatitis B virus. Diagnosed with another malignancy (other than malignancy for which transplant was performed) within 3 years of enrollment, with the exception of completely resected basal cell or squamous cell carcinoma of the skin, resected in situ cervical malignancy, resected breast ductal carcinoma in situ, or low-risk prostate cancer after curative resection. Relapse of the underlying cancer or post-transplant lymphoproliferative disease at the time of screening. Had previous exposure to belumosudil or known allergy/sensitivity to belumosudil or any other Rho-associated protein kinase 2 inhibitor. Taken other immunosuppressant drugs for GVHD, including mammalian target of rapamycin inhibitors (Note: Only steroids, calcineurin inhibitors, and ECP are acceptable). Corrected QT interval using Fridericia's formula >450 milliseconds.

Study Design and Treatment

[0114] Patients were enrolled into three sequential cohorts: cohort one received belumosudil 200 mg once daily, cohort two received belumosudil 200 mg twice daily (twice a day), and cohort three received belumosudil 400 mg once daily. (FIG. **1**) Before enrollment of the subsequent cohort, safety data in each previous cohort were analyzed after eight patients reached two months of treatment to assure that there was no safety signal. The 2-month timeframe was selected because all clinically significant belumosudil-related adverse events (AEs) to date had occurred in ≤36 days of starting belumosudil. No safety concerns were identified, allowing for planned dose escalation.

[0115] Belumosudil was administered orally in 28-day cycles until disease progression or unacceptable toxicity. Progression was defined per the 2014 NIH cGVHD Consensus Criteria. Long-term follow-up was conducted every 8 weeks until study closeout. After 4 weeks of belumosudil therapy, corticosteroid therapy could be tapered at the investigators' discretion. Screening was conducted within 28 days of the first study dose. Response was initially assessed after two cycles; however, this was amended to evaluate response on day 1 of each cycle, starting at cycle 2 day 1.

Study Endpoints

[0116] The primary efficacy endpoint was ORR, defined as the proportion of patients who achieved either a complete response (CR) or partial response (PR), per the 2014 NIH cGVHD Consensus Criteria, at any time point. Only response assessments before the next lines of therapy after belumosudil were counted toward ORR. All responses were assessed by the investigators. Secondary end points included the number and the percentage of patients with steroid-dependent cGVHD who had a best response of PR or CR, duration of response (DOR), response rate by organ system, LSS score, corticosteroid dose reductions, time to next treatment (TTNT), failure-free

survival (FFS), and overall survival (OS). The safety and tolerability of belumosudil were evaluated via AE assessments, physical examinations, vital sign measurements, laboratory tests, and electrocardiograms throughout the study. Predose samples were collected for pharmacodynamic (PD) evaluation, which included the assessment of immune cell subtypes in peripheral blood.

Statistical Analysis

[0117] With a sample size of 16 patients per cohort, the study had a >90% probability of >1 study participants experiencing an AE with an underlying rate of ≥14%, which was derived from the probability calculations of the assumed sample size. Assuming a best ORR of 25%, which was determined to be clinically meaningful, the study was expected to have approximately 90% probability to show a response in ≥2 patients per cohort. This study was not powered to show significant differences between cohorts with respect to efficacy, AEs, or PD analyses. The primary analysis was conducted using the safety population, defined as enrolled patients who received ≥1 dose of study medication. The Clopper-Pearson (exact) method was used to construct the two-sided 95% CI for ORR. The Kaplan-Meier (K-M) method was used to calculate estimates of FFS and OS.

Results. Subjects

[0118] A total of fifty-four patients were enrolled in sequential cohorts: 17 patients in cohort 1, 16 patients in cohort 2, and 21 patients in cohort 3 (FIG. **1**). As of the data cutoff for this analysis, the median duration of follow-up was 36 months in cohort 1, 32 months in cohort 2, and 24 months in cohort 3. The overall median duration of follow-up was 29 months (range, 1-39 months).

[0119] Demographics and baseline characteristics were overall comparable across cohorts (Table 1, Table 2). The median age at baseline was 52 years (range, 20-75 years). The median time from cGVHD diagnosis to treatment was longest in cohort 1 at 26 months (compared with 18 months and 16 months in cohorts 2 and 3, respectively). Seventy-eight percent of patients had severe cGVHD per investigator assessment. Half of the patients had involvement of ≥4 organs, and more patients in cohort 3 had lung involvement (48%) compared with those in cohorts 1 (24%) and 2 (19%). The baseline median corticosteroid dose (mg/kg/d prednisone equivalent) was 0.22, 0.19, and 0.17 across cohorts, respectively. Patients in cohort 1 had received a median of three prior lines of treatment, whereas patients in cohorts 2 and 3 had received a median of two prior lines of treatment. Seventy-three percent (35 of 48, data not available for six patients) of patients were refractory to their last line of treatment before study enrollment. The CONSORT diagram (FIG. **1**) shows patient disposition. The median duration of treatment was 8.5 months (range, 2-39 months) in cohort 1, 7.5 months (range, 1-35 months) in cohort 2, and 9 months (range, 1-29 months) in cohort 3. Twenty-eight percent of patients have received >18 months of belumosudil. Reasons for discontinuing belumosudil included cGVHD progression (n=22), voluntary withdrawal by patients (n=8), relapse of underlying disease (n=7), investigator decision (n=3), AEs considered to be possibly treatment related (n=3), and death (n=2). LTFU means long-term follow up.

TABLE-US-00002 TABLE 1 Baseline Demographics and Clinical Characteristics Cohort 1 Cohort 2 Cohort 3 KD025 200 mg KD025 200 mg KD025 400 mg Once Daily Twice a Day Once Daily Total Characteristic (n = 17) (n = 16) (n = 21) (N = 54) Median age, years (range) 50 (20-63) 55 (30-75) 46 (25-75) 52 (20-75) Male, n (%) 13 (77) 9 (56) 12 (57) 34 (63) Indication for transplant, n (%) AML 3 (18) 8 (50) 9 (43) 20 (37) ALL 3 (18) 2 (13) 3 (14) 8 (15) MDS 2 (12) 2 (13) 2 (10) 6 (11) Non-Hodgkin lymphoma 3 (18) 0 2 (10) 5 (9) Other non-Hodgkin lymphoma 0 2 (13) 1 (5) 3 (6) Others 6 (35) 2 (13) 4 (19) 12 (22) Conditioning intensity, n (%).sup.a Myeloablative 9 (53) 5 (31) 10 (48) 24 (44) Nonmyeloablative 7 (41) 8 (50) 10 (48) 25 (46) Unknown 1 (6) 3 (19) 1 (5) 5 (9) Stem-cell source, n (%).sup.a Peripheral blood 15 (88) 15 (94) 18 (86) 48 (89) Bone marrow 0 0 1 (5) 1 (2) Cord blood 1 (6) 0 0 1 (2) Unknown 1 (6) 1 (6) 2 (10) 4 (7) HLA matching of donor or recipient, n (%).sup.a Matched 14 (82) 13 (81) 18 (86) 45 (83) Partially matched 3 (18) 3 (19) 2 (10) 8 (15) Unknown 0 0 1 (5) 1 (2) CMV-positive serostatus (donor/recipient), n (%) +/+ 4 (24) 4

(25) 6 (29) 14 (26) +/− 1 (6) 3 (19) 0 4 (7) −/+ 6 (35) 4 (25) 6 (29) 16 (30) −/− 3 (18) 4 (25) 6 (29) 13 (24) At least 1 unknown 3 (18) 1 (6) 3 (14) 7 (13) Median time from cGVHD 26.4 (0.0-130.7) 18.0 (1.0-69.9) 16.0 (1.0-161.9) 20.0 (0.0-161.9) diagnosis to enrollment, months (range) cGVHD severity, n (%).sup.b Severe 12 (71) 14 (88) 16 (76) 42 (78) Moderate 5 (29) 2 (13) 4 (19) 11 (20) Mild 0 0 1 (5) 1 (2) Organ involvement Median No. of organs involved, 3 (2-6) 4 (1-7) 3 (2-7) 3 (2-7) n (range) ≥4 organs involved, n (%) 8 (47) 10 (63) 9 (43) 27 (50) Eyes, n (%) 14 (82) 11 (69) 17 (81) 42 (78) Skin, n (%) 13 (77) 12 (75) 15 (71) 40 (74) Mouth, n (%) 13 (77) 11 (69) 11 (69) 35 (65) Joints and/or fascia, n (%) 11 (65) 11 (69) 12 (57) 34 (63) Lungs, n (%) 4 (24) 3 (19) 10 (48) 17 (32) Upper GI, n (%) 2 (12) 4 (25) 2 (10) 8 (15) Esophagus, n (%) 2 (12) 0 4 (19) 6 (11) Lower GI, n (%) 1 (6) 2 (13) 1 (5) 4 (7) Liver, n (%) 0 2 (13) 0 2 (4) Median Karnofsky performance status, n (%) ≤50 0 0 1 (5) 1 (2) 60-70 4 (24) 4 (25) 6 (29) 14 (26) 80-90 13 (77) 12 (75) 14 (67) 39 (72) 100 0 0 0 0 Prior therapy characteristics Median prior LOTs, n 3 2 2 3 ≥2 prior LOTs, n (%) 15 (88) 9 (56) 14 (67) 38 (70) Refractory to prior LOT, n (%).sup.a 11/15 (73) 9/13 (69) 15/20 (75) 35/48 (73) Abbreviations: ALL, acute lymphocytic leukemia; AML, acute myelogenous leukemia; cGVHD, chronic graft-versus-host disease; CMV, cytomegalovirus; LOT, line of therapy; MDS, myelodysplastic syndrome. .sup.aDenominator excludes patients with unknown status (six patients in total). .sup.bDisease severity was determined using the Physician-reported Global cGVHD Activity Assessment Form.

TABLE-US-00003 TABLE 2 Additional Baseline Demographics Cohort 1 Cohort 2 Cohort 3 KD025 200 mg KD025 200 mg KD025 400 mg Once Daily Twice a Day Once Daily Total Characteristic (n = 17) (n = 16) (n = 21) (N = 54) Prior systemic cGVHD therapy type, No. (%) CS 17 (100) 16 (100) 21 (100) 54 (100) Tacrolimus 8 (47) 7 (44) 11 (52) 26 (48) Sirolimus 10 (59) 8 (50) 6 (29) 24 (44) Rituximab 8 (47) 3 (19) 5 (24) 16 (30) ECP 5 (29) 4 (25) 6 (29) 15 (28) MMF 4 (24) 4 (25) 4 (19) 12 (22) Cyclosporine 3 (18) 0 2 (10) 5 (9) Ibrutinib 1 (6) 0 3 (14) 4 (7) MTX 1 (6) 2 (13) 0 3 (6) Ixazomib 1 (6) 1 (6) 0 2 (4) ATG 1 (6) 0 0 1 (2) Ofatumumab 0 0 1 (5) 1 (2) Imatinib 1 (6) 0 0 1 (2) Ruxolitinib 0 0 1 (5) 1 (2) Continuing systemic cGVHD therapy type CS, No. (%) 17 (100) 16 (100) 21 (100) 54 (100) Mean prednisone equivalent dose 0.22 0.24 0.28 0.25 at enrollment, mg/kg/d CNI, No. (%) 7 (41) 6 (38) 12 (57) 25 (46) ECP, No. (%) 4 (24) 4 (25) 4 (19) 12 (22) Abbreviations: ATG, antithymocyte globulin; cGVHD, chronic graft-versus-host disease; CNI, calcineurin inhibitor; CS, corticosteroid; ECP, extracorporeal photopheresis; MMF, mycophenolate mofetil; MTX, methotrexate.

Efficacy

[0120] Overall response rate. In the safety population (N=54), the ORR (95% CI) was 65% (51% to 77%). The ORR (95% CI) was similar across cohorts: 65% (38% to 86%) in cohort 1, 69% (41% to 89%) in cohort 2, and 57% (34% to 78%) in cohort 3 (Table 3). Efficacy data for subgroups and secondary end points are presented as pooled data across cohorts.

TABLE-US-00004 TABLE 3 Efficacy and CS Reduction Cohort 1 Cohort 2 Cohort 3 KD025 200 mg KD025 200 mg KD025 400 mg Once Daily Twice a Day Once Daily Total Characteristic (n = 17) (n = 16) (n = 21) (N = 54) ORR, % (95% CI) 65 (38 to 86) 69 (41 to 89) 62 (38 to 82) 65 (51 to 77) Subgroup analyses, n/N (%, 95% CI) ≤2 prior LOTs 10/15 (67, 38 to 5/8 (63, 25 to 8/12 (67, 35 to 23/35 (66, 48 to 88) 92) 90) 81) Refractory to 7/11 (64, 31 to 6/9 (67, 30 to 9/15 (60, 32 to 22/35 (63, 45 to previous LOT 89) 93) 94) 79) ≤4 organs involved 4/8 (50, 16 to 8/10 (80, 44 to 7/9 (78, 40 to 19/27 (70, 50 to 84) 98) 97) 86) Severe cGVHD.sup.a 8/12 (67, 35 to 9/14 (64, 35 to 8/16 (50, 25 to 25/42 (60, 43 to 90) 87) 75) 74) Clinically significant improvement (LSS).sup.b Overall, n (%, 95% 9 (53, 28 to 77) 7 (44, 20 to 70) 11 (52, 30 to 27 (50, 36 to CI) 74) 64) Responder, n/N (%, 8/11 (73, 39 to 3/11 (27, 6 to 9/13 (69, 39 to 20/35 (57, 39 to 95% CI) 94) 61) 91) 74) Nonresponder, n/N 1/6 (17, 0.4 to 4/5 (80, 28 to 2/8 (25, 3 to 7/19 (37, 16 to (%, 95% CI) 64) 99) 65) 62) Proportion with CS 13 (76, 50 to 9 (56, 30 to 80) 14 (67, 43 to 36 (67, 53 to reduction, n (%, 95% 93) 85) 79) CI) Mean percent change in CS dose from baseline, % Overall −50 −36 −47 −45 Responder −63 −36 −63 −55 Nonresponder −26 −37 −19 −26 CS discontinuation, n 4 (24, 7 to

50) 2 (13, 2 to 38) 4 (19, 5 to 42) 10 (19, 9 to 31) (%, 95% CI) Abbreviations: cGVHD, chronic graft-versus-host disease; CS, corticosteroid; LOT, line of therapy; LSS, Lee Symptom Scale; ORR, overall response rate. .sup.aDisease severity was determined using the Physician-reported Global cGVHD Activity Assessment Form. .sup.bChanges in cGVHD symptom burden were measured by the LSS. Clinically meaningful improvement in symptom burden was defined as a decrease of at least seven points in LSS summary score.

[0121] Responses were achieved across key subgroups, with ORRs of 60% (25 of 42) in patients with severe cGVHD, 66% (23 of 35) in patients who had received ≥2 prior systemic lines of therapy, 63% (22 of 35) in patients who were refractory to their last lines of therapy before enrollment, and 70% (19 of 27) in patients with ≥4 organs involved (FIG. **2**). All responses at the patient level were PR; however, organ specific analyses showed that CR was achieved across all affected organs, with the exception of the lungs, where PR was the best response achieved (FIG. **3**A and FIG. **3**B). FIG. **3**B shows for the best response by organ that three partial responses were achieved in lung at the 400 mg once daily dose.

[0122] Responses were generally rapid, with >75% of all responses achieved by the first response assessment at week 8 (FIG. **4**). Four of 35 responses occurred after 24 weeks of belumosudil treatment, with late organ responses observed in the lungs, joints and/or fascia, and eyes (FIG. **5**).

[0123] Percentage of Participants With Overall Response (OR): OR was defined as the percentage of participants with complete response (CR) or partial response (PR). The OR determination of chronic graft versus host disease (cGVHD) was based on cGVHD response assessment performed by clinicians as per the 2014 National Institutes of Health (NIH) Consensus Development Project for Clinical Trials in cGVHD criteria. CR was defined as the resolution of all manifestations in each organ or site. PR was defined as the improvement in at least 1 organ or site without progression in any other organ or site; and cGVHD progression was defined as the clinically meaningful worsening in 1 or more organs regardless of improvement in other organs. Timeframe: From the date of first response until documented disease progression or death due to any cause or data cut-off, whichever occurred first (maximum duration: up to 64.2 months.

[0124] Analysis was performed on mITT population. Participants received belumosudil orally on Day 1, 8, 15, and 22 of each 28-day treatment cycle until disease progression, unacceptable toxicity, or death whichever occurred first (maximum duration: 64.2 months). The data is shown in the table below.

TABLE-US-00005 TABLE 4 OR Cohort 1: Cohort 2: Cohort 3: Belumosudil Belumosudil Belumosudil 200 mg QD 200 mg BID 400 mg QD Overall Number of 17 16 21 Participants Analyzed Percentage of 65 (38-86%) 69 (41-89%) 57 (34-78%) Participants With Overall Response Number (95% Confidence Interval) Unit of Measure = percentage of participants

[0125] Duration of Response (DOR). The DOR was defined as the time (in weeks) from first documentation of response to the time of first documentation of deterioration from best response (e.g., CR to PR, or PR to LR). LOR included the response status of unchanged (LOR-U), mixed (LOR-M), or progression (LOR-P). Per the 2014 NIH Consensus Development Project for Clinical Trials in cGVHD criteria; CR was defined as the resolution of all manifestations in each organ or site; PR was defined as the improvement in at least 1 organ or site without progression in any other organ or site; LOR-M was defined as CR or PR in at least one organ accompanied by progression in another organ, LOR-U was defined as outcomes that did not meet the criteria for CR, PR, progression or mixed response, LOR-P was defined as progression in at least one organ or site without a response in any other organ or site. Kaplan-Meier was used for the analysis. Timeframe: From the date of first response until documented disease progression or death due to any cause or data cut-off, whichever occurred first (maximum duration: up to 64.2 months.

[0126] Analysis was performed on responder population which included participants who received at least 1 dose of study medication and achieved a PR or CR response at any post-baseline response assessment. Participants received belumosudil orally on Day 1, 8, 15, and 22 of each 28-day

treatment cycle until disease progression, unacceptable toxicity, or death whichever occurred first (maximum duration: 64.2 months). The data is shown in the table below.

TABLE-US-00006 TABLE 5 DOR Cohort 1: Cohort 2: Cohort 3: Belumosudil Belumosudil Belumosudil 200 mg QD 200 mg BID 400 mg QD Overall Number of 11 11 12 Participants Analyzed DOR Median (95% 40 (8-na* %) 11 (2-35%) 16 (4-38%) Confidence Interval) Unit of Measure = weeks *95% CI upper limit not available due to 3 (27.3%) participants were censored

[0127] Time to next therapy (TTNT). The TTNT was defined as the time (in months) from first treatment to the time of new systemic cGVHD treatment. TTNT was censored by last response assessment or long term follow up assessment, whichever was earlier. Kaplan-Meier survival method was used for the analysis. Timeframe: From time of first treatment to the time of new systemic cGVHD treatment or long term follow-up assessment, whichever occurred first (maximum duration: up to 64.2 months). Analysis was performed on mITT population. The data is shown in the table below.

TABLE-US-00007 TABLE 6 TTNT Cohort 1: Cohort 2: Cohort 3: Belumosudil Belumosudil Belumosudil 200 mg QD 200 mg BID 400 mg QD Overall Number of 17 16 21 Participants Analyzed TTNT Median (95% 15 (5-NA* %) 10 (4-19%) 14 (3-NA %) Confidence Interval) Unit of Measure = months *95% confidence interval upper limit are not available due to high percentage of censoring.

[0128] Subsequent systemic cGVHD therapies included tacrolimus, sirolimus, ibrutinib, ruxolitinib, extracorporeal photopheresis, and mycophenolate mofetil.

FFS and OS. Failure-Free Survival (FFS) and Overall Survival (OS)

[0129] Failure-free survival was defined as the time (in months) from first dose of study drug to either the start of another new systemic treatment for cGVHD, relapse of the underlying disease or death. If no such events happened, FFS was censored by last response assessment or long term follow up assessment, whichever was the latest and available. Kaplan-Meier survival method was used for the analysis. Analysis was performed on mITT population. Timeframe: From first dose of study drug to either start of another new systemic treatment for cGVHD, relapse of the underlying disease or death or data cut-off, whichever occurred first (maximum duration: up to 64.2 months). Participants received belumosudil orally on Day 1, 8, 15, and 22 of each 28-day treatment cycle until disease progression, unacceptable toxicity, or death whichever occurred first (maximum duration: 64.2 months). The data is shown in the table below.

TABLE-US-00008 TABLE 7 FFS Cohort 1: Cohort 2: Cohort 3: Belumosudil Belumosudil Belumosudil 200 mg QD 200 mg BID 400 mg QD Overall Number of 17 16 21 Participants Analyzed FFS Median (95% 11 (4-na* %) 10 (4-19%) 10 (3-16%) Confidence Interval) Unit of Measure = months *not specified

[0130] Overall survival was defined as the time (in months) from first dose of study drug to the death due to any reason. If there was no death, OS was censored by last visit, last long term follow-up, or study cutoff date, whichever was the latest. Kaplan-Meier survival method was used for the analysis. Timeframe: From first dose of study drug to date of death from any cause or data cut-off, whichever occurred first (maximum duration: up to 64.2 months). Participants received belumosudil orally on Day 1, 8, 15, and 22 of each 28-day treatment cycle until disease progression, unacceptable toxicity, or death whichever occurred first (maximum duration: 64.2 months). The data is shown in the table below.

TABLE-US-00009 TABLE 8 OS Cohort 1: Cohort 2: Cohort 3: Belumosudil Belumosudil Belumosudil 200 mg QD 200 mg BID 400 mg QD Overall Number of 17 16 21 Participants Analyzed OS Median (95% NA (40-NA* %) NA (52-NA %) NA (23-NA %) Confidence Interval) Unit of Measure = months *OS medians and the corresponding 95% upper limits are not available due to the majority of the participants were still alive at the time of the final analysis.

