NDA Multidisciplinary Review and Evaluation

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA. FDA review was conducted in conjunction with other regulatory authorities under Project ORBIS. FDA collaborated with Australia's Therapeutic Goods Administration, Health Canada, Switzerland's Swissmedic, and the United Kingdom's Medicines and Healthcare products Regulatory Agency.

Application Number	**NDA 214783**
Application Type	Type 1
Priority or Standard	Priority
Submit Date	9/30/2020
Received Date	9/30/2020
PDUFA Goal Date	8/30/2021
Office/Division	OOD/DHM1
Review Completion Date	7/16/2021
Applicant	Kadmon Pharmaceutical, LLC
Established Name	Belumosudil
(Proposed) Trade Name	Rezurock™
Pharmacologic Class	Kinase inhibitor
Formulation	Tablet (200 mg)
Applicant Proposed Indication/Population	For the treatment of patients 12 years and older with chronic graft-versus-host disease (chronic GVHD) after failure of at least (b) (4) of systemic therapy.
Recommendation on Regulatory Action	Approval
Recommended Indication/Population	For the treatment of adult and pediatric patients 12 years and older with chronic graft-versus-host disease (chronic GVHD) after failure of at least two prior lines of systemic therapy
SNOMED CT for the Recommended Indication/Population	402356004
Recommended Dosing Regimen	200 mg given orally once daily

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GLOSSARY

ADME	absorption, distribution, metabolism, excretion
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
alloHCT	allogeneic hematopoietic cell transplantation
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
BCRP	breast cancer resistance protein
BID	twice daily
BLA	Biologics License Application
BSC	Best supportive care
C1D1	Cycle 1 Day 1
CFR	Code of Federal Regulations
cGVHD	chronic graft versus host disease
CI	confidence interval
CMQ	customized MedDRA query
CNI	calcineurin inhibitor
CR	complete response
CSR	clinical study report
DDI	drug-drug interaction
D07 PtR	duration of 7-point reduction
DOR	duration of response
EAER	exposure adjusted event rate
ECG	electrocardiogram
ECP	extracorporeal photopheresis
eGFR	estimated glomerular filtration rate
FDA	Food and Drug Administration
FFS	failure-free survival
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase
GLP	Good Laboratory Practice
GRMP	Good Review Management Practice
HGLT	high-level group term
HLT	high-level term
ICH	International Conference on Harmonization

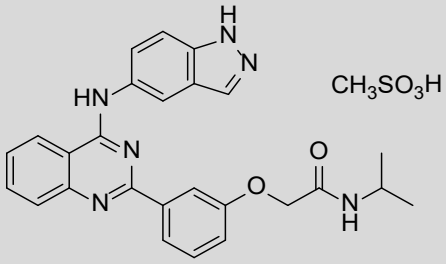
IL-2	Interleukin-2
IND	Investigational New Drug
IPF	idiopathic pulmonary fibrosis
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
IV	intravenous
KARA	Kadmon Algorithmic Response Assessments
LFT	liver function test
LSS	Lee Symptom Scale
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	New Drug Application
NIH	National Institutes of Health
NME	new molecular entity
NR	not reached
ORR	overall response rate
OS	overall survival
PK	pharmacokinetics
PP	per protocol
PPI	proton pump inhibitor
PR	partial response
PRO	patient reported outcome
PT	preferred term
QD	once daily
QOL	quality of life
QTc	QT interval corrected
RDI	Relative dose intensity
REMS	risk evaluation and mitigation strategy
ROCK	Rho-associated, coiled-coil containing protein kinase
SAE	serious adverse event
SAP	statistical analysis plan
SMQ	standardized MedDRA queries (
SOC	system organ class
$t_{½}$	half life
TEAE	treatment emergent adverse event
TTR	time to response
UGT	uridine diphosphate glucuronosyltransferase
ULN	upper limit of normal

1 EXECUTIVE SUMMARY

1.1 Product Introduction

Proposed Trade Name:	Rezurock™
Established Name:	Belumosudil
Also Known As:	KD025, SLx-2119, belumosudil mesylate
Chemical Name:	Mesylate is 2-{3-[4-(1H-indazol-5-ylamino)-2-quinazolinyl]phenoxy} -N-(propan-2-yl) acetamide methanesulfonate (1:1)
Molecular Formula:	$C_{27}H_{28}N_6O_5S_1$
Molecular Weight:	548.62 g/mol
Dosage Forms:	Tablet (200 mg)
Therapeutic Class:	Selective immunosuppressant
Chemical Class:	Small molecule
Pharmacologic Class:	Kinase inhibitor
Mechanism of Action:	Inhibitor of rho-associated, coiled-coil containing protein kinases 1 and 2 (ROCK1 and ROCK2) resulting in down-regulation of proinflammatory responses via regulation of STAT3/STAT5 phosphorylation and shifting Th17/Treg balance and inhibition of aberrant pro-fibrotic signaling

Chemical Structure:



NDA 214783 for belumosudil, a new molecular entity, was submitted under the 505(b)(1) pathway for the indication "for the treatment of patients 12 years and older with chronic graft-versus-host disease (chronic GVHD) after failure of at least (b) (4) of systemic therapy" using a dose of 200 mg given orally once daily.

The review team recommends approval of belumosudil for "treatment of adult and pediatric patients 12 years and older with chronic graft-versus-host disease (chronic GVHD) after failure of at least two prior lines of systemic therapy" using a dose of 200 mg given orally once daily until progression of chronic GVHD that requires new systemic therapy. The recommendation is based on the finding in Study KD025-213 of a 75% overall response rate with adequate durability. Additional studies are warranted to confirm safety with long-term use, to assess the effect on cardiac repolarization, to establish the appropriate dosages across the pediatric age range, and to determine the risk of increased toxicity associated with drug-drug interactions, race, and ethnicity.

1.2 Conclusions on the Substantial Evidence of Effectiveness

Study KD025-213 (NCT03640481) was a randomized, open-label, multicenter dose-ranging study of belumosudil for treatment of patients with chronic GVHD (cGVHD) who had failed two to five prior lines of systemic therapy and required additional treatment. Patients were excluded from the study if platelets were < 50 Gi/L, absolute neutrophil count < 1.5 Gi/L, AST or ALT > 3x ULN, total bilirubin > 1.5× ULN, QTc(F) > 480 ms, eGFR < 30 mL/min/1.73 m^2, or FEV1 ≤ 39%. Concomitant treatment with supportive care therapies for chronic GVHD was permitted. Concomitant treatment with GVHD prophylaxis and standard care systemic chronic GVHD therapies was permitted as long as the subject has been on a stable dose for at least 2 weeks prior to study. Initiation of new systemic chronic GVHD therapy while on study was not permitted.

Enrolled patients were randomized 1:1 to one of two oral dosages of belumosudil (200 mg daily and 200 mg twice daily), and randomization was stratified according to prior cGVHD treatment with ibrutinib (yes/no) and presence of severe cGVHD (yes/no). The primary objective was to evaluate efficacy as determined by achievement of overall response (ORR) that included complete or partial response (CR or PR) according to the 2014 NIH consensus criteria at any time on study. The results were to be assessed in each arm individually; the study was not powered to assess for differences in outcomes between arms. A sample size of 63 patients per arm was calculated to have 90% power with a 2-sided alpha 0.045 to exclude an ORR of 30% with a true ORR of 55%. The analysis set included all treated patients. An interim analysis was to occur when 126 patients completed 2 months on study, the primary analysis was to occur when 126 patients completed 6 months on study, and a follow-up analysis was to occur when 126 patients completed 12 months on study.

There were 132 patients randomized, 66 to each arm. Both arms met the objective of excluding a 30% ORR at both the interim and primary analyses. The Applicant proposed to recommend the belumosudil 200 mg daily dosage. The pharmacometrics analysis revealed a flat exposure-response relationship, and it was concluded that the dosage recommended by the Applicant was acceptable.

There were 65 patients with active cGVHD treated on the belumosudil 200 mg once daily arm in Study KD025-213. The patients has a median age of 53 years (range, 21-77 years), 65% were male, and 83% were Caucasian. The patients had been treated with a median of 3 (range, 2-6) prior lines of therapy, including 32% with ibrutinib and 31% with ruxolitinib; 78% were considered refractory to the last therapy. cGVHD was severe in 71%, the median global severity rating was 7 (range, 2-9), and the median Lee Symptom Scale (LSS) score was 27 (range, 7-56).

The efficacy of belumosudil was determined by ORR through Cycle 7 Day 1 as adjudicated by FDA using the updated dataset with 12 months of study follow-up. The ORR was 75% (95% CI: 63, 85). The responses were consistent across subgroups, including in patients who failed treatment with ibrutinib or ruxolitinib. The median time to first response was 1.8 months (95% CI: 1.0, 1.9). The median duration of response, calculated from first response to progression in any organ, death, or new systemic therapy for chronic GVHD, was 1.9 months (95% CI: 1.2, 2.9), and the median alternative measure of durability, defined as the time from first response to death or new systemic therapy, was not reached. In patients who achieved response, no death or new systemic therapy initiation occurred in 62% (95% CI: 46, 74) of patients for at least 12 months since response.

The ORR results in Study KD025-213 were supported by exploratory analyses of patient-reported symptom bother which showed at least a 7-point decrease in the LSS score by Cycle 7 Day 1 in 52% (95% CI: 40, 65) of patients. Additionally, the FDA-adjudicated ORR through Cycle 7 Day 1 in Study KD025-208, a supporting dose-escalation trial, was 59% (95% CI 33%, 82%) for the 17 patients treated with belumosudil 200 mg daily, the median duration of response was 5.6 months, and the median alternative measure of durability was not reached.

One potential weakness in the body of evidence is that nearly all the responses observed were only PRs. There were no CRs through Cycle 7 Day 1 in Study KD025-208, and the CR rate was only 6% (95% CI 2%, 15%) through Cycle 7 Day 1 in Study KD025-213.

Nonetheless, the PRs were durable, with extended periods of time without new treatment, and there was a substantial proportion of patients who achieved a clinically-meaningful improvement in the LSS, a patient-reported outcome. Additionally, despite all evidence coming from single-arm trials, the substantial ORR was reproducible across dosages in Study KD025-213 and across the two clinical trials in patients who had failed multiple other treatments.

Hence, the 75% ORR with a lower bound of 63% with durability in the 200 mg daily dosage arm of Study KD025-213, supported by the LSS results, the ORR in the 200 mg BID dosage arm, and the ORR in Study KD025-208 are considered substantial evidence of effectiveness.

The pharmacometrics analysis also showed no clinically significant differences in belumosudil pharmacokinetics with regard to weight over the range of 38.6 to 143 kg. On the basis of biology of treatment-refractory cGVHD and mechanism of action of belumosudil, the efficacy of belumosudil for treatment-refractory cGVHD can be extrapolated from the adequate and well-controlled studies in adults to postpubertal pediatric patients weighing at least 40 kg.

1.3 Benefit-Risk Assessment

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• cGVHD occurs in about 40% of patients after allogeneic hematopoietic stem cell transplantation. • Without treatment, cGVHD can cause severe multisystem tissue damage due to chronic inflammation and fibrosis. • The complications of cGVHD can be fatal.	cGVHD is a serous and life-threatening disease.
Current Treatment Options	• Standard first line treatment is steroids with or without a calcineurin inhibitor depending on the severity of the disease. • Ibrutinib is approved for treatment of cGVHD after 1 or more lines of therapy. ORR occurred in 67%, and the median duration of response was less than 20 weeks. • Almost half the patients require ≥ 3 lines of therapy, which are used off-label.	There is a need for new treatments for cGVHD.
Benefit	• KD025-213 was a two-cohort, single-arm, dose-ranging study that included 65 patients treated with belumosudil 200 mg daily for cGVHD failing ≥ 2 lines of therapy. • ORR (CR or PR) was achieved by 49 (75%) patients by Cycle 7 Day 1. Three (6%) patients had a CR. • The median duration of response was only 1.9 months, but 62% were alive without intervening need for new systemic therapy for at least 12 months since response. • A 7-point reduction in LSS score by Cycle 7 Day 1 was achieved by 52%.	Belumosudil 200 mg daily is an effective treatment of cGVHD failing 2 or more prior lines of therapy.
Risks and Risk Management	• There was 1 fatal adverse reaction. • Adverse reactions led to withdrawal in 18%. • The most common (≥ 20%) adverse reactions were infections, asthenia, nausea, diarrhea, dyspnea, cough, edema, hemorrhage, abdominal pain, musculoskeletal pain, headache, phosphate decreased, gamma glutamyl transferase increased, lymphocytes decreased, and hypertension. • The safety of long-term use has not been established. • There is not sufficient information regarding toxicities of belumosudil with drug-drug interactions, in patients with hepatic impairment, in racial and ethnic minorities, and in patients susceptible to QT prolongation. • The clinical trials included specific monitoring to mitigate serious toxicities.	The safety profile of 200 mg daily appears tolerable in the short term, but additional studies are needed to establish safe dosing in special populations.

cGVHD occurs in about 40% of patients after allogeneic hematopoietic stem cell transplantation (HSCT). Without treatment, cGVHD can cause severe multisystem tissue damage due to chronic

inflammation and fibrosis, which can be fatal. Standard first-line treatment is steroids with or without a calcineurin inhibitor, depending on the severity of the disease. Ibrutinib is the only approved treatment of cGVHD. Almost half the patients require 3 or more lines of therapy, which include multiple types of immunosuppressant drugs used off-label. There is a clear need for new drugs for treatment of cGVHD.

KD025-213 was a two-cohort, single-arm, dose-ranging study that included 65 patients treated with belumosudil 200 mg daily for cGVHD failing at least 2 lines of therapy. ORR (CR or PR) was achieved by 49 (75%) patients by Cycle 7 Day 1, and the median duration of response was only 1.9 months, but 62% were alive without intervening need for new systemic therapy for at least 12 months since response, and a 7-point reduction in LSS score by Cycle 7 Day 1 was achieved by 52%. These results show that belumosudil is active for the treatment of cGVHD that has failed multiple lines of therapy.

On the basis of mechanism of action, issues with wound healing were anticipated. Potential off-target inhibition of the mTOR pathway and UGT1A1 were also noted. Nonclinical studies identified the gastrointestinal tract, liver, kidneys, marrow and reproductive systems as potential targets for toxicity. In vitro, the potential for phototoxicity was observed.
In two clinical trials (Study KD025-213 and Study KD025-208), 83 adult patients with refractory or recurrent cGVHD were treated with belumosudil 200 mg once daily. The median duration of treatment was 9.2 months (range 0.5 to 44.7 months). A fatal adverse reaction was reported in one patient with severe nausea, vomiting, diarrhea and multi-organ failure. Permanent discontinuation due to adverse reactions occurred in 18% of patients. The most common (≥ 20%) adverse reactions, including laboratory abnormalities, were infections, asthenia, nausea, diarrhea, dyspnea, cough, edema, hemorrhage, abdominal pain, musculoskeletal pain, headache, phosphate decreased, gamma glutamyl transferase increased, lymphocytes decreased, and hypertension. Overall, belumosudil 200 mg daily appeared tolerable in the intended population using the monitoring and specific monitoring to mitigate serious toxicities.

The safety of long-term use has not been established. Additionally, there is not sufficient information regarding toxicities of belumosudil with drug-drug interactions, in patients with hepatic impairment, in racial and ethnic minorities, and in patients susceptible to QT prolongation. The safe dosage for small children is also unknown. Additional studies are required in these areas, and these can be accomplished postmarketing.

Given the observed response rate with durability, and with the mitigation strategies in place in labeling, the clinical benefit of belumosudil at this time appears to outweigh the risks of treatment of adult and pediatric patients 12 years and older with cGVHD after failure of at least two prior lines of systemic therapy.

1.4 Patient Experience Data

Patient Experience Data Relevant to this Application					
X	The patient experience data that was submitted as part of the application, include:				Section where discussed
	X	Clinical outcome assessment (COA) data, such as			
			X	Patient reported outcome (PRO)	8
			□	Observer reported outcome (ObsRO)	
			X	Clinician reported outcome (ClinRO)	8
			□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)			
	□	Patient-focused drug development or other stakeholder meeting summary reports			
	□	Observational survey studies designed to capture patient experience data			
	□	Natural history studies			
	□	Patient preference studies (e.g., submitted studies or scientific publications)			
	□	Other: (Please specify)			
□	Patient experience data that was not submitted in the application, but was considered in this review.				

2 THERAPEUTIC CONTEXT

2.1 Analysis of Condition

The Applicant's Position:

Chronic graft versus host disease (cGVHD) is a devastating complication of allogeneic hematopoietic cell transplantation (alloHCT) that develops in 30-50% of recipients [Lee et al 2017, Martin et al 2017, Flowers et al 2011, Arai et al 2015, Socie' et al 2014]. The estimated prevalence of cGVHD in the US based on the Medicare FFS and Pharmetrics commercial databases was approximately 14,000 patients in 2016 [Bachier et al 2019].
It is the leading cause of non-relapse mortality in transplant survivors [Arai et al 2015] and its impact includes physical, functional and psychosocial deficits, and poor quality of life (QOL) [Lee et al 2017].

Treatment of cGVHD is intended to reduce symptom burden, control objective manifestations of disease activity, and prevent damage and disability, without disproportionate toxicity related to the treatments themselves [Martin et al 2015].

Systemic therapy is indicated for patients with moderate or severe cGVHD according to the National Institutes of Health (NIH) consensus criteria: involvement of 3 or more organs, moderate or severe organ involvement in any organ, or any lung involvement [Jagasia et al 2015].

First-line therapy for the treatment of cGVHD has relied on corticosteroids with or without a calcineurin inhibitor (CNI). It is estimated that approximately 50 to 75% of patients with cGVHD will require at least second-line treatment [Lee 2017; Pelosi et al 2007]. Indications for second-line treatment include worsening manifestations of cGVHD in a previously affected organ, development of cGVHD in a previously unaffected organ, absence of improvement, and inability to taper corticosteroids or significant treatment-related toxicity [Inamoto et al 2014, Martin et al 2015].

Ibrutinib is approved in the U.S. for the treatment of adult patients with cGVHD after failure of one or more lines of systemic therapy based upon a single-arm study of 42 patients. This study demonstrated an overall response rate (ORR) of 67% with ibrutinib in a selected population of subjects with either >25% body surface area erythematous rash or a NIH mouth score > 4 [Miklos et al 2017]. Adverse events (AEs) led to treatment discontinuation in 14 patients (33%). The median duration of treatment was 1.8 months (range, 0.2–8.7 months) for patients who discontinued treatment due to unacceptable toxicity [Miklos et al 2017].

Beyond first-line treatment and treatment with ibrutinib, the efficacy of second-line agents is limited, with response rates of approximately 30% regardless of the agent that is chosen [Cutler et al 2017]. These include agents such as sirolimus, mycophenolate mofetil, methotrexate, extracorporeal photopheresis (ECP), rituximab, imatinib, bortezomib, and IL-2 [Lee et al 2017]. Clinical trials of ruxolitinib are ongoing. Furthermore, such therapies are associated with significant toxicities.

Chronic GVHD is a serious, potentially life threatening condition with significant unmet medical need after at least one line of systemic therapy.

The FDA's Assessment:
FDA agrees with the Applicant's conclusion that cGVHD is a serious, potentially life threatening condition.

Biology of chronic GVHD:

cGVHD is a multisystem disorder that is manifested by both inflammatory and fibrosing features. Experimental models have implicated both the innate and adaptive immune systems in the etiology. The pathogenesis is thought to evolve from an acute inflammatory response to tissue injury early posttransplant which evolves into chronic inflammation and dysregulation of both T and B cells with subsequent aberrant tissue repair and fibrotic reaction (Cooke KR et al 2017). It has been hypothesized that the thymus plays a major role in the development of

cGVHD, as it is responsible for the negative selection that limits expansion of alloreactive donor cells and pathogenic B cells. Although this has been cited as the basis for a lower incidence of cGVHD in children, who are more likely than adults to have a functioning thymus, there is no evidence that the natural history or response to treatment differs by age once cGVHD (and especially treatment-refractory cGVHD) occurs.

U.S. population of patients with chronic GVHD:

Table 1 below shows demographic and baseline patient characteristics of US Population Samples for patients with chronic GVHD based on US population reference of Bachier, et al. 2021.[1]

Table 1. Demographic and Baseline Patient Characteristics of US Population Sample

Characteristics	**cGVHD Patients n=5259**
Age (years)	
Median	58 Years
Sex	
Female	42%
Male	58%
Geographical Region Distribution	
Midwest	24-28%
Northeast	20-21%
South	30-37%
West	14-25%
Race Distribution	
Native American	0%
Hispanic	5%
White	82%
Asian	2%
Black	6%
Other	2%
Unknown	3%
Number of lines of systemic therapy for cGVHD	
One	95.7%
Two	70.9%
Three	46.8%
Four or more	29.2%

[1] Epidemiology and Treatment of Chronic Graft-Versus-Host Disease post-Allogeneic Hematopoietic Cell Transplantation (HCT): A US Claims Analysis. 2021.Transplantation and Cellular Therapy. https://www.tctjournal.org/action/showPdf?pii=S2666-6367%2820%2930101-9.

Characteristics	**cGVHD Patients n=5259**
Top Treatment Regimens within 12 months post-Diagnosis	
Steroid Only	22.3 - 28.2%
CNI Only	21.0 - 23.2%
Steroid + CNI	9.6 - 13.4%
mTOR inhibitors	5.4 - 8.6%
Steroid + mTOR inhibitors	4.2 - 4.7%
MMF	3.2 – 3.9%
Steroid + MMF	3.5 – 3.8%
ECP	2.3 -3.6%
Steroid + ECP	2.3%
Ibrutinib	0.5%
Ruxolitinib	0.5 – 2.5%
Other Regimen	15.7 -18.8%

Source: Reproduced based on the references of Bachier et al. 2019 Blood, and Bachier et al. 2021 Transplantation and Cellular Therapy. Abbreviations: CNI: calcineurin inhibitor; MMF: mycophenolate mofetil; ECP: extracorporeal photopheresis.

Scoring and Response Criteria for Chronic GVHD:

Scoring and response criteria are defined by the 2014 NIH Consensus Development Project on Criteria for Clinical Trials in cGVHD (Lee, et al 2015). Additionally, the Lee Symptom Scale (LSS) has been used as a tool to assess patient reported outcome in this population (Lee, et al 2002).

2.2 Analysis of Current Treatment Options

The Applicant's Position:

First-line treatment with systemic corticosteroids, with or without a calcineurin inhibitor, is standard for patients newly diagnosed with cGVHD when systemic therapy is indicated. Generally, patients are started on regimens of up to 1 mg/kg/day of prednisone at diagnosis with the goal of weaning the dosage down as quickly as possible due to tolerability and safety concerns. Prolonged systemic corticosteroid treatment causes significant toxicity, including weight gain, bone loss, myopathy, diabetes, hypertension, mood swings, cataract formation, and increased risk of infection. Inability to wean patients from high-dose corticosteroids, steroid dependence, persistent or worsening manifestations of cGVHD necessitate second-line treatment.

No consensus has been reached regarding the optimal choice of agents for second line and subsequent treatment of cGVHD. Treatment choices are based on physician experience, ease of use, need for monitoring, risk of toxicity, and potential exacerbation of preexisting comorbidity.

The Bruton's tyrosine kinase inhibitor, ibrutinib, is the only Food and Drug Administration (FDA)-approved treatment for cGVHD, and is approved for patients with cGVHD after failure of one or more lines of systemic therapy (Table 2). Other options for second line and later treatment include extracorporeal photopheresis (ECP), ruxolitinib, sirolimus, rituximab, imatinib, pentostatin, mycophenolate mofetil, methotrexate, and interleukin-2 (IL-2).

Table 2 Summary of Current FDA-Approved Treatment for Patients with cGVHD

Product (s) Name	Relevant Indication	Year of Approval And Type of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
Ibrutinib (IMBRUVICA)	Treatment of adult patients with cGVHD after failure of one or more lines of systemic therapy	August 2017 (NDA 205552/S-017)	420 mg orally once daily until cGVHD progression, recurrence of an underlying malignancy, or unacceptable toxicity	Single-arm trial of subjects with either >25% body surface area erythematous rash or a National Institutes of Health (NIH) mouth score > 4: ORR: 67% (95% CI: 51, 80) CR: 9/42 (21%) PR: 19/42 (45%)	Most common adverse reactions (≥20%) in patients with cGVHD: fatigue, bruising, diarrhea, thrombocytopenia, muscle spasms, stomatitis, nausea, hemorrhage, anemia, and pneumonia. Twenty-four percent of patients receiving IMBRUVICA in the cGVHD trial discontinued treatment due to adverse reactions (USPI (Section 6.1 Clinical Trials Experience).

The FDA's Assessment:

FDA agreed with the Applicant's statement that ibrutinib is the only FDA-approved treatment for cGVHD. Ibrutinib was been approved for the treatment of adult patients with chronic GVHD after failure of one or more lines of systemic therapy.[2] Ibrutinib efficacy assessments were based on NIH response criteria for cGVHD clinical trial, as defined by the 2014 NIH Consensus

[2] See USPI at https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=0dfd0279-ff17-4ea9-89be-9803c71bab44.

Development Project on Criteria for Clinical Trials in cGVHD (Lee, et al 2015), and labeling includes outcomes using a 7-point improvement in the Lee Symptom Scale (LSS) score.

National Comprehensive Cancer Network (NCCN) Guidelines suggested systemic agents for steroid-refractory chronic GVHD include: abatacept, alemtuzumab, calcineurin inhibitors (eg, tacrolimus, cyclosporine), etanercept, ECP, hydroxychloroquine, ibrutinib , imatinib, low-dose interleukin-2 (IL-2), low-dose methotrexate, mTOR inhibitors (eg, sirolimus), mycophenolate mofetil, pentostatin, rituximab, or ruxolitinib.[3] NCCN indicated that there was insufficient evidence to recommend one systemic agent as preferred over another, and that the agent is generally selected on the basis of institutional preference, physician experience, the drug's toxicity profile, prior treatments, drug-drug interactions, convenience and tolerability.

3 REGULATORY BACKGROUND

3.1 U.S. Regulatory Actions and Marketing History

The Applicant's Position:

Belumosudil (formerly referred to as KD025 or SLx-2119) is not currently registered (or approved) in the United States or in any part of the world. The clinical development program for belumosudil in cGVHD is being conducted under Investigational New Drug (IND) 125890 with the Division of Hematologic Malignancies 1 (DHM1), and the relevant regulatory history is included in Section 3.2.

The FDA's Assessment:

FDA agrees with the Applicant's statement that Belumosudil is not currently registered or approved in the United States or in any part of the world.

3.2 Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:

IND 125890 was submitted on December 10, 2015 and received a "Study May Proceed" letter from FDA on January 8, 2016. Belumosodil was granted Orphan Drug Designation for the "treatment of chronic graft versus host disease (cGVHD)" on October 5, 2017. FDA granted Breakthrough Therapy Designation for the "treatment of adult patients with chronic graft versus host disease (cGVHD) after failure of two or more lines of systemic therapy" on October

[3] See NCCN Clinical Practice Guidelines for Hematopoietic Cell Transplantation (HCT): Pre-Transplant Recipient Evaluation and Management of Graft-Versus-Host Disease. Version 1.2021 — January 28, 2021, available at NCCN.org https://www.nccn.org/professionals/physician_gls/pdf/hct.pdf

16, 2018, based on preliminary data from Study KD025-208 and in response to Kadmon's request dated August 17, 2018.

Below is a summary of Kadmon's key interactions with FDA in **Error! Reference source not found.**.

Table 3 Key FDA Interactions

Type of meeting	Date	Purpose of Meeting
Type B Meeting (pre-IND meeting)	May 28, 2015	Discussed the adequacy of the nonclinical program for KD025, design of the Study KD025-208, and general development plan.
Type C Meeting	March 22, 2018	Discussed the adequacy of a proposed clinical development plan as a basis for a regulatory approval in cGVHD. Based on FDA's agreement with the study design, Study KD025-213 was initiated in October 2018.
Type B Meeting (initial Breakthrough Designation Therapy meeting)	May 1, 2019	Discussed Kadmon's drug development program for belumosudil.
Type B Meeting (pre-NDA meeting)	March 12, 2020	Relevant agreements with FDA included discussion of Kadmon's drug development program for KD025 for purposes of an NDA submission: (1) 6-month data in the initial NDA and the 12-month data to be submitted in the 60-day update, (2) pooled efficacy data from Studies KD025-208 and KD025-213 and integrated safety data from the drug development program to support the NDA, and (3) discussion of Kadmon's participation in the Real-Time Oncoloy Review (RTOR) pilot program and Project Orbis.

The FDA's Assessment:

Belumosudil was developed (b) (4) . The clinical trials in patients with cGVHD were conducted under IND 125890. The regulatory activities pertinent to cGVHD are listed in the table below.

Table 4. Key US Presubmission/Submission Regulatory Activities

Date	Regulatory Activity
5/28/2015	Type B Meeting (pre-IND)
12/11/2015	IND 125890 received
8/11/2017	Preliminary Breakthrough Designation advice telecon
10/5/2017	Orphan Designation granted for "Treatment of graft-vs-host disease"
3/22/2018	Type C Meeting (EOP2)
6/19/2018	Preliminary Breakthrough Designation advice correspondence
10/16/2018	Breakthrough Designation granted for "treatment of adult patients with chronic graft versus host disease (cGVHD) after failure of two or more lines of systemic therapy"
5/1/2019	Type B Initial Breakthrough Designation Therapy Meeting
8/21/2019	Rezurock conditionally accepted as proprietary name
1/13/2020	Type B Meeting (CMC only) comments issued
3/12/2020	Type B Meeting (pre-NDA)
4/17/2020	Agreed iPSP
4/21/2020	Agreed RTOR timeline
5/20/2020	Initial RTOR section received
8/13/2020	Rezurock conditionally accepted as proprietary name
8/31/2020	FDA accepted plan for additional modules under RTOR rather than requesting rolling review
9/30/2020	NDA 214783 received
10/08/2020	Applicant Assessment Aid received
11/6/2020	Application Orientation Meeting
11/20/2020	Integrated Summary of Safety (ISS) datasets received
11/25/2020	60-Day Efficacy and Safety Update Reports received
12/16/2020	Current Integrated Summary of Efficacy (ISE) and ISS datasets received
1/9/2021	Midcycle Communication
3/5/2021	Major Amendment - Revised Efficacy and Safety datasets received
6/23/2021	Late Cycle Meeting

Source: FDA Analysis

The Applicant did not submit any requests for Special Protocol Assessment, so there were no formal agreements on size and design of the pivotal trial. Key advice provided by FDA to the Applicant during clinical development included:

- The lowest maximally effective dose should be chosen for development. A randomized dose-finding study was recommended. [EOP2]
- If response is an endpoint, active cGVHD should be required for eligibility. [PIND]

- Patients failing 2 or more therapies would be an acceptable target population for the pivotal study. [EOP2]
- The 2014 NIH consensus response criteria are acceptable. [EOP2, IBTD]
- At least 12 months of follow-up is needed to establish duration of response and to determine short-term safety. [EOP2, IBTD, PNDA]
- If the Lee Symptoms Score (LSS) results are to be used to support a claim, there should be a clear statistical analysis plan for the LSS in the pivotal study with justification for the analysis parameters. [PIND, EOP2, IBTD]
- A Thorough QT study should be conducted to assess the effect of belumosudil on cardiac conduction. [PIND, IBTD, PNDA]
- Justification for not conducting a carcinogenicity study should be submitted. [IBTD]

4 SIGNIFICANT ISSUES FROM OTHER REVIEW DISCIPLINES PERTINENT TO CLINICAL CONCLUSIONS ON EFFICACY AND SAFETY

4.1 Office of Scientific Investigations (OSI)

The Office of Scientific Investigations conducted inspections for Studies KD025-208 and KD025-213 at clinical sites in Boston, MA (Site 004), Denver, CO (Site 098), and San Antonio, TX (Site 079). These sites had the highest accrual and greatest center-level impact on the primary endpoint.

No substantial regulatory issues were found during inspection of Sites 004 and 079, and the final classification for these sites was No Action Indicated. Inspection of Site 098 revealed failure to conduct the investigation in accordance with the investigational plan and failure to maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation. A Form 483 was issued to the Investigator at Site 098, and the final classification was Voluntary Action Indicated. Subsequently, the site was closed by the Applicant, and subjects still on study were transferred to a different study site. The Investigator's response to the Form 483 was considered adequate. OSI concluded that although the inspection findings were regulatory violations, these findings did not appear to have a significant impact on the safety and efficacy analyses. To confirm this, additional sensitivity analyses will be conducted to exclude any potential bias from this site.

The Applicant (Kadmon) was also audited. A Form 483 was issued for failure to bring into compliance an investigator site (Site 098) who did not comply with the signed agreement, the

general investigational plan, and applicable regulatory requirements. The final classification for the Applicant inspection was Voluntary Action Indicated. The Applicant's response to the Form 483 and corrective action plan were considered adequate. Based on these inspection results, the study data derived from the inspected clinical sites were considered reliable by OSI in support of the requested indication.

4.2 Product Quality

Belumosudil drug product (Rezurock) is presented as a pale-yellow film-coated oblong tablet containing 200 mg of the free base equivalent to 242.5 mg of belumosudil mesylate. The tablets are debossed with "KDM" on one side and "200" on the other side. The inactive ingredients are 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. The drug product is supplied in bottles of 30 tablets with an expiry of 24 months when stored at USP controlled room temperature.

Several different formulations (10 mg and 100 mg capsules and 200 mg tablets) were used throughout clinical development. The Biopharmaceutics reviewer noted that the components and composition of the 200 mg tablet used in clinical trials were essentially the same as the components and composition of the to-be-marketed formulation, and that the manufacturing process used in the manufacture of the clinical tablet is identical to that of the commercial tablet. The Applicant included a comparative bioavailability (BA) study (Study KD025-106) to evaluate the relative BA of the tablet and capsule formulations in the fed state (with food effect). The Applicant also submitted the in vitro dissolution profile comparison between the capsule and tablet formulation. The Biopharmaceutics reviewer concluded that there was no statistically significant difference in terms of exposure when subjects were administered belumosudil tablets or belumosudil capsules in the BA study. Accordingly, no additional bridging studies were needed for the capsule formulation to the tablet formulation.

There were no outstanding safety issues identified for the manufacturing process or from the facilities inspections. The Applicant claimed a categorical exclusion from the requirement for an environmental assessment under U.S. Code of Federal Regulations Title 21 Part 25.31(b). Approval of the NDA was recommended by the Product Quality review team.

4.3 Clinical Microbiology

Not applicable.

4.4 Devices and Companion Diagnostic Issues

There was no device or companion diagnostic included in this application.

5 NONCLINICAL PHARMACOLOGY/TOXICOLOGY

5.1 Executive Summary

Belumosudil (also known as KD025 or Slx-2119) is an inhibitor of rho-associated coiled-coil containing kinase 2 (ROCK2). ROCK2 belongs to a serine/threonine kinase family that regulates multiple functions including cellular contraction, actin cytoskeleton remodeling, and pro-inflammatory cytokines. Proinflammatory cytokines IL-17 and IL-21, controlled by the ROCK2 signaling pathway, have been involved in the pathogenesis of chronic GVHD (cGVHD).

Belumosudil inhibited ROCK2 enzymatic activity (IC_{50}≤ 100 nM) with higher affinity compared to its family member ROCK1 (IC_{50} ≥3 µM). In kinase screen assays belumosudil inhibited casein kinase II (CK2) with an IC50 of 100 nM. Belumosudil inhibited the secretion of pro-inflammatory cytokines IL-21 and IL-17 by 90% and 60%, respectively, in anti-CD3/CD28 activated human peripheral blood mononuclear cells (PBMCs). Belumosudil-mediated inhibition of ROCK2 led to regulation of STAT3/STAT5 phosphorylation and transcriptional activity in ex-vivo or in vitro studies. Thus, inhibition of ROCK2 appears to shift the balance between T-helper 17 (Th17) cells and regulatory T cells (Tregs) in modulating immune homeostasis. Belumosudil was shown to inhibit aberrant pro-fibrotic signaling in vitro. In vivo studies in cGVHD mouse models demonstrated treatment with belumosudil resulted in improvement in cGVHD-related safety endpoints in the lung and skin. In addition, belumosudil reduced pulmonary fibrosis (one of the clinical manifestations of GVHD) and inflammation in a murine model of pulmonary fibrosis.

Safety pharmacology studies assessed the effects of belumosudil on cardiovascular, central nervous system (CNS), and respiratory function. Belumosudil blocked hERG (human ether-à-go-go-related gene) current in a concentration-dependent manner with an IC_{50} of 0.6 µM. Cardiovascular findings in toxicology studies consisted of increased weight of the heart; there was no apparent drug-related ECG findings in the repeat-dose general toxicology study in dogs. In a modified Irwin study to evaluate CNS function, there was a transient reduction in locomotor activity in rats treated with a single belumosudil dose of 350 mg/kg, consistent with the distribution of radioactivity to spinal nerve observed in a distribution study.

In a pulmonary safety pharmacology study, respiratory depressive effects were observed in male rats treated with a single belumosudil dose of 175 or 350 mg/kg.

The oral bioavailability of a single dose of belumosudil in rats was 16 to 53%. Following oral administration, the elimination half-life (t½) of belumosudil was 1 to 7 hours in animals and approximately 19 hours in humans. Human, rat and dog plasma protein binding were >90% for both the parent drug and the metabolites. Oral administration of [^{14}C]-belumosudil demonstrated distribution in the tissues associated with elimination (gastrointestinal tract, liver, kidney, urinary bladder), as well as in the adrenal gland, fur, lung, testes, spinal nerve, and uveal tract. Belumosudil was metabolized rapidly in rat and mouse liver microsome

preparations but was relatively stable in rabbit, dog, and human microsome preparations following 60 minutes of incubation. A mass balance study in male and female rats demonstrated that approximately 90% and <1% of belumosudil was excreted in the feces and urine, respectively.

Consistent with the intended clinical route of administration and intended dosing schedule, daily oral administration of belumosudil was assessed in repeat-dose general toxicology studies for up to 26 weeks in rats and up to 39 weeks in dogs. There were several unscheduled deaths in the rat and dog studies, and some of the deaths were due to drug-related injury to tissues including kidney (inflammation/necrosis of the cortical epithelium and/or the liver (multifocal biliary stasis).

In the 26-week rat study, belumosudil was administered by oral gavage at 50, 150, and 275 mg/kg/day with 4 weeks of recovery. Belumosudil-related toxicities were more prominent in the 3-month dog study than in the 39-week dog study. In the 3-month dog study, gelatin capsules of belumusodil were administered orally at 35, 70, and 125 mg/kg/day with 4 weeks of recovery. Following administration of belumosudil to rats and/or dogs, the adverse effects observed in one or both species included toxicities in the gastrointestinal (GI) tract (emesis, loose stools, and/or abnormal black contents, increase in salivation), liver (elevated liver enzymes, hypertrophy/increased organ weight, and cholestasis/inflammation), kidney (increased blood urea nitrogen [BUN] , tubular changes, pigmentation, intracellular protein droplets in the epithelium), hemolymphoid system (regenerative anemia), and reproductive system. The reproductive system toxicity involved both the male and female reproductive organs and associated tissues. In females, changes included lower uterine weights that correlated with uterine/cervical hypoplasia and decreased follicular development in rats at 275 mg/kg/day; findings were reversible. In males, toxicities included lower epididymis and testes weights associated with multifocal bilateral spermatozoan degeneration in the epididymis and testes, and multinucleated spermatids in the testes, and the changes were reversible. Other noteworthy findings in the rat included a significant decline in cholinesterase activity at a drug concentration (15 µg/mL) that is 6.5x the clinical Cmax at the recommended dose of 200 mg daily. This finding may be related to depressive respiratory effects and/or decreased locomotor activity observed in rats following single dose administration in the safety pharmacology studies. The decline in enzyme activity persisted at the high dose in females but was trending towards recovery in the absence of dosing.

A combined male and female fertility study was conducted in rats with belumosudil administered once daily at doses of 50, 150, or 275 mg/kg/day. Males were treated for 70 days prior to pairing through the mating and the post-mating period. Additional groups of treated males were allowed to recover for 77 days, following the treatment period. Females were treated starting 14 days prior to pairing through gestation day (GD) 7. In the treated males, significantly lower body weight gains were observed at 150 and 275 mg/kg/day. A dose of 275

mg/kg/day resulted in statistically significant effects on fertility and reproductive parameters compared to controls and historical control data and included abnormal sperm findings (reduced motility/count and increased percentage of abnormal sperm), testes/epididymis organ weight changes (small and decreased organ weights) and degenerative histopathology. While the fertility index in the treated males returned to normal on Day 77 of the recovery period, other changes in several reproductive parameters (e.g. organ weights and microscopic findings) were still present but tended to recover compared to the dosing period. At the dose of 275 mg/kg/day, adverse findings in female rats (treated with belumosudil or untreated but mated with treated males) included increased pre- or post-implantation loss and decreased number of viable embryos. In addition, females treated at 275 mg/kg/day had increased estrous cycle and decreased corpora lutea. Adverse changes in male and female reproductive organs also occurred in general toxicology studies; findings included spermatozoa degeneration at a belumosudil dose of 35 mg/kg/day (dogs) and decreased follicular development in ovaries at 275 mg/kg/day (rats). Effects were reversible in both male and female animals. Exposures at 275 mg/kg/day for male and female rats were approximately 8- and 9-fold higher, respectively, than at the recommended clinical dose based on AUC. Adverse changes in male and female reproductive organs also occurred in general toxicology studies; findings included spermatozoa degeneration at a belumosudil dose of 35 mg/kg/day in dogs and decreased follicular development in ovaries at 275 mg/kg/day in rats. Exposures at 35 mg/kg/day in dogs is approximately 0.5 times the recommended clinical dose based on AUC.

Embryofetal-fetal development (EFD) studies were conducted with belumosudil in pregnant rats and rabbits. Rats were administered daily oral doses of 25, 50, 150, and 300 mg/kg/day in a pilot study and doses of 15, 50, and 150 mg/kg/day in a pivotal GLP compliant study on GD 6-17. Toxicities including maternal and embryo-fetal development were more evident in the pilot study. Rabbits were administered daily oral doses of 50, 125, or 225 mg/kg/day on GD 6-18.

In the pilot EFD study inrats, daily oral administration of belumosudil at 25, 50, 150 or 300 mg/kg/day to pregnant rats on GD 6-17 resulted in maternal toxicity and embryo-fetal developmental effects. Maternal toxicity was most evident at 150 and 300 mg/kg/day doses, based on reductions in adjusted body weights. Post-implantation loss was non-dose dependent and occurred at 50 and 300 mg/kg/day doses. Embryo-fetal effects noted in one fetus each were characterized by absence of anus and tail, or whole-body edema at 50 mg/kg, omphalocele at 150 mg/kg/day, or dome-shaped head at 300 mg/kg. There was a lack of dose-response in the incidence of fetal malformations. The 50, 150, and 300 mg/kg groups had exposures that were 3, 5 and 9 times the exposures at the recommended clinical dose based on AUC.

In the GLP compliant study in rats, maternal toxicity characterized by dose-dependent decreased mean body weight change and reduced food consumption was observed at 50 and 150 mg/kg/day compared to control. Fetal toxicity included statistically significant decreased

mean fetal weights at 150 mg/kg/day compared to control, but were within the historical control data.

In the embryo-fetal development study in rabbits, daily administration of belumosudil at 50, 125, or 225 mg/kg/day on GD 6-18 resulted in maternal toxicity, mortality, increased fetal loss, and embryo-fetal developmental effects. Maternal toxicity was evident at 125 and 225 mg/kg/day doses based on reduced adjusted body weight gains and one mortality (on GD 9) at 225 mg/kg/day. Embryo-fetal findings occurred at doses ≥ 50 mg/kg/day and included spontaneous abortion, increased post-implantation loss, decreased percentage of live fetuses, decreased fetal body weight, and skeletal/external malformations. The malformations included short tail, ribs branched, fused or misshapen (deformed), sternebra(e) fused, neural arches fused, misaligned, and misshapen, and extra sternum sternebra(e), and visceral malformations (malpositioned ureter). The 50, 125, or 225 mg/kg/day doses resulted in exposures that were 0.07, 0.4, and 1 times, respectively, the exposures at the recommended clinical dose based on AUC.

Belumosudil was not mutagenic in the in vitro bacterial reverse mutation test or clastogenic in either the in vitro chromosomal aberrations assay in human peripheral lymphocytes or in the vivo bone marrow micronucleus assay in rats.

No carcinogenicity studies have been conducted with belumosudil. Given that the patient population includes subjects with non-cancerous conditions and long life expectancy, rodent studies should be conducted to determine the risk of carcinogenicity from belumosudil.

The nonclinical pharmacology and toxicology data submitted to this NDA are adequate to support the approval of belumosudil for the proposed indication.

5.2 Referenced NDAs, BLAs, DMFs

The Applicant's Position:

Belumosudil is a New Molecular Entity (NME) and there are no referenced NDAs, Biologics License Application (BLAs), or Drug Master Files (DMFs) related to nonclinical pharmacology or toxicology data for belumosudil.

The FDA's Assessment:

There are no referenced NDAs, BLAs, or DMFs related to the nonclinical pharmacology or toxicology of belumosudil.

5.3 Pharmacology

Primary pharmacology

The Applicant's Position:

Belumosudil is a selective Rho-associated, coiled-coil containing protein kinase-2 (ROCK2) inhibitor that is being evaluated for its potential as a therapy for patients with autoimmune and fibrotic disorders.

In vitro effects of belumosudil on the activity of ROCK1 and ROCK2 were evaluated in enzymes purified from cell supernatants or tissue homogenates and demonstrated selective inhibitory activity for ROCK2 ([IC_{50}]< 100 nM) compared to ROCK1 (IC_{50}> 3 µM). Further characterization of belumosudil inhibition of ROCK2 activity revealed it to be an adenosine triphosphate (ATP)-competitive interaction. Overall, the in vitro studies demonstrated that belumosudil is a potent, competitive, and selective inhibitor of ROCK2 (Study KD025-NCP-2).

Belumosudil has demonstrated an impact on the T-helper 17 (Th17) and Treg- immune responses as well as on the actin/myosin cytoskeletal network and collagen formation. In vitro immune cell activity data specifically demonstrate the role of belumosudil in controlling IL-21 and IL-17 secretion in human T cells via regulation that involves signal transducer and activator of transcription (STAT) 3, IRF4 and retinoid-related orphan receptor gamma t (RORγt)(Zanin-Zhorov et al 2014). Moreover, belumosudil leads to increased percentage of Forkhead box P3 (Foxp3)+ T cells via a STAT5-dependent mechanism and positively regulates the suppressive function of human regulatory T cells (Zanin-Zhorov et al 2014). This indicates that belumosudil plays an important role in modulating immune homeostasis and shifting the Th17/Treg balance towards the regulatory T cells phenotype. In addition, belumosudil exhibited therapeutically relevant activities in a wide range of cell types and showed pleiotropic anti-fibrotic potential by inhibiting aberrant extracellular matrix production and pro-fibrotic signaling (Study KD025 NCP-3).

In vivo, belumosudil has demonstrated efficacy in a variety of clinically relevant animal models of disease including chronic graft versus host disease, scleroderma , idiopathic pulmonary fibrosis (IPF), and other autoimmune diseases. Specifically belumosudil shows efficacy in the following studies that are relevant to cGVHD pathogenesis. Belumosudil significantly improved pulmonary function tests in cGVHD mice with bronchiolitis obliterans syndrome (BOS) (Study KD025-NCP-cGVHD-1). In line with the improvement in respiratory function, belumosudil reduced collagen and antibody deposition in the lung of treated mice. Belumosudil treatment significantly reduced the percentage of Tfh cells and plasma B cells while the percentage of Tregs was increased in the spleen (Flynn et al 2016). Compared to vehicle-treated mice, belumosudil treatment blocked the development of chronic sclerodermatous cGVHD and significantly decreases the GVHD score in mice (Study KD025-NCP-cGVHD-2, Flynn et al 2016). Thus, belumosudil affects both the immunological disbalance as well as significant tissue fibrosis in affected organs in models of cGVHD. The anti-fibrotic therapeutic benefits of belumosudil were also examined in a therapeutic model of pulmonary fibrosis induced with bleomycin in mice (Study KDM/01). Belumosudil has also demonstrated efficacy in a systemic lupus (SLE) model (Study 20131203-1, Weiss et al 2016) and a rheumatoid arthritis model (CIA) (Study KD025-NCP-CIA-1, Zanin-Zhorov et al 2014).

All nonclinical primary pharmacology studies were non-Good Laboratory Practice (GLP) consistant with regulatory expectations.

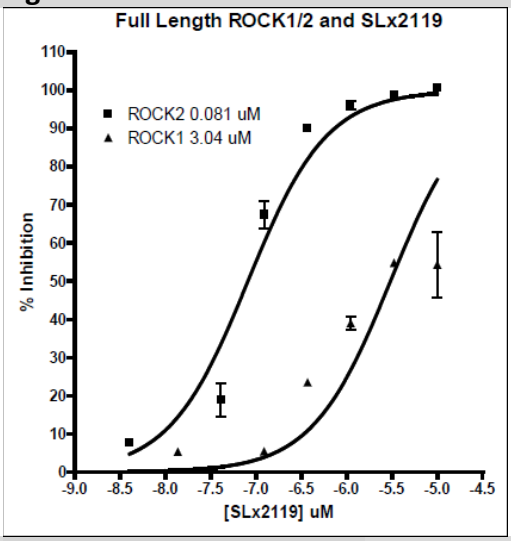
The FDA's Assessment:

FDA Please note different nomenclature used in the review: belumosudil (KD025, SLx-2119), metabolite KD025 m1 (SLx-3047), and second metabolite KD025 m2 (SLx-2131).

In Vitro Activity

The effects of belumosudil on the activity of ROCK1 and ROCK2 were evaluated in enzymes purified from cell supernatants or tissue homogenates (Study KD025-NCP-2). Full length rat ROCK1 and ROCK2 proteins were isolated from various tumor cell lines or tissues by immunoabsorption to 24-well microtiter plates pre-coated with antibodies specific for each isozyme. Reactions were initiated by the addition of S6 kinase substrate peptide, [γ33P]ATP, and belumusodil and incubated at 37°C for 20 minutes. Reactions were terminated by addition of phosphoric acid and the radioactivity was quantified using standard methods. The results show that belumosudil inhibited ROCK2 enzymatic activity with approximately 30-fold greater inhibition compared to ROCK1; i.e. an IC_{50} more than 30-fold lower than its inhibitory effect on ROCK1 (Figure 1). Table 5 shows the order of the inhibitory effect of belumosudil, its active metabolite KD025m1, and its second metabolite KD025m2 on ROCK enzymes. Fasudil and Y-27362 are included as reference ROCK inhibitors. The active metabolite KD025m1 inhibited ROCK2 with a comparable Ki value to belumosudil, while inhibition of ROCK2 by the second metabolite KD025m2 was approximately 6-fold lower.

Figure 1. Inhibition of ROCK 1 and ROCK 2 Enzymatic Activity by Belumosudil



(Excerpted from Applicant's NDA)

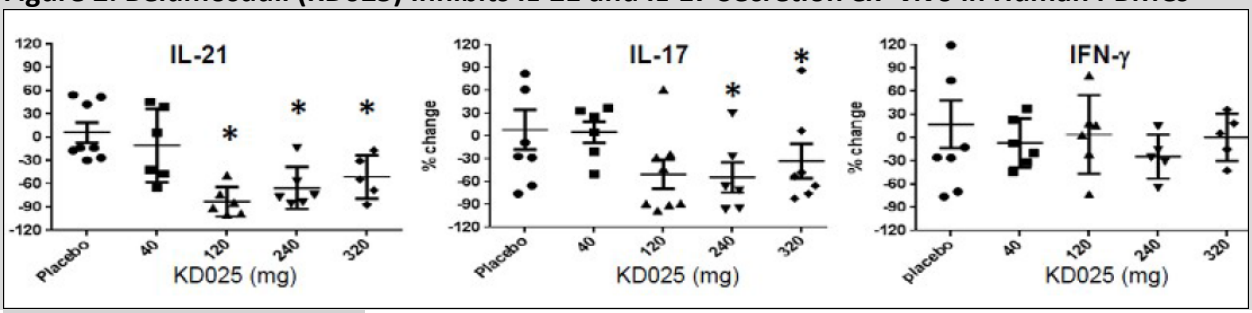
Table 5. Inhibition ROCK 2 by Belumosudil and the Metabolites KD025m1 and KD025m2

Enzyme	Ki (nM)				
	KD025	KD025m1	KD025m2	Y-27632	Fasudil
ROCK2	40±5	55±2	338±55	45±5	55±5

Inhibition of pro-inflammatory cytokines (Zanin-Zhorov 2014)

PBMCs were isolated from healthy subjects from a Phase 1 study after once daily oral administration with belumosudil at 120 mg, 240 mg, and 320 mg. PBMCs were activated ex vivo with anti-CD3/CD28 stimulation. The supernatants were analyzed for the secretion of IL-21, IL-17, and IFN-γ after 48 hours by enzyme-linked immunosorbent assay (ELISA). Both IL-21 and IL-17 production were reduced by 90 and 60%, respectively, in cells from belumosudil-treated individuals compared to placebo-treated subjects. There was no effect of belumosudil on IFN-γ secretion.

Figure 2. Belumosudil (KD025) Inhibits IL-21 and IL-17 Secretion ex- vivo in Human PBMCs

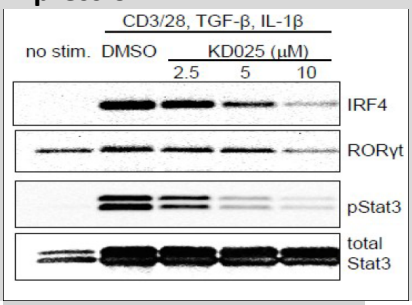


(Excerpted from Applicant's NDA)

Inhibition of STAT3 phosphorylation (Zanin-Zhorov 2014)

Human peripheral blood CD4+ T cells were treated with 2.5, 5, or 10 µM belumosudil and then stimulated by anti-CD3/28 mAbs, IL-1β (50 ng/mL) and TGF-β (5 ng/mL) for 48 hours. Nuclear extracts were prepared and analyzed by Western blotting. Belumosudil treatment resulted in suppression of phosphorylated STAT3 (pSTAT) and reduced levels of IRF4 and RORγt protein in a concentration-dependent manner, demonstrating inhibition of ROCK2 leads to down-regulation of STAT3 phosphorylation and transcriptional activity.

Figure 3. Belumosudil Inhibits STAT3 Phosphorylation, and Down-Regulates IRF4 and RORγt Expression



(Excerpted from Applicant's NDA)

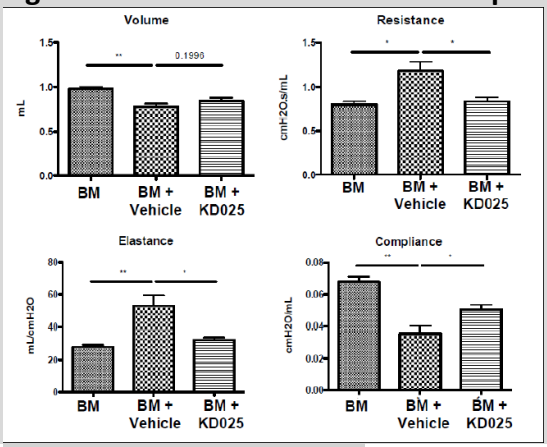
Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA. The FDA's position is highlighted in gray.

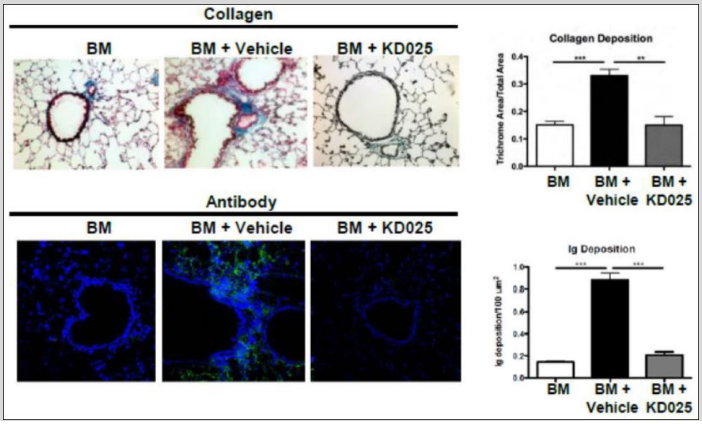
In Vivo Activity

The in vivo pharmacodynamic activity of belumosudil was assessed in cGVHD murine models that involve a wide spectrum of clinically relevant target organs including the lung, and skin (Study Nos. KD025-NCP-cGVHD-1, KD025-NCP-cGVHD-2, Flynn 2016). In addition, anti-fibrotic activity of belumosudil was also assessed in a pulmonary fibrosis model, as fibrosis is one of the clinical manifestation of cGVHD due to numerous inflammatory and infectious insults to the lung (Study No. KDM-01).

B10.BR recipient mice were conditioned with Cytoxan/total body radiation. Donor bone marrow (BM) from C57BI/6 mice was T-cell depleted with anti-Thy 1.2 mAb followed by rabbit complement treatment. On Day 0, recipient mice received 10^7 BM cells with or without allogeneic splenocytes (10^6 cells). On Day 28 after transplantation, a decrease in pulmonary function was noticed in the recipient mice and was characterized by an increase in airway resistance, which correlated with constriction, increased elastance and decreased compliance. Belumosudil at 100 mg/kg/day was administered intraperitoneally once a day for 28 days to one group of animals with established cGVHD with lung effects. Animals were observed for body weight changes twice weekly. Pulmonary function tests (PFTs) were performed on Day 56 by whole-body plethysmography. Histopathology of lung sections was conducted to assess collagen deposition, and immunofluorescence for antibody depositions. Flow cytometric analysis was conducted to determine the effect of belumosudil on CD4+ T follicular helper (Tfh) cells and germinal centers (GC) of B cells in spleens that are known to be activated during cGVHD disease initiation. Single cell suspensions of spleens were labeled with anti-CD4, anti-CXCR5 (Tfh cells are identified by high surface expression of the chemokine receptor CXCR5), and anti-PD1. In comparison with control mice, treatment with belumosudil at 150 mg/kg once daily (IP) significantly improved lung function in cGVHD mice, as was demonstrated by a decrease in resistance and elastance, and an increase in lung compliance compared to the vehicle-treated group with no effect on body weight and survival (Figure 4). Treatment with belumosudil was also shown to reduce both collagen and antibody deposition in the lung (Figure 4), and reduced the number of GC centers and Tfh cells in the spleen of GVHD mice (Figure 5). These studies demonstrate the therapeutic benefits of belumusodil cGVHD using nonclinical models.

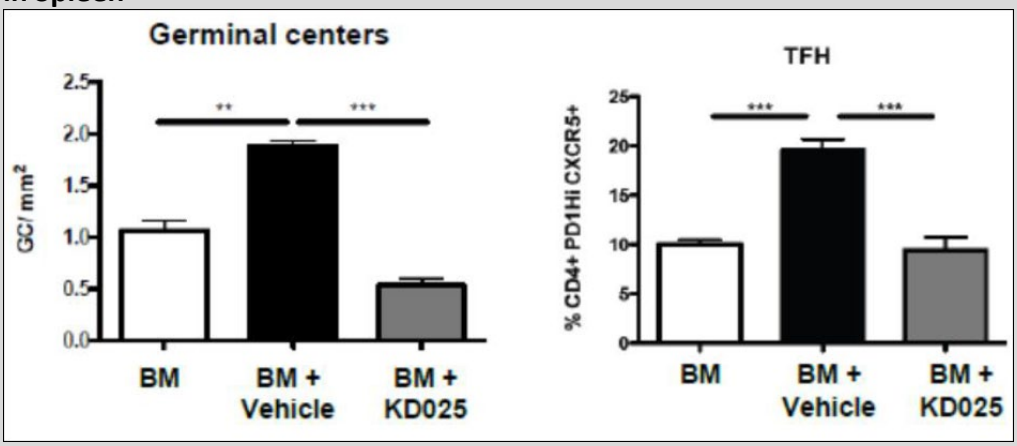
Figure 4. Effect of Belumosudil on Improving Lung Function in cGVHD Murine Model





(Excerpted from Applicant's NDA)

Figure 5. Effect of Belumosudil (KD025) on Germinal Centers and T Follicular Helper (Tfh) Cells in Spleen



(Excerpted from Applicant's NDA)

As noted by the Applicant, the therapeutic benefits of belumosudil were also demonstrated in an established model of scleroderma cGVHD (Scl cGVHD; Flynn 2016). Treatment with belumosudil at 150 mg/kg daily administered intraperitoneally to Scl cGVHD mice for ~3 weeks resulted in significant improvement in skin morphology (i.e., skin ulcers with alopecia less than 1 cm2 in area = 1; skin ulcers with alopecia 1–2 cm2 in area = 2; skin ulcers with alopecia greater than 2 cm2 in area = 3; mice lacking skin ulcers and alopecia received a score of 0) compared to vehicle control [4].

[4] Anderson BE, McNiff J, Yan J, et al. Memory CD41 T cells do not induce graft-versus-host disease. J Clin Invest. 2003;112(1):101-108.

Immunologic imbalance in cGVHD can lead to increased fibrosis in the lung. The anti-fibrotic therapeutic benefits of belumosudil were examined in a commonly utilized model of pulmonary fibrosis induced with bleomycin in mice (Study No. KDM-01). Pulmonary fibrosis was established at belumosudil treatment initiation. C57Bl/6 mice were treated orally with belumosudil (50, 100, or 150 mg/kg/day) or vehicle (0.4% carboxymethyl cellulose) for 13 days beginning 8 days after the administration of 2.25 U/kg of bleomycin into the lungs. Belumosudil has demonstrated anti-fibrotic effects on pulmonary fibrosis in a murine model of pulmonary fibrosis compared to both untreated and vehicle-treated groups. Belumosudil at 100 and 150 mg/kg significantly reduced mean lung wet weight, and significantly reduced pulmonary fibrosis and inflammation in comparison to vehicle-control therapy, demonstrating improved pulmonary function in murine model of pulmonary fibrosis.

Secondary Pharmacology

The Applicant's Position:

Secondary pharmacology for belumosudil was evaluated in multiple in vitro kinase screening assays (Study KD025-NCP-2), including the evaluation of kinase inhibition against a panel of approximately 220 kinases that were representative of the AGC, CMGC, TK, TKL, STE, CAMK, and CK1 kinase families. At maximum recommended clinical dose levels of 200 mg/day, a mean steady state C_{max} of 2390 ng/mL [5.3µM total drug] is achieved at that dose, which provides a sufficient safety margin versus the off-targets identified in vitro.

With the exception of ROCK2 (intended pharmacological target) and CK2 (IC_{50} approximately 100 nM), belumosudil IC_{50} values were generally above 5 µM for all other ATP-dependent kinases. In follow up cell based target engagement assays, belumosudil did not demonstrate pharmacologically relevant CK2 activity (IC_{50}>10uM) and it was concluded the reported in vitro CK2 inhibition is unlikely to contribute to the in vivo activity of belumosudil.

Belumosudil interaction with cell surface receptors and ion channels (Study KD025-NCP-2) was also evaluated through assessment of inhibition of radioligand binding and demonstated limited off target binding. Of the many targets evaluated, only two potentially active targets were identified: adenosine A_{2A} and A_3 receptors with IC_{50} values of 0.13-0.66 µM. In follow-up cell based functional assays, belumosudil was not an adenosine A_{2A} and A_3 receptor agonist. Belumosudil did not demonstrated pharmacologically relevant antagonist activity (IC_{50} >10µM) on adenosine A_3 receptor and the cellular IC_{50} for adenosine A_{2A} receptor antagonist activity was 0.350 µM. The expression of adenosine A_{2A} receptor is primarily restricted to the brain; Belumosudil is not brain penetrant and demonstrates no CNS-related toxicities, suggesting that adenosine A_{2A} receptor is not engaged by belumosudil in vivo. In conclusion, belumosudil is not expected to have pharmacologically relevant activity on adenosine A_{2A} and A_3 receptors.

In vitro, belumosudil treatment also inhibited the mTOR pathway, as demonstrated by the clear reduction in phosphorylation of the mTOR pathway effector kinase, S6K, in WI-38 human lung fibroblasts human connective tissue fibrosarcoma cell line HT1080. Results indicate that belumosudil likely reduces mTORC1 activity indirectly, through activation of the upstream inhibitory TSC complex in response to increased AMP-activated protein kinase (AMPK) activity.

All nonclinical secondary pharmacology studies were non-GLP consistent with regulatory expectations.

The FDA's Assessment:

Overall, the FDA concurs with the Applicant's assessment based on the results from study no. KD025-NCP-2 and KD025-NCP-3.

Safety Pharmacology

The Applicant's Position:

Formal GLP safety pharmacology studies have been conducted with belumosudil, evaluating hERG (*in vitro*) [Study (b) (4)090109.TVM), central nervous system (CNS)(rat) [Study 602031), respiratory (rat) (Study 8289751), and cardiovascular (dog) [Study 602029] function. Overall, the safety pharmacology data demonstrate low potential for belumosudil-related CNS, respiratory, or cardiovascular effects at clinically relevant exposures.

Central Nervous System: In the rat GLP CNS safety pharmacology study, no clinicaly relevant and/or adverse changes were observed in the functional observational battery after a single dose administration of 350 mg/kg (highest dose evaluated) to male and female rats.

Respiratory: In the rat GLP respiratory safety pharmacology study, no clinically relevant or adverse changes were observed in respiratory function (plethysmography) after administration of 350 mg/kg (highest dose evaluated) to male and female rats.

Cardiovascular: In vitro, belumosudil and KD025m1 (minor human metabolite) inhibited hERG channel activity modestly in a concentration-dependent manner with estimated IC_{50} of 0.6 µM [272 ng/mL free drug] and 1.5 µM [616 ng/ml free drug], respectively. KD025m2 (major human metabolite) had no inhibitory effect in this assay at concentrations up to 10 µM [4114 ng/ml free drug]. At the highest dose evaluated (150 mg/kg) in the dog cardiovascular safety pharmacology study, no evidence of changes in electrocardiogram (ECG) waveforms (PR, QRS, RR, QT, QTcV and HR-derived) was detected. In addition, in the 28-day, repeat-dose, dog general toxicology study, a dose of 200 (male)/125 (female) mg/kg had no ECG evidence of adverse cardiac effects. Based on the modest effects in the in vitro hERG assay and the lack of effects in vivo in dogs at belumosudil concentrations exceeding those evaluated in the in vitro hERG assay, the risk of QT interval corrected (QTc) prolongation is considered minimal and was not observed clinically (Section 0 and Section 8.3.4).

In the dog cardiovascular safety pharmacology study, belumosudil demonstrated low magnitude lowering of systolic blood pressure, diastolic blood pressure, and mean arterial pressure in female dogs at 150 mg/kg. These cardiovascular effects were low magnitude at exposures similar to those expected in human subjects at the recommended clinical dose and no blood pressure effects have been observed clinically (Section 8.3.5).

The FDA's Assessment:

We have noted some neurological, respiratory, and cardiovascular findings in the safety pharmacology studies. The cardiovascular effect was evident in the in vitro hERG assay (see above the Applicant's assessment). While the in vivo cardiovascular study did not show an apparent adverse finding, this might have been due to the study design. See below for additional information.

Neurological

In the rat CNS safety pharmacology study (Study No. (b) (4)-602031), at approximately 2 hours post-dose, there was a significant decrease in the total (↓53%) and ambulatory (↓69%) motor activity counts for the males at 350 mg/kg. Lower total (↓41%) and ambulatory (↓50%) motor activity counts were noted in the females at 350 mg/kg at the 1-hour post-dose interval (not statistically significant). Statistically significant lower body temperature was observed for the females at 350 mg/kg from 2 to 4 hours (up to 2.2 °C lower compared to pre-dose).

Respiratory

The Applicant conducted two GLP-compliant respiratory safety pharmacology studies, (GLP, (b) (4) 602030 and GLP, (b) (4) 8289751). In both studies, belumosudil was administered once orally to male and female Sprague Dawley rats at 50, 175, and 350 mg/kg and the effects on respiration rate, tidal volume and minute volume were evaluated.

In study (b) (4)-602030, lower minute volume was observed at 175 mg/kg, and lower respiratory frequency, lower tidal volume (in males only), and lower minute volume were observed in males and females at 350 mg/kg when compared to vehicle controls. The respiratory effects (e.g. minute volume and respiratory frequency decrease) at 350 mg/kg were more pronounced for the males and were considered adverse. The safety margin at 350 mg/kg in males with respiratory effects based on exposure (AUC_{0-24} 29110 ng·h/mL) was approximately 1.3X the human AUC at the recommended 200 mg dose.

A repeat (Study No.8289751) of the above respiratory safety pharmacology study failed to reproduce and/or confirm the adverse respiratory findings observed in males at doses ≥ 175 mg/kg during a head-out plethysmography evaluation of rats following the administration of belumosudil at doses ≤ 350 mg/kg.

The absence of respiratory findings in the repeat study was not due to a lack of exposure and the same rat strain was employed in both studies. Exposures to belumosudil at 350 mg/kg were higher (3-5 fold in males and females) based on AUC compared to the previous study despite the lack of any notable findings. The positive control increased tidal volume and decreased respiration rate in both studies, which confirms the sensitivity of the assay. The studies were conducted in two different CROs. The lack of findings may indicate a difference in assay proficiency between CROs.

Cardiovascular

We note that the ECG examinations in the 1-month dog study were unremarkable; however, assessments were estimated earlier than the Tmax post-dose; ECGs were assessed at 1-hour post-dose while the Tmax was 4-9 hours post-dose. Thus, the ECG evaluation was conducted at an inappropriate post-dose time.

Toxicokinetic Parameters in Dogs in One-Month Repeat Dose Study

Day	Dose (mg/kg/day)	$AUC_{0\text{-tlast}}$ (hr•ng/mL)	$AUC_{0\text{-tlast}}$/Dose (hr•ng/mL/mg/kg)	C_{max} (ng/mL)	C_{max}/Dose (ng/mL/mg/kg)	$t_{1/2}$ (hr)	T_{max} (hr)
1	25	452±317	18.1±12.7	90.9±53.9	3.64±2.16	2.66±1.26	6.86±4.30
	75	1200±1050	16.0±14.1	187±126	2.50±1.68	2.58	7.00±3.38
	200/125*	2830±2790	14.1±13.9	305±276	1.53±1.38	2.78±0.270	9.20±4.73
28	25	1350±763	54.0±30.5	278±150	11.1±5.99	1.90±0.597	4.38±1.69
	75	8010±4590	107±61.2	1000±457	13.4±6.09	2.69±0.476	6.00±2.19
	200/125*	14100±9450	113±75.6	1590±825	12.7±6.60	2.93±1.14	9.00±4.05

*Animals received 200 mg/kg/day from Day 1 through Day 15, were given a drug holiday until Day 19 and continued at 125 mg/kg/day until Day 28.