[0131] QOL assessment. Clinically meaningful improvement in LSS score, defined as a decrease of ≥7 points in the LSS summary score, during belumosudil treatment was observed in 50% of

patients. Thirty-five percent of all patients (37% of responders and 32% of nonresponders) reported a clinically meaningful improvement in LSS score on consecutive assessments.
[0132] Corticosteroid sparing. During belumosudil treatment, 67% of patients reduced corticosteroid dose and 19% completely discontinued corticosteroid therapy. The mean corticosteroid dose was reduced by 45%. The median time to corticosteroid therapy discontinuation was 29 weeks (range, 8-77 weeks). The mean corticosteroid dose reduction was 55% in responders and 26% in nonresponders (Table 3).
[0133] Best Overall Response (BOR). BOR was defined as the participants with either a CR or PR or lack of response (LOR), where LOR included the response status of unchanged (LOR-U), mixed (LOR-M), or progression (LOR-P). BOR was assessed per the 2014 NIH Consensus Development Project for Clinical Trials in cGVHD criteria. CR was defined as the resolution of all manifestations in each organ or site; PR was defined as the improvement in at least 1 organ or site without progression in any other organ or site; LOR-M was defined as CR or PR in at least one organ accompanied by progression in another organ, LOR-U was defined as outcomes that did not meet the criteria for CR, PR, progression or mixed response, LOR-P was defined as progression in at least one organ or site without a response in any other organ or site. Timeframe: From the date of randomization to the date of first documentation of progression or death due to any cause or data cut-off, whichever occurred first (maximum duration: up to 64.2 months). Analysis was performed on mITT population. The data is shown in the table below.
TABLE-US-00010 TABLE 9 BOR Cohort 1: Cohort 2: Cohort 3: Belumosudil Belumosudil Belumosudil 200 mg QD 200 mg BID 400 mg QD Overall Number of 17 16 21 Participants Analyzed Measure Type: Count of Participants Unit of measure = participants CR 0 (0%) 0 (0%) 0 (0%) PR 11 (65%) 11 (69%) 12 (57%) LOR-U 2 (12%) 3 (19%) 4 (19%) LOR-M 2 (12%) 1 (6%) 0 (0%) LOR-P 2 (12%) 1 (6%) 1 (5%)
[0134] Maximal Improvement from Baseline in Global Severity Rating (GSR) by Clinician-reported cGVHD Assessment. The GSR assessment was performed by asking the participants to rate their disease severity of cGVHD symptoms on a 0 to 10-point numeric rating scale, where score 0 indicated ‘not at all severe cGVHD symptoms’ and score 10 indicated ‘most severe cGVHD symptoms possible’. The response was defined using the scores from 9 organs: skin, eyes, mouth, esophagus, upper gastrointestinal (GI) track, lower GI tract, liver, lungs, and joints and fascia plus GSR. End of treatment (EOT) visit was performed within 3 days after the participant's last dose of study drug. Baseline value was defined as valid and last non-missing value obtained within 28 days prior to participant receiving first study medication. Timeframe: From Baseline up to end of treatment (i.e., up to 64.2 months). Analysis was performed on mITT population. Participants received belumosudil 200 mg orally QD on Day 1, 8, 15, and 22 of each 28-day treatment cycle until disease progression, unacceptable toxicity, or death whichever occurred first (maximum duration: 64.2 months). The data is shown in the table below.
TABLE-US-00011 TABLE 10 GSR Cohort 1: Cohort 2: Cohort 3: Belumosudil Belumosudil Belumosudil 200 mg QD 200 mg BID 400 mg QD Overall Number of 17 16 21 Participants Analyzed Measure Type: Count of Participants Unit of measure = participants −7 0 (0%) 0 (0%) 2 (10%) −6 0 (0%) 2 (13%) 0 (0%) −5 2 (12%) 2 (13%) 0 (0%) −4 2 (12%) 0 (0%) 3 (14%) −3 4 (24%) 0 (0%) 1 (5%) −2 2 (12%) 4 (25%) 4 (19%) −1 1 (6%) 2 (13%) 4 (19%) 0 5 (29%) 4 (25%) 3 (14%) 1 0 (0%) 1 (6%) 1 (5%) 3 0 (0%) 1 (6%) 0 (0%) missing 1 (6%) 0 (0%) 3 (14%)
[0135] Number of Participants With Maximal Improvement From Baseline in Symptom Activity by cGVHD Activity Assessment Participant Self-Report. cGVHD symptom severity was self-reported by participants. Participants were asked to rate their disease symptom severity over the last week on the following questions: skin itching at its worst, moth dryness at its worst, mouth pain at its worst, mouth sensitivity at its worst, main compliant on eyes, symptom severity on eyes. The severity rating was done on a 0 to 10-point numeric rating scare, where score 0 indicated ‘not at all severe cGVHD symptoms’ and score 10 indicated ‘most severe cGVHD symptoms possible’.

EOT visit was performed within 3 days after the participant's last dose of study drug. Baseline value was defined as valid and last non-missing value obtained within 28 days prior to participant receiving first study medication. Timeframe: From Baseline up to end of treatment (i.e., up to 64.2 months). Analysis was performed on mITT population. The data is shown in the table below.
TABLE-US-00012 TABLE 11 Number of Participants With Maximal Improvement From Baseline in Symptom Activity by cGVHD Activity Assessment Participant Self-Report Cohort 1: Cohort 2: Cohort 3: Belumosudil Belumosudil Belumosudil 200 mg QD 200 mg BID 400 mg QD Number of Participants With 17 16 21 Maximal Improvement From Baseline in Symptom Activity by cGVHD Activity Assessment Participant Self-Report Measure Type: Count of Participants Unit of measure = participants −8 0 (0%) 0 (0%) 1 (5%) −7 3 (18%) 2 (13%) 0 (0%) −6 0 (0%) 1 (6%) 4 (19%) −5 2 (12%) 0 (0%) 2 (10%) −4 2 (12%) 2 (13%) 1 (5%) −3 2 (12%) 2 (13%) 2 (10%) −2 2 (12%) 3 (19%) 2 (10%) −1 2 (12%) 2 (13%) 2 (10%) 0 1 (6%) 1 (6%) 0 (0%) 1 0 (0%) 0 (0%) 1 (5%) 2 0 (0%) 1 (6%) 2 (10%) 4 1 (6%) 0 (0%) 0 (0%) missing 2 (12%) 2 (13%) 4 (19%)
[0136] Best Response in Each Individual Organ. Best response was defined as the percentage of participants with CR or PR. Response was assessed per the 2014 NIH Consensus Development Project for Clinical Trials in cGVHD criteria; CR was defined as the resolution of all manifestations in each organ or site; PR was defined as the improvement in at least 1 organ or site without progression in any other organ or site. Organ response assessment was performed on 9 individual organs: skin, eyes, mouth, esophagus, upper GI, lower GI, liver, lungs, and joints and fascia. Timeframe: From date of randomization until disease progression or data cut-off, whichever occurred first (maximum duration: up to 64.2 months). Analysis was performed on mITT population. Here, ‘number analyzed’=participants with available data for each specified category. Here, ‘0’ in the number analyzed field signifies that none of the participants were available for the analysis at the specified time points. The data is shown in the table below:
TABLE-US-00013 TABLE 12 Best Response in Each Individual Organ Cohort 1: Cohort 2: Cohort 3: Belumosudil Belumosudil Belumosudil 200 mg QD 200 mg BID 400 mg QD Overall Number of 17 16 21 Participants Analyzed participant number analyzed (percentage of participants with best response in each individual organ) Skin 13 participants 12 participants 15 participants (23%) (17%) (13%) Eyes 14 participants 11 participants 17 participants (36%) (36%) (24%) Mouth 13 participants 11 participants 11 participants (46%) (46%) (46%) Esophagus 2 participants 0 participants 4 participants (50%) (25%) Upper GI tract 2 participants 4 participants 2 participants (100%) (100%) (50%) Lower GI tract 1 participant 2 participants 1 participant (0%) (100%) (0%) Liver 0 participants 2 participants 0 participants (50%) Lungs 5 participants 3 participants 10 participants (0%) (0%) (30%) Joints and Fascia 11 participants 11 participants 12 participants (55%) (46%) (42%)
Safety
[0137] Belumosudil was well-tolerated, with >56 patient-years of belumosudil exposure. The median relative dose intensity was 98% overall. The percentage of patients with a relative dose intensity >95% was 77%, 63%, and 71% across cohorts, respectively. Dose reductions occurred in 9% of patients, and the median duration of reduction was 97 days (range, 21-859 days). Dose interruptions occurred in 41% of patients, and the median duration of interruption was 10 days (range, 2-39 days).
[0138] AEs were consistent with those expected in a population of patients with advanced cGVHD receiving corticosteroid therapy. AEs reported in ≥20% of patients were upper respiratory infection (46%), diarrhea (33%), fatigue (33%), nausea (33%), increased liver function tests (33%), dyspnea (30%), headache (24%), peripheral edema (24%), cough (22%), and hypertension (20%) (Table 13). Serious AEs were reported in 43% of patients, and serious AEs reported in >1 patient were dyspnea (7%), lung infection (6%), hypoxia (4%), and influenza-like illness (4%). Sixty-one percent of patients had a grade ≥3 AE, with the most common being dyspnea (13%), increased liver function tests (7%), hyperglycemia (7%), and hypoxia (7%) (Table 13). Grade ≥3 cytopenias were

reported in two patients (4%). These occurred at relapse of underlying malignancy in patients who had otherwise maintained normal blood counts during their belumosudil treatment.
TABLE-US-00014 TABLE 13 Safety Overview Cohort 1 Cohort 2 Cohort 3 KD025 200 mg KD025 200 mg KD025 400 mg Once Daily Twice a Day Once Daily Total AE, No. (%) (n = 17) (n = 16) (n = 21) (N = 54) Any AE 17 (100) 16 (100) 16 (100) 53 (98) Grade ≥3 AE 9 (53) 10 (63) 14 (67) 33 (61) Drug-related AE 8 (47) 8 (50) 14 (67) 30 (56) SAE 5 (29) 6 (38) 12 (57) 23 (43) Death 0 0 2 (10) 2 (4) Drug-related SAE 0 0 0 0 All grade in ≥20% URI 9 (53) 9 (56) 7 (33) 25 (46) Diarrhea 6 (35) 5 (31) 7 (33) 18 (33) Nausea 6 (35) 4 (25) 8 (38) 18 (33) Fatigue 6 (35) 3 (19) 9 (43) 18 (33) ALT/AST increased 11 (65) 5 (31) 2 (10) 18 (33) Dyspnea 3 (18) 6 (38) 7 (33) 16 (30) Peripheral edema 3 (18) 4 (25) 6 (29) 13 (24) Headache 4 (24) 3 (19) 6 (29) 13 (24) Cough 1 (6) 4 (25) 7 (33) 12 (22) Hypertension 5 (29) 2 (13) 4 (19) 11 (20) Grade ≥3 in ≥5% Dyspnea 1 (6) 2 (13) 4 (19) 7 (13) Lung infection or 1 (6) 2 (13) 2 (10) 5 (9) pneumonia ALT/AST increased 2 (12) 2 (13) 0 4 (7) Hyperglycemia 2 (12) 0 2 (10) 4 (7) Hypoxia 1 (6) 1 (6) 2 (10) 4 (7) Anemia 2 (12) 1 (6) 0 3 (6) Abbreviations: AE, adverse event; SAE, serious adverse event; URI, upper respiratory tract infection.
[0139] No cases of cytomegalovirus (CMV) infection or reactivation were reported with belumosudil. Three patients discontinued belumosudil because of potentially drug-related AEs (cohort 1: diarrhea and headache; cohort 3: fatigue). Four patients, all in cohort 3, died during the study (secondary to relapse of leukemia, pneumonia (unknown pathogen), cardiac arrest, and cGVHD progression) with none of the deaths attributed to belumosudil. There was no dose response with respect to the observed AEs.
[0140] Reported Adverse Events. Timeframe: From first dose of study drug up to 28 days after the last dose of study drug (maximum duration: up to 64.2 months). Reported AEs and deaths were treatment emergent AEs that developed, worsened, or became serious from first dose of study drug up to 28 days after the last dose of study drug. All-cause mortality data collected during the study were assessed for all enrolled participants. Disease progression related death was not reported as AE. Participants received belumosudil 200 mg orally QD on Day 1, 8, 15, and 22 of each 28-day treatment cycle until disease progression, unacceptable toxicity, or death whichever occurred first (maximum duration: 64.2 months). The data is shown in the three tables below.
TABLE-US-00015 TABLE 14 All-Cause Mortality Cohort 1 200 mg QD Cohort 2 200 mg BID Cohort 3 400 mg QD Affected/At # Affected/At # Affected/At # Risk (%) Events Risk (%) Events Risk (%) Events Total All- 2/17 (11.76%) 3/16 (18.75%) 3/21 (14.29%) Cause Mortality
TABLE-US-00016 TABLE 15 Serious Adverse Events Cohort 1 200 mg QD Cohort 2 200 mg BID Cohort 3 400 mg QD Affected/At # Affected/At # Affected/At # Risk (%) Events Risk (%) Events Risk (%) Events Total 5/17 (29.41%) 6/16 (37.5%) 13/21 (61.9%) Blood and lymphatic system disorders Febrile neutropenia .sup.A † 0/17 (0%) 0 0/16 (0%) 0 1/21 (4.76%) 1 Cardiac disorders Cardiac arrest .sup.A † 0/17 (0%) 0 0/16 (0%) 0 1/21 (4.76%) 1 Pericardial effusion .sup.A † 0/17 (0%) 0 0/16 (0%) 0 1/21 (4.76%) 1 Gastrointestinal disorders Abdominal wall haematoma .sup.A † 0/17 (0%) 0 0/16 (0%) 0 1/21 (4.76%) 1 Small intestinal obstruction .sup.A † 0/17 (0%) 0 0/16 (0%) 0 1/21 (4.76%) 1 General disorders Influenza like illness .sup.A † 0/17 (0%) 0 0/16 (0%) 0 2/21 (9.52%) 2 Non-cardiac chest pain .sup.A † 0/17 (0%) 0 1/16 (6.25%) 2 0/21 (0%) 0 Immune system disorders Anaphylactic reaction .sup.A † 1/17 (5.88%) 1 0/16 (0%) 0 0/21 (0%) 0 Chronic graft versus host disease in skin .sup.A † 0/17 (0%) 0 1/16 (6.25%) 1 0/21 (0%) 0 Graft versus host disease in lung .sup.A † 0/17 (0%) 0 0/16 (0%) 0 1/21 (4.76%) 1 Infections and infestations Bacteraemia .sup.A † 0/17 (0%) 0 1/16 (6.25%) 1 0/21 (0%) 0 Cellulitis .sup.A † 0/17 (0%) 0 1/16 (6.25%) 1 0/21 (0%) 0 Citrobacter infection .sup.A † 0/17 (0%) 0 1/16 (6.25%) 1 0/21 (0%) 0 Pneumonia .sup.A † 1/17 (5.88%) 2 1/16 (6.25%) 1 3/21 (14.29%) 3 Pneumonia viral .sup.A † 0/17 (0%) 0 0/16 (0%) 0 1/21 (4.76%) 1 Stenotrophomonas infection .sup.A † 0/17 (0%) 0 1/16 (6.25%) 1 0/21 (0%) 0 Urinary tract infection .sup.A † 0/17 (0%) 0 1/16 (6.25%) 1 0/21 (0%) 0 Varicella zoster virus infection .sup.A † 0/17 (0%) 0 0/16 (0%) 0 1/21 (4.76%) 1 Investigations Influenza A

virus test positive .sup.A † 1/17 (5.88%) 1 0/16 (0%) 0 0/21 (0%) 0 Respirovirus test positive .sup.A † 0/17 (0%) 0 1/16 (6.25%) 1 0/21 (0%) 0 Metabolism and nutrition disorders Lipomatosis .sup.A † 1/17 (5.88%) 1 0/16 (0%) 0 0/21 (0%) 0 Musculoskeletal and connective tissue disorders Muscular weakness .sup.A † 0/17 (0%) 0 1/16 (6.25%) 1 0/21 (0%) 0 Neoplasms benign, malignant and unspecified (incl cysts and polyps) Acute lymphocytic leukaemia recurrent .sup.A † 0/17 (0%) 0 0/16 (0%) 0 1/21 (4.76%) 1 Leukaemia recurrent .sup.A † 0/17 (0%) 0 0/16 (0%) 0 1/21 (4.76%) 1 Metastases to meninges .sup.A † 1/17 (5.88%) 1 0/16 (0%) 0 0/21 (0%) 0 Myelodysplastic syndrome .sup.A † 0/17 (0%) 0 0/16 (0%) 0 1/21 (4.76%) 1 Nervous system disorders Lacunar infarction .sup.A † 0/17 (0%) 0 1/16 (6.25%) 1 0/21 (0%) 0 Renal and urinary disorders Acute kidney injury .sup.A † 0/17 (0%) 0 1/16 (6.25%) 1 0/21 (0%) 0 Proteinuria .sup.A † 1/17 (5.88%) 1 0/16 (0%) 0 0/21 (0%) 0 Urinary retention .sup.A † 0/17 (0%) 0 0/16 (0%) 0 1/21 (4.76%) 1 Respiratory, thoracic and mediastinal disorders Acute respiratory failure .sup.A † 1/17 (5.88%) 1 0/16 (0%) 0 0/21 (0%) 0 Dyspnoea .sup.A † 0/17 (0%) 0 1/16 (6.25%) 1 3/21 (14.29%) 3 Hypoxia .sup.A † 0/17 (0%) 0 0/16 (0%) 0 2/21 (9.52%) 2 Obliterative bronchiolitis .sup.A † 1/17 (5.88%) 1 0/16 (0%) 0 0/21 (0%) 0 Pleural effusion .sup.A † 0/17 (0%) 0 0/16 (0%) 0 1/21 (4.76%) 1 Social circumstances Pregnancy of partner .sup.A † 0/17 (0%) 0 0/16 (0%) 0 1/21 (4.76%) 1 Vascular disorders Embolism 0/17 (0%) 0 1/16 (6.25%) 1 0/21 (0%) 0 † Indicates events were collected by systematic assessment. .sup.A Term from vocabulary, MedDRA 24.1

TABLE-US-00017 TABLE 16 Other Adverse Events Frequency Threshold Above Which Other Events are Reported: 5% Cohort 1 200 mg QD Cohort 2 200 mg BID Cohort 3 400 mg QD Affected/At # Affected/At # Affected/At # Risk (%) Events Risk (%) Events Risk (%) Events Total 17/17 (100%) 16/16 (100%) 19/21 (90.48%) Blood and lymphatic system disorders Anaemia .sup.A † 5/17 (29.41%) 14 4/16 (25%) 8 0/21 (0%) 0 Blood loss anaemia .sup.A † 1/17 (5.88%) 1 0/16 (0%) 0 0/21 (0%) 0 Leukocytosis .sup.A † 1/17 (5.88%) 1 0/16 (0%) 0 1/21 (4.76%) 1 Thrombocytopenia .sup.A † 0/17 (0%) 0 1/16 (6.25%) 1 1/21 (4.76%) 1 Thrombocytosis .sup.A † 1/17 (5.88%) 1 0/16 (0%) 0 0/21 (0%) 0 Cardiac disorders Palpitations .sup.A † 1/17 (5.88%) 1 0/16 (0%) 0 1/21 (4.76%) 1 Pericardial effusion .sup.A † 1/17 (5.88%) 1 0/16 (0%) 0 0/21 (0%) 0 Tachycardia .sup.A † 0/17 (0%) 0 0/16 (0%) 0 2/21 (9.52%) 2 Ear and labyrinth disorders Vertigo .sup.A † 2/17 (11.76%) 2 0/16 (0%) 0 0/21 (0%) 0 Endocrine disorders Adrenal insufficiency .sup.A † 1/17 (5.88%) 2 0/16 (0%) 0 0/21 (0%) 0 Hyperthyroidism .sup.A † 0/17 (0%) 0 1/16 (6.25%) 1 1/21 (4.76%) 1 Hypogonadism .sup.A † 1/17 (5.88%) 1 0/16 (0%) 0 0/21 (0%) 0 Hypothyroidism .sup.A † 1/17 (5.88%) 2 1/16 (6.25%) 2 3/21 (14.29%) 4 Eye disorders Blepharitis .sup.A † 1/17 (5.88%) 1 0/16 (0%) 0 1/21 (4.76%) 2 Conjunctival haemorrhage .sup.A † 0/17 (0%) 0 1/16 (6.25%) 1 1/21 (4.76%) 1 Dry eye .sup.A † 2/17 (11.76%) 3 4/16 (25%) 4 2/21 (9.52%) 2 Eye irritation .sup.A † 1/17 (5.88%) 1 0/16 (0%) 0 0/21 (0%) 0 Eye pain .sup.A † 0/17 (0%) 0 2/16 (12.5%) 4 0/21 (0%) 0 Eye pruritus .sup.A † 0/17 (0%) 0 1/16 (6.25%) 1 0/21 (0%) 0 Eyelid margin crusting .sup.A † 1/17 (5.88%) 1 0/16 (0%) 0 0/21 (0%) 0 Glaucoma .sup.A † 0/17 (0%) 0 1/16 (6.25%) 1 0/21 (0%) 0 Lacrimation increased .sup.A † 0/17 (0%) 0 1/16 (6.25%) 1 0/21 (0%) 0 Macular degeneration .sup.A † 0/17 (0%) 0 1/16 (6.25%) 1 0/21 (0%) 0 Photophobia .sup.A † 0/17 (0%) 0 1/16 (6.25%) 1 2/21 (9.52%) 2 Ulcerative keratitis .sup.A † 0/17 (0%) 0 1/16 (6.25%) 1 0/21 (0%) 0 Vision blurred .sup.A † 0/17 (0%) 0 2/16 (12.5%) 2 4/21 (19.05%) 4 Gastrointestinal disorders Abdominal distension .sup.A † 1/17 (5.88%) 1 0/16 (0%) 0 1/21 (4.76%) 1 Abdominal pain .sup.A † 2/17 (11.76%) 2 2/16 (12.5%) 4 4/21 (19.05%) 6 Abdominal pain upper .sup.A † 1/17 (5.88%) 1 1/16 (6.25%) 1 0/21 (0%) 0 Anal incontinence .sup.A † 1/17 (5.88%) 2 0/16 (0%) 0 0/21 (0%) 0 Constipation .sup.A † 1/17 (5.88%) 1 1/16 (6.25%) 1 3/21 (14.29%) 4 Diarrhoea .sup.A † 6/17 (35.29%) 9 5/16 (31.25%) 10 7/21 (33.33%) 11 Dyspepsia .sup.A † 0/17 (0%) 0 2/16 (12.5%) 2 1/21 (4.76%) 1 Dysphagia .sup.A † 1/17 (5.88%) 1 3/16 (18.75%) 4 2/21 (9.52%) 3 Enamel anomaly .sup.A † 0/17 (0%) 0 1/16 (6.25%) 1 0/21 (0%) 0 Flatulence .sup.A † 0/17 (0%) 0 1/16 (6.25%) 2 1/21 (4.76%) 1 Gastric ulcer .sup.A † 0/17 (0%) 0 1/16 (6.25%) 1 0/21 (0%) 0 Gastrooesophageal reflux disease .sup.A † 2/17 (11.76%) 2 1/16 (6.25%) 1 2/21 (9.52%) 2 Nausea