(Excerpted from Applicant's NDA)

5.4 ADME/PK

The Applicant's Position:

Pharmacokinetics/Toxicokinetics

Nonclinical exposure data used for GLP safety pharmacology and GLP repeat-dose toxicokinetic analyses were assessed using fully validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) bioanalytical methods that were comparable to the methods utilized for human pharmacokinetics (PK) determination.

Following oral administration, the plasma $t_{½}$ of belumosudil was variable across the nonclinical studies with values of approximately 2 hours in mouse, 1-7 hours in rat and rabbit, and 1-5 hours in dog. Belumosudil and metabolite exposure generally increased in a dose or greater than dose proportional manner, and accumulation increased with higher doses. Accumulation

of belumosudil and metabolites was not observed in pregnant rats or rabbits. In rats, females exhibited higher belumosudil plasma exposure compared to males. No apparent sex differences were observed in dogs (mice and rabbits were not evaluated for sex differences).

Absorption

Belumosudil solubility decreased as pH increased between pH 2.0 and 6.8 (nonGLP, Study ADME-KAD-200402-Kinetic Solubility).

In mice, belumosudil was found to be rapidly absorbed with maximum concentrations of belumosudil and metabolites being reached within 1 hour after both single and repeat doses. Rate of absorption appeared to be slower in rats and dogs with maximum exposure observed predominantly between 2 and 8 hours for all analytes at every dose level following single or repeat oral administrations; variations in peak exposure tended to occur in rats where T_{max} was observed up to 24 hours for all analytes. The extent of absorption was variable in mice and rats with bioavailability (%F) of belumosudil at 12-85% between 10-150 mg free base/kg.

Distribution

In in vitro studies, belumosudil was > 99% bound to animal (mouse, rat, rabbit, dog) and human plasma proteins (NonGLP, Study ADME-KAD-200410-PPB and KDM/06).

In vivo distribution studies (Study KDM/01 [GLP] and KDM/03 [nonGLP]) performed in rats with oral administration of [^{14}C]-belumosudil demonstrated distribution primarily into tissues associated with elimination (gastrointestinal, liver, kidney, urinary bladder), as well as the adrenal gland and exocrine glandular tissue. All tissues demonstrated clearance and no appreciable radioactivity was observed in the brain. Melanin-containing tissues (uveal tract and pigmented skin) demonstrated higher tissue retention, indicating some affinity of belumosudil for melanin.

Metabolism:

In vitro, predicted hepatic clearance (CL) values ranged from about 15-87 mL/min/kg in mouse, rat, dog, and human liver microsomes and hepatocytes (nonGLP, Studies ADME-KAD-200420-LM and ADME-KAD-200420-Hepatocytes).

In in vitro studies conducted in mouse, rat, rabbit, dog, and human liver microsomes (nonGLP, Study ADME-KAD-200420-LM MetID) and hepatocytes (nonGLP, Study ADME-KAD-200420-Hep-MedID), 32 and 28 metabolites were detected across all species, respectively. No major human specific metabolites (>10%) were identified in vitro. Belumosudil [parent] and only 2 metabolites (M21[belumosudil glucuronide] and M28/KD025m2 [hydrolysis]) were observed at >5% peak area in human liver microsomes and hepatocytes.

In vivo, in preclinical studies belumosudil underwent hepatic metabolism after oral administration to form KD025m1 (considered a minor human metabolite) and KD025m2 (considered a major human metabolite). KD025m2 exposure levels after belumosudil

administration in preclinical tox species provided sufficient coverage relative to human exposure levels at the recommended clinical dose; therefore, KD025m2 was not considered a disproportionate human-only phase 1 metabolite.

Human metabolites were evaluated in KD025-108, a human Absorption, Metabolism and Excretion study (Section 6.3.1), demonstrating the presence of belumosudil (64%), KD025m2 and co-eluting *O*-dealkylated belumosudil sulfate was 11.5% (total), and a belumosudil glucuronide was 15% (KDM-05). The *O*-dealkylated belumosudil sulfate was detected in multiple other species in the liver microsome and hepatocyte in vitro studies and in in vivo studies (KDM-03). The glucuronide metabolite is not an acyl glucuronide and, thus, consistent with FDA Guidance *Safety Testing of Drug Metabolites* is not considered to be of toxicological concern.

Based on *in vitro* assessment (nonGLP, Studies XT174009 and XT184060), CYP3A4 (41.9%) was the predominant cytochrome P450 (CYP) isoform responsible for the metabolism of belumosudil although CYP2D6 (21.7%), CYP2C8 (14.2%), CYP1A2 (<5%), CYP2C19 (<5%), and uridine diphosphate glucuronosyltransferase (UGT)1A9 may also contribute to a lesser extent. Metabolism of belumosudil to KD025m1 was CYP3A4 and CYP2C8 dependent. Metabolism of belumosudil to KD025m2 was CYP3A4 dependent with further metabolism of KD025m2 dependent on UGT1A1 with no to little contribution from CYP enzymes.

Excretion

In a rat excretion study (nonGLP, Study KDM/03), [^{14}C]-belumosudil excretion was similar in male and female rats and was predominantly excreted via the fecal route (~90%), while urine accounted for a smaller proportion of excretion (<1%).

Drug Interactions:

The potential for metabolism- and transporter-based drug-drug interactions (DDI) was evaluated with in vitro systems to assess victim or perpetrator potential with co-administered drugs.

Belumosudil caused increases (greater than two-fold) in CYP1A2, CYP2B6 and CYP3A4 mRNA levels; however, the observed increases were less than 20% of the respective positive controls indicating low clinical significance. KD025m2 had minimal to no inductive effect on CYP1A2, CYP2B6 and CYP3A4 mRNA levels (nonGLP, Study XT173022).

In vitro (nonGLP, Study XT175017), belumosudil directly inhibited CYP2C8 (competitively) and CYP2C9 (competitively-noncompetitively) activities with IC_{50} values < 1 µM; it directly inhibited CYP1A2, CYP2C19, CYP2D6, and CYP3A4/5-mediated midazolam 1'-hydroxylation and testosterone 6β-hydroxylation activities with IC_{50} values > 1 µM. Belumosudil was a metabolism-dependent inhibitor of CYP1A2, CYP2C19, CYP2D6 and both CYP3A4/5 activities; the metabolism-dependent inhibition of CYP3A4/5-mediated midazolam 1'-hydroxylation by belumosudil was consistent with enzyme inactivation. KD025m2 directly inhibited CYP1A2,

CYP2C8, CYP2C9 and CYP3A4/5-mediated testosterone 6β-hydroxylation activities with IC_{50} values > 1 µM. KD025m2 was a metabolism-dependent inhibitor of both midazolam 1'-hydroxylation and testosterone 6β-hydroxylation CYP3A4/5 activities. The clinical implications of these findings are discussed in Section 0.

Belumosudil (nonGLP, Study XT178018) was an in vitro substrate of P-gp and inhibitor (IC_{50} < 1 µM) of P-gp, BCRP, OATP1B1, MATE and MATE2-K. KD025m2 was a substrate of BSEP, OATP1B1, OATP1B3, OAT1, OAT3 and MATE2-K. KD025m2 was an inhibitor of OATP1B1 (IC_{50} <1 µM) and had less potent inhibition (IC_{50} > 1 µM) of BCRP, BSEP, OATP1B3, OAT3, MATE1 and MATE2-K. The clinical implications of these findings are discussed in Section 0.

The FDA's Assessment:

Type of Study	Major Findings
Absorption	
Bioavailability of Belumosudil Following Intravenous and Oral Administration in Male Sprague-Dawley Rats (Non-GLP, SLx-PK-113-213) **Single dose study in beagle dogs/ (b) (4) -602029**	Sprague-Dawley (SD) rats were given single oral doses of 10, 30, 100, or 150 mg/kg. Plasma was analyzed for belumosudil and the metabolites KD025m1 and KD025m2. • Oral bioavailability for belumosudil ranged from 16% to 53%. •Tmax ranged from 0.5 hours to 2 hours for belumosudil and the two metabolites. • T½ ranged from 5 hours to 7.26 hours for belumosudil (from study KDM/03). Beagle dogs were given single gelatin capsules at dose levels of 25, 75, and 150 mg/kg. •Oral bioavailability for belumosudil could not be determined in dogs as there was no IV dosing to compare. •Tmax ranged from 2 hours to 12 hours for belumosudil and the two metabolites. • T½ ranged from 1 hours to 2.3 hours
Distribution	
Tissue Distribution Pattern Following a Single Oral Administration of [14C]-Belumosudil to Male Rats/Study KDM/01 [GLP]	Radioactivity of oral administration of [14C]- 150 mg/kg belumosudil demonstrated distribution primarily into tissues associated with elimination (gastrointestinal tract, liver, kidney, and urinary bladder), as well as into the adrenal gland, and exocrine glandular tissue. In addition, radioactivity was also observed in the spinal nerve of male albino rats at 1, 6, and 24 hours post-dose and this site-specific accumulation of belumosudil may likely represent the potential for locomotor impairment (see safety pharmacology study review No. (b) (4) -602031).

Type of Study	Major Findings

Tissue	Mean Rat Tissue Concentration (µg/g) of Belumosudil Over Time				
	1 h	6 h	24 h	72 h	120 h
Adrenal gland	47.5	30.2	10.9	0.888	BLQ
Aorta	13.2	14.2	5.29	BLQ	BLQ
Bone marrow	8.69	5.58	1.34	BLQ	BLQ
Brain	BLQ	BLQ	BLQ	BLQ	BLQ
Fur	BLQ	BLQ	BLQ	21.1	23.9
Gastricmucosa	69.5	20.5	3.07	BLQ	BLQ
Heart blood	7.49	4.77	1.68	BLQ	BLQ
Kidney: Cortex	32.9	19.2	9.99	1.31	BLQ
Kidney: Medulla	15.9	7.27	2.79	BLQ	BLQ
Liver	58.1	35.9	22.8	3.57	1.39
Lung	9.67	6.95	2.58	BLQ	BLQ
Sciatic nerve	0.765	2.88	0.868	BLQ	BLQ
Skeletal muscle	6.22	4.41	0.885	BLQ	BLQ
Skin: Non-pigmented	6.00	6.52	3.17	BLQ	BLQ
Spinal cord	BLQ	BLQ	BLQ	BLQ	BLQ
Spinal nerve	12.2	14.8	5.38	BLQ	BLQ
Spleen	12.7	7.29	1.75	BLQ	BLQ
Stomach contents	4553a	3129a	921	BLQ	BLQ
Testis	0.889	2.54	0.818	BLQ	BLQ
Uveal tract	6.52	3.51	1.05	BLQ	BLQ

[a]Above Limit of Accurate Quantification (>1052 µg equivalents/g)

Evaluation of Plasma Protein Binding (ADME-KAD-200410-PPB)

Species	Plasma Protein Binding (%)
	1 µM - 100 µM
Mouse	99.2-99.6
Rat	99.5-99.6
Rabbit	99.5-99.6
Dog	98.9-99.3
Human	99.8-100

Evaluation of Blood/Plasma Partitioning (ADME-KAD-200402-Blood Partition)

Species	Blood-to-Plasma Ratios
	1 µM
Mouse	0.91
Rat	0.92

Type of Study	Major Findings
	Rabbit 1.26 **Dog** 0.92 **Human** 0.71 • Placental transfer studies have not been conducted.
Metabolism	
Metabolic Stability of KD025 in Different Species of Liver Microsomes/ ADME-KAD-200420-LM	The in vitro metabolism of 1 µM belumosudil was evaluated in mouse, rat, rabbit, dog, and human liver microsomes following an incubation period of 60 minutes. Belumosudil was readily metabolized in rat and mouse liver preparations but was relatively stable in rabbit, dog and human preparations.

In Vitro Evaluation of Microsomal Metabolism of Belumosudil in Mouse, Rat, Rabbit, Dog, and Human Liver Microsomes

Species	Remaining Percentages at 60 min (%)	t1/2 (min)	In vitro CLint (µL/min/mg)	Predicted Hepatic CLint (mL/min/kg)
Mouse	0.00	3.11	445	30.1
Rat	0.00	2.60	533	86.7
Rabbit	15.6	22.9	60.6	36.6
Dog	18.3	24.7	56.1	25.3
Human	23.7	29.6	46.9	15.3

Metabolite Identification of KD025 in Different Species of Hepatocytes/ADME-KAD-200420-Heps MetID.

Metabolite Identification of Belumosudil in Liver Microsomes (Metabolites >5% in bold)

Metabolite (modification)	Belumosudil Metabolite Profile in Liver Microsomes				
	Mouse	**Rat**	**Rabbit**	**Dog**	**human**
M1 (De-lkylation+Oxidation)	-	-	X	-	-
M2	X	X	X	-	-

Type of Study	Major Findings				
De-alkylation					
(M4) De-alkylation+Hydrolysis	-	-	X	-	-
M5 De-alkylation+Glucuronidation	-	-	X	-	-
M6 De-alkylation+Oxidation +Glucuronidation	-	-	X	X	X
M7 De-alkylation+Oxidation+ Hydrogenation	-	-	-	X	-
M8 De-alkylation+Oxidation+ Glucuronidation	X	X	X	-	-
M9 Hydrolysis+Oxidation+ Hydrogenation	-	-	-	X	-
M10 De-alkylation+Glucuronidation	X	X	X	X	X
M11 Oxidation	-	-	X	X	-
M13 De-alkylation	X	X	X	-	-
M14 De-alkylation+Oxidation	-	-	X	X	-
M15 Hydrolysis+Glucuronidation	-	-	-	X	X
M16 De-alkylation+Methylation+ Oxidation	X	X	X	X	-
M18 Oxidation+Glucuronidation	X	X	X	X	X
M19 (KD)25M1 De-alkylation	X	**X (18.25%)**	**X (8.95%)**	**X (16.16%)**	X
M21	-	-	X	X	**X (6.14%)**

Type of Study	Major Findings				
Glucuronidation					
M22 Ribose Conjugation+ Phosphorylation	X	X	X	-	-
M23 Oxidation+Glucuronidation	X	X	X	X	-
M24 Hydrolysis+Oxidation	-	-	X	X	-
M26 Oxidation	X	-	X	X	X
M27 Oxidation+Hydrogenation	-	-	-	X	X
M28 (KD025M2) Hydrolysis	X	X	X	**X (16.55%)**	**X (10.97%)**
M29 Ribose Conjugation	X	X	-	-	-
M30 Glycine Conjugation	X	X	X	X	X
M31 Oxidation+Hydrogenation	-	-	-	X	-
M32 Oxidation	X	-	-	X	X
M35 Parent Drug	**X (54.20%)**	**X (53.09%)**	**X (66.98%)**	**X (48.68%)**	**X (69.12%)**
M36 De-alkylation+De-hydrogenation	**X (6.66%)**	**X (8.20%)**	**X (6.48%)**	X	X
M39 Hydrolysis+De-hydrogenation	X	X	X	X	X
M40 De-alkylation+De-hydrogenation	X	X	-	X	-
M42 De-hydrogenation	**X (27.00%)**	X	X	X	X
M44	X	-	X	-	-

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td colspan="2">Oxidation+De-hydrogenation</td></tr>
<tr><td colspan="2">Excretion</td></tr>
<tr><td>Excretion Studies Following A Single Oral Dose Administration to Male and Female Rats/KDM-03</td><td>
<table>
<tr><th colspan="4">[^{14C}]Belumosudil Recovery (%)</th></tr>
<tr><th>Urine</th><th>Feces</th><th>Cage Wash</th><th>Carcass</th></tr>
<tr><td>0.67</td><td>91.2</td><td>0.63</td><td>0.42</td></tr>
</table>
</td></tr>
<tr><td colspan="2">TK data from general toxicology studies</td></tr>
<tr><td>KD025: A 26-Week Oral Gavage Toxicity and Toxicokinetic Study in Rats with a 13-Week Interim Termination and a 4-Week Recovery Period/029502</td><td>
• Belumosudil exposure (mean Cmax and AUC0-24) increased with increasing dose in both sexes after a single dose (Day 1) and multiple doses (Days 91 and 179; at 13 and 26 weeks).
•Belumosudil exposures were higher in females with accumulation as the study progressed.
•After 26 weeks of dosing (Day 179), there was 2- to 4-fold accumulation from Day 1 in females.
<table>
<tr><th colspan="6">Belumosudil TK Parameters in 26-Week Repeat-Dose Study in Rats</th></tr>
<tr><th>Dose (mg/kg/day)</th><th>Study Day</th><th>Sex</th><th>Cmax (ng/mL)</th><th>Tmax (h)</th><th>AUC0-24h (h*ng/mL)</th></tr>
<tr><td rowspan="6">50</td><td rowspan="2">Day 1</td><td>M</td><td>4170</td><td>8.0</td><td>26700</td></tr>
<tr><td>F</td><td>3830</td><td>4.0</td><td>43400</td></tr>
<tr><td rowspan="2">Day 91</td><td>M</td><td>3640</td><td>4.0</td><td>24000</td></tr>
<tr><td>F</td><td>8670</td><td>8.0</td><td>60400</td></tr>
<tr><td rowspan="2">Day 179</td><td>M</td><td>2980</td><td>6.0</td><td>25000</td></tr>
<tr><td>F</td><td>7390</td><td>8.0</td><td>73500</td></tr>
<tr><td rowspan="6">125</td><td rowspan="2">Day 1</td><td>M</td><td>5030</td><td>6.0</td><td>60900</td></tr>
<tr><td>F</td><td>6220</td><td>2.0</td><td>81600</td></tr>
<tr><td rowspan="2">Day 91</td><td>M</td><td>10400</td><td>6.0</td><td>68300</td></tr>
<tr><td>F</td><td>15800</td><td>6.0</td><td>164000</td></tr>
<tr><td rowspan="2">Day 179</td><td>M</td><td>7100</td><td>6.0</td><td>61500</td></tr>
<tr><td>F</td><td>14900</td><td>8.0</td><td>167000</td></tr>
<tr><td rowspan="4">275</td><td rowspan="2">Day 1</td><td>M</td><td>8930</td><td>24.0</td><td>120000</td></tr>
<tr><td>F</td><td>9180</td><td>24.0</td><td>115000</td></tr>
<tr><td rowspan="2">Day 91</td><td>M</td><td>13900</td><td>6.0</td><td>162000</td></tr>
<tr><td>F</td><td>29600</td><td>12.0</td><td>394000</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td></td><td>
<table>
<tr><td></td><td>Day 179</td><td>M</td><td>10600</td><td>6.0</td><td>112000</td></tr>
<tr><td></td><td></td><td>F</td><td>29500</td><td>2.0</td><td>474000</td></tr>
</table>
</td></tr>
<tr><td>KD025: 3-Month Oral Toxicity and Toxicokinetic Study in Dogs with a 28-Day Recovery Period/029281</td><td>
Following repeated daily dosing for 3 months in dogs, belumosudil exposures were roughly 2-fold higher compared to Day 1, indicating some accumulation of belumosudil.
<table>
<tr><th colspan="6">Belumosudil TK Parameters in 3-Month Repeat-Dose Study in Dogs</th></tr>
<tr><th>Dose (mg/kg/day)</th><th>Study Day</th><th>Sex</th><th>Cmax (ng/mL)</th><th>Tmax (h)</th><th>AUC0-24h (h*ng/mL)</th></tr>
<tr><td>35</td><td>Day 1</td><td>M</td><td>1660</td><td>5.50</td><td>11600</td></tr>
<tr><td></td><td></td><td>F</td><td>1870</td><td>4.25</td><td>13100</td></tr>
<tr><td></td><td>Day 91</td><td>M</td><td>4910</td><td>4.25</td><td>25200</td></tr>
<tr><td></td><td></td><td>F</td><td>4620</td><td>5.00</td><td>23300</td></tr>
<tr><td>70</td><td>Day 1</td><td>M</td><td>2650</td><td>7.50</td><td>25700</td></tr>
<tr><td></td><td></td><td>F</td><td>2950</td><td>7.25</td><td>24200</td></tr>
<tr><td></td><td>Day 91</td><td>M</td><td>6170</td><td>3.75</td><td>44800</td></tr>
<tr><td></td><td></td><td>F</td><td>7250</td><td>8.50</td><td>50100</td></tr>
<tr><td>125</td><td>Day 1</td><td>M</td><td>4150</td><td>8.17</td><td>41600</td></tr>
<tr><td></td><td></td><td>F</td><td>5030</td><td>6.83</td><td>51400</td></tr>
<tr><td></td><td>Day 91[a]</td><td>M</td><td>NA</td><td>NA</td><td>NA</td></tr>
<tr><td></td><td></td><td>F</td><td>NA</td><td>NA</td><td>NA</td></tr>
</table>
NA not applicable.
[a] Due to adverse clinical signs at 125 mg/kg/day, 2 male dogs were sacrificed in moribund condition. Surviving dogs continued un-dosed and were euthanized and/or necropsied on Days 50/51.
</td></tr>
<tr><td>39 Week Oral Toxicity Study in Dogs with a 13 Week Interim Sacrifice and an 8 Week Recovery Period/8289750</td><td>
•There was a high degree of variability in the plasma concentrations of belumosudil in this study.
•Belumosudil exposure tended to increase in a greater than dose proportional manner in both sexes.
•The degree of belumosudil accumulation is difficult to determine considering the variable plasma concentrations.
<table>
<tr><th colspan="6">Belumosudil TK Parameters in 39-Week Repeat-Dose Study in Dogs</th></tr>
<tr><th>Dose (mg/kg/day)</th><th>Study Day</th><th>Sex</th><th>Cmax (ng/mL)</th><th>Tmax (h)</th><th>AUC0-24h (h*ng/mL)</th></tr>
<tr><td></td><td>Day 1</td><td>M</td><td>89.2</td><td>2.17</td><td>550</td></tr>
</table>
</td></tr>
</table>

Type of Study	Major Findings					
	5		F	112	3.00	574
		Week 13	M	120	3.50	537
			F	178	2.40	566
		Week 39	M	386	4.00	1180
			F	249	3.33	833
	20	Day 1	M	805	4.89	4570
			F	768	4.56	5600
		Week 13	M	1910	4.00	8660
			F	2300	4.22	11500
		Week 39	M	854	4.33	4040
			F	1480	3.75	8400
	40	Day 1	M	1700	6.83	11600
			F	858	5.36	8170
		Week 13	M	2120	3.63	14700
			F	1440	3.05	9700
		Week 39	M	2060	4.00	15500
			F	3220	3.58	22500

TK data from reproductive toxicology studies

KD025: A combination study of fertility and early embryonic development to implantation in Sprague-Dawley Rats/2420-008

Belumosudil Exposure in Oral Fertility and Early Embryonic Development to Implanation in Rats

Dose (mg/kg)	**50**		**150**		**275**	
Sex	**M**	**F**	**M**	**F**	**M**	**F**
AUC0-24 (ng.h/mL)	21600	26200	70100	99500	191000	209000
Relative Exposure (multiples of 22700*)	0.95	1.15	3.08	4.38	8.4	9.2

Pilot Embryo-l Developmental Toxicity Study in Sprague-Dawley Rats ((b) (4) 2420-004)

Belumosudil Exposure in Pilot Prenatal Development to implantation in Rats

Dose (mg/kg)	**25**	**50**	**150**	**300**
AUC0-24 (ng.h/mL)	20400	61800	120000	193000
Relative Exposure (multiples of 22700*)	0.89	2.72	5.28	8.5

Embryo Developmental

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td>Toxicity Study in New Zealand White Rabbits/ (b) (4) 2420-007</td><td>
<table>
<tr><td colspan="4">Belumosudil Exposure in Pilot Prenatal Development to implantation in Rabbits</td></tr>
<tr><td>Dose (mg/kg)</td><td>50</td><td>125</td><td>225</td></tr>
<tr><td>AUC0-24 (ng.h/mL)</td><td>1590</td><td>9290</td><td>23500</td></tr>
<tr><td>Relative Exposure (multiples of 22700*)</td><td>0.07</td><td>0.40</td><td>1.03</td></tr>
</table>
* In patients, belumosudil mean steady-state daily AUC is 22700 ng·h/mL following administration of the recommended dosage of 200 mg QD.
</td></tr>
</table>

5.5 Toxicology

5.5.1 General Toxicology

The Applicant's Position:

GLP-compliant rat and dog general toxicology/toxicokinetic studies of acute [Studies 0500-05015 and 1173-023 (nonGLP)], subchronic (1 and 3 month) [Studies 1173-028 , 1173-029 and 029281], and chronic (6-month rat and 9-month dog) [Studies 029502 and 8289750] duration have been completed. These studies were dosed orally (intended clinical route of administration) and utilized comparable and representative belumosudil drug substance. All definitive repeat-dose toxicology studies were conducted in accordance with GLP and currently accepted International Conference on Harmonization (ICH)/FDA guidelines.

The primary nonclinical toxicology finding in the range of or modestly above clinically relevant exposures were limited to changes in hepatic (transaminitis, hypertrophy/increased organ weight, and cholestasis/inflammation), renal (increased blood urea nitrogen [BUN], tubular changes, pigmentation, intracellular protein droplets in the epithelium), gastrointestinal (decreased appetite), and hematopoietic/immunologic (anemia with regeneration and thymic/splenic lymphoid depletion) systems.

The FDA's Assessment:

Toxicology studies including acute, short-term, and chronic studies were reviewed by FDA divisions supporting non-oncology indications. The relevant study reviews are summarized and modified below to fit the review for the current indication. A detailed review of the 26-week rat study and the 3-month dog study are included. Since the belumosudil-related toxicities were more prominent in the 3-month dog study than in the 39-week dog study, the 3-month study was chosen for the detailed review.

Study title/ Study number: 26 Week Oral Gavage Toxicity Study in Rats with a 13 Week Interim Sacrifice and a 4 Week Recovery Period/029502

Key Study Findings

- There were 7 deaths in belumosudil treated rats in the main study, 2 females at LD (50 mg/kg/day), and 5 females at HD (275 mg/kg/day). The cause of deaths at 2 HD rats is due to toxicities in the kidney characterized by inflammation/necrosis of the cortical epithelium. In addition, there were 5 deaths in toxicokinetic animals (male and female at 50 mg/kg/day, 2 females at 125 mg/kg/day and one male at 275 mg/kg/day)
- Belumosudil-induced toxicity was observed in multiple tissues including in GI tract (decreased appetite), liver, kidney, and reproductive organs in the surviving animals.
    - Dose-dependent decreases in body weight gain and food consumption at all doses.
    - Liver toxicity: Increased liver weights and diffuse hypertrophy of hepatocytes occurred at all doses; increases in GGT, ALP, and total bilirubin, and multifocal hepatocellular vacuolation at HD.
    - Kidney toxicity: Intracellular protein droplets in the epithelium of the outer stripe cortex occurred at all doses. In addition, tubular basophilia and gold pigmentation of the outer stripe cortex were observed at MD and HD.
    - Reproductive organ toxicity: Lower organ weights were observed in both sexes. Lower uterus weights correlated with uterine/cervical hypoplasia, and decreased follicular development was also observed in females at HD. In males, lower epididymis and testes weights correlated with sperm degeneration that increased in severity following the recovery period.
    - In the recovery necropsy, the incidence and severity were generally, except for spleen and testes, less than observed in animals terminated at the main necropsy.

Conducting laboratory and location: (b) (4)
GLP compliance: Yes

Methods	
Dose and frequency of dosing:	0, 50, 125 or 275 mg/kg/day for 13 or 26 weeks + 4 weeks recovery; once daily dosing
Route of administration:	Oral Gavage
Formulation/Vehicle:	0.4% methylcellulose 400 cp/water
Species/Strain:	Rat/Sprague-Dawley
Number/Sex/Group:	Main study: 10/sex/group (Control, LD, MD, HD) – Week 13 (Day 92, interim sacrifice)

	15/sex/group (Control, LD, MD, HD) – Week 26 (Day 183, terminal sacrifice) Recovery: 5/sex/group (Control and HD)– Interim (Week 17) and terminal (Week 30)
Age:	8 weeks
Satellite groups/ unique design:	Toxicokinetics: 3/sex/group control 18/sex/group (LD, MD, HD)
Deviation from study protocol affecting interpretation of results:	No

Observations and Results: changes from control

Parameters	**Major findings**
Mortality	

Mortality in Rats from the Main Study

Animal#	**Sex**	**Dose (mg/kg/day)**	**Day of Death**	**Cause of death (COD) Pathologists findings**
1236	Female	LD (50)	17	Found Dead COD: Gavage Error Microscopic findings: Decreased Thyroid Colloid
1253	Female	LD (50)	134	Moribund Sacrifice COD: Cage Related Injury (Malocclusion) Microscopic findings: adrenal hypertrophy, Liver hypertrophy, increased lymphocyte in the spleen, thymic depletion, decreased thyroid colloid and thyroid follicular hypertrophy
1387	Female	HD (275)	92	COD: Blood Collection Injury
1388	Female	HD (275)	85	Found Dead COD: Undetermined (Applicant's assessment) Microscopic findings: Minimal, diffuse, bilateral gold pigmentation of the epithelium of the proximal tubules localized to the outer stripe of the renal cortex; mild, diffuse, bilateral

				hypertrophy of the adrenal cortex; moderate, diffuse hypertrophy of centrilobular and midzonal hepatocytes; and mild, diffuse depletion of lymphocytes of the thymic cortex.
1298	Female	HD (275)	92	Moribund Sacrifice COD: Fractured Tibia Microscopic findings: Adrenal hypertrophy, basophilia and gold pigmentation outer stripe renal cortex tubules, liver hypertrophy, increased lymphocyte in the spleen, decreased thyroid colloid and thyroid follicular hypertrophy
1299	Female	HD (275)	159	Found Dead COD: Moderate, diffuse, bilateral, necrosis of kidneys Microscopic findings: adrenal hypertrophy moderate, diffuse, bilateral, necrosis of the epithelium lining the proximal tubules of the outer stripe renal cortex, liver hypertrophy, increased lymphocyte in the spleen, thymic depletion, decreased thyroid colloid and thyroid follicular hypertrophy.
1302	Female	HD (275)	36	Moribund Sacrifice COD: Related to solid skin mass - moderate, locally extensive acanthosis and hyperkeratosis. marked, locally extensive ulceration and marked, locally extensive, chronic dermal inflammation

Mortality in Toxicokinetics Study

Animal#	Sex	Dose (mg/kg/day)	Day of Death	Cause of death (COD) Pathologists finding
1139	Male	LD (50)	106	Moribund Sacrifice; Broken mandible
1326	Female	LD (50)	13	Found Dead; Inflated lungs
1343	Female	MD (125)	71	Found Dead; Thickened pericardium, enlarged heart and fluid in pericardial sac

				likely drug related.
1348	Female	MD (125)	143	Moribund Sacrifice; Thymus mass
1371	Female	HD (275)	14	Found Dead; Dark Red Inflated Lungs

[1]An abbreviated postmortem examination was performed on rats derived from the toxicokinetic groups that died or were sacrificed moribund on study.

Clinical Signs

Slight increase in salivation and dose-dependent increase in the incidence of hair loss in the belumosudil-treated animals.

Body Weights

Final mean body weights (Day 182) were lower in the belumosudil-treated animals than concurrent controls in both males (↓6% to 12%) and females (↓14% to 23%). An early (Week 1) decline in food consumption that persisted through Week 10 contributed to the lower body weights. Body weights in HD rats were trending towards recovery at the end of recovery period on Day 210.

Ophthalmoscopy

Unremarkable

Hematology

% Differences in Hematology Parameters Compared to Control

Dose (mg/kg/dose)	**50**		**125**		**275**	
	M	**F**	**M**	**F**	**M**	**F**
Analyte	**(%) Change vs. control mean**					
Day 92						
RBC (M/µL)	↓2	↓9**	↓9**	↓18**	↓24**	↓43**
HGB (g/dL)	↓1	↓8**	↓5**	↓14**	↓19**	↓36**
HCT (%)	↓1	↓9**	↓5**	↓13**	↓20**	↓35**
RET (109/L)	↑5	↑15	↑26*	↑55**	↑72**	↑244**
Platelets (K/ µL)					↑54**	↑51**
Day 183						
RBC (M/µL)	↓3	↓8**	↓11**	↓17**	↓21**	↓58**
HGB (g/dL)	↓1	↓6**	↓8**	↓13**	↓17**	↓46**
HCT (%)	↓1	↓6**	↓9**	↓12**	↓17**	↓42**
RET (109/L)	-	↑17	↑22**	↑92**	↑77**	↑311**
Platelets (K/ µL)	-	-	-	-	↑7	↑27**

(*p<0.05) (**p<0.01)

The changes in hematology tended to recover at the end of the recovery period on Day 210.

Clinical Chemistry

% Differences in Clinical Chemistry Parameters Compared to Control in Rats

Dose (mg/kg/dose)	50		125		275	
	M	F	M	F	M	F
Analyte	(%) Change vs. control mean					
Day 92						
CHE (U/L)	↓22	↓5	↓24	↓51**	↓29	↓68**
TBILI (mg/dL)	-	-	-	-	↑6	↑5*
GGT (U/L)	-	-	-	-	↑2**	↑18**
ALP (U/L)	-	-	-	-	↑1.3**	↑2**
Day 183						
CHE (U/L)	-	↓3	↓1	↓45**	↓8	↓69**
TBILI (mg/dL)	-	-	-	-	↑6	↑6*
GGT (U/L)	-	-	-	-	↑4**	↑18**
ALP (U/L)	-	-	-	-	↑1.1	↑2**
Day 211 (recovery)						
CHE (U/L)	-	-	-	-	↓15	↓45**

(*p<0.05) (**p<0.01)
CHE= Cholinesterase
The elevated TBILI, GGT, and ALP on Day 92 and Day 183 were compared to control and tended to normalize in the absence of dosing.

Urinalysis

MD and HD: There was an increased incidence and severity associated with the presence of leukocytes (dip-stick) in the urine of male and female rats.

Gross Pathology

Scheduled sacrifice: HD male: Enlarged liver (Day 183) associated microscopically with moderate, diffuse hypertrophy of the centrilobular and mid-zonal hepatocytes.
Recovery sacrifice: HD male: Bilateral small testes correlated microscopically with marked, diffuse bilateral degeneration of spermatogenic elements in the seminiferous tubules.

Organ Weights

Organ weight Changes Compared to Control in Rats

Dose (mg/kg/dose)	50		125		275	
Sex	M	F	M	F	M	F
Day 92						
Liver (g)	-	↑31%	-	↑74%	↑63%	↑161%
Heart (g)	-	↑43%	-	↑36%	↑15%	↑32%
Spleen (g)	-	-	-	↑20%	↑21%	↑68%

Thymus (g)	-	-	↓29%	-	-	↓37%
Adrenal Glands (g)	-	-	-	↑22%	-	↑32%
Kidneys (g)	-	-	-	-	-	↑11%
Thyroid (g)	↑9%	↑15%	↑11%	↑5%	↑26%	↑10%
Uterus (g)	NA	↓19%	NA	↓28%	NA	↓40%
Epididymides (g)	↓6%	NA	↓5%	NA	↓12%	NA
Testes (g)	-	NA	-	NA	↓4%	NA
Day 183						
Liver (g)	-	-	↑35%	↑47%	↑74%	↑105%
Heart (g)	-	-	↑14%	↑17%	↑16%	↑36%
Spleen (g)	-	-	-	↑20%	-	↑110%
Thymus (g)	-	↓28%	-	↓40%	↓26%	↓46%
Adrenal Glands (g)	-	↑19%	-	↑23%	-	↑24%
Kidneys (g)	-	-	-	↑10%	-	-
Thyroid (g)	-	-	-	-	↑16%	-
Uterus (g)	NA	↓18%	NA	↓26%	NA	↓44%
Epididymides (g)	-	NA	↓4%	NA	↓5%	NA
Testes (g)	-	NA	↓4%	NA	↓5%	NA

Increased liver, heart, kidney, and adrenal weights, and decreased thymus weights were observed on Day 92 and Day 183 and tended to recover at the end of the recovery period .

Histopathology

Histopathology findings Day 92 (interim) and Day 183 (Main Terminal Sacrifice)

Dose (mg/kg/day)		**0**		**50**		**125**		**275**	
Sex		**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
	n=Day 92	10	10	10	9	10	10	10	9
	n=Day 183	15	15	15	14	15	15	15	12
Tissue	Finding								
Histopathology – Interim Sacrifice (Day 92)									
Kidney									

Increased Intracellular Protein Droplets Outer Stripe Cortex	0	0	0	0	10 (6**/4***)	2*	10 (6**/4***)	1*
Multifocal Tubular Basophilia Outer Stripe Cortex	-	0	-	0	-	0	-	9*
Bilateral Gold Pigmentation Proximal Tubule Outer Stripe Cortex	-	0	-	0	-	0	-	5*
Liver								
Diffuse Hypertrophy Hepatocytes	0	0	0	0	10**	9**	8***	7***
Thymus								
Diffuse Depletion Thymic Cortex Lymphocytes	0	0	0	0	5**	7 (4*/3**)	10 (2*/8**)	7 (2*/5**)
Spleen								
Diffuse Increase in the Lymphocytes Associated with the Mantle Layer of Splenic Lymphoid Nodules	0	0	0	0	9**	7**	9**	9**
Adrenal Gland								
Diffuse Bilateral Hypertrophy of the Adrenal Cortex	0	0	0	0	0	9 (1*/8**)	10 (1*/9**)	9**
Multifocal Bilateral Necrosis	-	0	-	0	-	0	-	1**
Thyroid Gland								

Diffuse Bilateral Decrease in Colloid in Thyroid Follicles		0	0	2**	2*	10 (8**/2***)	3*	10 (5**/5***)	6 (2**/4***)
Diffuse Bilateral Hypertrophy Thyroid Follicle Lining Epithelium		0	0	1*	0	10 (6*/4**)	1*	10 (3*/7**)	6 (2*/4**)
Epididymides									
Multifocal Bilateral Degeneration Spermatozoal Elements Efferent Ducts		0	NA	0	NA	0	NA	2*	NA
Testes									
Multifocal Unilateral or Bilateral Degeneration Spermatogenic Seminiferous Tubule		0	NA	0	NA	2*	NA	4*	NA
Cervix	Hypoplasia		0		0		0		2***
Ovary									
Decreased Follicular Development (Bilateral)			0		0		0		4 (2**/2***)
Uterus	Hypoplasia		0		0		0		3 (1**/2***)
Histopathology – Terminal Sacrifice (Day 183)									
Kidney									
Increased Intracellular Protein Droplets Outer Stripe Cortex		0	0	1**	1*	12 (2*/9**) (1***)	0	15 (10**/5***)	0

Multifocal Tubular Basophilia Outer Stripe Cortex	0	0	0	0	14*	14*	13 (12*/1**)	12 (3*/9**)
Bilateral Gold Pigmentation Proximal Tubule Outer Stripe Cortex	0	0	0	0	3*	4*	2*	9*
Multifocal Tubular Dilatation	1*	3*	2*	2*	3*	2*	6 (5*/1**)	5 (3*/2**)
Liver								
Diffuse Hypertrophy Hepatocytes	0	0	14*	14 (1**/13***)	15**	15***	15 (1**/14***)	12***
Hepatocellular Vacuolation (Multifocal)	0	0	0	1*	0	0	1*	3*
Thymus								
Diffuse Depletion Thymic Cortex Lymphocytes	0	0	0	14 (4*/10**)	0	8**	14 (6*/8**)	3 (2**/1***)
Spleen								
Diffuse Increase Splenic Lymphocytes	0	0	0	8	13**	13**	13**	12**
Adrenal Gland								
Diffuse Bilateral Hypertrophy of the Adrenal Cortex	0	0	0	13**	0	14**	14 (3*/11**)	12**
Thyroid Gland								
Diffuse Bilateral Decrease in Colloid in Thyroid Follicles	0	0	8*	7 6*/1**)	14 (8*/6**)	14 (4*/8**) (2***)	15 (8**/7***)	11 (5**/6***)
Diffuse Bilateral Hypertrophy	0	0	0	1*	10*	7*	14 (4*/10**)	11

Thyroid Follicle Lining Epithelium									(4*/7**)
Epididymides									
Multifocal Bilateral Degeneration Spermatozoal Elements Efferent Ducts		0	NA	0	NA	0	NA	1*	NA
Testes									
Focal/Multifocal Unilateral or Bilateral Degeneration Spermatogenic Seminiferous Tubule		1*	NA	7*	NA	8*	NA	10 (9*/1**)	NA
Cervix	Hypoplasia		0		0		0		1***
Uterus	Hypoplasia		0		0		0		1***

Minimal (*) Mild (**) Moderate (***) Marked (****)

Recovery necropsy Day 120 (interim) and Day 211 (terminal) (Control and HD):

At the interim recovery necropsy (Day 120), the findings in the HD animals showed toxicities in kidney (minimal, increased intracellular protein droplets in the tubular epithelium of the outer stripe of the cortex and mild, increased intracellular protein droplets in the tubular epithelium of the outer stripe of the cortex), and male reproductive organs (minimal multifocal, bilateral degeneration in epididymides and testes).

At the terminal recovery necropsy (Day 211), findings in the HD animals in the adrenal glands (minimal, diffuse bilateral hypertrophy/mild, multifocal bilateral cystic degeneration of the adrenal cortex), , kidneys (minimal, multifocal basophilia of tubules in the outer stripe of the cortex, minimal, increased intracellular protein droplets in the tubular epithelium of the outer stripe of the cortex), liver (moderate, diffuse hypertrophy of centrilobular and midzonal hepatocytes), thyroid glands(diffuse bilateral decreased colloid, and diffuse, bilateral hypertrophy of the lining epithelium of the thyroid follicles), and male reproductive organs (moderate, diffuse, bilateral degeneration of spermatozoa elements, and minimal/marked

and diffuse, multifocal, bilateral degeneration of spermatogenic elements of the seminiferous tubules.

LD: low dose; MD: mid dose; HD: high dose.

Study title/ Study number: KD025: 3-Month Oral Toxicity and Toxicokinetic Study in Dogs with a 28-Day Recovery Period/029281

Key Study Findings

- The HD (125 mg/kg/day) was not tolerated, leading to the unscheduled euthanasia of two males on Day 21 and the discontinuation of dosing in the remaining dogs of this group. COD is likely due to adverse effects in kidney (multifocal, bilateral, infarcts, cast, and necrosis) and liver (multifocal biliary stasis)
- Belumosudil-induced toxicities included liver toxicity (multifocal centrilobular biliary stasis, diffuse atrophy of centrilobular hepatocytes and increased ALT/total bilirubin levels), kidney toxicity (gold/brown pigmentation in the epithelium of the renal proximal tubules), hemolymphoid system toxicity (decreased red cell mass (RBCs, HGB and HCT), increased platelet counts, lymphocyte depletion in the thymus and spleen and effects on spermatogenesis (spermatozoa degeneration of the epididymis and testicular seminiferous tubules) at the LD and MD on Day 92.
- Effects on the liver, and kidney were present at MD, while lymphoid organs, and reproductive organs tended to recover by Day 121 (end of the recovery period).

Conducting laboratory and location: (b) (4)
GLP compliance: Yes

Methods	
Dose and frequency of dosing:	0, 35, or 70 mg/kg for 13 weeks + 4 weeks Recovery 125 mg/kg (HD) for 20/21 days + 2 weeks Recovery; once daily dosing
Route of administration:	Oral, gelatin capsule; bulk drug weights were corrected for salt and purity (correction factor 1.23)
Formulation/Vehicle:	Control group received empty gelatin capsules
Species/Strain:	Dog/Beagle
Number/Sex/Group:	Main study: 5/sex/group (Control, LD and MD) – Day 92 2/sex (HD) – Terminal Day 51/50 8 males/10 males (HD) Terminal Day 51/50 – No Tissue/Necropsy Recovery: 3/sex/group (Control, LD and MD Only) – Day 121

	4/sex (Control) – Day 121 – No Tissue/Necropsy
Age:	7-8 Months / 4.8 to 9.2 kg (at randomization)
Deviation from study protocol affecting interpretation of results:	No

Observations and Results: changes from control

Parameters	Major findings
Mortality	Two male HD animals were euthanized moribund on Day 21 and the dosing was discontinued for the remaining animals in this group. Euthanasia at the HD was due to the poor body condition (↓28% body weight/↓36% food consumption) during the first week of dosing that continued until euthanasia, but the specific cause of moribundity was not identified. Both euthanized males presented with microscopic findings in bone marrow (hypocellularity), liver (multifocal biliary stasis), kidney (multifocal, bilateral infarcts, casts, necrosis), GI tract (black abnormal contents; likely hemorrhage), lymph nodes (diffuse depletion), and spleen (diffuse depletion of lymphocytes). Evidence of renal injury was observed in 1 of the 2 HD males terminated moribund.
Clinical Signs	Emesis, colored vomit, decreased food intake, decreased activity, thin body appearance, and decreased and unformed/loose feces were observed during the dosing phase and occurred with increased frequency in the belumosudil treated groups compared to control. Thin body and weight loss at HD prompted food supplementation.
Body Weights	Lower body weight gains corresponded with decreases in food consumption despite supplementation of diet with canned food at the LD and MD compared to control. HD: Mean body weights on Day 21/20 were reduced by ↓25% and ↓19% in males and females, respectively. MD: Mean body weights on Day 91 were reduced by ↓14% and ↓3% in males and females, respectively. LD: Unremarkable Body weights tended to increase at the end of the recovery period.
Ophthalmoscopy	Unremarkable
ECG	ECG examinations during Week 1, Week 13 and recovery (Week 17) did not reveal any abnormal findings at 4 hours post-dose. The selected examination time was consistent with the Tmax at the LD; however, at the higher dose levels (MD and HD), the Tmax values ranged from 7 to 8 hours.

Hematology

% Differences in Hematology Parameters Compared to Control in Dogs

Daily Dose (mg/kg)	35		70		125a	
Sex	M: 8	F: 8	M: 8	F: 8	M: 12	F: 12
RBC (M/µL)[b]	↓9%	↓9%	↓20%	↓24%	NA	NA
Hemoglobin (g/dL)[b]	↓6%	↓9%	↓18%	↓22%	NA	NA
Hematocrit (%)[b]	↓6%	↓9%	↓17%	↓21%	NA	NA

[a] Not tolerated; high dose cessation on Day 21; animals euthanized on Day 51 (limited histopathology and no TK conducted)
[b]percent difference from controls is shown.

Clinical Chemistry

Mean ALT tended to increase in males (↑2-Fold) and females (↑1.5-Fold) at the MD on Day 85 relative to predose values. Mean ALT values were trending towards recovery in both sexes following the recovery period (Day 121).
Total bilirubin was elevated at the MD in males (↑4-Fold) and females (↑8-Fold). Total bilirubin normalized in both sexes following the recovery period (Day 121).

Urinalysis

Unremarkable

Gross Pathology

Interim Recovery Termination on Day 50/51 - Exposed to 125 mg/kg - Day 1 to Day 21
Unremarkable
Terminal (Day 92) and Recovery Sacrifice (Day 121)
Unremarkable

Organ Weights

Interim Recovery Termination – Day 50/51
HD: Organ weights were not derived from control dogs during the interim sacrifice on Day 50/51. The Sponsor reported that the relative (to body/to brain) organ weights derived from the spleen and thymus were lower in the 2 males and 2 females terminated on Day 50/51 when compared to the terminal (Day 92) necropsy controls.
Terminal Sacrifice – Day 92

Dose (mg/kg/dose)	**35**		**70**		**125**	
Sex	M: 8	F: 8	M: 8	F: 8	M: 12[a]	F: 12[a]
Organ						
Liver (g/kg)b	↑37%**	↑17%	↑7%	↑13%	-	-
Thymus (g/kg)b	↓7%	↓13%	↓50%*	↓50%**	-	-
Spleen (g/kg)b	-	↓6%	↓22%	↓31%	-	-

	[a]Not tolerated; high dose cessation on Day 21; animals euthanized on day 51(Limited histopathology and no TK conducted [b]For treated groups, percent difference from controls is shown. "-" = no data
Histopathology	

Histopathology findings Day 92 (Main Terminal Sacrifice) in dogs following 3-month daily dosing

Daily Dose (mg/kg)		**0**		**35**		**70**		**125a**
Tissue	**Finding**	**M:5**	**F:5**	**M:5**	**F:5**	**M:5**	**F:5**	**M:0**
-Liver	Multifocal Biliary Stasis Localized to the Centrilobular Hepatocytes	0	0	0	0	3 (2*/1**)	5 (1*/4**)	-
	Diffuse Atrophy of Centrilobular Hepatocytes	0	0	0	0	1***	1***	-
Spleen	Diffuse Depletion of Lymphocytes Derived from the Periarteriolar Sheaths	0	0	4**	4**	5***	5**	-
Thymus	Diffuse Depletion of Lymphocytes Thymic Cortex	0	0	4 (3**/1***)	4**	5 (1**/2***) (2****)	5 (2**/3***)	-
Kidney	Pigmentation (Gold/brown) Proximal Tubule Cortex Bilateral and Multifocal	0	0	0	0	2 (1*/1**)	3*	-
Epididymis	Multifocal Bilateral	0	NA	1**	NA	1**	NA	-

	Spermatozoa Degeneration									
Testes	Multifocal Bilateral Degeneration of Spermatogenic Elements	0	NA	1**	NA	2**	NA	-		NA
	Multifocal Bilateral Multinucleated Spermatids (Symplasts)	0	NA	1**	NA	2**	NA	-		NA

Minimal (*) Mild (**) Moderate (***) Marked (****)
[a]Not tolerated; high dose cessation on Day 21; animals euthanized on day 51(Limited histopathology and no TK conducted

Recovery	**Interim Recovery Termination on Day 50/51- Exposed to HD - Day 1 to Day 21)** Findings of minimal to mild multifocal biliary stasis localized to the centrilobular hepatocytes, mild, diffuse depletion of lymphocytes of the periarteriolar sheaths of the splenic white pulp, and diffuse depletion of lymphocytes from the thymic cortex were observed. **Recovery Necropsy on Day 121 – Exposed to (Control, LD and MD Only) – Day 1- Day 92** Findings of minimal to mild multifocal biliary stasis localized to the centrilobular hepatocytes in the liver and minimal to mild multifocal bilateral gold/brown pigment in the kidney persisted at the MD. Other findings in the liver, spleen, thymus, and male reproductive organs were normal at the end of the recovery period.

General toxicology; additional studies

Study title/number: 4-Week Oral Toxicity Study of SLx-2119 in Rats with a 14-Day Recovery Period/1173-028

Belumosudil was administered once daily to Sprague Dawley rats (15/sex for vehicle and HD; 10/sex LD and MD) at doses of 0, 50, 150 or 375 mg/kg/day for 28 days. At the HD, one female

was found dead on study Day 11 and another was euthanized in extremis on study Day 21; an additional TK female was found dead on Day 20. The cause of the deaths appears to be treatment related. Test article-related clinical observations in these animals included decreased activity, hunched posture, pale skin, skin cold to touch, and distention of the abdomen. One low dose female was found dead on Day 26 with no clinical signs and pathology revealed lymphoma. Significant body weight loss was observed in the high dose males (↓33%) and females (↓79%) that persisted throughout the recovery period. There was a dose-dependent reduction in red cell mass in males and females at the MD and HD associated with microscopic findings of minimal erythrocytic or mixed hyperplasia in the bone marrow of females at the MD and males and females at the HD . There was elevated GGT (up to 17-fold) and ALP (up to 2-fold) in the HD animals. Significant increases in the liver weights at the MD in both males (36%) and females (66%) and the HD in both males (80%) and females (130%) correlated with microscopic findings of mild to severe panlobular hepatocyte hypertrophy in the MD and HD males and females. Other findings included a mild increase in BUN (up to 24%) in HD males and females, minimal to mild thymus apoptosis and lymphoid depletion in HD females, and mild to moderate bilateral degeneration/atrophy of the seminiferous tubules in HD in males. Minimal pan lobular hepatocellular hypertrophy was still present following the recovery period in HD males and females.

Study title/number: SLx-2119: A 4-Week Oral Toxicity of SLx-2119 in Dogs With a 14-Day Recovery Period / 1173-029

Gelatin capsules of belumosudil were orally administered to Beagle dogs (6/sex in vehicle and HD; 4/sex/group in LD and MD) once daily at doses of 0, 25, 75 or 200/125 mg/kg/day for 28 days. During Weeks 1 and 2, treatment-related emesis was noted in the MD and HD males and females. From Day 18, the HD treatment was reduced to 125 mg/kg and the frequency of emesis decreased but was still present in MD and HD animals. Thin body appearance observed in males at the HD and at the MD and HD in females was consistent with lower body weight gains (19% decrease in males and 12% decrease in females) and reduced food consumption. Additional clinical signs included lacrimation in males at the MD and HD and at all doses in females. Hematology findings included decreases in red cell mass and increases in reticulocytes, platelets and MCV. Increases in ALP (2-fold), GGT (1.4-fold), and total bilirubin (2-fold) occurred in males and females at the HD. A significant increase in the liver weights in males (48%) and females (26%) correlated to cholestasis (accumulation of bile within the cuniculi) with or without hepatocellular vacuolation. Cholestasis and associated liver weight increases over controls persisted at the end of the recovery period. In addition, reduced thymus weights correlated with increased incidence and/or severity of thymic lymphoid depletion in HD males and females. Thymic lymphoid depletion was not observed in recovery males or females.

Study title/ Study number: 39 Week Oral Toxicity Study in Dogs with a 13 Week Interim Sacrifice and an 8 Week Recovery Period/8289750

Gelatin capsules of belumosudil were orally administered to Beagle dogs (12/sex in vehicle and HD; 8/sex at LD; 10/sex at MD) once daily at doses of 0, 5, 20 or 40 mg/kg/day for 39-weeks. One group of animals were sacrificed at Week 13 (interim) with a recovery sacrifice on Week 17; a second group of animals were sacrificed at Week 39 (terminal) with a recovery sacrifice on Week 47. No unscheduled deaths occurred during the study. Clinical signs included emesis, excessive salivation, and vomitus during the dosing phase and occurred with increased frequency at the MD and HD. Thin body and weight loss at the HD prompted food supplementation. Final mean body weights (Day 274) were lower than in concurrent controls in both males (↓15%) and females (↓18%) and coincided with a decline in food consumption. Body weights tended to increase at the end of the recovery period. Hematology findings included transient increases (3- to 8-fold) in ALT levels in individual animals on Week 13 and Week 39 at the MD and HD. An increase in liver/gallbladder weights was noted in males given the MD but not the HD on Day 91. Microscopic findings on Week 13 included mononuclear cell infiltrates with increased severity in most of the HD males and degeneration/necrosis of hepatocytes at the MD and HD on Day 91, consistent with the increase liver enzymes.

5.5.2 Genetic Toxicology

The Applicant's Position:

Belumosudil is not considered genotoxic or mutagenic. There was no evidence of genotoxicity in the in vitro Bacterial Reverse Mutation Assay (GLP, Study AB44FM.503.BTL), the *in* vitro Mammalian Chromosome Aberration Test (GLP, Study AB44FM.341.BTL), or the in vivo Mammalian Erythrocyte Micronucleus Test mutagenicity assay (GLP, Study AB44FM.125.BTL).

The FDA's Assessment:

FDA concurs with the Applicant's assessment. Additional details regarding the studies are provided in the review below.

In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

Study title/ number: Bacterial Reverse Mutation Assay/AB44FM.503.BTL

Key Study Findings:

- Belumosudil did not increase the number of revertant colonies in the tester strains with or without metabolic activation up to 5000 µg per plate.
- Belumosudil precipitate was observed at ≥50 µg per plate, and toxicity (growth inhibition) resulting in a reduction in revertant count was observed at 500 µg per plate

with TA1535 in the absence of S9 in the toxicity-mutation assay.

Test system: Salmonella typhimurium strains TA98, TA100, TA1535, and TA1537, and Escherichia Coli strain WP2 uvrA in the presence or absence of rat liver S9 extract.
GLP compliance: Yes

Study is valid: Yes.

<u>In Vitro Assays in Mammalian Cells</u>

Study title/ number: *In Vitro* Mammalian Chromosome Aberration Test/AB44FM.341.BTL

The study was reviewed by another FDA division for a non-oncology indication. The review is summarized below to fit this assessment.

Key Study Findings:

- Belumosudil was negative for the induction of chromosome aberrations using human peripheral blood lymphocytes (HPBL).
- A visible precipitate was observed in the treatment medium at a concentration of 250 µg/mL. Cytotoxicity defined as at least a 50% reduction in the mitotic index in the treatment culture relative to the vehicle control, was observed at ≥50 µg/mL in the nonactivated and S9 activated 4-hour exposure groups, and also at ≥25 µg/mL in the 20-hour non-activated group in the definitive chromosome aberration assay.

Test system: Cultured HPBL with or without metabolic activation.

GLP compliance: Yes

Study is valid: Yes

<u>In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)</u>

Study title/ number: Mammalian Erythrocyte Micronucleus Test/AB44FM.125.BTL

Key Study Findings:

- A single oral administration of belumosudil at doses up to and including 2000 mg/kg did not induce an increase in the incidence of micronucleated polychromatic erythrocytes (MPCE) compared to vehicle control in either male or female rats.
- Belumosudil did not cause any noteworthy toxicities in mice up to 2000 mg/kg.

Test system: Rat

GLP compliance: Yes

Study is valid: Yes

5.5.3 Carcinogenicity

The Applicant's Position:

No carcinogenicity studies have been conducted with belumosudil based on the proposed indication.

The FDA's Assessment:

No carcinogenicity studies have been conducted with belumosudil. The Applicant submitted a request for a waiver of *in vivo* carcinogenicity studies for belumosudil for the treatment of chronic graft-versus-host (cGVHD) disease. The submission did not adequately address the carcinogenicity potential of belumosudil for chronic use. Given that the patient population includes subjects with non-cancerous conditions and long life expectancy, rodent studies should be conducted to determine the risk of carcinogenicity from belumosudil.

5.5.4 Reproductive and Developmental Toxicology

The Applicant's Position:

Fertility and Early Embryonic Development

This GLP fertility and early embryo-fetal developmental toxicity study (Study 2420-008) in Sprague-Dawley Rats was conducted with belumosudil to determine the toxic effect of belumosudil on female estrous cycle, tubal transport, implantation and development of the embryo, and to determine functional effects on male fertility. The study was conducted in accordance with GLP and currently accepted ICH/FDA guidelines.

Briefly, male rats treated with belumosudil at the highest dose evaluated (275 mg base/kg/day) for 70 days prior to mating (when mated to untreated females) had reduced fertility, abnormal sperm findings (reduced motility, reduced concentration, and increased percentage of abnormal sperm), and testes/epididymis organ changes (decreased organ weights and degenerative histopathology). Fertility indices and all sperm parameters in recovery males at 275 mg base/kg/day were comparable to concurrent controls at the end of recovery phase, indicating potential reversibility of these parameters. No adverse fertility changes were observed at lower dose levels (50 and 150 mg/kg/day). Male fertility findings were generally at higher then clinically relevant exposures. Area under the curve (AUC) at 275 mg base/kg (191000 ng.h/mL) and 150 mg base/kg (70100 ng.h/mL) was approximately 8.4 and 3 times, respectively, the exposure in humans at the recommended dose of 200 mg/day (22700 ng.h/mL).

Female fertility was not impacted when female rats were treated with belumosudil in this study at the highest dose evaluated (275 mg base/kg/day) for 14 days prior to mating and during early embryonic development (when mated to untreated males). Adverse belumosudil -related findings (increased post-implantation loss/resorptions and decreased number of viable embryos) regarding early embryonic development were observed at 275 mg base/kg/day. No adverse early embryo-fetal findings were observed at lower dose levels (50 and 150 mg/kg). AUC at 275 mg base/kg (209000 ng.h/mL) and 150 mg base/kg (99500 ng.h/mL) was approximately 9.2 and 4.4 times, respectively, the exposure in humans at the recommended dose of 200 mg/day (22700 ng.h/mL).

Embryo-Fetal Development

Published studies have shown that targeted ROCK2 receptor knockdown in homozygous knockout mice have placental dysfunction, intrauterine growth retardation, and fetal death [Pelosi et al 2007, Thumkeo et al 2003]. Belumosudil has also been evaluated in standard GLP rat and rabbit embryo-fetal toxicology studies (Studies 2420-006 and 2420-007). The studies were conducted in accordance with GLP and currently accepted ICH/FDA guidelines.

In the rat GLP embryo-fetal toxicity study (Study 2420-006), oral administration of belumosudil resulted in maternal toxicity (reduced body weight gain and low food consumption) at doses ≥ 50 mg/kg/day. Fetal effects included decreased fetal weight at ≥ 150 mg/kg/day (approximately 3.9 times the human exposure at the recommended clinical dose (200 mg once daily) based on AUC).

In the rabbit GLP embryo-fetal toxicity study (Study 2420-007), oral administration of belumosudil resulted in maternal toxicity (body weight loss, reduced body weight gain, low food consumption, and mortality) at doses ≥ 125 mg/kg/day. Fetal effects included abortions, increased post-implantation loss, decreased percentage of live fetuses, decreased fetal body weight, and skeletal/external malformations in fetuses at doses ≥ 125 mg/kg/day (approximately 0.4 times the human exposure at the recommended clinical dose (200 mg once daily) based on AUC).

In summary, belumosudil has demonstrated potential for embryo-fetal toxicity and/or malformations at clinically relevant exposures.

Pre- and Postnatal Development

No pre- and post-natal development studies have been conducted with belumosudil.

The FDA's Assessment:

The FDA agrees with the summary of the study results described above. Additional details of the GLP fertility/early embryonic development, embryo-fetal development in rats and rabbits etc., are included below. We note that the non-GLP pilot embryo-fetal developmental toxicity and toxicokinetic study in Sprague-Dawley rats (study number 2420-004) was not discussed.

This study was reviewed in detail due to findings of maternal toxicity, and fetal-developmental effects observed in the belumosudil treated animals.

Fertility and Early Embryonic Development

Study title/ number: KD025: A combination study of fertility and early embryonic development to implantation in Sprague-Dawley rats/2420-008
Key Study Findings

- Treated males:
  - Belumosudil induced generalized toxicity and statistically significant effects on fertility and reproductive indices at 275 mg/kg/day. Fertility indices returned to normal on Day 77 of the recovery period. The lower organ weights (testes and epididymis) and microscopic findings were still present at the end of the recovery period but tended to recover compared to dosing period.
- Treated females:
  - Adverse findings in female rats (treated with belumosudil or untreated but mated with treated males) included increased estrous cycle, decreased corpora lutea, increased post-implantation loss, increased number of resorptions, and decreased number of viable embryos were observed at 275 mg base/kg/day compared to concurrent control and historical control data.
- Exposures at 275 mg/kg/day for males (AUC0-24=191000 ng*hr/mL) and females (AUC024=209000 ng*hr/mL) were approximately 8- and 9-fold higher, respectively, than at the recommended clinical dose (AUC0-24=22700 ng*hr/ml).

Conducting laboratory and location	(b) (4)
GLP compliance:	Yes

Methods	
Dose and frequency of dosing:	Males: 0, 50, 150, or 275 mg/kg/day; once daily dosing for 70 days prior to pairing through mating (with untreated females) and post-mating period. Males designated for the recovery phase were dosed for 70 days, and then received a 77 day recovery period. Females: 0, 50, 150, or 275 mg/kg/day; once daily dosing starting 14 days prior to pairing through Gestation Day (GD) 7; females with no evidence of mating were dosed for 7 days following the completion of the mating period.
Route of administration:	Oral gavage (10 mL/kg)

<table>
<tr><td>Formulation/Vehicle:</td><td>0.4% (w/w) methylcellulose (400 cps) in distilled water</td></tr>
<tr><td>Species/Strain:</td><td>Rat/Crl:CD (SD)</td></tr>
<tr><td>Number/Sex/Group:</td><td>25/sex/group</td></tr>
<tr><td>Satellite groups:</td><td>Toxicokenetics: 10 males and 10 females at 50, 150, or 275 mg/kg/day and 3 males and 3 females in the vehicle control group were dosed daily via oral gavage for either 14 (females) or 70 (males) days.</td></tr>
<tr><td>Study design:</td><td>
<table>
<tr><th>Mating groups</th><th>Male</th><th>Female</th><th>Rationale</th></tr>
<tr><td>1</td><td>Untreated (n=25)</td><td>Treated (14 Days prior to mating through mating and to GD7) (n=25)</td><td>To evaluate specific female effects</td></tr>
<tr><td>2</td><td>Treated (70 Days prior to mating through mating to euthanasia) (n=25)</td><td>Untreated (n=25)</td><td>To evaluate specific male effects</td></tr>
<tr><td>3</td><td>Treated (70 Days) and allowed to recover (77 Days) N=25</td><td>Untreated (n=10)</td><td>To evaluate the long-term effects in males following recovery.</td></tr>
</table>
Females: For the treated females, the day on which positive evidence of copulation was observed was considered gestation day (GD) 0. Females with no evidence of mating were dosed for 7 days following the completion of the mating period.
Males: Untreated males were first paired with the treated females (first mating period) and then following 70 days of dosing, paired with untreated females (second mating period) until the GD13 uterine exams.
</td></tr>
</table>

	Males assigned to the recovery phase were dosed for 70 days and allowed to recover for 70 days prior to pairing with untreated females (1:1).
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Parameters	**Major findings**
Treated Males (Mated with Untreated Females)	
Mortality	There were no belumosudil-treatment related mortalities.
Clinical Signs	Abnormal feces (few/absent or discolored), salivation (at 150 and 275 mg/kg/day) and thin body at 275 mg/kg/day. In addition, significantly lower body weight gains and reduced food consumption occurred at 150 and 275 mg/kg/day compared to respective vehicle control groups.
Body Weights (g)	Lower mean body weight gains during some intervals in the test article-treated groups. Premating: Days 1-67, ↓9%, ↓26%** and ↓43% ** at 50, 150 and 275 mg/kg/day, respectively. Pairing (Days 71-95): During Days 92-95, ↓49%, ↓56% and ↓83% at 50, 150 and 275 mg/kg/day, respectively. ** statistically significant compared to control group.
Food consumption (g/animal/day)	Premating: At Week 10 ↓ 14%** at 275 mg/kg/day Post-mating: At Week 15 ↓ 10%** at 275 mg/kg/day ** statistically significant compared to control group.
Fertility	**Reproductive and Fertility Indices of Treated males**

Dose (mg/kg/day)	**0**	**50**	**150**	**275**
No. Evaluated	25	25	25	25
No. of Males Paired	25	24	25	25
No. of Males Mated	24	23	25	24
No. of Males Impregnating a Female	24	23	23	18
Male Mating Index (%)	96.0	95.8	100.0	96.0
Male Fertility Index (%)	96.0	95.8	92.0	72.0* (HCD 76-100%)
Male Fecundity Index (%)	100.0	100.0	92.0	75.0* (HCD 79-100%)

	Females with Confirmed Mating Day	24	24	24	25
	Mean Copulatory Interval (Days)	3.7	4.1	3.5	2.8
Necropsy findings					
	Dose (mg/kg/day)	**0**	**50**	**150**	**275**
	Macroscopic findings				
	Number Examined	24	24	25	25
	Epididymis Left				
	Small				
	Mild	0	0	0	6
	Moderate	0	0	0	2
	Epididymis, right				
	Small				
	Mild	0	0	0	2
	Moderate	0	0	0	3
	Organ Weights (%)				
	Number Examined	24	24	25	25
	Epididymis (g)	1.5	-1	-6*	-27**
	Epididymis/BWt (%)	0.2	+6	+8	-7
	Testes (g)	4	-2	-5	-18**
	Testes/BWt (%)	0.7	+5	+9	+6
	Microscopic Observations				
	Epididymis, left				
	Luminal cellular debris				
	Minimal	0	0	0	8
	Mild	0	0	0	9
	Testes, left				
	Degeneration/atrophy, seminiferous tubules				
	Minimal	1	0	0	8
	Mild	0	0	0	3
	Moderate	0	0	0	1
	Severe	0	0	0	4
	Sperm Evaluation				
	Sperm % motility	92	95	88	59** *(HCD 83.5- 97.2%)*

	Total Sperm Count per Cauda Epididymis x 10^8	3.4	3.2	3.3	2** *(HCD 2.6-3.9%)*
	Sperm Concentration per gram Cauda Epididymis x 10^8	10	10	11	7** *(HCD 8.4-12.4%)*
	% Abnormal	4	2.5	3.7	41.5** *(HCD 2.4-8.2%)*
	HCD = Historical Control Data				
Untreated Females (Mated with Treated Males)					
Necropsy Observations	Noteworthy findings were limited to a statistically significant decrease in mean number implantation sites, an increase in mean percent preimplantation loss, and a statistically significant decrease in mean number of viable embryos at 275 mg/kg/day.				
	Cesarean Section Observations				
	Dose (me/kg/day)	**0**	**50**	**150**	**275**
	Mean No. Implantation Sites	13.9	13.3	12.9	11.6**
	Mean % Preimplantation Loss	10.04	14.20	8.87	20.96
	Mean No. Viable Embryos	13.3	12.6	12.3	11.1**
	Mean % Postimplantation Loss	4.65	5.94	4.12	3.80
Treated Females (Mated with Untreated Males)					
Mortality	There were no test article related mortalities.				
Clinical Signs	Abnormal feces (few/absent or discolored) and thin body (premating/mating/gestation) at 275 mg/kg/day. In addition, significantly lower body weight gains and reduced food consumption occurred at 150 and 275 mg/kg/day compared to respective vehicle control groups.				
Body Weights (g)	Beginning on study day 4 and throughout the premating and gestation period, female mean body weights at 150 (3% to 5% lower) and 275 (6% to 13% lower) mg/kg/day were statistically lower in comparison to concurrent control values. A compensatory statistically higher mean body weight change was observed in these same groups following cessation of dosing (GD 7-10 and GD 10-13).				
Food consumption (g/animal/day)	AT 150 and 275 mg/kg, mean food consumption was statistically lower during the premating period (Week 1				

<table>
<tr><td></td><td>and/or 2), and during gestation period, correlated with mean body weight loss and/or lower mean body weight change .</td></tr>
<tr><td>Necropsy Observations</td><td>Uterine Examinations
<table>
<tr><th>Dose (me/kg/day)</th><th>0</th><th>50</th><th>150</th><th>275</th></tr>
<tr><td>Untreated Males</td><td>25</td><td>25</td><td>25</td><td>25</td></tr>
<tr><td>Necropsy Observations</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>Organ Weights (%)</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>Mean Estrous Cycle Length (Days)</td><td>4.3</td><td>4.7</td><td>4.7</td><td>5.4**
(HCD 4.0-5.2%)</td></tr>
<tr><td>No. of Cycles (Count)</td><td>2.4</td><td>2.3</td><td>2.3</td><td>2.1</td></tr>
<tr><td>No. Females Paired</td><td>25</td><td>25</td><td>25</td><td>25</td></tr>
<tr><td>No. Females Mated</td><td>25</td><td>25</td><td>25</td><td>25</td></tr>
<tr><td>No. Pregnant</td><td>25</td><td>25</td><td>25</td><td>24</td></tr>
<tr><td>Female Mating Index (%)</td><td>100.0</td><td>100.0</td><td>100.0</td><td>100.0</td></tr>
<tr><td>Female Fertility Index (%)</td><td>100.0</td><td>100.0</td><td>100.0</td><td>96.0</td></tr>
<tr><td>Female Fecundity Index (%)</td><td>100.0</td><td>100.0</td><td>100.0</td><td>96.0</td></tr>
<tr><td>No. of Females with Confirmed Mating Day</td><td>21</td><td>21</td><td>22</td><td>25</td></tr>
<tr><td>Mean Copulatory Interval (Days)</td><td>2.3</td><td>2.8</td><td>3.1</td><td>2.9</td></tr>
<tr><td colspan="5">Cesarean Section Observations</td></tr>
<tr><td>No. Evaluated</td><td>25</td><td>25</td><td>25</td><td>25</td></tr>
<tr><td>No. Not Pregnant</td><td>0</td><td>0</td><td>0</td><td>1</td></tr>
<tr><td>No. Pregnant</td><td>25</td><td>25</td><td>25</td><td>24</td></tr>
<tr><td>No. Aborted or with Total Resorption of Litter</td><td>0</td><td>0</td><td>0</td><td>2</td></tr>
<tr><td>No. Females with Viable Embryos on GD 13</td><td>21</td><td>21</td><td>22</td><td>22</td></tr>
</table></td></tr>
</table>

No. Pregnant with No Confirmed Mating Date	4	4	3	0	
Mean No. Corpora Lutea	17.7	17.2	16.0	15.0** *(HCD 15.1-20.0)*	
Mean No. Implantation Sites	13.6	15.6	14.6	13.1	
Mean % Preimplantation Loss	22.18	8.75	8.30	14.12	
Mean No. Viable Embryos	13.1	14.9	13.5	10.3	
Mean % Postimplantation Loss	3.55	4.20	8.44	19.42** *(HCD 2.7-11.0%)*	
Mean No. Resorptions	0.5	0.7	1.1	2.8*	

Recovery Males	
Clinical signs	There were no test article related mortalities. Clinical signs included salivation and thin body observed at 275 mg/kg/day. Lower mean body weight gains were observed at 150 and 275 mg/kg/day compared to control throughout the recovery phase. On Day 67 a statistically significant difference (-11% to -16%) was observed at 275 mg/kg/day compared to control. Necropsy findings included small testes and epididymis in 1/10 animals consistent with the decrease in absolute organ weight changes (testes -14%; epididymis -8%) at 275 mg/kg/day, which correlated microscopically with degeneration/atrophy and reduced sperm count/increased abnormal sperm, respectively.