.sup.A † 6/17 (35.29%) 10 4/16 (25%) 6 9/21 (42.86%) 12 Oesophageal ulcer .sup.A † 0/17 (0%) 0 1/16 (6.25%) 1 0/21 (0%) 0 Stomatitis .sup.A † 1/17 (5.88%) 2 1/16 (6.25%) 1 1/21 (4.76%) 1 Vomiting .sup.A † 2/17 (11.76%) 4 3/16 (18.75%) 3 4/21 (19.05%) 4 General disorders Asthenia .sup.A † 0/17 (0%) 0 1/16 (6.25%) 1 0/21 (0%) 0 Catheter site haemorrhage .sup.A † 1/17 (5.88%) 1 0/16 (0%) 0 0/21 (0%) 0 Chills .sup.A † 1/17 (5.88%) 1 1/16 (6.25%) 1 0/21 (0%) 0 Fatigue .sup.A † 6/17 (35.29%) 7 3/16 (18.75%) 7 10/21 (47.62%) 14 Generalised oedema .sup.A † 1/17 (5.88%) 1 0/16 (0%) 0 1/21 (4.76%) 1 Hypothermia .sup.A † 0/17 (0%) 0 1/16 (6.25%) 1 0/21 (0%) 0 Impaired healing .sup.A † 1/17 (5.88%) 1 0/16 (0%) 0 0/21 (0%) 0 Influenza like illness .sup.A † 1/17 (5.88%) 1 1/16 (6.25%) 2 0/21 (0%) 0 Non-cardiac chest pain .sup.A † 0/17 (0%) 0 3/16 (18.75%) 3 1/21 (4.76%) 1 Oedema .sup.A † 0/17 (0%) 0 1/16 (6.25%) 1 0/21 (0%) 0 Oedema peripheral .sup.A † 3/17 (17.65%) 3 4/16 (25%) 5 6/21 (28.57%) 6 Pain .sup.A † 3/17 (17.65%) 3 0/16 (0%) 0 1/21 (4.76%) 1 Pyrexia .sup.A † 1/17 (5.88%) 3 3/16 (18.75%) 6 3/21 (14.29%) 3 Immune system disorders Contrast media allergy .sup.A † 0/17 (0%) 0 2/16 (12.5%) 2 0/21 (0%) 0 Graft versus host disease in 1/17 (5.88%) 1 0/16 (0%) 0 0/21 (0%) 0 gastrointestinal tract .sup.A † Infections and infestations Bronchitis .sup.A † 1/17 (5.88%) 1 0/16 (0%) 0 1/21 (4.76%) 1 Conjunctivitis .sup.A † 0/17 (0%) 0 1/16 (6.25%) 1 3/21 (14.29%) 3 Corneal infection .sup.A † 0/17 (0%) 0 1/16 (6.25%) 2 0/21 (0%) 0 Epstein-Barr virus infection .sup.A † 1/17 (5.88%) 1 0/16 (0%) 0 0/21 (0%) 0 Fungal infection .sup.A † 1/17 (5.88%) 1 0/16 (0%) 0 0/21 (0%) 0 Genital infection fungal .sup.A † 0/17 (0%) 0 1/16 (6.25%) 1 0/21 (0%) 0 Hordeolum .sup.A † 1/17 (5.88%) 1 0/16 (0%) 0 1/21 (4.76%) 1 Influenza .sup.A † 2/17 (11.76%) 2 1/16 (6.25%) 2 2/21 (9.52%) 2 Oral candidiasis .sup.A † 2/17 (11.76%) 3 1/16 (6.25%) 1 0/21 (0%) 0 Pneumonia .sup.A † 1/17 (5.88%) 2 3/16 (18.75%) 3 0/21 (0%) 0 Pneumonia respiratory syncytial viral .sup.A † 0/17 (0%) 0 1/16 (6.25%) 1 0/21 (0%) 0 Pseudomonas infection .sup.A † 1/17 (5.88%) 1 1/16 (6.25%) 2 0/21 (0%) 0 Rash pustular .sup.A † 0/17 (0%) 0 1/16 (6.25%) 1 0/21 (0%) 0 Respiratory syncytial virus infection .sup.A † 0/17 (0%) 0 1/16 (6.25%) 1 2/21 (9.52%) 3 Respiratory tract infection .sup.A † 1/17 (5.88%) 1 0/16 (0%) 0 0/21 (0%) 0 Respiratory tract infection fungal .sup.A † 1/17 (5.88%) 1 0/16 (0%) 0 0/21 (0%) 0 Sinusitis .sup.A † 1/17 (5.88%) 1 2/16 (12.5%) 4 1/21 (4.76%) 1 Tinea pedis .sup.A † 0/17 (0%) 0 1/16 (6.25%) 1 0/21 (0%) 0 Upper respiratory tract infection .sup.A † 9/17 (52.94%) 16 9/16 (56.25%) 13 7/21 (33.33%) 9 Urinary tract infection .sup.A † 0/17 (0%) 0 2/16 (12.5%) 2 0/21 (0%) 0 Injury, poisoning and procedural complications Contusion .sup.A † 2/17 (11.76%) 2 2/16 (12.5%) 2 3/21 (14.29%) 4 Corneal abrasion .sup.A † 1/17 (5.88%) 1 0/16 (0%) 0 0/21 (0%) 0 Fall .sup.A † 2/17 (11.76%) 2 1/16 (6.25%) 1 1/21 (4.76%) 1 Ligament sprain .sup.A † 1/17 (5.88%) 1 0/16 (0%) 0 0/21 (0%) 0 Limb injury .sup.A † 1/17 (5.88%) 1 0/16 (0%) 0 1/21 (4.76%) 1 Overdose .sup.A † 1/17 (5.88%) 1 0/16 (0%) 0 0/21 (0%) 0 Skin abrasion .sup.A † 0/17 (0%) 0 0/16 (0%) 0 2/21 (9.52%) 2 Spinal compression fracture .sup.A † 1/17 (5.88%) 1 0/16 (0%) 0 0/21 (0%) 0 Tooth fracture .sup.A † 0/17 (0%) 0 1/16 (6.25%) 1 0/21 (0%) 0 Transfusion reaction .sup.A † 1/17 (5.88%) 1 0/16 (0%) 0 0/21 (0%) 0 Vascular access complication .sup.A † 0/17 (0%) 0 1/16 (6.25%) 1 0/21 (0%) 0 Investigations Alanine aminotransferase increased .sup.A † 6/17 (35.29%) 12 3/16 (18.75%) 4 2/21 (9.52%) 2 Aspartate aminotransferase increased .sup.A † 5/17 (29.41%) 8 2/16 (12.5%) 2 1/21 (4.76%) 1 Blood alkaline phosphatase increased .sup.A † 4/17 (23.53%) 6 1/16 (6.25%) 1 0/21 (0%) 0 Blood chloride decreased .sup.A † 0/17 (0%) 0 1/16 (6.25%) 1 0/21 (0%) 0 Blood cholesterol increased .sup.A † 1/17 (5.88%) 2 0/16 (0%) 0 1/21 (4.76%) 1 Blood creatine increased .sup.A † 0/17 (0%) 0 1/16 (6.25%) 1 0/21 (0%) 0 Blood creatine phosphokinase increased .sup.A † 1/17 (5.88%) 1 0/16 (0%) 0 0/21 (0%) 0 Blood creatinine increased .sup.A † 1/17 (5.88%) 1 1/16 (6.25%) 1 2/21 (9.52%) 2 Bronchoscopy .sup.A † 1/17 (5.88%) 1 0/16 (0%) 0 0/21 (0%) 0 Gamma-glutamyltransferase increased .sup.A † 4/17 (23.53%) 9 4/16 (25%) 4 0/21 (0%) 0 Glucose urine present .sup.A † 2/17 (11.76%) 3 0/16 (0%) 0 1/21 (4.76%) 3 Neutrophil count decreased .sup.A † 1/17 (5.88%) 1 0/16 (0%) 0 1/21 (4.76%) 1 Platelet count decreased .sup.A † 1/17 (5.88%) 3 0/16 (0%) 0 0/21 (0%) 0 Red blood cells urine positive .sup.A † 0/17 (0%) 0 1/16 (6.25%) 1 0/21 (0%) 0 Urine output

decreased .sup.A † 1/17 (5.88%) 1 1/16 (6.25%) 1 0/21 (0%) 0 Weight decreased .sup.A † 1/17 (5.88%) 1 0/16 (0%) 0 2/21 (9.52%) 4 Weight increased .sup.A † 3/17 (17.65%) 9 1/16 (6.25%) 2 1/21 (4.76%) 4 White blood cell count decreased .sup.A † 1/17 (5.88%) 1 0/16 (0%) 0 1/21 (4.76%) 2 Metabolism and nutrition disorders Decreased appetite .sup.A † 2/17 (11.76%) 4 2/16 (12.5%) 2 4/21 (19.05%) 4 Dehydration .sup.A † 2/17 (11.76%) 2 3/16 (18.75%) 4 2/21 (9.52%) 2 Hyperglycemia .sup.A † 2/17 (11.76%) 2 0/16 (0%) 0 3/21 (14.29%) 8 Hyperkalaemia .sup.A † 3/17 (17.65%) 7 2/16 (12.5%) 2 3/21 (14.29%) 4 Hypertriglyceridaemia .sup.A † 0/17 (0%) 0 1/16 (6.25%) 1 0/21 (0%) 0 Hyperuricaemia .sup.A † 1/17 (5.88%) 6 1/16 (6.25%) 2 3/21 (14.29%) 5 Hypocalcaemia .sup.A † 0/17 (0%) 0 1/16 (6.25%) 4 1/21 (4.76%) 1 Hypokalaemia .sup.A † 1/17 (5.88%) 1 2/16 (12.5%) 3 0/21 (0%) 0 Hypomagnesaemia .sup.A † 1/17 (5.88%) 1 1/16 (6.25%) 1 1/21 (4.76%) 1 Hyponatraemia .sup.A † 1/17 (5.88%) 1 0/16 (0%) 0 2/21 (9.52%) 2 Hypophosphataemia .sup.A † 1/17 (5.88%) 1 1/16 (6.25%) 1 1/21 (4.76%) 1 Obesity .sup.A † 2/17 (11.76%) 2 0/16 (0%) 0 0/21 (0%) 0 Type 2 diabetes mellitus .sup.A † 1/17 (5.88%) 1 0/16 (0%) 0 0/21 (0%) 0 Musculoskeletal and connective tissue disorders Arthralgia .sup.A † 1/17 (5.88%) 1 1/16 (6.25%) 1 5/21 (23.81%) 6 Back pain .sup.A † 0/17 (0%) 0 2/16 (12.5%) 2 1/21 (4.76%) 1 Joint range of motion decreased .sup.A † 0/17 (0%) 0 1/16 (6.25%) 1 1/21 (4.76%) 1 Muscle spasms .sup.A † 1/17 (5.88%) 1 0/16 (0%) 0 6/21 (28.57%) 6 Muscular weakness .sup.A † 4/17 (23.53%) 6 1/16 (6.25%) 1 2/21 (9.52%) 2 Musculoskeletal chest pain .sup.A † 1/17 (5.88%) 1 0/16 (0%) 0 1/21 (4.76%) 1 Myalgia .sup.A † 1/17 (5.88%) 2 1/16 (6.25%) 1 3/21 (14.29%) 3 Neck pain .sup.A † 1/17 (5.88%) 1 0/16 (0%) 0 0/21 (0%) 0 Osteonecrosis .sup.A † 1/17 (5.88%) 1 0/16 (0%) 0 0/21 (0%) 0 Osteopenia .sup.A † 0/17 (0%) 0 1/16 (6.25%) 1 0/21 (0%) 0 Osteoporosis .sup.A † 0/17 (0%) 0 1/16 (6.25%) 1 0/21 (0%) 0 Pain in extremity .sup.A † 2/17 (11.76%) 2 2/16 (12.5%) 3 4/21 (19.05%) 5 Tendonitis .sup.A † 0/17 (0%) 0 1/16 (6.25%) 1 0/21 (0%) 0 Thoracic spinal stenosis .sup.A † 1/17 (5.88%) 1 0/16 (0%) 0 0/21 (0%) 0 Neoplasms benign, malignant and unspecified (incl cysts and polyps) Basal cell carcinoma .sup.A † 0/17 (0%) 0 1/16 (6.25%) 1 0/21 (0%) 0 Hodgkin's disease recurrent .sup.A † 1/17 (5.88%) 1 0/16 (0%) 0 0/21 (0%) 0 Leukaemia recurrent .sup.A † 1/17 (5.88%) 1 0/16 (0%) 0 0/21 (0%) 0 Skin papilloma .sup.A † 1/17 (5.88%) 1 0/16 (0%) 0 0/21 (0%) 0 Squamous cell carcinoma of skin .sup.A † 0/17 (0%) 0 2/16 (12.5%) 2 0/21 (0%) 0 Nervous system disorders Balance disorder .sup.A † 0/17 (0%) 0 1/16 (6.25%) 1 0/21 (0%) 0 Dizziness .sup.A † 0/17 (0%) 0 1/16 (6.25%) 4 2/21 (9.52%) 2 Epidural lipomatosis .sup.A † 1/17 (5.88%) 1 0/16 (0%) 0 0/21 (0%) 0 Headache .sup.A † 4/17 (23.53%) 4 3/16 (18.75%) 3 6/21 (28.57%) 8 Hypoaesthesia .sup.A † 1/17 (5.88%) 2 0/16 (0%) 0 1/21 (4.76%) 1 Migraine .sup.A † 0/17 (0%) 0 1/16 (6.25%) 1 0/21 (0%) 0 Muscle spasticity .sup.A † 1/17 (5.88%) 1 0/16 (0%) 0 1/21 (4.76%) 1 Neuropathy peripheral .sup.A † 0/17 (0%) 0 1/16 (6.25%) 1 1/21 (4.76%) 2 Paraesthesia .sup.A † 0/17 (0%) 0 1/16 (6.25%) 1 1/21 (4.76%) 1 Peripheral sensory neuropathy .sup.A † 0/17 (0%) 0 1/16 (6.25%) 1 0/21 (0%) 0 Presyncope .sup.A † 0/17 (0%) 0 3/16 (18.75%) 3 0/21 (0%) 0 Restless legs syndrome .sup.A † 0/17 (0%) 0 1/16 (6.25%) 1 0/21 (0%) 0 Tremor .sup.A † 2/17 (11.76%) 3 1/16 (6.25%) 2 3/21 (14.29%) 4 Psychiatric disorders Anxiety .sup.A † 1/17 (5.88%) 1 2/16 (12.5%) 3 3/21 (14.29%) 3 Depression .sup.A † 0/17 (0%) 0 4/16 (25%) 4 3/21 (14.29%) 3 Insomnia .sup.A † 0/17 (0%) 0 0/16 (0%) 0 3/21 (14.29%) 3 Irritability .sup.A † 1/17 (5.88%) 1 0/16 (0%) 0 0/21 (0%) 0 Renal and urinary disorders Acute kidney injury .sup.A † 1/17 (5.88%) 4 2/16 (12.5%) 2 2/21 (9.52%) 6 Chronic kidney disease .sup.A † 1/17 (5.88%) 1 0/16 (0%) 0 0/21 (0%) 0 Haematuria .sup.A † 1/17 (5.88%) 1 1/16 (6.25%) 1 1/21 (4.76%) 2 Nephrotic syndrome .sup.A † 1/17 (5.88%) 1 1/16 (6.25%) 1 0/21 (0%) 0 Nocturia .sup.A † 1/17 (5.88%) 1 0/16 (0%) 0 0/21 (0%) 0 Pollakiuria .sup.A † 1/17 (5.88%) 1 0/16 (0%) 0 0/21 (0%) 0 Proteinuria .sup.A † 2/17 (11.76%) 2 1/16 (6.25%) 1 0/21 (0%) 0 Renal failure .sup.A † 0/17 (0%) 0 1/16 (6.25%) 1 0/21 (0%) 0 Urinary retention .sup.A † 0/17 (0%) 0 1/16 (6.25%) 2 0/21 (0%) 0 Urinary tract pain .sup.A † 0/17 (0%) 0 1/16 (6.25%) 1 1/21 (4.76%) 1 Reproductive system and breast disorders Benign prostatic hyperplasia .sup.A † 1/17 (5.88%) 1 0/16 (0%) 0 0/21 (0%) 0 Erectile dysfunction .sup.A † 2/17 (11.76%) 4 0/16 (0%) 0 0/21 (0%) 0 Gynaecomastia .sup.A †

0/17 (0%) 0 1/16 (6.25%) 1 0/21 (0%) 0 Testicular pain .sup.A † 1/17 (5.88%) 1 0/16 (0%) 0 0/21 (0%) 0 Testicular swelling .sup.A † 1/17 (5.88%) 1 0/16 (0%) 0 0/21 (0%) 0 Respiratory, thoracic and mediastinal disorders Acute respiratory distress syndrome .sup.A † 1/17 (5.88%) 1 0/16 (0%) 0 0/21 (0%) 0 Atelectasis .sup.A † 1/17 (5.88%) 1 0/16 (0%) 0 0/21 (0%) 0 Bronchial secretion retention .sup.A † 0/17 (0%) 0 1/16 (6.25%) 1 0/21 (0%) 0 Cough .sup.A † 1/17 (5.88%) 1 4/16 (25%) 5 7/21 (33.33%) 9 Dyspnoea .sup.A † 2/17 (11.76%) 2 5/16 (31.25%) 7 6/21 (28.57%) 6 Dyspnoea exertional .sup.A † 1/17 (5.88%) 1 0/16 (0%) 0 0/21 (0%) 0 Hypoxia .sup.A † 1/17 (5.88%) 1 2/16 (12.5%) 5 3/21 (14.29%) 3 Nasal congestion .sup.A † 3/17 (17.65%) 3 0/16 (0%) 0 1/21 (4.76%) 1 Oropharyngeal pain .sup.A † 1/17 (5.88%) 1 0/16 (0%) 0 1/21 (4.76%) 1 Orthopnoea .sup.A † 1/17 (5.88%) 1 0/16 (0%) 0 0/21 (0%) 0 Pleural effusion .sup.A † 1/17 (5.88%) 1 0/16 (0%) 0 1/21 (4.76%) 1 Productive cough .sup.A † 2/17 (11.76%) 2 2/16 (12.5%) 7 1/21 (4.76%) 2 Pulmonary mass .sup.A † 0/17 (0%) 0 1/16 (6.25%) 1 1/21 (4.76%) 1 Sinus pain .sup.A † 2/17 (11.76%) 2 0/16 (0%) 0 0/21 (0%) 0 Upper-airway cough syndrome .sup.A † 0/17 (0%) 0 2/16 (12.5%) 2 1/21 (4.76%) 1 Skin and subcutaneous tissue disorders Actinic keratosis .sup.A † 0/17 (0%) 0 1/16 (6.25%) 1 1/21 (4.76%) 1 Blister .sup.A † 0/17 (0%) 0 2/16 (12.5%) 3 1/21 (4.76%) 1 Drug eruption .sup.A † 0/17 (0%) 0 1/16 (6.25%) 1 0/21 (0%) 0 Dry skin .sup.A † 1/17 (5.88%) 1 0/16 (0%) 0 1/21 (4.76%) 1 Hair growth abnormal .sup.A † 1/17 (5.88%) 1 0/16 (0%) 0 0/21 (0%) 0 Hyperhidrosis .sup.A † 0/17 (0%) 0 1/16 (6.25%) 1 1/21 (4.76%) 1 Nail disorder .sup.A † 1/17 (5.88%) 1 0/16 (0%) 0 0/21 (0%) 0 Pruritus .sup.A † 1/17 (5.88%) 1 2/16 (12.5%) 4 0/21 (0%) 0 Rash .sup.A † 1/17 (5.88%) 2 1/16 (6.25%) 1 1/21 (4.76%) 1 Rash erythematous .sup.A † 0/17 (0%) 0 1/16 (6.25%) 1 0/21 (0%) 0 Rash maculo-papular .sup.A † 2/17 (11.76%) 2 0/16 (0%) 0 0/21 (0%) 0 Rosacea .sup.A † 0/17 (0%) 0 1/16 (6.25%) 1 0/21 (0%) 0 Skin lesion .sup.A † 0/17 (0%) 0 1/16 (6.25%) 1 0/21 (0%) 0 Vascular disorders Embolism .sup.A † 1/17 (5.88%) 1 0/16 (0%) 0 1/21 (4.76%) 1 Flushing .sup.A † 0/17 (0%) 0 1/16 (6.25%) 1 0/21 (0%) 0 Hot flush .sup.A † 1/17 (5.88%) 1 0/16 (0%) 0 0/21 (0%) 0 Hypertension .sup.A † 5/17 (29.41%) 8 2/16 (12.5%) 5 4/21 (19.05%) 6 Peripheral coldness .sup.A † 1/17 (5.88%) 1 0/16 (0%) 0 0/21 (0%) 0 Phlebitis .sup.A † 0/17 (0%) 0 1/16 (6.25%) 1 0/21 (0%) 0 Superior vena cava syndrome .sup.A † 0/17 (0%) 0 1/16 (6.25%) 2 0/21 (0%) 0 † Indicates events were collected by systematic assessment. .sup.A Term from vocabulary, MedDR A 24.1

[0141] Number of Participants With Treatment-emergent Adverse Events (TEAEs), and Treatment-emergent Serious Adverse Events (TESAEs). An adverse event (AE) was defined as any untoward medical occurrence in a participant who received study drug and did not necessarily have to have a causal relationship with the treatment. Serious adverse events (SAEs) was any untoward medical occurrence that at any dose: resulted in death, was life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, was a congenital anomaly/birth defect, was a medically important event. TEAEs were defined as AEs that developed, worsened or became serious during the TEAE period (defined as the time from the first dose of study treatment up to 28 days after the last dose of study drug). TEAEs included both SAEs and non-SAEs. Timeframe: From first dose of study treatment up to 28 days after the last dose of study drug (maximum duration: up to 64.2 months). Analysis was performed on safety population which included all participants who received at least 1 dose of study medication. Data is shown in the table below.

TABLE-US-00018 TABLE 17 Number of Participants With Treatment-emergent Adverse Events (TEAEs), and Treatment-emergent Serious Adverse Events (TESAEs) Cohort 1: Cohort 2: Cohort 3: Belumosudil Belumosudil Belumosudil 200 mg QD 200 mg BID 400 mg QD Number of Participants With 17 16 21 Treatment-emergent Adverse Events (TEAEs), and Treatment-emergent Serious Adverse Events (TESAEs) Measure Type: Count of Participants Unit of measure = participants TEAE 17 (100%) 16 (100%) 20 (95%) TESAE 5 (29%) 6 (38%) 13 (62%)

PD Analyses

[0142] In exploratory PD analyses of peripheral blood mononuclear cells across cohorts, the

percentage of CD41 Tregs demonstrated an increasing trend early on by cycle 2 day 1 of belumosudil treatment. A simultaneous decrease in Th17 cells was also observed. The Th17 cells continued to decrease through C4D1 and C6D25. The percentage of CD41 Tregs continued to increase through C4D1 and C7D1, as shown in (FIG. **6**). Because of the small sample size, correlative data with steroid dose were limited for any statistical analysis.

[0143] This study was the first to evaluate belumosudil treatment in human patients with cGVHD. All phenotypes of cGVHD, without requirements for inflammatory or fibrotic manifestations, were included. Patients with advanced multiorgan cGVHD treated with belumosudil achieved an overall response rate (ORR) of 65%, with (quality of life) QOL improvements, corticosteroid dose reductions, and limited toxicity. With relatively small sample sizes, there was no difference in the ORR across cohorts.

[0144] Belumosudil achieved response rates that were meaningful and consistent across subgroups, including patients with severe cGVHD, patients who had received ≥2 prior systemic lines of therapy, patients who were refractory to their last lines of therapy before enrollment, and patients with >4 organs involved. The ORR among patients with nonsevere cGVHD was 83%, suggesting that further studies of how belumosudil may benefit patients earlier in their disease are indicated. All responses at the patient level were PR; no CR was achieved. However, given the severity and extent of fibrotic cGVHD manifestations in this patient population, achieving CR in all organs was not expected, as some advanced fibrotic changes in the eyes, mouth, lungs, or joints and/or fascia can be irreversible. CR was observed in all organs except the lungs, where PR was achieved.

[0145] Belumosudil response kinetics suggest that most responders achieved responses rapidly within 8 weeks after receiving belumosudil. Belumosudil was well-tolerated, with a median DOR of 35 weeks across all responders. The ability to stay on therapy is dependent on the safety and long-term tolerability profile of the intervention. The median treatment duration was 8 months (range, 1-39 months). Twenty-eight percent of patients remained on belumosudil for >18 months. There was no reported CMV infection or reactivation, despite 57% of patients being CMV seropositive. The incidence of TEAEs and grade ≥3TEAEs was similar across cohorts. The combination of well-tolerated therapy and efficacy in inducing responses translated into a 2-year OS rate of 82%, a median TTNT of 14 months, and FFS rates of 76% and 47% at 6 and 12 months, respectively.

[0146] In a prospective study conducted by the cGVHD Consortium, the 12-month FFS rate with response (CR/PR) after first-line therapy was 12% to 15%. (Martin P J, Storer B E, Inamoto Y, et al: An endpoint associated with clinical benefit after initial treatment for chronic graft-versus-host disease. Blood 130:360-367, 2017) In this study (after 1-3 prior lines of therapy), the 12-month FFS rate with response was 24%.

[0147] In the study of the present example, Belumosudil therapy was associated with a corticosteroid-sparing effect. The current treatment paradigm relies on corticosteroids as the mainstay of therapy; however, the related long-term toxicities mandate the use of the lowest possible dose or discontinuation whenever possible. The use of corticosteroid therapy is tied to quality of life, as the side effect profile of corticosteroid therapy contributes to patient symptom burden. Corticosteroid dose reduction was observed across both responders and nonresponders to belumosudil. Approximately 20% of patients were able to discontinue corticosteroid therapy during belumosudil treatment. Even in the absence of an NIH-defined response, patients experienced clinical benefit, as evidenced by improvements in LSS score or reductions in corticosteroid doses.

[0148] Change from Baseline in Corticosteroids Dose. An EOT visit was performed within 3 days after the participant's last dose of study drug. Baseline value was defined as valid and last non-missing value obtained within 28 days prior to participant receiving first study medication. The mITT population was analyzed, with the ‘overall number of participants analyzed’=participants with available data for this outcome measure. Timeframe: baseline up to end of treatment (i.e., up to 64.2 months). The data is shown in the table below.

TABLE-US-00019 TABLE 18 Change From Baseline in Corticosteroids Dose Cohort 1: Cohort 2: Cohort 3: Belumosudil Belumosudil Belumosudil 200 mg QD 200 mg BID 400 mg QD Overall Number of 17 15 19 Participants Analyzed Change From Baseline −0.110 (0.101) −0.111 (0.147) −0.116 (0.152) in Corticosteroids Dose Mean (Standard Deviation) Unit of measure (milligrams per kilogram per day)

[0149] Change from Baseline in Calcineurin Inhibitor (CNI). Calcineurin inhibitors included systemic tacrolimus and cyclosporine. Number of participants who took CNI at Baseline and had reduction and discontinuation in CNI use as compared to Baseline during the study are reported in this outcome measure. EOT visit was performed within 3 days after the participant's last dose of study drug. Baseline value was defined as valid and last non-missing value obtained within 28 days prior to participant receiving first study medication. Timeframe: baseline up to end of treatment (i.e., up to 64.2 months). The data is shown in the table below.

TABLE-US-00020 TABLE 19 CNI Cohort 1: Cohort 2: Cohort 3: Belumosudil Belumosudil Belumosudil 200 mg QD 200 mg BID 400 mg QD Overall Number of 6 6 11 Participants Analyzed Participants with 5 (83%) 5 (83%) 6 (55%) reduction in CNI dose Participants who 0 (0%) 1 (17%) 3 (27%) discontinued CNI

[0150] Time to Response (TTR). Time-to-response was measured as the time (in weeks) from first dose of study drug to the time of first documentation of response. Response was defined as the subjects achieving a PR or CR at any post-baseline response assessment. Per the 2014 NIH Consensus Development Project for Clinical Trials in cGVHD criteria; CR was defined as the resolution of all manifestations in each organ or site and PR was defined as the improvement in at least 1 organ or site without progression in any other organ or site. Timeframe: from first treatment to the time of first documentation of response or data cut-off, whichever occurred first (maximum duration: up to 64.2 months). The analysis was performed on responder population. The data is shown in the table below:

TABLE-US-00021 TABLE 20 Cohort 1: Cohort 2: Cohort 3: Belumosudil Belumosudil Belumosudil 200 mg QD 200 mg BID 400 mg QD Overall Number of 11 11 12 Participants Analyzed TTR 8.14 (7.9 8.14 (4.1 8.07 (4.1 Median (Full Range) to 26.1) to 40.0) to 67.0) Unit of Measure (weeks)

[0151] In this study, responses were achieved in patients with fibrotic manifestations in the lungs, joints and/or fascia, and eyes. These responses were observed in some cases after. 24 weeks of treatment, further highlighting the need to sustain effective therapy to achieve clinical benefit, particularly in patients with difficult-to-treat disease. Because the lower belumosudil 200-mg once daily dose was equally safe and effective, it has been further compared in the study described in Example 2 against the 200-mg twice a day dose for final dose recommendation.

[0152] Change From Baseline in Overall Score on Lee cGvHD Symptom Scale at Specified Time Points. Lee cGVHD symptom scale, a patient-reported symptom scale used to measure symptom burden and has 7 subscales (Skin, Eyes and Mouth, Breathing, Eating and Digestion, Muscles and Joints, Energy, and Mental and Emotional) with ratings as follows: 0—Not at all, 1—Slightly, 2—Moderately, 3—Quite a bit, 4—Extremely, with lower values representing better outcome. Score for each subscale was normalized to a score ranged from 0 to 100, where higher score-worse symptoms. An overall score was calculated as average of these 7 subscales. EOT visit was performed within 3 days after the participant's last dose of study drug. Baseline value was defined as valid and last non-missing value obtained within 28 days prior to participant receiving first study medication. Timeframe: Baseline, Day 1 of Cycles 2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34, 35,36,37, 38,39,40,41,42,43,44,45,46,47,48, 49, 50,51,52,53, 54,55, 56, 57,58,59,60,61,62,63,67 and EOT (i.e., anytime up to 64.2 months). Analysis was performed on mITT population. Here, ‘number analyzed’=participants with available data for each specified category. Here, ‘0’ in the number analyzed field signifies that none of the participants were available for the analysis at the

specified time points. The data is shown in the table below.
TABLE-US-00022 TABLE 21 Change From Baseline in Overall Score on Lee cGvHD Symptom Scale at Specified Time Points Cohort 1: Cohort 2: Cohort 3: Belumosudil Belumosudil Belumosudil 200 mg QD 200 mg BID 400 mg QD Overall Number of Participants Analyzed 17 16 21 Change From Baseline in Overall Score on Lee cGvHD Symptom Scale at Specified Time Points Mean (Standard Deviation) Unit of measure: score on a scale Cycle 2, Day 1 Number Analyzed 0 participants 0 participants 8 participants — — −5.2 (6.3) Cycle 3, Day 1 Number Analyzed 16 participants 12 participants 16 participants −3.0 (8.5) 0.5 (7.3) −4.3 (8.2) Cycle 4, Day 1 Number Analyzed 0 participants 0 participants 9 participants — — −2.7 (8.2) Cycle 5, Day 1 Number Analyzed 13 participants 10 participants 12 participants −3.7 (11.0) −3.7 (7.0) −0.5 (10.8) Cycle 6, Day 1 Number Analyzed 0 participants 0 participants 12 participants — — −0.8 (9.3) Cycle 7, Day 1 Number Analyzed 10 participants 9 participants 12 participants −4.9 (8.4) −2.2 (8.8) −2.0 (12.3) Cycle 8, Day 1 Number Analyzed 0 participants 2 participants 11 participants — −7.1 (10.1) −2.9 (10.9) Cycle 9, Day 1 Number Analyzed 8 participants 7 participants 10 participants −3.7 (10.7) −4.2 (5.5) −3.6 (10.2) Cycle 10, Day 1 Number Analyzed 0 participants 4 participants 9 participants — −2.7 (6.1) −3.7 (9.9) Cycle 11, Day 1 Number Analyzed 7 participants 6 participants 9 participants −3.4 (11.5) −5.5 (6.0) −4.5 (6.1) Cycle 12, Day 1 Number Analyzed 2 participants 5 participants 8 participants −3.9 (8.1) −7.6 (7.7) −2.8 (6.0) Cycle 13, Day 1 Number Analyzed 6 participants 5 participants 21 participants −5.8 (14.7) −5.9 (8.8) −0.6 (7.1) Cycle 14, Day 1 Number Analyzed 5 participants 5 participants 7 participants −1.6 (17.1) −5.0 (7.3) −1.5 (7.7) Cycle 15, Day 1 Number Analyzed 6 participants 4 participants 7 participants −4.8 (15.8) −6.8 (7.0) −3.2 (8.2) Cycle 16, Day 1 Number Analyzed 5 participants 3 participants 4 participants −4.6 (16.1) −6.9 (7.6) 1.9 (7.9) Cycle 17, Day 1 Number Analyzed 5 participants 3 participants 5 participants −4.1 (17.2) −10.1 (5.5) 0.0 (12.5) Cycle 18, Day 1 Number Analyzed 5 participants 3 participants 3 participants −2.3 (17.6) −11.5 (8.4) −2.3 (7.8) Cycle 19, Day 1 Number Analyzed 5 participants 3 participants 4 participants −7.7 (19.6) −9.9 (7.8) −6.6 (9.9) Cycle 20, Day 1 Number Analyzed 5 participants 3 participants 3 participants −4.6 (22.0) −9.0 (10.3) −2.8 (5.6) Cycle 21, Day 1 Number Analyzed 5 participants 3 participants 4 participants −3.1 (19.1) −7.5 (10.7) −4.0 (7.9) Cycle 22, Day 1 Number Analyzed 5 participants 2 participants 3 participants −4.1 (18.9) −14.5 (9.1) −3.6 (5.0) Cycle 23, Day 1 Number Analyzed 5 participants 2 participants 4 participants −4.1 (19.1) −11.6 (9.3) −6.2 (7.7) Cycle 24, Day 1 Number Analyzed 4 participants 1 participants 2 participants −6.7 (21.0) −18.7 (—) −5.6 (5.7) Cycle 25, Day 1 Number Analyzed 2 participants 2 participants 3 participants 2.2 (18.8) −12.4 (8.2) −8.4 (3.4) Cycle 26, Day 1 Number Analyzed 3 participants 0 participants 1 participants 1.3 (14.3) — 0.2 (—) Cycle 27, Day 1 Number Analyzed 2 participants 2 participants 3 participants −3.5 (25.3) −13.2 (6.6) −6.0 (9.6) Cycle 28, Day 1 Number Analyzed 3 participants 0 participants 1 participants 4.4 (13.4) — 2.6 (—) Cycle 29, Day 1 Number Analyzed 2 participants 2 participants 2 participants −2.8 (23.7) −11.0 (7.3) −3.7 (13.0) Cycle 30, Day 1 Number Analyzed 2 participants 0 participants 0 participants 9.0 (7.5) — — Cycle 31, Day 1 Number Analyzed 2 participants 2 participants 1 participants −4.8 (27.9) −15.6 (4.3) −12.9 (—) Cycle 32, Day 1 Number Analyzed 2 participants 0 participants 0 participants 10.3 (6.9) — — Cycle 33, Day 1 Number Analyzed 2 participants 2 participants 1 participants 0.5 (20.7) −13.5 (9.0) −12.9 (—) Cycle 34, Day 1 Number Analyzed 2 participants 0 participants 0 participants 13.5 (3.6) — — Cycle 35, Day 1 Number Analyzed 2 participants 2 participants 1 participants −2.5 (23.3) −11.0 (12.4) −12.9 (—) Cycle 36, Day 1 Number Analyzed 2 participants 0 participants 0 participants 7.5 (6.4) — — Cycle 37, Day 1 Number Analyzed 2 participants 2 participants 0 participants −5.3 (29.0) −13.6 (8.1) — Cycle 38, Day 1 Number Analyzed 2 participants 0 participants 0 participants 9.1 (5.2) — — Cycle 39, Day 1 Number Analyzed 2 participants 2 participants 1 participants −6.2 (25.9) −14.3 (8.5) −12.9 (—) Cycle 40, Day 1 Number Analyzed 1 participants 0 participants 0 participants 2.7 (—) — — Cycle 41, Day 1 Number Analyzed 1 participants 1 participants 1 participants −25.7 (—) −19.3 (—)

−12.9 (—) Cycle 42, Day 1 Number Analyzed 1 participants 0 participants 0 participants 4.6 (—) — — Cycle 43, Day 1 Number Analyzed 1 participants 1 participants 1 participants −20.4 (—) −19.9 (—) −12.9 (—) Cycle 44, Day 1 Number Analyzed 1 participants 0 participants 0 participants 4.3 (—) — — Cycle 45, Day 1 Number Analyzed 0 participants 0 participants 1 participants — — −12.3 (—) Cycle 46, Day 1 Number Analyzed 1 participants 0 participants 0 participants 4.6 (—) — — Cycle 47, Day 1 Number Analyzed 1 participants 1 participants 1 participants −6.8 (—) −16.8 (—) −12.9 (—) Cycle 48, Day 1 Number Analyzed 1 participants 0 participants 0 participants 2.4 (—) — — Cycle 49, Day 1 Number Analyzed 0 participants 1 participants 1 participants — −15.4 (—) −14.3 (—) Cycle 50, Day 1 Number Analyzed 1 participants 0 participants 0 participants 4.5 (—) — — Cycle 51, Day 1 Number Analyzed 1 participants 0 participants 1 participants −12.0 (—) — −12.9 (—) Cycle 52, Day 1 Number Analyzed 1 participants 0 participants 0 participants 6.0 (—) — — Cycle 53, Day 1 Number Analyzed 1 participants 0 participants 0 participants −19.2 (—) — — Cycle 54, Day 1 Number Analyzed 1 participants 0 participants 0 participants 4.9 (—) — — Cycle 55, Day 1 Number Analyzed 1 participants 0 participants 0 participants −16.8 (—) — — Cycle 56, Day 1 Number Analyzed 1 participants 0 participants 0 participants 1.8 (—) — — Cycle 57, Day 1 Number Analyzed 1 participants 0 participants 0 participants −17.6 (—) — — Cycle 58, Day 1 Number Analyzed 1 participants 0 participants 0 participants 5.4 (—) — — Cycle 59, Day 1 Number Analyzed 1 participants 0 participants 0 participants −12.7 (—) — — Cycle 60, Day 1 Number Analyzed 1 participants 0 participants 0 participants 4.2 (—) — — Cycle 61, Day 1 Number Analyzed 1 participants 0 participants 0 participants −19.3 (—) — — Cycle 62, Day 1 Number Analyzed 1 participants 0 participants 0 participants 4.4 (—) — — Cycle 63, Day 1 Number Analyzed 1 participants 0 participants 0 participants −18.0 (—) — — Cycle 67, Day 1 Number Analyzed 1 participants 0 participants 0 participants −21.9 (—) — — EOT Number Analyzed 10 participants 8 participants 10 participants −4.3 (11.7) −2.4 (10.9) 2.5 (11.9)

[0153] Change From Baseline in Percent Predicted Forced Expiratory Volume in 1 Second (FEV1) at Each Specified Time Points. FEV1 was the volume of air exhaled from the lungs in the first second of a forced expiration as measured by spirometer. Baseline value was defined as valid and last non-missing value obtained within 28 days prior to participant receiving first study medication. EOT visit was performed within 3 days after the participant's last dose of study drug. Timeframe: Baseline, Day 1 of Cycles 2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,29,30,31,32,33,34,35, 36,37,38, 39,40,41,43, 47,48,49,51,52,53, 54, 55,56, 57,58,60,61,62,63,67, EOT (i.e., anytime up to 64.2 months). Analysis was performed on mITT population. Here, ‘number analyzed’=participants with available data for each specified category. Here, ‘0’ in the number analyzed field signifies that none of the participants were available for the analysis at the specified time points. The data is shown in the table below.

TABLE-US-00023 TABLE 22 Change From Baseline in Percent Predicted Forced Expiratory Volume in 1 Second (FEV1) at Each Specified Time Points Cohort 1: Cohort 2: Cohort 3: Belumosudil Belumosudil Belumosudil 200 mg QD 200 mg BID 400 mg QD Overall Number of Participants Analyzed 17 16 21 Change From Baseline in Percent Predicted Forced Expiratory Volume in 1 Second (FEV1) at Each Specified Time Points Mean (Standard Deviation) Unit of measure: percent predicted FEV1 Cycle 2, Day 1 Number Analyzed 0 participants 0 participants 4 participants — — −4.8 (6.7) Cycle 3, Day 1 Number Analyzed 16 participants 14 participants 12 participants 1.1 (4.8) −1.8 (7.1) −1.5 (6.2) Cycle 4, Day 1 Number Analyzed 0 participants 0 participants 21 participants — — −0.2 (8.4) Cycle 5, Day 1 Number Analyzed 13 participants 11 participants 12 participants −3.3 (8.0) −5.0 (6.5) 0.5 (5.9) Cycle 6, Day 1 Number Analyzed 0 participants 0 participants 8 participants — — −0.9 (6.4) Cycle 7, Day 1 Number Analyzed 11 participants 9 participants 13 participants −3.5 (4.6) −2.6 (9.4) −0.9 (11.8) Cycle 8, Day 1 Number Analyzed 0 participants 1 participants 7 participants — 1.0 (—) −1.1 (8.0) Cycle 9, Day 1 Number

Analyzed 9 participants 8 participants 10 participants −1.7 (6.8) −5.9 (11.7) −3.0 (11.8) Cycle 10, Day 1 Number Analyzed 0 participants 2 participants 6 participants — −6.0 (8.5) 2.7 (3.9) Cycle 11, Day 1 Number Analyzed 7 participants 6 participants 8 participants −4.3 (5.2) −4.0 (8.5) −4.4 (15.8) Cycle 12, Day 1 Number Analyzed 1 participants 1 participants 7 participants −2.0 (—) −1.0 (—) 0.3 (3.6) Cycle 13, Day 1 Number Analyzed 7 participants 4 participants 8 participants −5.9 (9.3) −2.5 (14.7) −3.5 (13.2) Cycle 14, Day 1 Number Analyzed 1 participants 1 participants 7 participants 2.0 (—) 0.0 (—) −5.1 (9.1) Cycle 15, Day 1 Number Analyzed 6 participants 3 participants 8 participants −6.7 (11.7) −2.3 (5.1) −6.1 (12.6) Cycle 16, Day 1 Number Analyzed 1 participants 2 participants 4 participants 2.0 (—) −8.0 (15.6) −4.5 (7.3) Cycle 17, Day 1 Number Analyzed 6 participants 3 participants 7 participants −5.3 (9.1) −6.0 (7.2) −7.9 (15.5) Cycle 18, Day 1 Number Analyzed 0 participants 2 participants 3 participants — −7.5 (10.6) 4.0 (6.0) Cycle 19, Day 1 Number Analyzed 6 participants 3 participants 4 participants −5.2 (9.9) −6.3 (5.5) 0.5 (8.5) Cycle 20, Day 1 Number Analyzed 0 participants 2 participants 3 participants — −8.0 (7.1) 4.0 (10.4) Cycle 21, Day 1 Number Analyzed 5 participants 1 participants 21 participants −7.4 (10.6) 0.0 (—) −10.0 (19.8) Cycle 22, Day 1 Number Analyzed 0 participants 2 participants 2 participants — −11.0 (1.4) −6.0 (17.0) Cycle 23, Day 1 Number Analyzed 3 participants 2 participants 4 participants −4.3 (14.6) −12.5 (4.9) −4.8 (11.2) Cycle 24, Day 1 Number Analyzed 1 participants 1 participants 1 participants 2.0 (—) −18.0 (—) −19.0 (—) Cycle 25, Day 1 Number Analyzed 2 participants 2 participants 3 participants −11.0 (15.6) −12.5 (3.5) −5.0 (11.4) Cycle 26, Day 1 Number Analyzed 1 participants 0 participants 0 participants 0.0 (—) — — Cycle 27, Day 1 Number Analyzed 2 participants 2 participants 2 participants −6.5 (13.4) −17.0 (9.9) −10.0 (17.0) Cycle 29, Day 1 Number Analyzed 2 participants 2 participants 2 participants −0.5 (9.2) 17.0 (11.3) 0.0 (1.4) Cycle 30, Day 1 Number Analyzed 1 participants 0 participants 0 participants 3.0 (—) — — Cycle 31, Day 1 Number Analyzed 2 participants 2 participants 1 participants −3.5 (12.0) −19.5 (10.6) −4.0 (—) Cycle 32, Day 1 Number Analyzed 1 participants 0 participants 0 participants 1.0 (—) — — Cycle 33, Day 1 Number Analyzed 2 participants 2 participants 0 participants 5.0 (5.7) −1.0 (33.9) — Cycle 34, Day 1 Number Analyzed 1 participants 0 participants 0 participants 2.0 (—) — — Cycle 35, Day 1 Number Analyzed 17 participants 2 participants 1 participants 5.0 (0.0) −2.5 (30.4) −4.0 (—) Cycle 36, Day 1 Number Analyzed 1 participants 0 participants 1 participants 3.0 (—) — 5.0 (—) Cycle 37, Day 1 Number Analyzed 1 participants 1 participants 0 participants −1.0 (—) −22.0 (—) — Cycle 38, Day 1 Number Analyzed 1 participants 0 participants 0 participants 1.0 (—) — — Cycle 39, Day 1 Number Analyzed 2 participants 2 participants 1 participants 10.0 (2.8) −23.0 (11.3) −5.0 (—) Cycle 40, Day 1 Number Analyzed 1 participants 0 participants 0 participants −1.0 (—) — — Cycle 41, Day 1 Number Analyzed 1 participants 0 participants 0 participants 15.0 (—) — — Cycle 43, Day 1 Number Analyzed 1 participants 1 participants 1 participants 16.0 (—) −21.0 (—) −7.0 (—) Cycle 47, Day 1 Number Analyzed 1 participants 0 participants 1 participants 5.0 (—) — −5.0 (—) Cycle 48, Day 1 Number Analyzed 1 participants 0 participants 0 participants 3.0 (—) — — Cycle 49, Day 1 Number Analyzed 1 participants 0 participants 1 participants 8.0 (—) — −2.0 (—) Cycle 51, Day 1 Number Analyzed 1 participants 0 participants 0 participants 8.0 (—) — — Cycle 52, Day 1 Number Analyzed 1 participants 0 participants 0 participants 0.0 (—) — — Cycle 53, Day 1 Number Analyzed 1 participants 0 participants 0 participants 9.0 (—) — — Cycle 54, Day 1 Number Analyzed 1 participants 0 participants 0 participants 4.0 (—) — — Cycle 55, Day 1 Number Analyzed 1 participants 0 participants 0 participants 13.0 (—) — — Cycle 56, Day 1 Number Analyzed 1 participants 0 participants 0 participants 4.0 (—) — — Cycle 57, Day 1 Number Analyzed 1 participants 0 participants 0 participants 13.0 (—) — — Cycle 58, Day 1 Number Analyzed 1 participants 0 participants 0 participants 5.0 (—) — — Cycle 60, Day 1 Number Analyzed 1 participants 0 participants 0 participants 4.0 (—) — — Cycle 61, Day 1 Number Analyzed 1 participants 0 participants 0 participants 10.0 (—) — — Cycle 62, Day 1 Number Analyzed 1 participants 0 participants 0 participants 2.0 (—) — — Cycle 63, Day 1 Number Analyzed 1

participants 0 participants 0 participants 13.0 (—) — — Cycle 67, Day 1 Number Analyzed 1 participants 0 participants 0 participants 14.0 (—) — — EOT Number Analyzed 12 participants 10 participants 9 participants −1.4 (9.0) −10.1 (15.7) −7.4 (14.9)

[0154] Change From Baseline in Percent Predicted Forced Vital Capacity (FVC) at Each Specified Time Points. FVC was the total amount of air (in liters) exhaled from the lungs during the lung function test measured by spirometer which assessed the change in lung function related to the disease status. Baseline value was defined as valid and last non-missing value obtained within 28 days prior to participant receiving first study medication. EOT visit was performed within 3 days after the participant's last dose of study drug. Timeframe: Baseline, Day 1 of Cycles 2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,29,30,31,32,33,34,35, 36,37,38, 39,40,41,43, 47,48,49,51,52,53, 54, 55,56, 57,58,60,61,62,63,67, EOT (i.e., anytime up to 64.2 months). Analysis was performed on mITT population. Here, ‘number analyzed’=participants with available data for each specified category. Here, ‘0’ in the number analyzed field signifies that none of the participants were available for the analysis at the specified time points. The data is shown in the table below.