Embryo-Fetal Development

Study title/ number KD025: A Pilot Prenatal Developmental Toxicity and Toxicokinetic Study in Sprague-Dawley Rats/2420-004

Key Study Findings

- Belumosudil caused both maternal toxicity and fetal toxicity
  - Maternal toxicity was characterized by decreased body weight gains and reduced food consumption at all doses.
  - Increased post-implantation loss (early resorptions) was observed at 300 mg/kg/day.

- Fetal toxicity was characterized by decreased fetal body weights and external fetal malformations.
  - External malformations were characterized by absence of anus and tail in 1 fetus and 1 fetus with whole body edema at 50 mg/kg/day, omphalocele in 1 fetus at 150 mg/kg/day, and dome shaped head in 1 fetus at 300 mg/kg/day. There was a lack of dose response in the incidence of fetal malformations.

Conducting laboratory and location:	(b) (4)
GLP compliance:	No

Methods	
Dose and frequency of dosing:	0, 25, 50, 150, or 300 mg/kg/day; once daily dosing starting GD 6 through GD 17
Route of administration:	Oral gavage (10 mL/kg)
Formulation/Vehicle:	0.4% (w/w) methylcellulose (400 cps) in distilled water
Species/Strain:	Rat/Crl:CD®(SD)
Number/Sex/Group:	5 females/group
Satellite groups:	Toxicokinetics: 3 females in control group and 6 females per group in the test article-treated groups
Study design:	Pregnant female rats (14 weeks of age) were dosed with belumosudil once daily on GD 6-17; scheduled necropsy/cesarean section conducted on GD 20.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Parameters	**Major findings**
Mortality	All maternal animals survived to the scheduled day of necropsy on GD 20.
Clinical Signs	300 mg/kg/day: Hunched posture, unkempt and/or thin body appearance from GD 11 to GD 20.
Body Weights (g)	Lower mean body weight gains in the test article-treated groups throughout the dosing period compared to control.

<table>
<tr><td></td><td>GD 6-20: ↓10%, ↓14%, ↓22%, ↓72%** at 25, 50, 150, and 300 mg/kg/day, respectively.
** statistically significant compared to control group.</td></tr>
<tr><td>Food consumption (g/animal/day)</td><td>Lower mean food consumption in the test article-treated groups throughout the dosing period compared to control.
GD 6-20: ↓7%, ↓11%, ↓23%**, ↓65%** at 25, 50, 150, and 300 mg/kg/day, respectively.
** statistically significant compared to control group.</td></tr>
<tr><td>Necropsy findings
Cesarean Section Data</td><td>
<table>
<tr><th>Dose (mg base/kg/day)</th><th>0</th><th>25</th><th>50</th><th>150</th><th>300</th></tr>
<tr><td>No. Evaluated</td><td>5</td><td>5</td><td>5</td><td>5</td><td>5</td></tr>
<tr><td>Gravid Uterine Weight (g)</td><td>84.0</td><td>82.5</td><td>75.5</td><td>74.2</td><td>64.1*</td></tr>
<tr><td>Adjusted Final Body Weight (g)</td><td>304.8</td><td>290.3</td><td>305.3</td><td>283.6</td><td>241.4**</td></tr>
<tr><td>Adjusted Body Weight Change (g)</td><td>46.0</td><td>34.1</td><td>36.9</td><td>27.8*</td><td>14.9**</td></tr>
<tr><td>No. Pregnant</td><td>5</td><td>5</td><td>5</td><td>5</td><td>5</td></tr>
<tr><td>No. Aborted or with Total Resorption of Litter</td><td>0</td><td>0</td><td>0</td><td>0</td><td>11</td></tr>
<tr><td>Mean No. Corpora Lutea</td><td>16.6</td><td>14.8</td><td>14.6</td><td>13.8</td><td>17.3</td></tr>
<tr><td>Mean No. Implantation Sites</td><td>13.4</td><td>13.8</td><td>13.0</td><td>12.8</td><td>13.4</td></tr>
<tr><td>Mean % Preimplantation Loss</td><td>16.80</td><td>6.79</td><td>10.57</td><td>6.24</td><td>17.71</td></tr>
<tr><td>Mean No. Viable Fetuses</td><td>12.8</td><td>13.2</td><td>11.6</td><td>12.2</td><td>10.0</td></tr>
<tr><td>Mean Fetal Sex Ratio (% Males)</td><td>53.8</td><td>53.1</td><td>46.5</td><td>41.1</td><td>44.3</td></tr>
<tr><td>Mean % Postimplantation Loss</td><td>4.41</td><td>4.00</td><td>11.62</td><td>4.51</td><td>24.51 (HCD 0-17%)</td></tr>
<tr><td>Mean No. Nonviable Fetuses</td><td>0.0</td><td>0.0</td><td>0.0</td><td>0.0</td><td>0.0</td></tr>
</table>
</td></tr>
</table>

	Litter Size (Mean No. per Animal)	12.8	13.2	11.6	12.2	10.0
	Mean No. Early Resorptions	0.6	0.6	1.4	0.6	3.4
	Mean No. Late Resorptions	0.0	0.0	0.0	0.0	0.0
Necropsy findings Offspring						
	Dose (mg base/kg/day)	0	25	50	150	300
	No. Litters/Fetuses Evaluated	5/64	5/66	5/58	5/61	41/50
	Mean Fetal Body Weight (Least Square Mean) (g)					
	Males	4.64	4.52	4.68	4.28	3.52**
	Females	4.36	4.19	4.39	4.18	3.34 **
	Males + Females	4.50	4.37	4.50	4.22	3.42 **
	External Malformation					
	Body, Anus, Absent					
	No. Litters (%)	0	0	1(20)	0	0
	No. Fetuses (%)	0	0	1(1.7)	0	0
	Body, Entire, Edema					
	No. Litters (%)	0	0	1(20)	0	0
	No. Fetuses (%)	0	0	1(1.7)	0	0
	Body, Umbilicus, Omphalocele					
	No. Litters (%)	0	0	0	1(20)	0
	No. Fetuses (%)	0	0	0	1(1.6)	0
	Head, Entire, Dome shaped					
	No. Litters (%)	0	0	0	0	1(25)
	No. Fetuses (%)	0	0	0	0	1(2.0)
	Tail, Entire, Absent					
	No. Litters (%)	0	0	1(20)	0	0
	No. Fetuses (%)	0	0	1(1.7)	0	0
	1 one female was with all resorptions.					

Study title/number KD025: An Embryo-Fetal Developmental Toxicity Study in New Zealand White Rabbits with a Toxicokinetic Evaluation/2420-007

Key Study Findings:

- Belumosudil caused both maternal toxicity and fetal toxicity.
  - Maternal toxicity included body weight loss, reduced body weight gain, low food consumption, and mortality at 225 mg/kg/day.
  - Abortions at 225 mg/kg, dose-related increases in postimplantation loss (comprised of early and late resorptions) at 125 and 225 mg base/kg/day, and decreases in viable fetuses/litter size.
  - Fetal toxicity characterized by decreased fetal body weights and fetal developmental effects (external, visceral, and skeletal fetal malformations/variations) occurred at 125 and 225 mg/kg/day.
    - External malformations were characterized by short tail (entire), and skeletal malformations included ribs branched, fused or misshapen (deformed); sternebra(e) fused, and neural arches fused, misaligned, and misshapen.
    - In addition, visceral malformations (malpositioned ureter) and skeletal variations (sternebra(e) fused) were also observed at 50 mg/kg/day.

Conducting laboratory and location:	(b) (4)
GLP compliance:	Yes

Methods	
Dose and frequency of dosing:	0, 50, 125, or 225 mg/kg/day; once daily dosing starting GD 6 through GD 18
Route of administration:	Oral gavage (10 mL/kg)
Formulation/Vehicle:	0.4% (w/w) methylcellulose (400 cps) in distilled water
Species/Strain:	Rabbit/New Zealand White (NZW)
Number/Sex/Group:	23 females/group
Satellite groups:	Toxicokinetics: 4 females in control group and 6 females per group in the test article-treated groups
Study design:	Pregnant female rabbits were dosed with belumosudil once daily on GD 6-18; scheduled necropsy/cesarean section conducted on GD 29.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

<table>
<tr><th>Parameters</th><th>Major findings</th></tr>
<tr><td>Mortality</td><td>Main Study Maternal Survival
<table>
<tr><td>Dose (mg/kg/day)</td><td>0</td><td>50</td><td>125</td><td>225</td></tr>
<tr><td>Number Females on Study</td><td>23</td><td>23</td><td>23</td><td>23</td></tr>
<tr><td>Number Not Pregnant</td><td>0</td><td>1</td><td>3</td><td>0</td></tr>
<tr><td>Number Aborted (GD 19)</td><td>0</td><td>0</td><td>1</td><td>1</td></tr>
<tr><td>Number Died (GD 9)</td><td>0</td><td>0</td><td>0</td><td>1</td></tr>
<tr><td>Number with All Resorptions (litter loss) GD 29</td><td>0</td><td>0</td><td>0</td><td>2</td></tr>
<tr><td>Number Litters with Viable Fetuses GD 29</td><td>23</td><td>22</td><td>19</td><td>19</td></tr>
</table></td></tr>
<tr><td>Clinical Signs</td><td>Red material in pan and bedding at 125 and 225 mg/kg/day; thin body appearance at 225 mg/kg/day.</td></tr>
<tr><td>Body Weights</td><td>Statistically significant lower mean body weight gains at125 mg/kg /mean body weight loss at 225 mg/kg was noted during the dosing period compared to control.
GD 6-19: ↓16%, ↓68%**, ↓117%** at 50, 125, and 225 mg/kg/day, respectively.
** statistically significant compared to control group.

Adjusted BW changes occurred at 125 and 225 mg/kg doses, suggesting maternal toxicity at these dose levels.</td></tr>
<tr><td>Food Consumption</td><td>Lower mean food consumption in the test article-treated groups throughout the dosing period compared to control.
GD 6-20: ↓9%, ↓34%**, ↓50%** at 50, 125, and 225 mg/kg/day, respectively.
** statistically significant compared to control group.</td></tr>
<tr><td>Necropsy findings Cesarean Section Data</td><td>
<table>
<tr><th>Dose (mg/kg/day)</th><th>0</th><th>50</th><th>125</th><th>225</th></tr>
<tr><td>No. Evaluated</td><td>23</td><td>23</td><td>23</td><td>23</td></tr>
<tr><td>No. Not Pregnant</td><td>0</td><td>1</td><td>3</td><td>0</td></tr>
<tr><td>Mean No. Corpora Lutea</td><td>9.3</td><td>9.2</td><td>9.9</td><td>9.8</td></tr>
<tr><td>Mean No. Implantation Sites</td><td>8.7</td><td>8.7</td><td>8.7</td><td>8.9</td></tr>
<tr><td>Mean % Preimplantation Loss</td><td>6.04</td><td>5.64</td><td>11.97</td><td>8.71</td></tr>
<tr><td>Mean No. Viable Fetuses</td><td>8.4</td><td>8.5</td><td>8.0</td><td>7.4</td></tr>
</table></td></tr>
</table>

	Mean Fetal Sex Ratio (% Males)	55.4	52.2	50.7	54.4
	Mean % Post-implantation Loss	4.07	2.42	7.42	17.72 (*HCD 2-10)*
	Mean No. Nonviable Fetuses	0.0	0.0	0.0	0.0
	Litter Size (Mean No. per Animal)	8.4	8.5	8.0	7.4
	Mean No. Early + Late Resorptions	0.3	0.2	0.7	1.5*
	Mean No. Early Resorptions	0.3	0.2	0.5	1.4*
	Mean No. Late Resorptions	0.1	0.0	0.2	0.0

Necropsy findings Offspring

Mean Fetal Body Weight (Least Square Mean) (g)				
Dose (mg/kg/day)	**0**	**50**	**125**	**225**
Males	42.05	41.64	41.61	38.92*
Females	39.24	40.25	41.14	38.94
Males + Females	40.96	40.97	41.09	38.60
Fetal Observations				
No. Litters/Fetuses Evaluated	23/193	22/186	19/152	19/156

Fetal Malformations				
External Malformation				
Tail, Entire, Short				
No. Litters (%)	0 (0.0)	0 (0.0)	0 (0.0)	2 (10.5) *(HCD 5%)*
No. Fetuses (%)	0 (0.0)	0 (0.0)	0 (0.0)	5 (3.2) *(HCD 0.6%)*
Visceral Malformations				
Ureter, Malpositioned				
No. Litters (%)	0 (0.0)	1 (4.5)	4 (21.1)	5 (26.3) *(HCD 42.1)*
No. Fetuses (%)	0 (0.0)	1 (0.5)	7 (4.6)	5 (3.2) *(HCD 7.7)*
Skeletal Malformations				
Rib(s), Branched				
No. Litters (%)	0 (0.0)	0 (0.0)	1 (5.3)	4 (21.1)* *(HCD 5%)*
No. Fetuses (%)	0 (0.0)	0 (0.0)	1 (0.7)	4 (2.6) (HCD 0.5%)
Rib(s), Fused				
No. Litters (%)	0 (0.0)	0 (0.0)	0 (0.0)	3 (15.8) *(HCD 14.3%)*

No. Fetuses (%)	0 (0.0)	0 (0.0)	0 (0.0)	4 (2.6) *(HCD 1.7)*
Rib(s), Misshapen				
No. Litters (%)	0 (0.0)	0 (0.0)	0 (0.0)	3 (15.8) *(HCD 5.9%)*
No. Fetuses (%)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.9) *(HCD 0.7%)*
Sternum, Sternebra(e), Fused				
No. Litters (%)	1 (4.3)	4 (18.2)	2 (10.5)	6 (31.6) *(HCD 26.1)*
No. Fetuses (%)	1 (0.5)	6 (3.2)	6 (3.9)	7 (4.5) *(HCD 3.9%)*
Thoracic Vertebra(e), Neural arch(es), Fused				
No. Litters (%)	0 (0.0)	0 (0.0)	1 (5.3)	2 (10.5) *(HCD 9.5%)*
No. Fetuses (%)	0 (0.0)	0 (0.0)	1 (0.7)	3 (1.9) *(HCD 1.1%)*
Thoracic Vertebra(e), Neural arch(es), Misaligned				
No. Litters (%)	0 (0.0)	0 (0.0)	0 (0.0)	2 (10.5) *(HCD 5.3%)*
No. Fetuses (%)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.3) *(HCD 0.6%)*
Thoracic Vertebra(e), Neural arch(es), Misshapen				
No. Litters (%)	0 (0.0)	0 (0.0)	0 (0.0)	4 (21.1)* *(HCD 9.5%)*
No. Fetuses (%)	0 (0.0)	0 (0.0)	0 (0.0)	4 (2.6) *(HCD 1.1%)*
Skeletal Variations				
Cervical Vertebra(e), Centra, Hemicentric				
No. Litters (%)	0 (0.0)	0 (0.0)	0 (0.0)	4 (21.1)* *(HCD 5.3%)*
No. Fetuses (%)	0 (0.0)	0 (0.0)	0 (0.0)	4 (2.6) *(HCD 0.6%)*
Sternum, Sternebra(e), Extra				
No. Litters (%)	0 (0.0)	0 (0.0)	0 (0.0)	4 (21.1)* *(HCD 5.3%)*

	No. Fetuses (%)	0 (0.0)	0 (0.0)	0 (0.0)	7 (4.5) *(HCD 1.5%)*

Study title/number KD025: An Embryo-Fetal Developmental Toxicity Study in Sprague-Dawley Rats with a Toxicokinetic Evaluation/2420-006

A GLP compliant study of belumosudil was conducted to determine the embryo-fetal developmental toxicity, including the teratogenic potential, in Sprague-Dawley rats. Rats were dosed with belumosudil once daily via oral gavage from GD 6-17 at dose levels of 0, 15, 50 and 150 mg/kg/day (25 pregnant female rats/group, Main Study). One female at 150 mg kg/day was euthanized in extremis as the result of a suspected gavage injury on GD 15. There were no belumosudil-related maternal or embryo-fetal toxicities observed at 15 mg/kg/day. At 50 and 150 mg/kg/day, a dose dependent decrease in mean body weight change (up to 27%) and reduced food consumption (up to 28%) were observed compared to control. Fetal toxicity included statistically significant decreased mean fetal weights at 150 mg/kg/day compared to control, but within the historical control data. Maternal exposures at the 50 mg/kg/day dose were approximately 4 times the human clinical exposure based on AUC at the recommended human dose.

5.5.5 Other Toxicology Studies

The Applicant's Position:

Phototoxicity

Standard and tiered phototoxicity testing/risk assessment strategies consistent with ICH-S10 guidance were conducted on belumosudil. Belumosudil has demonstrated photo-absorbance between 290 and 370 nm (nonGLP, Study 20082808), some distribution into the skin and uveal tract based on the rat quantitative whole body autoradiography [QWBA] studies with [^{14}C]-KD025 (Section 5.4), and positive phototoxic potential in the *in vitro* 3T3 Neutral Red Uptake Assay (GLP, Study 20082809). [^{14}C]-KD025 distribution in partially-pigmented rats demonstrated higher tissue retention in melanin-containing tissues (uveal tract and pigmented skin), indicating some affinity of belumosudil for melanin.

While in vitro phototoxicity testing and animal distribution studies are important for potential hazard identification to inform clinical monitoring, clinical data should be considered in the overall phototoxicity risk assessment and should supersede nonclinical data (ICH/FDA-S10 guidance). In standard reporting of AEs in Phase 1/2 clinical studies, belumosudil has not demonstrated any clinically significant phototoxicity (Section 0).

The FDA's Assessment:

FDA concurs with the Applicant's assessment that belumosudil was positive in the in vitro phototoxicity studies.

6 CLINICAL PHARMACOLOGY

6.1 Executive Summary

The FDA's Assessment:

Belumosudil (REZUROCK, formerly referred to as KD025) is a Rho-associated, coiled-coil containing protein kinase-2 (ROCK2) inhibitor. The Applicant is seeking approval of REZUROCK for the treatment of chronic graft-versus-host disease (cGVHD) after failure of two or more lines of systemic therapy, for patients 12 years and older. The proposed REZUROCK dosing regimen is one tablet (200 mg belumosudil) taken orally once daily with food.

The Clinical Pharmacology section of the NDA is supported by the evaluation of pharmacokinetics (PK), exposure-response relationships for efficacy and safety and the population PK (popPK) analysis based on data from studies in healthy subjects and from two pivotal studies in patients with cGVHD: Study KD025-208 (a Phase 2a dose-ranging, safety and tolerability study) and Study KD025-213 (a Phase 2 safety and efficacy study). The registration trial KD025-213 evaluated two dosing regimens: REZUROCK 200 mg once daily (QD) versus REZUROCK 200 mg twice daily (BID). Based on the efficacy and safety results in the Phase 2a and Phase 2 studies in patients with cGVHD and the comparative PK assessment of REZUROCK QD and BID in the Phase 2 study, the proposed REZUROCK dosing regimen of 200 mg QD, once daily with food, is acceptable.

Analysis of the data showed a meaningful decrease in belumosudil exposure in the presence of concomitant proton pump inhibitors (PPIs) or a strong CYP3A inducer in a study in healthy subjects (Study KD025-107) and from the two pivotal studies in patients with cGVHD. Because of this decreased exposure, the FDA recommends 200 mg BID in the presence of concomitant strong CYP3A inducers and PPIs. Preliminary data in patients with mild and moderate hepatic impairment (HI) showed no change in mild HI, but higher exposures in patients with moderate HI. No data for patients with severe hepatic impairment is available. Based on the limited data, differences in belumosudil exposure were observed between black and white healthy subjects, with a higher number safety events in black patients.

Recommendation:

The proposed REZUROCK dosing regimen of 200 mg administered as a single tablet orally once daily with food is acceptable. This NDA is approvable from a Clinical Pharmacology standpoint. However, there are several key Clinical Pharmacology review issues that need to be addressed by post marketing requirements (PMRs). Specific recommendations/comments are summarized in the table below.

PMC or PMR	Review Issue	Recommendations and Comments
☐ PMC ☐ PMR	General dosing	Rifampicin, a strong CYP3A inducer, reduced belumosudil Cmax by 60% and overall exposure by 72%. Therefore, belumosudil should be administered at 200 mg BID in the presence of strong CYP3A inducers.
☐ PMC ☐ PMR	General dosing	In vivo studies showed that concomitant use of rabeprazole reduced the Cmax of belumosudil by 87% and AUC by 80% and concomitant use of omeprazole reduced the Cmax of belumosudil by up to 68%, and AUC by 50%. PopPK analysis also showed 48% lower relative bioavailability from PPI coadministration. Therefore, belumosudil should be administered at 200 mg BID in the presence of PPIs.
☐ PMC ☒ PMR	Drug-drug interactions	The results from the IC50 shift assay showed that belumosudil was a mechanism-based inhibitor of CYP1A2, CYP2C19 and CYP2D6. The IC50 generated in this study is not suitable for assessing mechanism-based inhibition potential of belumosudil on these enzymes for the labeling purpose. A potential risk of belumosudil to increase the concentration of concomitant substrate drugs that are used in this patient population has not been estimated. The Applicant should conduct an in vitro mechanism-based inhibition study (such as the two-step dilution method) estimating the inactivation parameters (k_{inact} and K_I) of CYP1A2, CYP2C19 and CYP2D6 enzymes and measuring nonspecific binding of belumosudil to assess the potential of drug interaction with belumosudil on these enzymes in accordance with the FDA Guidance for Industry titled "*In Vitro Drug Interaction Studies – Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions.*"
☐ PMC ☒ PMR	Drug-drug interactions	In vitro studies showed belumosudil inhibits the UGT1A1 enzyme. This inhibitory effect indicates a potential risk of increasing the concentration of concomitant substrate drugs, that are used in this patient population, to toxic levels. The Applicant should conduct a clinical pharmacokinetic trial evaluating the effect of repeat doses of belumosudil on the single dose pharmacokinetics of a UGT1A1 substrate to assess the potential for excessive drug toxicity. This trial should be designed and conducted in accordance with the FDA Guidance for Industry titled, *"Clinical Drug Interaction Studies – Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions."*
☐ PMC ☒ PMR	Drug-drug interactions	In vitro studies showed belumosudil inhibits P-gp, BCRP and OATP1B1 transporters. This inhibitory effect indicates a potential risk of increasing the concentration of concomitant substrate drugs, that are used in this patient population, to toxic levels. The Applicant should conduct a clinical pharmacokinetic trial evaluating the effect of repeat doses of belumosudil on the single dose pharmacokinetics of sensitive substrates (P-gp, BCRP and OATP1B1) to assess the potential for

		excessive drug toxicity. This trial should be designed and conducted in accordance with the FDA Guidance for Industry titled, *"Clinical Drug Interaction Studies – Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions."*
☐ PMC ☒ PMR	Hepatic impairment	Belumosudil is primarily eliminated in feces (85%). However, the Applicant's dedicated study to assess the impact of hepatic impairment on belumosudil exposure is ongoing and does not include subjects with severe hepatic impairment. Furthermore, for population PK analysis, there were no patients with cGVHD with moderate or severe hepatic impairment. Therefore, there exists a potential risk of toxic belumosudil exposure levels in patients with cGVHD with moderate or severe hepatic impairment. The Applicant should complete the clinical pharmacokinetic trial to determine a safe and appropriate dose of belumosudil in subjects with mild, moderate, and severe hepatic impairment. This trial should be designed and conducted in accordance with the FDA Guidance for Industry titled "Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling." The final report should include assessment of subjects with mild, moderate and severe hepatic impairment.
☐ PMC ☒ PMR	Cardiac electrophysiology	The Applicant did not conduct a thorough QT (TQT) study to evaluate the impact of belumosudil exposure on the QT/QTc interval. Therefore, there is a potential risk of belumosudil causing cardiotoxicity. The Applicant should conduct a thorough QT/QTc trial to evaluate the effect of repeat doses of belumosudil on the QT/QTc interval to address the potential for excessive drug toxicity. This trial should be designed and conducted in accordance with the ICH E14 guidance for industry titled "E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for NonAntiarrhythmic Drugs, and E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs -Questions and Answers (R3)."
☐ PMC ☒ PMR	Racial and ethnic minorities	In the registrational trial of belumosudil for the treatment of patients with cGVHD, higher rates of Grade 3 adverse events (cardiac disorders, gastrointestinal disorders, vascular disorders) were reported in Black patients compared to White patients. In addition, belumosudil exposure was higher in healthy Black subjects compared to healthy White subjects in safety/tolerability/PK studies. The data in the clinical trial is limited by the small number of non-white patients enrolled in the trial. This clinical trial is required to determine the PK and safety of belumosudil in non-White patients with cGVHD and determine if a dosage modification is needed. The Applicant should conduct a clinical trial in a sufficient number of Black patients with chronic graft versus host disease to assess the risk of cardiac toxicities and further characterize Grade 3 toxicities including gastrointestinal and vascular

		disorders associated with the use of belumosudil. This study should characterize the exposure (including PK data), safety, and efficacy of belumosudil.
☒ PMC ☐ PMR	Racial and ethnic minorities	The data in the clinical trial is limited by the small number of non-white patients enrolled in the trial. This clinical trial is required to determine the PK and safety of belumosudil in non-White patients with cGVHD and determine if a dosage modification is needed. The Applicant should conduct a clinical trial among U.S. racial and ethnic minorities to assess the safety of belumosudil. This study should characterize the PK exposure, safety, and efficacy of belumosudil.

6.2 Summary of Clinical Pharmacology Assessment

6.2.1 Pharmacology and Clinical Pharmacokinetics

Data:
The clinical pharmacology program to support the use of belumosudil in cGVHD consists of 12 clinical studies (10 Phase 1 trials and 2 Phase 2 trials), with 10 having been completed and 2 are ongoing (Section 0). An additional 2 clinical studies have been completed in subjects with psoriasis. Fourteen in vitro studies using human biomaterials have also been completed. PBPK modeling is in progress (Sections 0 and 0). Belumosudil and the KD025m2 and KD025m1 metabolites were assayed in all of the completed clinical studies.

The belumosudil clinical studies include single- and multiple-dose administration of belumosudil at doses ranging from 20 to 1000 mg; healthy subjects and subjects with cGVHD and psoriasis; evaluation of food effect; metabolism, distribution, and excretion studies; PK in subjects with hepatic impairment; characterization/evaluation of victim and perpetrator drug-drug interactions; and population pharmacokinetics (popPK) and exposure-response analyses. The results of these studies are summarized in Section 6.3.1.

The Applicant's Position:

The PK of belumosudil and the KD025m2 (major) and KD025m1 (minor) metabolites has been well characterized. The available clinical pharmacology package is sufficient to assess the effects of intrinsic and extrinsic factors on belumosudil PK and to support the safety, efficacy and dosing recommendation of 200 mg belumosudil once daily (QD) administered with food in the cGVHD population.

The FDA's Assessment:

The FDA agrees with the Applicant's position on the sufficiency of the clinical pharmacology package to support a 200 mg QD dose with food in the cGVHD population. There are several

outstanding issues described in subsequent sections. Also refer to Table 1 in Section 6.3.1 for a summary of general pharmacology and pharmacokinetic (PK) characteristics of belumosudil.

6.2.2 General Dosing and Therapeutic Individualization

General Dosing
Data:

Three belumosudil dosing regimens (each administered with food) were evaluated in the Phase 2 studies in cGHVD subjects (Studies KD025-208 and KD025-213): 200 mg QD, 200 mg twice daily (BID), and 400 mg QD.

In Study KD025-208, belumosudil achieved an ORR of 64.7% for 200 mg QD, 68.8% for 200 mg BID, and 61.9% for 400 mg QD (n=54 total); (Section 8.1.1). In Study KD025-213, belumosudil achieved clinically meaningful and statistically significant ORR of 72.7% and 74.2% for treatment arms 200 mg QD and 200 mg BID, respectively (n=132 total; Section 8.1.2). Belumosudil was well tolerated in the Phase 2 cGVHD studies (Section 0).

In the exposure-response analysis, safety and efficacy variables were plotted against the post hoc exposure estimates (maximum concentration [C_{max}] and area under the curve during a 24-hour period [AUC_{0-24}]) and total daily dose for subjects with cGVHD in Studies KD025-208 and KD025-213. Exposure-efficacy relationships were evaluated for overall response, duration of response, Lee Symptom Scale (LSS) score reduction, Global Severity Rating (GSR) reduction, and individual organ responses (Population PK Report NPS3067-PKPD001). At the range of exposures observed in these studies, the exposure-efficacy relationships were flat. Exposure-safety relationships were evaluated for headache, fatigue, abnormal liver function, nausea, and diarrhea. These relationships were also flat.

The Applicant's Position:
The clinical safety and efficacy data, exposure-response analyses, and clinical pharmacology support a belumosudil dose of 200 mg QD administered with food in the cGVHD population.

At the range of exposures observed in Studies KD025-208 and KD025-213, the exposure-efficacy relationships were flat. The exposure-safety relationships were also flat, indicating a wide range of tolerable exposures.

The FDA's Assessment:

FDA agrees with the Applicant's position that safety, efficacy, exposure-response and clinical pharmacology data supports a belumosudil dose of 200 mg QD (once daily) administered with food in patients with cGVHD. While food decreases the rate and increases the extent of belumosudil absorption, the pivotal clinical studies were conducted with belumosudil given with food. Refer to Section 6.3.2 for FDA's evaluation.

Therapeutic Individualization

Data:

The data regarding the impact of intrinsic and extrinsic factors on belumosudil PK are described in Sections 0 and 0, respectively. The data regarding the variety of patient characteristics included in the Phase 2 studies is described in Section 0.

The Applicant's Position:

No dose adjustments are required for demographic characteristics, renal impairment, hepatic impairment, concomitant medications that are CYP3A4 inhibitiors or inducers, or concomitant proton pump inhibitor (PPI) use (Sections 0 and 0).

The FDA's Assessment:

The FDA agrees that no dose adjustments are required by age, body size or renal function. However, the FDA does not agree that no dose adjustments are necessary for concomitant CYP3A inducers and concomitant PPIs. For hepatic impairment, there is insufficient information to determine the need for dose adjustments. Please refer to Section 6.3.2 for FDA's evaluation.

Outstanding Issues

Data:

Current data do not indicate a risk of QT prolongation at therapeutic exposures. A thorough QT study (KD025-110) is ongoing (Cardiac Electrophysiology in Section 6.3.1). This study will include belumosudil doses of 200 and 1000 mg, moxifloxacin, and placebo, consistent with ICH E14.

Subjects with severe hepatic impairment are still enrolling in Study KD025-109 (Section 0).

PBPK modeling to further characterize belumosudil as a perpetrator in drug-drug interactions is ongoing (Section 0).

The Applicant's Position:

Based on available data, a large effect on QT at therapeutic exposures can be ruled out. The ongoing thorough QT study will confirm this observation and allow for a small effect on QT to be evaluated.

Assessment of PK in patients with severe hepatic impairment is on-going (Study KD025-109).

The potential inhibition of belumosudil and CYP3A4 (time dependent) and CYP3A4 gut, P-gp, BCRP, OATP1B1, MATE1, and MATE2K is being further evaluated in PBPK modeling (Section 0).

The FDA's Assessment:

The FDA has the following outstanding issues to be resolved with a PMR and/or PMC

- There is insufficient data to assess the impact of belumosudil exposures on QT. Until the results from the thorough QT/QTc (TQT) study have been assessed, the risk of QT prolongation at therapeutic belumosudil exposures is unknown.
- There is insufficient information to evaluate the exposure and safety of belumosudil in patients with moderate and severe hepatic impairment.
- The effect of belumosudil's inhibition of metabolic enzymes (CYP1A2, CYP2C19, CYP2D6 and UGT1A1) and transporters (P-gp, BCRP, OATP1Bs, and MATEs) have not been adequately characterized.

6.3 Comprehensive Clinical Pharmacology Review

6.3.1 General Pharmacology and Pharmacokinetic Characteristics

Data and Sponsor's Position:

An overview of the ADME properties, clinical pharmacokinetics, and DDI potential of belumosudil is provided below.

Absorption

Following a single oral dose of belumosudil 200 mg administered as a tablet in the hAME study (Study KD025-108), the geometric mean absolute bioavailability based on AUC_{inf} oral/AUC_{inf} IV was 64%. Belumosudil is a Biopharmaceutics Classification System (BCS) Class IV compound.

Across all studies, median time to maximum concentration (t_{max}) values for belumosudil and both metabolites generally ranged from 2 to 4 hours, indicating rapid absorption of belumosudil and rapid appearance of KD025m2 and KD025m1.

Belumosudil solubility decreased as pH increased between pH 2.0 and 6.8 (nonGLP, Study ADME-KAD-200402-Kinetic Solubility). Assessment of absorption when co-administered with a PPI (gastric pH-modifying agent) is described in Section 0.

In in vitro studies, KD025 was a substrate of P-gp only and not a substrate of the other transporters evaluated (BCRP, OATP1B1, and OATP1B3).

Systemic exposure of belumosudil was increased when administered under the fed state (Studies KD025-105 and KD025-106; Section 0).

Distribution

Belumosudil and its metabolites KD025m1 and KD025m2 were evaluated for human plasma protein binding using [^{14}C]KD025 in equilibrium dialysis. Belumosudil was extensively bound to proteins in human plasma (mean 99.88% bound). [^{14}C]-KD025 was preferentially bound to human serum albumin (99.91%) compared to α_1-acid glycoprotein (98.64%). KD025m1 and KD025m2 are also extensively bound to human plasma proteins (fraction bound >99%).

In the hAME study (Study KD025-108), following intravenous (IV) administration of 100 µg [^{14}C]-KD025 solution for infusion, the apparent volume of distribution observed was higher than total body water, supporting that [^{14}C]-KD025 is distributed into tissue. Whole blood:plasma ratios (0.53 to 1.16 over the entire sampling range) indicated minimal to no preferential distribution of total radioactivity into the cellular components of whole blood.

Following 200 mg belumosudil tablet administration (Study KD025-107 and Study KD025-108), the geometric mean (%CV) Vz/F estimated from noncompartmental analyses ranged from 184 (67.7%) to 251 (51.3%) L. The volume of distribution for the central compartment was estimated as 29.7 L and the volume of distribution for the peripheral compartment was estimated as 78.8 L in the popPK analysis. In the popPK analysis, no covariate effects on the central or peripheral volumes of distribution were significant.

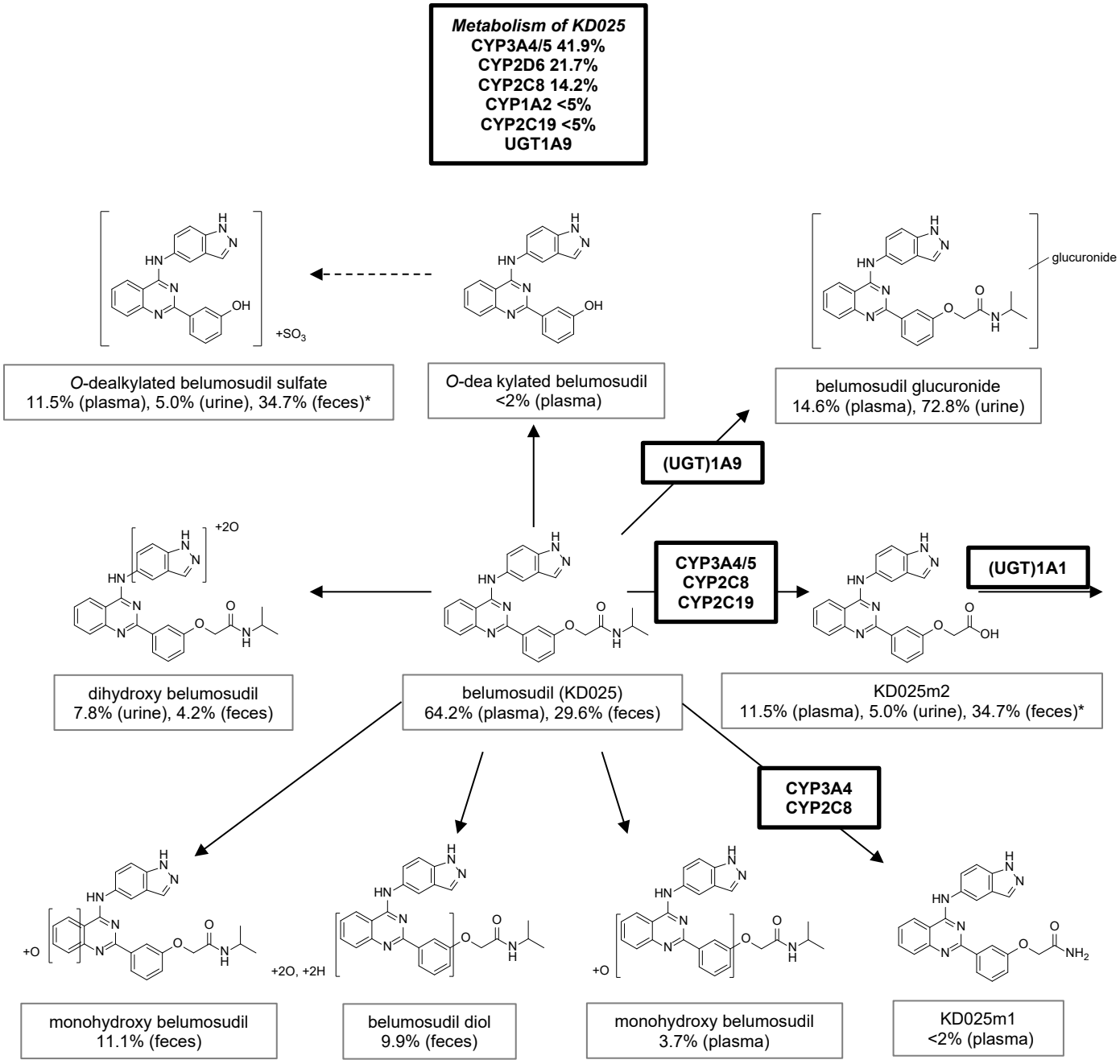
Metabolism

Following oral administration, 2 metabolites of belumosudil have been assayed in several clinical studies: an active minor metabolite, KD025m1, and a relatively less active major metabolite, KD025m2. These 2 metabolites were also formed in liver microsomes and hepatocytes from all species examined. Based on *in vitro* assessment, CYP3A4 (41.9%) was the predominant cytochrome P450 (CYP) isoform responsible for the metabolism of belumosudil although CYP2D6 (21.7%), CYP2C8 (14.2%), CYP1A2 (<5%), CYP2C19 (<5%), and UGT1A9 may also contribute to a lesser extent. Metabolism of belumosudil to KD025m2 was CYP3A4 dependent with metabolism of KD025m2 dependent on UGT1A1 with no to little contribution from CYP enzymes. Metabolism of belumosudil to KD025m1 was CYP3A4 and CYP2C8 dependent.

KD025m2 and KD025m1 rapidly appeared in plasma (median T_{max} generally ranged from 1 to 6 hours) and were readily eliminated (geometric mean $t_{½}$ ~2 to 14 hours) following belumosudil administration across all studies. The major metabolite, KD025m2, had a C_{max} value approximately 20% of the parent and an AUC value approximately 15% of the parent. The minor metabolite, KD025m1, had C_{max} and AUC values <5% and <2% of the parent, respectively. C_{max} and AUC for both metabolites increased with dose; some accumulation of KD025m2 was observed (<2x higher on Day 28) and minimal to no accumulation of KD025m1 was observed following multiple doses (Study KD025-103).

In the hAME study (Study KD025-108), following oral administration of 200 mg [^{14}C]-KD025 capsule, a mean of ~90% of total radioactivity was recovered over a 216 hour sampling period. Of the total plasma radioactivity, belumosudil was 64%, KD025m2 and co-eluting *O*-dealkylated belumosudil sulfate was 11.5% (total), and a belumosudil glucuronide was 15% (KDM-05). The *O*-dealkylated belumosudil sulfate was detected in multiple other species in the liver microsome and hepatocyte in vitro studies and in in vivo studies (KDM-03) The glucuronide metabolite is not an acyl glucuronide and, thus, consistent with FDA Guidance *Safety Testing of Drug Metabolites* is not considered to be of toxicological concern. The proposed human metabolic pathway for the belumosudil is presented in Figure 6.

Figure 6 Proposed Biotransformation Pathway for Belumosudil in Humans



*These two compounds co-elute and the percentage refers to the total contr bution of both components.
Sources: Report XT174009, Report XT184060, Report KDM-05 (Study KD025-108)

Excretion

The hAME study (Study KD025-108) confirmed that the majority of total radioactivity was recovered in feces (85%), with <5% recovered in urine (absolute bioavailability of 64% based on AUC_{inf} oral/AUC_{inf} IV). This indicates minimal renal elimination and that the predominant route of clearance of [^{14}C]-KD025 and associated metabolites is biliary and/or intestinal.

Following 200 mg belumosudil tablet administration to healthy subjects (Study KD025-107 and Study KD025-108), the geometric mean (%CV) CL/F ranged from 367 to 402 (33.3 to 40.2%) mL/min (22 to 24 L/h). Across all studies, the terminal $t_{½}$ ranged from ~4 to 11 hours following single or multiple dose administration, indicating rapid elimination of the drug. In the popPK analysis, the typical value of CL/F was estimated as 21.1 L/h in healthy subjects. CYP3A4 induction resulted in a CL/F of 60.8 L/h and CYP3A4 inhibition in healthy subjects resulted in a CL/F of 16.2 L/h. Subjects with cGVHD had a 53.4% lower CL/F compared to healthy volunteers (9.83 L/h).

Dose Proportionality

Overall, exposure of belumosudil (C_{max} and AUC) appears to be slightly greater than dose proportional over the 20 to 500 mg QD dose range, but less than dose-proportional for doses above 500 mg in healthy subjects (AUC_{0-24} <1.2x the 500 mg exposure for a 1.6x or 2x dose). In cGVHD subjects, the increase between 200 and 400 mg is approximately proportional.

Pharmacokinetics in Patients

In the popPK analysis, there was a significant effect of cGVHD subjects on CL/F relative to healthy subjects (53.4% lower). A small increase in relative bioavailability between healthy fasted subjects and GVHD subjects in the fed state was also observed in popPK analysis.

Victim Drug-Drug Interactions

A Phase 1 DDI study (KD025-107) has been completed to determine the effects of itraconazole (CYP3A4 inhibitor; 200 mg QD), rifampicin (CYP3A4 inducer; 600 mg QD), rabeprazole (strong PPI; 20 mg BID), and omeprazole (moderate PPI; 20 mg QD) on the PK of belumosudil and its metabolites following oral administration in healthy male subjects (Section 0).

Perpetrator Drug-Drug Interactions

In vitro assessment of DDIs for belumosudil as perpetrator have been conducted and physiologically based pharmacokinetic (PBPK) modeling is ongoing to further evaluate these effects (Section 0).

Hepatic Impairment

In the ongoing hepatic impairment study (KD025-109), the exposure in subjects with mild and moderate hepatic impairment had exposure ≤1.51x the exposure observed in normal subjects (Section 0).

Renal Impairment

In Study KD025-108, the majority of total radioactivity was recovered in feces (85%) and <5% was recovered in urine, suggesting there is minimal renal elimination (Section 0).

Cardiac Electrophysiology

Based on the totality of data, including preclinical data, concentration-QT analysis, and review of clinical safety data, there is no evidence for an increased risk of QT interval prolongation and a large effect of belumosudil on QT interval can be excluded. A thorough QT study (KD025-110) in healthy subjects is ongoing and will allow for the evaluation of small effects of belumosudil on QT interval.

The Applicant's Position:

The Applicant's Position is inserted in the Data and Sponsor's Position above.

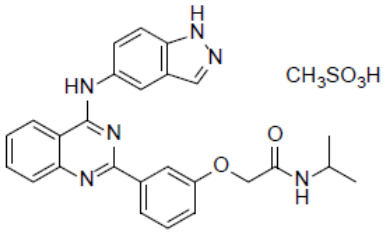
The FDA's Assessment:

The FDA generally agrees with the Applicant's assessment on general pharmacology and pharmacokinetic characteristics of belumosudil. The general overview of belumosudil ADME and clinical PK information are presented in Table 6.

The Applicant submitted a PBPK report as part of a major amendment. FDA reviewed the report and concluded that the PBPK modeling was adequate to evaluate the effects of belumosudil on the substrates of CYP2C9 and CYP3A and CYP2C8 that are not substrates of OATP1B; however, the PBPK modeling was inadequate to evaluate the inhibition potential of belumosudil on P-gp, BCRP, OATP1Bs, and MATEs.

The PBPK model could not adequately investigate the effects of belumosudil on substrates of CYP1A2, CYP2C19 and CYP2D6. Although the results from the IC50 shift assay showed that belumosudil was a mechanism-based inhibitor of CYP1A2, CYP2C19 and CYP2D6, an in vitro mechanism-based inhibition study (such as the two-step dilution method) estimating the inactivation parameters (k_{inact} and K_I) of CYP1A2, CYP2C19 and CYP2D6 enzymes and measuring nonspecific binding of belumosudil to assess the potential of drug interaction with belumosudil will be necessary for assessing mechanism-based inhibition potential of belumosudil on these enzymes. Refer to Section 16.4.1 for the Physiologically Based Pharmacokinetic (PBPK) Modeling Analysis.

Table 6. Summary of General Pharmacology and Pharmacokinetic Characteristics of Belumosudil

Physical and Chemical Properties	
Chemical Structure and Formula	 Chemical structure of belumosudil Belumosudil free base has a molecular weight of 452.5 g/mole. It is formulated as a mesylate salt with an empirical formula of $C_{27}H_{28}N_6O_5S$ and a molecular weight of 548.6 g/mole. Belumosudil has low solubility and low permeability, making it a biopharmaceutic classification Class 4 compound. The solubility of belumosudil decreases significantly with increase in pH. Belumosudil is available as an immediate-release oral tablet.
Pharmacology	
Mechanism of Action	Belumosudil is a Rho-associated, coiled-coil containing protein kinase-2 (ROCK2) selective small molecule kinase inhibitor.
Active Moieties	Belumosudil
QT Prolongation	The effect of belumosudil on the QTc interval has not been adequately characterized.
General Information	
Bioanalysis	Validated bioanalytical assays (LC-MS/MS) were used to determine concentrations of belumosudil and inactive metabolite KD025m2 and KD025m1 in human plasma.
Healthy vs. Patients	Dose escalation study KD025-208 and registration trial KD025-213 were conducted in patients with cGVHD. The following studies were conducted in healthy males: Food effect and comparative bioavailability (KD025-106), DDI (KD025-107), hAME or absorption/ metabolism/excretion (KD025-108). Study KD025-109 (preliminary data received) evaluated belumosudil PK in healthy subjects and subjects with mild or moderate hepatic impairment. A finalized report has not been submitted. Exposure to belumosudil was greater than dose proportional up to doses of 500 mg in healthy subjects. Doses of 200 and 400 mg are approximately dose proportional in patients with cGVHD. Compared to healthy subjects, cGHVD patients have a ~53% reduction in CL/F (9.83 L/h) based on popPK analysis.

Drug Exposure at Steady State Following the Therapeutic Dosing Regimen	Based on patients with cGVHD in studies KD025-208 and KD025-213, population PK analysis predicted mean AUC_{0-24} (SD) and Cmax (SD) at steady state following 200 mg QD belumosudil with food to be 22700 ng*hr/mL (10900) and 2390 ng/mL (1040), respectively.
Dose Proportionality	In dose escalation study KD025-208, for Cohorts 1 (200 mg QD) and 3 (400 mg QD), a 2-times increase in dose corresponded to <1.4-times increase in Cmax and AUC_{0-6} in cycle 1 and an approximately 1.7-times increase in Cmax and AUC_{0-6} in cycle 2.
Accumulation	Population PK simulation of exposure following 200 mg QD and BID regimens of belumosudil indicated no appreciable accumulation of belumosudil at steady state as observed in studies KD025-208 and KD025-213. The extent of accumulation is less than 2-fold for both QD and BID regimens. The simulations indicate a slightly higher accumulation for the BID regimen compared to QD. • 200 mg QD mean accumulation ratio (SD): 1.35 (0.479) • 200 mg BID mean accumulation ratio (SD): 1.84 (1.18)
Variability	Population PK analysis determined the following inter-individual variabilities (%CV): 52.7% for CL/F and 149.9% for V2/F. Registration trial KD025-213 provided the following geometric CV: • 200 mg QD – 127% to 154% for Cmax; 123% to 153% for AUC_{0-6} • 200 mg BID – 99.9% to 177% for Cmax; 108% to 204% for AUC_{0-6}
Absorption	
Median T_{max}	In pivotal study KD025-208, median Tmax (hours) for belumosudil at steady state was 2.53 for 200 mg QD and 2.47 for 200 mg BID. For registration trial KD025-213, median Tmax (hours) was 1.98 for 200 mg QD and 1.26 for 200 mg BID.
Food effect (Fed/fasted)	Food decreases the rate and increases the extent of belumosudil absorption. Exposure (AUC and Cmax) in the fed state is ~2x that in the fasted state, and Tmax is delayed 0.5 to 2 hours. Belumosudil is recommended to be administered with food.
Distribution	
Volume of Distribution	Based on population PK analysis estimates, central volume of distribution is 29.7 L and peripheral volume of distribution was estimated to be 78.8 L.
Plasma Protein Binding	Belumosudil and its metabolites KD025m1 and KD025m2 are >99% bound to human plasma proteins with a free fraction of <1%.
Blood to Plasma Ratio	Belumosudil had a blood to plasma ratio of 0.71.
As Substrate of Transporters	In *in vitro* studies showed belumosudil to be a substrate of P-gp only and not a substrate of the other transporters evaluated (BCRP, OATP1B1, and OATP1B3).
Elimination	

Terminal Elimination Half-Life	Population PK analysis determined a t½ of 19.0 hours for 200 mg QD and 200 mg BID.
Metabolism	
Fraction Metabolized (% dose)	In hAME study KD025-108, a mean of 90% total radioactivity was recovered in plasma. In plasma, belumosudil accounted for 64% of total drug-related material, KD025m2 and co-eluting O-dealkylated belumosudil sulfate was 11.5%, and a belumosudil glucuronide was 15%.
Primary Metabolic Pathway(s)	CYP3A4, found in the liver and the intestine, is the predominant CYP isoform responsible for belumosudil metabolism (41.9%). CYP2D6 (21.7%), CYP2C8 (14.2%), CYP1A2 (<5%), CYP2C19 (<5%), and UGT1A9 contribute to a lesser extent.
Excretion	
Primary Excretion Pathways (% dose) ±SD	The predominant route of belumosudil clearance and associated metabolites is biliary and/or intestinal, as 85% of drug material was recovered in feces.
Interaction liability (Drug as Perpetrator)	
Inhibition/Induction of Metabolism	PBPK analyses indicate belumosudil drug interactions are expected to be minimal with moderate CYP3A inhibitors, CYP2C9 substrates or CYP2C8 substrates that are not substrates of OATP1B, and weak with the moderate CYP3A inducer efavirenz or CYP3A substrates. In vitro studies indicate potential interactions with UGT1A1, UGT1A9, CYP1A2, CYP2C19 and CYP2D6, however these interactions were not further investigated by the Applicant in their PBPK analyses.
Inhibition/Induction of Transporter Systems	In vitro evaluations showed belumosudil to inhibit the transporters BCRP, P-gp and OATP1B1. The applicant has not assessed inhibition of transporter systems in patients. PBPK analyses were inadequate to confirm a negative DDI effect of belumosudil on the exposure of substrates of P-gp, BCRP, OATP1B, and MATEs due to lack of quantitative in vitro to in vivo extrapolation for the in vitro transporter inhibition parameters and/or limitations identified in the PBPK models of these transporter substrates.

Cmax=maximum plasma concentration; t1/2=elimination half-life; Tmax=time to maximum plasma concentration; CL/F= elimination clearance; V2/F = central volume of distribution

6.3.2 Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Data:

Results from the Phase 2 studies in subjects with cGVHD demonstrate clinically meaningful and similar ORR at 3 dose levels (200 mg QD, 200 mg BID, and 400 mg QD [all administered with food]; Section 0). Exposure-efficacy analyses for these studies indicate a flat relationship.

The Applicant's Position:
The flat exposure-efficacy relationships (Section 0) at the range of exposures observed in Studies KD025-208 and KD025-213 and the similarity of ORR across the tested dose levels supports the selection of 200 mg QD with food.

The FDA's Assessment:
The FDA agrees with the Applicant's position that the clinical pharmacology information provides sufficient supportive evidence of effectiveness and safety to support the 200 mg once daily dosing *with food.*

Efficacy

The FDA agrees with the Applicant assessment that the clinical pharmacology program demonstrates supportive evidence of effectiveness. In registration trial KD025-213, 200 mg QD resulted in an overall response rate (ORR) of 75%, which was comparable to the 70% with 200 mg BID. Additional information regarding the efficacy assessment of belumosudil in Study KD025-213 is provided in Section 8.2.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Data:

A variety of patient characteristics were included in Studies KD025-208 and KD025-213. Baseline characteristics demonstrate that ~50% all subjects had ≥4 organs affected in both studies, including both inflammatory and fibrotic manifestations of cGVHD; 65% of all patients had received ≥2 prior lines of cGVHD therapy in Study KD025-208; and 73% of all subjects were refractory to the line of therapy received immediately prior to enrollment in Study KD025-213. Concomitant medications reflective of the cGHVD population (including PPIs [Section 0]) were included in these studies and no demographics had significant effects on belumosudil PK in the popPK analysis (Section 0).

The exposure-response analysis demonstrated no trend with safety or efficacy variables across the range of exposures observed at the dose levels included in the Phase 2 studies.

The Applicant's Position:
The variety of patient characteristics included in Studies KD025-208 and KD025-213 are reflective of the cGVHD population and did not affect safety or efficacy. The exposure-response analyses support the proposed dose of 200 mg QD in the general cGVHD population. The exposure-efficacy relationships were flat. The exposure-safety relationships were also flat, indicating a wide range of tolerable exposures.

The FDA's Assessment:

The FDA agrees with the Applicant's position that 200 mg QD, with food, is an appropriate dose for the general cGVHD population.

Dose response analysis showed that a higher rate of Grade 4/life threatening (19%) and Grade 5/fatal (19%) TEAEs was observed in the 400 mg QD cohort compared to 200 mg QD and 200 mg BID (Table 7). It should be noted that 400 mg QD lead to a higher Cmax and AUC compared to 200 mg QD and 200 mg BID. In addition, based on FDA's independent analyses, positive trends were observed in probability of TEAE Grade 4+ versus AUC, probability of TEAE leading to drug interruption versus AUC, and probability of TEAE leading to drug withdrawal versus AUC. Furthermore, the increased AEs under 400 mg QD may also have been driven by Cmax.

Table 7. Summary of Safety from Studies KD025-208 and KD025-213

	200 mg QD (N = 83)	200 mg BID (N = 82)	400 mg QD (N = 21)
Grade ≥ 3 TEAE	53.0%	48.8%	66.7%
TEAE leading to dose interruption	28.9%	29.3%	38.1%
TEAE leading to drug withdrawal	25.3%	18.3%	38.1%
Grade 3 (severe) TEAEs	44.6%	41.5%	28.6%
Grade 4 (life threatening) TEAEs	3.6%	6.1%	19.0%
Grade 5 (fatal) TEAEs	4.8%	1.2%	19.0%
Grade ≥ 3 infections/infestations*	18.1%	15.9%	28.6%
Grade ≥ 3 metabolism disorders**	16.9%	9.8%	14.3%
Grade ≥ 3 respiratory disorders	13.3%	6.1%	28.6%
Grade ≥ 3 GI disorders	14.5%	6.1%	9.5%

Given the comparable efficacy and safety profiles between the 200 mg QD and BID dosing regimens (See Section 8.2), the serious safety events seen at the 400 mg QD dosing regimen, and the lower exposure observed with 200 mg QD, the proposed dose of 200 mg once daily, with food, is acceptable for the general patient population.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

Data:

Demographics

Sex, age, body weight, race, and ethnicity were evaluated for inclusion in the popPK model but significant effects were not detected.

Hepatic Impairment

In the ongoing hepatic impairment study (KD025-109), the exposure in subjects with mild and moderate hepatic impairment had exposure ≤1.51x the exposure observed in normal subjects. Supporting a lack of large effect of hepatic impairment on belumosudil clearance, liver enzymes, and bilirubin were not significant covariates on CL/F in the popPK analysis. Evaluation of belumosudil PK in subjects with severe hepatic impairment is ongoing (KD025-109).

Renal Impairment

In Study KD025-108, the majority of total radioactivity was recovered in feces (85%) and <5% was recovered in urine, suggesting there is minimal renal elimination. In the popPK analysis, there was no significant effect of estimated glomerular filtration rate (eGFR) or creatinine clearance on belumosudil CL/F. Each of the cGVHD studies (KD025-208 and KD025-213) allowed for enrollment subjects with mild (Study KD25-208 n=28 subjects and Study KD025-213 n=59 subjects with eGFR ≥60 and <90 mL/min/1.72m^2 at baseline) and moderate renal impairment (Study KD25-208 n=24 subjects and Study KD025-213 n=9 subjects with eGFR ≥30 and <60 mL/min/1.72m^2 at baseline).

The Applicant's Position:

No belumosudil dose adjustments are required based on demographic characteristics or renal impairment. No dose adjustment is needed for subjects with mild or moderate hepatic impairment (C_{max} and AUC ≤1.51x exposure in subjects with normal hepatic function). Evaluation of belumosudil PK in subjects with severe hepatic impairment is ongoing.

The exposure-responses analyses further support the recommendation for no dose adjustment to account for these intrinsic factors.

The FDA's Assessment:

The FDA agrees with the Applicant that no dose adjustments are required based on sex, age, body weight and renal impairment.

Pediatrics

The FDA finds the Applicant's recommended dose of belumosudil 200 mg QD to be acceptable for pediatric patients 12 years of age or older with cGVHD. Use of belumosudil in this age group is supported by evidence from pivotal studies in adults and popPK analysis demonstrating that

age and body weight had no clinically meaningful effect on the PK of belumosudil. The exposure of drug substance is expected to be similar between adults and pediatric patients that are 12 years of age and older. Further, the course of disease is sufficiently similar in adult and pediatric patients to allow extrapolation of data in adults to pediatric patients. Weight range included in the popPK analysis was 38.6 to 143 kg, and no body weight effect was identified on the clearance of belumosudil. Based on the CDC growth chart, the median body weight for 12 year old females is 41.5 kg.

Race and Ethnicity

The FDA does not agree with the Applicant's assessment on the impact of race and ethnicity on the exposure of belumosudil given that the data in the clinical trial is limited by the small number of non-white patients enrolled in the trial. The distribution of race out of 186 patients treated in the studies is shown in Table 8. In the pivotal studies, higher rates of Grade 3 AEs (cardiac disorders, gastrointestinal disorders, vascular disorders) were reported in Black patients compared to White patients (Table 9).

Table 8. Distribution of race across pivotal studies

	Study KD025-208 (54 patients treated)	**Study KD025-213 (132 patients treated)**
Race	**N (%)**	**N (%)**
White	47 (87%)	112 (85%)
Black	2 (3.7%)	7 (5.3%)
American Indian or Alaska Native	2 (3.7%)	2 (1.5%)
Asian Indian		1 (0.8%)
Chinese		1 (0.8%)
Other Asian		1 (0.8%)
Non-white (Unreported/ Unknown)		8 (6%)
Other	3 (5.6%)	

Table 9. Rates of three AE categories by worst grade between White and Black patients

Studies KD025-208 and KD025-213	**Grade 3 Cardiac Disorders**	**Grade 3 GI Disorders**	**Grade 3 Vascular Disorders**
White patients	3.1%	11%	9.0%
Black patients	**11%**	**22%**	**11%**

Data from Study KD025-101 and KD025-102 were used to compared exposures between White and Black subjects for the 500 mg QD cohorts. Belumosudil exposure was higher in healthy Black subjects compared to healthy White subjects in safety/tolerability/PK studies (Table 10).

Table 10. Belumosudil exposure in healthy White and Black subjects from two safety/tolerability/PK studies (500 mg QD cohorts)

Studies KD025-101 and KD025-102, 500 mg QD	Day 1 AUC24 GM, ng•h/mL	Day 7, 8 AUC24 GM, ng•h/mL (n)
White subjects (7)	15643	18375
Black subjects (5)	**25653**	**25576**

Given the limited information in non-white patients and the potential for higher rates of safety events, a PMR will be issued for the Applicant to conduct a clinical trial in a sufficient number of Black patients with cGVHD to assess the safety of belumosudil. This study should characterize the exposure (including PK data), safety, and efficacy of belumosudil. Given the limited number of non-white patients, a PMC to characterize the exposure (including PK data), safety, and efficacy of belumosudil in other U.S. racial and ethnic minorities will be conducted.

Hepatic impairment

The FDA does not agree with the Applicant's position that there is a lack of a large effect of hepatic impairment on belumosudil clearance and that no dose adjustments are required for hepatic impairment. The impact of moderate and severe hepatic impairment, as defined by the NCI-ODWG classification, in patients with cGVHD on belumosudil exposure is unknown, as none of the 352 subjects in the popPK dataset had moderate or severe hepatic impairment: 303 had normal hepatic function and 49 had mild hepatic impairment.

The evaluation of the relationship between hepatic impairment and clearance indicated no effect of mild hepatic impairment on clearance compared to normal hepatic function.

The PK and safety of belumosudil as a single 200 mg dose was assessed in otherwise healthy subjects with mild and moderate hepatic impairment (Child-Pugh classification) in the dedicated hepatic impairment study KD025-109. This study is currently ongoing and a final report has not been submitted. Preliminary data for hepatic impairment study showed mean PK exposure (AUC) of belumosudil to be approximately 50% higher in subjects with moderate hepatic impairment compared to subjects with normal function, indicating that a dose adjustment may be necessary once the final report is available.

Given the interim status of the dedicated hepatic impairment study, which included preliminary data showing higher belumosudil exposure in subjects with moderate HI, a PMR will be issued

for the Applicant to complete their clinical PK trial to determine a safe and appropriate dose of belumosudil in subjects with mild, moderate and severe hepatic impairment. The final report should include assessments of subjects with mild, moderate and severe hepatic impairment.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Data:

Food Effect

Systemic exposure of belumosudil was increased when administered under the fed state (C_{max} and AUC_{inf} geometric mean ratios of 2.52 and 2.92, respectively in Study KD025-105 [capsule], and C_{max} and AUC_{0-24} geometric mean ratios of 2.25 and 1.99, respectively in Study KD025-106 [tablet; to-be-marketed form]). Median t_{max} was delayed by 0.5 hours when belumosudil tablet was administered with food.

In the popPK analysis, a net effect of fed status, concomitant CYP3A4 inducer and inhibitor use, and disease status on relative bioavailability was estimated. In cGVHD subjects, belumosudil was administered with food. Therefore, the increase in exposure (due to lower clearance estimated in cGVHD subjects) is indistinguishable from the food effect. The results from the controlled Phase 1 food effect studies are more conclusive regarding a food effect on the relative bioavailability of belumosudil than the popPK model.

Victim Drug-Drug Interactions

CYP3A4 induction and inhibition: Co-administration of belumosudil with rifampicin resulted in decreased exposure of belumosudil and KD025m2 (belumosudil C_{max} and AUC GMR of 0.41 and 0.28, respectively; KD025m2 C_{max} and AUC GMR of 0.45 and 0.33, respectively), but an increase in exposure of KD025m1 (C_{max} and AUC GMR of 2.3 and 2.5, respectively). Co-administration of belumosudil with itraconazole resulted in a small increase in belumosudil exposure and decrease in KD025m2 exposure (belumosudil C_{max} and AUC GMR of 1.20 and 1.25, respectively; KD025m2 C_{max} and AUC GMR of 0.66 and 0.67, respectively).

PPI: A delay and reduction in absorption was observed when belumosudil was co-administered with a moderate or strong PPI. Exposure of both the parent and associated metabolites decreased significantly when administered with either PPI (~53 to 68% with omeprazole, ~80 to 87% with rabeprazole). In the popPK analysis, concomitant PPI use (all strengths pooled together) resulted in a 48% reduction in relative bioavailability.

Perpetrator Drug-Drug Interactions

Enzyme Inhibition: Based on in vitro CYP inhibition data (belumosudil concentration range 0.025 to 25 µM; ~10 to ~10300 ng/mL), belumosudil R values meet the threshold for further evaluation for CYP3A4/5 time dependent inhibition and gut inhibition. This potential interaction is being investigated further with PBPK modeling. KD025m1 and KD025m2 AUCs are <20% belumosudil exposure and, therefore, their CYP inhibition potential need not be further evaluated (FDA Guidance for Industry: In Vitro Drug Interaction Studies – Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions, January 2020).

Enzyme Induction: At in vitro concentrations higher than clinically relevant (3 to 30 µM; ~1360 to ~13600 ng/mL), belumosudil caused increases in CYP1A2, CYP2B6, and CYP3A4 mRNA that were less than 20% of the respective positive controls, indicating low clinical significance. KD025m2 had minimal to no inductive effect on CYP1A2, CYP2B6, and CYP3A4 mRNA levels at 0.3 to 100 µM (~123 to ~41000 ng/mL).

Transporter Inhibition: Belumosudil is a potential inhibitor of P-gp, BCRP, and OATP1B1. These potential interactions are being further evaluated in the ongoing PBPK analysis.

Belumosudil meets the threshold for further evaluation for P-gp inhibition; however, of the 7 concomitant medications most used (i.e., used in >9 subjects in Study KD025-208 and >14 subjects in Study KD025-213) in the cGVHD population, only 2 are labeled to be used with caution when co-administered with a P-gp inhibitor (sirolimus [which is labeled to use with caution when administered with P-gp inhibitors] and cyclosporin [which is labeled for potential P-gp interactions and advises therapeutic monitoring when concomitant drugs that may perpetrate interactions are co-administered]).

The R value assessment indicates that belumosudil meets the threshold for further evaluation for breast cancer resistance protein (BCRP) inhibition. However, compounds that are known substrates of BCRP are not likely to be heavily used in the cGVHD population and those most commonly used in Studies KD025-208 and KD025-213 are not labeled for dose adjustment.

Using the worst-case estimate of complete solubility of 200 mg in 250 mL water, belumosudil has an OATP1B1 estimate above the cut off. The intestinal concentration used in this assessment was 0.8 mg/mL (200 mg/250 mL) which is >27x the reported solubility for belumosudil in fed and fasted simulated intestinal fluid (0.029 and 0.003 mg/mL, respectively); using these solubilities as maximum intestinal concentrations and, thus, maximal input of new drug to the hepatic vein, and 0.12% unbound, the OATP1B1 value drops below the cutoff. The OATP1B1 substrates most commonly used in Studies KD025-208 and KD025-213 are not labeled for dose adjustment when administered with OATP1B1 inhibitors.

The R values for MATE and MATE2K are near the threshold for further evaluation. MATE1 or MATE2K substrates are not likely concomitant medications in the cGVHD population. Those

that were used in Studies KD025-208 and KD025-213 are not labeled for dose adjustment with MATE/MATE2K inhibitors.

Transporter Induction: Belumosudil is not an inducer of CYP3A4 in vitro and therefore was not evaluated for P-gp induction.

The Applicant's Position:

Food Effect

The belumosudil should be administered with food. There is increased exposure after fed administration and the Phase 2 studies were conducted with fed administration.

Victim Drug-Drug Interactions

CYP3A4 Induction and Inhibition: These clinical study results indicate that CYP34A enzymes impact the metabolism of belumosudil; however, no dose adjustment is needed for concomitant CYP3A4 inducer or inhibitor administration given the flat exposure-efficacy and exposure-safety relationships across the evaluated exposure range.