TABLE-US-00024 TABLE 23 Change From Baseline in Percent Predicted Forced Vital Capacity (FVC) at Each Specified Time Points Cohort 1: Cohort 2: Cohort 3: Belumosudil Belumosudil Belumosudil 200 mg QD 200 mg BID 400 mg QD Overall Number of Participants Analyzed 17 16 21 Change From Baseline in Percent Predicted Forced Vital Capacity (FVC) at Each Specified Time Points Mean (Standard Deviation) Unit of measure: percent predicted FVC Cycle 2, Day 1 Number Analyzed 0 participants 0 participants 21 participants — — −5.5 (9.9) Cycle 3, Day 1 Number Analyzed 16 participants 14 participants 12 participants 0.5 (3.8) −2.4 (6.0) −3.0 (6.7) Cycle 4, Day 1 Number Analyzed 0 participants 0 participants 6 participants — — −0.2 (8.6) Cycle 5, Day 1 Number Analyzed 13 participants 11 participants 12 participants −0.5 (7.1) −4.3 (5.2) 1.6 (6.3) Cycle 6, Day 1 Number Analyzed 0 participants 0 participants 8 participants — — 0.8 (9.5) Cycle 7, Day 1 Number Analyzed 11 participants 9 participants 13 participants −2.9 (5.2) −1.3 (6.4) 2.3 (9.7) Cycle 8, Day 1 Number Analyzed 0 participants 1 participants 7 participants — 2.0 (—) 0.4 (8.9) Cycle 9, Day 1 Number Analyzed 9 participants 8 participants 10 participants 0.4 (5.1) −2.9 (5.5) −0.8 (9.5) Cycle 10, Day 1 Number Analyzed 0 participants 2 participants 6 participants — −5.0 (8.5) 4.7 (4.9) Cycle 11, Day 1 Number Analyzed 7 participants 6 participants 8 participants −1.1 (7.3) −2.7 (5.6) −4.4 (12.0) Cycle 12, Day 1 Number Analyzed 1 participants 1 participants 7 participants 2.0 (—) 1.0 (—) 0.7 (5.8) Cycle 13, Day 1 Number Analyzed 7 participants 4 participants 8 participants −2.4 (7.9) −3.3 (15.4) −4.9 (9.8) Cycle 14, Day 1 Number Analyzed 1 participants 1 participants 7 participants 11.0 (—) 2.0 (—) −2.7 (7.1) Cycle 15, Day 1 Number Analyzed 6 participants 3 participants 8 participants −3.7 (10.4) −3.3 (5.5) −4.8 (11.5) Cycle 16, Day 1 Number Analyzed 1 participants 2 participants 4 participants 16.0 (—) −6.0 (19.8) −6.5 (6.5) Cycle 17, Day 1 Number Analyzed 6 participants 3 participants 7 participants −3.2 (6.3) −3.0 (11.8) −5.6 (12.8) Cycle 18, Day 1 Number Analyzed 0 participants 2 participants 3 participants — −7.5 (9.2) 4.0 (4.0) Cycle 19, Day 1 Number Analyzed 6 participants 3 participants 4 participants −2.3 (6.8) −5.3 (4.7) 0.8 (5.1) Cycle 20, Day 1 Number Analyzed 0 participants 2 participants 3 participants — −10.5 (2.1) −2.0 (5.6) Cycle 21, Day 1 Number Analyzed 5 participants 1 participants 5 participants −3.2 (8.1) −3.0 (—) −6.6 (17.0) Cycle 22, Day 1 Number Analyzed 0 participants 2 participants 2 participants — −11.0 (0.0) −6.0 (8.5) Cycle 23, Day 1 Number Analyzed 3 participants 2 participants 4 participants 0.0 (12.3) −11.0 (2.8) −1.8 (10.6) Cycle 24, Day 1 Number Analyzed 1 participants 1 participants 1 participants 4.0 (—) −13.0 (—) −15.0 (—) Cycle 25, Day 1 Number Analyzed 2 participants 2 participants 3 participants −7.0 (11.3) −10.5 (3.5) −1.3 (11.7) Cycle 26, Day 1 Number Analyzed 1 participants 0 participants 0 participants 4.0 (—) — — Cycle 27, Day 1 Number Analyzed 2 participants 2 participants 2 participants −2.0 (4.2) −18.0 (12.7) −4.0 (21.2) Cycle 29, Day 1 Number Analyzed 2 participants 1 participants 2 participants 2.5 (4.9) −11.0 (—) 6.0 (1.4) Cycle 30, Day 1 Number Analyzed 1

participants 0 participants 0 participants 4.0 (—) — — Cycle 31, Day 1 Number Analyzed 2 participants 2 participants 1 participants 1.5 (3.5) −15.5 (7.8) −4.0 (—) Cycle 32, Day 1 Number Analyzed 1 participants 0 participants 0 participants 2.0 (—) — — Cycle 33, Day 1 Number Analyzed 2 participants 2 participants 0 participants 11.0 (0.0) −17.5 (7.8) — Cycle 34, Day 1 Number Analyzed 1 participants 0 participants 0 participants 6.0 (—) — — Cycle 35, Day 1 Number Analyzed 2 participants 2 participants 1 participants 11.0 (5.7) −15.0 (11.3) −3.0 (—) Cycle 36, Day 1 Number Analyzed 1 participants 0 participants 1 participants 5.0 (—) — 2.0 (—) Cycle 37, Day 1 Number Analyzed 1 participants 1 participants 0 participants 7.0 (—) −24.0 (—) — Cycle 38, Day 1 Number Analyzed 1 participants 0 participants 0 participants 2.0 (—) — — Cycle 39, Day 1 Number Analyzed 2 participants 2 participants 1 participants 12.5 (0.7) −20.5 (12.0) −1.0 (—) Cycle 40, Day 1 Number Analyzed 1 participants 0 participants 0 participants 3.0 (—) — — Cycle 41, Day 1 Number Analyzed 1 participants 0 participants 0 participants 15.0 (—) — — Cycle 43, Day 1 Number Analyzed 1 participants 1 participants 1 participants 17.0 (—) −18.0 (—) −4.0 (—) Cycle 47, Day 1 Number Analyzed 1 participants 0 participants 1 participants 5.0 (—) — −2.0 (—) Cycle 48, Day 1 Number Analyzed 1 participants 0 participants 0 participants 5.0 (—) — — Cycle 49, Day 1 Number Analyzed 1 participants 0 participants 1 participants 6.0 (—) — 2.0 (—) Cycle 51, Day 1 Number Analyzed 1 participants 0 participants 0 participants 9.0 (—) — Cycle 52, Day 1 Number Analyzed 1 participants 0 participants 0 participants 3.0 (—) — — Cycle 53, Day 1 Number Analyzed 1 participants 0 participants 0 participants 8.0 (—) — — Cycle 54, Day 1 Number Analyzed 1 participants 0 participants 0 participants 5.0 (—) — — Cycle 55, Day 1 Number Analyzed 1 participants 0 participants 0 participants 13.0 (—) — Cycle 56, Day 1 Number Analyzed 1 participants 0 participants 0 participants 7.0 (—) — Cycle 57, Day 1 Number Analyzed 1 participants 0 participants 0 participants 14.0 (—) Cycle 58, Day 1 Number Analyzed 1 participants 0 participants 0 participants 7.0 (—) — — Cycle 60, Day 1 Number Analyzed 1 participants 0 participants 0 participants 8.0 (—) — — Cycle 61, Day 1 Number Analyzed 1 participants 0 participants 0 participants 12.0 (—) — — Cycle 62, Day 1 Number Analyzed 1 participants 0 participants 0 participants 5.0 (—) — — Cycle 63, Day 1 Number Analyzed 1 participants 0 participants 0 participants 12.0 (—) — — Cycle 67, Day 1 Number Analyzed 1 participants 0 participants 0 participants 14.0 (—) — — EOT Number Analyzed 12 participants 10 participants 9 participants −2.5 (10.3) −8.4 (9.2) −7.8 (14.7)

[0155] Change From Baseline in Percent Predicted Hemoglobin (HGB) Corrected Diffusing Capacity of Lung for Carbon Monoxide (DLco) at Each Specified Time Points. DLco is a measurement of the ability of the lungs to transfer gases from the air to the blood. Change from baseline in diffusing capacity of the lung for carbon monoxide (percent predicted hemoglobin level corrected) was reported for this measure. Baseline value was defined as valid and last non-missing value obtained within 28 days prior to participant receiving first study medication. EOT visit was performed within 3 days after the participant's last dose of study drug. Timeframe: Baseline, Day 1 of Cycles 2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,29,30,31,32,33,34,35, 36,37,38, 39,40,41,43, 47,48,49,51,52,53, 54, 55,56, 57,58,60,61,62,63,67, EOT (i.e., anytime up to 64.2 months). Analysis was performed on mITT population. Here, ‘number analyzed’=participants with available data for each specified category. Here, ‘0’ in the number analyzed field signifies that none of the participants were available for the analysis at the specified time points. The data is shown in the table below.

TABLE-US-00025 TABLE 24 Change From Baseline in Percent Predicted Hemoglobin (HGB) Corrected Diffusing Capacity of Lung for Carbon Monoxide (DLco) at Each Specified Time Points Cohort 1: Cohort 2: Cohort 3: Belumosudil Belumosudil Belumosudil 200 mg QD 200 mg BID 400 mg QD Overall Number of Participants Analyzed 17 16 21 Change From Baseline in Percent Predicted Hemoglobin (HGB) Corrected Diffusing Capacity of Lung for Carbon Monoxide (DLco) at Each Specified Time Points Mean (Standard Deviation) Unit of measure: Percent Predicted HGB

Corrected DLco Cycle 2, Day 1 Number Analyzed 0 participants 0 participants 4 participants — — −5.243 (9.830) Cycle 3, Day 1 Number Analyzed 14 participants 14 participants 9 participants 4.545 (22.991) −0.638 (7.059) −3.928 (9.492) Cycle 4, Day 1 Number Analyzed 0 participants 0 participants 5 participants — — 0.278 (9.683) Cycle 5, Day 1 Number Analyzed 12 participants 12 participants 9 participants 4.635 (23.989) −4.462 (23.621) −4.111 (9.138) Cycle 6, Day 1 Number Analyzed 0 participants 0 participants 7 participants — — −3.143 (10.385) Cycle 7, Day 1 Number Analyzed 10 participants 8 participants 7 participants 1.521 (19.836) 6.184 (9.436) −4.275 (11.464) Cycle 8, Day 1 Number Analyzed 0 participants 1 participants 6 participants — 3.554 (—) −3.787 (11.983) Cycle 9, Day 1 Number Analyzed 9 participants 8 participants 8 participants −4.514 (7.401) 2.570 (8.902) −2.540 (11.897) Cycle 10, Day 1 Number Analyzed 0 participants 2 participants 5 participants — 4.343 (3.144) 1.328 (8.887) Cycle 11, Day 1 Number Analyzed 6 participants 6 participants 7 participants −0.625 (7.262) 6.582 (10.695) −2.720 (10.920) Cycle 12, Day 1 Number Analyzed 1 participants 1 participants 6 participants 0.531 (—) 4.076 (—) −1.378 (6.364) Cycle 13, Day 1 Number Analyzed 7 participants 4 participants 7 participants −5.548 (12.175) 1.882 (7.522) 2.091 (13.290) Cycle 14, Day 1 Number Analyzed 1 participants 1 participants 6 participants 12.916 (—) 0.358 (—) 0.309 (11.651) Cycle 15, Day 1 Number Analyzed 6 participants 3 participants 7 participants 0.228 (15.731) 1.125 (5.927) −5.309 (11.514) Cycle 16, Day 1 Number Analyzed 1 participants 2 participants 4 participants 48.465 (—) −6.618 (15.443) −6.840 (15.053) Cycle 17, Day 1 Number Analyzed 6 participants 3 participants 6 participants −1.018 (9.226) 8.458 (6.229) −10.865 (13.346) Cycle 18, Day 1 Number Analyzed 0 participants 2 participants 3 participants — 15.543 (11.753) −3.174 (3.106) Cycle 19, Day 1 Number Analyzed 6 participants 3 participants 3 participants −2.293 (5.763) 1.824 (8.539) −2.020 (2.436) Cycle 20, Day 1 Number Analyzed 0 participants 1 participants 3 participants — −14.692 (—) −13.517 (5.936) Cycle 21, Day 1 Number Analyzed 5 participants 1 participants 4 participants −2.778 (8.187) −10.661 (—) −12.354 (12.800) Cycle 22, Day 1 Number Analyzed 0 participants 2 participants 2 participants — 3.347 (3.560) −17.222 (16.947) Cycle 23, Day 1 Number Analyzed 2 participants 2 participants 3 participants 0.354 (1.844) −15.184 (20.181) −2.219 (10.614) Cycle 24, Day 1 Number Analyzed 1 participants 1 participants 1 participants 6.945 (—) −18.095 (—) −11.430 (—) Cycle 25, Day 1 Number Analyzed 2 participants 2 participants 1 participants −4.461 (19.865) 6.289 (2.469) −13.392 (—) Cycle 26, Day 1 Number Analyzed 1 participants 0 participants 0 participants 4.715 (—) — — Cycle 27, Day 1 Number Analyzed 2 participants 2 participants 1 participants −8.047 (24.788) −9.914 (15.387) −11.154 (—) Cycle 29, Day 1 Number Analyzed 2 participants 2 participants 1 participants −6.701 (1.671) −18.814 (24.960) 8.613 (—) Cycle 31, Day 1 Number Analyzed 2 participants 2 participants 1 participants 2.343 (20.988) −0.800 (17.528) 10.833 (—) Cycle 32, Day 1 Number Analyzed 1 participants 0 participants 0 participants 5.586 (—) — — Cycle 33, Day 1 Number Analyzed 2 participants 2 participants 0 participants 9.901 (9.954) −5.962 (10.550) — Cycle 34, Day 1 Number Analyzed 1 participants 0 participants 0 participants 4.863 (—) — — Cycle 35, Day 1 Number Analyzed 2 participants 2 participants 1 participants 13.867 (1.309) −0.426 (6.677) 5.088 (—) Cycle 36, Day 1 Number Analyzed 1 participants 0 participants 1 participants 4.166 (—) — 10.372 (—) Cycle 37, Day 1 Number Analyzed 1 participants 1 participants 0 participants 9.306 (—) −19.228 (—) — Cycle 39, Day 1 Number Analyzed 2 participants 2 participants 1 participants 14.754 (0.649) −6.813 (12.810) 5.902 (—) Cycle 40, Day 1 Number Analyzed 1 participants 0 participants 0 participants 5.586 (—) — — Cycle 41, Day 1 Number Analyzed 1 participants 0 participants 0 participants 22.884 (—) — — Cycle 43, Day 1 Number Analyzed 1 participants 1 participants 1 participants 15.213 (—) 8.775 (—) 16.351 (—) Cycle 47, Day 1 Number Analyzed 1 participants 0 participants 0 participants 9.660 (—) — — Cycle 49, Day 1 Number Analyzed 1 participants 0 participants 0 participants −3.599 (—) — — Cycle 51, Day 1 Number Analyzed 1 participants 0 participants 0 participants 11.734 (—) — — Cycle 53, Day 1 Number Analyzed 1 participants 0 participants 0 participants 10.292 (—) — Cycle 55, Day 1 Number Analyzed 1 participants 0 participants 0 participants

16.550 (—) — — Cycle 61, Day 1 Number Analyzed 1 participants 0 participants 0 participants 17.682 (—) — — Cycle 62, Day 1 Number Analyzed 1 participants 0 participants 0 participants 4.170 (—) — — Cycle 63, Day 1 Number Analyzed 1 participants 0 participants 0 participants 26.215 (—) — — Cycle 67, Day 1 Number Analyzed 1 participants 0 participants 0 participants 41.384 (—) — — EOT Number Analyzed 9 participants 6 participants 7 participants −1.962 (11.426) 0.985 (5.919) −10.371 (14.208)

[0156] Change From Baseline in Percent Predicted Total Lung Capacity (TLC) at Each Specified Time Points. TLC is the volume of air in the lungs upon the maximum effort of inspiration. Baseline value was defined as valid and last non-missing value obtained within 28 days prior to participant receiving first study medication. EOT visit was performed within 3 days after the participant's last dose of study drug. Timeframe: Baseline, Day 1 of Cycles 2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,29,30,31,32,33,34,35, 36,37,38, 39,40,41,43, 47,48,49,51,52,53, 54, 55,56, 57,58,60,61,62,63,67, EOT (i.e., anytime up to 64.2 months). Analysis was performed on mITT population. Here, ‘number analyzed’=participants with available data for each specified category. Here, ‘0’ in the number analyzed field signifies that none of the participants were available for the analysis at the specified time points. The data is shown in the table below.

TABLE-US-00026 TABLE 25 Change From Baseline in Percent Predicted Total Lung Capacity (TLC) at Each Specified Time Points Cohort 1: Cohort 2: Cohort 3: Belumosudil Belumosudil Belumosudil 200 mg QD 200 mg BID 400 mg QD Overall Number of Participants Analyzed 17 16 21 Change From Baseline in Percent Predicted Total Lung Capacity (TLC) at Each Specified Time Points Mean (Standard Deviation) Unit of measure: Percent Predicted TLC Cycle 2, Day 1 Number Analyzed 0 participants 0 participants 4 participants — — −9.0 (13.4) Cycle 3, Day 1 Number Analyzed 14 participants 12 participants 12 participants 1.6 (11.9) 1.9 (8.5) −0.6 (14.8) Cycle 4, Day 1 Number Analyzed 0 participants 0 participants 6 participants — — 3.3 (14.0) Cycle 5, Day 1 Number Analyzed 13 participants 9 participants 10 participants −2.6 (16.8) −7.2 (10.5) −1.7 (11.2) Cycle 6, Day 1 Number Analyzed 0 participants 0 participants 7 participants — — −4.4 (11.6) Cycle 7, Day 1 Number Analyzed 11 participants 7 participants 12 participants −3.7 (6.6) −4.4 (6.3) −2.6 (13.4) Cycle 8, Day 1 Number Analyzed 0 participants 1 participants 6 participants — −5.0 (—) −0.2 (12.9) Cycle 9, Day 1 Number Analyzed 9 participants 8 participants 10 participants −2.9 (6.1) −6.0 (8.5) −0.9 (15.8) Cycle 10, Day 1 Number Analyzed 0 participants 2 participants 5 participants — −18.5 (6.4) 3.6 (14.7) Cycle 11, Day 1 Number Analyzed 7 participants 6 participants 8 participants 0.7 (4.3) −5.2 (11.2) −3.0 (19.7) Cycle 12, Day 1 Number Analyzed 1 participants 1 participants 6 participants −9.0 (—) 0.0 (—) −8.0 (14.2) Cycle 13, Day 1 Number Analyzed 7 participants 4 participants 8 participants −0.3 (7.1) −10.3 (18.7) −3.3 (17.6) Cycle 14, Day 1 Number Analyzed 1 participants 1 participants 6 participants 23.0 (—) −7.0 (—) −5.8 (16.5) Cycle 15, Day 1 Number Analyzed 6 participants 3 participants 7 participants −2.8 (10.8) −1.0 (5.6) −7.0 (12.0) Cycle 16, Day 1 Number Analyzed 1 participants 2 participants 4 participants −3.0 (—) −14.0 (12.7) −15.5 (9.5) Cycle 17, Day 1 Number Analyzed 5 participants 3 participants 7 participants −3.0 (6.2) −17.0 (11.4) −18.1 (15.6) Cycle 18, Day 1 Number Analyzed 0 participants 2 participants 3 participants — −16.0 (8.5) 0.0 (13.9) Cycle 19, Day 1 Number Analyzed 5 participants 3 participants 4 participants −4.6 (6.1) −7.7 (10.5) −7.0 (5.4) Cycle 20, Day 1 Number Analyzed 0 participants 2 participants 3 participants — −9.5 (16.3) −9.3 (15.4) Cycle 21, Day 1 Number Analyzed 3 participants 1 participants 5 participants 0.3 (9.3) −18.0 (—) −14.4 (24.0) Cycle 22, Day 1 Number Analyzed 0 participants 2 participants 2 participants — −18.5 (6.4) −21.0 (14.1) Cycle 23, Day 1 Number Analyzed 3 participants 2 participants 4 participants 0.0 (8.7) −21.0 (19.8) −2.8 (18.8) Cycle 24, Day 1 Number Analyzed 1 participants 1 participants 1 participants 0.0 (—) −15.0 (—) −34.0 (—) Cycle 25, Day 1 Number Analyzed 2 participants 2 participants 3 participants −3.0 (7.1) −19.5 (13.4) −6.3 (24.1) Cycle 26, Day 1 Number Analyzed 1 participants 0 participants 0 participants 0.0 (—) — — Cycle 27, Day 1

Number Analyzed 2 participants 2 participants 2 participants 5.5 (16.3) −24.0 (12.7) −14.5 (24.7) Cycle 29, Day 1 Number Analyzed 2 participants 2 participants 2 participants −1.0 (17.0) −27.5 (21.9) 12.0 (14.1) Cycle 30, Day 1 Number Analyzed 1 participants 0 participants 0 participants 7.0 (—) — — Cycle 31, Day 1 Number Analyzed 2 participants 1 participants 1 participants 7.5 (17.7) −36.0 (—) 17.0 (—) Cycle 32, Day 1 Number Analyzed 1 participants 0 participants 0 participants 1.0 (—) — — Cycle 33, Day 1 Number Analyzed 2 participants 1 participants 0 participants 14.0 (11.3) −39.0 (—) — Cycle 34, Day 1 Number Analyzed 1 participants 0 participants 0 participants 2.0 (—) — — Cycle 35, Day 1 Number Analyzed 2 participants 2 participants 1 participants 10.5 (7.8) −23.5 (16.3) 13.0 (—) Cycle 36, Day 1 Number Analyzed 1 participants 0 participants 1 participants 6.0 (—) — −6.0 (—) Cycle 37, Day 1 Number Analyzed 1 participants 1 participants 0 participants −7.0 (—) −41.0 (—) — Cycle 38, Day 1 Number Analyzed 1 participants 0 participants 0 participants 2.0 (—) — — Cycle 39, Day 1 Number Analyzed 2 participants 2 participants 1 participants 24.0 (28.3) −30.0 (21.2) 23.0 (—) Cycle 40, Day 1 Number Analyzed 1 participants 0 participants 0 participants 0.0 (—) — — Cycle 41, Day 1 Number Analyzed 1 participants 0 participants 0 participants 38.0 (—) — — Cycle 43, Day 1 Number Analyzed 1 participants 1 participants 1 participants 33.0 (—) −16.0 (—) 21.0 (—) Cycle 47, Day 1 Number Analyzed 1 participants 0 participants 1 participants 19.0 (—) — 25.0 (—) Cycle 48, Day 1 Number Analyzed 1 participants 0 participants 0 participants −13.0 (—) — — Cycle 49, Day 1 Number Analyzed 1 participants 0 participants 1 participants 5.0 (—) — 1.0 (—) Cycle 51, Day 1 Number Analyzed 1 participants 0 participants 0 participants 15.0 (—) — — Cycle 52, Day 1 Number Analyzed 1 participants 0 participants 0 participants 1.0 (—) — — Cycle 53, Day 1 Number Analyzed 1 participants 0 participants 0 participants 15.0 (—) — — Cycle 54, Day 1 Number Analyzed 1 participants 0 participants 0 participants 4.0 (—) — — Cycle 55, Day 1 Number Analyzed 1 participants 0 participants 0 participants 29.0 (—) — — Cycle 56, Day 1 Number Analyzed 1 participants 0 participants 0 participants 9.0 (—) — — Cycle 57, Day 1 Number Analyzed 1 participants 0 participants 0 participants 18.0 (—) — — Cycle 58, Day 1 Number Analyzed 1 participants 0 participants 0 participants 5.0 (—) — — Cycle 60, Day 1 Number Analyzed 1 participants 0 participants 0 participants −3.0 (—) — — Cycle 61, Day 1 Number Analyzed 1 participants 0 participants 0 participants 5.0 (—) — — Cycle 62, Day 1 Number Analyzed 1 participants 0 participants 0 participants −1.0 (—) — — Cycle 63, Day 1 Number Analyzed 1 participants 0 participants 0 participants 12.0 (—) — — Cycle 67, Day 1 Number Analyzed 1 participants 0 participants 0 participants 12.0 (—) — — EOT Number Analyzed 10 participants 7 participants 8 participants 5.2 (27.5) −2.4 (15.0) −12.6 (20.1)

[0157] Change From Baseline in Percent Predicted Residual Volume (RV) at Each Specified Time Points. RV is the volume of air remaining in the lungs after maximum forceful expiration. Baseline value was defined as valid and last non-missing value obtained within 28 days prior to participant receiving first study medication. EOT visit was performed within 3 days after the participant's last dose of study drug. Timeframe: Baseline, Day 1 of Cycles 2,3,4,5,6,7,8,9,10,11,12,13,14,15,16, 17,18, 19,20,21,22,23,24,25,26,27,29,30,31,32,33,34,35, 36,37,38, 39,40,41,43, 47,48,49,51,52,53, 54, 55,56, 57,58,60,61,62,63,67, EOT (i.e., anytime up to 64.2 months). Analysis was performed on mITT population. Here, ‘number analyzed’=participants with available data for each specified category. Here, ‘0’ in the number analyzed field signifies that none of the participants were available for the analysis at the specified time points. The data is shown in the table below.

TABLE-US-00027 TABLE 26 Change From Baseline in Percent Predicted Residual Volume (RV) at Each Specified Time Points Cohort 1: Cohort 2: Cohort 3: Belumosudil Belumosudil Belumosudil 200 mg QD 200 mg BID 400 mg QD Overall Number of 17 16 21 Participants Analyzed Change From Baseline in Percent Predicted Residual Volume (RV) at Each Specified Time Points Mean (Standard Deviation) Unit of measure: percent predicted RV Cycle 2, Number 0 participants 0 participants 4 participants Day 1 Analyzed — — −18.0 (30.1) Cycle 3, Number 14 participants 12 12 Day 1 Analyzed participants participants Cycle 4, Number 0.2 (22.2) −4.6 (18.8)

9.0 (34.4) Day 1 Analyzed 0 participants 0 participants 6 participants — — 17.8 (29.0) Cycle 5, Number 13 participants 11 10 Day 1 Analyzed participants participants 5.2 (24.5) −11.5 (26.9) −3.7 (29.8) Cycle 6, Number 0 participants 0 participants 7 participants Day 1 Analyzed — — −10.9 (37.5) Cycle 7, Number 11 participants 8 participants 12 Day 1 Analyzed participants 4.9 (29.1) −9.9 (17.1) −7.5 (33.0) Cycle 8, Number 0 participants 1 participants 6 participants Day 1 Analyzed — −28.0 (—) 2.5 (39.7) Cycle 9, Number 9 participants 8 participants 10 Day 1 Analyzed participants 6.4 (27.4) −19.9 (24.3) 0.1 (35.6) Cycle 10, Number 0 participants 2 participants 5 participants Day 1 Analyzed — −47.5 (0.7) 1.4 (38.2) Cycle 11, Number 7 participants 6 participants 8 participants Day 1 Analyzed 22.1 (29.6) −10.5 (28.3) 5.4 (38.0) Cycle 12, Number 1 participants 1 participants 6 participants Day 1 Analyzed −28.0 (—) −5.0 (—) −22.2 (49.9) Cycle 13, Number 7 participants 4 participants 8 participants Day 1 Analyzed 20.3 (19.9) −27.0 (35.6) 0.3 (32.6) Cycle 14, Number 1 participants 1 participants 6 participants Day 1 Analyzed 78.0 (—) −31.0 (—) −6.5 (36.3) Cycle 15, Number 6 participants 3 participants 7 participants Day 1 Analyzed 20.3 (27.4) −0.7 (18.1) −16.7 (22.3) Cycle 16, Number 1 participants 2 participants 4 participants Day 1 Analyzed 0.0 (—) −36.5 (13.4) −27.5 (31.9) Cycle 17, Number 5 participants 3 participants 7 participants Day 1 Analyzed 13.6 (27.8) −47.3 (25.1) −39.1 (26.2) Cycle 18, Number 0 participants 2 participants 3 participants Day 1 Analyzed — −42.0 (0.0) −7.3 (33.7) Cycle 19, Number 5 participants 3 participants 4 participants Day 1 Analyzed 5.4 (28.7) −19.7 (18.0) −23.5 (18.7) Cycle 20, Number 0 participants 2 participants 3 participants Day 1 Analyzed — −7.5 (37.5) −22.0 (44.3) Cycle 21, Number 3 participants 1 participants 5 participants Day 1 Analyzed 8.3 (10.0) −44.0 (—) −30.2 (51.2) Cycle 22, Number 0 participants 2 participants 2 participants Day 1 Analyzed — −33.0 (19.8) −41.0 (46.7) Cycle 23, Number 3 participants 1 participants 4 participants Day 1 Analyzed 0.3 (5.1) −72.0 (—) 1.5 (44.8) Cycle 24, Number 1 participants 1 participants 1 participants Day 1 Analyzed −4.0 (—) −17.0 (—) −78.0 (—) Cycle 25, Number 2 participants 2 participants 3 participants Day 1 Analyzed 1.0 (9.9) −34.0 (31.1) −23.3 (56.0) Cycle 26, Number 1 participants 0 participants 0 participants Day 1 Analyzed −3.0 (—) — — Cycle 27, Number 2 participants 2 participants 2 participants Day 1 Analyzed 19.5 (41.7) −39.5 (20.5) −41.0 (28.3) Cycle 29, Number 2 participants 1 participants 2 participants Day 1 Analyzed −13.0 (42.4) −13.0 (—) 17.5 (40.3) Cycle 30, Number 1 participants 0 participants 0 participants Day 1 Analyzed 21.0 (—) — — Cycle 31, Number 2 participants 1 participants 1 participants Day 1 Analyzed 15.0 (43.8) −93.0 (—) 61.0 (—) Cycle 32, Number 1 participants 0 participants 0 participants Day 1 Analyzed 5.0 (—) — — Cycle 33, Number 2 participants 1 participants 0 participants Day 1 Analyzed 14.5 (36.1) −70.0 (—) — Cycle 34, Number 1 participants 0 participants 0 participants Day 1 Analyzed −1.0 (—) — — Cycle 35, Number 2 participants 2 participants 1 participants Day 1 Analyzed 3.5 (36.1) −34.5 (33.2) 47.0 (—) Cycle 36, Number 1 participants 0 participants 1 participants Day 1 Analyzed 17.0 (—) — −20.0 (—) Cycle 37, Number 1 participants 1 participants 0 participants Day 1 Analyzed −54.0 (—) −70.0 (—) — Cycle 38, Number 1 participants 0 participants 0 participants Day 1 Analyzed 8.0 (—) — — Cycle 39, Number 2 participants 2 participants 1 participants Day 1 Analyzed 43.0 (89.1) −43.0 (42.4) 81.0 (—) Cycle 40, Number 1 participants 0 participants 0 participants Day 1 Analyzed −1.0 (—) — — Cycle 41, Number 1 participants 0 participants 0 participants Day 1 Analyzed 80.0 (—) — — Cycle 43, Number 1 participants 1 participants 1 participants Day 1 Analyzed 58.0 (—) −26.0 (—) 75.0 (—) Cycle 47, Number 1 participants 0 participants 1 participants Day 1 Analyzed 42.0 (—) — 87.0 (—) Cycle 48, Number 1 participants 0 participants 0 participants Day 1 Analyzed −50.0 (—) — — Cycle 49, Number 1 participants 0 participants 1 participants Day 1 Analyzed −14.0 (—) — −5.0 (—) Cycle 51, Number 1 participants 0 participants 0 participants Day 1 Analyzed 22.0 (—) — — Cycle 52, Number 1 participants 0 participants 0 participants Day 1 Analyzed −4.0 (—) — — Cycle 53, Number 1 participants 0 participants 0 participants Day 1 Analyzed 22.0 (—) — — Cycle 54, Number 1 participants 0 participants 0 participants Day 1 Analyzed 4.0 (—) — — Cycle 55, Number 1 participants 0 participants 0 participants Day 1 Analyzed 53.0 (—) — —

Cycle 56, Number 1 participants 0 participants 0 participants Day 1 Analyzed 17.0 (—) — — Cycle 57, Number 1 participants 0 participants 0 participants Day 1 Analyzed 18.0 (—) — — Cycle 58, Number 1 participants 0 participants 0 participants Day 1 Analyzed 4.0 (—) — — Cycle 60, Number 1 participants 0 participants 0 participants Day 1 Analyzed −20.0 (—) — — Cycle 61, Number 1 participants 0 participants 0 participants Day 1 Analyzed −18.0 (—) — — Cycle 62, Number 1 participants 0 participants 0 participants Day 1 Analyzed −8.0 (—) — — Cycle 63, Number 1 participants 0 participants 0 participants Day 1 Analyzed 6.0 (—) — — Cycle 67, Number 1 participants 0 participants 0 participants Day 1 Analyzed 2.0 (—) — — EOT Number 11 participants 8 participants 8 participants Analyzed 6.3 (24.3) 10.6 (34.9) −18.5 (32.6)

[0158] Pharmacokinetics (PK): Maximum Observed Plasma Concentration (Cmax) of Pharmacokinetics (PK): Maximum Observed Plasma Concentration (Cmax) of Belumosudil and Its Metabolites (KD025 m1 and KD025m2). Cmax was the maximum observed plasma concentration, obtained by a non-compartmental analysis. Cmax data for Belumosudil and its metabolites KD025 m1 and KD025m2 are reported in this outcome measure. Timeframe: Cycles 1 and 2: pre-dose (0 hour), 1, 2, 3, 4, 5, and 6 hours post-dose on Day 1. Analysis was performed on PK population which included all participants who received at least one dose of study drug and had at least 1 post-dose PK sample drawn. Here, ‘number analyzed’=participants with available data for each specified category. The data is shown in the table below.

TABLE-US-00028 TABLE 27 Pharmacokinetics (PK) Cmax Cohort 1: Cohort 2: Cohort 3: Belumosudil Belumosudil Belumosudil 200 mg QD 200 mg BID 400 mg QD Overall Number of 17 16 21 Participants Analyzed Pharmaco- kinetics (PK): Maximum Observed Plasma Concentration (Cmax) of Belumosudil and Its Metabolites (KD025m1 and KD025m2) Geometric Mean (Geometric Coefficient of Variation) Unit of measure: nanograms per milliliter Belumosudil: Number 16 16 21 Cycle 1 Analyzed participants participants participants Day 1 2500 (60.1%) 1400 (98.5%) 2960 (69.7%) Belumosudil: Number 16 14 16 Cycle 2 Analyzed participants participants participants Day 1 2020 (101%) 1890 (120%) 3270 (63.0%) KD025m1: Number 6 6 14 Cycle 1 Analyzed participants participants participants Day 1 44.4 (67.9%) 34.8 (58.8%) 63.9 (59.4%) KD025m1: Number 7 5 participants 11 Cycle 2 Analyzed participants participants Day 1 36.2 (43.0%) 45.0 (38.6%) 55.8 (82.1%) KD025m2: Number 15 14 17 Cycle 1 Analyzed participants participants participants Day 1 208 (93.1%) 99.2 (112%) 388 (82.3%) KD025m2: Number 15 13 16 Cycle 2 Analyzed participants participants participants Day 1 158 (150%) 145 (147%) 265 (154%)

[0159] Pharmacokinetics (PK): Time of the Maximum Observed Plasma Concentration (Tmax) of Belumosudil and Its Metabolites (KD025 ml and KD025m2). Tmax was defined as time to reach maximum observed plasma concentration, obtained by a non-compartmental analysis. Tmax data for Belumosudil and its metabolites KD025 ml and KD025m2 are reported in this outcome measure. Timeframe: Cycles 1 and 2: pre-dose (0 hour), 1, 2, 3, 4, 5, and 6 hours post-dose on Day 1. Analysis was performed on PK population. Here, ‘number analyzed’=participants with available data for each specified category. The data is shown in the table below.

TABLE-US-00029 TABLE 28 Pharmacokinetics (PK) Tmax Cohort 1: Cohort 2: Cohort 3: Belumosudil Belumosudil Belumosudil 200 mg QD 200 mg BID 400 mg QD Overall Number of 17 16 21 Participants Analyzed Pharmaco- kinetics: Time of the Maximum Observed Plasma Concentration (Tmax) of Belumosudil and Its Metabolites (KD025m1 and KD025m2) Median (Full Range) Unit of measure: hours Belumosudil: Number 16 16 21 Cycle 1 Analyzed participants participants participants Day 1 2.12 (0.98 to 3.43 (1.97 to 3.03 (1.85 to 5.00) 6.00) 6.00) Belumosudil: Number 16 14 16 Cycle 2 Analyzed participants participants participants Day 1 2.53 (0 to 2.47 (0 to 2.66 (1.00 to 4.87) 5.83) 6.02) KD025m1: Number 6 6 14 Cycle 1 Analyzed participants participants participants Day 1 2.50 (1.00 to 1.75 (1.08 to 1.98 (0.90 to 3.98) 5.95) 4.95) KD025m1: Number 7 5 11 Cycle 2 Analyzed participants participants participants Day 1 2.98 (1.17 to 2.05 (1.08 to 2.17 (1.00 to 3.03) 5.83) 4.03) KD025m2: Number 15 14 17 Cycle 1

Analyzed participants participants participants Day 1 2.82 (1.93 to 3.00 (2.00 to 2.98 (1.85 to 5.00) 6.00) 6.00) KD025m2: Number 15 13 16 Cycle 2 Analyzed participants participants participants Day 1 2.98 (0 to 2.00 (1.05 to 3.03 (1.98 to 3.93) 5.07) 6.02)

[0160] Pharmacokinetics (PK): The Area Under the Plasma Concentration Versus Time Curve From Time 0 to 6 Hours Post-dose (AUC0-6 hr) of Belumosudil and Its Metabolites (KD025 ml and KD025m2). AUC0-6 hr was defined as area under the plasma concentration versus time curve from time 0 to 6 hours post-dose, obtained by a non-compartmental analysis from the concentration-time data. AUC0-6 hr data for Belumosudil and its metabolites KD025 ml and KD025m2 are reported in this outcome measure. Timeframe: Cycles 1 and 2: pre-dose (0 hour), 1, 2, 3, 4, 5, and 6 hours post-dose on Day 1. Analysis was performed on PK population. Here, 'number analyzed'=participants with available data for each specified category. The data is shown in the table below.

TABLE-US-00030 TABLE 29 Pharmacokinetics (PK) AUCO-6 hr Cohort 1: Cohort 2: Cohort 3: Belumosudil Belumosudil Belumosudil 200 mg QD 200 mg BID 400 mg QD Overall Number of 17 16 21 Participants Analyzed Pharmaco- kinetics: The Area Under the Plasma Con- centration Versus Time Curve From Time 0 to 6 Hours Post-dose (AUC0-6 hr) of Belumosudil and Its Metabolites (KD025m1 and KD025m2) Geometric Mean (Geometric Coefficient of Variation) Unit of measure: hours* nanograms per milliliter Belumosudil: Number 16 16 21 Cycle 1 Analyzed participants participants participants Day 1 8350 4960 11500 (60.3%) (108%) (97.3%) Belumosudil: Number 16 14 16 participants Cycle 2 Analyzed participants participants 12000 Day 1 7090 (95.9%) 7190 (115%) (68.8%) KD025m1: Number 6 6 14 Cycle 1 Analyzed participants participants participants Day 1 140 (72.3%) 114 (60.8%) 216 (61.9%) KD025m1: Number 7 5 11 Cycle 2 Analyzed participants participants participants Day 1 123 (38.2%) 160 (31.3%) 178 (72.9%) KD025m2: Number 15 14 17 Cycle 1 Analyzed participants participants participants Day 1 565 (90.8%) 282 (125%) 1150 (97.1%) KD025m2: Number 15 13 16 Cycle 2 Analyzed participants participants participants Day 1 471 (145%) 513 (122%) 923 (144%)

Example 2: A Phase II Randomized Study of Belumosudil

Subject Eligibility

[0161] Eligible subjects were allogeneic hematopoietic cell transplant recipients aged ≥12 years with persistent cGVHD manifestations after receiving 2 to 5 prior systemic lines of therapy. Subjects were required to be receiving stable corticosteroid therapy for 2 weeks prior to screening and to have a Karnofsky or Lansky Performance Status Scale score ≥60. Certain concurrent immunosuppressive medications were allowed because drug-drug interactions were not anticipated. Subjects were excluded if they had a relapse of their underlying malignancy, had a forced expiratory volume in 1 second (FEV1)≤39% or an NIH lung symptom score of 3, had developed posttransplant lymphoproliferative disease, had liver transaminases (aspartate aminotransferase [AST] or alanine transaminase [ALT])>3 times the upper limit of normal, had a total bilirubin >1.5 times the upper limit of normal for any reason, or were currently receiving ibrutinib.

Study Design and Treatment

[0162] Screening for eligibility was conducted within 14 days of cycle 1 day 1. Treatment consisted of belumosudil 200 mg daily (Arm A) or 200 mg twice daily (Arm B) administered orally in subjects with cGVHD (FIG. **7**). Randomization was stratified (1:1) by cGVHD severity and prior exposure to ibrutinib. Belumosudil was administered continuously in 28-day treatment cycles until clinically significant progression of cGVHD or unacceptable toxicity. Progression was defined using an organ-specific cGVHD response assessment, as defined by the 2014 NIH Consensus Development Project on Criteria for Clinical Trials in cGVHD, referred to as the 2014 NIH Consensus Criteria. After ≥2 weeks on belumosudil, corticosteriod therapy could be tapered at the discretion of the investigator. Subjects who did not achieve a response after 12 cycles of belumosudil treatment should be withdrawn if in the Investigator's judgment there is no evidence of clinical benefit.

Study Endpoints

[0163] The primary endpoint was best ORR at any time, defined as the proportion of subjects who achieved complete response (CR) or partial response (PR) according to the 2014 NIH Consensus Criteria. All responses were assessed by the study site investigators. Secondary endpoints included duration of response (DOR), time to response, changes in LSS summary score, failure-free survival (FFS), corticosteroid dose reductions, and overall survival (OS). DOR was measured from the time of initial PR or CR until documented progression from best response of cGVHD, time from initial response to start of additional systemic cGVHD therapy, or death. The 7-day LSS summary score was calculated based on the developer recommendations and was compared with the score from baseline; an improvement ≥7 points was considered clinically meaningful. FFS was defined as the interval between the start of belumosudil and the addition of a new cGVHD Therapy, relapse, or NRM. The safety of belumosudil was evaluated by adverse event (AE) and serious AE (SAE) assessments. Relative dose intensity (RDI) was used as a surrogate measure of drug tolerability and was defined as actual dose intensity/planned dose intensity, where dose intensity was defined as the cumulative dose over the duration of exposure (mg/d). Actual dose intensity captured the sum of actual doses received over the duration of exposure and incorporated dose reductions and/or interruptions.

Statistical Analysis

[0164] The sample size was based on the primary efficacy end point (best ORR), with 1 planned interim analysis and a target ORR of 55%. With a target sample size of 63 subjects per treatment arm and an estimated 10% dropout rate, each treatment arm was estimated to have about 90% power to yield a 95% confidence interval (CI) of ORR that excluded 30% as the lower bound. Based on consultation with key opinion leaders, a 30% ORR was considered clinically meaningful in this heavily pretreated population with cGVHD and unmet medical needs. The Hochberg procedure was used for multiplicity adjustment for the primary end point of best ORR. The primary analysis was conducted using the modified intent-to-treat (mITT) population, defined as randomized subjects who received ≥1 dose of belumosudil. Interim, primary, and follow-up analyses were planned at about 2, 6, and 12 months, respectively, after 126 subjects were enrolled in the mITT population. Here, we report data from the 12-month analysis. CI was calculated using the Clopper-Pearson interval (exact) method.

Results

Subject Characteristics

[0165] A total of 132 subjects were enrolled in the clinical study. Overall, baseline demographics and clinical characteristics were comparable across treatment arms (Table 30). At enrollment, the median subject age was 56 years (range, 21-77). The median time from cGVHD diagnosis to enrollment was 28 months (range, 2-162). Thirty-one percent of subjects had moderate cGVHD at screening, and 67% had severe cGVHD, based on the 2014 NIH Consensus Criteria; 52% had involvement of >4 organs. Thirty-six percent of subjects had lung involvement at baseline, with 38% of these subjects having an NIH lung symptom score of 2. Subjects were previously treated with a median of 3 systemic lines of therapy. Seventy-two percent of subjects (n=79) had cGVHD refractory to their last systemic lines of therapy, 34% (n=45) had previously received ibrutinib, 29% (n=38) had previously received ruxolitinib, and 72% (n=95) had received ≥3 prior lines of therapy. The baseline median corticosteroid dose was 0.2 mg/kg per day (range, 0.03-1.07) of prednisone equivalent. The baseline mean corticosteroid dose was 0.25 mg/kg per day (range, 0.03-1.07) of prednisone equivalent.

TABLE-US-00031 TABLE 30 Baseline demographics and clinical characteristics Belumosudil Belumosudil 200 mg twice 200 mg daily daily Total Characteristic (n = 66) (n = 66) (N = 132) Age, median (range), y 53 (21-77) 57 (21-77) 56 (21-77) Males 42 (64) 33 (50) 75 (57) Indication for transplant AML 28 (42) 25 (38) 53 (40) ALL 7 (11) 12 (18) 19 (14) MDS 8 (12) 5 (8) 13 (10) CML 5 (8) 3 (5) 8 (6) Myelofibrosis 3 (5) 2 (3) 5 (4) CLL 2 (3) 2 (3) 4 (3) Non-Hodgkin 3 (5) 4 (7) 7 (5)

lymphoma and DLBCL Other 7 (11) 11 (17) 18 (14) Conditioning intensity Myeloablative 41 (62) 42 (64) 83 (63) Nonmyeloablative 22 (33) 22 (33) 44 (33) Unknown 3 (5) 2 (3) 5 (4) Stem cell source Peripheral blood 57 (86) 63 (96) 120 (91) Bone marrow 6 (9) 3 (5) 9 (7) Cord blood 0 0 0 Unknown 3 (5) 0 3 (2) HLA matching of donor/recipient Matched 57 (86) 62 (94) 119 (90) Partially matched 8 (12) 3 (5) 11 (8) Unknown 0 1 (2) 1 (1) Missing 1 (2) 0 1 (1) CMV-positive serostatus (donor/recipient) +/+ 23 (35) 16 (24) 39 (30) i) +/− 3 (5) 8 (12) 11 (8) ii) −/+− 18 (27) 17 (26) 35 (27) iii) −/− 13 (20) 16 (24) 29 (22) 1 unknown 3 (5) 3 (5) 6 (5) Unknown/unknown 5 (8) 6 (9) 11 (8) Missing 1 (2) 0 1 (1) iv) Time from 25 (2-162) 30 (4-144) 29 (2-162) cGVHD diagnosis to enrollment, median (range), mo NIH cGVHD severity* Severe 46 (70) 43 (65) 89 (67) Moderate 18 (27) 23 (35) 41 (31) Mild 2 (3) 0 2 (2) Organ involvement No. of organs 4 (0-7) 4 (2-7) 4 (0-7) involved, median (range) ≥4 organs involved 33 (50) 35 (53) 68 (52) Skin 55 (83) 55 (83) 110 (83) Joints/fascia 51 (77) 49 (74) 100 (76) Eyes 48 (73) 49 (74) 97 (74) Mouth 30 (46) 42 (64) 42 (64) Lungs 24 (36) 23 (35) 47 (36) Esophagus 19 (29) 12 (18) 31 (24) Upper GI 13 (20) 10 (15) 23 (17) Lower GI 6 (9) 7 (11) 13 (10) Liver 9 (14) 4 (6) 13 (10) Baseline global severity rating 0 1 (2) 0 1 (1) 1 0 0 0 2 2 (3) 1 (2) 3 (2) 3 3 (5) 2 (3) 5 (4) 4 8 (12) 3 (5) 11 (8) 5 6 (9) 8 (12) 14 (11) 6 12 (18) 14 (21) 26 (20) 7 11 (17) 20 (30) 31 (24) 8 19 (29) 14 (21) 33 (25) 9 4 (6) 3 (5) 7 (5) 10 0 1 (2) 1 (1) Median Karnofsky Performance Status 60-70 10 (15) 19 (29) 29 (22) 80-90 52 (79) 43 (65) 95 (72) 100 4 (6) 4 (6) 8 (6) Prior therapy characteristics Median prior LOTs, n 3 4 3 2 prior LOTs 23 (35) 14 (21) 37 (28) 3 prior LOTs 13 (20) 17 (26) 30 (23) 4 prior LOTs 15 (23) 14 (21) 29 (22) 5 prior LOTs 14 (21) 19 (29) 33 (25) ≥6 prior LOTs 1 (2) 2 (3) 3 (2) Refractory to prior LOT 44 (79) 35 (65) 79 (72) Prior systemic cGVHD therapy type CS (prednisone) 65 (99) 65 (99) 130 (99) Tacrolimus 40 (61) 42 (64) 82 (62) ECP 31 (47) 32 (49) 63 (48) Sirolimus 29 (44) 33 (50) 62 (47) Ibrutinib 22 (33) 23 (35) 45 (34) Ruxolitinib 20 (30) 18 (27) 38 (29) MMF 18 (27) 15 (23) 33 (25) Rituximab 15 (23) 13 (20) 28 (21) MTX 3 (5) 3 (5) 6 (5) Cyclosporine 4 (6) 3 (5) 5 (4) Imatinib 3 (5) 1 (2) 4 (3) Ixazomib 0 1 (2) 1 (1) Ofatumumab 0 1 (2) 1 (1) Concomitant systemic cGVHD therapy type† CS 65 (99) 66 (100) 131 (99) CNI 24 (36) 25 (38) 49 (37) ECP 17 (26) 22 (33) 39 (30) Sirolimus 17 (26) 18 (27) 35 (27) MMF 11 (17) 2 (3) 13 (10) Imatinib 1 (2) 1 (2) 2 (2) Rituximab 1 (2) 0 1 (1) Ruxolitinib 1 (2) 0 1 (1) Other systemic 9 (14) 13 (20) 22 (17) cGVHD therapies Prednisone- 0.20 0.20 0.20 equivalent dose at (0.03-0.95) (0.03-1.07) (0.03-1.07) enrollment, median (range), mg/kg/d Unless otherwise noted, data are n (%). Percentages may not add to 100% because of rounding. ALL, acute lymphocytic leukemia; AML, acute myelogenous leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myelogenous leukemia; CMV, cytomegalovirus; DLBCL, diffuse large B-cell lymphoma; GI, gastrointestinal; MDS, myelodysplastic syndrome; MMF, mycophenolate mofetil; MTX, methotrexate. *Disease severity was determined using NIH Global Severity of cGVHD scoring. †Classified as concomitant systemic cGVHD medications on cycle 1 day 1.