PPI: The clinical study results indicate that an increase in gastric pH led to decreased solubility of belumosudil thus resulting in decreased absorption of belumosudil; however, no dose adjustment is needed for concomitant PPI use given the flat exposure-efficacy relationships across the evaluated exposure range.

Perpetrator Drug-Drug Interactions

The potential inhibtion of belumosudil and CYP3A4 (time dependent) and CYP3A4 gut, P-gp, BCRP, OATP1B1, MATE1, and MATE2K is being further evaluated in PBPK modeling. The risk of belumosudil inhibition by transporters is low, as only 2 drugs commonly used in the cGVHD population are labeled for dose adjustment with transporter inhibition.

The FDA's Assessment:

Food Effect

FDA agrees with the Applicant's position regarding the food effect.

The effect of food on belumosudil when given with food was evaluated under Study KD025-106, a 3-way crossover, open-label study in healthy subjects who were dosed in either the fasted or fed (high fat breakfast) state. The high fat breakfast included 144 kcal from protein, 280 kcal from carbohydrates, and 486 kcal from fat. Results showed a half-life of 11.16 h in the fasted state and 6.98 h in the fed state. Administration of 200 mg belumosudil tablet in the fed state resulted in an increased exposure in terms of Cmax and AUC when compared to the fasted state. It should be noted that based on popPK analysis, patients with cGVHD had approximately

53% lower CL/F compared to healthy volunteers.

Drug-drug interactions – Belumosudil as a victim

The FDA does not agree with the Applicant's position that no dose adjustments are required for concomitant CYP3A4 inducers or PPIs.

CYP3A Inducers

The FDA notes that rifampicin, a strong CYP3A inducer, significantly reduced belumosudil Cmax by approximately 60% and overall exposure by approximately 72%. Population PK (popPK) analysis also showed that oral clearance (CL/F) with concomitantly administered CYP3A4 inducers was 2.88 times the CL/F in healthy volunteers without CYP3A4 inducers. Additional information regarding the population PK analysis is provided in Section 16.4.2.

Given that CYP3A4 inducers significantly reduce belumosudil exposure, the FDA recommends that belumosudil 200 mg be administered twice daily (BID) with food when administered concomitantly with strong CYP3A4 inducers.

Proton-pump Inhibitors

The Applicant evaluated the impact of PPIs on belumosudil exposure in healthy subjects in Study KD025-107. In Part 1, subjects received multiple doses of 20 mg rabeprazole followed by a single dose of belumosudil 200 mg in the fed state. In Part 2, subjects received multiple doses of 20 mg omeprazole followed by a BID dose (once every 12 hours) of belumosudil 200 mg in the fed state. The PPI rabeprazole reduced belumosudil Cmax by up to 87% and overall exposure by up to 80%. The impact of co-administered rabeprazole and omeprazole on belumosudil exposure is shown in Table 11.

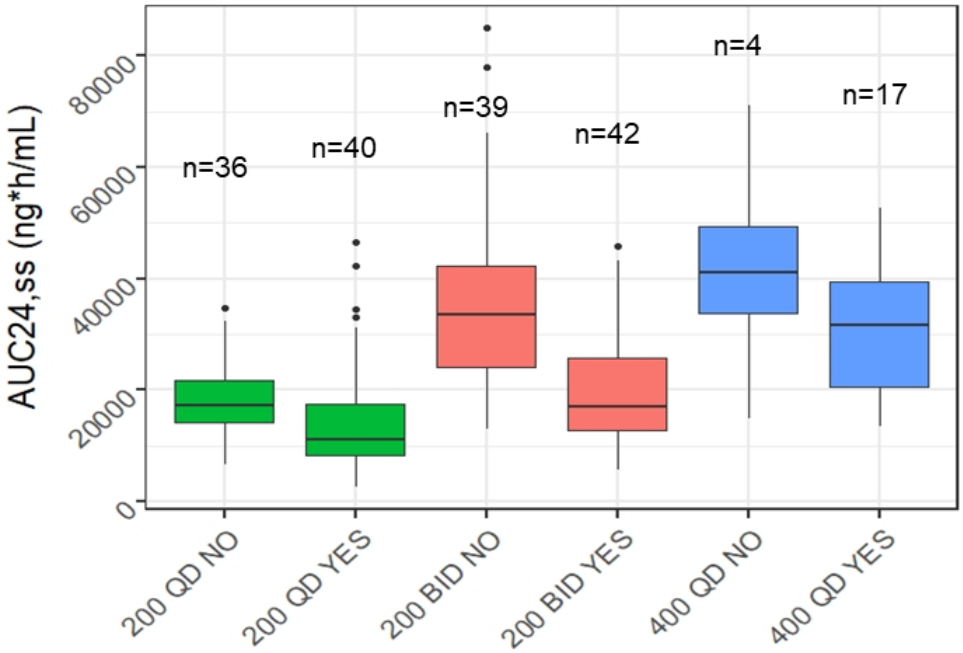
Table 11. Impact of Co-administered PPIs on belumosudil exposure, expressed as GMR

	PPI	Cmax GMR (90% CI)	AUCinf GMR (90% CI)
Belumosidil 200 mg QD (n = 32)	Rabeprazole	13% (11.2% – 15.1%)	20.2% (18% – 22.6%)
Belumosudil 200 mg BID (n = 36)	Omeprazole	32.1% (23.9% – 43%)	53.5% (45.9% – 62.4%)

In addition, the PopPK analysis showed that concomitant PPI administration had a statistically significant effect on exposure by reducing belumosudil bioavailability by approximately 48% compared to no PPI administration. Out of the 178 patients with cGVHD included in the E-R analysis, 9 patients had concomitant administration of either esomeprazole or rabeprazole, which decreased belumosudil exposure up to 80% (categorized as "strong" PPIs in the studies), and only 5 of these patients received 200 mg QD.

Given that 200 mg QD is the lowest dose studied and the significant reduction of belumosudil exposure expected with co-administration of these strong PPIs, there is a potential for compromised efficacy following the 200 mg QD belumosudil and co-administration of strong PPIs, such as esomeprazole and rabeprazole used in the studies. To reduce the risk of lower efficacy in patients with the extremely low exposures with coadministration of strong PPIs, a higher dosing regimen was considered. Due to the lack of definition of weak/moderate/strong PPIs in the clinical practice, dose adjustment only for strong PPIs concomitant use is not practical. The dose adjustment was determined based on the pooled exposure from the mixed weak/moderate/strong PPIs usage. PPK analysis using the data from the two pivotal studies indicated that with the concomitant use of PPIs, the dosing regimen of 200 mg BID is expected to provide closer AUC24,ss compared to that following 200 mg QD without concomitant PPIs use, while the AUC24,ss following 400 mg QD with concomitant use of PPIs would be much higher than that following 200 mg QD without concomitant PPIs use (Figure 2). As such, a dose adjustment to 200 mg BID in the presence of concomitant PPIs would potentially prevent exposures that would fall below the AUC0-24,ss observed during the pivotal studies. Given that Study KD025-208 showed the highest rate of Grade 4 and 5 treatment-emergent adverse events (TEAEs) to occur in the 400 mg QD cohort (19% of patients), as well as the positive E-R trend for safety, 400 mg QD is not a recommended dose adjustment with concomitant PPIs.

Figure 7. Comparison of AUC24 at steady-state in each belumosudil dosing regimen with or without concomitant use of PPIs



Drug-drug interactions – Belumosudil as a perpetrator

CYP enzymes

The Applicant only conducted in vitro studies and did not conduct a clinical evaluation of belumosudil as a perpetrator. Plasma concentration of concomitant medications relevant to patients with cGVHD that are substrates of CYP3A4 (e.g. tacrolimus, cyclosporine, sirolimus) were not determined in pivotal studies KD025-208 and KD025-213.

The Applicant conducted PBPK analyses to evaluate the effects of moderate CYP3A inhibitors and inducers on the PK of belumosudil, and the effects of belumosudil on the substrates of CYP3A, CYP2C9 and CYP2C8. FDA reviewed the PBPK report and concluded the following:

- The effect of moderate CYP3A inhibitors on belumosudil PK is minimal
- The effect of moderate CYP3A inducers on belumosudil PK is weak
- The effect of belumosudil on substrates of CYP3A and CYP2C9 is minimal
- The effect of belumosudil on substrates of CYP2C8 that are not substrates of OATP1B1 is minimal

Refer to FDA's review of the Applicant's physiologically based pharmacokinetic (PBPK) modeling analysis in Section 14.4.1.

It should be noted that the Applicant did not adequately investigate belumosudil inhibition of CYP1A2, CYP2C19 and CYP2D6. The results from the IC50 shift assay (Study XT175017) showed that belumosudil was a mechanism-based inhibitor of CYP1A2, CYP2C19 and CYP2D6. However, the IC50 generated in the in vitro study is not suitable for assessing mechanism-based inhibition potential of belumosudil on these enzymes for the labeling purpose. A potential risk of belumosudil to increase the concentration of concomitant substrate drugs that are used in this patient population has not been estimated.

A PMR will be issued for the Applicant to conduct an in vitro mechanism-based inhibition study (such as the two-step dilution method) estimating the inactivation parameters (k_{inact} and K_I) of CYP1A2, CYP2C19 and CYP2D6 enzymes and measuring nonspecific binding of belumosudil to assess the potential of drug interaction with belumosudil on these enzymes.

UGT1A1 enzyme

In vitro studies (Study Report ADME-KAD-200630-UGT Inhibition) showed belumosudil to be a potent inhibitor of the UGT1A1 enzyme, with an IC50 of 0.06 μM. Belumosudil was predicted to inhibit UGT1A1 at clinically relevant concentrations, which indicates a potential risk of

increasing the concentration of concomitant substrate drugs, that are used in this patient population, to toxic levels.

A PMR will be issued for the Applicant to conduct a clinical PK trial evaluating the effect of repeat doses of belumosudil on the single dose PK of a UGT1A1 substrate to assess the potential for excessive drug toxicity.

Transporters

The Applicant only conducted in vitro studies and did not conduct a clinical evaluation of the impact of belumosudil on other transporter substrates. Plasma concentration of concomitant medications relevant to patients with cGVHD that are substrates of the P-gp transporter (e.g. sirolimus) were not determined in pivotal studies KD025-208 and KD025-213.

The Applicant conducted PBPK analyses to evaluate the effects of belumosudil on the exposure of transporter substrates. FDA concluded that the Applicant's PBPK analyses were inadequate to predict the effect of belumosudil on the exposure of substrates of P-gp, BCRP, OATP1B, and MATEs due to uncertainty in the *in vitro* to *in vivo* extrapolation for the *in vitro* transporter inhibition parameters and/or limitations identified in the PBPK models of these transporter substrates. Refer to FDA's review of the Applicant's physiologically based pharmacokinetic (PBPK) modeling analysis in Section 14.4.1.

A PMR will be issued for the Applicant to conduct a clinical PK trial evaluating the effect of repeat doses of belumosudil on the single dose PK of sensitive substrates (P-gp, BCRP and OATP1B1) to assess the potential for excessive drug toxicity.

7 SOURCES OF CLINICAL DATA

7.1 Table of Clinical Studies

The Applicant's Position:

All studies pertinent to the evaluation of efficacy and safety of belumosudil are summarized in Table 12.

Table 12 Listing of Clinical Trials Relevant to this NDA for Belumosudil

Trial Identity [NCT no.]	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety							
KD025-213 [NCT03640481]	Open-label, randomized 1:1	Test product: Belumosudil tablet 200 mg Dosage regimen: 200 mg QD (Arm A) 200 mg BID (Arm B) Route: Oral	Primary: ORR as defined by 2014 NIH Consensus Development Project for Clinical Trials in cGVHD Secondary: DOR, Change in Lee Symptom Scale Score, Response rate by organ system, TTR, TTNT, % subjects w/ best response of PR and % subjects with best response of CR Change in corticosteroid dose, Change in calcineurin inhibitor dose, FFS, OS, Change in symptom activity using the cGVHD Activity Assessment Patient Self-Report, Pharmacokinetics	28 day cycles until disease progression or unacceptable toxicity; follow-up for survival (FFS/ OS) continued every 12 weeks until death, lost to follow-up, patient withdrawal	Total: 132 Arm A: 66 Arm B: 66	Patients with cGVHD after failure of two to five lines of systemic therapy	33 Centers, 28 enrolling centers 1 country (USA)

KD025-208 [NCT02841995]	Open-label, Dose-escalation	Test products: Belumosudil capsule 100 mg or belumosudil tablet 200 mg Dosage regimen: 200 mg QD (Cohort 1) 200 mg BID (Cohort 2) 400 mg QD (Cohort 3) Route: Oral	Primary: Overall Response Rate (ORR) as per 2014 NIH Consensus Development Project for Clinical Trials in cGVHD criteria Secondary: % subjects w/ best response of PR or CR, DOR, TTR, Response rate by organ system, LSS, FFS, TTNT, OS, Change in corticosteroid dose, Change in CNI dose, Change in symptom activity based on cGVHD Activity Assessment Patient Self-Report, PFTs, Pharmacokinetics	28 day cycles until disease progression or unacceptable toxicity; follow-up for survival (FFS/ OS) continued every 8 weeks until death, lost to follow-up, patient withdrawal	Total: 54 Cohort 1: 17 Cohort 2: 16 Cohort 3: 21	Patients with cGVHD after failure of one to three lines of systemic therapy	7 Centers 1 country (USA)
Additional Studies to Support Safety							
KD025-205 [NCT02106195]	Open-label	Test Product: Belumosudil capsule 100 mg Dosage Regimen: 200 mg QD Route: Oral	Primary: Evaluate safety and tolerability of 200 mg QD Secondary: Assess decereases in PASI, achieve improvement in PGA	4 weeks	Total: 8	Male and female subjects with moderately severe psoriasis vulgaris	1 center 1 country (USA)
KD025-206 [NCT02317627]	Open-label	Test Product: Belumosudil capsule 100 mg Dosage Regimen: 3 daily doses: Cohort 1: 400 mg QD Cohort 2: 200 mg BID	Primary: Evaluate safety and tolerability of 3 daily dose regimens Secondary: Assess amount of decrease in PASI, assess changes in PGA, assess changes in DLQI, assess PK of KD025	12 weeks of dosing with 30 day Follow-up after end of treatment	Total: 38 Cohort 1: 13 Cohort 2: 13	Subjects with psoriasis vulgaris who had failed a first-line of therapy	9 centers 1 country (USA)

		Cohort 3: 400 mg BID Route: Oral			Cohort 3: 12		
KD025-211 [NCT02852967]	Double-blind, randomized, placebo controlled	Test Product: Belumosudil tablet 200 mg Dosage Regimen: 5 dose cohorts in a 1:1:1:1:1 manner: Cohort 1: 200 mg QD Cohort 2: 200 mg BID Cohort 3: 400 mg QD Cohort 4: 600 mg daily Cohort 5: matching Placebo BID	Primary: Assess number of subjects that reach PASI 75 after 16 weeks compared with placebo Secondary: Assess changes in absolute PASI; assess mean percent change in PASI; assess safety and tolerability of KD025; assess changes in PGA; assess changes in DLQI	16 weeks of double-blind treatment with option to continue for 32 weeks of open label treatment; follow-up 30 days post final dose	Total: 110 Cohort 1: 23 Cohort 2: 22 Cohort 3: 21 Cohort 4: 26 Cohort 5: 18	Adult male and female subjects with moderate to severe chronical plaque psoriasis	16 centers, 14 enrolling centers 1 country (USA)
KD025-207 [NCT02688647]	Open-label, randomized	Test Product: Belumosudil capsule 100 mg or belumosudil tablet 200 mg Dosage Regimen: 400 mg QD Route: Oral	Primary: Evaluate change in FVC from baseline to 24 weeks in subject with IPF compared with best supportive care (BSC); Evaluate safety and tolerability of KD025 when administered 24 weeks in subject with IPF compared with BSC Secondary: Evaluate change in 6-minute walk distance; Evaluate occurrence of acute	24 weeks with option to continue and follow-up occurring 30 days after final dose; up to 96 weeks	Total: 76 enrolled	Adult male and postmenopausal/surgically sterilized female subjects with idiopathic pulmonary fibrosis	11 Centers, 10 Enrolling centers 1 country (USA)

			exacerbation of IPF throughout treatment; Evaluate change in severity of lung fibrosis as measured by quantitative HRCT; Evaluate percentage of subject with disease progression before or at 24 weeks				
SLx-2119-09-01	Randomized, double-blind, dose escalating	Test product: Belumosudil capsule 10 mg or 100 mg Dosage regimen: Single dose of belumosudil 20 mg, 40 mg, 80 mg, 160 mg and placebo Route: Oral	Primary: Determine safety and tolerability of escalating single oral doses Secondary: Determine the plasma levels and its metabolites after administration of escalating single oral doses	1 Day	Total: 32 SLx-2119 (belumosudil): 24 Placebo: 8	Healthy male subjects	1 center 1 country (USA)
KD025-101	Randomized, placebo controlled	Test Product: Belumosudil 10 mg capsule or 100 mg capsule Dosage regimen: 40 mg, 80 mg, 120 mg, 160 mg, 240 mg, 320 mg, 400 mg, 500 mg and placebo Route: Oral	Primary: Safety and tolerability of single and multiple doses of belumosudil Secondary: Determine PK in plasma of belumosudil after single and multiple doses	1 day single dose and 7 days multiple dose	Total: 64 Belumosudil: 48 Placebo: 16	Healthy male subjects	1 center 1 country (USA)
KD025-102	Randomized,	Test Product:	Primary: Determine safety and	7 days	Total: 32	Healthy male	1 center

	double-blind, placebo controlled	Belumosudil capsule 100 mg Dosing regimen: 500 mg QD 800 mg QD 500 mg BID 1000 mg QD placebo Route: Oral	tolerability of multiple doses and regimens Secondary: Determine the pharmacokinetics after multiple-dose administration		Belumosudil: 24 Placebo: 8	and post-menopausal female subjects	1 country (USA)
KD025-103	Randomized, double-blind placebo controlled	Test Product: Belumosudil capsule 100 mg Dose regimen: 500 mg QD 800 mg QD 500 mg BID 1000 mg QD Route: Oral	Primary: Determine safety and tolerability of 500 mg administered BID for 28 days Secondary: Determine pharmacokinetics of 500 mg administered BID for 28 days, Evaluate exploratory pharmacodynamics of 500 mg administered BID	28 days	Total: 8 Belumosudil: 6 Placebo: 2	Healthy male and post-menopausal female subjects	1 center 1 country (USA)
Other studies pertinent to review of efficacy or safety (e.g., clinical pharmacological studies)							
KD025-105	Open-label, two period, crossover	Test Product: Belumosudil capsule 100 mg Dosage regimen: 500 mg Route: Oral	Primary: Determine safety and tolerability of single dose of 500 mg belumosudil administered orally under fed and fasted conditions Secondary: Determine pharmacokinetics of a single dose of 500 mg belumosudil	2 days (single dose on 2 separate occasions)	Total: 12	Healthy male subjects	1 center 1 country (USA)

			administered orally under fed and fasted conditions				
KD025-106 [NCT02557139]	Open-label, three-period, crossover	Test Product: Belumosudil capsule 100 mg and belumosudil tablet 200 mg Dosage Regimen: 2x100 mg capsule fasted 200 mg tablet fed 200 mg tablet fasted Route: Oral	Primary: Determine the PK parameters of belumosudil tablet formulation in the fed and fasted states Secondary: Determine the effect of a high fat meal on the bioavailability of belumosudil tablet formulation, Assess the relative bioavailability of a tablet to a capsule formulation of belumosudil, Assess and compare variability in Cmax and AUC for all 3 belumosudil treatments, Provide additional safety and tolerability information for belumosudil	3 days (single dose on 3 separate occasions)	Total: 23	Healthy male subjects	1 center 1 country (UK)
KD025-107 [NCT03530995]	Open-label, two part	Test Product: Belumosudil tablet 200 mg, itraconazole 100 mg, rifampicin 300 mg, rabeprazole 20 mg and omeprazole 20 mg Dosage regimen: Part 1: Period 1: Belumosudil 200 mg Period 2: Itraconazole 200 mg QD and itraconazole 200 mg plus	Primary Part 1: Determine the effect of itraconazole, rifampicin and rabeprazole on the PK of once daily orally administered belumosudil Secondary Part 1: Provide additional information on safety and tolerability of QD orally administered belumosuidl Primary Part 2: Determine effect of omeprazole on PK of a single day twice daily(BID;	Part 1: 4 days (single dose on 4 separate occasions) Part 2: 2 days (twice daily dose on 2 separate occasions)	Total: 73 Part 1: 35 Part 2: 38	Healthy male subjects	1 center 1 country (UK)

		belumosudil 200 mg QD Period 3: Rabeprazole 20 mg BID and rabeprazole 20 mg plus belumosudil 200 mg QD Period 4: Rifampicin 600 mg QD and rifampicin 600 20 mg plus belumosudil 200 mg QD Part 2: Period 1: Belumosudil 200 mg BID Period 2: Omeprazole 20 mg QD, belumosudil 200 mg BID plus omeprazole 20 mg QD Route: Oral	every 12 h [Q12h]) dose of belumosudil administered orally Secondary Part 2: Provide additional information on safety and tolerability of single day BID dose of belumosudil administered orally				
KD025-108 [NCT03907540]	Open-label, two part	Test Product: Belumosudil tablet 200 mg, [^{14}C]-KD025 solution for infusion,	Primary Part 1: Determine absolute oral bioavailability of belumosudil	Part 1: Single oral dose of belumosudil followed by an IV	Total: 5	Healthy male subjects	1 center 1 country (UK)

		20 µg/mL and [^{14}C]-KD025 tablet 200 mg Dosage regimen: Part 1: Single oral dose of belumosudil followed by IV infusion of [^{14}C]-KD025 Part 2: Single dose of [^{14}C]-KD025 capsule Route: Oral, IV	Secondary Part 1: Obtain information regarding oral PK of total radioactivity, belumosudil and its metabolites KD025m1 and KD025m2 in plasma and Obtain information regarding IV PK of [^{14}C]-KD025 in plasma Primary Part 2: Determine the mass balance recovery after a single oral dose of carbon-14 [^{14}C]-KD025 and Provide plasma, urine and fecal samples for metabolite profiling and structural identification Secondary Part 2: Determine the route and rates of elimination of [^{14}C]-KD025 and associated total radioactivity, Evaluate extent of distribution of total radioactivity into blood cells, Assess qualitative and quantitative metabolic profile of [^{14}C]-KD025 and carry out the structural elucidation of main metabolites in plasma, Provide additional safety and tolerability information for belumosudil	infusions of [^{14}C]-KD025 Part 2: Single dose of [^{14}C]-KD025 capsule			
KD025-109 [NCT04166942]	Single-dose, Open-label	Test Product: Belumosudil tablet	Primary: Assess PK of belumosudil following single	1 day	Total: 40	Group 1: normal	3 centers 1 country

		200 mg Dosage Regimen: 200 mg Route: Oral	oral dose of belumosudil in subject groups Secondary: Evaluate safety and tolerability of single oral dose of belumosudil in subject groups, Assess PK of belumosudil metabolites following single oral dose of belumosudil in subject groups		Group 1: 16 Group 2: 8 Group 3: 8 Group 4: 8	hepatic function Group 2: mild hepatic impairment Group 3: moderate hepatic impairment Group 4: severe hepatic impairment	(USA)
KD025-110	Cross over, positive controlled and placebo controlled study	Test Product: Belumosudil tablet 200 mg Dosage Regimen: 200 mg 1000 mg Moxifloxacin Placebo Route: Oral	Primary: Evaluate effects of therapeutic and supratherapeutic concentrations of belumosudilon cardiac repolarization Secondary: assess effects of therapeutic and supratherapeutic belumosudil on HR, PR interval, QRS duration, t-wave morphology; evaluate plasma concentration on QT/QTc interval; evaluate assay sensitivity of effect of positive control on QT/QTc interval; assess PK of belumosudil; evaluate safety and tolerability	4 days (single dose on 4 separate occasions)	Total: up to 32	Healthy male and female subjects on non-child bearing potential	1 center 1 country (USA)

7.2 Review Strategy

The FDA's Assessment:

The applicant submitted data from 15 clinical studies. Of the 16 studies listed in the table above, there were no data from Study KD025-110 in this submission. The key materials used in the review of efficacy and safety include:

- NDA 214783
- Relevant published literature

Information submitted to NDA 214783 after 6/25/2021 was not included in this review.

The data from Studies KD025-208 and KD025-213 were used for the review of efficacy. The Assessment Aid prepared by the applicant was received on 10/08/2020, and it included analyses conducted with a data cut as of 02/19/2020. FDA's analyses utilized the data sets received 12/16/2020 with a data cut as of 08/19/2020. Because of these major differences in the data used for the efficacy analyses, the results of FDA's analyses are grouped separately at the end of Sections 8.1.1 and 8.1.2 as highlighted in gray. See FDA's section on Data Quality and Integrity for each study for discussion of additional data issues.

The data from all 15 clinical studies submitted were used in the review of safety. Details of the approach to the review of safety are described in Section 8.3. As indicated above, the applicant and FDA used data sets with different data cut dates. Because of the differences in the data used for the safety analyses, the results of FDA's safety analyses are grouped separately at the end of Section 8.3 as highlighted in gray.

Analyses by the statistical reviewers were performed using R (3.6.3) and SAS 9.4 (SAS Institute, Inc., Cary, NC). Analyses by the clinical reviewers were performed using JMP 15.2.1 (SAS Institute, Inc., Cary, NC). MedDRA Adverse Events Diagnostic (MAED) v3.0 (FDA, Silver Spring, MD) was used to assess for safety signals.

8 STATISTICAL AND CLINICAL EVALUATION

8.1 Review of Relevant Individual Trials Used to Support Efficacy

The Applicant's Description
The clinical development program to support the efficacy evaluation of belumosudil in the treatment of GVHD includes 2 clinical studies of subjects with cGVHD, KD025-208 and KD025-213.

8.1.1 Study KD025-208

Study KD025-208: A Phase 2a, Dose-Escalation, Open-Label Study to Evaluate the Safety, Tolerability, and Activity of KD025 in Subjects with Chronic Graft Versus Host Disease

TRIAL DESIGN

The Applicant's Description

Trial Design

Study KD025-208 is an ongoing Phase 2a, open-label, dose-escalation study of belumosudil in subjects with cGVHD who have received 1 to 3 prior lines of systemic cGVHD therapy. The key objective was evaluating the efficacy of different dose levels of belumosudil in cGVHD to inform future development of the agent. Subjects were enrolled with inflammatory and fibrotic manifestations of cGVHD involving all organs evaluated by the 2014 NIH consensus criteria.

Key eligibility

The FDA's Assessment:

Th key inclusion criteria were: Adult male or female subjects who were at least 18 years of age; who had an allogeneic bone marrow transplant or hematopoietic cell transplantation; were receiving glucocorticoid therapy and calcineurin therapy or glucocorticoid therapy alone for cGVHD at study entry; had persistent active cGVHD manifestations after at least 2 months of steroid therapy; had 1 to 3 prior lines of systemic treatment for cGVHD (extracorporeal photopheresis was not counted as prior systemic therapy); had a Karnofsky Performance Scale (KPS) score of >40; had adequate organ and bone marrow function; and had adequate safety laboratory values were enrolled in the study.

Treatment plan

The FDA's Assessment:

The subjects received orally administered belumosudil 200 mg once daily (QD) (Cohort 1), belumosudil 200 mg twice daily (BID) (Cohort 2), or belumosudil 400 mg QD (Cohort 3). Study drug was administered with food, in 28-day cycles until disease progression or unacceptable toxicity occurred. From Protocol Amendment 5.0 (29 May 2018) onward, subjects who had a

response assessment of "Lack of Response (LR) - Mixed (LR-M)" were permitted to continue treatment with belumosudil and remain in the study if the Investigator considered continued treatment to be in the subject's best interest.

Monitoring plan

The FDA's Assessment:

Prior to the enrollment of subsequent cohorts, the safety data in each previous cohort were evaluated after 8 subjects had reached 2 months of treatment. As this was an open-label study, safety data were continuously monitored. Study drug was administered in 28-day cycles until disease progression or unacceptable toxicity occurred, followed by a 28-Day Follow-Up visit and subsequent Long-Term Follow-Up every 8 weeks until study closeout.

Study Endpoints

The primary efficacy endpoint is ORR, per the 2014 NIH Consensus Development Project on Clinical Trials in cGVHD (hereafter referred to as the 2014 NIH Response Criteria).

The secondary endpoints include duration of response (DOR), time to response (TTR), response by organ system, LSS, changes in corticosteroid and CNI dose, failure-free survival (FFS), and overall survival (OS).

The FDA's Assessment:

FDA's assessment of efficacy will rely on ORR through Cycle 7 Day 1, as opposed to ORR at any time (as prespecified by the Applicant). FDA will consider two definitions of duration of response: 1) time from response to progression, new systemic therapy, or death and 2) time from response to new systemic therapy or death. Refer to Section 8.2 for more details.

Statistical Analysis Plan and Amendments

The Applicant's Description:

Statistical Analysis Plan

Primary and secondary efficacy endpoints are assessed in the modified intent-to-treat (mITT) population, which includes all subjects who have received at least 1 dose of study drug. The responder population includes subjects in the mITT population who achieve a response of partial response (PR) or complete response (CR) at any postbaseline response assessment. The nonresponder population includes any subject in the mITT population who is not a responder.

The primary efficacy endpoint of ORR is defined as the proportion of subjects who achieve a PR or CR as their best overall response, as assessed by the Investigator. A 2-sided 95% confidence interval (CI) is estimated using the Clopper-Pearson method.

The secondary endpoints of DOR, FFS, TTNT, and OS are estimated and summarized using the Kaplan-Meier method. Median values are estimated from the 50th percentile of the corresponding Kaplan-Meier estimates.

Subgroup analyses for the endpoints of ORR and DOR were conducted for the following subgroups: number of prior line therapies, number of organs involved at baseline, baseline disease severity, concomitant medication with a PPI taken on C1D1 (yes/no); and refractory to most recent line of therapy prior to enrollment (yes/no).

Safety assessments included AEs, serious adverse events (SAEs), vital sign measurements, clinical laboratory evaluations (hematology and chemistry), and ECGs.

Amendments

The original statistical analysis plan (SAP; v1.0) was dated 30 November 2017. There were 4 amendments to the original SAP (v2.0, dated 06 June 2019; v2.1, dated 12 August 2019; v2.2, dated 23 September 2019; and v2.3, dated 29 October 2019). The key changes are summarized below.

The major changes in v2.0 (06 June 2019) were the following:

- There was a change of study design that included the removal of the expansion cohort;
- More definitions of DOR were added;
- Some secondary efficacy endpoints were added and rearranged; and
- The calculation of symptom score for the LSS was corrected.

The major changes in v2.1 (12 August 2019) were the following:

- A subsection called “Missing event dates” was added;
- The censoring rule for DOR, TTNT, and FFS was clarified; and
- The definition of discontinuation of corticosteroid was clarified.

The major changes in v2.2 (23 September 2019) were the following:

- OS analysis was added as a secondary efficacy endpoint; and
- In the subgroup analysis, refractory was added to prior line status.

The major change in v2.3 (29 October 2019) was the following:

- LSS was changed from an exploratory endpoint to a secondary endpoint.

The FDA's Assessment:

FDA agreed with the Applicant' description of the Statistical Analysis Plan.

Subjects returned to the study site within 3 days after the subject's last dose of study drug to complete all EOT visit assessments. This may have occurred at the visit at which disease progression was diagnosed.

Subjects who discontinued treatment prematurely also were asked to come to the clinic for EOT visit assessments.

If subjects responded but had to be taken off study drug due to toxicity, they were considered as responders if there was a response EOT assessment. And if there was PD at EOT assessment, that would count as a DOR event.

The Applicant clarified on 01 December 2020 that in Study KD025-208 a subject who only showed response at EOT was counted as a responder.

This response criteria assessment at EOT was different from Study KD025-213 (see Section 8.1.2 below).

Protocol Amendments

The Applicant's Description:

The original protocol was dated 22 December 2015 and no subjects were enrolled under this version. There were 7 amendments to the CSP (Amendment 1, dated 22 February 2016; Amendment 2, dated 15 July 2016; Amendment 3, dated 06 June 2017; Amendment 4, dated 19 October 2017; Amendment 4.1, dated 26 October 2017; Amendment 5, dated 29 May 2018; Amendment 6, dated 15 October 2018; and Amendment 7, dated 28 October 2019). It should be noted that Amendment 4 (19 October 2017) was never implemented at any of the 7 clinical sites. Amendment 4.1 (26 October 2017) was the subsequent institutional review board (IRB)-approved protocol implemented post-Amendment 3 (06 June 2017) at all 7 clinical sites. The key changes are summarized below for each amendment.

Under Amendment 1 (22 February 2016), 0 subjects were enrolled. The major changes in Amendment 1 were the following:

- The study design changed from Phase 2 to Phase 2a, randomized to nonrandomized, dose ranging to dose escalation, and efficacy to activity design;
- Doses to be studied changed from 200 mg QD, 400 mg QD, and 400 mg BID to 200 mg

QD, 200 mg BID, and 400 mg QD;

- Safety data were to be evaluated after 8 subjects had reached 2 months of treatment prior to dose escalation;
- Inclusion criteria were clarified to note that subjects may have been receiving glucocorticoid therapy and calcineurin therapy or glucocorticoid therapy alone for cGVHD at study entry;

Under Amendment 2 (15 July 2016), 38 subjects were enrolled. The major changes in Amendment 2 were the following:

- The timing with regard to assessment of response criteria was modified;
- Inclusion criterion #5 was modified to include subjects with a Karnofsky Performance Score of >40;
- Inclusion criteria related to pregnancy, female subjects of childbearing potential, and/or male subjects who were sexually active and partners of premenopausal women were expanded and clarified.

Under Amendment 3 (06 June 2017), 9 subjects were enrolled. The major changes in Amendment 3 were the following:

- An option to allow subjects with stable disease from baseline at Week 24 to continue treatment with KD025 for up to Week 48 at the same dose level was added;
- The definition of the EOT visit was changed; and
- The screening period was changed from 29 days to 28 days.

Under Amendment 4 (19 October 2017), 0 subjects were enrolled. The major changes in Amendment 4 were the following:

- The duration of dosing with KD025 was extended from 48 weeks to 96 weeks to provide potential benefit of KD025 for subjects in whom cGVHD had not progressed;
- Assessments during C6D25 (End of Primary Treatment) visit were removed since they were not relevant with the extension of KD025 dosing that was added;
- The primary activity outcome was clarified to reflect a primary endpoint of ORR and not a landmark response rate analysis.

Under Amendment 4.1 (26 October 2017), 7 subjects were enrolled. The major change in Amendment 4.1 was the following:

- It was clarified that medications that prolong the QT/QTc interval were not prohibited but should be used with caution in subjects who were receiving KD025.

Under Amendment 5 (29 May 2018), 0 subjects were enrolled. The major changes in Amendment 5 were the following:

- The expansion cohort was removed and enrollment was limited to the first 3 cohorts;
- Instructions for managing subjects who had a "lack of response mixed" (LR-M) response assessment were added to permit continued treatment with KD025 and participation in the study if the Investigator considered continued treatment to be in the subject's best interest, and only after approval from the Medical Monitor and documentation of the subject's willingness to continue;
- It was updated that treatment with KD025 could exceed 96 weeks (the time limit was removed) to allow treatment to continue until progression of disease or unacceptable toxicity.

Under Amendment 6 (15 October 2018), no subjects were enrolled. The major changes in Amendment 6 were the following:

- The allowance of subjects to receive 2 cycles worth of study drug along with 2 study drug diaries and allowance to return to the clinic at the next odd cycle for assessments and study drug accountability was added instead of requiring subjects to visit the clinic at every cycle after 24 cycles, and the option for Investigators and/or subjects to come into the clinic at 1 or more even cycles was added and subjects who did not come into the clinic on even cycles would be contacted via telephone by study staff to document any new AEs and concomitant medications was added;
- The definition of disease progression was clarified and updated to include the addition of a new systemic cGVHD therapy for analysis purposes which stated that the addition of a new systemic cGVHD therapy was considered a KD025 treatment failure and progression of cGVHD.

Under Amendment 7 (28 October 2019), 0 subjects were enrolled. The major changes in Amendment 7 were the following:

- OS, TTNT, and change in symptom burden/bother using the LSS were included as secondary endpoints (LSS was formerly an exploratory endpoint);
- It was updated that PK and pharmacodynamic samples were not required to be collected at the end-of-treatment visit; and
- It was updated that CYP3A4 strong inducers were prohibited and other CYP3A4 inducers/inhibitors were to be used with caution.

The FDA's Assessment:

FDA agreed with the Applicant's summary of Protocol Amendments.

FDA noted that the following Protocol Amendment was important and affected the assessment of response and duration of response. From the original protocol KD025-208 through Protocol Amendment 3.0 (06 June 2017), response was assessed on Day (D) 1 of Cycles (C) 1, 3, and 5; at the D25-28 visit of C6; and then every odd-numbered cycle thereafter starting on C9D1, as well as the End of Treatment (EOT) visit. Under Protocol Amendment 4.1 (26 October 2017), this schedule was changed and response criteria were assessed on D1 of each cycle starting at the C2D1 visit as well as the EOT visit.

STUDY RESULTS - APPLICANT'S POSITION

Compliance with Good Clinical Practices

The Applicant's Position:

The study was conducted in accordance with the Declaration of Helsinki and with all applicable laws and regulations of the locale and country where the study was conducted, and in compliance with GCP Guidelines.

Informed consent was obtained in writing from each subject or legally acceptable representative of the subject, before conducting any study-specific procedures. The study was described by the Investigator or designee, who answered any questions, and written information was also provided.

Data Quality and Integrity

The Applicant's Position:

Accurate and reliable data collection was ensured by verification and cross-checking of the electronic case report form (eCRF) against the Investigator's records by the study monitor

(source document verification) and by maintenance of a drug-dispensing log by the Investigator. Collected data were entered into a computer database and subject to electronic and manual quality assurance procedures.

Clinical research associates conducted periodic on-site visits to ensure adherence to the protocol, review eCRFs and site source documents for accuracy and completeness of information, examine site records for documentation of study drug receipt and administration, observe the progress of the study, and review Investigator files for required documents.

AEs and medical/surgical history were coded to system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) (v20.0). Concomitant medications were coded to American Therapeutic Chemical (ATC) class and PT using the Wordl Health Organization (WHO) Drug Dictionary (March 2017, B2 Format).

A central laboratory performed all study-related laboratory tests. The Investigator reviewed all laboratory reports and filed copies with the subject's chart.

Financial Disclosure

The Applicant's Position:

None of the investigators participating in the study had any disclosable financial arrangements. As a result, there were no concerns regarding the overall integrity of data.

Patient Disposition

Data:

In total, 54 subjects were included in the Study KD025-208 mITT population. A summary of analysis populations in the mITT population is presented in Table 13.

Table 13 Analysis Populations in Study KD025-208

	Belumosudil			
Population, n (%)	**200 mg QD**	**200 mg BID**	**400 mg QD**	**Overall**
mITT	17 (100)	16 (100)	21 (100)	54 (100)
Responder	11 (64.7)	11 (68.8)	13 (61.9)	35 (64.8)
Nonresponder	6 (35.3)	5 (31.3)	8 (38.1)	19 (35.2)

Abbreviations: BID = twice daily; mITT = modified intent-to-treat; QD = once daily.
Notes: The data cutoff date was 19 February 2020.
Sources: CSR KD025-208, Table 1.1.1.

For the overall population (mITT population), the median (minimum, maximum) of follow-up duration was 28.8 (0.7, 38.7) months.

As of the cutoff date for this analysis (19 February 2020), 47 (87.0%) subjects have discontinued from treatment and 7 (13.0%) subjects have remained on treatment with belumosudil. The most common reason for treatment discontinuation was disease progression (22 [40.7%] subjects). As of the cutoff date for this analysis, a total of 37 (68.5%) subjects were participating in the study, either being actively treated with belumosudil or being followed for survival (in long-term follow-up). A total of 17 (31.5%) subjects have discontinued from the study.

The Applicant's Position:

The proportion of subjects who have discontinued the study and the reasons for discontinuation are within expectations for the population under study.

Protocol Violations/Deviations

Data:

There were no events that met the definition of serious non-compliance during the study through the reporting period (19 February 2020). There were 42 major deviations reported through the reporting period that fell under the following categories: inclusion/ exclusion, investigational product, and subject not withdrawn as per protocol.

The Applicant's Position:

The protocol deviations observed during this study did not change the overall interpretation of the study results

Table of Demographic Characteristics

Data:

Demographic and other baseline disease characteristics for the mITT population in Study KD025-208 are summarized in Table 14.

Table 14 Demographic and Other Baseline Disease Characteristics: Study KD025-208 – mITT Population

	Belumosudil			
Category	**200 mg QD N = 17**	**200 mg BID N = 16**	**400 mg QD N = 21**	**Overall N = 54**
Age (years), n	17	16	21	54
Median	50.0	55.0	46.0	51.5
Min, max	20, 63	30, 75	25, 75	20, 75

Category	Belumosudil			
	200 mg QD N = 17	200 mg BID N = 16	400 mg QD N = 21	Overall N = 54
Sex, n (%)				
Female	4 (23.5)	7 (43.8)	9 (42.9)	20 (37.0)
Male	13 (76.5)	9 (56.3)	12 (57.1)	34 (63.0)
Karnofsky Performance Status, n (%)				
50	0	0	1 (4.8)	1 (1.9)
60	1 (5.9)	0	2 (9.5)	3 (5.6)
70	3 (17.6)	4 (25.0)	4 (19.0)	11 (20.4)
80	7 (41.2)	6 (37.5)	7 (33.3)	20 (37.0)
90	6 (35.3)	6 (37.5)	7 (33.3)	19 (35.2)
Number of prior lines of cGVHD therapy[a]				
Median	3.0	2.0	2.0	2.5
Time from most recent transplant to cGVHD diagnosis[b] (months), n	17	16	21	54
Median	9.8	7.3	7.9	7.9
Min, max	2.8, 48.3	1.9, 27.1	1.0, 28.1	1.0, 48.3
Time from cGVHD diagnosis to enrollment (months), n	17	16	21	54
Median	26.4	18.0	16.0	20.0
Min, max	0, 130.7	1.0, 69.9	1.0, 161.9	0, 161.9
Severe NIH cGVHD at screening[c], n (%)	12 (70.6)	14 (87.5)	16 (76.2)	42 (77.8)
Number of organs involved at baseline, n	17	16	21	54
Median	3.0	4.0	3.0	3.5
Min, max	2, 6	1, 7	2, 7	1, 7
≥ 4	8 (47.1)	10 (62.5)	9 (42.9)	27 (50.0)
Organs involved at baseline				
Skin, n (%)	13 (76.5)	12 (75.0)	15 (71.4)	40 (74.1)
Eyes, n (%)	14 (82.4)	11 (68.8)	17 (81.0)	42 (77.8)
Mouth, n (%)	13 (76.5)	11 (68.8)	11 (52.4)	35 (64.8)
Esophagus, n (%)	2 (11.8)	0 (0)	4 (19.0)	6 (11.1)
Upper GI, n (%)	2 (11.8)	4 (25.0)	2 (9.5)	8 (14.8)
Lower GI, n (%)	1 (5.9)	2 (12.5)	1 (4.8)	4 (7.4)
Liver, n (%)	0 (0)	2 (12.5)	0 (0)	2 (3.7)
Lung, n (%)	4 (23.5)	3 (18.8)	10 (47.6)	17 (31.5)
Joints and fascia, n (%)	11 (64.7)	11 (68.8)	12 (57.1)	34 (63.0)
GSR, n	16	16	21	53
Median	7.0	6.5	7.0	7.0
Min, max	3, 9	4, 8	4, 9	3, 9
Median baseline corticosteroid dose (mg/kg/day)	0.22	0.19	0.17	0.19
Subjects who took corticosteroids concomitantly at baseline, n (%)	17 (100)	16 (100)	21 (100)	54 (100)
Subjects who took CNIs concomitantly at baseline, n (%)	6 (35.3)	6 (37.5)	11 (52.4)	23 (42.6)

Category	Belumosudil			
	200 mg QD N = 17	200 mg BID N = 16	400 mg QD N = 21	Overall N = 54
Subjects who received ECP concomitantly at baseline, n (%)	3 (17.6)	3 (18.8)	3 (14.3)	9 (16.7)
BoR to the last systemic cGVHD treatment before enrolling in study, n (%)				
Complete response	0	0	0	0
Partial response	4 (23.5)	4 (25.0)	5 (23.8)	13 (24.1)
Stable disease	11 (64.7)	7 (43.8)	10 (47.6)	28 (51.9)
Progressive disease	0	2 (12.5)	5 (23.8)	7 (13.0)
Unknown/missing	2 (11.8)	3 (18.8)	1 (4.8)	6 (11.1)
Refractory to prior line[d]	11 (73.3)	9 (69.2)	15 (75.0)	35 (72.9)

Abbreviations: BID = twice daily; BoR = best overall response; cGVHD = chronic graft versus host disease; CNI = calcineurin inhibitor; CR = complete response; ECP = extracorporeal photopheresis; GI = gastrointestinal; GSR = global severity rating; max = maximum; min = minimum; mITT = modified intent-to-treat; NIH = National Institutes of Health; PD = progressive disease; PR = partial response; QD = once daily; SD = stable disease.
Note: The data cutoff date was 19 February 2020.
[a] Including ECP.
[b] Time from most recent transplant to cGVHD diagnosis (months) = (date of cGVHD diagnosis - date of most recent transplant +1)/365.25 □ 12.
[c] Severe was defined as at least 1 organ with an NIH Activity Assessment score of 3 or lung score of □□2 at baseline.
[d] Formula for calculation of the percentages of subjects who were refractory: (PD+SD)/(PD+SD+CR+PR).
Sources: CSR KD025-208, Tables 2.1.1, 2.1.3, 2.1.4, 2.1.5.1, 3.1.1, 5.6.1.1, and 5.7.1, and Listing 2.1.5.2.

The Applicant's Position:

Overall, there were no notable differences in baseline characteristics across the 3 dosing cohorts. The study population was reflective of real-world patients, with advanced, complex cGVHD.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Data:

Treatment Compliance

The RDI was used to assess treatment compliance. Overall, the median RDI was 98.3%: 99.1% for Cohort 1, 96.6% for Cohort 2, and 99.1% for Cohort 3. A majority of subjects had an RDI >95% (38 [70.4%] subjects) (CSR Post-text Table 4.1.1.).

Systemic cGVHD Concomitant Medications
Table 15 summarizes the concomitant corticosteroid and CNI medications taken for cGVHD in the mITT Population.

Table 15 Concomitant Systemic Medications for Chronic Graft Versus Host Disease by ATC1 Class, Preferred Term, and Cohort: Study KD025-208 – mITT Population

ATC1 Class Preferred Term	Cohort 1 200 mg QD N=17 n (%)	Cohort 2 200 mg BID N=16 n (%)	Cohort 3 400 mg QD N=21 n (%)	Overall N=54 n (%)
Corticosteroid	17 (100)	16 (100)	21 (100)	54 (100)
Tacrolimus	7 (41.2)	6 (37.5)	11 (52.4)	24 (44.4)
Ciclosporin	0 (0)	0 (0)	1 (4.8)	1 (1.9)
ECP treatment	4 (23.5)	4 (25.0)	4 (19.0)	12 (22.2)

Statistical notes:
Medications were coded using WHO Drug Dictionary, version March 2017, B2 Format.
A subject with multiple medications within an ATC1 class or preferred term was counted only once for that ATC1 class or preferred term.
The table is sorted in descending order of frequency in the overall column by ATC1 class and by preferred term within each ATC1 class.
ATC = Anatomical Therapeutic Chemical; BID = twice daily; CNI = calcineurin inhibitor; ECP = extracorporeal photopheresis; mITT = modified Intent-to-Treat; QD = once daily; WHO = World Health Organization.
Sources: CSR Post-text Tables 2.1.6.2, 3.1.1 and 3.1.2, data cutoff date of 19 February 2020.

Concomitant Medications of Interest
In total, 32 subjects were taking PPIs at C1D1: 8 subjects in Cohort 1, 9 subjects in Cohort 2, and 15 subjects in Cohort 3. The PPIs taken included esomeprazole magnesium, pantoprazole sodium sesquihydrate, pantoprazole, esomeprazole, omeprazole, omeprazole magnesium, and lansoprazole.

Rescue Medication Use
Not applicable.

The Applicant's Position:

Treatment compliance, as assessed by relative dose intensity (RDI), was high across treatment cohorts, with an overall median RDI of 98.3%. The concomitant medication profiles of the 3 cohorts were within expectations for the population under study.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data:

Overall Response Rate
The primary efficacy endpoint of this study was the ORR, defined by the 2014 NIH Consensus Development Project on Clinical Trials in cGVHD, as assessed by Investigators. Overall response rate, including ORR within 6 months of initiation of treatment, and best overall response for the mITT population are summarized Table 16.

Table 16 Overall Response Rate: Study KD025-208 – mITT Population

Variable/Category	Belumosudil			
	200 mg QD N = 17	200 mg BID N = 16	400 mg QD N = 21	Overall N = 54
ORR (CR or PR), n (%)	11 (64.7)	11 (68.8)	13 (61.9)	35 (64.8)
95% CI of ORR[a]	(38.3, 85.8)	(41.3, 89.0)	(38.4, 81.9)	(50.6, 77.3)
Best overall response				
Complete response	0	0	0	0
Partial response	11 (64.7)	11 (68.8)	13 (61.9)	35 (64.8)
Lack of response				
Unchanged	2 (11.8)	3 (18.8)	4 (19.0)	9 (16.7)
Mixed	3 (17.6)	1 (6.3)	0	4 (7.4)
Progression	1 (5.9)	0	1 (4.8)	2 (3.7)
No response assessment	0	1 (6.3)	3 (14.3)	4 (7.4)
ORR (CR or PR) within 6 months of treatment, n (%)	10 (58.8)	10 (62.5%)	11 (52.4)	31 (57.4)
Complete response	0	0	0	0
Partial response	10 (58.8)	10 (62.5%)	11 (52.4)	31 (57.4)
95% CI of ORR[a]	(32.9, 81.6)	(35.4, 84.8)	(29.8, 74.3)	(43.2, 70.8)

Abbreviations: BID = twice daily; cGVHD = chronic graft versus host disease; CI = confidence interval; CR = complete response; ECP = extracorporeal photopheresis; mITT = modified intent-to-treat; ORR = overall response rate; PR = partial response; QD = once daily.
Note: The data cutoff date was 19 February 2020.
[a] The 95% CIs (2-sided) were calculated using the Clopper-Pearson exact method.
[b] The percentages were calculated based on the number of subjects in the specific subgroup in the mITT Population.
[c] ECP was not included as a prior line of systemic cGVHD therapy.
Source: CSR KD025-208, Tables 5.1.1, 5.1.1.1, and 5.1.2.

The Applicant's Position:

Belumosudil demonstrated clinical activity and a treatment effect at all three dose levels evaluated, with consistent response rates overall as well as in subgroup populations of heavily pre-treated subjects with severe disease refractory to prior line of treatment. Not only did belumosudil show high percentage of overall response, but the responses were clinically meaningful, as demonstrated by the results of secondary efficacy analyses. Robust responses were observed whether subjects had received only 1 or multiple prior lines of therapy.

Efficacy Results – Secondary and other relevant endpoints

Data:

Results for the secondary efficacy endpoints of DOR, TTR, response by organ system, LSS score, FFS, TTNT, OS, and change in corticosteroid dose are summarized in Table 17. Responses were achieved across all organ systems, with CRs in all organs systems except for lung and GSR, where PRs were observed. Improvements in LSS and corticosteroid dose reductions were observed in both responders and nonresponders.

Table 17 Secondary Efficacy Endpoints: Study KD025-208 – mITT Population

Variable	Belumosudil 200 mg QD N = 17	Belumosudil 200 mg BID N = 16	Belumosudil 400 mg QD N = 21	Belumosudil Overall N = 54
Duration of response (responders), n	11	11	13	35
Median (weeks)				
Primary/secondary (95% CI)	40.0 (8.1, NR)	10.9 (4.1, 35.1)	19.9 (4.1, 43.1)	19.9 (8.1, 38.1)
Tertiary (95% CI)	NR (20.3, NR)	34.2 (5.9, 58.9)	74.4 (5.0, 108.3)	53.4 (33.3, NR)
Quaternary (95% CI)	NR (8.6, NR)	12.6 (4.1, 35.1)	38.1 (5.0, 100.9)	35.1 (12.9, 100.9)
Time-to-response (weeks)	11	11	13	35
Median	8.1	8.1	8.0	8.1
Min, max	7.9, 26.1	4.1, 40.0	3.1, 67.0	3.1, 67.0
Response by organ system[a], % (n/total)				
Skin	23.1 (3/13)	16.7 (2/12)	13.3 (2/15)	17.5 (7/40)
Eyes	35.7 (5/14)	36.4 (4/11)	23.5 (4/17)	31.0 (13/42)
Mouth	53.8 (7/13)	45.5 (5/11)	45.4 (5/11)	48.6 (17/35)
Esophagus	50.0 (1/2)	0 (0/0)	50.0 (2/4)	50.0 (3/6)
Upper GI	100 (2/2)	100 (4/4)	50.0 (1/2)	87.5 (7/8)
Lower GI	100 (1/1)	100 (2/2)	0 (0/1)	75.0 (3/4)
Liver	0 (0/0)	50.0 (1/2)	0 (0/0)	50.0 (1/2)
Lungs	0 (0/4)	0 (0/3)	30.0 (3/10)	17.6 (3/17)
Joints and fascia	54.5 (6/11)	45.5 (5/11)	50.0 (6/12)	50.0 (17/34)
GSR	58.8 (10/17)	50.0 (8/16)	47.6 (10/21)	51.9 (28/54)
Lee Symptom Scale score, n (%)				
Subjects with a 7-PtR[b] from baseline	9 (52.9)	7 (43.8)	11 (52.4)	27 (50.0)
Subjects with a 7-PtR from baseline on 2 consecutive assessments	5 (29.4)	5 (31.3)	9 (42.9)	19 (35.2)
Failure-free survival (months)				
Median (95% CI)	15.2 (6.4, NR)	9.8 (4.0, 19.02)	10.5 (2.7, 26.7)	10.7 (7.4, 19.0)
6 months (95% CI)	0.82 (0.55, 0.94)	0.80 (0.50, 0.93)	0.67 (0.43, 0.83)	0.76 (0.62, 0.85)
12 months (95% CI)	0.53 (0.28, 0.73)	0.40 (0.16, 0.63)	0.48 (0.26, 0.67)	0.47 (0.33, 0.60)
Time-to-next treatment (months)				
Number of subjects initiating a new systemic therapy for cGVHD, n (%)	8 (47.1)	11 (68.8)	10 (47.6)	29 (53.7)
Median (95% CI)	22.0 (6.6, NR)	9.8 (4.0, 19.0)	14.2 (8.2, NR)	14.2 (9.8, NR)
Overall survival				
Number of deaths	3 (17.6)	2 (12.5)	6 (28.6)	11 (20.4)
6 months OS (95% CI)	1.00 (1.0, 1.0)	1.00 (1.0, 1.0)	0.86 (0.62, 0.95)	0.94 (0.84, 0.98)

Variable	Belumosudil			
	200 mg QD N = 17	200 mg BID N = 16	400 mg QD N = 21	Overall N = 54
12 months (95% CI)	0.94 (0.65, 0.99)	0.94 (0.63, 0.99)	0.86 (0.62, 0.95)	0.91 (0.79, 0.96)
Corticosteroid dosing				
Median greatest reduction (%)	-62.5	-50.0	-50.0	-50.0
Min, max	-100, 0	-100, 75.00	-100, 0	-100, 75.00
Subjects who discontinued corticosteroid usage, n (%)	4 (23.5)	2 (12.5)	3 (14.3)	9 (16.7)

Abbreviations: BID = twice daily; cGVHD = chronic graft versus host disease; CI = confidence interval; GI = gastrointestinal; GSR = global severity rating; max = maximum; min = minimum; NRA = not reached; OS = overall survival; 7-PtR = 7-point reduction; QD = once daily.
Note: The data cutoff date was 19 February 2020.
[a] Response = CR or PR.
[b] The 7-PtR is a ≥ 7-point reduction.
Source: CSR KD025-208, Tables 5.2.1.1, 5.2.1.2, 5.2.1.3, 5.2.1.4, 5.3.1, 5.4.1.1, 5.5.1, 5.6.1.1, 5.8.1, 5.9.1, and 5.12.1.1.

The Applicant's Position:

Secondary efficacy analyses were supportive of the primary analyses. cGVHD responses to belumosudil appeared to be clinically meaningful based on several measures of disease activity and symptom burden. Responses were durable, and subjects reported improvement in LSS and were able to reduce their doses of corticosteroids. Clinical benefit was observed in both responders and non-responders.

Efficacy Results – Exploratory and COA (PRO) endpoints

Data:

Exploratory objectives included evaluation of changes in the expression of cytokines (including IL-17A, IL-21, and IL 2) in plasma after belumosudil administration; and changes in percentage of immune-cell subtypes (including Th17 and Treg cells) in whole blood after belumosudil administration.

The Applicant's Position:

Exploratory PD analyses are consistent with the proposed MoA with numerical increases in Tregs and decreases in TH17 cells.

Additional Analyses Conducted on the Individual Trial

The Applicant's Position:

Not applicable.

STUDY RESULTS - FDA'S POSITION

Compliance with Good Clinical Practices

FDA agreed with the Applicant's summary of Compliance with Good Clinical Practice.

Financial Disclosure

There were 120 investigators identified for the Study KD025-208. There were no clinical investigators with disclosable financial arrangements reported. See Appendix 16.2.

Data Quality and Integrity

See the section on Data Quality and Integrity under Study KD025-213 for details on the issues identified, the procedures used to resolve the issues, and the final data used for the analyses.

Patient Disposition

Table 18 shows Subject Disposition including reasons for discontinuation of belumosudil treatment in patients with chronic GVHD in Study KD025-208. The most common reasons for treatment discontinuation were progression of chronic GVHD (29%) and recurrence of the underlying malignancy (18%) in patients with chronic GVHD treated with belumosudil 200 mg once daily.

Table 18. Study KD025-208: Subject Disposition in Safety Population of Chronic GVHD

	Belumosudil			
Parameter n (%)	**200 mg QD (N = 17)**	**200 mg BID (N = 16)**	**400 mg QD (N = 21)**	**Total cGVHD (N = 54)**
Treatment Ongoing	2 (12)	1 (6)	2 (10)	5 (9)
Treatment Discontinued	15 (88)	15 (94)	19 (90)	49 (91)
Reasons for discontinuation				
Adverse Event	2 (12)	0	1 (5)	3 (6)
Death	4 (24)	2 (13)	7 (33)	13 (24)
Recurrence of underlying malignancy	3 (18)	0	4(19)	7 (13)
Failure to Meet Continuation Criteria	0	0	0	0
Lost to Follow-Up	2 (12)	1 (6)	2 (10)	5 (9)
Noncompliance to Protocol	1 (6)	0	0	1 (2)
Other	1 (6)	1 (6)	0	2 (4)
Physician Decision	2 (12)	0	1 (5)	3 (6)

	Belumosudil			
Parameter n (%)	**200 mg QD (N = 17)**	**200 mg BID (N = 16)**	**400 mg QD (N = 21)**	**Total cGVHD (N = 54)**
Progression of chronic GVHD	5 (29)	11 (69)	7 (33)	23 (43)
Withdrawal By Subject	2 (12)	3 (19)	3 (14)	8 (15)

Source: FDA Analysis. Abbreviations: QD, once daily; BID, twice daily; cGVHD = chronic graft versus host disease.

Protocol Violations/Deviations

FDA agrees with the Applicant's summary for Protocol Violations/Deviations.

Demographic Characteristics and Baseline Characteristics

FDA acknowledges the Applicant's Table of Demographic Characteristics for Study KD025-208 above. FDA analyzed datasets and the Applicant's responses to information requests, and additional demographics and baseline disease characteristics for the Study KD025-208 population are summarized in Table 19 below.

Table 19. Study KD025-208: Demographic and Baseline Disease Characteristics

	Belumosudil			
Category	**200 mg QD N = 17**	**200 mg BID N = 16**	**400 mg QD N = 21**	**Overall N = 54**
Age, Median, Years (minimum, maximum)	50 (20, 63)	55 (30, 75)	46 (25, 75)	51.5 (20, 75)
Age ≥ 65 Years, n (%)	0	6 (37.5)	5 (23.8)	11 (20.4)
Sex				
Male, n (%)	13 (76.5)	9 (56.3)	12 (57.1)	34 (63.0)
Race, n (%)				
White	15 (88.2)	14 (87.5)	18 (85.7)	47 (87.0)
Black	0	0	2 (9.5)	2 (3.7)
Other or Not Reported	2 (11.8)	2 (12.5)	1 (4.8)	5 (9.3)
Median (range) time (months) from cGVHD diagnosis to enrollment	26.4 (0, 130.7)	18.0 (1.0, 69.9)	16.0 (1.0, 161.9)	20.0 (0, 161.9)
Number of Organs Involved at Baseline				
≥ 4 Organs Involved, n (%)	8 (47.1)	10 (62.5)	10 (47.6)	28 (51.9)
Median (range) Number of Prior Lines of cGVHD Therapy	3 (1, 4)	2 (1, 3)	2 (1, 4)	2.5 (1, 4)
Number of Prior Lines of Therapy, n (%)				
1	2 (11.8)	7 (43.8)	7 (33.3)	16 (29.6)
2	3 (17.6)	2 (12.5)	6 (28.6)	11 (20.4)
3	10 (58.8)	7 (43.8)	7 (33.3)	24 (44.4)
4	2 (11.8)	0	1 (4.8)	3 (5.6)

Category	Belumosudil			
	200 mg QD N = 17	200 mg BID N = 16	400 mg QD N = 21	Overall N = 54
Prior chronic GVHD treatment with ibrutinib, n (%)	2 (11.8	0	3 (14.3)	4 (7.4)
Prior chronic GVHD treatment with ruxolitinib, n (%)	0	0	1 (4.8)	1 (1.9)
Refractory to the Last Systemic cGVHD Therapy prior to enrollment to study, n (%[a])	11/15 (73.3)	9/13 (69.2)	15/20 (75.0)	35/48 (72.9)
Severe chronic GVHD, n (%)	12 (70.6)	14 (87.5)	16 (76.2)	42 (77.8)
Median (range) Global Severity Rating	7 (3, 9)	6.5 (4, 8)	7 (4, 9)	7 (3, 9)
Median (range) Lee Symptom Scale Score at baseline	25.8 (8.6, 46.2)	26.2 (10.9, 41.6)	21.4 (6.8, 62.4)	23.8 (6.8, 62.4)
Concomitant systemic cGVHD therapies* on Study Day 1, n (%)	17 (100)	15 (93.8)	21 (100)	53 (98.1)
Corticosteroids alone	10 (58.8)	7 (43.8)	6 (28.6)	23 (42.6)
Corticosteroids and other drugs	7 (41.2)	8 (50.0)	15 (71.4)	30 (55.5)
Corticosteroids + Tacrolimus +/- other	6 (35.3)	6 (37.5)	9(42.9)	21 (38.9)
Corticosteroids + MMF +/- other	0	0	1 (4.8)	1 (1.9)
Corticosteroids + ECP +/- other	2 (11.8)	2 (12.5)	2 (9.5)	6 (11.1)
Corticosteroids + Sirolimus +/- other	0	0	0	0
mTOR inhibitor**				
Sirolimus alone	0	0	0	0
Sirolimus and other drugs	0	0	0	0
Everolimus alone	0	0	0	0
Everolimus and other drugs	0	0	0	0

Sources: FDA analysis.
* FDA Analysis results of NDA datasets for combination variations of concomitant medications.
** There was no subject who received mTOR inhibitor sirolimus. There was no subject who received other mTOR inhibitors such as Everolimus.
[a] Denominator excludes patients with unknown status
Abbreviations: QD, once daily; BID, twice daily; cGVHD = chronic graft versus host disease; ECP, extracorporeal photopheresis; MMF, mycophenolate mofetil; CNI, calcineurin inhibitor; MTX, methotrexate; mTORi, mammalian target of rapamycin (mTOR) inhibitor.

Table 20 below shows the FDA's additional analysis for baseline common concomitant medications for chronic GVHD therapy on Study Day 1 in Study KD025-208. Additional subgroup efficacy analyses are performed for these subpopulations with Concomitant Therapies for chronic GVHD as baseline: Steroids Alone; Steroid + CNI; Steroid + ECP; Steroid + mTORi; or Other/Multiple.

Table 20. Study KD025-208: FDA Additional Analysis for Baseline Concomitant Medications

Category	Belumosudil			
	200 mg QD N = 17	200 mg BID N = 16	400 mg QD N = 21	Overall N = 54
Concomitant systemic cGVHD therapies on Study Day 1, n (%)	17 (100)	16 (100)	21 (100)	54 (100)
Corticosteroids alone	10 (58.8)	8 (50.0)	7 (33.3)	25 (46.3)
Steroids and CNI	5 (29.4)	4 (25.0)	8 (38.1)	17 (31.5)
Steroids and ECP	1 (5.9)	1 (6.3)	2 (9.5)	4 (7.4)
Steroids and mTORi	0	0	0	0
Other/Multiple	1 (5.9)	3 (18.8)	4 (19.0)	8 (14.8)

Sources: FDA Analysis results of NDA datasets for combination variations of concomitant medications.
Abbreviations: QD, once daily; BID, twice daily; cGVHD = chronic graft versus host disease; ECP, extracorporeal photopheresis; CNI, calcineurin inhibitor; mTORi, mammalian target of rapamycin (mTOR) inhibitor.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Table 21 shows the dose-intensity by cycle for each arm in Study KD025-208 as reported by the Applicant.

Table 21. Study KD025-208: Belumosudil Dose Intensity by Cycle

	Cohort 1 200 mg QD N = 17			Cohort 2 200 mg BID N = 16			Cohort 3 400 mg QD N = 21		
	Dose intensity category			Dose intensity category			Dose intensity category		
Cycle	N*	< 80% n (%)	80-100% n (%)	>100% n (%)	N*	< 80% n (%)	80-100% n (%)	>100% n (%)	N*	< 80% n (%)	80-100% n (%)	>100% n (%)
1	17	0	17 (100.0%)	0	16	2 (12.5%)	14 (87.5%)	0	21	3 (14.3%)	18 (85.7%)	0
2	17	0	17 (100.0%)	0	15	2 (13.3%)	13 (86.7%)	0	19	3 (15.8%)	16 (84.2%)	0
3	17	2 (11.8%)	15 (88.2%)	0	14	2 (14.3%)	12 (85.7%)	0	16	3 (18.8%)	13 (81.3%)	0
4	16	1 (6.3%)	15 (93.8%)	0	13	1 (7.7%)	12 (92.3%)	0	15	5 (33.3%)	10 (66.7%)	0
5	14	0	14 (100.0%)	0	12	1 (8.3%)	11 (91.7%)	0	14	2 (14.3%)	12 (85.7%)	0
6	14	0	14 (100.0%)	0	11	1 (9.1%)	10 (90.9%)	0	14	3 (21.4%)	11 (78.6%)	0
7	12	0	12 (100.0%)	0	10	1 (10.0%)	8 (80.0%)	1 (10.0%)	14	2 (14.3%)	12 (85.7%)	0
8	11	0	11 (100.0%)	0	9	0	9 (100.0%)	0	13	2 (15.4%)	11 (84.6%)	0
9	10	0	10 (100.0%)	0	8	0	8 (100.0%)	0	11	1 (9.1%)	10 (90.9%)	0
10	9	0	9 (100.0%)	0	7	0	7 (100.0%)	0	11	1 (9.1%)	10 (90.9%)	0
11	8	0	8 (100.0%)	0	7	0	7 (100.0%)	0	11	1 (9.1%)	10 (90.9%)	0
12	8	1 (12.5%)	7 (87.5%)	0	6	1 (16.7%)	5 (83.3%)	0	10	1 (10.0%)	9 (90.0%)	0

Source: Applicant's Table 4.1.1.1 (208) in 9/11/2020 response to an Information Request

Table 22 shows the salvage therapies administered after start of study treatment.

Table 22. Study KD025-208: Salvage Therapies

Treatment	Belumosudil 200 mg QD N = 17		Belumosudil 200 mg BID N = 16		Belumosudil 400 mg QD N = 21	
ECP	2	12%	4	25%	3	14%
Ibrutinib	2	12%	6	38%	3	14%
Steroids	2	12%	0	0%	3	14%
Montelukast	1	6%	0	0%	0	0%
Mycophenolate	1	6%	2	13%	2	10%
PUVA	1	6%	1	6%	0	0%
Investigational	1	6%	1	6%	2	10%
Tacromilus	1	6%	1	6%	3	14%
TLI	1	6%	1	6%	2	10%
FAM	0	0%	1	6%	0	0%
Interleukin-2	0	0%	1	6%	0	0%
Rituximab	0	0%	1	6%	2	10%
Sirolimus	0	0%	2	13%	0	0%

Source: FDA Analysis

Efficacy Results – Primary Endpoint

The FDA acknowledges the Applicant's assessment of overall response rate (ORR) in the section above. FDA assessed the ORR occurring through Cycle 7 Day 1 (see discussion in Section 8.2.1). Table 23 shows the results using the FDA-adjusted responses. All responses were PR. For the 200 mg QD dose group, ORR was 10/17, 59% (95% CI: 33%, 82%).

Table 23. Study KD025-208: ORR through Cycle 7 Day 1 per FDA Adjudication by Dose Group

Response	Belumosudil 200 mg QD N=17	Belumosudil 200 mg BID N=16	Belumosudil 400 mg QD N=21
ORR,* n, % (95% CI)[1]	10, 59% (33%, 82%)	7, 44% (20%, 70%)	10, 48% (26%, 70%)

*All were PR
[1]95% Confidence interval, estimated using the Clopper-Pearson method
Source: Reviewer's analysis.

Efficacy Results – Secondary and Other Relevant Endpoints

Duration of Response

For responses that began through Cycle 7 Day 1, Table 24 shows duration of response by dose group: time from response to any organ progression from the last assessment, new systemic therapy, or death, whichever occurs first. Median duration of response is 5.6 (95% CI: 1.6, 11.1) months in the 200 mg QD group.

Reviewer's comment: Results should be interpreted with caution due to low number of events (10 or fewer) and high uncertainty in all dose groups.