[0166] The CONSORT diagram (FIG. **7**) shows subject disposition. The median duration of treatment was 10 months (range, 0.4-22.0), and the median follow-up was 14 months (range, 1-22). Forty-four percent of subjects had received treatment for >12 months. At the time of the data analysis, 37% of subjects continued to receive belumosudil. Reasons for discontinuation included progression of cGVHD (n=21), voluntary withdrawal (n=13), AEs (n=16), physician decision (n=11), progression of underlying malignancy (n=5), death due to underlying malignancy or disease progression (n=4), other (n=7), and nonadherence to study drug (n=3).

Efficacy

[0167] The best ORR for belumosudil 200 mg daily and 200 mg twice daily was 74% (95% CI, 62-84) and 77% (95% CI, 65-87), respectively (Table 6). High ORRs (61-85%) were observed in all subgroups (FIG. **8**). Pooled responses across arms, unless stated otherwise. Efficacy of belumosudil was maintained, irrespective of prior ibrutinib (n=46) or ruxolitinib (n=38) therapy. The ORR for the subgroup with prior ruxolitinib therapy was 68% (95% CI, 51-83). The ORR (95% CI) for the subgroup with prior ibrutinib therapy was 74% (95% CI, 59-86).

TABLE-US-00032 TABLE 31 Efficacy end points in both arms within mITT population Belumosudil, Belumosudil, 200 mg 200 mg twice daily daily Total Efficacy end point (n = 66) (n = 66) (N = 132) ORR 49 (74) 51 (77) 100 (76) 95% Cl 62-84 65-87 68-83 ORR for responses 47 (71) 48 (73) 95 (72) occurring within 6 mo of treatment 95% Cl 59-82 60-83 64-80 CR 2 (3) 1 (2) 3 (2) PR 45 (68) 47 (71) 92 (70) ORR for responses 49 (74) 50 (76) 99 (75) occurring within 12 mo of treatment 95% Cl 62-84 64-86 67-82 CR 4 (6) 2 (3) 6 (5) PR 45 (68) 48 (73) 93 (71) Clinically significant improvement from baseline (LSS)* Overall 39 (59) 41 (62) 80 (61) Responder, n/N (%) 34/49 (69) 36/51 (71) 70/100 (70) Nonresponder, n/N (%) 5/17 (29) 5/15 (33) 10/32 (31) FFS at 6 mo (95% CI), % 73 (61-83) 76 (63-84) 75 (66-81) FFS at 12 mo (95% CI), % 57 (44-68) 56 (43-67) 56 (47-64) Proportion with CS reduction 42 (64) 44 (67) 86 (65) Median CS reduction 38 50 50 from baseline to greatest reduction, % Mean change in CS dose from baseline, % Overall −43 −48 −45 Responder −49 −58 −54 Nonresponder −22 −10 −16 CS discontinuation 13 (20) 15 (23) 28 21) Unless otherwise noted, data are n (%). *Changes in cGVHD symptom burden were measured using LSS. Clinically meaningful improvement in symptom burden was defined as a decrease ≥7 points in LSS score.

[0168] Best ORR, including CR, was evaluated across all affected organs. In the mITT population, organ-specific analyses demonstrated a best ORR of 37% in the skin, 42% in the eyes, 55% in the mouth, 39% in the liver, 26% in the lungs, 71% in the joints/fascia, 52% in the upper gastrointestinal (GI) tract, 69% in the lower GI tract, and 45% in the esophagus (FIG. **9**; Table 32). Overall, 7 subjects achieved CR in all affected organs. Of the 12 subjects with lung responses, 3 were scored as CR based on normalization of FEV1 (median increase, 23%; range, 18-25), with an additional 3 CRs based on a reduction in NIH lung symptom score from 1 to 0 in the absence of pulmonary function tests. Six additional subjects had PR, with a ≥10% increase in FEV1 (median increase for all subjects achieving PR, 10%; range, 0-15) or a reduction in NIH lung symptom score of 1 point when pulmonary function tests were unavailable. Of the 41 subjects with skin responses, 11 had a decrease in sclerotic features, 15 had a decrease in body surface area involvement, and 13 had improvements in body surface area involvement and sclerotic features. Two subjects had skin responses according to the investigator's clinical assessment, not according to the 2014 NIH Consensus Criteria.

TABLE-US-00033 TABLE 32 Summary of ORR by dose and organ system Belumosudil, Belumosudil, 200 mg QD 200 mg BID Total Organ system, n (%) (n = 66) (n = 66) (N = 132) Joints and fascia 51 (77) 49 (74) 100 (76) CR 10 (20) 10 (20) 20 (20) PR 28 (55) 23 (47) 51 (51) ORR 38 (75) 33 (67) 71 (71) Lower GI 6 (9) 7 (11) 13 (10) CR 4 (67) 4 (57) 8 (62) PR 0 1 (14) 1 (8) ORR 4 (67) 5 (71) 9 (69) Mouth 30 (45) 42 (64) 72 (55) CR 15 (50) 17 (41) 32 (44) PR 1 (3) 7 (17) 8 (11) ORR 16 (53) 24 (57) 40 (56) Upper GI 13 (20) 10 (15) 23 (17) CR 7 (54) 4 (40) 11 (48) PR 1 (8) 0 1 (4) ORR 8 (62) 4 (40) 12 (52) Esophagus 19 (29) 12 (18) 31 (23) CR 9 (47) 5 (42) 14 (45) PR 0 0 0 ORR 9 (47) 5 (42) 14 (45) Eyes 48 (73) 49 (74) 97 (73) CR 8 (17) 6 (12) 14 (14) PR 8 (17) 19 (39) 27 (28) ORR 16 (33) 25 (51) 41 (42) Liver 9 (14) 4 (6) 13 (10) CR 2 (22) 2 (50) 4 (31) PR 1 (11) 0 1 (8) ORR 3 (33) 2 (50) 5 (39) Skin 55 (83) 55 (83) 110 (83) CR 8 (15) 10 (18) 18 (16) PR 10 (18) 13 (24) 23 (21) ORR 18 (33) 23 (42) 41 (37) Lungs 24 (36) 23 (35) 47 (36) CR 4 (17) 2 (9) 6 (13) PR 3 (13) 3 (13) 6 (13) ORR 7 (29) 5 (22) 12 (26) BID, twice a day; CR, complete response; GI, gastrointestinal; ORR, overall response rate; PR, partial response; QD, every day.

[0169] The overall median time to response was 5 weeks (range, 4-66) (FIG. **10**A). Ninety-one percent of responses occurred within 6 months of treatment, with the remaining 9% of responses seen after 6 to 12 months of treatment. Fifty-nine percent of responders maintained responses for ≥20 weeks. The median DOR was 54 weeks in the responder population. The overall FFS rate was 75% (95% CI, 66-81) and 56% (95% CI, 47-64) at 6 and 12 months, respectively (FIG. **10**B). Overall, low rates of nonrelapse mortality (NRM) (7%) and relapse (3%) were observed. The most common failure event was the initiation of a new systemic cGVHD therapy (38%). The 2-year OS rate was 89% (95% CI, 82-93) (FIG. **10**C).

[0170] During treatment with belumosudil, 65% of subjects reduced their corticosteroid dose. The mean corticosteroid dose was reduced by 45% in the mITT population, with a mean corticosteroid dose reduction of 54% in responders. Twenty-one percent of subjects discontinued corticosteroid therapy. In addition, 22% of those subjects successfully discontinued calcineurin inhibitor (CNI) therapy, and 20% and 21% of subjects discontinued sirolimus and mycophenolate mofetil, respectively.

[0171] Clinically meaningful improvement (>7-point reduction) in 7-day LSS summary score from baseline with belumosudil 200 mg daily and 200 mg twice daily was observed in 59% and 62% of them ITT population, respectively. This improvement was observed in 69% and 71% of responders in the belumosudil 200 mg daily and 200 mg twice-daily arms, respectively, as well as in 29% and 33% of nonresponders, respectively.

Safety

[0172] Belumosudil was well tolerated, with a median RDI of 99.7%. Eighty-one percent of subjects received an RDI >95%. AEs were consistent with those expected in patients with cGVHD receiving corticosteroid therapy and other immunosuppressive therapies (ISTs) (Table 8). Thirty eight percent of subjects had >1 SAE; the most common was pneumonia (7%). The most common (≥5%) grade 3 or 4 AEs were pneumonia (8%), hypertension (6%), and hyperglycemia (5%). Twenty-four percent of subjects had increased liver function tests (LFTs); at baseline, 5% of subjects had increased g-glutamyltransferase (GGT), 5% of subjects had increased AST, 3% of subjects had increased ALT, 3% of subjects had increased LFTs, and 1% of subjects had increased bilirubin. The most common liver-related AE was increased GGT (12%). Of the 83 subjects who discontinued treatment, 28 (21%) discontinued because of overall AEs, 16 (12%) discontinued because of possible drug-related AEs, 5 (4%) discontinued because of progression of underlying malignant disease, and 21 (16%) discontinued because of progression of cGVHD. Fourteen subjects died during the study; 2 from multiorgan failure and infection possibly related to belumosudil, 2 from cardiac arrest, 2 from respiratory failure, 1 from hemothorax resulting from lung biopsy, 1 from acute myeloid leukemia recurrence, and 6 during long-term follow-up (LTFU) (>28 days after last dose). Grade ≥3 anemia was reported in 3% of subjects, neutropenia was reported in 2% of subjects, and thrombocytopenia was reported in 2% of subjects. There was 1 case of Epstein-Barr viremia that required treatment and 1 case of cytomegalovirus (CMV) reactivation; both were unrelated to belumosudil treatment.

TABLE-US-00034 TABLE 33 Safety overview Belumosudil, Belumosudil, 200 mg 200 mg twice daily daily Total AE (n = 66) (n = 66) (N = 132) Any AE 65 (99) 66 (100) 131 (99) Grade ≥3 AEs 37 (56) 34 (52) 71 (54) Drug-related AEs 49 (74) 40 (61) 89 (67) SAEs 27 (41) 23 (35) 50 (38) Deaths* 8 (12) 6 (9) 14 (11) Drug-related SAEs 5 (8) 2 (3) 7 (5) All grades in ≥20% of subjects (overall) Fatigue 30 (46) 20 (30) 50 (38) Diarrhea 23 (35) 21 (32) 44 (33) Nausea 23 (35) 18 (27) 41 (31) Cough 20 (30) 17 (26) 37 (28) Upper respiratory tract infection 17 (26) 18 (27) 35 (27) Dyspnea 21 (32) 12 (18) 33 (25) Headache 13 (20) 18 (27) 31 (24) Peripheral edema 17 (26) 13 (20) 30 (23) Vomiting 18 (27) 10 (15) 28 (21) Muscle spasms 13 (20) 13 (20) 26 (20) Grade ≥3 in ≥5% of subjects in either arm Pneumonia 6 (9) 4 (6) 10 (8) Hypertension 4 (6) 4 (6) 8 (6) Hyperglycemia 3 (5) 3 (5) 6 (5) Liver-related AEs 12 (18) 19 (29) 31 (24) GGT increased 6 (9) 10 (15) 16 (12) AST increased 5 (8) 8 (12) 13 (10) ALT increased 4 (6) 7 (11) 11 (8) Blood alkaline phosphatase 4 (6) 6 (9) 10 (8) increased Hypoalbuminemia 2 (3) 2 (3) 4 (3) Transaminases increased 1 (2) 1 (2) 2 (2) Bilirubin conjugated increased 1 (2) 0 1 (1) LFT increased 1 (2) 0 1 (1) All data are n (%). *Six subjects died during long-term follow-up (LTFU) (>28 days after last dose).

[0173] The study of the present Example 2 demonstrated promising efficacy and a favorable safety profile for belumosudil therapy in patients with steroid-refractory (SR) cGVHD. The study population, consisting of subjects with severe cGVHD with multiorgan involvement and fibrotic manifestations who were treated after a median of 3 prior systemic lines of therapy, achieved best

ORRs of 74% and 77% in the 200-mg daily and 200-mg twice-daily treatment arms, respectively.
[0174] Responses to belumosudil were sustained and clinically meaningful, regardless of response to prior treatment, severity of cGVHD, and number of organs involved. Responses were observed in all organs, which was clinically significant because CR and PR were achieved in difficult-to-treat organs, such as the lungs and liver, as well as in organs with fibrotic manifestations, such as the skin. cGVHD greatly impairs quality of life, especially in patients with fibrotic multiorgan involvement, which can be challenging to treat. The CR and PR observed, along with improvements in LSS, limited interactions, and lack of drug toxicities, are promising results that demonstrate that belumosudil treatment may have the potential to improve overall patient well-being. Seven subjects achieved CR in all affected organs. CR in all affected organs can be difficult to achieve in cGVHD because of the irreversible changes that occur in several organs, most notably the eyes and the lungs. The clinical benefit and tolerability of belumosudil therapy demonstrate the potential to halt the expected cycling of therapies for cGVHD seen in clinical practice. Responses were sustained in 59% of responders for ≥20 weeks at the 12-month analysis. The median DOR was 54 weeks in responders at the 12-month analysis.
[0175] In a patient population that is vulnerable to AEs and infections from immunosuppressive therapy (IST), belumosudil was well tolerated, allowing most subjects to remain on therapy to achieve clinically meaningful results and improvement in quality of life, which could be maintained with continued treatment. Only 12% of subjects discontinued belumosudil because of possible drug-related AEs. The median duration of treatment was 10 months (range, 0.4-22.0), and 37% of subjects continued to receive belumosudil after this time point, AEs were manageable, with few grade ≥3 SAEs attributable to belumosudil. The SAE rates were comparable between the two treatment arms. Many current cGVHD treatment options are immunosuppressive and, consequently, increase the risk of infection and may cause hematologic toxicities, including leukopenia, anemia, and thrombocytopenia. Grade ≥3 cytopenias were present in <4% of subjects, and there was only one report of cytomegalovirus (CMV) reactivation that was unrelated to belumosudil treatment. Cytopenias and CMV infection present as serious complications of cGVHD and cGVHD therapeutics; thus, the low rates of grade ≥3 cytopenias and CMV infection rates are promising features of the safety profile of belumosudil.
[0176] In the present study, all subjects received belumosudil. Requiring randomization to best available therapy was not deemed appropriate, because subjects had previously progressed following >2 systemic lines of therapy, where response rates were historically low. Indeed, subjects in this study had already attempted a median of three prior lines of best available therapy for cGVHD before enrollment, with the use of ECP (48%), ibrutinib (34%), ruxolitinib (29%), and rituximab (21%), among other agents. The best ORR was 75% in subjects who were refractory to their last lines of therapy.
[0177] Based on the similar efficacy and safety observed in this study, 200 mg daily is the preferred dosage for the treatment of SR cGVHD. Although the 200-mg twice-daily dose showed higher responses in certain organs, such as the skin, and slightly fewer AEs, the difference compared with the 200-mg daily dose was not deemed significant.
Example 3: Combined Analysis of Lung-Specific Responses in Subjects Treated with Belumosudil
Methods. Subjects and Study Design
[0178] Subjects enrolled in the clinical studies described in Examples 1 and 2 served as the population for the combined analysis.
[0179] Patients with BOS were identified as: 1) % predicted forced expiratory volume in 1 second (% FEV1) of £79% at enrollment, and 2) clinician attribution of lung disease due to cGVHD. Subjects were excluded from the study of Example 2 if they had a % FEV1<40% or an NIH lung symptom score of 3.
[0180] In Example 1, lung function assessments were conducted at baseline and on Day 1 of each cycle for patients with suspected of known lung involvement. In Example 2, lung function

assessments were conducted at baseline and at the time of response assessments: Day 1 of cycles 2-5 and then on Day 1 of every other cycle thereafter.

[0181] The severity of cGVHD was graded according to the 2014 NIH Consensus Criteria. (Jagasia M H, Greinix H T, Arora M, Williams K M, Wolff D, Cowen E W et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group report. Biol Blood Marrow Transplant 2015; 21 (3): 389-401 e381). Treatment responses were defined using an organ-specific cGVHD response assessment, as defined by the 2014 NIH Consensus Criteria. (Lee S J, Wolff D, Kitko C, Koreth J, Inamoto Y, Jagasia M 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 (6): 984-999). According to these criteria, a complete response (CR) in the lung is defined as normal % FEV1 after previous involvement or in the absence of PFTs, a NIH lung Symptom Score of 0 after previous involvement. Partial response (PR) in the lung is defined as an increase by 10% predicted absolute value of % FEV1 or in the absence of PFTs, a decrease in NIH Lung Symptom Score by 1 or more points. Progression of lung disease is defined as a decrease by 10% predicted absolute value of % FEV1 or in the absence of PFTs, an increase in NIH Lung Symptom Score by 1 or more points, except 0 to 1.

[0182] The analysis of the present example evaluated the treatment effect of belumosudil in subjects with BOS, given the unique mechanism of ROCK2 inhibition to potentially address both the inflammatory and fibrotic physiology of BOS. (Kitko C L, White E S, Baird K. Fibrotic and sclerotic manifestations of chronic graft-versus-host disease. Biol Blood Marrow Transplant 2012; 18 (1 Suppl): S46-52). Furthermore, multiple lung-specific metrics were analyzed in order to better characterize longitudinal changes in pulmonary function and patient symptoms.

Statistical Analysis

[0183] Baseline characteristics were reported descriptively. Univariable and multivariable logistic regression analysis was performed to investigate clinical factors (listed in Table 1) that were associated with NIH lung response. Correlation analysis was performed to assess correlation among lung response metrics. All testing was two-sided at the significance level of 0.05. All analyses were performed using SAS 9.3 (SAS Institute Inc., Cary, NC), and R v3.5.2 (the CRAN project).

Results. Subject Characteristics

[0184] A total of 66 subjects with BOS were identified from the clinical studies described in Examples 1 and 2. Six subjects were excluded from this analysis for not having a subsequent pulmonary function test evaluation beyond baseline and one subject was reclassified as not having BOS. Of the 59 evaluable subjects, 17 (29%) were enrolled in the study described in Example 1 and 42 (71%) were enrolled in the study described in Example 2. The dose of belumosudil was either 200 mg daily (n=27, 46%), 200 mg twice daily (n=23, 39%), or 400 mg daily (n=9, 15%).

[0185] The baseline demographics and clinical characteristics are shown in Table 34. The median age at enrollment was 42.5 years (range, 26-77). Allogeneic HCT was predominantly performed with myeloablative conditioning (n=44, 75%) and peripheral blood stem cells (n=54, 92%) from an HLA-matched donor (n=53, 90%). The median time from cGVHD diagnosis to enrollment was 22 months (range, 1-161). NIH cGVHD global severity score at enrollment was moderate (n=11, 19%) or severe (n=48, 81%). Most subjects (n=39, 66%) had at least 4 organs involved at enrollment. The median number of prior lines of systemic therapy was 3 (range, 1-6). Overall cGVHD response to the line of systemic therapy prior to enrollment was partial response (n=12, 20%), stable disease (n=25, 42%), progressive disease (n=12, 20%) or unknown (n=10, 17%). The median number of cycles of belumosudil therapy received on trial was 14 (range, 1-57). At the time of analysis, 16 subjects remained on therapy. The reason for belumosudil discontinuation included: progressive cGVHD (n=18), adverse event (n=8), underlying disease relapse (n=6), subject withdrawal (n=4),

physician discretion (n=4), noncompliance (n=2), and death (n=1). Thirty-one subjects (53%) experienced at least 1 respiratory infection (any grade) while on treatment, with 11 subjects experiencing 32 episodes. These infections were categorized as upper respiratory infections (n=33) or pneumonia (n=13). Eleven subjects experienced .sup.33 grade respiratory infection, for which belumosudil treatment was interrupted or discontinued in 6 cases. With a median follow-up among survivors of 27 months (range, 1.8-55), the 2-year overall survival is 82% (95% CI: 70, 90).
TABLE-US-00035 TABLE 34 Baseline demographics and clinical characteristics Characteristic Value Number of subjects 59 Age, median (range), y 49 (26-77) Sex, n (%) Male 33 (56) Female 26 (44) HLA matching of donor/recipient, n (%) Matched 53 (90) Partially matched 6 (10) Conditioning intensity, n (%) Myeloablative 44 (75) Nonmyeloablative 13 (22) Unknown 2 (3) Stem cell source, n (%) Peripheral blood 54 (92) Bone marrow 4 (7) Unknown 1 (1) Median time from cGVHD to enrollment 22 (1-161) (range), m Clinical trial enrollment, n (%) KD025-208 17 (29) KD025-213 42 (71) Belumosudil dose, n (%) 200 mg daily 27 (46) 200 mg twice daily 23 (39) 400 mg daily 9 (15) NIH cGVHD global severity, n (%) Moderate 11 (19) Severe 48 (81) Number of organs involved, n (%) <4 20 (34) ≥4 39 (66) Median lines of prior therapy (range), n 3 (1-6) Response to last systemic therapy prior to enrollment, n (%) Partial response 12 (20) Stable disease 25 (42) Progressive disease 12 (20) Unknown 10 (17) Median number of cycles of belumosudil 14 (1-57) therapy (range), n NIH lung score at baseline, n (%) 1 (FEV1 60-79%) 30 (51) 2 (FEV1 40-59%) 23 (39) 3 (FEV1 <40%) 6 (10) Abbreviations: cGVHD: chronic graft-versus-host disease; FEV1: forced expiratory volume in the first second; m: months; n: number; NIH: National Institutes of Health; y: year;
BOS Responses According to NIH Criteria
TABLE-US-00036 TABLE 35 Definitions of lung metrics Categorized Metric Definition Measurements Best NIH Best response by 2014 NIH Complete response (CR) response response criteria (using Partial response (PR) % FEV1 or NIH symptom No response (NR) score in the absence of PFTs) Best NIH Best response by 2014 NIH Complete response (CR) response by PFT response criteria (using Partial response (PR) % FEV1 definitions alone) No response (NR) Best NIH lung Best NIH lung score 0 score achieved, defined by 2014 1 NIH criteria 2 3 Best NIH lung Best NIH lung symptom 0 symptom score achieved, defined by 1 score 2014 NIH criteria 2 3 Best %FEV1 Best absolute improvement ≥10% response in % FEV1 as compared to baseline 1-<10% ≤0% Best % Best relative improvement ≥10% improvement in in FEV1 (L) compared to 1-<10% FEV1 in L baseline ≤0% Unknown Best improvement Best absolute improvement ≥200 in mL in FEV1 (mL) compared to 1-200 baseline ≤0 Unknown Best improvement Best absolute improvement ≥20 decrease Lee lung in Lee Symptom Score for 10-15 decrease score Lung, as compared to 5 decrease baseline No change or increase
[0186] Patients with BOS had a % predicted forced expiratory volume in 1 second (% FEV1) of £79% at enrollment and clinician attribution of lung disease due to cGVHD. The NIH cGVHD lung score at enrollment was 1 (n=30, 59%), 2 (n=23, 39%), or 3 (n=6, 10%). According to NIH response criteria, the best ORR for pulmonary cGVHD was 32% (PR 17%, CR15%) as shown in FIG. **17**. The median time to first NIH lung response was 5 cycles (range, 3-39), while the median time to best NIH lung response was 7 cycles (range, 3-41). In 3 of the 19 responders, subjects met NIH criteria for lung progression (median 4 cycles; range, 3-7) before later meeting criteria for response (median 11 cycles; range, 4-21). The trial described in Example 2 was designed to allow subjects to continue therapy until clinically meaningful progression occurred, thus permitting continued administration of belumosudil.
[0187] The NIH response criteria are based on % FEV1 or in the absence of PFTs, a NIH Lung Symptom Score. The NIH lung response was defined by the measurement of % FEV1 alone for 12 subjects (63%). In the absence of an % FEV1, the NIH symptom score was used to define NIH response in 5 subjects (26%). In 2 subjects, the NIH response was upgraded from a PR (according to % FEV1) to CR based on the NIH symptom score. When evaluating NIH response with PFTs

alone, the best ORR for lung cGVHD was 24% (PR 14%, CR 10%).