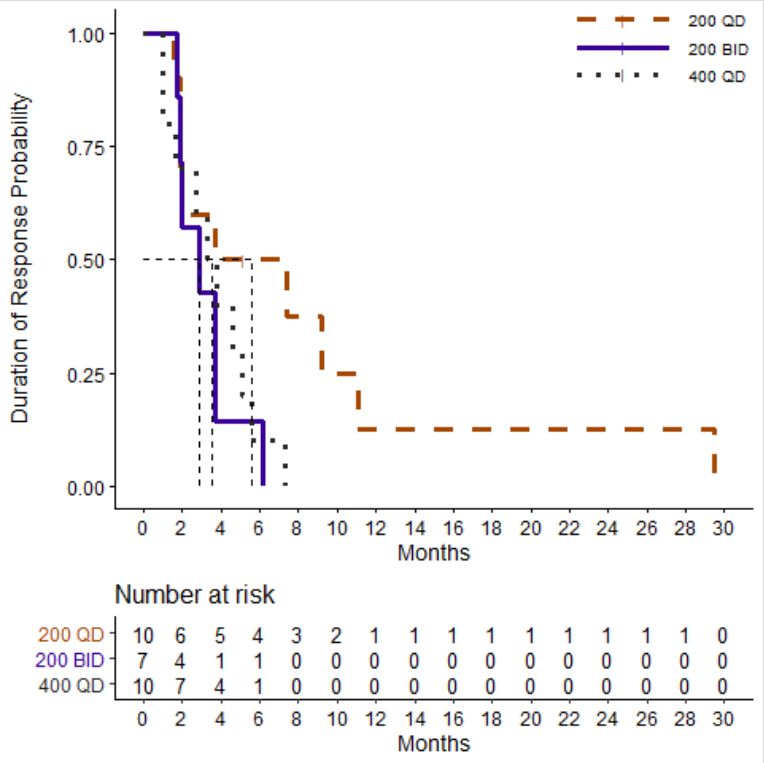
Table 24. Study KD025-208: Duration of Response per FDA Adjudication by Dose Group

	Belumosudil		
	200 mg QD	**200 mg BID**	**400 mg BID**
	N=10	N=7	N=10
Events, n (%)	9 (90%)	7 (100%)	10 (100%)
Median, months (95% CI)[1]	5.6 (1.6, 11.1)	2.9 (1.7, 3.7)	3.5 (1.0, 5.1)

[1]Median as estimated per Kaplan-Meier methodology, confidence interval estimated using the Brookmeyer and Crowley method.
Source: Reviewer's analysis.

Figure 8 shows the Kaplan-Meier plot of duration of response for responses that began through Cycle 7 Day 1.

Figure 8. Study KD025-208: Kaplan Meier Plot of Duration of Response per FDA Adjudication



Source: Reviewer's analysis.

Alternative Measure of Durability

Table 25 shows durability of response by dose group: time from response to new systemic therapy or death, whichever occurs first.

Table 25. Study KD025-208: Durability of Response per FDA Adjudication by Dose Group

	Belumosudil		
	200 mg QD N=10	**200 mg BID** N=7	**400 mg BID** N=10
Events, n (%)	4 (40%)	5 (71%)	9 (90%)
Median, months (95% CI)[1]	NE (1.6, NE)	12.2 (3.8, NE)	7.6 (1.1, 26.4)

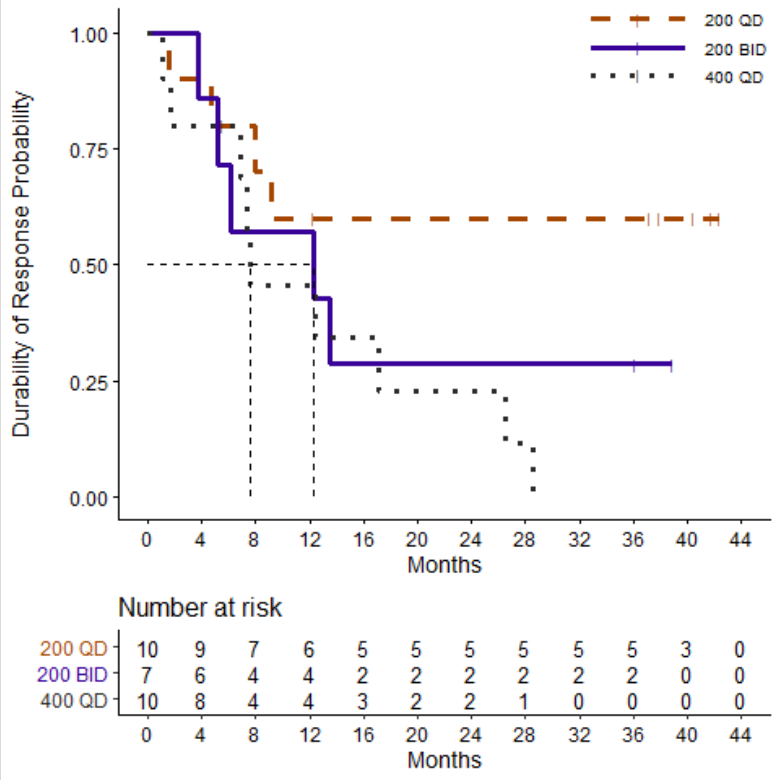
[1]Median as estimated per Kaplan-Meier methodology, confidence interval estimated using the Brookmeyer and Crowley method.
Source: Reviewer's analysis.

Median durability of response is non-estimable in the 200 mg QD group. Durability of response

was longer than six months in 80% (95% CI: 41%, 95%) and longer than 12 months in 60% (95% CI: 25%, 83%) of patients in the 200 mg QD group. Figure 9 shows the durability of response Kaplan-Meier plot. The number of events is 10 or fewer in all dose groups.

Reviewer's comment: Results should be interpreted with caution due to low number of events (10 or fewer) and high uncertainty in all dose groups.

Figure 9. Study KD025-208: Kaplan Meier Plot of Durability of Response per FDA Adjudication



Source: Reviewer's analysis.

Subpopulations

Table 26 shows ORR by subgroups. Study KD025-208 was not designed to compare subgroups and does not contain sufficient information on patients in each treatment group to determine if subgroup outcomes differ.

Table 26. Study KD025-208: ORR per FDA Adjudication by Subgroup

Variable	Group	Belumosudil		
		200 mg QD	200 mg BID	400 mg QD
Age	<65 years	10/17, 59% (33,82)	5/10, 50% (19,81)	6/16, 38% (15,65)
	>=65 years	NA	2/6, 33% (4,78)	4/5, 80% (28,99)
Sex	Female	2/4, 50% (7,93)	4/7, 57% (18,90)	4/9, 44% (14,79)
	Male	8/13, 62% (32,86)	3/9, 33% (7,70)	6/12, 50% (21,79)
Race	Other	2/2, 100% (16,100)	NA	1/1, 100% (3,100)
	White	8/15, 53% (27,79)	6/14, 43% (18,71)	8/18, 44% (22,69)
	American Indian or Alaska Native	NA	1/2, 50 (1,99)	NA
	Black or African-American	NA	NA	1/2, 50% (1,99)
Number of Lines of prior therapy	1	1/2, 50% (1,99)	4/7, 57% (18,90)	3/7, 43% (10,82)
	2	2/3, 67% (9,99)	1/2, 50% (1,99)	3/6, 50% (12,88)
	3	5/10, 50% (19,81)	2/7, 29% (4,71)	4/7, 57% (18,90)
	4	2/2, 100% (16,100)	NA	0/1, 0% (0,98)
Prior ibrutinib	No	9/16, 56% (30,80)	7/16, 44% (20,70)	8/18, 44% (22,69)
	Yes	1/1, 100% (3,100)	NA	2/3, 67% (9,99)
Prior ruxolitinib	No	10/17, 59% (33,82)	7/16, 44% (20,70)	10/20, 50% (27,73)
	Yes	NA	NA	0/1, 0% (0,98)
Best response to the last prior cGVHD treatment	Partial Response	2/4, 50% (7,93)	3/4, 75% (19,99)	3/5, 60% (15,95)
	Stable Disease	6/11, 55% (23,83)	3/7, 43% (10,82)	4/10, 40% (12,74)
	Unknown	2/2, 100% (16,100)	0/3, 0% (0,71)	1/1, 100% (3,100)
	Progressive Disease	NA	1/2, 50% (1,99)	2/5, 40% (5,85)
Time from cGVHD diagnosis to enrollment (months)	<=20	3/7, 43% (10,82)	5/9, 56% (21,86)	6/11, 55% (23,83)
	>20	7/10, 70% (35,93)	2/7, 29% (4,71)	4/10, 40% (12,74)
Severe cGVHD at screening	No	2/5, 40% (5,85)	2/2, 100% (16,100)	3/5, 60% (15,95)
	Yes	8/12, 67% (35,90)	5/14, 36% (13,65)	7/16, 44% (20,70)
Baseline corticosteroid dose level (PE mg/kg/day)	<=0.19	7/7, 100% (59,100)	5/8, 62% (24,91)	5/12, 42% (15,72)
	>0.19	3/10, 30% (7,65)	2/8, 25% (3,65)	5/9, 56% (21,86)
Takes proton pump inhibitor medication	No	3/9, 33% (7,70)	5/7, 71% (29,96)	1/6, 17% (0,64)
	Yes	7/8, 88% (47,100)	2/9, 22% (3,60)	9/15, 60% (32,84)
Number of organs involved at baseline	<=4	9/15, 60% (32,84)	6/13, 46% (19,75)	6/16, 38% (15,65)
	>4	1/2, 50% (1,99)	1/3, 33% (1,91)	4/5, 80% (28,99)
Lung involvement at baseline	No	6/13, 46% (19,75)	6/12, 50% (21,79)	5/10, 50% (19,81)
	Yes	4/4, 100% (40,100)	1/4, 25% (1,81)	5/10, 50% (19,81)
	Unknown	NA	NA	0/1, 0% (0,98)

Variable	Group	Belumosudil		
		200 mg QD	200 mg BID	400 mg QD
Baseline GFR (mL/min/1.72 m^2)	60<=GFR<90	5/8, 62% (24,91)	5/10, 50% (19,81)	4/10, 40% (12,74)
	GFR<60	1/1, 100% (3,100)	1/3, 33% (1,91)	2/5, 40% (5,85)
	GFR>=90	4/8, 50% (16,84)	1/3, 33% (1,91)	4/6, 67% (22,96)

Responders/N, % (95% Confidence Interval, estimated using the Clopper-Pearson method)
Source: Reviewer's analysis.

Reviewer's Comment: Study KD025-208 does not contain sufficient information on patients in each treatment group to determine if subgroup outcomes differ. As the study was not designed to assess differential ORR in any particular subgroup, the results presented above should be regarded as exploratory only.

Efficacy Results – Exploratory and Other COA (PRO) Endpoints

The protocol stipulated that the Lee cGVHD Symptom Scale "will be assessed on Day 1 of Cycles 2-5, then on Day 1 of every other cycle thereafter and EOT. The questionnaire consists of 30 items over 7 domains: skin, eyes and mouth, breathing, eating and digestion, muscles and joints, energy, and mental and emotional. Each question is scored 0, 1, 2, 3, or 4. A domain score will be calculated for each domain by taking the mean of all items completed if more than 50% were answered and normalizing to a 0 to 100 scale. A summary score will be calculated as average of all non-missing domain scores if more than 50% of them are non-missing. A higher score indicates more bothersome symptoms. A 7-point difference on the summary score of cGVHD symptom scale has been found to be clinically meaningful." (Source: Statistical Analysis Plan v2.3, p24)

The period for calculating 7-point change from baseline was from Cycle 1, Day 1 through Cycle 7, Day 1 or initiation of new systemic therapy, whichever occurred first. Table 27 shows reporting compliance.

Table 27. Study KD025-208: Lee cGVHD Symptom Scale Compliance

Visit	Compliance
CYCLE 1, DAY 1	52 / 54, 96%
CYCLE 2, DAY 1	8 / 10, 80%
CYCLE 3, DAY 1	46 / 46, 100%
CYCLE 4, DAY 1	10 / 14, 71%
CYCLE 5, DAY 1	38 / 40, 95%
CYCLE 6, DAY 1	14 / 15, 93%
CYCLE 7, DAY 1	34 / 35, 97%
28 DAY FOLLOW-UP	0 / 16, 0%

Visit	Compliance
END OF TREATMENT	37 / 42, 88%
UNSCHEDULED	3 / 4, 75%

Source: Reviewer's analysis.

At least a 7-point decrease in the Lee Symptom Scale summary score through Cycle 7 Day 1 was reported by 6/17, 35% (95% CI: 14, 62) of the patients in the 200 mg QD group.

Reviewer's comment: Study KD025-208 was an open-label study. Patient-reported outcomes in open-label studies may be impacted by patients' knowledge of the treatment received. Moreover, no placebo group was present in the study to assess any potential advantage in patient-reported outcomes. Results of this exploratory analysis should be interpreted with caution.

Additional Analyses Conducted on the Individual Trial

Biomarkers

Blood samples were collected prior to dosing on Cycle 1 Day 1, Cycle 2 Day 1, Cycle 4 Day 1 and Cycle 7 Day 1, the EOT visit and at the 28-Day Follow-Up visit. Testing was performed for plasma cytokines, intracellular cytokines, and lymphocyte subset enumeration. The stated hypothesis was that treatment with belumosudil may result in plasma IL-17A and plasma IL-21 decrease, TH17 decrease, CD3+CD4+CD25+CD127lowFoxP3+ (Treg) increase, and IFNγ decrease (Study KD025-208 Clinical Study Report Appendix 16.1.13 Section 2). The Applicant concluded that "Exploratory PD analyses are consistent with the proposed MoA with numerical increases in Tregs and decreases in TH17 cells." (Study KD025-208 Clinical Study Report Section 13.1).

Clinical TL Review Comment: The small number of patients at any dose precludes credible assessments for a biomarker-response relationship.

8.1.2 Study KD025-213

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

TRIAL DESIGN

The Applicant's Description:

Trial Design

Study KD025-213 an ongoing, pivotal, Phase 2, randomized, open-label study in subjects with active cGVHD who receive belumosudil after at least 2 prior lines of systemic therapy.

Subjects were randomized to receive 200 mg QD or 200 mg BID of belumosudil. These doses were selected based on the safety and efficacy of belumosudil in a similar patient population in Study KD025-208. Randomized subjects may or may not have received previous treatment with ibrutinib for cGVHD (target was for ≥ 10% of the enrolled population having previously received ibrutinib). As with Study KD025-208, the design for Study KD025-213 is open-label with a requirement for concomitant use of corticosteroids.

Key eligibility

The FDA's Assessment:

The key inclusion criteria were adults and adolescents who: Had undergone allogeneic hematopoietic cell transplantation; Had previously received at least 2 prior lines of systemic therapy for cGVHD; Had received glucocorticoid therapy with a stable dose for at least 2 weeks prior to screening; and Had persistent cGVHD manifestations and for whom systemic therapy for cGVHD was indicated.

Treatment plan

The FDA's Assessment:

The eligible subjects were randomized (1:1) to 1 of 2 treatment arms: Arm A: belumosudil 200 mg QD; or Arm B: belumosudil 200 mg BID.

Monitoring plan

The FDA's Assessment:

Th Subjects received belumosudil treatment in 28-day cycles until clinically significant progression of cGVHD (defined as progression that required the addition of new systemic therapy for cGVHD), histologic recurrence of underlying malignancy, unacceptable toxicity, Investigator decision, subject preference/withdrawal of consent, loss of follow-up, Sponsor decision, or death (whichever occurred first).

Study Endpoints

Primary and secondary efficacy endpoints and analysis populations were similar to those for Study KD025-208.

The FDA's Assessment:

FDA's assessment of efficacy will rely on ORR through Cycle 7 Day 1 as opposed to ORR at any time (as prespecified by the Applicant). FDA will consider two definitions of duration of response: 1) time from response to progression, new systemic therapy, or death and 2) time from response to new systemic therapy or death. Refer to Section 8.2 for more details.

Statistical Analysis Plan and Amendments

The Applicant's Description:

Statistical Analysis Plan

As in Study KD025-208, primary and secondary efficacy endpoints are assessed in the mITT population. Responder and nonresponder subsets of that population also were used for subgroup analyses.

For the primary efficacy endpoint of ORR, point estimates, various CIs (Clopper-Pearson [exact] method) and unadjusted and Hochberg adjusted p-values corresponding to the null hypothesis of ORR ≤ 30% versus the alternative hypothesis of ORR > 30% by treatment arms are reported. Secondary efficacy analyses were analyzed similarly to those in Study KD025-208.

Safety assessments included AEs, SAEs, vital sign measurements, clinical laboratory evaluations (hematology and chemistry), and ECGs. Clinically significant physical examination (PE) findings were captured as AEs.

Amendments

The original SAP (v1.0) was dated 08 March 2019. There were 2 amendments to the original SAP (v2.0, dated 16 August 2019 and v2.1, dated 26 June 2020). The key changes are summarized below.

The major changes in Amendment 1 (16 August 2019) were the following:

- The study design was updated to include an additional formal interim analysis with alpha spending 0.0025;
- The definitions of DOR were updated;
- Secondary efficacy endpoints were added and rearranged.

The major changes in Amendment 2 (26 June 2020) were the following:

- Censoring rules of new systemic cGVHD treatments for organ and overall response, corticosteroid usage, and LSS were added;

- Additional analyses were added, including the following:
    - ORR and DOR for responses occurring within the first 6 months of treatment with belumosudil;
    - Organ responses according to baseline NIH/severity score;
    - Landmark FFS with CR/PR at 6 and 12 months; and
    - Time to corticosteroid discontinuation.

The FDA's Assessment:

FDA agreed with the Applicant's statement of Statistical Analysis Plan and Amendments.

The primary efficacy endpoint was the ORR (overall response rate), as defined by the 2014 NIH Consensus Development Project on Clinical Trials in cGVHD. See Section 8.2 for a discussion of endpoints.

Protocol Amendments

The Applicant's Description:

The original protocol (v1.0) was dated 25 June 2018 and 135 subjects were enrolled under this protocol (135 subjects randomized and 132 dosed). There were 2 amendments to the original protocol (v2.0, Amendment 1, dated 26 June 2019 and v3.0, Amendment 2, dated 01 June 2020). The key changes are summarized below.

The major changes in Amendment 1 (26 June 2019) were the following:

- TTR and TTNT were added as secondary objectives and secondary efficacy endpoints
- The dosage and administration procedures were updated as follows:
    - Specified that subjects may have returned to the clinic every other treatment cycle starting on C19D1; and
- Guidance on how to dose and report an AE in the event of vomiting was added;
- Safety was added as a secondary endpoint and the primary safety outcome was added as the percentage of subjects in each arm who experienced AEs;
- Inclusion criteria was updated to include subjects who were 12 years of age or older instead of subjects who were 18 years of age or older.

The major changes in Amendment 2 (01 June 2020) were the following:

- The study design was updated as follows:

  - The study enrollment period was revised from 12 to 24 months; and
  - The anticipated study close out was revised to occur approximately 4 years after the first subject enrolled.
- The number of subjects to be enrolled was updated from 126 to 166. The additional 40 subjects to include 20 adolescents and 20 adults to be enrolled into a site-specific Companion Study;
- Analyses were added to be conducted to include adolescent subjects and Companion Study subjects approximately 6 months after the completion of enrollment of the respective subjects.

The FDA's Assessment:

FDA agreed with the Applicant's statement of Protocol Amendments.

In Study KD025-213, subjects returned to the study site within 7 days after the subject's last dose of study drug to complete all EOT assessments. This may occur at the visit at which disease progression is diagnosed. Response was assessed on D1 of C2 through C5, then on D1 of every other cycle thereafter and at the EOT visit.

The Applicant clarified on 01 December 2020 (Response to Information Request) that "there is one assessment criteria difference between Study KD025-208 and Study KD025-213. In Study KD025-208 a subject who only shows response at End of Treatment (EOT) is counted as a responder. In Study KD025-213, and also in the Integrated Summary of Efficacy, a subject who only shows response at End of Treatment (EOT) is not counted as a responder." (See also Section 8.1.1 above).

STUDY RESULTS - APPLICANT'S POSITION

Compliance with Good Clinical Practices

The Applicant's Position:

The study was conducted in accordance with the Declaration of Helsinki and with all applicable laws and regulations of the locale and country where the study was conducted, and in compliance with GCP Guidelines.

Quality and Integrity

The Applicant's Position:

Data quality and integrity measures followed in Study KD025-213 mirror those described above for Study KD025-208 (Section 0).

Financial Disclosure

The Applicant's Position:

None of the investigators participating in the study had any disclosable financial arrangements. As a result, there were no concerns regarding the overall integrity of data.

Patient Disposition

Data:

A summary of subject enrollment in the mITT population is presented in Table 28.

Table 28 Analysis Populations in Study KD025-213

	Belumosudil		
Population, n (%)	**200 mg QD**	**200 mg BID**	**Overall**
mITT	66 (100)	66 (100)	132 (100)
Responder	48 (72.7)	49 (74.2)	97 (73.5)
Nonresponder	18 (27.3)	17 (25.8)	35 (26.5)

Abbreviations: BID = twice daily; mITT = modified intent-to-treat; QD = once daily.
Notes: The data cutoff date was 19 February 2020.
Sources: CSR KD025-213, Table 1.1.1.

Overall, 221 subjects were screened for the study and 132 subjects were included in the mITT population: 66 subjects each were in the 200 mg QD and 200 mg BID arms.

As of the data cutoff date, 33 subjects (50.0%) in the 200 mg QD arm and 37 subjects (56.1%) in the 200 mg BID arm remained on treatment with belumosudil. Of the 33 subjects (50.0%) in the 200 mg QD arm who discontinued from treatment, 25 were still being followed for FFS and survival; median duration of follow-up was 8.0 months (range, 0.6, 15.4). In the 200 mg BID arm, 24 of the 29 subjects (43.9%) who discontinued from treatment were still being followed for FFS and survival; median duration of follow-up was 7.9 months (range, 0.9, 17.5). The most common reasons for treatment discontinuation in the 200 mg QD and BID arms were AE and withdrawal by subject (7 subjects each, 10.6%) and cGVHD disease progression (10 subjects, 15.2%), respectively.

The Applicant's Position:

The proportion of subjects who have discontinued the study and the reasons for discontinuation are within expectations for the population under study.

Protocol Violations/Deviations

Data:

Overall, there were 28 CSR-reportable protocol deviations: 1 in the study exclusion category, 1 in the restricted concomitant medication category, 4 in the safety reporting category, 5 in the subject not withdrawn category, 5 in the informed consent category, and 12 in the study inclusion category.

The Applicant's Position:

The protocol deviations observed during this study did not change the overall interpretation of the study results.

Table of Demographic Characteristics

Data:

Demographics and other baseline disease characteristics for the mITT population are summarized in Table 29.

Table 29 Demographic and Baseline Disease Characteristics: Study KD025-213– mITT Population

Category	Belumosudil		
	200 mg QD N = 66	200 mg BID N = 66	Overall N = 132
Age (years), n	66	66	132
Median	53.0	57.0	55.5
Min, max	21, 77	21, 77	21, 77
Sex, n (%)			
Female	24 (36.4)	33 (50.0)	57 (43.2)
Male	42 (63.6)	33 (50.0)	75 (56.8)
Karnofsky Performance Status, n (%)			
60	3 (4.5)	2 (3.0)	5 (3.8)
70	7 (10.6)	17 (25.8)	24 (18.2)
80	33 (50.0)	25 (37.9)	58 (43.9)
90	19 (28.8)	18 (27.3)	37 (28.0)
100	4 (6.1)	4 (6.1)	8 (6.1)
Time from most recent transplant to cGVHD diagnosis[a] (months), n	66	66	132
Median	6.9	6.7	6.8
Min, max	1.0, 29.5	0, 48.8	0, 48.8
Number of prior lines of cGVHD therapy			
Median	3.0	4.0	3.0
Prior ibrutinib	22 (33.3)	23 (34.8)	45 (34.1)

Category	Belumosudil		
	200 mg QD N = 66	200 mg BID N = 66	Overall N = 132
Prior ruxolitinib[b]	20 (30.3)	18 (27.3)	38 (28.8)
Refractory to the last systemic cGVHD treatment prior to enrollment to study (SD or PD)[c]	45/56 (80.4)	34/53 (64.2)	79/109 (72.5)
Time from cGVHD diagnosis to enrollment (months)[d], n	66	66	132
Median	25.2	30.2	28.9
Min, max	1.9, 162.4	3.7, 144.1	1.9, 162.4
Severe NIH cGVHD at screening[e], n (%)	46 (69.7)	43 (65.2)	89 (67.4)
Number of organs involved at baseline, n	66	66	132
Median	3.5	4.0	4.0
Min, max	0, 7	1, 7	0, 7
≥ 4	33 (50.0)	35 (53.0)	68 (51.5)
Organs involved at baseline, n (%)			
Skin	55 (83.3)	55 (83.3)	110 (83.3)
Eyes	48 (72.7)	49 (74.2)	97 (73.5)
Mouth	30 (45.5)	41 (62.1)	71 (53.8)
Esophagus	19 (28.8)	12 (18.2)	31 (23.5)
Upper GI	13 (19.7)	10 (15.2)	23 (17.4)
Lower GI	6 (9.1)	7 (10.6)	13 (9.8)
Liver	9 (13.6)	4 (6.1)	13 (9.8)
Lung	24 (36.4)	23 (34.8)	47 (35.6)
Joints and fascia	51 (77.3)	49 (74.2)	100 (75.8)
GSR, n	66	66	132
Median	7.0	7.0	7.0
Min, max	0, 9	2, 10	0, 10
Median baseline corticosteroid dose (mg/kg/day)	0.17	0.22	0.18
Concomitant systemic cGVHD therapies[f,g], n (%)	66 (100)	66 (100)	132 (100)
Prednisone	63 (95.5)	65 (98.5)	128 (97.0)
Tacrolimus	23 (34.8)	25 (37.9)	48 (36.4)
Sirolimus	18 (27.3)	18 (27.3)	36 (27.3)
MMF	11 (16.7)	2 (3.0)	13 (9.8)
ECP[h]	19 (28.8)	22 (33.3)	41 (31.1)
BoR to the last systemic cGVHD treatment before enrolling in study, n (%)			
Complete response	0	1 (1.5)	1 (0.8)
Partial response	11 (16.7)	18 (27.3)	29 (22.0)
Stable disease	28 (42.4)	18 (27.3)	46 (34.8)
Progressive disease	17 (25.8)	16 (24.2)	33 (25.0)
Unknown/missing	10 (15.2)	12 (18.2)	22 (16.7)
Missing	0	1 (1.5)	1 (0.8)

Category	Belumosudil		
	200 mg QD N = 66	200 mg BID N = 66	Overall N = 132

Abbreviations: BID = twice daily; cGVHD = chronic graft versus host disease; CR = complete response; ECP = extracorporeal photopheresis; GI = gastrointestinal; GSR = global severity rating; max = maximum; min = minimum; mITT = modified Intent-to-Treat; MMF = mycophenolate mofetil; NIH = National Institutes of Health; PD = progressive disease; PR = partial response; QD = once daily; SD = stable disease; WHO = World Health Organization.
Note: The data cutoff date was 19 February 2020.
[a] Time from most recent transplant to cGVHD diagnosis (months) = (date of cGVHD diagnosis - date of most recent transplant +1)/365.25 □ 12.
[b] Includes prior therapy with ruxolitinib and ruxolitinib phosphate.
[c] Formula for calculation of the percentages of subjects who were refractory: (PD+SD)/(PD+SD+CR+PR).
[d] Time from cGVHD diagnosis to enrollment (months) = (date of informed consent – date of cGVHD diagnosis +1)/365.25*12.
Subjects with missing or unknown status were excluded.
[e] Severe was defined as at least 1 organ with a National Institutes of Health Activity Assessment score of 3 or a lung score of □ 2 at baseline.
[f] Medications were coded using WHO Drug Dictionary, version March 2017, B2 Format.
[g] A subject with multiple medications within a medication type or preferred term was counted only once for that medication type or preferred term.
[h] ECP was coded as "photopheresis."
Sources: CSR KD025-213, Tables 2.1.1, 2.1.3, 2.1.4, 2.1.5, 3.1.3, and 3.1.4.

The Applicant's Position:

Overall, there were no notable differences between treatment arms in demographic/baseline characteristics.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Data:

Treatment Compliance

The RDI was used to assess treatment compliance. The median RDI was 99.7%. In total, 110 (83.3%) subjects had an RDI >95%: 54 (81.8%) subjects in Arm A and 56 (84.8%) subjects in Arm B (Post-text Table 4.1.1).

Systemic cGVHD Concomitant Medications

Table 30 summarizes systemic cGVHD concomitant therapies by type of medication and PT for ≥5 subjects overall in the mITT Population.

Table 30 Chronic Graft Versus Host Disease Systemic Therapies by Type of Medication and Preferred Term (≥5 Subjects Overall): Study KD025-213– mITT Population

Type of Medication Preferred Term	Arm A 200 mg QD N=66 n (%)	Arm B 200 mg BID N=66 n (%)	Overall N=132 n (%)
Subjects with any cGVHD medication	66 (100)	66 (100)	132 (100)
Prednisone	63 (95.5)	65 (98.5)	128 (97.0)
Tacrolimus	23 (34.8)	25 (37.9)	48 (36.4)
ECP[a]	19 (28.8)	22 (33.3)	41 (31.1)
Sirolimus (systemic)	18 (27.3)	18 (27.3)	36 (27.3)
MMF	11 (16.7)	2 (3.0)	13 (9.8)

Statistical notes:
[a]ECP was coded as "photopheresis."
Medications were coded using WHO Drug Dictionary, version March 2017, B2 Format.
A subject with multiple medications within a medication type or preferred term was counted only once for that medication type or preferred term.
The table is sorted in descending order of frequency in the overall column by medication type and by preferred term within each ATC class.
The results presented are based on the data cutoff date of 19 February 2020.
ATC = Anatomical Therapeutic Chemical; BID = twice daily; cGVHD = chronic graft versus host disease; ECP = extracorporeal photopheresis; mITT = modified Intent-to-Treat; MMF = mycophenolate mofetil; QD = once daily; WHO = World Health Organization.
Sources: CSR Post-text Tables 3.1.3 and 3.1.4

Rescue Medication Use

Not applicable.

The Applicant's Position:

Treatment compliance, as assessed by RDI, was high in the 2 treatment arms, with an overall median RDI of 99.7%. The concomitant medication profiles of the 2 treatment arms were within expectations for the population under study.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data:

Overall response rate, including ORR within 6 months of initiation of treatment, and best overall response for the mITT population are summarized in Table 31.

Partial response was the most common best responses observed, though some responses of CR were observed in this population with advanced cGVHD.

Table 31 Overall Response Rate: Study KD025-213 – mITT Population

Variable/Category	Belumosudil 200 mg QD N = 66	Belumosudil 200 mg BID N = 66	Belumosudil Overall N = 132
ORR (CR or PR), n (%)	48 (72.7)	49 (74.2)	97 (73.5)
Exact method 95% CI of ORR	(60.4, 83.0)	(62.0, 84.2)	(65.1, 80.8)
Best overall response			
Complete response	3 (4.5)	1 (1.5)	4 (3.0)
Partial response	45 (68.2)	48 (72.7)	93 (70.5)
Lack of response			
Unchanged	14 (21.2)	10 (15.2)	24 (18.2)
Mixed	0	3 (4.5)	3 (2.3)
Progression	1 (1.5)	2 (3.0)	3 (2.3)
No response assessment	3 (4.5)	2 (3.0)	5 (3.8)
ORR (CR or PR) within 6 months of treatment, n (%)	46 (69.7)	48 (72.7)	94 (71.2)
Complete response	2 (3.0)	1 (1.5)	3 (2.3)
Partial response	44 (66.7)	47 (71.2)	91 (68.9)
Exact method 95% CI of ORR	(57.1, 80.4)	(60.4, 83.0)	(62.7, 78.8)

Abbreviations: BID = twice daily; CI = confidence interval; CR = complete response; mITT = modified intent-to-treat; ORR = Overall Response Rate; PR = partial response; QD = once daily.
Notes: 2-sided, exact CI was calculated using the Clopper Pearson method. The data cutoff date was 19 February 2020.
Source: CSR KD025-213, Tables 5.1.1, 5.1.1.1, and 5.1.2.

The Applicant's Position:

Belumosudil doses at 200 mg QD and 200 mg BID demonstrated clinically meaningful responses in a population of subjects with advanced, heavily pre-treated cGVHD. The point estimates and 95% CIs all exceeded 60%.

Efficacy Results – Secondary and other relevant endpoints

Data:

Results for the secondary efficacy endpoints of DOR, TTR, response by organ system, LSS score, FFS, TTNT, OS, and change in corticosteroid dose are summarized in Table 32.

Responses were achieved across all organ systems, with CRs in all organs systems. Improvements in LSS and corticosteroid dose reductions were observed in both responders and nonresponders. In the 200 mg QD and BID arms, 11 subjects (16.7%) and 13 subjects (19.7%), respectively, discontinued corticosteroid usage.

Table 32 Secondary Efficacy Endpoints: Study KD025-213– mITT Population

Variable	Belumosudil 200 mg QD N = 66	Belumosudil 200 mg BID N = 66	Belumosudil Overall N = 132
Duration of response (responders), n	48	49	97
Median (weeks)			
Primary/secondary (95% CI)	21.1 (9.4, NR)	32.0 (12.6, NR)	22.1 (16.1, NR)
Tertiary (95% CI)	NR (NR, NR)	NR (NR, NR)	NR (NR, NR)
Quaternary (95% CI)	NR (16.1, NR)	NR (NR, NR)	NR (NR, NR)
Time-to-response (weeks), n	48	49	97
Median	4.4	4.4	4.4
Min, max	3.7, 40.6	3.7, 40.1	3.7, 40.6
Response by organ system[a], % (n/total)			
Skin	29.1 (16/55)	40.0 (22/55)	34.5 (38/110)
Eyes	29.2 (14/48)	49.0 (24/49)	39.2 (38/97)
Mouth	50.0 (15/30)	51.2 (21/41)	50.7 (36/71)
Esophagus	36.8 (7/19)	41.7 (5/12)	38.7 (12/31)
Upper GI	53.8 (7/13)	40.0 (4/10)	47.8 (11/23)
Lower GI	50.0 (3/6)	71.4 (5/7)	61.5 (8/13)
Liver	33.3 (3/9)	25.0 (1/4)	30.8 (4/13)
Lungs	20.8 (5/24)	17.4 (4/23)	19.1 (9/47)
Joints and fascia	70.6 (36/51)	67.3 (33/49)	69.0 (69/100)
GSR	39.4 (26/66)	53.0 (35/66)	46.2 (61/132)
Lee Symptom Scale score, n (%)			
Subjects with a 7-PtR[b] from baseline	36 (54.5)	40 (60.6)	76 (57.6)
Subjects with a 7-PtR from baseline on 2 consecutive assessments	26 (39.4)	22 (33.3)	48 (36.4)
PROMIS[c], n (%)			
Mental Health Raw Score Subjects with a ≥ 4.7-PtR from baseline	34 (51.5)	25 (37.9)	59 (44.7)
Physical Health Raw Score Subjects with a ≥ 4.7-PtR from baseline	21 (31.8)	23 (34.8)	44 (33.3)
Failure-free survival (months)			
Median (95% CI)	NR (10.2, NR)	NR (NR, NR)	NR (NR, NR)
6 months (95% CI)	0.74 (0.61, 0.83)	0.81 (0.70, 0.89)	0.77 (0.69, 0.84)
Time-to-next treatment (months)			
Number of patients who initiated new systemic therapy for cGVHD, n (%)	13 (19.7)	13 (19.7)	26 (19.7)
Median (95% CI)	NR (NR, NR)	NR (NR, NR)	NR (NR, NR)
Overall survival			
Number of deaths	5 (7.6)	3 (4.5)	8 (6.1)
Median (95% CI)	NR (NR, NR)	NR (NR, NR)	NR (NR, NR)
6 months OS (95% CI)	0.94 (0.85, 0.98)	0.97 (0.88, 0.99)	0.95 (0.90, 0.98)
Corticosteroid dosing			
Median greatest reduction (%)	-25.0	-50.0	-33.3
Min, max	-100, 0	-100, 33.3	-100, 33.3

Variable	Belumosudil 200 mg QD N = 66	Belumosudil 200 mg BID N = 66	Belumosudil Overall N = 132
Subjects who discontinued corticosteroid usage, n (%)	11 (16.7)	13 (19.7)	24 (18.2)

Abbreviations: 4.7-PtR = 4.7 point reduction; 7-PtR = 7-point reduction; BID = twice daily; cGVHD = chronic graft versus host disease; CI = confidence interval; GI = gastrointestinal; GSR = global severity rating; max = maximum; min = minimum; NR = not reached; OS = overall survival; PROMIS = Patient-Reported Outcomes Measurement Information System; QD = once daily.
Note: The data cutoff date was 19 February 2020.
[a] Response = CR or PR.
[b] The 7-PtR is a ≥ 7-point reduction.
[c] Change from baseline in PROMIS Global Health subscore was an exploratory efficacy endpoint.
Source: CSR KD025-213, Tables 5.2.1.1, 5.2.1.2, 5.2.1.3, 5.2.1.4, 5.3.1, 5.4.1.1, 5.5.1.1, 5.6.1.1, 5.8.1, 5.8.2, 5.9.1, and 5.12.2.

Efficacy Results – Exploratory and COA (PRO) endpoints

Data:

Kadmon Algorithmic Response Assessments (KARA)

In addition to ORR assessed by Investigators, the Sponsor conducted response assessments (KARA) programmatically according to NIH-defined response criteria for each individual organ, including GSR, then assigned overall response according to cGVHD response definitions. Analyses of ORR and DOR were repeated with KARA. Results observed in the KARA analyses were similar to the Investigator assessments. The concordance of overall response between KARA and the Investigator assessment was 100% for the 200-mg QD and 200-mg BID groups. .

The Applicant's Position:

The KARA exploratory/sensitivity analyses yielded results similar to the primary analysis.

[To the Applicant: Insert text here]

Additional Analyses Conducted on the Individual Trial

Data:

Not applicable.

The Applicant's Position:

Not applicable.

STUDY RESULTS - FDA'S POSITION

Compliance with Good Clinical Practices

FDA agreed with the Applicant's statement of Compliance with Good Clinical Practices.

Financial Disclosure

There were 455 investigators identified for the Study KD025-213. There were no clinical investigators with disclosable financial arrangements reported. See Appendix 16.2.

Data Quality and Integrity

The major components needed for the response assessment included the scoring or test results for each organ system, the comment on whether abnormalities were due to solely to an unrelated disorder, and whether a new systemic therapy was instituted.

The Applicant provided the first new systemic therapy date in the variable adsl.CMGVHDDT. FDA disagreed with the dates of first new systemic therapy for multiple patients largely due to the following factors:

- FDA considered institution of or increase in steroids to a dose of at least 1 PE mg/kg/day (+/- 10%) as a new systemic therapy, but the Applicant considered only institution of a new steroid at any dose (but not an increase in dose) as new systemic therapy.
- FDA considered montelukast as a systemic therapy for cGVHD.
- FDA did not consider supportive care drugs, such as pilocarpine or saliva substitutes, as new systemic therapy.
- The Applicant identified multiple incorrect entries due to programming errors (Response to Information Request received 1/8/2021).

The final FDA-adjudicated list of first new systemic therapy was sent to the Applicant in an Information Request on 2/25/2021 (see DARRTS entry dated 7/9/2021).

The Applicant submitted in adrs.xpt the response assessments by the investigators and by an algorithmic approach (Kadmon Algorithmic Response Assessment; KARA). FDA identified the following major issues with KARA:

- The initial iteration of KARA included that Clinician Overall Severity Score as an element for the response assessment. However, the 2014 NIH criteria clearly indicate that only the organ-based outcomes were to be considered in the overall response determination.
- The initial iteration also assessed loss of response as measured in comparison to baseline. However, this does not take into account patients who achieve a response and then

worsened, which would require that the duration of response (DOR) be calculated from the nadir value for each individual organ.

On 3/5/2021, the Applicant provided a revised data file with the assessment of response based on organ system alone and the assessment of DOR calculated from nadir for the individual organs. This submission was part of the Major Amendment.

FDA also used an algorithmic approach to identify responders and determine the DOR. The FDA analysis of efficacy used all available data, including assessments at unscheduled visits (e.g., out-of-window) and end-of-therapy visits. Discrepancies between the revised KARA assessments and FDA's algorithm were adjudicated by the clinical review team at the data element level. Following clarifications by the Applicant for cases of differences for response or duration of response, the final FDA-adjudicated responses were conveyed to the Applicant in fadj.xpt sent on 6/1/2021, and the results are memorialized in the file kadj.xpt received in SDN 82 on 6/7/2021.

Patient Disposition

Table 33 shows Subject Disposition including reasons for discontinuation of belumosudil treatment in patients with chronic GVHD. The most common reasons for treatment discontinuation were progression of chronic GVHD (14%) and recurrence of the underlying malignancy (8%) in patients with chronic GVHD treated with belumosudil 200 mg once daily.

Table 33. Study KD025-213: Subject Disposition

Parameter	Belumosudil		
	200 mg QD (N = 66)	200 mg BID (N = 66)	Total cGVHD (N = 132)
Treatment Ongoing	23 (35)	27 (41)	50 (38)
Treatment Discontinued	43 (65)	39 (59)	82 (62)
Reasons for discontinuation			
Adverse Event	8 (12)	8 (12)	16 (12)
Death	8 (12)	6 (9)	14 (11)
Recurrence of underlying malignancy	**5 (8)**	0	5 (4)
Failure to Meet Continuation Criteria	1 (2)	0	1 (1)
Lost to Follow-Up	2 (3)	0	2 (2)
Noncompliance to Protocol	1 (2)	2 (3)	3 (2)
Other	4 (6)	3 (5)	7 (5)
Physician Decision	7 (11)	4 (6)	11 (8)
Progression of chronic GVHD	**9 (14)**	12 (18)	21 (16)
Withdrawal By Subject	6 (9)	9 (14)	15 (11)

Protocol Violations/Deviations

FDA agreed with the Applicant's statement for Protocol Violations/Deviations.

Demographic Characteristics and Baseline Characteristics

FDA acknowledges the Applicant's table of demographics in the section above and agrees with the Applicant's statement that there were no notable differences between treatment arms in demographic/baseline.

FDA analyzed datasets and the Applicant's responses to information requests, and additional demographics and baseline disease characteristics for the Study KD025-213 population are summarized in Table 34 below.

Table 34. Study KD025-213: Demographic and Baseline Disease Characteristics:

	Belumosudil		
Category	**200 mg QD N = 66**	**200 mg BID N = 66**	**Overall N = 132**
Age, Median, Years (minimum, maximum)	53 (21, 77)	57 (21, 77)	55.5 (21, 77)
Age ≥ 65 Years, n (%)	17 (25.8)	20 (30.3)	37 (28)
Sex			
Male, n (%)	42 (63.6)	33 (50.0)	75 (56.8)
Race, n (%)			
White	55 (83.3)	57 (86.4)	112 (84.8)
Black	6 (9.1)	1 (1.5)	7 (5.3)
Other or Not Reported	5 (7.6)	8 (12.1)	13 (9.8)
Median (range) time (months) from cGVHD diagnosis to enrollment	25.2 (1.9, 162.4)	30.2 (3.7, 144.1)	28.1 (1.9, 162.4)
Number of Organs Involved at Baseline			
≥ 4 Organs Involved, n (%)	33 (50.0)	35 (53.0)	68 (51.5)
Median (range) Number of Prior Lines of cGVHD Therapy	3 (2, 6)	4 (2, 6)	3 (2, 6)
Number of Prior Lines of Therapy, n (%)			
2	23 (34.8)	14 (21.2)	37 (28.0)
3	13 (19.7)	17 (25.8)	30 (22.7)
4	15 (22.7)	14 (21.2)	29 (22.0)
5	14 (21.2)	19 (28.8)	33 (25.0)
6	1 (1.5)	2 (3.0)	3 (2.3)
Prior chronic GVHD treatment with ibrutinib, n (%)	22 (33.3)	24 (36.4)	46 (34.8)
Prior chronic GVHD treatment with ruxolitinib, n (%)	20 (30.3)	18 (27.3)	38 (28.8)
Refractory to the Last Systemic cGVHD Therapy prior to enrollment to study, n (%[a])	44/56 (78.6)	35/54 (64.8)	79/110 (71.8)
Severe chronic GVHD, n (%)	46 (69.7)	43 (65.2)	89 (67.4)

Category	Belumosudil		
	200 mg QD N = 66	**200 mg BID N = 66**	**Overall N = 132**
Median (range) Global Severity Rating	7 (0, 9)	7 (2, 10)	7 (0, 10)
Median (range) Lee Symptom Scale Score at baseline	26.8 (7.2, 56.3)	23.5 (7.7, 59.8)	25.7 (7.2, 59.8)
Concomitant systemic cGVHD therapies* on Study Day 1, n (%)	66 (100)	66 (100)	132 (100)
Corticosteroids alone	18 (27.3)	24 (36.4)	42 (31.8)
Corticosteroids and other drugs	46 (69.7)	41 (62.1)	87 (65.9)
Corticosteroids + Tacrolimus +/- other	25 (37.9)	28 (42.4)	53 (40.2)
Corticosteroids + MMF +/- other	10 (15.2)	1 (1.5)	11 (8.3)
Corticosteroids + ECP +/- other	11 (16.7)	10 (15.2)	21 (15.9)
Corticosteroids + Sirolimus +/- other	14 (21.2)	14 (21.2)	28 (21.2)
mTOR inhibitor**			
Sirolimus alone	0	0	0
Sirolimus and other drugs	14 (21.2)	14 (21.2)	28 (21.2)
Everolimus alone	0	0	0
Everolimus and other drugs	0	0	0

Sources: FDA analysis.
* FDA Analysis results of NDA datasets for combination variations of concomitant medications.
** There was no subject who received mTOR inhibitor sirolimus alone. There was no subject who received other mTOR inhibitors such as Everolimus.
[a] Denominator excludes patients with unknown status
Abbreviations: QD, once daily; BID, twice daily; cGVHD = chronic graft versus host disease; ECP, extracorporeal photopheresis; MMF, mycophenolate mofetil; CNI, calcineurin inhibitor; MTX, methotrexate; mTORi, mammalian target of rapamycin (mTOR) inhibitor.

Table 35 shows the Applicant's additional analysis for baseline common concomitant medications for chronic GVHD therapy on Study Day 1 in Study KD025-213.

Table 35. Study KD025-213: Applicant's Analysis for Baseline Concomitant Medications

Category	Belumosudil		
	200 mg QD N = 66	**200 mg BID N = 66**	**Overall N = 132**
Median (range) Corticosteroid Dose at Baseline (PE mg/kg)[a]	0.19 (0.03, 0.95)	0.20 (0.03, 1.07)	
Concomitant chronic GVHD Therapy, n (%)	66 (100)	66 (100)	132 (100)
Corticosteroids alone	11 (16.7)	11 (16.7)	22 (16.7)
Only corticosteroids and GVHD prophylaxis	11 (16.7)	10 (15.2)	21 (15.9)
Corticosteroids, GVHD prophylaxis and GVHD treatment	55 (83.3)	55 (83.3)	110 (83.3)
Extracorporeal photopheresis	18 (27.3)	22 (23.3)	40 (30.3)
Other treatments [b]	51 (77.3)	52 (78.8)	103 (78.0)

Category	Belumosudil		
	200 mg QD N = 66	200 mg BID N = 66	Overall N = 132

Sources: Reproduced from the Table [adh7_t_1_1_b] in the Applicant's Response to Information Request submitted on 03/25/2020.
[a] Prednisone equivalents mg/kilogram/day
[b] Other treatments include systemic use of sirolimus, calcineurin inhibitor, imatinib, methotrexate, mycophenolate mofetil, FAM (fluticasone, azithromycin, montelukast), rituximab, ruxolitinib, ibrutinib.
Abbreviations: QD, once daily; BID, twice daily; cGVHD = chronic graft versus host disease.

However, FDA could not confirm the numbers provided by the Applicant in Table 35 above because of missing information for some medications, such as exactly which CNI was used in prophylaxis or concomitant treatment for chronic GVHD on Study Day 1.

Table 36 below shows the FDA's additional analysis for the common concomitant medications for chronic GVHD therapy on Study Day 1 in Study KD025-213.

Table 36. Study KD025-213: FDA's Analysis for Baseline Concomitant Medications

Category	Belumosudil		
	200 mg QD N = 66 or *N =65	200 mg BID N = 66	Overall N = 132
Median (range) Corticosteroid Dose at Baseline (PE mg/kg)[a]	0.19 (0.03, 0.95) *0.19 (0.03, 0.95)	0.20 (0.03, 1.07)	0.19 (0.03, 1.07)
Concomitant chronic GVHD Therapy, n (%)	66 (100) *65 (100)	66 (100)	132 (100)
Corticosteroids alone	18 (27.3) *17 (26.2)	25 (37.9)	43 (32.6)
Steroids and CNI	13 (19.7) *13 (20.0)	14 (21.2)	27 (20.5)
Steroids and ECP	5 (7.6) *5 (7.7)	4 (6.1)	9 (6.8)
Steroids and mTORi	10 (15.2) *10 (15.4)	8 (12.1)	18 (13.6)
Other/Multiple	20 (30.3) *20 (30.8)	15 (22.7)	43 (32.6)

Sources: FDA Analysis
*Subject KD025-213-(b) (6) (no active cGVHD documented at baseline) was excluded from the total number of patients (N=66) in the 200 mg QD group.
[a] Prednisone equivalents mg/kilogram/day.
Abbreviations: QD, once daily; BID, twice daily; cGVHD = chronic graft versus host disease; ECP, extracorporeal photopheresis; CNI, calcineurin inhibitor; mTORi, mammalian target of rapamycin (mTOR) inhibitor.

In the Study KD025-213, among 66 subjects who received Belumosudil 200 mg QD, one subject (KD025-213-(b) (6)) had no active cGVHD documented at baseline. Table 37 below shows additional demographics and baseline disease characteristics of 65 subjects who received Belumosudil 200 mg QD in Study KD025-213.

Table 37. Study KD025-213: Demographic and Baseline Disease Characteristics for the Evaluable Population

Category	Belumosudil 200 mg QD N = 66	Belumosudil 200 mg QD *N = 65
Age, Median, Years (minimum, maximum)	53 (21, 77)	*53 (21, 77)
Age ≥ 65 Years, n (%)	17 (25.8)	*17 (26.2)
Sex		
Male, n (%)	42 (63.6)	*42 (64.6)
Race, n (%)		
White	55 (83.3)	*54 (83.1)
Black	6 (9.1)	* 6 (9.2)
Other or Not Reported	5 (7.6)	*5 (7.7)
Median (range) time (months) from cGVHD diagnosis to enrollment	25.2 (1.9, 162.4)	*25.3 (1.9, 162.4)
Number of Organs Involved at Baseline		
≥ 4 Organs Involved, n (%)	**33** (**50.0**)	***31** (47.6)
Median (range) Number of Prior Lines of cGVHD Therapy	3 (2, 6)	*3 (2, 6)
Number of Prior Lines of Therapy, n (%)		
2	23 (34.8)	*23 (35.4)
3	13 (19.7)	*12 (18.5)
4	15 (22.7)	*15 (23.1)
5	14 (21.2)	*14 (21.5)
6	1 (1.5)	*1 (1.5)
Prior chronic GVHD treatment with ibrutinib, n (%)	22 (33.3)	*21 (32.3)
Prior chronic GVHD treatment with ruxolitinib, n (%)	20 (30.3)	*20 (30.8)
Refractory to the Last Systemic cGVHD Therapy prior to enrollment to study, n (%[a])	**44**/56 (**78.6**)	***43**/55 (**78.2**)
Severe chronic GVHD, n (%)	46 (69.7)	*46 (70.8)
Median (range) Global Severity Rating	7 (0, 9)	*7 (2, 9)
Median (range) Lee Symptom Scale Score at baseline	26.8 (7.2, 56.3)	*26.8 (7.2, 56.3)

Sources: FDA analysis.
*Subject KD025-213-(b) (6) (no active cGVHD documented at baseline) was excluded from the total number of patients (N=66) in the 200 mg QD group.
Abbreviations: QD, once daily; BID, twice daily; cGVHD, chronic graft versus host disease.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The Study KD025-213 has an exclusion criterion: "Subject had not been on a stable dose/regimen of systemic cGVHD treatments for at least 2 weeks prior to screening." FDA interprets this to mean that patients may have started a new GVHD therapy 2 weeks + 1 day prior to study start. Since the time to response for cGVHD is much longer than 2 weeks, that means some of the responses may have been due to a new therapy starting only slightly more than 2 weeks before the study.

FDA adjudicated concomitant medications that the patients taking on study day 1. Table 38 below shows the range of durations (started 56 days or less from study day 1) of those concomitant medications prior to study start.

Table 38. Study KD025-213: Durations of cGVHD Medications Prior to Study

Durations of Concomitant Medications for GVHD	Belumosudil		
	200 mg QD N = 66	200 mg BID N = 66	Overall N = 132
24-28 days prior to study start date, n (%)	1 (1.5)	3 (4.5)	4 (3.0)
29-56 days prior to study start date, n (%)	5 (7.6)	1 (1.5)	6 (4.5)

Table 39 below shows the details of those concomitant medications (started 56 days or less from study day 1) prior to study start.

Table 39. Study KD025-213: cGVHD Medications Started 24-56 Days Prior to Study

USUBJID	Treatment	Start Prior to Study	Belumosudil Arm
KD025-213 (b) (6)	Sirolimus	-55	KD025 200 mg QD
KD025-213	Sirolimus	-50	KD025 200 mg QD
KD025-213	Tacromilus	-50	KD025 200 mg QD
KD025-213	Sirolimus	-41	KD025 200 mg QD
KD025-213	ECP	-30	KD025 200 mg QD
KD025-213	Mycophenolate	-24	KD025 200 mg QD
KD025-213	ECP	-51	KD025 200 mg BID
KD025-213	ECP	-28	KD025 200 mg BID
KD025-213	Sirolimus	-27	KD025 200 mg BID
KD025-213	Sirolimus	-26	KD025 200 mg BID

Table 40 shows the dose-intensity by cycle for each arm in Study KD025-213 as reported by the Applicant.

Table 40. Study KD025-213: Dose Intensity by Cycle

	200 mg QD N = 66				200 mg BID N = 66			
		Dose intensity category				Dose intensity category		
Cycle	N*	< 80% n (%)	80-100% n (%)	>100% n (%)	N*	< 80% n (%)	80-100% n (%)	>100% n (%)
1	66	2 (3.0%)	63 (95.5%)	1 (1.5%)	66	1 (1.5%)	65 (98.5%)	0
2	64	5 (7.8%)	59 (92.2%)	0	63	3 (4.8%)	60 (95.2%)	0
3	61	5 (8.2%)	56 (91.8%)	0	57	3 (5.3%)	54 (94.7%)	0
4	52	3 (5.8%)	49 (94.2%)	0	52	5 (9.6%)	47 (90.4%)	0
5	47	2 (4.3%)	45 (95.7%)	0	49	3 (6.1%)	46 (93.9%)	0
6	43	5 (11.6%)	38 (88.4%)	0	44	1 (2.3%)	43 (97.7%)	0
7	41	7 (17.1%)	34 (82.9%)	0	41	1 (2.4%)	40 (97.6%)	0
8	36	3 (8.3%)	32 (88.9%)	1 (2.8%)	36	1 (2.8%)	35 (97.2%)	0
9	27	3 (11.1%)	24 (88.9%)	0	26	0	26 (100.0%)	0
10	22	2 (9.1%)	20 (90.9%)	0	23	0	23 (100.0%)	0
11	17	3 (17.6%)	14 (82.4%)	0	18	1 (5.6%)	17 (94.4%)	0
12	10	2 (20.0%)	8 (80.0%)	0	15	0	15 (100.0%)	0

Source: Applicant's Table 4.1.1.1 (213) in 9/11/2020 response to an Information Request

Table 41 shows the salvage therapies administered after start of study treatment.

Table 41. Study KD025-213: Salvage Therapies

Treatment	Belumosudil	
	200 mg QD N = 66	200 mg BID N = 66
ECP	4 6%	7 11%
Ibrutinib	4 6%	5 8%
Steroids	4 6%	4 6%
Sirolimus	3 5%	1 2%
Rituximab	2 3%	3 5%
Investigational	1 2%	0 0%
Itacitinib	1 2%	1 2%
Methotrexate	1 2%	0 0%
Mycophenolate	0 0%	1 2%

Source: FDA analysis

Efficacy Results – Primary Endpoint

The FDA acknowledges the Applicant's assessment of overall response rate (ORR) in the section above. FDA assessed the ORR occurring through Cycle 7 Day 1 (see discussion in Section 8.2.1). Table 42 shows response by dose group. ORR in 200 mg QD group is 49/65, 75% (95% CI: 63%, 85%).

Table 42. Study KD025-213: ORR by Cycle 7 Day 1 per FDA Adjudication by Dose Group

Response	Belumosudil	
	200 mg QD N=65	200 mg BID N=66
ORR[1]	49/65, 75% (63,85)	46/66, 70% (57,80)
CR	4/65, 6% (2,15)	1/66, 2% (0,8)
PR	45/65, 69% (57,80)	45/66, 68% (56,79)

[1] Responders/N, % (95% Confidence Interval, estimated using the Clopper-Pearson method)
Source: Reviewer's analysis.

Efficacy Results – Secondary and Other Relevant Endpoints

For responses that began through Cycle 7 Day 1, Table 43 shows duration of response: time from response to any organ progression from the last assessment, new systemic therapy, or death, whichever occurs first. The median time to first response in the responders was 1.8 months (95% CI: 1.0, 1.9). Median duration of response is 1.9 (95% CI: 1.2, 2.9) months in 200 mg QD group.

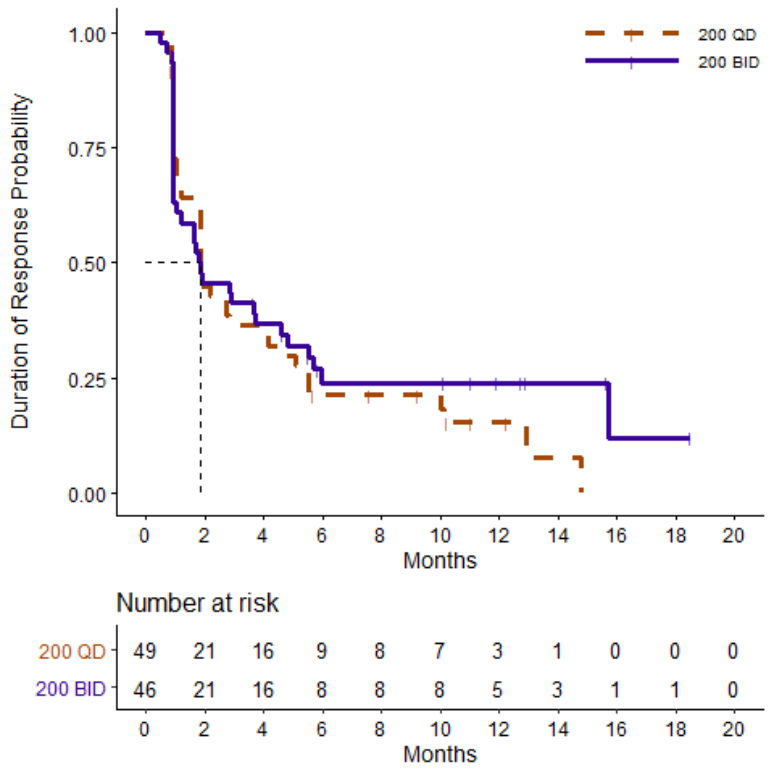
Table 43. Study KD025-213: Duration of Response per FDA Adjudication

	Belumosudil	
	200 mg QD	200 mg BID
	N=49	N=46
Events, n (%)	41 (84%)	35 (76%)
Median, months (95% CI)[1]	1.9 (1.2, 2.9)	1.8 (1.0, 4.6)

[1]Median as estimated per Kaplan-Meier methodology, confidence interval estimated using the Brookmeyer and Crowley method.
Source: Reviewer's analysis.

Figure 10 shows the Kaplan-Meier plot for duration of response for responses that began through Cycle 7 Day 1.

Figure 10. Study KD025-213: Kaplan Meier Plot of Duration of Response per FDA Adjudication



Source: Reviewer's analysis.

Alternative Measure of Durability

For responses that began through Cycle 7 Day 1, Table 44 shows durability of response by dose group: time from response to new systemic therapy or death, whichever occurs first. Median durability of response is non-estimable in the 200 mg QD group. Durability of response was longer than six months in 79% (95% CI: 64%, 88%) and longer than 12 months in 62% (95% CI: 46%, 74%) of patients in the 200 mg QD group. Figure 11 shows the Kaplan-Meier plot for the durability of response Kaplan-Meier plot.

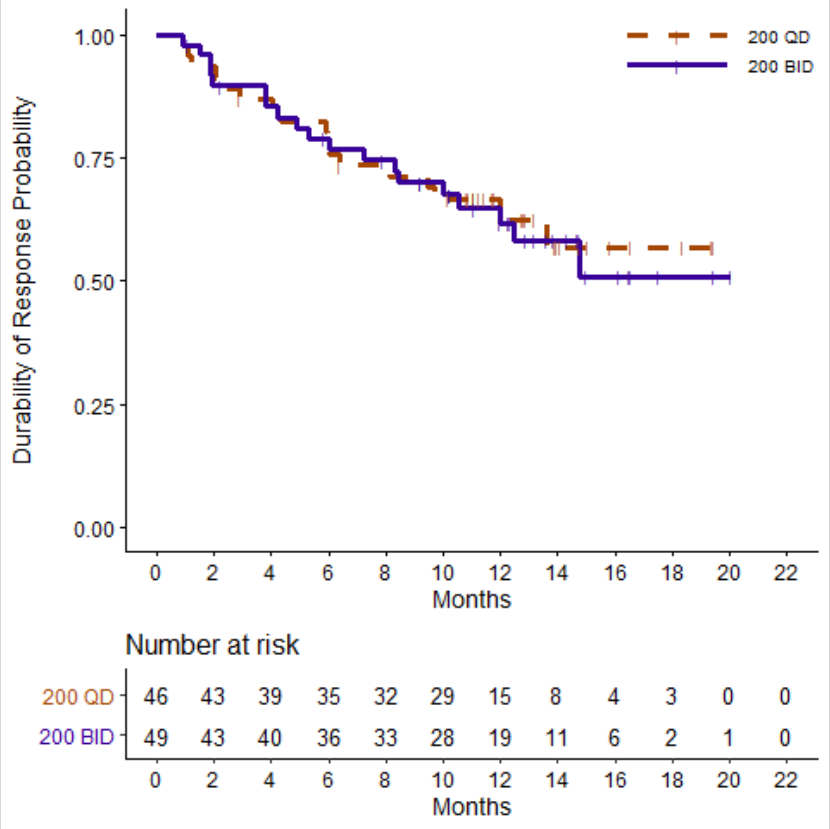
Reviewer's Comment: Since median durability of response was not reached, percentage of patients without an event is reported for 6- and 12-month timepoints, as these milestones provide context when the median has not been reached. The description should not be misinterpreted as a measure of clinical benefit.

Table 44. Study KD025-213: Durability of Response per FDA Adjudication

	Belumosudil	
	200 mg QD	**200 mg BID**
	N=49	**N=46**
Events, n (%)	19 (39%)	17 (37%)
Median, months (95% CI)[1]	NE (10.5, NE)	NE (12.0, NE)

[1]Median as estimated per Kaplan-Meier methodology, confidence interval estimated using the Brookmeyer and Crowley method.
Source: Reviewer's analysis.

Figure 11. Study KD025-213: Kaplan Meier Plot of Durability of Response per FDA Adjudication



Source: Reviewer's analysis.

Subpopulations

Table 45 shows ORR by subgroup. Study KD025-213 was not designed to compare subgroups and does not contain sufficient information on patients in each treatment group to determine if subgroup outcomes differ.

Table 45. Study KD025-213: ORR per FDA Adjudication by Subgroup

Variable	Group	Belumosudil	
		200 mg BID	200 mg QD
Age	< 65 years	32/46, 70% (54,82)	40/48, 83% (70,93)
	>= 65 years	14/20, 70% (46,88)	9/17, 53% (28,77)
Sex	Female	23/33, 70% (51,84)	17/23, 74% (52,90)
	Male	23/33, 70% (51,84)	32/42, 76% (61,88)
Race	American Indian or Alaska Native	2/2, 100% (16,100)	NA
	Black or African-American	0/1, 0% (0,98)	6/6, 100% (54,100)
	Chinese	1/1, 100% (3,100)	NA
	Other Asian	1/1, 100% (3,100)	NA
	Unknown	4/4, 100% (40,100)	3/4, 75% (19,99)
	White	38/57, 67% (53,79)	40/54, 74% (60,85)
	Asian Indian	NA	0/1, 0% (0,98)
Number of Lines of prior therapy	2	9/14, 64% (35,87)	16/23, 70% (47,87)
	3	13/17, 76% (50,93)	11/12, 92(% 62,100)
	4	9/14, 64% (35,87)	12/15, 80% (52,96)
	5	13/19, 68% (43,87)	9/14, 64% (35,87)
	6	2/2, 100% (16,100)	1/1, 100% (3,100)
Prior ibrutinib	No	30/42, 71% (55,84)	32/44, 73% (57,85)
	Yes	16/24, 67% (45,84)	17/21, 81% (58,95)
Prior ruxolitinib	No	32/48, 67% (52,80)	36/45, 80% (65,90)
	Yes	14/18, 78% (52,94)	13/20, 65% (41,85)
Best response to the last prior cGVHD treatment	Complete Response	0/1, 0% (0,98)	NA
	Partial Response	11/18, 61% (36,83)	9/12, 75% (43,95)
	Progressive Disease	15/17, 88% (64,99)	16/17, 94% (71,100)
	Stable Disease	11/18, 61% (36,83)	16/26, 62% (41,80)
	Unknown	9/12, 75% (43,95)	8/10, 80% (44,97)
Time from cGVHD diagnosis to enrollment (months)	<= 28	21/29, 72% (53,87)	31/35, 89% (73,97)
	> 28	25/37, 68% (50,82)	18/30, 60% (41,77)
Severe cGVHD at screening	No	17/23, 74% (52,90)	14/19, 74% (49,91)
	Yes	29/43, 67% (51,81)	35/46, 76% (61,87)
Baseline corticosteroid dose level (PE mg/kg/day)	<= 0.19	23/33, 70% (51,84)	21/32, 66% (47,81)
	> 0.19	23/33, 70% (51,84)	28/33, 85% (68, 95)
Takes proton pump inhibitor medication	No	26/34, 76% (59,89)	22/33, 67% (48,82)
	Yes	20/32, 62% (44,79)	27/32, 84% (67,95)
Number of organs involved at baseline	<= 4	36/47, 77% (62,88)	32/43, 74% (59,86)
	> 4	10/19, 53% (29,76)	17/22, 77% (55,92)
Lung involvement at baseline	No	31/43, 72% (56,85)	33/41, 80% (65,91)
	Yes	15/23, 65% (43,84)	16/24, 67% (45,84)

Variable	Group	Belumosudil	
		200 mg BID	200 mg QD
Baseline GFR ($mL/min/1.72m^2$)	GFR >=9 0	14/21, 67% (43,85)	18/23, 78% (56,93)
	60 <= GFR < 90	23/29, 79% (60,92)	24/30, 80% (61,92)
	GFR < 60	9/16, 56% (30,80)	7/12, 58% (28,85)

Responders/N, % (95% Confidence Interval, estimated using the Clopper-Pearson method)
Source: Reviewer's analysis.

Reviewer's Comment: Study KD025-213 was not designed to assess differential ORR in any particular subgroup, the results presented above should be regarded as exploratory only.

Efficacy Results – Exploratory and COA (PRO) Endpoints

"Lee cGVHD Symptom Scale will be assessed on Day 1 of Cycles 2-5, then on Day 1 of every other Cycle thereafter and EOT. The questionnaire consists 30 items of 7 domains: skin, eyes and mouth, breathing, eating and digestion, muscles and joints, energy, and mental and emotional. Each question is scored 0, 1, 2, 3 or 4. A domain score will be calculated for each domain by taking the mean of all items completed if more than 50% were answered and normalizing to a 0 to 100 scale. A summary score will be calculated as average of all nonmissing domain scores if more than 50% of them are nonmissing. A higher score indicated more bothersome symptoms. 7 points difference on the summary score of cGVHD symptom scale was found to be clinically meaningful." Source: Statistical Analysis Plan v1.0, p19

The period for calculating 7-point change from baseline was from Cycle 1, Day 1 through Cycle 7, Day 1 or initiation of new systemic therapy, whichever occurred first. Table 46 shows reporting compliance.

Table 46. Study KD025-213: Lee cGVHD Symptom Scale Compliance

Visit	Compliance
CYCLE 1, DAY 1	124 / 131, 95%
CYCLE 2, DAY 1	121 / 127, 95%
CYCLE 3, DAY 1	117 / 118, 99%
CYCLE 4, DAY 1	102 / 103, 99%
CYCLE 5, DAY 1	93 / 95, 98%
CYCLE 7, DAY 1	81 / 84, 96%
END OF TREATMENT	60 / 79, 76%
UNSCHEDULED	35 / 35, 100%

Source: Reviewer's analysis.

At least a 7-point decrease in the Lee Symptom Scale summary score through Cycle 7 Day 1 was reported by 52% (95% CI: 40, 65) of the patients in the 200 mg QD group.

Reviewer's comment: Study KD025-213 was an open-label study. Patient-reported outcomes in open-label studies may be impacted by patient's knowledge of the treatment received. Moreover, no placebo group was present in the study to assess any potential advantage in patient-reported outcomes. Results of this exploratory analysis should be interpreted with caution.

Additional Analyses Conducted on the Individual Trial

Supplementary Analysis Excluding Site 098

Protocol violations were identified for study site 098 (See Section 4.1). Table 47 shows ORR excluding site 098.

Table 47. Study KD025-213: ORR Excluding Study Site 098 per FDA Adjudication

		Belumosudil	
		200 mg QD	200 mg BID
Response		N=59	N=63
ORR[1]		44/59, 75% (62,85)	44/63, 70% (57,81)
	CR	3/59, 5% (1,14)	1/63, 2% (0,9)
	PR	41/59, 69% (56,81)	43/63, 68% (55,79)

[1]Responders/N, % (95% Confidence Interval, estimated using the Clopper-Pearson method)
Source: Reviewer's analysis.

Biomarkers

The Applicant provided no analyses of biomarkers in Study KD025-213.

8.2 Integrated Review of Effectiveness

8.2.1 Assessment of Efficacy Across Trials

APPLICANT'S POSITION

Methods

The Applicant's Position:

This section presents integrated data from the two Phase 2 studies, KD025-208 and KD025-213 with all belumosudil dose groups (200 mg QD, 200 mg BID, 400 mg QD, 200 mg QD/BID, and overall), in support of the efficacy of belumosudil in the treatment of patients with cGVHD after failure of at least 1 prior line of systemic cGVHD therapy. Brief details of the integrated analyses are summarized below; full details are in the SAP for the Integrated Summary of Effectiveness (ISE).

The data cutoff dates for CSR KD025-208 and CSR KD025-213 are the same as the data cutoff date for the ISE, 19 February 2020. However, the dates of data extract may differ for the clinical study reports (CSRs) and the ISE. While all data for events up to and including the cutoff date are included in analysis, ISE data were extracted at a later timepoint and may not exactly match data presented in the individual CSRs. Differences, if present, are expected to be minimal.

The primary population for efficacy analysis is the mITT population, defined as all subjects who received at least 1 dose of study medication. The mITT population was used for all integrated efficacy analyses.

In addition, the following populations were used for subgroup analyses:

- Responder: The responder population was defined as subjects in the mITT population that achieved a PR or CR at any post-baseline response assessment.
- Nonresponder: The nonresponder population was comprised of subjects in mITT population who were not responders.

The primary efficacy endpoint of Study KD025-208 and Study KD025-213 study is the ORR, with response status as assessed by investigators based on the 2014 NIH Consensus Development Project on Clinical Trials in cGVHD.

The ORR is defined as the proportion of subjects with a best response meeting the overall response criteria assessment of CR or PR at any post-baseline response assessment.

Primary Endpoints

Data:

Best overall response and ORR for the mITT- Phase 2 analysis group (P2AG, which includes all subjects from Study KD025-208 and Study KD025 213) population are summarized in Table 48. The primary efficacy endpoint was met, as the null hypothesis of ORR ≤ 30% was rejected. For subjects in the 200 mg QD and BID groups, ORR was 71.1% (95% CI: 60.1, 80.5) and 72.0% (95% CI: 60.9, 81.3), respectively. Overall, ORR was 69.9% (95% CI: 62.8, 76.4). The lower bound of the 95% CIs for the 200 mg QD and BID groups and all subjects exceeded 60%.

Among subjects in the 200 mg QD group, best responses of CR and PR were achieved by 3 subjects (3.6%) and 56 subjects (67.5%), respectively.

Within 6 months of treatment, the ORR among subjects in the 200 mg QD and BID groups was 67.5% (95% CI: 56.3, 77.4) and 69.5% (95% CI: 58.4, 79.2), respectively. Overall, ORR was 66.1% (95% CI: 58.8, 72.9). The lower bound of the 95% CIs for the 200 mg QD and BID groups and all subjects exceeded 55%. Best responses of CR and PR with belumosudil 200 mg QD were achieved within 6 months of treatment by 2 subjects (2.4%) and 54 subjects (65.1%), respectively.

Table 48 Best Overall Response on Treatment and Best Overall Response within 6 Months of Treatment – mITT Population, Phase 2 Analysis Group

	Belumosudil				
Variable	**200 mg QD N = 83**	**200 mg BID N = 82**	**Combined 200 mg N = 165**	**400 mg QD N = 21**	**Overall N = 186**
Best overall response on treatment					
ORR (CR or PR), n (%)	59 (71.1)	59 (72.0)	118 (71.5)	12 (57.1)	130 (69.9)
95% CI of ORR[a]	(60.1, 80.5)	(60.9, 81.3)	(64.0, 78.3)	(34.0, 78.2)	(62.8, 76.4)
One-sided p-value[b]	<0.0001	<0.0001	<0.0001	0.0087	<0.0001
Best overall response					
Complete response	3 (3.6)	1 (1.2)	4 (2.4)	0	4 (2.2)
Partial response	56 (67.5)	58 (70.7)	114 (69.1)	12 (57.1)	126 (67.7)
Lack of response					
Unchanged	16 (19.3)	13 (15.9)	29 (17.6)	4 (19.0)	33 (17.7)
Mixed	3 (3.6)	4 (4.9)	7 (4.2)	0	7 (3.8)
Progression	2 (2.4)	2 (2.4)	4 (2.4)	1 (4.8)	5 (2.7)
No response assessment	3 (3.6)	4 (4.9)	7 (4.2)	4 (19.0)	11 (5.9)
Overall response rate within 6 months of treatment					
ORR (CR or PR), n (%)	56 (67.5)	57 (69.5)	113 (68.5)	10 (47.6)	123 (66.1)
CR	2 (2.4)	1 (1.2)	3 (1.8)	0	3 (1.6)
PR	54 (65.1)	56 (68.3)	110 (66.7)	10 (47.6)	120 (64.5)
95% CI of ORR[a]	(56.3, 77.4)	(58.4, 79.2)	(60.8, 75.5)	(25.7, 70.2)	(58.8, 72.9)
One-sided p-value[b]	<0.0001	<0.0001	<0.0001	0.0676	<0.0001

Abbreviations: BID = twice daily; CI = confidence interval; CR = complete response; mITT = modified intent-to-treat; ORR = overall response rate; PR = partial response; QD = once daily.
Note: Response assessments performed on or after initiation of new systemic therapy for cGVHD are excluded from the analysis.
[a]95% CI and p-value are calculated using Clopper-Pearson exact method.
[b]Null hypothesis: ORR ≤ 30%).
Source: ISE Table 3.1.1A1 and Table 3.1.2A1.

The Applicant's Position:

As assessed by best overall response and ORR, belumosudil demonstrated clinically meaningful activity and a treatment effect at all dose levels evaluated.

Secondary and Other Endpoints

Data:

Duration of Response

Primary/Secondary DOR

Kaplan-Meier and landmark statistics for primary and secondary DOR in the responder-P2AG population are summarized in Table 48.

The primary and the secondary methods of analysis are similar, but the primary method counts deterioration from best response (e.g., a CR to PR) as a loss of response, while the secondary method requires loss of response. As there are a limited number of CRs, the differences between the 2 methods of analysis are minimal.

Median primary/secondary DOR among subjects in the 200 mg QD group was 24.1 weeks (95% CI: 11.4, not reached [NR]). There were 59 subjects (responders) in the analysis of DOR. In the 200 mg QD group, 31 subjects had an event and 28 were censored. The Kaplan-Meier estimates of DOR at 12 and 24 weeks were 64% and 50%, respectively, for the 200 mg QD group. At the time of the data cutoff, 34 subjects (57.6%) in the 200 mg QD group had a sustained response to treatment of 12 weeks or longer and 22 subjects (37.3%) had a sustained response to treatment of 24 weeks or longer.

Quaternary DOR

Kaplan-Meier and landmark analyses of quaternary DOR enabled summation of multiple response episodes for a given subject and reflect the waxing and waning nature of cGVHD.

In the responder-P2AG population, median quaternary DOR was not reached among subjects in the 200 mg QD group as 38 subjects (64.4%) were still in response as of the data cutoff.

Kaplan-Meier estimates of quaternary DOR at 12 and 24 weeks was 71% and 64%, respectively, in the 200 mg QD group. At the time of the data cutoff, 37 subjects (62.7%) in the 200 mg QD group had a sustained response to treatment of 12 weeks or longer and 26 subjects (44.1%) had a sustained response to treatment of 24 weeks or longer.

Tertiary DOR

Tertiary DOR was defined as the time from first documentation of response to the time of initiation of new systemic cGVHD therapy (i.e., TTNT), which is clinically important because it reflects patient management.

Kaplan-Meier and landmark statistics showed median tertiary DOR was not reached among subjects in the 200 mg QD group as 47 subjects (79.7%) had not initiated new systemic therapy for cGVHD as of the data cutoff. Of the 47 subjects, 44 (74.6%) were still on study and 3 (5.1%) were lost to follow up.

Kaplan-Meier estimates of tertiary DOR at 12 and 24 weeks were 89% and 83%, respectively, in the 200 mg QD group. At the time of the data cutoff, 48 subjects (81.4%) and 39 subjects (66.1%) in the 200 mg QD group had a sustained response to treatment of 12 and 24 weeks or longer, respectively.

Duration of Response Across Methodologies

Several measures of durability of response provide interesting perspectives on the impact of belumosudil on the course of cGVHD.

A comparison of Kaplan-Meier and landmark statistics for primary/secondary, quaternary, and tertiary DOR for the responder-P2AG population is summarized in Table 49. The methods for calculating DOR each provide different perspectives on the impact of belumosudil on the course of cGVHD and therefore produce notably different results. Median primary DOR is 22.1 weeks (overall), indicating this as the time from first documentation of response to time of first deterioration of best response. Median quaternary DOR, which accounts for the waxing and waning nature of cGVHD, is 52.3 weeks (overall), revealing the time from first documentation of response to the time of first documentation of lack of response but with durations summed for multiple response/lack of response episodes. Among all subjects, median tertiary DOR was not reached as 95 subjects (73.1%) had not initiated a new systemic cGVHD therapy.

Table 49 Kaplan-Meier and Landmark Statistics for Primary/Secondary, Quaternary, and Tertiary Duration of Response – Responder Population, Phase 2 Analysis Group

	Belumosudil					
	Primary/Secondary		Quaternary		Tertiary	
Variable	200 mg QD N=59	Overall N = 130	200 mg QD N=59	Overall N = 130	200 mg QD N=59	Overall N = 130
Duration of response, n (%)						
Censored	28 (47.5)	56 (43.1)	38 (64.4)	79 (60.8)	47 (79.7)	95 (73.1)
Still on treatment/study	21 (35.6)	42 (32.3)	28 (47.5)	58 (44.6)	44 (74.6)	90 (69.2)
End of treatment/study	7 (11.9)	14 (10.8)	10 (16.9)	21 (16.2)	3 (5.1)	5 (3.8)
Event: deterioration from best response/ documentation of LR	26 (44.1)	64 (49.2)	15 (25.4)	38 (29.2)	–	–
Event: new treatment[a]	5 (8.5)	10 (7.7)	6 (10.2)	13 (10.0)	11 (18.6)	32 (24.6)
Event: death	–	–	–	–	1 (1.7)	3 (2.3)

Kaplan-Meier estimate (weeks)						
25th, 75th percentiles	8.1, NR	8.1, 76.3	8.6, NR	12.4, NR	40.0, NR	35.1, NR
Median (95% CI)	24.1 (11.4, NR)	22.1 (16.1, 40.0)	NR (22.14, NR)	52.3 (35.14, NR)	NR (NR, NR)	NR (58.9, NR)
Kaplan-Meier estimate of duration of response (95% CI)						
12 weeks	0.64 (0.50, 0.75)	0.64 (0.55, 0.72)	0.71 (0.57, 0.81)	0.77 (0.69, 0.84)	0.89 (0.78, 0.95)	0.90 (0.84, 0.94)
24 weeks	0.50 (0.36, 0.63)	0.49 (0.40, 0.58)	0.64 (0.50, 0.76)	0.62 (0.52, 0.70)	0.83 (0.70, 0.91)	0.81 (0.73, 0.87)
36 weeks	0.45 (0.31, 0.58)	0.43 (0.33, 0.52)	0.62 (0.47, 0.73)	0.59 (0.49, 0.68)	0.77 (0.61, 0.87)	0.73 (0.62, 0.81)
48 weeks	0.39 (0.24, 0.55)	0.36 (0.25, 0.46)	0.56 (0.39, 0.70)	0.54 (0.43, 0.64)	0.72 (0.55, 0.84)	0.67 (0.55, 0.76)
Number of subjects with sustained response[b], n (%)						
≥ 12 weeks	34 (57.6)	77 (59.2)	37 (62.7)	91 (70.0)	48 (81.4)	110 (84.6)
≥ 24 weeks	22 (37.3)	45 (34.6)	26 (44.1)	53 (40.8)	39 (66.1)	82 (63.1)
≥ 36 weeks	11 (18.6)	25 (19.2)	15 (25.4)	31 (23.8)	22 (37.3)	48 (36.9)
≥ 48 weeks	4 (6.8)	12 (9.2)	6 (10.2)	17 (13.1)	12 (20.3)	26 (20.0)

Abbreviations: BID = twice daily; CI = confidence interval; NR = not reached; QD = once daily.
Note: CI is calculated using the Kaplan-Meier method.
[a]New systemic chronic graft versus host disease treatment is considered loss of response if occurring within 2 cycles (56 days) after last assessment.
[b]Number and percentage are based on using landmark analysis without adjustment for censoring. Primary, secondary, and quaternary were censored by last assessment. Tertiary was censored by last assessment or long-term follow up, whichever was latest.
Source: ISE Tables 3.3.1A1, 3.3.2A1, 3.3.3A1, and 3.3.4A1.

Time to Response

Median TTR in the responder-P2AG population was 7.9 weeks (range, 3.7-40.6) among subjects in the 200 mg QD group. By 10 weeks, 50 subjects (84.7%) in the 200 mg QD group had achieved a response.

A median TTR of approximately 8 weeks is a rapid response. It is notable, that 3 subjects in the 200 mg QD group and 10 subjects overall had late responses, occurring after 24 weeks of treatment. Rapid responses are known to occur most frequently in inflammatory disease while response is expected to take longer with more advanced disease manifestations disease.

Response by Organ System

The integrated analysis of best response by individual organ system and baseline organ severity score for the mITT-P2AG population showed that among subjects in the 200 mg QD group, responses (including CR) were achieved across all organ systems and in GSR.

Responses to treatment were generally rapid, occurring during the first 8 weeks. Late responses tend to reflect response in organ systems with more fibrotic involvement, as advanced/severe disease requires sustained therapy to achieve a response. Subjects in the 200 mg QD group had a median TTR of approximately 8 weeks or shorter in the skin, eyes, mouth, esophagus, upper GI, lower GI, liver, and joints and fascia.

Median GSR TTR was 12.0 weeks in 35 subjects in the 200 mg QD group.

Late organ system responses occurring after more than 24 weeks of treatment in the 200 mg QD group were observed, including 5 patients with responses in the eyes; 3 in the skin and joints and fascia; 2 in the mouth; and 1 each in the esophagus, lower GI, liver, and lungs. In the 200 mg QD group, 6 responses occurred after more than 24 weeks of treatment, according to GSR.

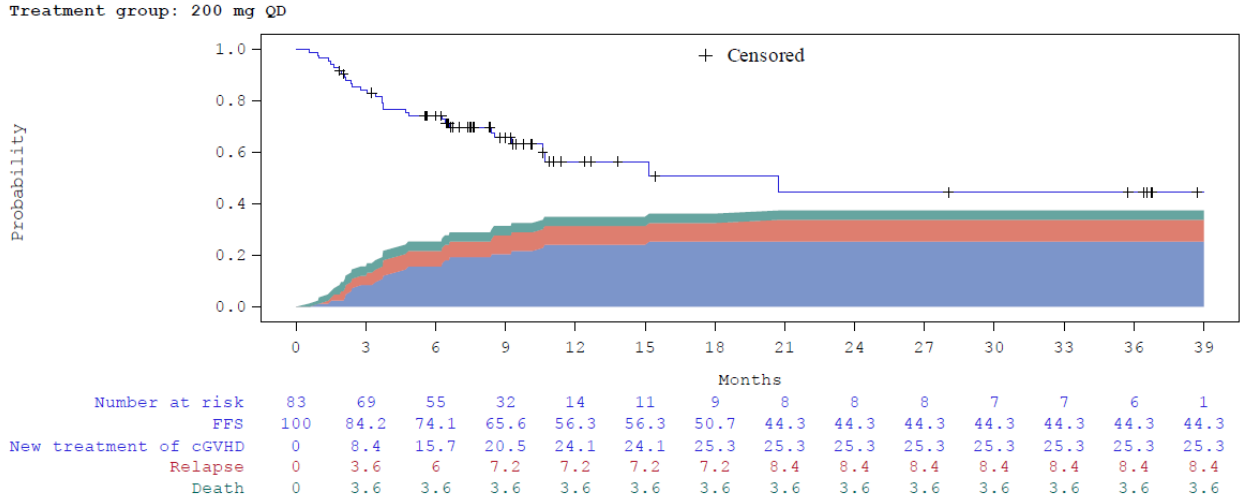
Lee Symptom Scale
On the LSS, which is a measure of cGVHD symptom burden, a 7-point reduction (7 PtR) increase from baseline is considered a clinically meaningful improvement. In the mITT-P2AG population, 45 subjects (54.2%) in the 200 mg QD group experienced a clinically meaningful improvement at least once. There were 31 subjects (37.3%) in the 200 mg QD group who experienced a clinically meaningful improvement on at least 2 consecutive assessments. The median duration of a 7-point reduction (DO7) PtR was 14.3 weeks (range, 0-120) in the 200 mg QD group. Thirty-six subjects (43.4%) in the 200 mg QD group had a DO7 PtR ≥ 8 weeks.

The LSS results were analyzed separately for responders and nonresponders. As assessed by LSS, 6 subjects (25.0%) in the 200 mg QD group experienced clinically meaningful improvement at least once. There were 4 subjects (16.7%) in the 200 mg QD group who experienced clinically meaningful improvement on at least 2 consecutive assessments. The median DO7-PtR was 12.4 weeks (range, 4-16). Four subjects (16.7%) in the 200 mg QD group had a DO7 PtR ≥ 8 weeks.

Failure-Free Survival
Figure 12 is a Kaplan-Meier plot for FFS for subjects receiving belumodusil 200 mg QD. Median FFS among subjects in the mITT-P2AG population in the 200 mg QD group was 20.7 months (95% CI: 10.6, NR).

Among subjects in the 200 mg QD group, 52 subjects (62.7%) were censored; 48 subjects were ongoing on the study and 4 had discontinued from the study. Failure events were new systemic therapy for cGVHD (21 subjects, 25.3%), nonrelapse mortality (3 subjects, 3.6%), and recurrent malignancy (7 subjects, 8.4%). Failure-free survival at 6, 12, 18, and 24 months was 74%, 56%, 51%, and 44%, respectively, though it is notable the median duration of follow-up is approximately 8 months and a number of subjects were censored in the 6 to 12 month range.

Figure 12 Kaplan-Meier Plots for Failure-free Survival in the Belumosudil 200-mg QD Group – mITT Population, Phase 2 Analysis Group



Number at risk	83	69	55	32	14	11	9	8	8	8	7	7	6	1
FFS	100	84.2	74.1	65.6	56.3	56.3	50.7	44.3	44.3	44.3	44.3	44.3	44.3	44.3
New treatment of cGVHD	0	8.4	15.7	20.5	24.1	24.1	25.3	25.3	25.3	25.3	25.3	25.3	25.3	25.3
Relapse	0	3.6	6	7.2	7.2	7.2	7.2	8.4	8.4	8.4	8.4	8.4	8.4	8.4
Death	0	3.6	3.6	3.6	3.6	3.6	3.6	3.6	3.6	3.6	3.6	3.6	3.6	3.6

Abbreviations: cGVHD = chronic graft versus host disease; FFS = failure free survival; mITT = modified intent-to-treat; QD = once daily.
Note: The data cutoff date was 19 February 2020.
Source: ISE Figure 3.4A1.

Failure-free survival with CR/PR at 6 months was achieved in less than 42% of subjects (estimated 22%-42%) after first line treatment.

Time to Next Treatment

Median TTNT for subjects in the mITT-P2AG population in the 200 mg QD group was not reached (95% CI: 15.18, NR). Among subjects in the 200 mg QD group, 22 subjects (26.5%) received a new systemic therapy for cGVHD. At baseline, overall, over 20% of subjects had received prior treatment with ruxolitinib, while more than 25% had received prior treatment with ibrutinib. It is notable that Investigators elected to continue subjects—even those who had not received ruxolitinib or ibrutinib—on belumosudil, suggesting that Investigators saw some clinical benefit in continued belumosudil dosing despite other available options.

Overall Survival

For subjects in the mITT-P2AG population in the 200 mg QD group, median OS was not reached at the time of the data cutoff. Among subjects in the 200 mg QD group, 8 (9.6%) died; 75 subjects were censored, including 70 who were alive and 5 who were lost to follow-up.

The Applicant's Position

Secondary and exploratory endpoint analyses supported the primary analysis. Corticosteroid dose reductions and discontinuations were demonstrated among both responders and non-responders.

Subpopulations

Data:

Evaluation of ORR was performed for the following pre-specified subgroups: age group, gender, race, number of organs involved at baseline, severe cGVHD, number of prior lines of therapy, prior use of ibrutinib, prior use of ruxolitinib, refractory to prior line of cGVHD treatment, duration of cGVHD before enrollment, and baseline glomerular filtration rate (GFR).

Overall Response Rate

Among subjects in the 200 mg QD group, there were numerical differences in ORR in the subgroups analyses of age group and number of prior lines of therapy.

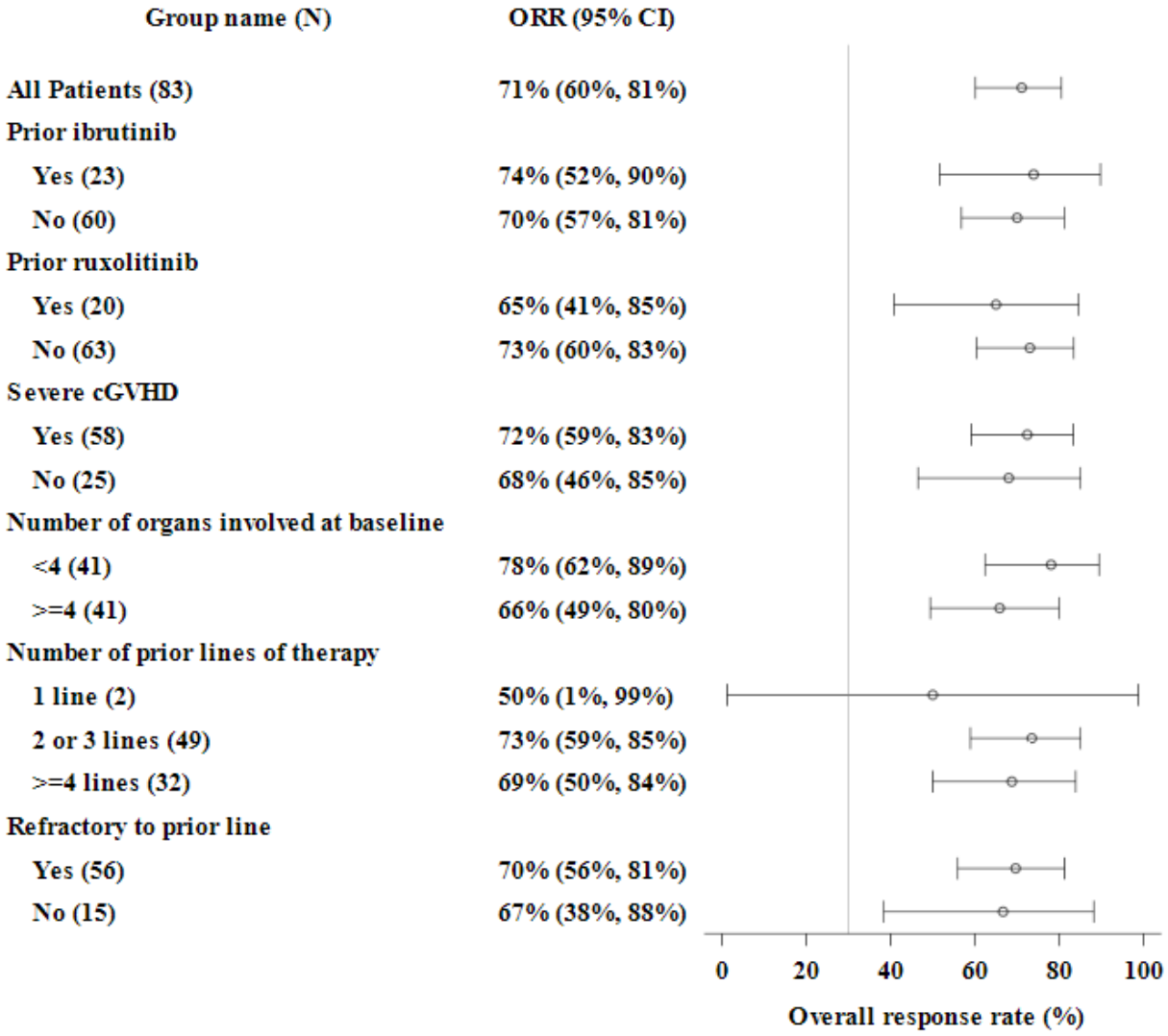
With respect to the subgroup analysis of age group, the ORR for subjects ≥ 65 years of age (N = 17) was 53% (95% CI: 28, 77). Although the lower bound of this CI crosses 30%, the point estimate is meaningful, and the CI is wide given the number of subjects. For subjects < 65 years of age (N = 66), ORR was 76% (95% CI: 64, 86).

With respect to the subgroup analysis of number of lines of prior therapy, robust responses were observed in subjects who had received < 4 and ≥ 4 lines of prior therapy. When pooled across number of lines (i.e., combining 1 line with 2 or 3 lines) and compared with subjects with ≥ 4 lines of prior therapy, no meaningful differences in ORR were observed with belumosudil. Pooled across all dose levels, the ORR in subjects who had 1 prior line of therapy (n=16) was 63% (95% CI: 35, 85). Subjects in the combined 200 mg QD and 200 mg BID group (n=9) had an ORR of 67% (95% CI: 30, 93).

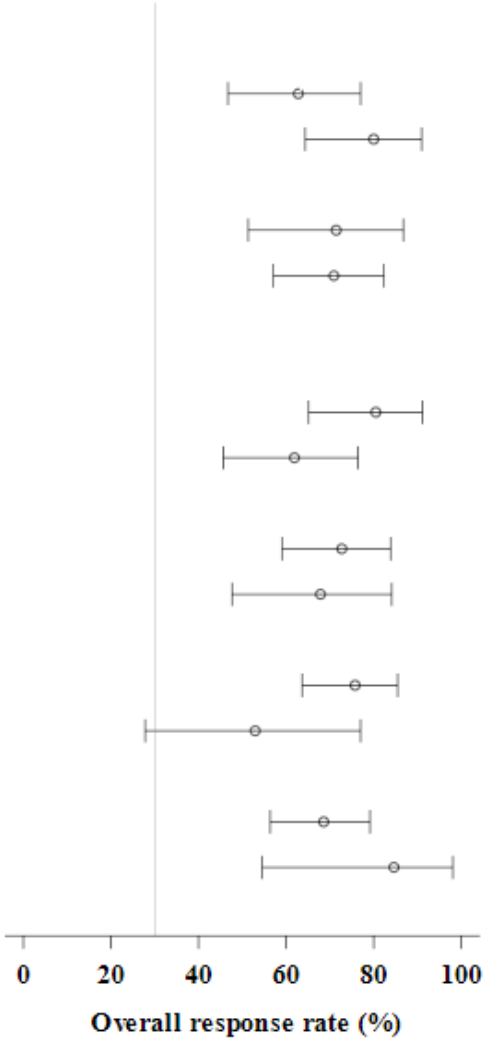
Among all subjects, there were no meaningful differences in ORR to belumosudil across subgroups based on age, gender, race, number of organs involved at baseline, severe cGVHD, prior use of ibrutinib, prior use of ruxolitinib, refractory to prior line of cGVHD treatment, duration of cGVHD before enrollment, and baseline GFR.

A forest plot of the ORR to treatment with belumosudil by subgroup for subjects in the 200 mg QD group (mITT-P2AG) is presented in Figure 13.

Figure 13 Forest Plot of Overall Response Rate by Subgroup – 200 mg QD dose, mITT Population, Phase 2 Analysis Group



Group name (N)	ORR (95% CI)
Duration of cGVHD before enrollment	
> 50th percentile (43)	63% (47%, 77%)
<= 50th percentile (40)	80% (64%, 91%)
Lung involvement at baseline	
Yes (28)	71% (51%, 87%)
No (55)	71% (57%, 82%)
Take concomitant medication proton pump inhibitor (PPI) on C1D1	
Yes (41)	80% (65%, 91%)
No (42)	62% (46%, 76%)
Gender	
Male (55)	73% (59%, 84%)
Female (28)	68% (48%, 84%)
Age	
<65 (66)	76% (64%, 85%)
>=65 (17)	53% (28%, 77%)
Race	
White (70)	69% (56%, 79%)
Non-white (13)	85% (55%, 98%)



Abbreviations: BID = twice daily; C1D1 = Cycle 1 Day 1; cGVHD = chronic graft versus host disease; mITT = modified intent-to-treat; QD = once daily.
Notes: CIs were calculated using the Clopper-Pearson interval (exact) method. The vertical bar references 30%, which was considered clinically meaningful in an unmet need population. The data cutoff date was 19 February 2020.
Source: ISE Figure 3.1A1.

The Applicant's Position:

Among subjects in the 200 mg QD group, there were significant differences in ORR in the subgroups analyses of age group and number of prior lines of therapy. As demonstrated by the forest plots, the 95% CIs for each comparison are inclusive of 30%, indicating statistically significant differences in ORR in these observed subgroups.

Dose/Dose Response

Data:

See the overall response rates by dosing groups in Table 48.

The Applicant's Position:

No dose response was observed. As assessed by best overall response and ORR, belumosudil demonstrated clinically meaningful activity and a treatment effect at all dose levels evaluated.

Durability of Response

The Applicant's Position:

Belumosudil induced durable responses in subjects with cGVHD. Based on results of Studies KD025-208 and KD025-213 in subjects who received belumosudil 200 mg QD, median DOR (primary) was 24.1 weeks (95% CI: 11.4, NA). No dose change was necessary to achieve durable responses.

Persistence of Effect

The Applicant's Position:

There are no known tolerance effects associated with belumosudil treatment.

Additional Efficacy Considerations

FDA'S POSITION

Methods

The Applicant proposed the indication "for the treatment of patients 12 years and older with chronic graft-versus-host disease (chronic GVHD) after failure of at least (b) (4) of systemic therapy".

Issues with the clinical development program: The clinical development program for cGVHD included two trials:

- Study KD025-213, a randomized dose-ranging trial of belumosudil for treatment of patients with cGVHD failing 2 - 5 prior lines of therapy, was the pivotal trial. The study was powered to exclude an ORR of 30% if the true ORR was 55% in each of two arms assessing different dosages.

- Study KD025-208, a single-arm dose-escalation trial of belumosudil for treatment of patients with cGVHD failing 1 - 3 prior lines of therapy, was supportive. The efficacy outcomes were planned to be reported descriptively.

A weakness in the program is that there is only one adequate and well-controlled trial, and it is a single-arm study. At the Initial Comprehensive Breakthrough Meeting on 5/1/2019, FDA indicated the, in general, for a single pivotal study to support an NDA, the trial should be well-designed, well-conducted, internally consistent and provide statistically persuasive efficacy findings such that a second trial would be ethically or practically impossible to perform. A major strength of the program is that the Applicant attended closely to dose optimization. Additionally, eligibility for the trials required failure of multiple prior lines of therapy; as ibrutinib is the only drug approved for treatment of cGVHD, a durable response in a refractory population would be considered beneficial. As such, FDA also indicated that data from Studies KD025-208 and KD025-213 together may be adequate.

Issues with the pivotal trial design: The primary efficacy endpoint for Study KD025-213 was ORR (CR or PR) per the 2014 NIH Consensus Development Project on Clinical Trials in cGVHD at anytime on study. FDA was in agreement with the use of the 2014 NIH consensus criteria, but indicated at the pre-NDA meeting on March 12, 2020, that ORR through Cycle 7 Day 1 (C7D1) would be considered the basis of efficacy, as the 6-month window allows sufficient time for development of a response without continuing a treatment that poses risks without efficacy. Table 50 shows a comparison of the elements of efficacy assessment as described in the Applicant's SAP in comparison to the advice provided by FDA prior to submission of the NDA.

Table 50. Study KD025-213: Applicant's SAP vs FDA's Assessment

	Applicant's SAP	FDA's Assessment
Primary endpoint	• ORR at any time on study	• ORR starting by C7D1
Analysis set	• All patients who received at least one dose of study drug	• All patients with active disease at baseline who received at least one dose of study drug
Adjudication	• Primary - Investigator • Additional - Algorithmic	• Algorithmic with manual adjudication for discrepancies with the Applicant's results
Definition - ORR	• 2014 NIH consensus criteria based on organ response criteria and clinician overall severity score	• 2014 NIH consensus criteria based on organ response criteria and occurring by C7D1
Definition - Duration of response (DOR)	• Time from first documentation of response to the time of first documentation of deterioration from best ORR, initiation of new systemic therapy for cGVHD, or death	• Interval from first response by C7D1 to progression in any organ, death, or new systemic therapies for chronic GVHD
Definition - Alternate measure of durability	• Time from first documentation of response to the time of initiation of new systemic cGVHD therapy or death	• Interval from first response by C7D1 to death or new systemic therapies for chronic GVHD
Definition - PRO response (using LSS)	• Summary score and domain scores by visit • Change from baseline by visit • Number and percent of subjects with a ≥7-point reduction from baseline • Number and percent of subjects with a ≥7-point reduction from baseline on 2 consecutive assessments	• ≥7-Point reduction from baseline by C7D1

Source: FDA analysis

Additionally, the Applicant utilized the Investigator's response for the primary analysis. FDA performed an algorithmic assessment of response using the raw data for the organ criteria with manual adjudication for discrepancies with the Applicant's results.

Patient Population

The demographics and baseline disease characteristics are outlined in the tables in Sections 8.1.1 and 8.1.2. The reviewers conclude that the study population was representative of the patients with cGVHD in practice as summarized in Section 2.1. Of note, one subject (KD025-213-(b) (6)) in Study KD025-213 had no active cGVHD documented at baseline and is excluded from FDA's final efficacy analysis set. Additionally, there were no patients in Study KD025-213 failing only one line of therapy, so the reviewers concluded that the accrued population did not support the Applicant's proposed broad intended population.

Primary Endpoint

The primary objective of Study KD025-213 was to evaluate efficacy as determined by achievement of ORR at any time on study. The results were to be assessed in each arm individually; the study was not powered to assess for differences in outcomes between arms. A sample size of 63 patients per arm was calculated to have 90% power with a 2-sided alpha 0.045 to exclude an ORR of 30% with a true ORR of 55%. An interim analysis was to occur when 126 patients completed 2 months on study, and the primary analysis was to occur when 126 patients completed 6 months on study. As described in Tables 24 and 25 of the Study KD025-213 Clinical Study Report, for both arms, the point estimates of the ORR were greater than 55% and the lower bound of the ORR 95% CI exceeded 30% at both the interim and primary analyses, so the study was considered positive per the Sponsor's statistical analysis plan.

FDA considers a CR or PR by C7D1 to be representative of a clinically meaningful response. The Applicant provided supplemental analyses for ORR by C7D1. Table 51 shows the Applicant's analysis of ORR by C7D1 from the primary analysis dataset and FDA's adjudicated ORR by C7D1 from the final analysis dataset for the 200 mg daily dosage arm in Study KD025-213 as well as the supporting data from Study KD025-208. The FDA-adjudicated ORR by C7D1 was 75% (95% CI: 63, 85) in the 200 mg daily arm in the pivotal trial, and the results from the supporting study were consistent.

Table 51. Belumosudil 200 mg Daily: Efficacy Outcomes Through C7D1

	Study KD025-213 Pivotal Study		Study KD025-208 Supporting Information	
	Applicant n=66	**FDA n=65**	**Applicant n=17**	**FDA n=17**
Response				
ORR by C7D1 (95% CI)	46 (70%) (57, 80)	49 (75%) (63, 85)	10 (59%) (33, 82)	10 (59%) (33, 82)
CR	2 (3%)	4 (6%)	0	0
PR	44 (67%)	45 (69%)	10 (59%)	10 (59%)
Persistence of Effect				
Median Duration of Response	21.1 weeks	1.9 months	40 weeks	5.6 months
Median Alternate Measure of Durability	NR	NR	NR	NR
PRO				
7-point LSS reduction by C7D1	34 (52%)	34 (52%)	-	6 (35%)

Source: Applicant's Tables 16 and 31, and Response to Information Request received 5/13/2021; otherwise, FDA reviewer's analyses
Abbreviations: NR, not reached.

Subpopulations

Tables 26 and 45 show FDA's subgroup analysis for ORR by C7D1 in Studies KD025-208 and KD025-213. The ORR results are consistent across subgroups defined by demographics, prior treatment, and baseline disease characteristics.

Persistence of Effect

Table 51 shows the median durations of response (DOR) as reported by the Applicant and as calculated by FDA. Note the differences is the definitions used for duration of response as described in Table 50 above. FDA calculated that the DOR was only 1.9 months (8 weeks) for the 49 responders in the pivotal trial. Although the median DOR is quite short, the definition of DOR does not take into account that cGVHD may flare and resolve without additional treatment. An additional measure of the durability of response would be the time to death or new systemic therapy. For the 49 responders, the median time to either death or new systemic therapy for cGVHD (new cGVHD drug or increase in steroids) was not reached, but no death or new systemic therapy initiation occurred in 62% (95% CI: 46, 74) of patients for at least 12 months since response. The reviewers considered the persistence of response to be clinically meaningful by this measure and recommend that both the classical DOR and the alternative measure of durability be displayed in the USPI, including the 12-month point-in-time outcome. This is not to suggest that 12-month duration of response is a clinical benefit, but rather it is to provide context to the durability when the median is not yet reached with the limited follow-up.

Secondary and Other Endpoints

A 7-point reduction in the LSS score is of clinical interest in patients undergoing treatment for cGVHD. Table 51 shows the FDA's analyses of the LSS score changes through C7D1 in Studies KD025-213 and KD025-208. FDA found that 34 (52%) patients reported a 7-point reduction in the LSS score. The reviewers acknowledge that this may be an overestimate due to the fact that the study was open-label, so the results may have been impacted by the patient's knowledge of the treatment received. In addition, the results are limited by the absence of a placebo control arm; it is unclear how much of the observed improvement is due to belumosudil alone and how much is due to the natural history of the disease.

Dose/Dose Response

Based on preliminary data from Study KD025-206 in patients with psoriasis, belumosudil was considered tolerable at doses up to 400 mg daily. In order to assess the impact of split dosing,

belumosudil doses of 200 mg once daily, 200 mg twice daily, and 400 mg daily were chosen for Study KD025-208, the dose-escalation trial in patients with cGVHD (Study KD025-208 Clinical Study Report Section 7.2).

As described in Section 8.1.1, all three dose levels of belumosudil tested in Study KD025-208 were active, so given the adequate efficacy and tolerability, the two lower doses were chosen for the dose-ranging study, Study KD025-213 (Study KD025-213 Clinical Study Report Section 9.4.4). As described in Section 8.1.2, the results of Study KD025-213 confirmed the activity of both the 200 mg daily and 200 mg twice daily dosages, and although the study was not powered to demonstrate a difference between arms, there did not appear to be a substantial difference in ORR through C7D1 (75% vs 70%, respectively). Thus, the review team finds the Applicant's recommended dosage of 200 mg daily to be acceptable from the perspective of efficacy.

Additional Efficacy Considerations

Biomarker Studies

As described in Section 8.1.1, cytokines and lymphocyte subsets were measured serially in Study KD025-208, but the small number of patients precluded credible assessments for a biomarker-response relationship. No immune biomarker data were submitted for Study KD025-213. Additionally, no biomarker data for disease activity/tissue injury were submitted. Therefore, there are no biomarker data to provide supporting evidence of the activity of belumosudil in cGVHD.

Evidence of Clinical Activity in Other Diseases

There are no randomized controlled trials in any disease that demonstrated a clinical benefit following treatment with KD025. Among the clinical trials listed in Table 12, there were two randomized Phase 2 trials:

- Study KD025-207 is a randomized, Phase 2, open-label, multicenter study to evaluate the safety, tolerability, and activity of KD025 400 mg daily in comparison to best supportive care in patients with idiopathic pulmonary fibrosis (IPF). The study was reported as on-going at the time of submission of this NDA, and no results were available.

- Study KD025-211 is a Phase 2, randomized, double-blind, placebo-controlled, dose-finding study to evaluate the safety, tolerability, and efficacy of belumosudil in adults with moderate to severe chronic plaque psoriasis. The primary objective was to assess the number of subjects that reach a 75% reduction in the Psoriasis Area and Severity Index

(PASI 75) after 16 weeks of treatment. Patients were randomized equally across placebo or belumosudil 200 mg daily, 200 mg twice daily, 400 mg daily or 400 mg q AM/ 200 mg q PM.

(b) (4)

Thus, at the present time, there is no evidence that belumosudil is active in any other disorder.

Extrapolation to Pediatric Patients

No data on the use of belumosudil in children were submitted in this application. As described the Section 2.1, the pathogenesis and natural history of cGVHD are the same in pediatric and adult patients. Additionally, the approach to treatment as described in Section 2.2 is similar for pediatric and adult patients. Therefore, the reviewers conclude that given the biological comparability of the disease across the age range, it would be reasonable to extrapolate efficacy from the adequate and well-controlled study in adults to pediatric patients if exposure can be matched. Based on the pharmacometric analysis, there were no clinically significant differences in belumosudil pharmacokinetics with regard to weight over the range of 38.6 to 143 kg (Appendix 16.4), so exposure would be adequate for patients within the weight range of the adults accrued to these trials. By contrast, there are no data on safety or PK for smaller pediatric patients. Consequently, the extent of extrapolation is limited, and additional studies are needed to determine an effective dose for the smaller pediatric patients

8.2.2 Integrated Assessment of Effectiveness

APPLICANT'S POSITION

The Applicant's Position:

Belumosudil inhibits ROCK2, and therefore reduces pro-inflammatory cytokines IL-17 and IL-21. ROCK2 inhibition is thought to 'rebalance' the immune system away from pro-inflammatory to a more regulated state. Pre-clinical studies have provided support for ROCK2 inhibition having a potential role in ameliorating cGVHD.

The primary data in support of the proposed indication for the belumosudil are based on the Phase 2/2A clinical studies in subjects with cGVHD who have received at least 1 prior line of systemic therapy (Studies KD025-208 and KD025-213). Analyses of this subject population, which is directly representative of the clinically complex, real-world patient population, and therefore generalizable to that population, comprises the core of the evaluation of the efficacy and safety profiles for the intended indication.

The proposed labeled dose of belumosudil for the treatment of cGVHD is 200 mg QD administered with food. Based on the totality of data, including combined PK and exposure-response analyses and clinical data, 200 mg QD provides the lowest efficacious dose in cGVHD patients, supporting this dose for the proposed marketing application.

As established by the 2014 NIH Response Criteria and with regulatory precedent, ORR is a clinically meaningful outcome measure in subjects with cGVHD. The observed ORR for belumosudil is impressive when compared to historically reported response rates and it is notable that almost all responses occurred during the first 6 months of treatment. Most patients achieved a response of PR; a response of CR was not necessarily anticipated because of the advanced cGVHD, often with fibrotic manifestations, observed in this patient population. Belumosudil doses of 200 mg QD and 200 mg BID demonstrated clinically meaningful responses in a population of subjects with advanced, heavily pre-treated cGVHD. The overall ORR (95% CI) for the mITT Population was 71.1% (60.1, 80.5) among subjects who received belumosudil 200 mg QD.

Responses were durable. Kaplan-Meier and landmark analyses of quaternary DOR, which enable summation of multiple response episodes for a given subject, showed median quaternary DOR was not reached among subjects in the 200 mg QD group as 38 subjects (64.4%) were still in response as of the data cutoff. Kaplan-Meier estimates of quaternary DOR at 12 and 24 weeks were 71% and 64%, respectively, in the 200 mg QD group. At the time of the data cutoff, 37 subjects (62.7%) in the 200 mg QD group had a sustained response to treatment of 12 weeks or longer and 26 subjects (44.1%) had a sustained response to treatment of 24 weeks or longer.

Similarly, median tertiary DOR (initiation of new systemic cGVHD therapy or death as censoring events) was not reached among subjects in the 200 mg QD group as 47 subjects (79.7%) had not initiated new systemic therapy for cGVHD as of the data cutoff. Of the 47 subjects, 44 (74.6%) were still on study and 3 (5.1%) were lost to follow up. Kaplan-Meier estimates of tertiary DOR at 12 and 24 weeks were 89% and 83%, respectively, in the 200 mg QD group.

The integrated analysis of best response by individual organ system and baseline organ severity score in subjects with cGVHD showed that among subjects in the 200 mg QD and BID groups, responses (including CR) were achieved across all organ systems and in GSR. Robust responses were observed whether subjects had received only 1 or multiple prior lines of therapy.

Subjects in all integrated analysis populations benefited from treatment with belumosudil, with 46% of nonresponders who received 200 mg QD being able to reduce their corticosteroid dose. Both 66% of responders and 25% of nonresponders experienced a clinically meaningful improvement in QOL, as assessed by the LSS.

While persistence of response to belumosudil by DOR, TTNT, and FFS provide examples of Investigator assessments, persistence of efficacy was also demonstrated by subject assessment, as reflected by LSS score data. Among responder subjects in the mITT population who received

belumosudil 200 mg QD, 45.8% experienced clinically meaningful improvement on at least 2 consecutive assessments.

Among all subjects, there were no meaningful differences in belumosudil ORR across subgroups based on age, gender, race, number of organs involved at baseline, severe cGVHD, prior use of ibrutinib, prior use of ruxolitinib, refractory to prior line of cGVHD treatment, duration of cGVHD before enrollment, or baseline GFR.

FDA'S POSITION

The 75% ORR by C7D1 with a lower bound of 63% and substantial durability in the 200 mg daily dosage arm of Study KD025-213, in addition to a 7-point reduction in LSS score in 52% of patients, establishes the activity of belumosudil for treatment of adult and pediatric patients 12 years and older with cGVHD after failure of at least two prior lines of systemic therapy. Although the 59% ORR by C7D1 in Study KD025-208 is supportive evidence of effectiveness, that study is not considered adequate and well-controlled, so the results should not be displayed in the USPI. Additional studies are needed to determine an effective dose in smaller pediatric patients.

8.3 Review of Safety

APPLICANT'S POSITION

8.3.1 Safety Review Approach

The safety analysis presented here is based on data from the Phase 2/2A clinical studies in subjects with cGVHD with at least 1 prior lines of systemic therapy (Studies KD025--208 and KD025-213), Analysis Group 1.

Supporting safety data for belumosudil are provided in Analysis Group 2 from a single Phase 2 study in subjects with IPF (Study KD025-207); Analysis Group 3, 3 Phase 2 studies in subjects with psoriasis (Studies KD025-205, KD025-206, and KD025-211); and 8 Phase 1 trials that have been conducted with belumosudil in Phase 1 studies (Studies 2119-09-01, KD025-101, KD025-102, KD025-103, KD025-105, KD025-106, KD025-107, and KD025-108).

A Phase 1 hepatic impairment study is ongoing (KD025-109); results from the mild and moderate hepatic impairment and normal hepatic function groups are provided. In addition, a Phase 1 study to investigate the effects of belumosudil on QTc interval (KD025-110) will commence in 2020. Results from this recently initiated study are not yet available.

Results from non-cGVDH studies for individual safety parameters are not discussed at length here, but an overall summary is provided in Section 0.

The Applicant's Position:

The available safety data allow for a suitable assessment of the safety profile of belumosudil at a dose of 200 mg QD, which is the proposed dose to treat cGVHD, supported by safety data from doses of 200 mg BID, and 400 mg QD. The overall safety of belumosudil treatment for patients with cGVHD who have received previous systemic therapy is characterized in this section.

8.3.2 Review of the Safety Database

Overall Exposure

Data:

The median duration of treatment with belumosudil in the 186 subjects with cGVHD was 6.83 months (range: 0.39-38.74 months), with 84 subjects (45.2%) having been exposed to belumosudil for ≥ 6 to 12 months and 31 subjects (16.7%) treated for ≥ 12 months. The median duration of treatment was similar between the 200 mg QD and 200 mg BID groups (6.87 and 6.69 months, respectively); the median duration of treatment was slightly longer at 9.00 months for subjects in the 400 mg QD group. Table 52 is a summary of treatment exposure from cGVHD studies with belumosudil.

The cumulative duration of exposure was 57.3 patient-years in the 200 mg QD group and 131.0 patient-years in all belumosudil-treated subjects.

Table 52 Treatment Exposure from Phase 2 cGVHD Studies with Belumosudil (Safety Population)

	cGVHD			
Parameter	**200 mg QD N=83 n (%)**	**200 mg BID N=82 n (%)**	**400 mg QD N=21 n (%)**	**All Belumosudil N=186 n (%)**
Duration of Treatment (months)				
n	83	82	21	186
Mean	8.29	7.68	12.10	8.45
SD	7.16	5.85	9.92	7.08
Median	6.87	6.69	9.00	6.83
Min, Max	0.46, 38.74	0.39, 34.92	0.69, 29.40	0.39, 38.74
Exposure Ranges, n (%)				
0 to 6 months	33 (39.8)	31 (37.8)	7 (33.3)	71 (38.2)
≥ 6 to 12 months	39 (47.0)	41 (50.0)	4 (19.0)	84 (45.2)
≥ 12 months	11 (13.3)	10 (12.2)	10 (47.6)	31 (16.7)
Overall Exposure (mg)				
n	83	82	21	186

Mean	48452	90517	133048	76548
SD	43142	70306	111158	71610
Median	40000	81100	104000	55700
Min, Max	2800, 235800	2800, 419200	8400, 315400	2800, 419200
Cumulative Duration (Patient-Years)	57.32	52.49	21.17	130.99

Abbreviations: BID=twice daily; cGVHD=chronic graft versus host disease; Max=maximum; Min=minimum; SD=standard deviation; QD=once daily.
Source: ISS Table 1.1ABC

The Applicant's Position:

Exposure to belumosudil was within the range planned in the study protocols and is adequate to support characterization of the safety profile of belumosudil. Within the overall population of subjects with cGVHD, 17% were treated for ≥ 12 months.

Relevant Characteristics of the Safety Population

Data:

The study population of subjects with cGVHD reflects the clinically complex patient population with an unmet medical need. As required by the cGVHD study protocols, all subjects had undergone alloHCT. Subjects were pre-treated, with at least one prior line of systemic cGVHD therapy. Among subjects in the 200 mg QD group, the median number of organs involved at baseline was 3.0 (range, 0-7). Over half of subjects in each dose group had involvement of the skin, eyes, mouth, and joints and fascia. The median GSR in the 200-mg dose group was 7.0 and most subjects in the 200 mg QD group (70%) had severe cGVHD at screening. Among subjects in the 200 mg QD cohort, median time from transplant to cGVHD diagnosis was 9.8 months. Median time from cGVHD diagnosis to study enrollment was 26.4 months. Median number of prior lines of systemic cGVHD therapy was 3.0 and 73% of subjects were refractory to their prior line of therapy.

The Applicant's Position:

Baseline characteristics for subjects with cGVHD are reflective of the disease under study and generally well balanced across dose groups.

Adequacy of the Safety Database

The Applicant's Position:

Over 600 subjects have been exposed to at least one dose of belumosudil in clinical trials. Belumosudil has been administered to 402 subjects, through 19 February 2020 in multi-dose

phase 2a/2 studies, with 31 subjects who have cGVHD were treated for ≥ 12 months. Over all 3 populations, 57 of the 402 subjects were treated for ≥ 12 months, with over 250 patient-years of exposure. The size of the database is considered adequate to identify most common AEs, support the benefit-risk assessment and represent the target patient population. Additional data of subject with 1 year exposure will be presented in the 60-day Safety Update Report.

8.3.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The Applicant's Position:

Clinical study sites are monitored to verify accurate and reliable data collection by checking the eCRF against the Investigator's records. Collected data were entered into a database and subject to quality assurance procedures.

Clinical research associates conducted periodic on-site visits to ensure adherence to the protocol, review eCRFs and site source documents for accuracy and completeness of information, examine site records for documentation of study drug receipt and administration, observe the progress of the study, and review Investigator files for required documents.
No significant issues have been identified regarding the quality or integrity of the submitted data that had an effect on the risk-benefit balance. Please refer to the Addendum to the Summary of Clinical Safety, the Clinical Reviewer's Guide, and the Analysis Data Reviewer's Guide for additional information regarding certain ongoing safety data reviews.

Categorization of Adverse Events

The Applicant's Position:

For the purpose of safety analyses, all TEAEs were assessed for seriousness (serious vs non-serious), severity as measured in Grades using the 5-point National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0, and causality with respect to study drug.

The number and percentage of patients who experienced at least 1 TEAE were summarized by MedDRA SOC, PT, maximum severity, and relationship to study drug. Also presented were SAEs, events leading to dose modification (dose interruption, dose reductions and drug discontinuation), TEAEs assessed as related to study drug, and TEAEs of severity Grade ≥ 3. First onset of TEAEs were also assessed in each of 4 different treatment periods: 0 to 6 months; > 6 to 12 months; > 12 to 24 months, and > 24 months. SAEs leading to death were summarized by dose-group, SOC, PT and time to onset.

AEs were coded according to MedDRA Version 20.0.

Adverse events of special interest (AESIs) were selected based on mechanism of action (effects on immune system), nonclinical toxicology profile and emerging clinical data. Standardized MedDRA queries (SMQs), customized MedDRA queries (CMQs), SOCs, high-level group terms (HLGTs), high-level terms (HLTs) were used to define the AESIs.

Routine Clinical Tests

The Applicant's Position:

Data from central and local laboratories were combined. The summaries included all laboratory assessments collected through 28 days after study treatment discontinuation.
Key assessments included routine clinical laboratory tests (hematology, chemistry), vital signs, and ECG assessments.

Selected laboratory data were combined with TEAE data for the evaluation of some AESI.

8.3.4 Safety Results

Deaths

Data:

Among subjects with cGVHD, 9 (4.8%) of 186 subjects experienced a TEAE leading to death within 28 days of ending study treatment; 4 of these subjects were treated with 200 mg QD. Of these 9 subjects, 8 were assessed as not related to belumosudil, as they were due to recurrence of malignancy, progression of cGVHD, or other underlying disorder (Table 53). One case ((b) (6) in Subject 213- (b) (6)) was reported as a suspected unexpected serious adverse reaction (SUSAR), with fatal event of multiorgan dysfunction syndrome assessed as related to belumosudil by the Investigator (Sponsor assessment was unlikely related). (NB: This event was changed to unlikely related by the site at the time of the Intergated Summary of Safety [ISS] data extraction and was subsequently changed back to possibly related by the Investigator. Therefore, the text of Modules 2.5 and 2.7.4 have more up-to-date data than the tables for this event.)

Table 53 Summary of Subjects who Died within 28 Days of Ending Study Treatment (Safety Population, Analysis Group 1)

Treatment Group Subject Number Study	Treatment Duration (Months)	Primary Cause of Death (Preferred Term)	Relationship to Study Drug by Investigator	Time from Last Dose (Days)	Comments
Belumosudil 400 mg QD (b) (6) KD025-208	0.7	Leukemia recurrent	Not related	5	74-year-old female had relapse of AML on Study Day 8
Belumosudil- 400 mg QD (b) (6) KD025-208	2.2	Lung infection	Not related	1	28-year-old female, with cGVHD involving lung, hospitalized with suspected pneumonia and skin infection, and required repeated intubations due to hypoxia.
Belumosudil 400 mg QD (b) (6) KD025-208	0.7	Cardiac arrest	Not related	1	25-year-old male with cardiomegaly, hypertension, acute respiratory failure, found unresponsive at home of suspected cardiac arrest.
Belumosudil 400 mg QD (b) (6) KD025-208	14.2	GVHD in lung	Not related	2	63-year-old male with progression of cGVHD.
Belumosudil 200 mg QD (b) (6) KD025-213	1.0	Haemothorax	Not related	1	49-year-old male hospitalized for pneumatosis of colon, related to cGVHD; died from hemothorax due to lung biopsy.
Belumosudil 200 mg QD (b) (6) KD025-213	1.5	Aspiration Respiratory failure	Not related Not related	12	72-year-old male with recurrent aspiration events, left-sided pneumothorax requiring chest tube placement, and non-ST elevation myocardial infarction due to demand ischemia.
Belumosudil 200 mg QD (b) (6) KD025-213	0.5	Septic shock Multiple organ dysfunction syndrome	Unlikely related Possibly related[1]	4	75-year old male w/ aspiration, acute kidney injury, etc.; per autopsy, died of AML complicated by neutropenic shock secondary to acute pneumonia.

Treatment Group Subject Number Study	Treatment Duration (Months)	Primary Cause of Death (Preferred Term)	Relationship to Study Drug by Investigator	Time from Last Dose (Days)	Comments
Belumosudil 200 mg QD (b) (6) KD025-213	1.3	Acute myeloid leukemia recurrent	Not related	17	51-year-old male had relapse of AML.
Belumosudil 200 mg BID (b) (6) KD025-213	0.4	Cardiac arrest	Unlikely related	15	65-year-old male experienced upper GI haemorrhage, anaemia, pleural effusion, dyspnea, and oedema right arm; died from cardiac arrest after 'do not resuscitate' order instituted.

Abbreviations: AML=acute myeloid leukemia; BID=twice daily; cGVHD=chronic Graft versus Host Disease; GI=gastrointestinal; QD=once daily.
[1]This suspected unexpected serious adverse reactions (SUSAR) was reported as an expedited report. The event of multiple organ dysfunction syndrome was initially assessed as related to study drug by the Investigator. The event causality was changed to unlikely related at the time data were extracted for this report. The event was subsequently changed to back to possibly related. The fatal event was assessed as unlikely related by the Sponsor.
Source: ISS Listing 1.1.1ABC, CSR KD025-208, Listing 4.1.1, CSR KD025-213, Listing 4.1.1, and CSR KD025-207, Listing 6.2.1, CSR KD025-211 Listing 4.1.1, and Listing 4.3.1.

The Applicant's Position:

The majority of the deaths were associated with the underlying malignancy, cGVHD, or other pre-existing condition and were assessed as unrelated.

Serious Adverse Events

Data:

In the pooled cGVHD analysis group, SAEs were reported in 37.3% of subjects in the 200 mg QD group and in 36.0% of all belumosudil-treated subjects (Table 54). Overall, most SAEs were reported in the Infections and Infestations SOC (16.9% in 200 mg QD and 17.2% in the all belumosudil group) and in the Respiratory Disorders SOC (7.2% 200 mg QD and 7.0% in the all belumosudil group). This is reflected in the overall most commonly (> 2 subjects) reported SAEs by PT which were pneumonia (5.4%); dyspnoea (3.8%); lung infection (3.2%); and cellulitis, acute kidney injury, and sepsis (each 1.6%).

Table 54 Serious Treatment-Emergent Adverse Events ≥ 2 Subjects by Preferred Term (Safety Population, Analysis Group 1)

	Belumosudil			
System Organ Class Preferred term	**200 mg QD N=83 n (%)**	**200 mg BID N=82 n (%)**	**400 mg QD N=21 n (%)**	**All N=186 n (%)**
Subjects with at least one serious TEAE	31 (37.3)	24 (29.3)	12 (57.1)	67 (36.0)
Infections and infestations	14 (16.9)	14 (17.1)	4 (19.0)	32 (17.2)
Pneumonia	7 (8.4)	3 (3.7)	0	10 (5.4)
Lung infection	1 (1.2)	3 (3.7)	2 (9.5)	6 (3.2)
Cellulitis	1 (1.2)	2 (2.4)	0	3 (1.6)
Sepsis	2 (2.4)	1 (1.2)	0	3 (1.6)
Rhinovirus infection	2 (2.4)	0	0	2 (1.1)
Staphylococcal bacteraemia	2 (2.4)	0	0	2 (1.1)
Respiratory, thoracic and mediastinal disorders	6 (7.2)	4 (4.9)	3 (14.3)	13 (7.0)
Dyspnoea	1 (1.2)	3 (3.7)	3 (14.3)	7 (3.8)
Hypoxia	0	0	2 (9.5)	2 (1.1)
Pulmonary embolism	1 (1.2)	1 (1.2)	0	2 (1.1)
Gastrointestinal disorders	5 (6.0)	3 (3.7)	2 (9.5)	10 (5.4)
Abdominal pain	0	2 (2.4)	0	2 (1.1)
Diarrhoea	2 (2.4)	0	0	2 (1.1)
Nausea	1 (1.2)	1 (1.2)	0	2 (1.1)
Small intestinal obstruction	1 (1.2)	0	1 (4.8)	2 (1.1)
Vomiting	1 (1.2)	1 (1.2)	0	2 (1.1)
General disorders and administration site conditions	6 (7.2)	2 (2.4)	2 (9.5)	10 (5.4)
Pyrexia	4 (4.8)	0	0	4 (2.2)

System Organ Class Preferred term	Belumosudil 200 mg QD N=83 n (%)	Belumosudil 200 mg BID N=82 n (%)	Belumosudil 400 mg QD N=21 n (%)	Belumosudil All N=186 n (%)
Influenza like illness	0	0	2 (9.5)	2 (1.1)
Cardiac disorders	2 (2.4)	4 (4.9)	1 (4.8)	7 (3.8)
Cardiac arrest	0	1 (1.2)	1 (4.8)	2 (1.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (3.6)	0	3 (14.3)	6 (3.2)
Acute myeloid leukaemia recurrent	2 (2.4)	0	0	2 (1.1)
Renal and urinary disorders	3 (3.6)	1 (1.2)	1 (4.8)	5 (2.7)
Acute kidney injury	2 (2.4)	1 (1.2)	0	3 (1.6)
Vascular disorders	2 (2.4)	3 (3.7)	0	5 (2.7)
Hypotension	1 (1.2)	1 (1.2)	0	2 (1.1)
Musculoskeletal and connective tissue disorders	0	3 (3.7)	0	3 (1.6)
Back pain	0	2 (2.4)	0	2 (1.1)

Abbreviations: BID=twice daily; TEAE=treatment-emergent adverse events; QD=once daily.
Source: ISS Table 4.3.2A

Treatment-related SAEs were identified in a total of 7.2% of subjects with cGVHD in the 200 mg QD dose and 3.8% in the all belumosudil group. All SAEs were reported in 1 subject, including cellulitis, infectious colitis, lung infection, pneumonia, staphylococcal bacteraemia, upper respiratory tract infection, pyrexia, microangiopathic haemolytic anaemia, diarrhoea, nausea, and vomiting.

The Applicant's Position:

The majority of the SAEs resolved and were assessed as not related. Some SAEs are associated with cGVHD or other underlying disease.

Dropouts and/or Discontinuations Due to Adverse Effects
Data:

Study Drug Interruption

In the pooled cGVHD analysis group, 27.7% of subjects in the 200 mg QD group and 29.6 % of all belumosudil-treated subjects had a study drug interruption due to TEAEs during the study, most frequently due to infections (14%) and gastrointestinal disorder (7.0%).

The most frequently reported (> 2 subjects overall) TEAEs leading to study drug interruption in the all belumosudil group included pneumonia (4.3%); influenza, lung infection, diarrhoea, and vomiting (2.2% each); and nausea, dyspnoea, and GGT increased, (1.6%).

Treatment-related TEAEs leading to study drug interruption occurred in 17 (9.1%) of 186 subjects with cGVHD who received belumosudil. The most frequently reported (> 1 subject overall) treatment-related TEAEs leading to study drug interruption included ALT increased, diarrhoea, nausea, and vomiting (2 subjects, 1.1% each). No treatment-related TEAEs leading to study drug interruption occurred in > 2 subjects overall.

The overall incidence of treatment-related TEAEs leading to study drug interruption was generally lower in subjects with 200 mg QD (9.6%) and 200 mg BID (6.1%) dosing than in subjects whose starting dose was 400 mg QD (19.0%).

Study Drug Dose Reductions

Dose reductions due to TEAEs were uncommon in the pooled cGVHD analysis group; reported in 2.4% of subjects in the 200 mg QD group and 3.8% of all belumosudil-treated. The only TEAE reported leading to dose reduction in > 1 subject was fatigue (3 subjects, 1.6%). In subjects treated with 200 mg QD, dose reductions took place in 2 subjects due to TEAEs of blood creatinine increased and neuropathy peripheral. The incidence of TEAEs leading to study drug dose reductions was generally lower in subjects with 200 mg QD and 200 mg BID dosing than in subjects whose starting dose was 400 mg QD.

All TEAEs reported as leading to study drug dose reductions in subjects with cGVHD who received belumosudil were assessed as treatment-related.

Study Drug Discontinuation

In the pooled cGVHD analysis group, discontinuation of belumosudil due to TEAEs was reported in 25.3% of subjects in the 200 mg QD group and 23.7% of all belumosudil-treated subjects (Table 55).

Table 55 Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation (≥ 2 Subjects) by System Organ Class and Preferred Term (Safety Population, Analysis Group 1)

	Belumosudil			
System organ class Preferred term	200 mg QD N=83 n (%)	200 mg BID N=82 n (%)	400 mg QD N=21 n (%)	All N=186 n (%)
Subjects with at least one TEAE leading to study drug discontinuation	21 (25.3)	15 (18.3)	8 (38.1)	44 (23.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5 (6.0)	0	5 (23.8)	10 (5.4)
AML recurrent	2 (2.4)	0	1 (4.8)	3 (1.6)
Plasma cell myeloma	1 (1.2)	0	1 (4.8)	2 (1.1)
Gastrointestinal disorders	3 (3.6)	2 (2.4)	0	5 (2.7)
Nausea	2 (2.4)	0	0	2 (1.1)

General disorders and administration site conditions	2 (2.4)	1 (1.2)	1 (4.8)	4 (2.2)
Fatigue	1 (1.2)	1 (1.2)	1 (4.8)	3 (1.6)
Infections and infestations	1 (1.2)	2 (2.4)	1 (4.8)	4 (2.2)
Cellulitis	1 (1.2)	1 (1.2)	0	2 (1.1)
Investigations	2 (2.4)	2 (2.4)	0	4 (2.2)
AST increased	0	2 (2.4)	0	2 (1.1)
Nervous system disorders	3 (3.6)	1 (1.2)	0	4 (2.2)
Headache	2 (2.4)	1 (1.2)	0	3 (1.6)
Respiratory, thoracic and mediastinal disorders	2 (2.4)	2 (2.4)	0	4 (2.2)
Dyspnoea	0	2 (2.4)	0	2 (1.1)

Abbreviations: AML=acute myeloid leukaemia; AST=aspartate aminotransferase; BID=twice daily, TEAE=treatment-emergent adverse events; QD=once daily.
Source: ISS Table 4.3.3A

Treatment-related TEAEs leading to study drug discontinuation occurred in 10.8% of subjects in the 200 mg QD group and in 8.6% of all belumosudil-treated subjects. The incidence of treatment-related TEAEs leading to study drug discontinuation was generally lower in subjects with 200 mg BID (7.3%) and 400 mg QD (4.8%) dosing than in subjects whose starting dose was 200 mg QD (10.8%).

The most frequently reported (> 1 subject overall) treatment-related TEAEs leading to study drug discontinuation included headache (2.4% 200 mg QD and 1.6% all belumosudil), nausea (2.4% 200 mg QD and 1.1% all belumosudil), fatigue (1.2% 200 mg QD and 1.6% all belumosudil), cellulitis (1.2% 200 mg QD and 1.1% all belumosudil), dyspnoea (0 200 mg QD and 1.1% all belumosudil), and aspartate aminotransferase (AST) increased (0 200 mg QD and 1.1% all belumosudil). No treatment-related TEAEs leading to study drug discontinuation occurred in > 3 subjects overall.

The Applicant's Position:

The most common AE leading to study drug discontinuation was recurrence of the underlying malignancy. Others are events that may be associated with cGVHD.

The Applicant's Position:

The types and frequencies of AEs that led to dose interruption or dose reduction were within expectations for the population under study. The TEAEs that most frequently led to dose interruption were pneumonia (4.8%) and fatigue (1.6%), respectively.

Significant Adverse Events

The Applicant's Position:

Adverse Events of Special Interest

See Section 0 for description of AESI.

Grade ≥ 3 TEAEs

Grade ≥ 3 TEAEs occurred in 50.6% in the cGVHD 200 mg QD dose group and 51.6% in the all belumosudil group. Most were in the SOC Infection and infestations (15.7% and 17.2% respectively) and SOC Metabolism and nutrition disorder (16.9% and 13.4%, respectively). The most frequently reported Grade ≥ 3 TEAEs (≥ 2% overall) were pneumonia (7.2% 200 mg QD and 5.9% all belumosudil), dyspnoea (3.6% 200 mg QD and 5.4% all belumosudil), hyperglycaemia (6.0% 200 mg QD and 5.4% all belumosudil), and hypertension (6.0% 200 mg QD and 4.8% all belumosudil). The most frequently reported Grade ≥ 3 TEAEs in subjects with cGVHD receiving belumosudil 200 mg QD were generally consistent with those expected in a population of subjects with advanced cGVHD being treated with corticosteroids and other immunosuppressants. There were a small number of Grade 4 events; these were mainly recurrence of malignancy or infection. Few Grade 4 TEAEs were assessed as related to belumosudil.

Treatment Emergent Adverse Events and Adverse Reactions
Data:

The most commonly reported TEAEs (≥ 10% of belumosudil-treated subjects) are summarized for subjects with cGVHD by PT in Table 56. In the pooled cGVHD analysis group, the majority of the most commonly reported TEAEs were consistent with cGVHD symptoms or sequelae of GVHD, including gastrointestinal events, infections, and respiratory events. In the 200 mg group, the most common events were fatigue (38.6%), diarrhoea (32.5%), upper respiratory tract infection (28.9%), nausea (27.7%), and dyspnoea (26.5%).