BOS Responses According to Evaluation of FEV1

[0188] The trajectory of all % FEV1 evaluations collected on study are shown in FIG. **16**. The best change in % FEV1 from baseline is shown in FIG. **12**. Twenty-three subjects (39%) experienced .sup.3 5% absolute improvement in % FEV1 and 13 subjects (22%) experienced .sup.3 10% absolute improvement in % FEV1 from baseline while on treatment with belumosudil. A best absolute improvement in % FEV1 of .sup.3 5% from baseline was observed in subjects regardless of baseline NIH lung score (Score 1 (n=17, 57%); Score 2 (n=3, 13%); Score 3 (n=3, 50%). An absolute improvement in % FEV1 of .sup.3 5% from baseline was observed in 84% of responders by NIH criteria and 18% of non-responders, respectively. All 13 subjects with .sup.3 10% absolute improvement in % FEV1 were responders by NIH criteria (per definition). For subjects with a best improvement in % FEV1 by .sup.3 5%, 14 of the 23 responses were maintained over two consecutive FEV1 evaluations. For subjects with a best improvement in % FEV1 by .sup.3 10%, 9 of the 13 responses were maintained over two consecutive FEV1 evaluations.

[0189] The absolute FEV1 measurement was recorded for subjects enrolled in the study of Example 2 only. Fifteen subjects (36%) experienced at least a 200 mL improvement in FEV1 from baseline during treatment with belumosudil. This improvement was observed in subjects with a baseline lung score of 1 (n=10, 41%) or 2 (n=5, 31%) only. A 200 mL improvement in FEV1 from baseline was observed in 66% of responders by NIH criteria and 19% of non-responders, respectively. Nine of these 15 responses were maintained over two consecutive FEV1 evaluations.

Lee Symptom Scale Scores for Lung

[0190] The best change in the LSS scores for lung from baseline is shown in FIG. **13**. Following the methodology used for the LSS, we identified a 10-point difference (half a standard deviation from baseline scores) as being a clinically meaningful organ-specific change in this dataset. (Lee S et al. Development and validation of a scale to measure symptoms of chronic graft-versus-host disease. Biol Blood Marrow Transplant 2002; 8 (8): 444-452; Teh C et al. Reliability and Validity of the Modified 7-Day Lee Chronic Graft-versus-Host Disease Symptom Scale. Biol Blood Marrow Transplant 2020; 26 (3): 562-567.) Forty subjects (68%) experienced a clinically meaningful improvement (10-point reduction) in the LSS lung score. Clinically meaningful improvements were observed in subjects regardless of baseline NIH lung score (Score 1 (n=20, 66%); Score 2 (n=14, 61%); Score 3 (n=6, 100%). A clinically meaningful improvement was observed in 68% of responders by NIH criteria and 68% of non-responders, respectively.

Analysis of Subgroups and Predictors of Response

[0191] There was a correlation between response and baseline NIH lung score. The best ORR was 50% (PR 23%, CR 27%) for baseline NIH lung score 1, 17% (PR 13%, CR 4%) for baseline NIH lung score 2, and 0% for NIH lung score 3 (Table 36).

TABLE-US-00037 TABLE 36 Lung-specific NIH response according to lung score at baseline. NIH Lung Score at Number of baseline subjects PR rate CR rate Best ORR 1 30 23% 27% 50% (7 of 30) (8 of 30) (15 of 30) 2 23 13% 4% 17% (3 of 23) (1 of 23) (4 of 23) 3 6 0% 0% 0% (0 of 6) (0 of 6) (0 of 6) Total 17% 15% 32% (10 of 59) (9 of 59) (19 f 59) Abbreviations: CR: complete response; NIH: National Institutes of Health; ORR: overall response rate; PR: partial response

[0192] Logistic regression analysis was performed to identify clinical factors that were associated with lung-specific responses according to NIH criteria (Table 37). Univariable analysis identified male sex, lower baseline NIH cGVHD lung score, and overall cGvHD PR to last treatment prior to belumosudil as predictors of response. These variables remained significant in multivariable analysis (male sex, OR 14.07, p=0.0037; NIH lung score 1, OR 5.65, p=0.028; PR to prior line of therapy, OR 7.89, p=0.024).

TABLE-US-00038 TABLE 37 Logistic regression analysis for predictors of NIH lung response Univariable Multivariable p- p- OR 95% CI value OR 95% CI value Belumosudil 200 mg QD vs 1.67 0.49 5.62 0.41 dose 200 mg BID 400 mg QD vs 1.42 0.27 7.52 0.68 200 mg BID Age <50 vs

≥50 0.90 0.30 2.69 0.85 Sex Male vs 7.22 1.81 28.8 0.005 14.07 2.36 83.70 0.0037 Female HLA donor match Partially 2.31 0.42 12.7 0.34 matched vs Matched Response to last PR vs 4.36 1.11 17.2 0.036 7.89 1.31 47.71 0.024 systemic therapy no PR Conditioning MAC vs 3.14 0.62 16.0 0.17 Intensity NMA NIH severity at Moderate vs 3.23 0.84 12.40 0.088 2.80 0.50 15.79 0.24 enrollment Severe Number of organs ≥4 vs <4 1.68 0.50 5.61 0.4 involved at enrollment NIH lung score 1 vs 2 4.33 1.32 16.6 0.023 at enrollment 3 vs 2 0.33 0.002 3.85 0.5 NIH lung score 1 vs (2 or 3) 5.67 1.63 19.70 0.006 5.65 1.35 29.60 0.028 at enrollment Time from <24 vs ≥24 0.73 0.24 2.19 0.57 cGVHD to <36 vs ≥36 1.35 0.44 4.13 0.6 enrollment in months Abbreviations: BID: twice daily; cGVHD: chronic graft-versus-host disease; CI: confidence interval; HLA: human leukocyte antigen; MAC: myeloablative conditioning; NIH: National Institutes of Health; NMA: non-myeloablative; OR: odds ratio; PR: partial response; QD: daily

Correlation Between Metrics for Lung-Specific Response

[0193] Correlations between multiple metrics for BOS response were investigated (NIH criteria, NIH PFT response criteria, NIH lung symptom score, absolute improvement in FEV1, LSS score for lung; definitions are provided in Table 35). A heatmap demonstrating best changes in lung response metrics in 59 patients is shown in FIG. **14**. When examining the association between NIH lung score (score 0-3) and NIH lung symptom score (score 0-3), 24 pairs (41%) are concordant and 35 pairs (59%) are discordant. The NIH lung symptom score is lower than NIH lung score in 32 of 35 discordant pairs. In addition, LSS lung scores are not correlated with other metrics. For best lung response by NIH criteria, 12 of 19 (63.2%) responders and 27 of 40 (67.5%) non-responders (p=0.77) had at least 10 point reduction in LSS lung score. For best improvement in % FEV1, 14 of 23 (61%) with 35% and 25 of 36 (69%) with <5% % FEV1 showed clinically meaningful improvement in LSS lung score (p=0.58) (FIG. **13**).

[0194] To further assess correlation among metrics, measurements from all timepoints captured while on treatment were aggregated. Of 583 paired samples between NIH lung score (based on % FEV1) and NIH symptom score, 285 pairs (49%) were concordant and 295 pairs (51%) were discordant. Among discordant pairs, 266 pairs had lower NIH lung symptom scores and 29 pairs had higher NIH lung symptom score (FIG. **15**A), indicating NIH lung symptom score largely overestimates the response in subjects with predominantly less advanced disease. As expected, FEV1 in liter is better associated with % FEV1 and NIH lung score than with NIH lung symptom score (FIGS. **15**G, **15**B and **15**D). For example, no paired samples with NIH lung score 0 had FEV1<2L, whereas 31 of 99 paired samples with NIH lung symptom score 0 had FEV1<2L. LSS lung score is largely dissociated with NIH lung score 31 and NIH lung symptom score in general (FIGS. **15**E and **15**F). Most of paired samples between % FEV1 and LSS lung score fall below the diagonal line (FIG. **15**D) and there was a dissociation between FEV1 in liter and LSS lung score (FIG. **15**F).

[0195] The discordance observed between the NIH lung score (based on % FEV1) and the NIH symptom score suggests that the symptom score largely overestimates the PFT response in subjects with predominantly less advanced disease. Additionally, the LSS lung score is largely dissociated with NIH lung score 31 and NIH lung symptom score in general.

[0196] In this combined analysis of the studies of Examples 1 and 2, belumosudil was associated with a best ORR of 32% for BOS, according to 2014 NIH Response Criteria, in a population with predominantly less advanced disease. Response rates were inversely proportional to NIH cGVHD lung score, with highest response rates for subjects with baseline lung score of 1. No responses were observed for subjects with a baseline lung score of 3. Furthermore, both lower baseline NIH cGVHD lung scores and overall cGVHD partial response to previous line of systemic therapy prior to enrollment were associated with higher rates of organ-specific response in multivariable analysis. This highlights the importance of initiating treatment for patients with early stages of disease, as more advanced disease may have irreversible fibrotic change and lung destruction. In subjects with responses, the median time to best response was 7 cycles (range, 3-41), suggesting

that BOS, as compared to inflammatory-like manifestations of cGVHD, may require longer periods of treatment to achieve responses. While on treatment, the trajectory of FEV1 measurements is rarely linear. As noted in this analysis, only 60-70% of 5% or 10% improvements in absolute % FEV1 are achieved on consecutive evaluations. Nonetheless, the responses in FEV1 suggest a clinically meaningful improvement in lung function for a subset of subjects with earlier forms of BOS.

[0197] The present analysis did not identify a significant correlation between measurements of FEV1 (% FEV1 or FEV1 in L) and symptom measures (NIH Symptom Score or LSS lung score) in predominantly mild or moderate disease, raising questions about such metrics can best be integrated when evaluating treatment responses. First symptoms are usually a late sign of BOS and may not manifest until a more significant decrease in pulmonary function has occurred. Thus, the NIH response criteria use of the NIH symptom score in the absence of FEV1 measurement may lead to an overestimation of response, especially in patients with less advanced disease. In this data set, the NIH Symptom Score was used to define or upgrade clinical response in 7 of the 19 subjects (37%) who achieved a NIH response. Additionally, it may be that the clinical meaning of symptoms scores is dependent on the clinical setting. For example, in BOS, symptom measures may carry more weight in patients with more advanced disease, in which significant FEV1 response is less likely. Given the limited size of lack of standardized follow-up in many cGVHD data sets, it remains unknown how individual metrics (PFT, symptoms) and other measurements (functional assessments, biological markers) can be integrated to refine response criteria for BOS.

[0198] The data of the present example show that belumosudil is associated with lung-specific clinical responses for subjects with mild to moderate BOS, including, but not limited to, early BOS.

[0199] Example 4: This example describes a Phase III study to evaluate the efficacy of oral belumosudil in adult participants with chronic lung allograft dysfunction (CLAD) following bilateral lung transplantation

[0200] This study will evaluate the efficacy and safety of belumosudil treatment in male or female participants ≥18 years of age with CLAD Stages 1 or 2, at least 1 year post bilateral lung transplantation.

Subject Eligibility

[0201] Eligible patients are participants at least 18 years of age, who are recipients of bilateral lung transplant and have evidence of progressive CLAD Stages 1 and 2 (forced expiratory volume in 1 second (FEV1) from >50% to 80% of post-transplant peak) with concomitant azithromycin therapy and standard-of-care regimen of immunosuppression.

[0202] Inclusion Criteria. Participants are eligible to be included in the study only if all of the following criteria apply. Participant must be at least 18 years of age at the time of signing the informed consent. Participant type and disease characteristics: Participant ≥1 year post bilateral lung transplant at the time of screening. Participants diagnosed with CLAD within 9 months prior to screening. Participants presenting with CLAD Stage 1 or 2: FEV1 from >50% to 80% of PTBL at screening and at randomization. Participants presenting with progressive CLAD. Participants willing to continue all standard-of-care treatment per center protocols. Participants who have received at least 6 weeks of azithromycin following the diagnosis of CLAD. Participant body mass index ≥18 kg/m.sup.2.

[0203] Exclusion Criteria. Participants are excluded from the study if any of the following criteria apply. Medical Conditions: FEV.sub.1≤50% of the post-transplant baseline value (CLAD 3 and 4). Participant who are enrolled in other clinical trials. Participants who are intolerant to belumosudil or any of its components. Any condition that can affect the ability to perform pulmonary function testing. Lung function decline that can be explained by non-CLAD causes. Diagnosed or treated for malignancy within 3 years prior to randomization with the exception of complete resection of basal cell carcinoma or squamous cell carcinoma of the skin, an in-situ malignancy, or low risk prostate cancer after curative therapy. Untreated symptomatic gastroesophageal reflux disease (GERD).

Baseline resting oxygen saturation of <88% on room air or use of supplemental oxygen at rest. Known prolongation of the QT interval (>480 msec).
[0204] Prior/concomitant therapy. Participants who have received therapy for CLAD other than azithromycin and standard-of-care immunosuppressants.
[0205] Received any investigational drugs, or any investigational device or procedure, or prohibited therapy for this study. Participant has had previous exposure to belumosudil.
[0206] Other exclusion criteria. Sensitivity to any of the study interventions, or components thereof, or drug or other allergy that, in the opinion of the Investigator, contraindicates participation in the study. Participants with known hypersensitivity to azithromycin, erythromycin, any macrolide, or ketolide drug are excluded from the study.
Study Design and Treatment
[0207] Patients will receive either belumosudil or placebo during the 26-week double-blind treatment period. Participants will have been treated with azithromycin and will receive ongoing azithromycin treatment in addition to standard of care immunosuppressive therapy. This study will assess the effect of belumosudil 200 mg orally QD (or 200 mg BID in case participants take strong CYP3A inducers or proton pump inhibitors) or placebo on lung function decline as assessed by the percentage of participants with a lung function decline. For example, a lung function decline may be assessed by changes in FEV1 over the study period.
[0208] The study will consist of a screening period of up to 4 weeks followed by a 26-week double-blind treatment period. After the completion of the 26-week double-blind treatment period, all study participants will be offered to enroll in an OLE period of belumosudil 200 mg orally (QD; or BID in case participants take strong CYP3A inducers or proton pump inhibitors) for 26 weeks.
Study Endpoints
[0209] Endpoint Objectives: To demonstrate the efficacy of belumosudil compared with placebo in Stage 1 and 2 CLAD progression following bilateral lung transplantation and to assess how belumosudil affects lung function in participants with CLAD; to demonstrate the efficacy of belumosudil compared with placebo on lung function as measured by FEV1 in participants with CLAD following bilateral lung transplantation, other measurements of lung function may be used such as forced vital capacity (FVC), total lung capacity (TLC), and diffusion capacity of the lung for carbon monoxide (DLCO); to evaluate the effects of belumosudil on CLAD progression (Time to CLAD progression during the double-blind treatment period); to evaluate the effects of belumosudil on patient-reported outcomes (PROs) such as change from baseline to Week 26 in patient reported outcomes; to assess the safety of belumosudil in participants with CLAD after bilateral lung transplant (Treatment-emergent adverse events (TEAEs), adverse events of special interest (AESIs), and laboratory results).
[0210] Although the present invention has been described in some detail by way of illustration and example for purposes of clarity and understanding, the descriptions and examples should not be construed as limiting the scope of the invention. The disclosures of all patent and scientific literature cited herein are expressly incorporated herein in their entirety by reference.

Claims

1. A method of treating a subject diagnosed with chronic lung allograft dysfunction (CLAD) following lung transplantation, the method comprising administering a therapeutically effective amount of 2-{3-[4-(1H-indazol-5-ylamino)-2-quinazolinyl]phenoxy}-N-(propan-2-yl) acetamide, or a pharmaceutically acceptable salt thereof (belumosudil) to the subject in need thereof.
2. The method of claim 1, wherein the CLAD comprises bronchiolitis obliterans syndrome (BOS).
3. The method of claim 1, wherein the CLAD comprises restrictive allograft syndrome (RAS).
4. The method of any one of claims 1-2, wherein the subject has mild BOS or moderate BOS.
5. The method of claim 4, wherein the subject has mild BOS.

6. The method of claim 4, wherein the subject has moderate BOS.
7. The method of any one of claims 1-6, wherein the CLAD is stage 1 or 2.
8. The method of any one of claims 1-6, wherein the belumosudil is administered to the subject at a dose selected from 200 mg daily and 200 mg twice daily.
9. The method of claim 8, wherein the belumosudil is administered to the subject at 200 mg daily as a single dose.
10. The method of claim 8, wherein the belumosudil is administered to the subject in two doses of 200 mg each.
11. A method of treating a subject diagnosed with bronchiolitis obliterans syndrome (BOS) following lung transplantation, the method comprising administering a therapeutically effective amount of 2-{3-[4-(1H-indazol-5-ylamino)-2-quinazolinyl]phenoxy}-N-(propan-2-yl) acetamide, or a pharmaceutically acceptable salt thereof (belumosudil) to the subject in need thereof.
12. The method of claim 11, wherein the subject has mild BOS or moderate BOS.
13. A method of treating a subject diagnosed with bronchiolitis obliterans syndrome (BOS) following allogeneic hematopoietic stem cell transplantation, the method comprising administering a therapeutically effective amount of 2-{3-[4-(1H-indazol-5-ylamino)-2-quinazolinyl]phenoxy}-N-(propan-2-yl) acetamide, or a pharmaceutically acceptable salt thereof (belumosudil) to the subject in need thereof, wherein the subject has mild BOS or moderate BOS.
14. The method of any one of claims 12-13, wherein the subject has mild BOS.
15. The method of any one of claims 12-13, wherein the subject has moderate BOS.
16. The method of any one of claims 13-15, wherein the belumosudil is administered in a 28-day cycle.
17. The method of any one of claims 11-16, wherein the belumosudil is administered to the subject at a dose selected from 200 mg daily, 200 mg twice daily, and 400 mg daily.
18. The method of claim 17, wherein the dose is 200 mg daily.
19. The method of claim 17, wherein the dose is 200 mg twice daily.
20. The method of claim 17, wherein the dose is 400 mg daily.
21. The method of any one of claims 11-20, wherein the subject experiences a treatment response in the lung that is defined by at least one of the NIH Lung Symptom Score and pulmonary function tests.
22. The method of claim 21, wherein a treatment response in the lung is defined solely by pulmonary function tests.
23. The method of claim 21, wherein a treatment response in the lung is defined solely by NIH Lung Symptom Score.
24. The method of any one of claims 1-23, wherein the treatment response in the lung is defined by measurement of % FEV1.
25. The method of claim 24, wherein the subject experiences an improvement in % FEV1 from baseline during treatment with belumosudil.
26. The method of claim 25, wherein the subject experiences ≥5% absolute improvement in % FEV1 from baseline during treatment with belumosudil.
27. The method of any one of claims 25-26, wherein the subject experiences ≥10% absolute improvement in % FEV1 from baseline during treatment with belumosudil.
28. The method of any one of claims 24-27, wherein the subject experiences at least a 200 mL improvement in FEV1 from baseline during treatment with belumosudil.
29. The method of any one of claims 24-28, wherein FEV1 is evaluated at baseline and on day 1 of each cycle starting at cycle 2 day 1.
30. The method of any one of claims 24-29, wherein the improvement is maintained over at least two consecutive FEV1 evaluations.
31. The method of claim 21, wherein the subject experiences a treatment response in the lung that is defined by an upgrade from a partial response according to measurement of the % FEV1 alone to

a complete response according to measurement of the NIH Lung Symptom score.
32. The method of claim 21 or 23, wherein the subject has a baseline NIH Lung Symptom score of 1 prior to treatment with belumosudil.
33. The method of claim 21 or 23, wherein the subject has a baseline NIH Lung Symptom of 2 prior to treatment with belumosudil.
34. The method of claim 21 or 23, wherein the subject has a baseline NIH Lung Symptom score of 3 prior to treatment with belumosudil.
35. The method of any one of claim 21, 23, or 32-34, wherein the subject experiences an improvement in NIH Lung symptom score during treatment with belumosudil.
36. The method of claim 35, wherein the subject experiences NIH Lung symptom score of 0 during treatment with belumosudil.
37. The method of claim 35, wherein the subject experiences NIH Lung symptom score of 1 during treatment with belumosudil.
38. The method of claim 35, wherein the subject experiences NIH Lung symptom score of 2 during treatment with belumosudil.
39. The method of any one of claim 13-23 or 31-38, wherein the subject experiences a treatment response in the lung that is defined by the Lee Symptom Scale lung score.
40. The method of claim 39, wherein the subject experiences at least a 10-point reduction in the Lee Symptom Scale lung subscore from baseline during treatment with belumosudil.
41. The method of any one of claim 13-23 or 31-40 wherein the subject has chronic graft-versus-host disease and has failed at least two prior lines of systemic therapy for the chronic graft-versus-host disease.
42. The method of claim 41, wherein the subject has failed two to five prior lines of systemic therapy for the chronic graft-versus-host disease.
43. The method of any one of claims 41-42, wherein the subject experienced a partial response to last treatment for the graft-versus-host disease prior to belumosudil.
44. The method of any one of claims 41-43, wherein the prior lines of systemic therapy for the chronic graft-versus-host disease have been discontinued.
45. The method of any one of claims 41-44, wherein the prior lines of systemic therapy are selected from the group consisting of prednisone, tacrolimus, ECP, sirolimus, ibruitinib, ruxolitinib, MMF, rituximab, MTX, cyclosporine, imatinib, ixazomib, and ofatumumab.
46. The method of any one of claims 41-45, wherein the cGVHD is steroid-refractory (SR) cGVHD.
47. The method of any one of claims 1-46, wherein the subject is receiving concomitant corticosteroid therapy.
48. The method of claim 47, wherein the dose of the concomitant corticosteroid therapy is reduced after at least 1 cycle of the belumosudil treatment.
49. The method of claim 47, wherein the concomitant corticosteroid therapy is discontinued after at least 1 cycle of the belumosudil treatment.
50. The method of any one of claim 11-23 or 31-49, wherein the belumosudil is administered as a 28-day cycle, and wherein the number of cycles ranges from 3 to 15 to the subject in need thereof.
51. The method of any one of claims 24-30, wherein the belumosudil is administered at a dose selected from 200 mg daily and 200 mg twice daily.
52. The method of any one of claims 50-51, wherein the subject has mild BOS or moderate BOS.
53. The method of claim 52, wherein the subject has mild BOS.
54. The method of claim 52, wherein the subject has moderate BOS.
55. The method of claim 50 wherein the number of cycles ranges from 5 to 11.
56. The method of claim 50 or 55, wherein the number of cycles ranges from 5 to 7.
57. The method of any one of claims 13-20, wherein the allogeneic hematopoietic stem cell transplantation was performed with myeloablative conditioning and peripheral blood stem cells

from an HLA-matched donor.

58. The method of any one of claims **1**-**58**, wherein the subject is a human.