Table 56 Most Common (≥ 10% Incidence Rate) Treatment-emergent Adverse Events by Preferred Term (Safety Population, Analysis Group 1)

System Organ Class Preferred Term	Belumosudil			
	200 mg QD N=83 n (%)	200 mg BID N=82 n (%)	400 mg QD N=21 n (%)	All N=186 n (%)
Subjects with at least 1 TEAE	82 (98.8)	81 (98.8)	20 (95.2)	183 (98.4)
Gastrointestinal Disorders	56 (67.5)	54 (65.9)	16 (76.2)	126 (67.7)
Diarrhoea	27 (32.5)	23 (28.0)	7 (33.3)	57 (30.6)
Nausea	23 (27.7)	21 (25.6)	8 (38.1)	52 (28.0)
Vomiting	18 (21.7)	11 (13.4)	4 (19.0)	33 (17.7)
Abdominal pain	10 (12.0)	8 (9.8)	4 (19.0)	22 (11.8)
Infections and Infestations	53 (63.9)	48 (58.5)	15 (71.4)	116 (62.4)

System Organ Class Preferred Term	Belumosudil 200 mg QD N=83 n (%)	Belumosudil 200 mg BID N=82 n (%)	Belumosudil 400 mg QD N=21 n (%)	Belumosudil All N=186 n (%)
Upper respiratory tract infection	24 (28.9)	25 (30.5)	7 (33.3)	56 (30.1)
Respiratory, thoracic and mediastinal disorders	49 (59.0)	46 (56.1)	14 (66.7)	109 (58.6)
Dyspnoea	22 (26.5)	17 (20.7)	7 (33.3)	46 (24.7)
Cough	20 (24.1)	17 (20.7)	7 (33.3)	44 (23.7)
Productive cough	9 (10.8)	9 (11.0)	1 (4.8)	19 (10.2)
General disorders and administration site conditions	49 (59.0)	39 (47.6)	15 (71.4)	103 (55.4)
Fatigue	32 (38.6)	20 (24.4)	9 (42.9)	61 (32.8)
Oedema peripheral	20 (24.1)	15 (18.3)	6 (28.6)	41 (22.0)
Pyrexia	14 (16.9)	8 (9.8)	3 (14.3)	25 (13.4)
Musculoskeletal and connective tissue disorders	42 (50.6)	38 (46.3)	13 (61.9)	93 (50.0)
Muscle spasms	13 (15.7)	11 (13.4)	6 (28.6)	30 (16.1)
Arthralgia	11 (13.3)	8 (9.8)	5 (23.8)	24 (12.9)
Pain in extremity	8 (9.6)	7 (8.5)	4 (19.0)	19 (10.2)
Investigations	39 (47.0)	38 (46.3)	12 (57.1)	89 (47.8)
GGT increased	9 (10.8)	13 (15.9)	0	22 (11.8)
ALT increased	10 (12.0)	9 (11.0)	2 (9.5)	21 (11.3)
AST increased	10 (12.0)	9 (11.0)	1 (4.8)	20 (10.8)
Metabolism and nutrition disorders	37 (44.6)	29 (35.4)	11 (52.4)	77 (41.4)
Hyperglycaemia	11 (13.3)	12 (14.6)	3 (14.3)	26 (14.0)
Decreased appetite	12 (14.5)	4 (4.9)	4 (19.0)	20 (10.8)
Nervous system disorders	30 (36.1)	35 (42.7)	9 (42.9)	74 (39.8)
Headache	15 (18.1)	19 (23.2)	6 (28.6)	40 (21.5)
Vascular disorders	25 (30.1)	26 (31.7)	5 (23.8)	56 (30.1)
Hypertension	15 (18.1)	12 (14.6)	4 (19.0)	31 (16.7)
Blood and lymphatic system disorders	13 (15.7)	13 (15.9)	4 (19.0)	30 (16.1)
Anaemia	10 (12.0)	11 (13.4)	0	21 (11.3)

Abbreviations: ALT=Alanine aminotransferase; AST=aspartate aminotransferase; BID=twice daily; BSC=best supportive care, cGVHD=chronic graft versus host disease; GGT=gamma-glutamyltransferase; IPF=Idiopathic Pulmonary Fibrosis; MedDRA=Medical Dictionary for Regulatory Activities; TEAE=treatment-emergent adverse events; QD=once daily.
Source: ISS Table 4.3.1A

In the pooled cGVHD analysis group, treatment-related TEAEs were reported in 66.3% of subjects in the 200 mg QD group and in 60.8% of all belumosudil-treated subjects (Table 57). Most of the TEAEs were in the Gastrointestinal SOC (25.3% of the 200 mg QD group and 21% in the all belumosudil group) and the SOC General Disorders and Administration Site Conditions (21.7% of the 200 mg QD group and 21.0% in the all belumosudil group) including fatigue (18.1% 200 mg QD and 17.2% all belumosudil), pyrexia (3.6% 200 mg QD and 2.2% all belumosudil), and oedema peripheral (2.4% 200 mg QD and 2.2% all belumosudil). The following treatment-related gastrointestinal TEAEs were observed: nausea (12.0% in 200 mg QD, 11.3% in all belumosudil), diarrhoea (7.2% in 200 mg QD, 5.9% in all belumosudil), vomiting (7.2% in 200 mg QD, 4.3% in all belumosudil), and constipation (4.8% in 200 mg QD, 2.7% in all belumosudil).

Table 57 Treatment-Related Treatment-Emergent Adverse Events (≥ 2% of All Belumosudil-Treated Subjects) by System Organ Class and Preferred Term (Safety Population, Analysis Group 1)

System Organ Class Preferred term	Belumosudil			
	200 mg QD N=83 n (%)	200 mg BID N=82 n (%)	400 mg QD N=21 n (%)	All N=186 n (%)
Subjects with at least one related TEAE	55 (66.3)	44 (53.7)	14 (66.7)	113 (60.8)
General disorders and administration site conditions	18 (21.7)	18 (22.0)	3 (14.3)	39 (21.0)
Fatigue	15 (18.1)	14 (17.1)	3 (14.3)	32 (17.2)
Oedema peripheral	2 (2.4)	2 (2.4)	0	4 (2.2)
Pyrexia	3 (3.6)	1 (1.2)	0	4 (2.2)
Gastrointestinal disorders	21 (25.3)	13 (15.9)	5 (23.8)	39 (21.0)
Nausea	10 (12.0)	8 (9.8)	3 (14.3)	21 (11.3)
Diarrhoea	6 (7.2)	5 (6.1)	0	11 (5.9)
Vomiting	6 (7.2)	1 (1.2)	1 (4.8)	8 (4.3)
Constipation	4 (4.8)	1 (1.2)	0	5 (2.7)
Investigations	18 (21.7)	16 (19.5)	3 (14.3)	37 (19.9)
AST increased	6 (7.2)	7 (8.5)	0	13 (7.0)
ALT increased	5 (6.0)	6 (7.3)	1 (4.8)	12 (6.5)
GGT increased	5 (6.0)	3 (3.7)	0	8 (4.3)
Blood alkaline phosphatase increased	2 (2.4)	4 (4.9)	0	6 (3.2)
Platelet count decreased	2 (2.4)	3 (3.7)	0	5 (2.7)
Lymphocyte count decreased	2 (2.4)	2 (2.4)	0	4 (2.2)
Weight decreased	1 (1.2)	2 (2.4)	1 (4.8)	4 (2.2)
Nervous system disorders	13 (15.7)	15 (18.3)	4 (19.0)	32 (17.2)
Headache	7 (8.4)	5 (6.1)	4 (19.0)	16 (8.6)
Neuropathy peripheral	3 (3.6)	2 (2.4)	0	5 (2.7)
Musculoskeletal and connective tissue disorders	9 (10.8)	6 (7.3)	4 (19.0)	19 (10.2)
Muscle spasms	2 (2.4)	2 (2.4)	3 (14.3)	7 (3.8)
Arthralgia	1 (1.2)	3 (3.7)	2 (9.5)	6 (3.2)

System Organ Class Preferred term	Belumosudil			
	200 mg QD N=83 n (%)	200 mg BID N=82 n (%)	400 mg QD N=21 n (%)	All N=186 n (%)
Metabolism and Nutrition disorders	10 (12.0)	6 (7.3)	2 (9.5)	18 (9.7)
Hyperglycaemia	4 (4.8)	2 (2.4)	1 (4.8)	7 (3.8)
Decreased appetite	4 (4.8)	1 (1.2)	0	5 (2.7)
Infections	10 (12.0)	6 (7.3)	1 (4.8)	17 (9.1)
Upper respiratory tract infection	3 (3.6)	2 (2.4)	1 (4.8)	6 (3.2)
Respiratory, thoracic and mediastinal disorders	6 (7.2)	6 (7.3)	2 (9.5)	14 (7.5)
Cough	2 (2.4)	4 (4.9)	1 (4.8)	7 (3.8)
Dyspnoea	3 (3.6)	1 (1.2)	0	4 (2.2)
Vascular disorders	3 (3.6)	6 (7.3)	0	9 (4.8)
Hypertension	1 (1.2)	3 (3.7)	0	4 (2.2)

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; BID=twice daily; GGT=gamma-glutamyltransferase; TEAE=treatment-emergent adverse events; QD=once daily.
Source: ISS Table 4.3.4A

Identification of adverse drug reactions (ADRs) was based on analysis of multiple factors including frequency, severity, seriousness, Investigator causality assessment and drug discontinuations. This assessment is complicated by the lack of a comparator arm, various signs and symptoms of cGVHD, recurrence of malignancies and the toxicities of cGVHD treatments used as concomitant medications in these studies. Supplemental studies with comparator arms, although different patient populations, were utilized to enhance this analysis. Due to differences in exposure rates between belumosudil and the comparator arms (best supportive care [BSC] and placebo in the IPF analysis group and the psoriasis analysis group, respectively), exposure adjusted event rate data were also included in the review. The comparator arms in both analysis groups had limited patient-years of exposure, limiting their usefulness especially in less frequent events.

Potential ADRs identified are alanine aminotransferase (ALT) increased, AST increased, diarrhoea, fatigue, nausea, pneumonia, and vomiting. Other TEAEs being considered are anaemia, arthralgia, dizziness, headache, pruritus, pyrexia, and upper respiratory tract infection. The ADRs will be further refined with the additional data to be analysed in the Safety Update Report.

The Applicant's Position:

Common TEAEs, related TEAEs and potential ADRs are provided.

Laboratory Findings
Data:

Review of safety laboratory results showed no clinically meaningful changes from baseline in

mean hematology or clinical chemistry parameters observed in any subject population. Laboratory findings associated with AESI are described in Section 0.

The Applicant's Position:

No clinically meaningful changes from baseline in safety laboratory parameters were observed. Laboratory data associated with AESI are presented separately.

Vital Signs
Data:

Body weight, temperature, and heart rate showed some fluctuations during study treatment across study populations, but these changes were generally small and not clinically meaningful.

See Section 0 of this document for discussion of hypotension events.

The Applicant's Position:

No clinically meaningful changes from baseline in vital signs parameters were observed.

QT/Electrocardiograms (ECGs)

Data:

QTc Prolongation and Cardiac Arrhythmia

The safety data of belumosudil were examined to evaluate the potential for QTc prolongation per the ICH Harmonised Tripartite Guideline (E14 guideline), utilizing the searches SMQ Torsade de pointes/QT prolongation (broad) and SMQ Cardiac arrhythmias (broad).

ECG Results:

In the pooled cGVHD analysis group, the results from the categorical analyses of maximum post-baseline absolute QTcF showed that the majority of subjects had a maximum post-baseline absolute QTcF of ≤ 450 msec; 81.7% overall and 84.3%, 75.6%, and 90.5% 200 mg QD, 200 mg BID and 400 mg QD dose groups, respectively. Five subjects (2.7%) had a maximum value of > 480 but ≤ 500 msec and 3 subjects (1.6%) had a maximum value of > 500 msec (2 treated with 200 mg QD and 1 with 200 mg BID). There were no subjects with a maximum on-treatment value of > 480 who had a TEAE potentially indicative of QTc prolongation.

In the pooled cGVHD analysis group, the majority (97.3%) had less than 60 msec increase from baseline for their maximum change. Three subjects (3.6%) in the 200 mg QD group and one subject (1.2%) in the 200 mg BID group had an increase of ≥ 60 msec. None of these subjects had TEAEs potentially related to QTc prolongation.

Adverse Events:

In the pooled cGVHD analysis group, AEs within the SMQ (broad) torsades de pointes/QT prolongation were reported in 3.6% of subjects in the 200 mg QD group and 3.8% of all belumosudil-treated subjects, including syncope (2 subjects, 2.4% 200 mg QD and 4 subjects 2.2% all belumosudil), cardiac arrest (0 200 mg QD and 2 subjects, 1.1% all belumosudil), and electrocardiogram QT prolonged (2 subjects, 2.4% 200 mg QD and 2 subjects, 1.1% all belumosudil). The events of cardiac arrest and syncope were assessed as Grade ≥ 3.

Two subjects (Subject (b) (6) from Study KD025-208 and Subject (b) (6) from Study KD025-213) experienced TEAEs of cardiac arrest (fatal) with no evidence the events were related to QTc prolongation.

Four subjects had TEAEs of syncope (1 of whom also had a TEAE of QT prolongation) and 1 subject had a TEAE of QT prolongation without any associated clinical signs or symptoms reported as TEAEs. The 4 syncope events were all assessed as severe, non-serious, and not related to study drug. No dose modifications were made and 3 of the 4 subjects recovered.

Two subjects, both receiving belumosudil 200 mg QD, reported 3 events of ECG QT prolonged. All 3 events were assessed as non-serious and mild to moderate in severity. The events were considered unlikely related or not related to study drug and no dose modifications were made; each subject recovered from a single event with 1 subject experiencing a second and unresolved event.

In the pooled cGVHD analysis group, AEs within the SMQ cardiac arrhythmia broad were reported in 24 (12.9%) subjects. The most commonly reported events within this SMQ were tachycardia (8 subjects, 4.3%), syncope and sinus tachycardia (4 subjects, 2.2% each), and palpitations (3 subjects, 1.6%).

The Applicant's Position:

There were no events of torsades de pointe, sudden death, ventricular tachycardia, ventricular fibrillation, ventricular flutter or seizures. Although there were sporadic reports of QTc prolongation among 186 patients assessed at approximately monthly intervals, there does not appear to be a signal of QTc prolongation based on ECG findings or TEAEs in association with belumosudil. Of note, a Thorough QT study (KD025-110) is being performed to commence in 2020.

Immunogenicity

Not applicable.

8.3.5 Analysis of Submission-Specific Safety Issues

8.2.5.1 Adverse Events of Special Interest

Data

Adverse events of special interest were selected based on mechanism of action (MOA), non-clinical toxicology profile, and emergent clinical data. The selected AESI terms include:

- Hepatic events/Increased liver function tests
- Infections
- Hematologic events (anemia, neutropenia/leukopenia, and thrombocytopenia)
- Malignancy/neoplasm (relapse of underlying malignancy and second neoplasm)
- Hypotension
- Impaired wound healing.

Hepatic Events/Elevated Liver Function Test

Liver impairment is a potential risk associated with belumosudil based on nonclinical safety findings and emergent clinical data. As such, hepatic events were explored using preidentified search criteria for the AESIs.

Liver disorders were identified using the SMQ-Drug Related Hepatic Disorders (narrow) and the SMQ Liver Related Investigations, signs, and symptoms – comprehensive search (narrow). Both SMQ searches provided the same results and only the latter search will be described. Reports of Grade ≥ 3 elevations of ALT, AST, or bilirubin based on both TEAE and laboratory data are also presented.

In the pooled cGVHD analysis group, AEs within the SMQ (narrow) liver related investigations were reported in 22.9% of subjects in the 200 mg QD group and 24.2% of all belumosudil-treated subjects. The most commonly reported PTs included GGT increased (10.8% 200 mg QD and 11.8% all belumosudil), ALT increased (12.0% 200 mg QD and 11.3% all belumosudil), and AST increased (12.0% 200 mg QD and 10.8% all belumosudil).

Results of the search identified only liver function test (LFT) abnormalities and no major hepatic disorders.

The majority of TEAEs in the SMQ were reported as mild and none were reported as SAEs. Grade ≥ 3 events were reported in 4.8% of subjects in both the 200 mg QD and all belumosudil groups. In addition to LFT increases, 1 subject reported ascites.

Most of these events were mild in intensity and subjects recovered, with few dose interruptions, dose reductions, or study drug discontinuations. None of the LFT increases was assessed as serious. Grade 3 events were limited and there were no Grade 4 or 5 events of ALT, AST, or bilirubin elevations, with few Grade 4 gamma-glutamyl transferase (GGT) elevations. There was a balance between those events assessed as related and unrelated. The subjects who did have drug interruptions due to ALT, AST, or bilirubin increases had positive

dechallenges and none had a positive rechallenge. Bilirubin increased was reported only in subjects with baseline hepatic impairment.

Increased liver function test events were searched using the HLGT Hepatobiliary Investigations both including and excluding the PT of GGT increased. In addition, results from the search using SMQ Liver Related Investigations, Signs and Symptoms showed that GGT increases were not seen in other populations with the exposure-adjusted event rate being higher in the BSC arm than the belumosudil arm in the IPF analysis group. For these reasons, results presented below are for the analysis excluding GGT increased.

In the pooled cGVHD analysis group, this analysis identified 18.1% of subjects in the 200 mg QD group and 16.7% of all belumosudil-treated subjects with events in this category which primarily included reports of ALT increased (12.0% 200 mg QD and 11.3% all belumosudil) and AST increased (12.0% 200 mg QD and 10.8% all belumosudil).

Most were mild and recovered with no change in study drug. Three subjects experienced a Grade 3 event in this search: 3 of these subjects had AST increase and 2 had ALT increases. Of the Grade 3 elevations, none were reported as SAEs, all recovered, and all were assessed as possibly related to treatment with study drug.

For events within this category, there were no dose reductions. Study treatment was interrupted in 2 subjects: Subject 208-(b) (6) for concurrent Grade 3 AEs of ALT increased and AST increased and Subject 213(b) (6) for a mild AE of ALT increased. These events were assessed as not serious and possibly related to study drug; both subjects recovered. There was a positive dechallenge and a negative rechallenge for both (Data on file). Study drug was discontinued in 3 subjects; Subject 213-(b) (6) for Grade 3 AE of AST increased, Subject 213(b) (6) for Grade 2 AE of transaminases increased, and Subject 213-(b) (6) had concurrent Grade 1 AEs of AST increased, and ALT increased. All events were assessed as not serious and possibly related to study drug; Subject 213(b) (6) was the only subject who had not recovered by the data cutoff date.

Laboratory data were generally consistent with TEAE reporting for the Grade ≥ 3 events.

A review of the LFT elevations increased indicated that of the 31 subjects with events in the hepatobiliary investigations HLGT (excluding GGT increased), 8 events were associated with recurrence of underlying malignancy in 6 subjects.

Concomitant medications were also reviewed as a possible factor effecting LFTs; 4 subjects were taking rivaroxaban at the time of their LFT elevation (excluding GGT increased). Three subjects started the medication prior to entering the study (Subjects 208-(b) (6), 213(b) (6), and 213-(b) (6)), however, 1 subject had an LFT increase 6 days after starting treatment with rivaroxaban (Subject 213(b) (6)). Other concomitant medications, including treatment of cGVHD, have been associated with hepatotoxicity. The time to onset of the first event was generally within the first month of treatment.

The hepatic risk, to date, is limited to LFT increases; more severe hepatic disorders have not been identified in these data. No subject met the criteria for Hy's law.

In summary, LFT increases were identified in belumosudil treated subjects confounded by underlying disease pathophysiology and concomitant medications. They were generally mild, transient and manageable, resolving with few dose modifications or discontinuations. The Sponsor will continue to monitor these events.

Infections

Infections are a potential risk due to the mechanism of action (immune-modulator) of belumosudil. The analysis was done with data from pre-specified search criteria.

In the pooled cGVHD analysis group, the overall incidence of infection events for subjects administered 200 mg QD was generally similar to that of all belumosudil-treated subjects. The most frequently reported infection events included upper respiratory tract infection (28.9% 200 mg QD and 30.1% all belumosudil), pneumonia (10.8% 200 mg QD and 9.1% all belumosudil), influenza (3.6% 200 mg QD and 5.9% all belumosudil), conjunctivitis (2.4% 200 mg QD and 4.3% all belumosudil), lung infection (2.4% 200 mg QD and 4.3% all belumosudil), sinusitis (4.8% 200 mg QD and 4.3% all belumosudil), bronchitis (2.4% 200 mg QD and 3.2% all belumosudil), cellulitis (3.6% 200 mg QD and 3.2% all belumosudil), rhinovirus infection (3.6% 200 mg QD and 3.2% all belumosudil), oral candidiasis (3.6% 200 mg QD and 2.7% all belumosudil), urinary tract infection (200 mg QD and 2.2% all belumosudil), and candida infection (2.4% 200 mg QD and 2.2% all belumosudil).

A Grade ≥3 infections was experienced by 15.7% of subjects in the 200-mg QD group and 17.2% of subjects in the all belumosudil group. The most frequently reported Grade ≥3 infections were pneumonia (7.2% 200 mg QD and 5.9% all belumosudil) and lung infection (1.2% 200 mg QD and 3.2% all belumosudil).

The majority of infection events were viral, followed in frequency by bacterial infections. Fungal and opportunistic infections were uncommon and there were no reports of CMV infection or reactivation.

The majority of infections were mild or moderate, nonserious and were assessed as not related to belumosudil. Most subjects recovered and few required dose interruption or drug discontinuation. Two subjects suffered in the cGVHD population experienced fatal infections (lung infection, septic shock in the cGVHD population). Both were assessed as not related to belumosudil and had multiple comorbidities which contributed to the events and the outcome.

Overall, while infection is a potential risk due to the mechanism of action as immune-modulator, this is confounded by the increased risk of infection after allogeneic transplants and immunosuppressive standard of care in the cGVHD patient population, these results indicate

that the incidence of infections are manageable with belumosudil treatment. The Sponsor will continue to monitor infection events.

Hematologic Events

Hematopoietic impairment is a potential risk associated with belumosudil based on the mechanism of action (effects on the immune system), nonclinical safety findings, and events of interest occurring in the target population seen in emergent clinical data. As such, hematopoietic events were explored using preidentified search criteria for the AESIs. Laboratory shift analyses were also conducted to review changes in hematology parameters, including hemoglobin, platelets, leukocytes, and neutrophils.

In the pooled cGVHD analysis group, almost 17% of subjects had at least one TEAE of cytopenia (anemia, thrombocytopenia, neutropenia or leukopenia or cytopenias affecting more than one cell line). The most commonly reported of hematopoietic events included anaemia (12.0% 200 mg QD and 11.3% all belumosudil), platelet count decreased (4.8% 200 mg QD and 4.3% all belumosudil), lymphocyte count decreased (2.4% 200 mg QD and 2.7% all belumosudil), and white blood cell count decreased (3.6% 200 mg QD and 2.7% all belumosudil).

In the pooled cGVHD analysis group, a total of 12% of subjects in the 200 mg QD group and 11.8% of all belumosudil-treated subjects experienced an SMQ haematopoietic erythropenia event, including anaemia (12% 200 mg QD and 11.3% all belumosudil) and haematocrit decreased (0 200 mg QD and 1.1% all belumosudil). Grade 3 events in this category were reported in 4.8% of subjects in the 200 mg QD group and 3.8% of all belumosudil-treated subjects; all Grade 3 events were anaemia events. There were no Grade 4 or Grade 5 events.

No subject experienced a Grade ≥ 3 anaemia event on laboratory tests and 4.8% of subjects in the 200 mg QD group and 3.8% of all belumosudil-treated subjects had at least 1 Grade ≥ 3 TEAE or Grade ≥ 3 anaemia on laboratory tests.

In the pooled cGVHD analysis group, a total of 4.8% of subjects in the 200 mg QD group and 5.4% of all belumosudil-treated subjects experienced an event in the SMQ haematopoietic thrombocytopenia, including platelet count decreased (4.8% 200 mg QD and 4.3% all belumosudil) and thrombocytopenia (0 200 mg QD and 1.1% all belumosudil). Grade ≥ 3 events in this category were reported in 3.6% of subjects in the 200 mg QD group and 1.6% of all belumosudil-treated subjects; all Grade ≥ 3 events were platelet count decreased events.

Grade 3 thrombocytopenia events on laboratory tests were reported in 4.8% of subjects in the 200 mg QD group and 3.2% of all belumosudil-treated subjects; 4.8% of subjects in the 200 mg QD group and 3.2% of all belumosudil-treated subjects had at least 1 Grade 3 TEAE or Grade ≥ 3 thrombocytopenia on laboratory tests. There were no Grade 4 or Grade 5 events.

In the pooled cGVHD analysis group, a total of 6.0% of subjects in the 200 mg QD group and 5.9% of all belumosudil-treated subjects experienced an event in the SMQ haematopoietic leukopenia, including lymphocyte count decreased (2.4% 200 mg QD and 2.7% all belumosudil),

white blood cell count decreased (3.6% 200 mg QD and 2.7% all belumosudil), neutrophil count decreased (1.2% 200 mg QD and 1.6% all belumosudil), and febrile neutropenia (0 200 mg QD and 0.5% all belumosudil). Grade ≥ 3 events in this category were reported in 2.4% of subjects in the 200 mg QD group and 1.6% of all belumosudil-treated subjects; Grade ≥ 3 events included white blood cell count decreased (2.4% 200 mg QD and 1.1% all belumosudil), febrile neutropenia (0 200 mg QD and <1% all belumosudil), and neutrophil count decreased (0 200 mg QD and <1% all belumosudil).

In the pooled cGVHD analysis group, 1 (0.5%) subject (400 mg QD) experienced a neutropenia HLT event; the event of febrile neutropenia was assessed as a Grade ≥ 3 event. Two (1.1%) subjects experienced at least 1 Grade ≥ 3 neutropenia event on laboratory tests and 2 (1.1%) subjects had at least 1 Grade ≥ 3 neutropenia HLT event or Grade ≥ 3 neutropenia on laboratory tests.

No subject in the 200 mg QD group reported a neutropenia event.

In summary, cytopenias were identified in the cGVHD population. No subjects discontinued or required dose modification and only 1 subject had a dose interruption event indicating hematologic cytopenia events are manageable. Confounding factors include that some TEAEs were associated with recurrence of the underlying malignancies. Additionally, systemic treatments for cGVHD such as tacrolimus, sirolimus and mycophenolate mofetil are associated with cytopenias. The low incidence in the IPF analysis group and no events in the pooled psoriasis analysis group to date, support that the cytopenias may be due to underlying factors and disorders within the cGVHD population.

Malignancies/Neoplasms (Recurrent malignancy and Secondary neoplasm)

Malignancies/neoplasms are a potential risk associated with belumosudil based on the mechanism of action (immune modulator), and events of interest occurring in the target population. Recurrence of underlying malignancy was identified using the SMQ malignant or unspecified tumours (narrow). These results were medically reviewed against the verbatim term and the subjects' medical history to identify events of recurrences of the underlying malignancy. The SOC neoplasm benign, malignant and unspecified was used to identify newly occurring neoplasms. The recurrent malignancies identified in subjects were excluded from the results presented.

The incidence of malignancy TEAEs was low. The most commonly reported (≥ 2 subjects) events within this category included AML recurrent (2.4% 200 mg QD and 1.6% all belumosudil), leukaemia recurrent (1.2% 200 mg QD and 1.1% all belumosudil), and plasma cell myeloma (1.2% 200 mg QD and 1.1% all belumosudil).

The most commonly reported (≥ 2 subjects) secondary neoplasms (excluding recurrent malignancies) included squamous cell carcinoma of the skin (0 200 mg QD and 1.1% all belumosudil); all other secondary neoplasms were reported in 1 subject each.

No signal for increased recurrence of malignancies or secondary neoplasms has been identified to date. The Sponsor will continue to closely monitor these events.

Hypotension

Based on the on-target effect of pan-ROCK inhibitors and the observed lowering of blood pressure in nonclinical studies, hypotension is a potential risk with belumosudil treatment.

In the pooled cGVHD analysis group, this analysis identified 4.8% of subjects in the 200 mg QD group and 4.3% of all belumosudil-treated subjects with events in this category; the events reported were 3.6% and 3.8% subjects with cases of hypotension and 1.2% and 0.5% subjects with orthostatic hypotension in the 200 mg QD group and all belumosudil-treated population, respectively.

The majority of hypotension events were considered mild or moderate; 4 of the 7 hypotension events were assessed as Grade 3 AEs.

In addition, blood pressure measurements were evaluated for systolic blood pressure < 90 mmHg in subjects with cGVHD; 2.4% of subjects in the 200 mg QD group and 2.7% of all belumosudil-treated subjects experienced at least one systolic blood pressure < 90 mmHg.

Overall, 7.2% of subjects in the 200 mg QD group and 6.5% of all belumosudil-treated subjects experienced at least one TEAE of hypotension CMQ or systolic blood pressure < 90 mmHg; of, these, Grade ≥ 3 TEAEs of hypotension CMQ or systolic BP < 90 mmHg was reported in 4.8% of subjects in the 200 mg QD group and 4.3% of all belumosudil-treated subjects.

Review of decreases from baseline in systolic and diastolic blood pressure in subjects with cGVHD did not reveal substantial changes.

Several of the subjects had confounding factors, such as underlying disorders or acute infection. In the cGVHD population, oral sensitivity and dysphagia commonly lead to poor oral intake and nausea and vomiting contribute to dehydration potentially leading to hypotension. In several subjects, these confounding factors contributed to the hypotension.

Given the confounding effects of cGVHD and the low incidence in the other populations, hypotension is not considered an identified risk based on data to date. The Sponsor will continue to monitor this event through routine pharmacovigilance.

Impaired Wound Healing

Impaired wound healing is a potential risk due to the antifibrotic mechanism of action of belumosudil. Impaired wound healing events were searched using the HLT healing abnormal not otherwise classified (NEC). Overall, few impaired wound healing events were seen.

This analysis identified 1 (0.5%) subject with cGVHD with events in this category; the event reported was a single case of impaired healing which occurred in the first month of treatment

with belumosudil 200 mg QD. The event was considered mild in severity and assessed by the Investigator as not related to study drug; the subject recovered and required no dose modification.

8.3.6 Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

No patient-reported outcomes were collected.

8.3.7 Safety Analyses by Demographic Subgroups

Data:

The following subgroups were used for analysis of TEAEs:

- Gender (female / male)
- Race (White or Caucasian / others)
- Age group (≥ 65 years / < 65 years)
- Body mass index (BMI) group (< 25 kg/m^2 / 25 to < 30 kg /m^2 / ≥ 30 kg/m^2)
- Baseline hepatic impairment (normal / > upper limit of normal [ULN] [AST>ULN or ALT>ULN or total bilirubin>ULN])
- Baseline renal impairment (normal –GFR > 90 mL/min / 1.73 m^2/ Mild - GFR 60-90 mL/min / 1.73 m^2 / Moderate - GFR < 60 mL/min/1.73 m^2)
- Concomitant PPI use on C1D1 (yes / no)
- Concomitant CYP3A4 inhibitor use on C1D1 (yes / no)
- Maximum on-treatment QTcF value (≤ 450 ms / > 450 to 480 ms / > 480 to 500 ms / > 500 ms)
- Maximum on-treatment change in QTcF value from baseline (≤ 0 ms / > 0 to ≤ 30 ms / > 30 to ≤ 60 ms / > 60 ms)

Specific to cGVHD (Analysis Group 1):

- Severe cGVHD at screening (yes / no)
- Number of prior lines of therapy (≤ 3 / > 3)
- Duration of cGVHD before enrollment (> 50 percentile / ≤ 50 percentile).

The Applicant's Position:

Overall, analysis of TEAEs across the selected subgroups revealed no remarkable differences in the type or frequency of TEAEs experienced. Evaluation of differences in the incidence of TEAEs was often limited by the relative sizes of the subgroups being compared.

Drug-Demographic Interactions

TEAEs by Sex

TEAEs by Age

TEAEs by Race

All studies were performed in Europe. No racial or ethnic data was collected as part of any study. Therefore, no comparisons can be made.

Drug-Disease Interactions

[Insert text here.]

Drug-Drug Interactions

[Insert text here.]

8.3.8 Specific Safety Studies/Clinical Trials

The Applicant's Position:

The belumosudil safety discussion focuses on pooled data from the 2 studies in subjects with cGVHD, Studies KD025-208 and KD025-213. These data are supplemented with the study in IPF subjects (KD025-207; included in Analysis Group 2) and the pooled data in psoriasis (Studies KD025-205, KD025-206, and KD025-211; included in Analysis Group 3). Overall, 68 subjects with IPF and 148 subjects with psoriasis were included the analysis of safety.

IPF

Subjects in Study KD025-207 are analyzed according to the doses administered: 400 mg QD (belumosudil as randomized + BSC after crossover) and BSC (BSC censored by crossover date).

The median duration of treatment with belumosudil in the 68 subjects with IPF was 10.5 months (range: 0.03-24.44 months), with 16 subjects (23.5%) having been exposed to belumosudil for ≥ 6 to 12 months and 26 subjects (38.2%) treated for ≥ 12 months. The median duration of treatment for the BSC group was expectedly shorter at 5.55 months, as subjects who experienced progressive disease at any time in the first 6 months were allowed to switch to treatment with belumosudil. The cumulative duration of belumosudil exposure was 63.9 patient-years and 10.1 patient-years for BSC. Therefore, exposure adjusted event rates (EAER) were utilized for comparisons.

Overall, the incidence of TEAEs for belumosudil-treated subjects with IPF was similar to

belumosudil-treated subjects with cGVHD. However, belumosudil-treated subjects with IPF experienced a greater number of TEAEs (98.5% belumosudil vs 79.2% BSC), related TEAEs (44.1% belumosudil vs 8.3% BSC), SAEs, (51.5% belumosudil vs 16.7% BSC), and Grade ≥ 3 TEAEs (44.1% belumosudil vs 20.8% BSC) when compared to BSC-treated subjects with IPF. The incidence of TEAEs may differ due to the fact that belumosudil-treated subjects were allowed to extend treatment up to 24 weeks beyond BSC treatment.

There were no cases of severe hepatoxicity, such as hepatitis, in subjects treated with belumosudil in any analysis group. There have been no belumosudil-treated subjects' findings that meet the criteria of Hy's Law. Exposure adjusted event rate data indicate that GGT increases were higher in the BSC group, while AST and ALT elevations were higher in the belumosudil group. There were not elevations of bilirubin. The frequency of hematologic TEAEs was low in subjects with IPF, which suggests the majority of cytopenias are due to the underlying disorders of patients within the cGVHD patient population. Analysis of LFT results and other AESIs in subjects with IPF revealed no definitive safety concerns.

Psoriasis

The median duration of treatment with belumosudil in the 148 subjects with psoriasis was 3.07 months (range: 0.03-12.19 months), with 46 subjects (31.1%) having been exposed to belumosudil for ≥ 6 to 12 months and 1 subject (0.7%) treated for ≥ 12 months. The median duration of treatment for the placebo group was similar (3.07 months). The cumulative duration of exposure was 61.3 patient-years in the belumosudil group and 4.8 patient-years in the placebo group.

In general, the types and incidence of the most commonly reported TEAEs in the pooled psoriasis analysis group was greater in all belumosudil-treated subjects in comparison to the placebo group. The common TEAEs (≥ 5%) reported in all belumosudil-treated subjects included ALT increase (7.4%), nausea (7.4%), headache (6.1%), viral upper respiratory tract infection (5.4%), and vomiting (5.4%). No TEAEs were reported in more than 2 subjects in the placebo group.

Although the types of commonly reported events were similar in subjects with cGVHD and subjects with psoriasis, the incidence for most of these commonly reported TEAEs was higher in subjects with cGVHD compared to subjects with psoriasis.

There were no cases of severe hepatoxicity, such as hepatitis, in subjects treated with belumosudil in any analysis group. There have been no belumosudil-treated subjects' findings that meet the criteria of Hy's Law. Exposure adjusted event rates of GGT, AST and ALT increases were higher in the placebo arm than in the belumosudil treated, however, these were in only 1 subject for each event. The number of subjects and exposure in the placebo arm were limited.

The frequency of hematologic TEAEs was low in subjects with psoriasis, which suggests the

majority of cytopenias are due to the underlying disorders of patients within the cGVHD patient population. Analysis of LFT results and other AESIs in subjects with psoriasis revealed no definitive safety concerns.

8.3.9 Additional Safety Explorations

Human Carcinogenicity or Tumor Development
Not applicable.

Human Reproduction and Pregnancy
The Applicant's Position:

No information is available on the safety or efficacy of belumosudil in pregnant or lactating females. It is unknown if belumosudil is excreted in milk.

Pediatrics and Assessment of Effects on Growth
The Applicant's Position:

No information is available on the safety or efficacy of belumosudil in pediatric subjects.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound
The Applicant's Position:

There is no specific experience in the management of belumosudil overdose in patients. There is no known antidote for overdoses with belumosudil. Single doses up to 1000 mg have been given with acceptable tolerability in healthy volunteers. Appropriate supportive treatment should be given.

Based on the belumosudil mechanism of action, lack of activity on known targets associated with abuse or dependence, and lack of brain exposure of belumosudil, the potential for abuse and dependence with belumosudil is considered minimal.

8.3.10 Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The Applicant's Position:

Belumosudil has not been approved by any regulatory authority and remains an investigational agent.

Expectations on Safety in the Postmarket Setting

Data:

The Applicant's Position:

Analysis of the safety data including the potential risks indicate that most are generally manageable with limited dose modifications or drug discontinuations. As described in the belumosudil Risk Management Plan, no important identified risks have been accessed and the risks can be adequately monitored through routine pharmacovigilance.

8.3.11 Integrated Assessment of Safety

The Applicant's Position:

The safety profile of belumosudil 200 mg QD has been characterized based on safety data from analyses of the pooled cGVHD studies, which were supplemented by safety data from studies in IPF and psoriasis. Overall, TEAEs were generally reversible and manageable.

A total of 402 subjects have received at least 1 dose of belumosudil across the 3 indications, as of the data lock date of 19 February 2020. There were 186 subjects with cGVHD treated with belumosudil; 83 of whom received the target dose of 200 mg QD. The cumulative duration of exposure in this group was 57.3 patient-years (131 patient-years among all belumosudil-treated subjects).

Almost all subjects experienced at least one TEAE. The most common adverse events by SOC in the 200 mg QD group were Gastrointestinal disorders (67.5%), Infections and infestations (63.9%), Respiratory (59.0%), and General disorders (59.0%). The most commonly reported events (> 20%) in subjects with cGVHD receiving belumosudil 200 mg QD were fatigue (38.6%), diarrhoea (32.5%), upper respiratory tract infection (28.9%), nausea (27.7%), and dyspnoea (26.5%), and cough and oedema peripheral (24.1% each).

The most frequently reported Grade ≥ 3 TEAEs in subjects with cGVHD receiving belumosudil 200 mg QD were generally consistent with those expected in a population of subjects with advanced cGVHD being treated with corticosteroids and other immunosuppressants, including pneumonia (7.2%), dyspnoea (3.6%), hyperglycaemia (6.0%), and hypertension (6.0%). There were a small number of Grade 4 events; these were mainly recurrence of malignancy or infection. Few Grade 4 TEAEs were assessed as related to belumosudil.

Adverse events of special interest have been identified and characterized. They are hepatic event/elevated liver function tests, infections, hematologic events, malignancy/neoplasm, hypotension, and impaired healing. None have been assessed as important identified risks at this time.

In summary, the safety profile of belumosudil 200 mg QD has been characterized based on safety data from analyses of the pooled cGVHD studies, which was supplemented by safety data from studies in IPF and psoriasis. Overall, TEAEs were generally reversible and manageable. The most commonly reported events were consistent with those seen in the

cGVHD patient population and systemic immunosuppression. Belumosudil 200 mg QD has shown to have an acceptable safety profile consistent with that expected in cGVHD, a serious disease with limited therapeutic options.

FDA'S POSITION

8.3.1 Safety Review Approach

FDA's analyses are based on data cumulative through the Safety Update Report submitted 11/25/2020 and revised ISS datasets submitted through 3/5/2021.

Selection of Safety Population for Review

The safety database was comprised of 694 participants in 15 clinical studies, including 618 who received belumosudil initially and 76 who received placebo or best supportive care initially. See Section 7.1 for an overview of the design of each study.

Table 58 shows number of patients by dose in the 6 clinical trials in GVHD, idiopathic pulmonary fibrosis (IPF) and psoriasis. There were 417 participants in these clinical trials; 375 were treated with belumosudil and 42 with placebo or best supportive care.

Table 58. Patient Trials: Number of Patients by Dose Cohort

Dose Cohort	N	Study by Diagnosis						
		cGVHD			IPF	Psoriasis		
		KD025-208	KD025-213	All cGVHD	KD025-207*	KD025-205	KD025-206	KD025-211*
0	**42**	0	0	**0**	24	0	0	18
200 mg QD	**114**	17	66	**83**	0	8	0	23
200 mg BID	**117**	16	66	**82**	0	0	13	22
400 mg QD	**106**	21	0	**21**	51	0	13	21
400 mg BID	**12**	0	0	**0**	0	0	12	0
600 mg QD	**26**	0	0	**0**	0	0	0	26
Total	**417**	54	132	**186**	75	8	38	110

Source: FDA Analysis
*Placebo- or best supportive care-controlled trials
The cells highlighted in red are supportive of the safety of the proposed dose. The cells highlighted in blue is used for analyses of safety by dose.

All study participants are considered in the assessment of fatal adverse events. The 83 patients highlighted in the red cells in Table 58 provide the main analysis cohort to assess safety of the recommended dose in patients with cGVHD, the intended population. The 186 patients highlighted in the blue cell are used for the analysis of safety by dose in the intended population. The detailed results of analyses of safety in patients with IPF or psoriasis are

provided separately in Section 8.3.8; the results in these studies will be used as supportive information.

There were 277 participants in the 9 volunteer studies; 243 received belumosudil and 34 received placebo. Table 59 shows the number of participants by dose cohort. The detailed results of analyses of safety in the volunteer studies is provided separately in Section 8.3.8; the results in these studies will be used as supportive information.

Table 59. Volunteer Studies: Number of Subjects by Dose Cohort

Dose Cohort	N	Study								
		KD025-101*	KD025-102*	KD025-103*	KD025-105	KD025-106	KD025-107	KD025-108	KD025-109	SLx-2119-09-01*
0	34	16	8	2	0	0	0	0	0	8
20 mg QD	6	0	0	0	0	0	0	0	0	6
40 mg QD	12	6	0	0	0	0	0	0	0	6
80 mg QD	12	6	0	0	0	0	0	0	0	6
120 mg QD	6	6	0	0	0	0	0	0	0	0
160 mg QD	12	6	0	0	0	0	0	0	0	6
200 mg QD	91	0	0	0	0	23	35	5	28	0
200 mg BID	38	0	0	0	0	0	38	0	0	0
240 mg QD	6	6	0	0	0	0	0	0	0	0
320 mg QD	6	6	0	0	0	0	0	0	0	0
400 mg QD	6	6	0	0	0	0	0	0	0	0
500 mg QD	24	6	6	0	12	0	0	0	0	0
500 mg BID	12	0	6	6	0	0	0	0	0	0
800 mg QD	6	0	6	0	0	0	0	0	0	0
1000 mg QD	6	0	6	0	0	0	0	0	0	0
All	277	64	32	8	12	23	73	5	28	32

Source: FDA Analysis.
*Placebo-controlled studies

Anticipated Safety Issues

There are no approved ROCK2 inhibitors to inform expected class-related safety concerns. Based on the mechanism of action (MOA) and secondary pharmacology studies:

- The MOA involves fibrotic pathways and Th17 cells, so impaired wound healing and infections were anticipated.
- In secondary pharmacology studies, belumosudil also inhibited the mTOR pathway. Therefore, specific safety analyses has been performed for subjects who received mTOR inhibitors as concomitant systemic cGVHD therapies.
- Belumosudil also inhibited UGT1A1 at concentrations that could be achieved clinically (Applicant's 4/28/2021 response to Information Request), so transient isolated hyperbilirubinemia was also anticipated.

There were safety issues identified during nonclinical toxicology phase of drug development as requiring particular attention in the safety evaluation for the drug.

- In animals studies of belumosudil, the toxicities were observed in the gastrointestinal (GI) tract (emesis, loose stools, and/or abnormal black contents, increase in salivation), liver (elevated liver enzymes, hypertrophy/increased organ weight, and cholestasis/inflammation), kidney (increased blood urea nitrogen [BUN], tubular changes, pigmentation, intracellular protein droplets in the epithelium), hemolymphoid system (regenerative anemia), and reproductive system (See Section 5.1).
- In safety pharmacology studies in dogs, belumosudil was associated with lowering of the blood pressure.
- In reproductive toxicity studies, belumosudil was associated with embryo-fetal toxicity and impaired male fertility.
- Photoabsorbance and the potential for phototoxicity was observed in vitro, and the drug distributed to photo-sensitive areas such as skin and uveal tract.

There were no clinical holds for safety during the development program. The main emerging toxicity during clinical development was elevations of liver transaminases.

Based on key safety issues identified from the nonclinical testing and clinical development program, the safety Adverse Events of Special Interest in subjects with cGVHD were developed (See Section 8.3.4 below).

8.3.2 Review of the Safety Database

Overall Exposure

Table 60 shows treatment exposures of belumosudil in patients with cGVHD. Only 41% of the patients treated with 200 mg daily were on therapy for more than 1 year. The duration of exposure for patients with IPF or psoriasis is as described in the Applicant's section above.

Table 60. cGVHD Safety Population: Duration of Treatment with Belumosudil

Months	200 mg QD (N = 83)	200 mg BID (N = 82)	400 mg QD (N = 21)	Total cGVHD (N = 186)
Duration of Treatment				
Median Months	9.2	10.6	9.0	0.4
Range	0.5 – 44.7	0.4 – 38.9	0.7 – 35.4	0.4 – 44.7
Exposure Ranges, n (%)				
< 6 Months	33 (39.8)	31 (37.8)	7 (33.3)	71 (38.2)
≥ 6 to 12 Months	16 (19.3)	14 (17.1)	4 (19.0)	34 (18.3)
≥ 12 Months	34 (41.0)	37 (45.1)	10 (47.6)	81 (43.5)

Source: FDA Analysis. Abbreviations: QD, once daily; BID, twice daily; cGVHD = chronic graft versus host disease.

Clinical Reviewer Comment: Although the exposure may be sufficient to determine the initial safety profile of belumosudil in the intended population, given that patients may be on treatment for an extended period, additional data would be needed to confirm long-term safety.

Relevant Characteristics of the Safety Population

Table 61 shows the demographics and characteristics by dose and schedule for all 186 patients with cGVHD treated with belumosudil.

Table 61. cGVHD Safety Population: Demographics

Characteristics	200 mg QD (N = 83)	200 mg BID (N = 82)	400 mg QD (N = 21)	Total cGVHD (N = 186)
Age (years)				
Median	53	57	46	54.5
Range	20 - 77	21 - 77	25 -75	20 - 77
Age Group, n (%)				
<65 Years	66 (79.5)	56 (68.3)	16 (76.2)	138 (74.2)
>=65 Years	17 (20.5)	26 (31.7)	5 (23.8)	48 (25.8)
Sex, n (%)				
Male	55 (66.3)	42 (51.2)	12 (57.1)	109 (58.6)
Female	28 (33.7)	40 (48.8)	9 (42.9)	77 (41.4)
Race, n (%)				
White	70 (84.3)	71 (86.6)	18 (85.7)	159 (85.5)
Black/African American	6 (7.2)	1 (1.2)	2 (9.5)	9 (4.8)
Asian	1 (1.2)	2 (2.4)	0	3 (1.6)
American Indian or Alaska Native	0	4 (4.9)	0	4 (2.2)
Other	2 (2.4)	0	1 (4.8)	3 (1.6)
Unknown	4 (4.8)	4 (4.9)	0	8 (4.3)
Ethnicity				
Hispanic/Latino	10 (12.1)	11 (13.4)	3 (14.3)	24 (12.9)
Not Hispanic/Latino	73 (87.9)	66 (80.5)	18 (85.7)	157 (84.4)
Not Reported	0	5 (6.1)	0	5 (2.7)
BMI Group				
<25 kg/m^2	34 (43.6)	22 (30.6)	4 (22.2)	60 (35.7)
25 to <30 kg/m^2	26 (33.3)	28 (38.8)	10 (55.6)	64 (38.1)
>= 30 kg/m^2	18 (23.1)	22 (30.6)	4 (22.2)	44 (26.2)

Source: FDA Analysis
Abbreviations: QD, once daily; BID, twice daily; cGVHD = chronic graft versus host disease; BMI, body mass index.

Table 62 shows the baseline characteristics of chronic GVHD and common concomitant medications in all 186 patients treated with belumosudil at 3 dose regimens.

Table 62. cGVHD Safety Population: Baseline Disease Characteristics

Characteristics	200 mg QD (N = 83)	200 mg BID (N = 82)	400 mg QD (N = 21)	Total cGVHD (N = 186)
Time from transplant to cGVHD diagnosis				
Median (months)	7.1	6.7	7.8	6.9
Range	1.0 - 48.3	1.8 – 48.8	1.0 – 28.1	1.0 – 48.8
Prior aGVHD (yes), n (%)	55 (67.1)	60 (73.2)	13 (61.9)	128 (69.2)
Number of prior lines of therapy for cGVHD				
Median	3	3	2	3
Range	1 - 6	1 - 6	1 - 4	1 - 6
Group of Number of prior lines of therapy for cGVHD, n (%)				
Group <=3	51 (46.7)	47 (40.5)	20 (90.9)	118 (46.8)
Group >3	32 (53.9)	35 (59.5)	1 (9.1)	68 (53.2)
Prior ibrutinib (yes), n (%)	23 (27.2)	24 (29.3)	3 (14.3)	50 (26.9)
Prior ruxolitinib (yes), n (%)	20 (24.1)	18 (21.9)	1 (4.8)	39 (20.9)
Severity of cGVHD at screening, n (%)				
Mild	2 (2.4)	0	1 (4.8)	3 (1.6)
Moderate	23 (27.7)	25 (30.5)	4 (19.0)	52 (28.0)
Severe	58 (69.9)	57 (69.5)	16 (76.2)	131 (70.4)
Number of organs involved at baseline				
Median	6	7	2	6
Range	1 - 7	1 - 7	5 - 7	1 - 7
Concomitant systemic cGVHD therapies on Study Day 1, n (%)	83 (100)	81 (98.8)	21 (100)	185 (99.5)
Corticosteroids alone	28 (33.7)	31 (37.8)	6 (28.6)	65 (34.9)
Corticosteroids and other drugs	53 (63.9)	49 (59.8)	15 (71.4)	117 (62.9)
Corticosteroids + Tacrolimus +/- other	31 (37.3)	34 (41.5)	9 (42.9)	74 (39.8)
Corticosteroids + MMF +/- other	10 (12.0)	1 (1.2)	1 (4.8)	12 (6.5)
Corticosteroids + ECP +/- other	13 (15.7)	12 (14.6)	2 (9.5)	27 (14.5)
Corticosteroids + Sirolimus +/- other	14 (16.9)	14 (17.1)	0	28 (15.1)
mTOR inhibitor* Sirolimus alone	0	0	0	0
Sirolimus and other drugs	14 (16.9)	14 (17.1)	0	28 (15.1)
Everolimus alone	0	0	0	0
Everolimus and other drugs	0	0	0	0

Source: FDA Analysis.
Abbreviations: QD, once daily; BID, twice daily; cGVHD = chronic graft versus host disease; ECP, extracorporeal photopheresis; MMF, mycophenolate mofetil; CNI, calcineurin inhibitor; MTX, methotrexate; mTORi, mammalian target of rapamycin (mTOR) inhibitor.
* There was no subject who received mTOR inhibitor sirolimus alone. There was no subject who received other mTOR inhibitors such as Everolimus.

Due to the problems with discrepancies in new systemic therapy calls and dates as discussed in Section 8.1 above, descriptions of the concomitant medications and analyses of safety by concomitant medications should be interpreted with caution.

Table 63 shows the demographics of the participants in the studies in patients with IPF, patients with psoriasis, and healty volunteers.

Table 63. Demographics in IPF, Psoriasis and Healthy Volunteers Studies

	IPF and Psoriasis (n=231)		Volunteers (n=277)	
Age				
Median age (range)	55 years (19-89 years)		36 years (18-69 years)	
Age >=65 years	71	31%	7	3%
Sex				
Male	151	65%	263	95%
Female	80	35%	14	5%
Race				
White	207	90%	172	62%
Black	12	5%	94	34%
Asian	8	3%	5	2%
Other	4	2%	6	2%
Population				
Psoriasis	156	68%		
IPF	75	32%		
Hepatic Impairment			17	6%
Healthy Volunteer			260	94%
Source: FDA analysis				

Adequacy of the Safety Database

The size of the safety database for cGVHD (n=186) will allow for detection of common adverse reactions and to support the benefit-risk assessment. The small number of patients limits the ability to detect rare events, but it is considered adequate given that the safety profile established in other disease (or volunteer) settings. There were dose-ranging studies, so safety can be assessed by dose as well.

The study population in this NDA submission would be considered relevant to the US patient population (Table 1 above in Section 2.1), with similar age, sex and race distribution, and number of prior lines of chronic GVHD systemic therapies (including prednisone, tacrolimus, sirolimus, MMF, and ECP). However, there were higher percentages of patients in this submission received ibrutinib (27% vs. 0.5%) or ruxolitinib (21% vs. 2.5%) for chronic GVHD therapy than that in the US population sample (see FDA's position in Section 2.1). The demographics of the safety database demonstrate adequate representation of the target patient population with the notable exception of the absence of pediatric patients.

The duration of treatment in the safety population is adequate to provide assessment of adverse reactions in the short term. The median duration of follow-up of the safety database was 14.7 months (range: 0.56 - 44.2).

Clinical Reviewer Comment: Due to the lack of data on the safety of belumosudil during long-term use, additional data may be required.

8.3.3 Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

See Section 7.2 regarding the datasets used for the safety analyses. Additionally, the ISS data file adlb.xpt submitted 12/16/2020 was noted to have multiple missing values in the numeric fields as well as errors in grading. A corrected ISS adlb.xpt was received 3/5/2021 as part of a major amendment. The corrected version was used for the analyses in this section.

Categorization of Adverse Events

AEs were reported using the investigator's verbatim term and coded by the Applicant using Medical Dictionary for Regulatory Activities (MedDRA) version 20.0 terms. The events were graded using the NCI-CTCAE version 5.0. Treatment-emergent adverse (TEAE) events included all events occurring within 28 days after the last dose of belumosudil.

FDA compared verbatim terms to (MedDRA) terms for AEs, and no irregularities were identified. If GVHD was in the AE term or the lower level term, the event was not included in the analysis. Additionally, terms related to relapse of the primary malignancy were not considered adverse events. In order to improve the accuracy of estimating the risk of adverse reactions, grouped terms were used by FDA for some analyses, as described in Section 14.5 [Grouped Terms Use for Safety Analyses].

Based on mechanism of action (effects on immune system), nonclinical toxicology profile and emerging early clinical trial data, the events of hypersensitivity, hepatotoxicity, infections, prolonged QT and cardiac arrhythmias, cytopenias, impaired wound healing, second malignancies, and hypotension were chosen by the Applicant as Adverse Events of Special Interest (AESIs). Standardized MedDRA queries (SMQs), customized MedDRA queries (CMQs), SOCs, high-level group terms (HLGTs), high-level terms (HLTs) were used to define the AESIs as described by the Applicant above. FDA also assessed PTLD, graft failure and relapse in detail.

Routine Clinical Tests

The schedules of safety monitoring for Studies KD025-208 and KD025-213 are described in section 8.1 above. The schedule of examinations and testing was adequate to assess the risks of safety events.

8.3.4 Safety Results

Deaths

Table 64 below shows total of deaths by protocol for patients with cGVHD, IPF or psoriasis. There were no deaths in the volunteer studies.

Table 64. Patient Studies: Deaths

			Deaths		Deaths <= 30 days from last dose	
STUDYID	**TRT01A**	**N**	**n**	**%**	**n**	**%**
KD025-205	KD025 200 mg QD	8	0	0%	0	0%
KD025-206	KD025 200 mg BID	13	0	0%	0	0%
	KD025 400 mg QD	13	0	0%	0	0%
	KD025 400 mg BID	12	0	0%	0	0%
KD025-207	BSC	24	3	13%	2	8%
	KD025 400 mg QD	51	8	16%	7	14%
KD025-208	KD025 200 mg QD	17	4	24%	0	0%
	KD025 200 mg BID	16	2	13%	0	0%
	KD025 400 mg QD	21	7	33%	5	24%
KD025-211	Placebo BID	18	0	0%	0	0%
	KD025 200 mg QD	23	1	4%	1	4%
	KD025 200 mg BID	22	0	0%	0	0%
	KD025 400 mg QD	21	0	0%	0	0%
	KD025 600 mg/day	26	0	0%	0	0%
KD025-213	KD025 200 mg QD	66	8	12%	4	6%
	KD025 200 mg BID	66	6	9%	4	6%

Source: FDA analysis

Clinical TL Review Comment: Although there appears to be an excess in treatment-emergent deaths in the 400 mg daily dose level of Studies KD025-207 and KD025-208, the numbers of patients treated is small, and the effect was not consistent across protocols.

In the planned safety population, there were total of 46 adverse events (AEs) that resulted in deaths of 26 subjects: including 43 AEs that resulted in death of 23 subjects within 30 days from the last dose of belumosudil.

The Applicant stated that only one subject's cause of death was related to the study drug in subjects with cGVHD. FDA adjudicated the root cause of death under four categories:
1) recurrent primary malignancy, 2) active primary disease (GVHD vs psoriasis vs IPF) ,
3) unrelated (car accident), 4) fatal adverse reaction to the drug. Table 65 shows the FDA-adjudicated root causes of death for fatal adverse reaction within 28 days from the last dose of belumosudil.

Table 65. Patient Studies: FDA Adjudication of Cause of Death*

STUDYID	USUBJID	DX	Death - Study day	Death - Days from last dose	Applicant's COD	FDA adjudicated COD
KD025-207	KD025-207 (b) (6)	IPF	171	10	Sepsis, acute respiratory failure, and IPF	Primary - IPF
KD025-207	KD025-207	IPF	625	0	IPF	Primary - IPF
KD025-207	KD025-207	IPF	651	6	Acute respiratory failure and pneumonia	Unrelated - lung cancer
KD025-207	KD025-207	IPF	201	1	Hypoxemic respiratory failure	Primary - IPF
KD025-207	KD025-207	IPF	266	25	Cardiac arrest	Unrelated - CAD pre-existing
KD025-207	KD025-207	IPF	340	8	Acute respiratory failure and Cardiac failure congestive	Unrelated - CAD pre-existing
KD025-207	**KD025-207**	**IPF**	**41**	**0**	**Unknown causes**	**AR - sudden unexplained death**
KD025-207	KD025-207	IPF	326	26	Acute Respiratory Failure	Primary - IPF
KD025-208	KD025-208	cGVHD	925	0	Pericardial effusion	Primary -GVHD
KD025-208	KD025-208	cGVHD	25	4	Relapse of AML	Unrelated - AML pre-existing
KD025-208	KD025-208	cGVHD	68	0	Pneumonia and skin infection	Primary -GVHD
KD025-208	**KD025-208**	**cGVHD**	**22**	**0**	**Cardiac Arrest**	**AR - sudden unexplained death**
KD025-208	KD025-208	cGVHD	434	1	Progression of cGVHD	Primary -GVHD
KD025-211	KD025-211	Psoriasis	111	0	Natural causes (hypertensive and atherosclerotic cardiovascular disease and morbid obesity)	Unrelated - CAD pre-existing
KD025-213	KD025-213	cGVHD	26	14	Cardiac Arrest	Primary -GVHD
KD025-213	KD025-213	cGVHD	292	19	Infection related to cGVHD	Primary -GVHD

KD025-213	**KD025-213-(b) (6)**	**cGVHD**	**276**	**0**	**Cardiac Arrest**	**AR - sudden unexplained death**
KD025-213	KD025-213-	cGVHD	30	0	Hemothorax	Unrelated - Procedural
KD025-213	KD025-213-	cGVHD	57	11	Respiratory failure	Primary -GVHD
KD025-213	**KD025-213**	**cGVHD**	**17**	**3**	**Neutropenic shock secondary to acute pneumonia**	**AR - Gastrointestinal toxicity and multiorgan failure**
KD025-213	KD025-213-	cGVHD	56	16	Relapse of AML	Unrelated - AML pre-existing
KD025-213	KD025-213-	cGVHD	237	0	Respiratory arrest	Unrelated – COVID-19

Source: FDA analysis.
*Limited to death within 30 days from the last dose of belumosudil
Abbreviations: Dx, diagnosis primary disease; COD, causes of death; cGVHD, chronic Graft versus Host Disease; IPF, idiopathic pulmonary fibrosis; CAD, coronary artery disease; AML, acute myeloid leukemia; N/V/D , nausea, vomiting, diarrhea; MOF, multiorgan failure; COVID-19, coronavirus disease 2019.

There were **four** fatal adverse events for which FDA could not exclude a possible relation to belumosudil:

Case 1: Subject KD025-207-(b) (6) was a 73 year-old male treated with belumosudil 400 mg QD for idiopathic pulmonary fibrosis (IPF). He had medical history of diabetes, chronic kidney disease, hypertension, aortic aneurysm, obstructive sleep apnea, and melanoma. On the study day 41, the subject died "naturally due to unknown causes" as per the investigator. No signs or symptoms were reported, and an autopsy was not performed. FDA could not exclude a possible relation to belumosudil for the sudden unexplained death.

Case 2: Subject KD025-208-(b) (6) was a 25 year-old male treated with belumosudil 400 mg QD for chronic GVHD. His medical history included thrombocytopenia, hyperglycemia, hemorrhagic stroke, seizure, acute respiratory failure, and hypertension. On study day 22, the subject experienced cardiac arrest at home. The cause of the death was cardiac arrest as per the investigator. An autopsy was not performed. FDA could not exclude a possible relation to belumosudil for the sudden unexplained death.

Case 3: Subject KD025-213-(b) (6) was a 60 year-old male treated with belumosudil 200 mg BID for chronic GVHD. His medical history included hyperglycemia and hypertension. On study day 276, the subject suffered a cardiac arrest. The cause of the death was cardiac arrest as per the investigator. An autopsy was not performed. FDA could not exclude a possible relation to belumosudil for the sudden unexplained death.

Case 4: Subject KD025-213-(b) (6) was a 75 year-old male treated with belumosudil 200 mg QD for chronic GVHD after allogeneic hematopoietic stem cell transplantation for AML. His other medical history included hyperlipidemia, hypertension, chronic kidney injury, proteinuria, hyperkalemia, and thrombocytopenia. At study baseline, the neutrophil and platelet counts were normal. On study day 15, the subject was admitted after 3 days of nausea and vomiting and 8-9 days of diarrhea. The neutrophil and platelet counts were still normal. On study day 16,

he was intubated for acute respiratory failure. Chest X-ray showed pneumonia, and an abdominal X-ray showed dilated loops of small bowel with air-fluid levels. Despite maximal supportive care, the subject's condition declined, and he expired on study day 17 with multi-organ failure. Blood culture remained negative. Autopsy revealed no recurrent leukemia; the bowel showed multifocal erythematous lesions but no GVHD; and cultures from the lung tissue grew *K. oxytoca*. The Applicant consider the event MOF at least possibly related to study drug. FDA agrees that multi-organ failure was the proximate cause of death with gastrointestinal toxicity at least possibly related to study drug being the root cause of death.

Serious Adverse Events

The most common System Organ Class (SOC) for SAEs was infections and infestations. Table 66 below shows the SAEs by SOC by dose reported in at least 2 patients.

Table 66. cGVHD Safety Population: SAEs by SOC Terms

	200 mg QD (N=83)		200 mg BID (N=82)		400 mg QD (N=21)	
SOC Terms*	**n**	(%)	**n**	(%)	**n**	(%)
Any SAE	32	38.6	29	35.4	13	61.9
Infections and infestations	14	16.9	15	18.3	5	23.8
Respiratory, thoracic and mediastinal disorders	7	8.4	5	6.1	4	19.0
Gastrointestinal disorders	5	6.0	4	4.9	2	9.5
General disorders and administration site conditions	5	6.0	2	2.4	2	9.5
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3	3.6	0	0	3	14.3
Renal and urinary disorders	3	3.6	1	1.2	1	4.8
Cardiac disorders	2	2.4	5	6.1	2	9.5
Injury, poisoning and procedural complications	2	2.4	1	1.2	0	0
Metabolism and nutrition disorders	2	2.4	0	0	0	0
Vascular disorders	2	2.4	3	3.7	0	0

Source: FDA Analysis. *Terms = AEDECOD for System Organ Class (SOC).

Table 67 below shows the SAEs by grouped terms reported in more than 2% of patients.

Table 67. cGVHD Safety Population: SAEs by Grouped Terms

SAEs	200 mg QD (N=83)		200 mg BID (N=82)		400 mg QD (N=21)	
Grouped Terms*	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Infections	12	14.5	10	12.2	3	14.3
Bacterial infection	3	3.6	4	4.9	0	0
Hemorrhage	3	3.6	1	1.2	1	4.8
Pyrexia	3	3.6	0	0	0	0
AML recurrent	2	2.4	0	0	0	0
Diarrhea	2	2.4	1	1.2	0	0
Renal failure	2	2.4	1	1.2	0	0
Thrombosis	2	2.4	3	3.7	0	0
Viral infection	2	2.4	3	3.7	0	9.5
Dyspnoea	1	1.2	4	4.9	3	14.3
Abdominal pain	0	0	2	2.4	0	0
Cardiac arrest	0	0	2	2.4	1	4.8
Musculoskeletal pain	0	0	2	2.4	0	0

Source: FDA Analysis. AML, Acute myeloid leukemia.
*See Section 16.5.1 Grouped Terms Use for Safety Analyses.

Dropouts and/or Discontinuations Due to Adverse Effects

Table 68 shows the TEAE leading to drug withdrawal of belumosudil treatment by dose in 2 or more patients in the cGVHD population, after excluding AE terms describing relapse, malignancy or cGVHD.

Table 68. cGVHD Safety Population: TEAEs with Drug Withdrawal

	200 mg QD (N=83)		200 mg BID (N=82)		400 mg QD (N=21)	
Grouped Terms*	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Any TEAE with withdrawal**	15	18.1	17	20.7	5	6.0
Nausea	3	3.6	0	0.0	0	0.0
Headache	2	2.4	1	1.2	0	0.0
Liver function test abnormal	1	1.2	2	2.4	0	0.0
Dyspnoea	0	0.0	2	2.4	0	0.0

Source: FDA Analysis. *See Section 16.5.1 Grouped Terms Use for Safety Analyses.
** Excluded AE terms describing relapse, malignancy or cGVHD.

There were few dose reductions, but one third had TEAEs resulting in drug interruption. Table 69 shows the TEAE leading to dose interruption by dose in 2 or more patients in the cGVHD population.

Table 69. cGVHD Safety Population: TEAEs with Dose Interruption

	200 mg QD (N=83)		200 mg BID (N=82)		400 mg QD (N=21)	
Grouped Terms*	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Any TEAE with dose interruption**	24	28.9	27	32.5	8	9.6
Infection	9	10.8	9	11.0	1	4.8
Diarrhoea	3	3.6	2	2.4	0	0.0
Asthenia	2	2.4	1	1.2	1	4.8
Dyspnoea	2	2.4	2	2.4	0	0.0
Food poisoning	2	2.4	0	0.0	0	0.0
Haemorrhage	2	2.4	0	0.0	0	0.0
Hypotension	2	2.4	0	0.0	0	0.0
Liver function test abnormal	2	2.4	3	3.7	0	0.0
Nausea	2	2.4	3	3.7	0	0.0
Oedema	2	2.4	0	0.0	0	0.0
Pyrexia	2	2.4	0	0.0	0	0.0
Renal failure	2	2.4	3	3.7	0	0.0
Abdominal pain	1	1.2	2	2.4	0	0.0
Viral infection	1	1.2	6	7.3	1	4.8
Pericardial effusion	0	0	2	2.4	0	0

Source: FDA Analysis. *See Section 16.5.1 Grouped Terms Use for Safety Analyses.
** Excluded AE terms describing relapse, malignancy or cGVHD.

Table 70 below shows the TEAE leading to dose reductions by dose in 2 or more patients in the cGVHD population.

Table 70. cGVHD Safety Population: TEAEs with Dose Reduction

	200 mg QD (N=83)		200 mg BID (N=82)		400 mg QD (N=21)	
Grouped Terms*	**n**	(%)	**n**	(%)	**n**	(%)
Any TEAE with dose reduction**	3	3.6	4	4.8	2	2.4
Asthenia	0	0	2	2.4	1	4.8

Source: FDA Analysis. *See Section 16.5.1 Grouped Terms Use for Safety Analyses.
** Excluded AE terms describing relapse, malignancy or cGVHD.

Significant Adverse Events

The Table 71 shows selected Adverse Events of Special Interest (AESI) in increasing order of time to onset.

Table 71. cGVHD Safety Population: Adverse Events of Special Interest

	200 mg QD (N=83)			200 mg BID (N=82)			400 mg QD (N=21)		
AESI	**n**	**%**	**Time to onset Median Days (Range)**	**n**	**%**	**Time to onset Median Days (Range)**	**n**	**%**	**Time to onset Median Days (Range)**
QT Prolongation	2	2	36 (1-71)	1	1	51 (51-51)	0	0	
Hypotension	4	5	40 (1-149)	4	5	99 (40-210)	1	5	208 (208-208)
Thrombocytopenia	4	5	40 (1-267)	7	9	30 (13-294)	1	5	198 (198-198)
Drug Related Hepatic Disorders	22	27	57 (1-391)	20	24	20 (1-309)	4	19	341 (1-757)
Cardiac Arrhythmias	5	6	66 (1-279)	4	5	57 (3-386)	1	5	430 (430-430)
Infective Pneumonia	10	12	68 (15-279)	14	17	99 (3-363)	4	19	235 (55-878)
Infections - Pathogen Unspecified	44	53	70 (1-299)	44	53	59 (2-427)	13	62	99 (34-323)
Viral Infectious Disorders	17	20	86 (5-327)	18	22	237 (3-478)	7	33	279 (36-969)
Neoplasms	9	11	93 (39-327)	7	9	174 (29-346)	5	24	471 (8-813)
Erythropenia	10	12	101 (12-266)	12	15	81 (1-278)	1	5	8 (8-8)
Leukopenia	6	7	102 (1-267)	6	7	30 (28-57)	1	5	404 (404-404)
Neoplasms Malignant	8	10	103 (39-631)	2	2	241 (174-307)	4	19	337 (8-813)
Fungal Infectious Disorders	8	10	105 (29-282)	5	6	22 (15-141)	1	5	281 (281-281)
Bacterial Infectious Disorders	13	16	111 (1-360)	8	10	96 (18-332)	2	10	178 (161-194)
General Hypersensitivity	18	22	158 (15-614)	14	17	134 (1-309)	1	5	40 (40-40)
Anaphylactic Reaction	1	1	187 (187-187)	0	0		0	0	
Neutropenia	1	1	253 (253-253)	1	1	28 (28-28)	1	5	502 (502-502)

Source: FDA Analysis. Abbreviations: QD = once daily; BID=twice daily; AESI = adverse events of special interest; CAR_ARR = Cardiac arrhythmias; CAR_QT = Cardiac Torsade de pointes/QT prolongation; G_ANAPH = General Anaphylactic reaction; G_HYPER = General Hypersensitivity; G_HYPOT = General Hypotension; HEM_CYT = Hematopoietic cytopenias affecting more than one type of blood cell; HEM_ERY = Hematopoietic erythropenia; HEM_LEU = Hematological leukopenia; HEM_NEU = Hematological Neutropenia;HEM_THR = Hematological thrombocytopenia; HEP_HEP = Hepatic Drug related hepatic disorders; INF_BAC = Infection Bacterial infectious disorders; INF_FUN = Infection Fungal infectious disorders; INF_PAT = Infection Infections - pathogen unspecified; INF_PNE = Infection Infective pneumonia; INF_VIR = Infection Viral infectious disorders; NEO_MAL = Neoplasms Malignant or unspecified tumors; NEO_NEO = Neoplasms benign, malignant and unspecified.

The following tables summarize details for individual AESI (hepatic events, infections, hypersensitivity, cardiac events, hypotension, hematologic events, and malignancy/neoplasm), by the Preferred Terms.

Hepatic events (hepatobiliary investigations - Liver function analyses):

Table 72 shows details of AESI by Preferred Terms for hepatic events (hepatobiliary investigations and Liver function analyses).

Table 72. cGVHD Safety Population: Preferred Terms for Hepatic Events

Preferred Terms	200 mg QD (N=83)		200 mg BID (N=82)		400 mg QD (N=21)	
	n	(%)	n	(%)	n	(%)
With at least one TEAE of Hepatic events HLGT	20	24.1	22	26.8	4	19.0
ALT increased	10	12.1	10	12.2	2	9.5
AST increased	10	12.1	10	12.2	1	4.8
GGT increased	10	12.1	14	17.1	0	0
Transaminases increased	1	1.2	1	1.2	1	4.8
Liver function test increased	1	1.2	0	0	0	0
Bilirubin conjugated increased	1	1.2	0	0	0	0
Blood bilirubin increased	0	0	0	0	1	4.8
Cholangitis	0	0	1	1.2	0	0
Cholelithiasis	0	0	1	1.2	0	0
Ascites	0	0	0	0	1	4.8

Source: FDA Analysis.
Abbreviations: QD = once daily; BID=twice daily; HLGT = high level group term; TEAE = treatment-emergent adverse events; ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT=gamma-glutamyl transferase.

The Applicant recommends monitoring liver tests monthly for (b) (4) treatment with KD-025. To support this recommendation, they provided an analysis of time to first abnormal liver test (Response to Labeling Comments received 6/14/2021) (Table 73).

Table 73. cGVHD Safety Population: Time to First Event for Each Hepatic Adverse Events

Treatment Group: 200 mg QD (N = 83)

	0 to <1 month n/N (%)	1 to <2 months n/N (%)	2 to <3 months n/N (%)	3 to <6 months n/N (%)	6 to <9 months n/N (%)	9 to <12 months n/N (%)
ALT increased	10 (12.0%)	2 (2.4%)	0	3 (3.6%)	4 (4.8%)	1 (1.2%)
AST increased	8 (9.6%)	4 (4.8%)	4 (4.8%)	3 (3.6%)	2 (2.4%)	0
Bilirubin increased	1 (1.2%)	0	0	1 (1.2%)	0	1 (1.2%)

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Source: Response to Labeling Comments received 6/14/2021

Review Comment: Elevated liver tests is a substantial risk that would warrant monitoring.

Infections (Infections and infestations):

Table 74 shows the summary of infection events for the AESI Infections. See Appendix 16.5 for a detailed list of Infection Events (Infections and infestations).

Table 74. cGVHD Safety Population: Summary of Infection Events

	Belumosudil					
	200 mg QD (N=83)		200 mg BID (N=82)		400 mg QD (N=21)	
Infection	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
With at least one TEAE of infection event	54	65	51	62	15	71
All-grade infections						
Infections (pathogen not specified)	44	53	44	54	13	62
Viral infections	16	19	18	22	7	33
Bacterial infections	13	16	8	10	2	10
Fungal infections	8	10	5	6	1	5
Grade 3 - 5 infections						
Infections (pathogen not specified)	13	16	11	13	3	14
Viral infections	3	4	5	6	3	14
Bacterial infections	3	4	3	4	1	5
Fungal infections	0	0	0	0	0	0

Source: FDA Analysis. Abbreviations: QD = once daily; BID=twice daily; SOC, System Organ Class; HLGT = high level group term; TEAE = treatment-emergent adverse events.

Hypersensitivity:
Table 75 shows details of AESI by Preferred Terms for hypersensitivity.

Table 75. cGVHD Safety Population: Preferred Terms for Hypersensitivity

Preferred Term	**200 mg QD (N=83)**		**200 mg BID (N=82)**		**400 mg QD (N=21)**	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**
With at least one TEAE of Hypersensitivity SMQ narrow	11	13.3	15	18.3	1	4.8
Pruritus	9	10.8	11	13.3	0	0
Stomatitis	4	4.8	5	6.0	1	1.2
Rash	4	4.8	4	4.8	1	1.2
Blister	4	4.8	3	3.6	1	1.2
Rash maculo-papular	4	4.8	2	2.4	0	0
Wheezing	4	4.8	2	2.4	1	1.2

Preferred Term	200 mg QD (N=83)		200 mg BID (N=82)		400 mg QD (N=21)	
	n	(%)	n	(%)	n	(%)
Conjunctivitis	2	2.4	3	3.6	3	3.6
Contrast media allergy	2	2.4	1	1.2	0	0
Erythema	2	2.4	1	1.2	0	0
Face oedema	2	2.4	0	0	0	0
Skin exfoliation	2	2.4	0	0	0	0
Dermatitis	2	2.4	0	0	0	0
Dermatitis allergic	1	1.2	3	3.6	0	0
Drug eruption	1	1.2	2	2.4	0	0
Eosinophilia	1	1.2	1	1.2	0	0
Erythema multiforme	1	1.2	1	1.2	0	0
Flushing	1	1.2	1	1.2	0	0
Generalised oedema	1	1.2	0	0	1	1.2
Mouth ulceration	1	1.2	0	0	1	1.2
Rash erythematous	1	1.2	0	0	0	0
Rash pustular	1	1.2	0	0	0	0
Respiratory arrest	1	1.2	0	0	0	0
Respiratory failure	1	1.2	0	0	0	0
Acute respiratory failure	1	1.2	0	0	1	1.2
Anaphylactic reaction	1	1.2	0	0	0	0
Asthma	1	1.2	0	0	0	0
Choking	0	0	2	2.4	1	1.2
Dermatitis bullous	0	0	2	2.4	0	0
Dermatitis exfoliative	0	0	1	1.2	0	0
Eye swelling	0	0	1	1.2	0	0
Localised oedema	0	0	1	1.2	0	0
Periorbital oedema	0	0	1	1.2	0	0
Pruritus generalised	0	0	1	1.2	0	0
Rash generalised	0	0	1	1.2	0	0
Rhinitis allergic	0	0	1	1.2	0	0
Seasonal allergy	0	0	0	0	1	1.2

Source: FDA Analysis.
Abbreviations: QD = once daily; BID=twice daily, HLGT = high level group term; TEAE = treatment-emergent adverse events; SMQ, Standardised MedDRA (Medical Dictionary for Regulatory Activities) Query.

Cardiac events:

Table 76 shows details of AESI by Preferred Terms for cardiac events.

Table 76. cGVHD Safety Population: Preferred Terms for Cardiac events

Preferred Term	200 mg QD (N=83)		200 mg BID (N=82)		400 mg QD (N=21)	
	n	(%)	n	(%)	n	(%)
With at least one TEAE of Cardiac events SOC	11	13.3	15	18.3	5	23.8
Tachycardia	4	4.8	4	4.9	2	9.5
Sinus tachycardia	2	2.4	1	1.2	1	4.8
Atrial fibrillation	1	1.2	2	2.4	0	0
Palpitations	1	1.2	1	1.2	1	4.8
Myocardial infarction	1	1.2	0	0.0	0	0
Cardiac failure congestive	1	1.2	0	0.0	0	0
Pericardial effusion	1	1.2	2	2.4	1	4.8
Bradycardia	0	0	1	1.2	0	0
Cardiac arrest	0	0	2	2.4	1	4.8
Mitral valve incompetence	0	0	1	1.2	1	4.8
Acute coronary syndrome	0	0	1	1.2	0	0
Myocardial ischaemia	0	0	1	1.2	0	0
Cardiac failure	0	0	1	1.2	0	0
Left ventricular dysfunction	0	0	1	1.2	0	0
Left ventricular hypertrophy	0	0	2	2.4	0	0

Source: FDA Analysis. Abbreviations: QD = once daily; BID=twice daily; SOC, System Organ Class; HLGT = high level group term; TEAE = treatment-emergent adverse events.

Hypotension:

Table 77 shows details of AESI by Preferred Terms for hypotension.

Table 77. cGVHD Safety Population: Preferred Terms for Hypotension

Preferred Terms	200 mg QD (N=83)		200 mg BID (N=82)		400 mg QD (N=21)	
	n	(%)	n	(%)	n	(%)
With at least one TEAE of Hypotension PT	4	4.8	4	4.9	1	4.8
Hypotension	3	3.6	4	4.9	1	4.8
Orthostatic hypotension	1	1.2	0	0	0	0

Source: FDA Analysis
Abbreviations: QD = once daily; BID=twice daily, HLGT = high level group term; TEAE = treatment-emergent adverse events; PT, Preferred Term.

Hematologic events (anemia, neutropenia/leukopenia, and thrombocytopenia):

Table 78 shows details of AESI by Preferred Terms for hematologic events.

Table 78. cGVHD Safety Population: Preferred Terms for Hematologic events

Preferred Terms	200 mg QD (N=83)		200 mg BID (N=82)		400 mg QD (N=21)	
	n	(%)	n	(%)	n	(%)
With at least one TEAE of Hematologic events SOC	14	16.9	16	19.5	4	19.1
Anaemia	10	12.1	12	14.6	0	0
Platelet count decreased	4	4.8	5	6.1	0	0
Leukocytosis	3	3.6	0	0	1	4.8
White blood cell count decreased	3	3.6	1	1.2	0	4.8
Lymphocyte count decreased	2	2.4	3	3.7	0	0
Iron deficiency anaemia	1	1.2	1	1.2	0	0
Increased tendency to bruise	1	1.2	0	0	0	4.8
Thrombocytosis	1	1.2	0	0	0	0
Neutropenia	1	1.2	1	1.2	0	0
Blast cell count increased	1	1.2	0	0	0	0
Neutrophil count decreased	1	1.2	1	1.2	0	4.8
Microangiopathic haemolytic anaemia	0	0	1	1.2	0	0
Thrombocytopenia	0	0	2	2.4	1	4.8
Nucleated red cells	0	0	1	1.2	0	0
Eosinophilia	0	0	1	1.2	0	0
Leukopenia	0	0	1	1.2	0	0
Febrile neutropenia	0	0	0	0	1	4.8
Haematocrit decreased	0	0	1	1.2	1	4.8
Haematocrit increased	0	0	1	1.2	0	0
Neutrophil count increased	0	0	0	0	1	4.8
White blood cell count increased	0	0	0	0	1	4.8

Source: FDA Analysis. Abbreviations: QD = once daily; BID=twice daily; HLGT = high level group term; TEAE = treatment-emergent adverse events.

AESI of Malignancy/Neoplasms:

Table 79 shows details of AESI by Preferred Terms for malignancy/neoplasms.
See also Section 8.3.9 Additional Safety Explorations: Human Carcinogenicity or Tumor Development.

Table 79. cGVHD Safety Population: Preferred Terms for Malignancy/ Neoplasms

Preferred Terms	200 mg QD (N=83)		200 mg BID (N=82)		400 mg QD (N=21)	
	n	(%)	n	(%)	n	(%)
With at least one TEAE of Malignancy/Neoplasms SOC HLGT	9	10.8	4	4.9	5	23.8
Acute myeloid leukaemia recurrent	2	2.4	0	0	1	4.8
Leukaemia recurrent	1	1.2	0	0	1	4.8
Acute lymphocytic leukaemia recurrent	1	1.2	0	0	0	0
Hodgkin's disease recurrent	1	1.2	0	0	0	0
Metastases to meninges	1	1.2	0	0	0	0
Plasma cell myeloma	1	1.2	0	0	1	4.8
Cervix carcinoma stage 0	1	1.2	0	0	0	0
Vulval cancer stage 0	1	1.2	0	0	0	0
Papillary tumour of renal pelvis	0	0	1	1.2	0	0
Basal cell carcinoma	0	0	1	1.2	0	0
Squamous cell carcinoma of skin	0	0	2	2.4	0	0
Acute lymphocytic leukaemia refractory	0	0	0	0	1	4.8
Myelodysplastic syndrome	0	0	0	0	1	4.8

Source: FDA Analysis. Abbreviations: QD = once daily; BID=twice daily; SOC, System Organ Class; HLGT = high level group term; TEAE = treatment-emergent adverse events.

Treatment Emergent Adverse Events and Adverse Reactions

At least one TEAE was reported in all (100%) patients with chronic GVHD in dose groups (200 mg QD, 200 mg BID, and 400 mg QD). The numbers of patients with a TEAE are shown in Table 80 by SOC in decreasing order of incidence.

Table 80. cGVHD Safety Population: TEAEs by SOC Terms

	200 mg QD (N=83)		200 mg BID (N=82)		400 mg QD (N=21)	
SOC Terms	**n**	(%)	**n**	(%)	**n**	(%)
Gastrointestinal disorders	59	71.1	57	69.5	17	81.0
Infections and infestations	54	65.1	51	62.2	15	71.4
General disorders and administration site conditions	53	63.9	43	52.4	15	71.4

	200 mg QD (N=83)		200 mg BID (N=82)		400 mg QD (N=21)	
Respiratory, thoracic and mediastinal disorders	50	60.2	49	59.8	15	71.4
Musculoskeletal and connective tissue disorders	44	53.0	44	53.7	14	66.7
Investigations	42	50.6	40	48.8	12	57.1
Metabolism and nutrition disorders	41	49.4	34	41.5	11	52.4
Skin and subcutaneous tissue disorders	34	41.0	35	42.7	9	42.9
Injury, poisoning and procedural complications	32	38.6	23	28.0	6	28.6
Nervous system disorders	31	37.3	38	46.3	9	42.9
Vascular disorders	27	32.5	29	35.4	5	23.8
Eye disorders	20	24.1	20	24.4	7	33.3
Psychiatric disorders	15	18.1	18	22.0	7	33.3
Renal and urinary disorders	15	18.1	19	23.2	5	23.8
Blood and lymphatic system disorders	14	16.9	16	19.5	4	19.0
Cardiac disorders	11	13.3	15	18.3	5	23.8
Reproductive system and breast disorders	10	12.0	5	6.1	1	4.8
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	9	10.8	5	6.1	5	23.8
Endocrine disorders	8	9.6	4	4.9	4	19.0
Ear and labyrinth disorders	7	8.4	4	4.9	1	4.8
Immune system disorders	6	7.2	6	7.3	3	14.3
Hepatobiliary disorders	0	0	2	2.4	0	0

Source: FDA Analysis.

Table 81 shows the most common all-grade TEAEs by Grouped Terms occurring in ≥ 5% of patients with chronic GVHD.

Table 81. cGVHD Safety Population: Common (≥ 5%) All-Grade TEAEs

TEAEs	**200 mg QD (N=83)**	**200 mg BID (N=82)**	**400 mg QD (N=21)**
Grouped Terms*	**n (%)**	**n (%)**	**n (%)**
Infection	44 (53)	44 (54)	13 (62)
Asthenia	38 (46)	26 (32)	10 (48)
Nausea	35 (42)	26 (32)	9 (43)
Diarrhea	29 (35)	26 (32)	7 (33)
Dyspnea	27 (33)	21 (26)	7 (33)
Cough	25 (30)	26 (32)	8 (38)
Oedema	22 (27)	21 (26)	6 (29)
Liver function test abnormal	20 (24)	22 (27)	4 (19)
Haemorrhage	19 (23)	17 (21)	1 (5)
Abdominal pain	18 (22)	10 (12)	5 (24)
Musculoskeletal pain	18 (22)	26 (32)	6 (29)
Headache	17 (21)	22 (27)	6 (29)

TEAEs Grouped Terms*	200 mg QD (N=83) n (%)	200 mg BID (N=82) n (%)	400 mg QD (N=21) n (%)
Hypertension	17 (21)	13 (16)	4 (19)
Viral infection	16 (19)	18 (22)	7 (23)
Pyrexia	15 (18)	9 (11)	3 (14)
Decreased appetite	14 (17)	7 (9)	4 (19)
Muscle spasms	14 (17)	13 (16)	6 (29)
Bacterial infection	13 (16)	8 (10)	2 (10)
Dysphagia	13 (16)	4 (5)	2 (10)
Arthralgia	12 (15)	9 (11)	5 (24)
Hyperglycaemia	12 (14)	12 (15)	3 (14)
Anaemia	10 (12)	12 (15)	0
Nasal congestion	10 (12)	8 (10)	1 (5)
Rash	10 (12)	10 (12)	1 (5)
Fall	9 (11)	9 (11)	1 (5)
Pruritus	9 (11)	11 (13)	0
Renal failure	9 (11)	19 (23)	4 (19)
Abdominal distension	8 (10)	0	1 (5)
Blood alkaline phosphatase increased	8 (10)	7 (8)	0
Constipation	8 (10)	7 (9)	3 (14)
Dehydration	8 (10)	5 (6)	2 (10)
Dry mouth	8 (10)	5 (6)	2 (10)
Fungal infection	8 (10)	5 (6)	1 (5)
Muscular weakness	8 (10)	5 (5)	2 (10)
Chills	7 (8)	3 (4)	0
Dry eye	7 (8)	7 (9)	2 (10)
Stomatitis	7 (8)	6 (7)	2 (10)
Tachycardia	7 (8)	7 (9)	3 (14)
Hypokalaemia	6 (7)	4 (5)	0
Insomnia	6 (7)	4 (5)	3 (14)
Myalgia	6 (7)	3 (4)	3 (14)
Skin ulcer	6 (7)	2 (2)	2 (10)
Weight decreased	6 (7)	1 (1)	1 (5)
Dizziness	5 (6)	9 (11)	2 (10)
Gastrooesophageal reflux disease	5 (6)	4 (5)	2 (10)
Hyperkalaemia	5 (6)	4 (5)	3 (14)
Hypophosphataemia	5 (6)	4 (5)	1 (5)
Hypoxia	5 (6)	3 (4)	1 (5)
Neuropathy peripheral	5 (6)	6 (7)	1 (5)
Rhinorrhoea	5 (6)	5 (6)	0
Thrombosis	5 (6)	12 (15)	1 (5)
Anxiety	4 (5)	5 (6)	3 (14)
Blood creatine phosphokinase increased	4 (5)	2 (2)	0
Blood lactate dehydrogenase increased	4 (5)	6 (7)	0
Erythema	4 (5)	2 (2)	0
Gastritis	4 (5)	1 (1)	1 (5)
Hot flush	4 (5)	3 (4)	0

TEAEs Grouped Terms*	200 mg QD (N=83) n (%)	200 mg BID (N=82) n (%)	400 mg QD (N=21) n (%)
Hypocalcaemia	4 (5)	2 (2)	1 (5)
Hypomagnesaemia	4 (5)	4 (5)	1 (5)
Hyponatraemia	4 (5)	1 (1)	2 (10)
Hypotension	4 (5)	4 (5)	1 (5)
Pain	4 (5)	3 (4)	1 (5)
Platelet count decreased	4 (5)	5 (6)	0
Toothache	4 (5)	0	1 (5)
Trismus	4 (5)	0	0
Visual impairment	4 (5)	7 (9)	4 (19)
Weight increased	4 (5)	1 (1)	1 (5)
Hypomagnesaemia	4 (5)	4 (5)	1 (5)
Non-cardiac chest pain	3 (4)	6 (7)	1 (5)
Confusional state	3 (4)	5 (6)	0
Tremor	3 (4)	4 (5)	3 (14)
Blood cholesterol increased	3 (4)	1 (1)	1 (5)
Dry skin	3 (4)	2 (2)	1 (5)
Ear pain	3 (4)	1 (1)	1 (5)
Leukocytosis	3 (4)	0	1 (5)
Limb injury	3 (4)	1 (1)	1 (5)
Oropharyngeal pain	3 (4)	3 (4)	1 (5)
Paraesthesia	3 (4)	3 (4)	1 (5)
Upper-airway cough syndrome	3 (4)	2 (2)	1 (5)
White blood cell count decreased	3 (4)	1 (1)	1 (5)
Hypertriglyceridaemia	2 (2)	5 (6)	0
Syncope	2 (2)	5 (6)	1 (5)
Cataract	2 (2)	1 (1)	1 (5)
Glucose urine present	2 (2)	0	1 (5)
Hiatus hernia	2 (2)	0	1 (5)
Hyperhidrosis	2 (2)	1 (1)	1 (5)
Hypoaesthesia	2 (2)	1 (1)	1 (5)
Hypoalbuminaemia	2 (2)	2 (2)	1 (5)
Hypogammaglobulinaemia	2 (2)	0	1 (5)
Joint range of motion decreased	2 (2)	2 (2)	1 (5)
Peripheral swelling	2 (2)	0	1 (5)
Syncope	2 (2)	5 (6)	1 (5)
Urinary retention	2 (2)	2 (2)	1 (5)
Vitiligo	2 (2)	0	1 (5)
Influenza like illness	1 (1)	6 (7)	2 (10)
Hyperuricaemia	1 (1)	3 (4)	3 (14)
Pleural effusion	1 (1)	2 (2)	2 (10)
Acute respiratory failure	1 (1)	0	1 (5)
Alopecia	1 (1)	1 (1)	1 (5)
Ataxia	1 (1)	0	1 (5)
Blepharitis	1 (1)	0	1 (5)
Blister	1 (1)	3 (4)	1 (5)

TEAEs Grouped Terms*	200 mg QD (N=83) n (%)	200 mg BID (N=82) n (%)	400 mg QD (N=21) n (%)
Bone pain	1 (1)	1 (1)	1 (5)
Dyspepsia	1 (1)	3 (4)	1 (5)
Haemorrhoids	1 (1)	1 (1)	1 (5)
Influenza virus test positive	1 (1)	0	1 (5)
Iron deficiency	1 (1)	1 (1)	1 (5)
Muscle spasticity	1 (1)	0	1 (5)
Neutrophil count decreased	1 (1)	0	1 (5)
Palpitations	1 (1)	1 (1)	1 (5)
Pericardial effusion	1 (1)	2 (2)	1 (5)
Rotator cuff syndrome	1 (1)	0	1 (5)
Seasonal allergy	1 (1)	0	1 (5)
Small intestinal obstruction	1 (1)	0	1 (5)
Depression	0	8 (10)	3 (14)
Photophobia	0	1 (1)	2 (10)
Skin abrasion	0	1 (1)	2 (10)
Actinic keratosis	0	1 (1)	1 (5)
Amnesia	0	0	1 (5)
Ascites	0	0	1 (5)
Cardiac arrest	0	2 (2)	1 (5)
Cataract operation	0	0	1 (5)
Catheter site pain	0	1 (1)	1 (5)
Cerebellar syndrome	0	0	1 (5)
Choking	0	0	1 (5)
Coordination abnormal	0	0	1 (5)
Diabetes mellitus	0	1 (1)	1 (5)
Dysaesthesia	0	0	1 (5)
Febrile neutropenia	0	0	1 (5)
Flatulence	0	0	1 (5)
Groin pain	0	0	1 (5)
Haematocrit decreased	0	1 (1)	1 (5)
Hypercalcaemia	0	0	1 (5)
Hypermagnesaemia	0	1 (1)	1 (5)
Hyperthyroidism	0	1 (1)	1 (5)
Hypovolaemia	0	0	1 (5)
Lip pain	0	0	1 (5)
Local swelling	0	0	1 (5)
Lower respiratory tract congestion	0	2 (2)	1 (5)
Malnutrition	0	0	1 (5)
Memory impairment	0	0	1 (5)
Mitral valve incompetence	0	1 (1)	1 (5)
Mood altered	0	0	1 (5)
Neutrophil count increased	0	0	1 (5)
Obstructive airways disorder	0	0	1 (5)
Oesophageal pain	0	0	1 (5)
Oral dysaesthesia	0	1 (1)	1 (5)

TEAEs Grouped Terms*	200 mg QD (N=83) n (%)	200 mg BID (N=82) n (%)	400 mg QD (N=21) n (%)
Oral pain	0	1 (1)	1 (5)
Post herpetic neuralgia	0	0	1 (5)
Prostatic obstruction	0	0	1 (5)
Pulmonary fibrosis	0	0	1 (5)
Pulmonary pain	0	0	1 (5)
Secretion discharge	0	0	1 (5)
Skin hyperpigmentation	0	0	1 (5)
Skin hypertrophy	0	0	1 (5)
Skin induration	0	0	1 (5)
Skin tightness	0	1 (1)	1 (5)
Streptococcus test positive	0	0	1 (5)
Thrombocytopenia	0	2 (2)	1 (5)
Tricuspid valve incompetence	0	0	1 (5)
Urinary incontinence	0	1 (1)	1 (5)
Urinary tract pain	0	1 (1)	1 (5)
White blood cell count increased	0	0	1 (5)
Wheezing	0	3 (4)	1 (5)

Source: FDA Analysis. *See Section 16.5.1 Grouped Terms Use for Safety Analyses.

Table 82 shows the most common grade 3-5 TEAEs by Grouped Terms occurring in all-grade TEAEs occurring in ≥ 2% of patients with chronic GVHD.

Table 82. cGVHD Safety Population: Common (≥ 2%) Grade ≥ 3 TEAEs

TEAEs	200 mg QD (N=83)		200 mg BID (N=82)		400 mg QD (N=21)	
Grouped Terms*	n	(%)	n	(%)	n	(%)
Infection	13	16	11	13	3	14
Hypertension	6	7	4	5	0	0
Hyperglycaemia	5	6	3	4	2	10
Anaemia	4	5	3	4	0	0
Diarrhoea	4	5	1	1	0	0
Dyspnoea	4	5	4	5	4	19
Haemorrhage	4	5	1	1	0	0
Hypoxia	4	5	1	1	2	10
Liver function test abnormal	4	5	4	5	0	0
Asthenia	3	4	4	5	1	5
Bacterial infection	3	4	3	4	1	5
Musculoskeletal pain	3	4	2	2	0	0
Nausea	3	4	2	2	0	0
Platelet count decreased	3	4	0	0	0	0
Thrombosis	3	4	3	4	0	0

TEAEs	200 mg QD (N=83)		200 mg BID (N=82)		400 mg QD (N=21)	
Grouped Terms*	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Viral infection	3	4	5	6	3	14
Arthralgia	2	2	0	0	0	0
Blood cholesterol increased	2	2	0	0	0	0
Fall	2	2	0	0	0	0
Hypertriglyceridaemia	2	2	2	2	0	0
Hyponatraemia	2	2	0	0	1	5
Hypotension	2	2	1	1	1	5
Osteonecrosis	2	2	0	0	0	0
Renal failure	2	2	3	4	0	0
Syncope	2	2	1	1	1	5
Tachycardia	2	2	1	1	0	0
White blood cell count decreased	2	2	0	0	0	0
Cardiac arrest	0	0	2	2	1	5
Headache	0	0	2	2	0	0
Pleural effusion	0	0	0	0	2	10
Ascites	0	0	0	0	1	5
Cataract operation	0	0	0	0	1	5
Choking	0	0	0	0	1	5
Cough	0	0	0	0	1	5
Febrile neutropenia	0	0	0	0	1	5
Hypermagnesaemia	0	0	0	0	1	5
Hyperuricaemia	0	0	0	0	1	5
Leukocytosis	0	0	0	0	1	5
Neutrophil count decreased	0	0	0	0	1	5
Oedema	1	1	0	0	1	5
Pericardial effusion	0	0	1	1	1	5
Rotator cuff syndrome	0	0	0	0	1	5
Small intestinal obstruction	1	1	0	0	1	5
Streptococcus test positive	0	0	0	0	1	5

Source: FDA Analysis. *See Section 16.5.1 Grouped Terms Use for Safety Analyses.

See also the Section 8.3.11 [Integrated Assessment of Safety] below for the table that shows the most common all-grade (all-grade TEAEs occurring in > 10% of subjects), and grade 3-5 TEAEs by Grouped Terms.

The most common TEAEs included infection, asthenia, nausea, diarrhea, dyspnea, cough, edema, liver function test abnormal, hemorrhage, abdominal pain, musculoskeletal pain and headache.

Although TEAEs occurred in a substantial proportion of subjects, grade 3 or above TEAEs were uncommon, with the exception of infection which occurred in 16%.

Overall, however, there was not much difference among the 3 dosages in the safety profile.

Laboratory Findings

The Laboratory results were analyzed again, based on the Updated ABLB dataset submitted by the Applicant on 03/05/2021, in the major amendment NDA214783.56. The Applicant did state the following about new ADLB: "c) Baseline flag field is now present in adlb.xpt to identify baseline lab tests. d) All labs have a baseline value where available, ABLFL and BASETYPE variables are used to identify baseline records. e) We have updated adlb.xpt by using CTCAE V4.03 rather than CTCAE v5, which revises baseline grades. f) The version of adlb.xpt provided with this response has results graded using CTCAE v4 as requested."

However, the Applicant did not provide CTCAE grades for many laboratory tests of neutrophil abnormality, especially failed to grading neutrophil abnormality results at baseline and follow-up visits in the Study KD025-213; although the Applicant provided a statement in their IR response submitted on 03/25/2020 that " CTC grade is not calculated for laboratory test neutrophils of KD025-213 study, since the lower limit of normal is conflict with CTCAE criterion."

FDA recalculated CTCAE grades using CTCAE V4.03 for all the laboratory test results of neutrophils in both Study KD025-213 and Study KD025-208, based on lab test results in the Updated ABLB dataset submitted by the Applicant on 03/05/2021.

Table 83 shows the proportions of patients with shifts from Grades 0-1 to Grades 2-4 or Grades 3-4 in the tested laboratory parameters, based on analysis of datasets including the updated ADLB received on 03/05/2020. The table shows number of patients with grade 0-1 abnormality at baseline, number (percentage) with shift from baseline grades 0-1 to maximum grades 2-4 on study, and number (percentage) with shift from baseline grades 0-1 to maximum grade 3-4 on study in the tested laboratory parameters.

Table 83. cGVHD Safety Population: Shift Table for Laboratory Abnormalities

	200 mg QD (N=83) n (%)			200 mg BID (N=82) n (%)			400 mg QD (N=21) n (%)		
	Grade 0-1 Baseline	Grade 2-4 Max Post	Grade 3-4 Max Post	Grade 0-1 Baseline	Grade 2-4 Max Post	Grade 3-4 Max Post	Grade 0-1 Baseline	Grade 2-4 Max Post	Grade 3-4 Max Post
Parameter	**(N)**	**N (%)**	**N (%)**	**(N)**	**N (%)**	**N (%)**	**(N)**	**N (%)**	**N (%)**
Magnesium Decreased	83	2 (2)	0	82	1 (1)	0	21	0	0
Aspartate Aminotransferase Increased	83	1 (1)	1 (1)	82	6 (7)	1 (1)	21	0	0
Creatine Kinase Increased	83	1 (1)	1 (1)	81	4 (5)	1 (1)	21	0	0
Calcium Increased	83	0	0	82	0	0	21	0	0
Direct Bilirubin Increased	83	0	0	82	0	0	21	0	0
Eosinophils Increased	83	0	0	82	0	0	21	0	0
Hemoglobin Increased	83	0	0	82	0	0	21	0	0
Lactate Dehydrogenase Increased	81	0	0	81	0	0	17	0	0
Magnesium Increased	83	0	0	82	2 (2)	2 (2)	21	0	0
Sodium Increased	83	0	0	82	0	0	21	0	0
Urate Increased	83	0	0	82	0	0	21	0	0
Bilirubin Increased	83	0	0	82	1 (1)	1 (1)	21	1 (5)	0
Potassium Decreased	83	0	0	82	1 (1)	1 (1)	21	2 (10)	2 (10)
Lymphocytes Increased	80	7 (9)	1 (1)	79	9 (11)	1 (1)	18	1 (6)	0
Sodium Decreased	83	7 (8)	7 (8)	82	2 (2)	2 (2)	21	1 (5)	1 (5)
Creatinine Increased	83	3 (4)	0	82	4 (5)	0	21	1 (5)	0
Neutrophil count Decreased*	83	7(8)	3(4)	82	3 (4)	0	21	2 (10)	2 (10)
Alkaline Phosphatase Increased	80	7 (9)	0	80	2 (3)	0	21	2 (10)	0
Leukocytes Decreased	83	6 (7)	2 (2)	82	3 (4)	0	21	2 (10)	2 (10)

	200 mg QD (N=83) n (%)			200 mg BID (N=82) n (%)			400 mg QD (N=21) n (%)		
	Grade 0-1 Base line	Grade 2-4 Max Post	Grade 3-4 Max Post	Grade 0-1 Base line	Grade 2-4 Max Post	Grade 3-4 Max Post	Grade 0-1 Base line	Grade 2-4 Max Post	Grade 3-4 Max Post
Parameter	**(N)**	**N (%)**	**N (%)**	**(N)**	**N (%)**	**N (%)**	**(N)**	**N (%)**	**N (%)**
Albumin Decreased	82	5 (6)	0	82	5 (6)	1 (1)	21	2 (10)	0
Glucose Decreased	83	3 (4)	1 (1)	82	4 (5)	1 (1)	21	2 (10)	0
Potassium Increased	82	6(7)	1 (1)	81	5 (6)	1 (1)	21	3 (14)	0
Alanine Aminotransferase Increased	83	6 (7)	2 (2)	82	2 (2)	1 (1)	21	5 (24)	0
Hemoglobin Decreased	79	9 (11)	1 (1)	75	14 (19)	1 (1)	19	2 (10)	1 (5)
Calcium Decreased	82	10 (12)	1 (1)	82	15 (18)	5 (6)	21	2 (10)	2 (10)
Platelets Decreased	82	8 (10)	4 (5)	82	1 (1)	0	17	3 (18)	2 (12)
Gamma Glutamyl Transferase Increased	47	10 (21)	5 (11)	56	15 (27)	3 (5)	17	4 (24)	2 (12)
Phosphate Decreased	76	21 (28)	5 (7)	75	18 (24)	5 (7)	19	4 (21)	2 (11)
Lymphocytes Decreased	62	18 (29)	8 (13)	67	21 (31)	3 (4)	18	7 (39)	4 (21)
Glucose Increased	63	24 (38)	7 (11)	71	25 (35)	7 (10)	18	6 (33)	0

Source: FDA Analysis of datasets including the Updated ADLB received on 03/05/2021.
*FDA recalculate CTCAE grades using CTCAE V4.03 for all the laboratory test results of neutrophils in both Study KD025-213 and Study KD025-208.

On 03/25/2021, in the amendment NDA214783.65 [\\CDSESUB1\evsprod\NDA214783\65], the Applicant provided two separate shift tables for the selected laboratory abnormalities, one table for "Low Neutrophils" for Study KD025-213 only (including a note: "CTC grade is not calculated for laboratory test neutrophils of KD025-213 study, since the lower limit of normal is conflict with CTCAE criterion"), and a second table with neutrophil data for Study KD025-208 only. See also APPENDICES Section 16.5.2 for The Applicant's shift tables.

Clinical Reviewer Comment: Overall, severe abnormalities in key laboratory tests were 2% or less with the exception of thrombocytopenia, but that finding in the 200 mg QD cohort was no reproducible in the 200 mg BID cohort. The laboratory tests data may not establish any clinically meaningful laboratory adverse reactions at this time.

Vital Signs

The Applicant reported that no clinically relevant changes from baseline in vital signs were observed in Study KD025-208 Study and Study KD025-213 (KD025-208 Clinical Study Report Section 12.6.1, and KD025-213 Clinical Study Report Section 12.6).

FDA reviewed the submission including ADVS datasets. In view of hypotension being a potential risk, further analyses of blood pressure were undertaken. A systolic blood pressure < 90 mm Hg was reported for 2%, 4% and 0% of patients on belumosudil 200 mg QD, 200 mg BID and 400 mg QD, respectively. A diastolic blood pressure < 60 mm Hg was reported for 34%, 28% and 5% of patients on belumosudil 200 mg QD, 200 mg BID and 400 mg QD, respectively.

QT/Electrocardiograms (ECGs)

FDA reviewed the ECG analysis datasets including ADEG. The incidence of subjects whose maximum post baseline absolute QT interval corrected for heart rate using Fridericia's formula (QTcF) values were evaluated by the following categories: ≤ 450 msec, > 450 to ≤ 480 msec, > 480 to ≤ 500 msec, and > 500 msec. The incidence of subjects whose maximum post baseline increase from baseline in QTcF were summarized in the following categories: ≤ 0, > 0 to ≤ 30 msec, > 30 to ≤ 60 msec, and > 60 msec.

The majority of subjects in the cGVHD analysis group had a maximum post-baseline absolute QTcF of ≤ 450 msec. Table 84 shows the maximum post-baseline absolute QTcF, and the maximum QTcF increase from baseline QTcF in subjects with chronic GVHD.

Table 84. cGVHD Safety Population: Maximum QTcF Increase from Baseline

QTcF	**200 mg QD (N=83)**		**200 mg BID (N=82)**		**400 mg QD (N=21)**	
Maximum QTcF	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
≤450 msec	66	79.5	58	70.7	19	90.5
>450 to ≤480 msec	12	14.5	20	24.4	1	4.8
>480 to ≤500 msec	3	3.6	1	1.2	1	4.8
>500 msec	2	2.4	2	2.4	0	0
Maximum QTcF Change from Baseline	n	(%)	n	(%)	n	(%)
≤0 msec	7	8.4	9	11.0	9	42.9
>0 to ≤30 msec	63	75.9	58	70.7	9	42.9
>30 to ≤60 msec	10	12.0	13	15.9	2	9.5
>60 msec	3	3.6	2	2.4	0	0

Source: FDA Analysis. Abbreviations: QD = once daily; BID = twice daily; cGVHD, chronic Graft versus Host Disease; QTcF = corrected QT interval using Fridericia's formula.

There were reports of QTc prolongation among the subjects with chronic GVHD treated with belumosudil.

Clinical Reviewer Comment: Available data of ECG findings may not establish a significant signal of QTc prolongation in association with belumosudil treatment.

Immunogenicity

Not applicable.

8.3.5 Analysis of Submission-Specific Safety Issues

See Section above about AESI. There were no other submission-specific safety issues.

8.3.6 Safety Analyses by Subgroups

Drug-Demographic Interactions

The Applicant did not provide statements for Drug-Demographic Interactions by Age, and by Sex. For Drug-Demographic Interactions by Race, the Applicant stated that " All studies were performed in Europe. No racial or ethnic data was collected as part of any study. Therefore, no comparisons can be made".

FDA analyzed the NDA submission datasets and provided the following subgroup analyses for the patients with cGVHD who received belumosudil 200 mg once daily.

Table 85 shows the TEAEs by age group in decreasing order of the difference in incidence between age groups (<65 year old vs >= 65 years old). Only TEAE with a risk difference $\geq$ 10% are shown. Older adult appeared to have more cardiac events, but the number of patients is too small for firm conclusions.

Table 85. cGVHD Safety Population: TEAEs by Age Group

	< 65 years old (N=66)		≥ 65 years old (N=17)		Risk Difference (%)
Grouped Terms*	**n**	(%)	**n**	(%)	(%)
Tachycardia	3	5	4	24	-19
Decreased appetite	9	14	5	29	-16
Haemorrhage	13	20	6	35	-16
Insomnia	3	5	3	18	-13
Laceration	0	0	2	12	-12

	< 65 years old (N=66)		≥ 65 years old (N=17)		Risk Difference (%)
Abdominal pain	13	20	5	29	-10
Chills	7	11	0	0	11
Stomatitis	7	11	0	0	11
Arthralgia	11	17	1	6	11
Headache	15	23	2	12	11
Pruritus	8	12	0	0	12
Musculoskeletal pain	16	24	2	12	12
Muscle spasms	13	20	1	6	14
Nasal congestion	10	15	0	0	15
Nausea	30	45	5	29	16
Asthenia	33	50	5	29	21
Source: FDA Analysis. *See Section 16.5.1 Grouped Terms Use for Safety Analyses.					

Table 86 shows the TEAEs by gender in decreasing order of the difference in incidence. Only TEAE with a risk difference ≥ 10% are shown. Females appeared to have more gastrointestinal toxicities, and males had more respiratory events.

Table 86. cGVHD Safety Population: TEAEs by Gender

	Females (N=28)		Males (N=55)		Risk Difference (%)
Grouped Terms*	**n**	**(%)**	**n**	**(%)**	**(%)**
Abdominal pain	3	11	15	27	-17
Muscular weakness	0	0	8	15	-15
Musculoskeletal pain	4	14	14	25	-11
Renal failure	1	4	8	15	-11
Nausea	10	36	25	45	-10
Pruritus	5	18	4	7	11
Infection	17	61	27	49	12
Diarrhoea	12	43	17	31	12
Dry mouth	5	18	3	5	12
Bacterial infection	7	25	6	11	14
Oedema	11	39	11	20	19
Dyspnoea	13	46	14	25	21
Source: FDA Analysis. *See Section 16.5.1 Grouped Terms Use for Safety Analyses.					

Table 87 shows the TEAEs by race in decreasing order of the difference in incidence. Only TEAE with a risk difference ≥ 10% are shown. Patients who were not White race appeared to have more gastrointestinal and respiratory events, but the numbers of patients who were not White race is too small for firm conclusions.

Table 87. cGVHD Safety Population: TEAEs by Race

	White (N=70)		Not White (N=13)		Risk Difference (%)
Grouped Terms*	**n**	**(%)**	**n**	**(%)**	**(%)**
Decreased appetite	8	11	6	46	-35
Dyspnoea	20	29	7	54	-25
Nausea	27	39	8	62	-23
Blood creatine phosphokinase increased	1	1	3	23	-22
Pain	1	1	3	23	-22
Headache	12	17	5	38	-21
Abdominal pain	13	19	5	38	-20
Cough	19	27	6	46	-19
Dysphagia	9	13	4	31	-18
Arthropod bite	0	0	2	15	-15
Eye swelling	0	0	2	15	-15
Pruritus	6	9	3	23	-15
Pollakiuria	1	1	2	15	-14
Diarrhoea	23	33	6	46	-13
Hypomagnesaemia	2	3	2	15	-13
Toothache	2	3	2	15	-13
Hypophosphataemia	3	4	2	15	-11
Musculoskeletal pain	14	20	4	31	-11
Myalgia	4	6	2	15	-10
Weight decreased	4	6	2	15	-10
Asthenia	31	44	7	54	-10
Tachycardia	7	10	0	0	10
Liver function test abnormal	18	26	2	15	10
Muscle spasms	13	19	1	8	11
Dry mouth	8	11	0	0	11
Oedema	20	29	2	15	13
Viral infection	15	21	1	8	14
Hypertension	16	23	1	8	15
Infection	42	60	2	15	45

Source: FDA Analysis. *See Section 16.5.1 Grouped Terms Use for Safety Analyses.

Table 88 shows the TEAEs by ethnicity in decreasing order of the difference in incidence. Only TEAE with a risk difference $\geq$ 15% are shown. Patients who were Hispanic Or Latino appeared

to have more yypertension gastrointestinal toxicities, but the number of patients who were Hispanic Or Latino is too small for firm conclusions.

Table 88. cGVHD Safety Population: TEAEs by Ethnicity

	Not Hispanic Or Latino (N=73)		Hispanic Or Latino (N=10)		Risk Difference (%)
Grouped Terms*	**n**	**(%)**	**n**	**(%)**	**(%)**
Hypertension	12	16	5	50	-34
Diarrhoea	23	32	6	60	-28
Bacterial infection	9	12	4	40	-28
Asthenia	31	42	7	70	-28
Cough	20	27	5	50	-23
Abdominal pain	14	19	4	40	-21
Musculoskeletal pain	14	19	4	40	-21
Nausea	29	40	6	60	-20
Erectile dysfunction	0	0	2	20	-20
Glucose urine present	0	0	2	20	-20
Obesity	0	0	2	20	-20
Sinus pain	0	0	2	20	-20
Vertigo	0	0	2	20	-20
Oropharyngeal pain	1	1	2	20	-19
Blood creatine phosphokinase increased	2	3	2	20	-17
Pain	2	3	2	20	-17
Weight increased	2	3	2	20	-17
Haemorrhage	18	25	1	10	15
Dysphagia	13	18	0	0	18
Muscle spasms	14	19	0	0	19

Source: FDA Analysis. *See Section 16.5.1 Grouped Terms Use for Safety Analyses.

Table 89 shows the TEAEs by Body Mass Index (BMI) in decreasing order of the difference in incidence. Only TEAE with a risk difference $\geq$ 10% between patients of obese group (BMI >= 30 kg/m^2) verses patients of not overweight group (BMI <25 kg/m^2) are shown, also including a column of overweight group (BMI 25 to <30 kg/m2) between those 2 BMI groups.

Obese patients with BMI >= 30 kg/m^2 appeared to have more events of abdominal pain with risk difference (RD) of -27% versus patients with BMI <25 kg/m^2, hypertension (RD -24%), and infections (RD of -20%). Patients with BMI <25 kg/m^2 appeared to have more events of

abnormal liver function test with RD of 13% versus obese patients, viral infection (RD 15%), and increased blood alkaline phosphatase (RD 18%).

Table 89. cGVHD Safety Population: TEAEs by BMI

	BMI < 25 kg/m^2) (N=34)		BMI 25 to <30 kg/m^2 (N=26)		BMI >= 30 kg/m^2) (N=18)	
Grouped Terms*	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Abdominal pain	6	18	3	12	8	44
Hypertension	5	15	4	15	7	39
Infection	14	41	18	69	11	61
Cough	9	26	6	23	8	44
Asthenia	11	32	14	54	9	50
Skin ulcer	0	0	3	12	3	17
Rhinorrhoea	1	3	1	4	3	17
Decreased appetite	3	9	6	23	4	22
Dizziness	0	0	3	12	2	11
Anxiety	0	0	1	4	2	11
Non-cardiac chest pain	0	0	1	4	2	11
Oropharyngeal pain	0	0	1	4	2	11
Upper-airway cough syndrome	0	0	1	4	2	11
Pain in jaw	0	0	0	0	2	11
Abdominal distension	2	6	3	12	3	17
Fungal infection	2	6	3	12	3	17
Pruritus	2	6	3	12	3	17
Weight decreased	2	6	1	4	3	17
Arthralgia	4	12	4	15	4	22
Bacterial infection	6	18	6	23	1	6
Liver function test abnormal	10	29	4	15	3	17
Viral infection	9	26	5	19	2	11
Blood alkaline phosphatase increased	6	18	1	4	0	0

Source: FDA Analysis. *See Section 16.5.1 Grouped Terms Use for Safety Analyses. BMI, Body Mass Index.

Table 90 shows the TEAEs by concomitant systemic cGVHD therapy with mTOR inhibitor on Study Day 1, in decreasing order of the difference in incidence. Only TEAE with a risk difference $\geq$ 10% are shown. Patients who received concomitant systemic cGVHD therapy with mTOR inhibitor appeared to have more edema toxicities, but the number of patients is too small for firm conclusions.

Table 90. cGVHD Safety Population: TEAEs by Concomitant Therapy with mTOR inhibitor

	No mTOR inhibitor (N=69)		With mTOR inhibitor (N=14)		Risk Difference (%)
Grouped Terms*	**n**	**(%)**	**n**	**(%)**	**(%)**
Oedema	13	19	9	64	-45
Abdominal distension	4	6	4	29	-23
Asthenia	29	42	9	64	-22
Rhinorrhoea	2	3	3	21	-19
Hypertension	12	17	5	36	-18
Insomnia	3	4	3	21	-17
Chills	4	6	3	21	-16
Decreased appetite	10	14	4	29	-15
Peripheral sensory neuropathy	0	0	2	14	-14
Ear pain	1	1	2	14	-13
Pyrexia	11	16	4	29	-13
Pain	2	3	2	14	-11
Nasal congestion	7	10	3	21	-11
Dizziness	3	4	2	14	-10
Headache	13	19	4	29	-10
Hypoxia	3	4	2	14	-10
Diarrhoea	23	33	6	43	-10
Dysphagia	12	17	1	7	10
Viral infection	15	22	1	7	15

Source: FDA Analysis. *See Section 16.5.1 Grouped Terms Use for Safety Analyses.

Drug-Disease Interactions

Not applicable.

8.3.7 Clinical Outcomes Assessments Informing Tolerability/Safety

There were no patient-reported outcomes data submitted for informing tolerability/safety.

8.3.8 Specific Safety Studies/Clinical Trials

Adverse Events in Controlled Clinical Trials

Study KD025-207 is a randomized, Phase 2, open-label, multicenter study to evaluate the safety, tolerability, and activity of belumosudil 400 mg daily (n=51) in comparison to best

supportive care (n=25) in patients with idiopathic pulmonary fibrosis (IPF). The design is described in Table 12. The study was reported as on-going at the time of submission of this NDA. Deaths are discussed in Section 8.3.4. In this trial, crossover was allowed after 24 weeks of treatment. During the first 24-week period, the incidence was at least 10% higher in the belumosudil arm for all-grade Oedema (10% vs 0%) and at least 5% higher for Grade >= 3 Dyspneoa (10% vs 0%).

Study KD025-211 is a Phase 2, randomized, double-blind, placebo-controlled, dose-finding study to evaluate the safety, tolerability, and efficacy of belumosudil in adults with moderate to severe chronic plaque psoriasis. The design is described in Table 12. Deaths are discussed in Section 8.3.4, In this trial, crossover was allowed after 16 weeks of treatment. Table 91 shows the all-grade TEAE that occurred with an incidence at least 10% higher in any belumosudil arm in comparison to the control arm during the first 16-week treatment period. Liver function test abnormal was the only Grade >= 3 TEAE at least 5% higher with belumosudil than in the control arm (12% with belumosudil 600 mg/day vs 0% in the control arm).

Table 91. Study KD025-211: All-Grade TEAE by Dose

	Belumosudil				Control n=19
	200 mg qD n=23	200 mg BID n=22	400 mg qD n=21	600 mg/day n=26	
PT*	**%**	**%**	**%**	**%**	**%**
Liver function test abnormal	26	5	5	15	11
Headache	0	9	10	8	0
Infection	22	18	19	8	11
Nausea	0	18	5	8	5
Viral infection	4	14	5	4	0

Source: FDA analysis; Analysis limited to the first 16-week treatment period
*Includes grouped terms

Clinical TL Review Comment: The controlled trials in IPF and psoriasis revealed no additional adverse reactions for belumosudil. It was noteworthy that the comparative results in Study KD025-211 was not consistent across dose groups. The duration of follow-up, however, (16-24 weeks) is relatively short and would not address uncertainty about toxicities with long-term use.

Time Dependency for Adverse Events

We do not have enough follow up information to assess time dependency for adverse events. We recommend PMR/PMC for long-term follow-up for safety.

Dose Dependency for Adverse Events

Dose-Safety in GVHD Trials

The belumosudil 200 mg QD, 200 mg BID, and 400 mg QD dosages have similar safety profile of adverse events. See also Section 8.3.4 for adverse events analyses by dosages of belumosudil 200 mg QD, 200 mg BID and 400 mg QD in patients with cGVHD.

Dose-Safety in Trials for Other Diseases

The clinical trials of belumosudil in patients with IPF and psoriasis are listed in Table 12. Study KD025-207 allowed crossover after the initial 24-week period for assessment of efficacy. For Study KD025-211, after the initial 16-week period for assessment of efficacy, patients on the control arm could crossover to belumosudil, and patients originally on belumosudil were allowed to continue treatment. The belumosudil dose for the second treatment period was 400 mg daily. This analysis includes safety outcomes from both periods of treatment based on the actual dose of belumosudil for the treatment period.

Forty-four (9%) patients had an adverse event that resulted in belumosudil withdrawal. The most common adverse event resulting in withdrawal was Liver function test abnormal; the incidence of withdrawal due to Liver function test abnormal was not dose-relate, ranging from 4% at 400 mg daily to 19% at 200 mg daily to 33% at 400 mg BID.

Table 92 shows the incidence of all-grade TEAE by dose occurring in at least 5% in patients with IPF or psoriasis at any dose in decreasing order at the highest dose.

Table 92. IPF and Psoriasis Studies: All-Grade TEAE by Dose

	Belumosudil Dose				
TEAE*	**200 mg QD (n=31)**	**200 mg BID (n=35)**	**400 mg QD (n=152)**	**600 mg/day (n=26)**	**400 mg BID (n=12)**
Liver function test abnormal	26%	11%	16%	15%	42%
Infection	10%	14%	27%	8%	25%
Headache	0%	3%	7%	8%	17%
Viral infection	3%	9%	18%	4%	8%
Nausea	3%	14%	13%	4%	8%
Pruritus	0%	3%	4%	4%	8%
Arthralgia	0%	0%	4%	4%	8%
Bacterial infection	0%	0%	4%	4%	8%
Diarrhoea	3%	3%	14%	0%	8%
Musculoskeletal pain	3%	0%	11%	0%	8%
Asthenia	0%	3%	8%	0%	8%
Paranasal sinus discomfort	0%	0%	0%	0%	8%
Thrombosis	0%	3%	7%	4%	0%

Table 92. IPF and Psoriasis Studies: All-Grade TEAE by Dose

	Belumosudil Dose				
TEAE*	**200 mg QD (n=31)**	**200 mg BID (n=35)**	**400 mg QD (n=152)**	**600 mg/day (n=26)**	**400 mg BID (n=12)**
Dizziness	0%	3%	6%	4%	0%
Ligament sprain	0%	6%	1%	4%	0%
Dyspnoea	0%	0%	17%	0%	0%
Cough	0%	0%	14%	0%	0%
Haemorrhage	0%	6%	7%	0%	0%
Tachycardia	0%	0%	6%	0%	0%
Acute respiratory failure	0%	0%	5%	0%	0%
Anxiety	0%	0%	5%	0%	0%
Oropharyngeal pain	0%	6%	2%	0%	0%
Dyspepsia	0%	6%	1%	0%	0%

Source: FDA analysis; results limited to PTs with incidence of 5% or higher at any dose
*Includes grouped terms

Table 93 shows the proportions of study participants with Grades 2-4 laboratory abnormalities for selected analytes by decreasing incidence at the highest dose. ALT was also elevated at Grades 3-4 across all doses (3%, 6%, 3%, 19% and 25%, respectively) and ALT at the three highest doses (2%, 15% and 8%, respectively). There were no Grades 3-4 bilirubin elevations, and there were no Hy's Law cases.

Table 93. IPF and Psoriasis Studies: Selected Grades 2-4 Laboratory Abnormalities by Dose

	Belumosudil Dose				
Parameter	**200 mg QD (n=31)**	**200 mg BID (n=35)**	**400 mg QD (n=152)**	**600 mg/day (n=26)**	**400 mg BID (n=12)**
ALT Increased	10%	11%	9%	19%	42%
AST Increased	6%	9%	5%	19%	33%
GGT Increased	6%	0%	7%	12%	17%
Bilirubin Increased	3%	0%	1%	0%	8%
Creatinine kinase Increased	3%	3%	5%	4%	8%
GFR Decreased	6%	3%	14%	4%	8%
Hemoglobin Decreased	0%	0%	1%	0%	8%
Lymphocytes Decreased	0%	3%	2%	4%	0%
Neutrophils Decreased	0%	3%	0%	0%	0%
Platelets Decreased	0%	0%	0%	0%	0%

Source: FDA analysis

Clinical TL Comment: The analysis of safety in patients with IPF or psoriasis confirms that elevated transaminases and GI toxicity are adverse reactions of belumosudil. Infections may also be adverse reactions. The high rate of cough and dyspnea in this population may be symptoms of the disease (IPF) rather than a true adverse reaction.

Dose-Safety in Healthy Volunteer Studies

The volunteer studies are listed in Table 12. There were 5 participants in the volunteer studies who withdrew due to adverse reactions, including 3 due to elevated transaminases (200 mg and 500 mg BID), 1 due to an elevated creatinine kinase (240 mg), and 1 due to peripheral neuropathy (200 mg).

For the analysis of TEAEs, all participants in Study KD025-107 were excluded, since they received additional drugs concomitantly with belumosudil. The individuals with hepatic impairment in Study KD025-109 were also excluded. For the remaining 154 study participants, individual doses ranged from 20 mg to 1000 mg. The number of days of dosing ranged from 1 to 28. The duration of follow-up from start of dosing ranged from 7 to 58 days. Table 94 shows the common (≥ 4% in any dose pool) all-grade TEAE among healthy volunteers treated with belumosudil given as a single dose, as multiple doses less then 200 mg daily, as multiple doses of 200 to 400 mg, and at multiple doses of 500 mg daily or higher.

Table 94. Volunteer Studies: All-Grade TEAE by Dose Pool

		Multiple doses of Belumosudil		
PT	Single Dose of Belumosudil (N = 36)	< 200 mg (N = 24) (%)	200 - 400 mg (N = 46) (%)	≥ 500 mg (N = 48) (%)
Liver function test abnormal	0	0	4	6
Viral upper respiratory tract infection	0	0	4	6
Diarrhoea	3	0	0	6
Abdominal pain	0	0	0	4
Nausea	0	0	0	4
Headache	0	4	2	2
Rash	3	0	4	0
Blood creatine phosphokinase increased	0	0	4	0
Musculoskeletal pain	0	4	2	0
Dermatitis contact	0	4	0	0
Lip blister	0	4	0	0
Nasal congestion	0	4	0	0
Peripheral swelling	0	4	0	0

Source: FDA analysis; results limited to PTs with incidence of 4% or higher in any dose pool
*Includes grouped terms

Table 95 shows the proportions of study participants with Grade > 1 laboratory abnormalities for selected analytes. There appeared to be a dose-related decrease in the incidence of anemia and lymphocytopenia. Elevated transaminases were observed at all dose levels. Most abnormalities were Grade 1. There was 1 individual with Grade 2 ALT increased, 1 with Grade 3

AST increased, 2 with Grade 2 bilirubin increased, and 1 with Grade 3 neutrophils decrease. There were no Hy's Law cases.

Table 95. Volunteer Studies: Selected All-Grade Laboratory Abnormalities by Dose Pool

LAB	Single Dose of Belumosudil (n=35)*	Multiple doses of Belumosudil		
		< 200 mg (n=24)	200 - 400 mg (n=46)	≥ 500 mg (n=48)
	%	%	%	%
ALT Increased	3%	13%	24%	6%
AST Increased	0%	8%	9%	8%
Bilirubin Increased	3%	4%	0%	6%
GGT Increased	3%	4%	4%	2%
Hemoglobin Decreased	11%	4%	4%	54%
Lymphocytes Decreased	0%	0%	0%	17%
Neutrophils Decreased	6%	25%	15%	6%
Platelets Decreased	0%	0%	4%	2%

Source: FDA analysis
*Percentage of individuals with data when results were missing for some participants.

Clinical TL Comment: The analysis of safety in healthy volunteers confirms that elevated transaminases and GI toxicity are adverse reactions of belumosudil. The findings of lymphocytopenia and anemia represent new potential adverse reactions that would be difficult to ascertain in patients with cGVHD.

Study KD025-109 is an on-going study of the PK of a single 200 mg dose of belumosudil with hepatic impairment. Safety data were available from 8 individuals with mild impairment, 8 with moderate impairment, 1 with severe impairment, and 11 with normal hepatic function. There were no TEAEs reported to date that were at least possibly related to study drug. There was a trend for worsening any-grade bilirubin increased, hemoglobin decreased, and platelets decrease with increasing hepatic impairment, but in the absence of a control arm, it was not possible to discern if the effects were due to the drug or the underlying hepatic disease.

Drug-Drug Interactions

See Section 8.3.6 for subgroup analyses for subjects who received mTOR inhibitor as concomitant systemic cGVHD therapies.

Study KD025-107 was a nonrandomized, sequential-period PK study of belumosudil in combination with itraconazole, rabeprazole, rifampin or omeprazole. There was insufficient follow-up to allow for a credible assessment of toxicity when belumosudil was used in combination with these drugs.

8.3.9 Additional Safety Explorations

Human Carcinogenicity or Tumor Development

In the pooled chronic GVHD analysis group, malignant or unspecified neoplasma were reported in 9 (10.8%) subjects in the 200 mg QD group and 4.9% of subjects in the belumosudil 200mg BID treated subjects. The most commonly reported (≥ 2 subjects) events within this category included AML recurrent (2.4% of the belumosudil 200 mg QD treated subjects.

Human Reproduction and Pregnancy

Based on findings from animal studies and the mechanism of action, belumosudil can cause fetal harm when administered to pregnant women. There are no available human data on belumosudil use in pregnant women to evaluate for a drug-associated risk.

Pediatrics and Assessment of Effects on Growth

The Applicant has not submitted pediatric safety data.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Not applicable.

8.3.10 Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Not applicable.

Expectations on Safety in the Postmarket Setting

Adverse reactions leading to dose interruption occurred in 33% of patients. The adverse reactions leading to dose interruption in ≥ 2% were infections (11%), diarrhea (4%), and asthenia, dyspnea, hemorrhage, hypotension, liver function test abnormal, nausea, pyrexia, edema, and renal failure with (2% each).

The most common (≥ 20%) adverse reactions of belumosudil are infections, asthenia, nausea, diarrhea, dyspnea, cough, edema, hemorrhage, abdominal pain, musculoskeletal pain, headache, and hypertension.

However, the median duration of belumosudil treatment in the two clinical trials (Study KD025-213 and Study KD025-208) was only 9.2 months (range 0.5 to 44.7 months). The recommended duration of belumosudil treatment is until disease progression.

Due to the lack of data on the safety of belumosudil for long-term use, additional data for long-term safety are required. Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's safety profile during long-term use.

8.3.11 Integrated Assessment of Safety

The FDA's Assessment:

As this was a single-arm trial, all adverse events not clearly unrelated to treatment were considered adverse reactions. Additionally, for a true estimate of risks, grouped terms were used as described in Section 8.3.3. No data were submitted for pediatric patients. Based on the review of the safety database of 618 patients or healthy volunteers treated with belumosudil, there were no adverse reactions that rose to the level of seriousness that would warrant a warning.

The primary population for the common adverse events included the 83 patients with cGVHD treated with belumosudil 200 mg daily. The median duration of treatment was 9.2 months (range 0.5 to 44.7 months). Table 96 below shows the summary of major safety events in this population.

Table 96. Summary Of The Major Safety Events

Safety Events	Belumosudil 200 mg daily N=83
Any TEAE	99 %
Grade 3-5 TEAE	55%
TEAE resulting in drug interruption	29 %
TEAE resulting in drug withdrawal	18 %
Fatal adverse reaction	1 %

Source: FDA Analysis

The adverse reactions which resulted in permanent discontinuation of belumosudil in > 3% of patients included nausea (4%). The adverse reactions leading to dose interruption in ≥ 2% were infections (11%), diarrhea (4%), and asthenia, dyspnea, hemorrhage, hypotension, liver function test abnormal, nausea, pyrexia, edema, and renal failure with (2% each).

Table 97 summarizes the adverse reactions in patients with cGVHD treated with belumosudil at dose of 200 mg once daily.

Table 97. Nonlaboratory Adverse Reactions in > 10% Patients with cGVHD

	Belumosudil 200 mg daily (N=83)	
Adverse Reaction	**All Grades (%)**	**Grades 3-4 (%)**
Infections and infestations		
Infection (pathogen not specified)	53	16
Viral infection	19	4
Bacterial infection	16	4
General disorders and administration site conditions		
Asthenia	46	4
Edema	27	1
Pyrexia	18	1
Gastrointestinal		
Nausea	42	4
Diarrhea	35	5
Abdominal pain	22	1
Dysphagia	16	0
Respiratory, thoracic and mediastinal		
Dyspnea	33	5
Cough	30	0
Nasal congestion	12	0
Vascular		
Hemorrhage	23	5
Hypertension	21	7
Musculoskeletal and connective tissue		
Musculoskeletal pain	22	4
Muscle spasm	17	0
Arthralgia	15	2
Nervous system		
Headache	21	0
Metabolism and nutrition		
Decreased appetite	17	1
Skin and subcutaneous		
Rash	12	0
Pruritus	11	0

Source: FDA analysis

Table 98 is a shift table for selected laboratory abnormalities in patients with cGVHD treated with belumosudil at dose of 200 mg once daily.

Table 98. Selected Laboratory Abnormalities in Patients with cGVHD

	Belumosudil 200 mg once daily		
	Grade 0-1 Baseline	Grade 2-4 Max Post	Grade 3-4 Max Post
Parameter	**(N)**	**(%)**	**(%)**
Chemistry			
Phosphate Decreased	76	28	7
Gamma Glutamyl Transferase Increased	47	21	11
Calcium Decreased	82	12	1
Alkaline Phosphatase Increased	80	9	0
Potassium Increased	82	7	1
Alanine Aminotransferase Increased	83	7	2
Creatinine Increased	83	4	0
Hematology			
Lymphocytes Decreased	62	29	13
Hemoglobin Decreased	79	11	1
Platelets Decreased	82	10	5
Neutrophil Count Decreased	83	8	4

Source: FDA analysis

Overall, the safety profile for belumosudil 200 mg daily appears tolerable for patients with cGVHD. Additional data are needed to assess the safety of long-term administration of belumosudil.

SUMMARY AND CONCLUSIONS

8.4 Statistical Issues

The FDA's Assessment:

Table 99 summarizes key efficacy issues. Efficacy issues were resolved by FDA adjudication of response and duration of response, adjudication of new systemic therapy initiation, and assessment of efficacy by separate cohorts. Additionally, the patient-reported improvement in Lee Symptom Scale summary score may be overestimated because patients were not blinded to treatment assignment. Due to this potential issue in treatment blinding, lack of a control group, and the exploratory nature of the patient-reported outcomes analysis, from a statistical

perspective, the statistical team does not recommend including Lee Symptom Scale summary score results in the label.

Table 99. Efficacy Issues

Issue	Impact	Solution
1. Discrepancy: Investigator vs NIH Criteria-based response per Kadmon Algorithmic Response Assessment (KARA)	ORR, DOR	FDA adjudication of organ-based and overall response
2. Discrepancy: FDA vs KARA organ-based assessment	ORR, DOR	FDA organ-based assessment algorithm creation
3. Inadequate Assessment: FDA vs Applicant overall response assessment	ORR, DOR	FDA adjudication of overall response
4. Inadequate Documentation: Subsequent anti-cGVHD therapy and increase in steroids	ORR, DOR	FDA adjudication of subsequent therapy initiation
5. Inadequate Analysis: Complete pooling of heterogeneous groups for efficacy (i.e., differences in population and dosage)	Integrated efficacy assessment	Efficacy assessment by separate cohorts

Source: Reviewer's Analysis

8.5 Conclusions and Recommendations

The FDA's Assessment:

The accepted clinical benefit of a treatment for recurrent or refractory cGVHD is CR or PR within 6 months of treatment and with durability. The response rate of 75% in Study KD025-213 with durability provides substantial evidence of effectiveness of belumosudil 200 mg daily for treatment of chronic GVHD, and the results in Study KD025-208 are supportive. The safety profile of the recommended dosage is tolerable in the intended population. Approval is recommended.

9 ADVISORY COMMITTEE MEETING AND OTHER EXTERNAL CONSULTATIONS

The FDA's Assessment:

This application was not discussed by an Advisory Committee.

10 PEDIATRICS

The Applicant's Position:

An agreed initial Pediatric Study Plan (Agreed iPSP) for chronic Graft-Versus-Host-Disease (cGVHD) was issued by FDA on April 17, 2020.

The FDA's Assessment:

The Applicant has not submitted pediatric safety data. The adolescent Cohort of Study KD025-213 has not enrolled any adolescents prior to the data cutoff.

In the initial Pediatric Study Plan (Agreed iPSP) issued by FDA on April 17, 2020, 20 subjects ages ≥ 12 - 17 years will be enrolled to the KD025-213 study, 10 to be treated with each of the dose levels, 200 mg QD and 200 mg BID, to assess for safety, efficacy and PK. Safety and PK assessments will be the same as those for adult subjects.

The Applicant also planned Pediatric Clinical Studies, including a pediatric formulation PK study in adults (Study 1); and efficacy/safety study in pediatric patients (Study 2): (b) (4)

11 LABELING RECOMMENDATIONS

Summary of Significant Labeling Changes		
Section	**Applicant's Proposed Labeling**	**FDA's proposed Labeling**
Highlights	Indications and Usage Adverse Reactions	FDA added the established pharmacologic class ("kinase inhibitor") in accordance with 21CFR201.57(a)(6). FDA added laboratory abnormalities to the most common adverse reaction statements (i.e., phosphate decreased, gamma glutamyl transferase increased, lymphocytes decreased).
1. Indications and Usage	REZUROCK is indicated for the treatment of patients 12 years and older with chronic graft-versus-host disease (chronic GVHD) after failure of at least (b) (4) of systemic therapy.	REZUROCK is indicated for the treatment of adult and pediatric patients 12 years and older with chronic graft-versus-host disease (chronic GVHD) after failure of at least two prior lines of systemic therapy.

2. Dosage and Administration	**2.1 Recommended Dosage** The recommended dose of REZUROCK is 200 mg given orally once daily.	FDA added "until progression of chronic GVHD that requires new systemic therapy." to provide the required duration of use. FDA added instructions for the patient to swallow tablets whole and not to cut, crush, or chew tablets. FDA revised statements to clarify REZUROCK has not been studied in patients with pre-existing severe renal or hepatic impairment and removed "(b) (4)" and "(b) (4)" statements that were not required.
2. **Dosage and Administration**	**2.2 Dose Modifications for Adverse Reactions**	FDA revised AST and ALT monitoring criteria from "(b) (4)" to "at least monthly". FDA revised to clarify that REZUROCK should be resumed at the recommended dose after recovery of adverse reactions.
2. **Dosage and Administration**	No drug interaction labeling proposed by Applicant in this subsection.	**2.3 Dosage Modification Due to Drug Interactions** FDA added this section and required dosage modifications for REZUROCK when administered with strong CYP3A inducers and proton pump inhibitors.
5. Warnings and Precautions	**5.1 Embryo-Fetal Toxicity**	FDA added fetal harm may occur "based on mechanism of action" (in addition to findings in animals). FDA added "adverse developmental outcomes revised" and revised (b) (4)" to "fetal malformations".
6. Adverse Reactions	**6.1 Clinical Trial Experience**	FDA revised this subsection to reflect exposure to patients (n=83) who received the recommended dose of REZUROCK (200 mg once daily) and removed (b) (4) FDA added a fatal adverse reaction

		statement (one patient with severe nausea, vomiting, diarrhea and multi-organ failure). FDA revised the permanent discontinuation and dose interruption statements due to adverse reactions (ARs); and revised the ARs included and incidence rates reported based on FDA safety review findings. FDA added "asthenia, dyspnea, hemorrhage, liver function test abnormal, nausea, edema, and renal failure with (2% each)" to the adverse reactions leading to dose interruption statement. FDA updated the common adverse reactions table based on FDA safety review findings and FDA grouped terms. These revisions resulted in new AR terms for infections (pathogen not specified, viral, and bacterial), hemorrhage, musculoskeletal pain, rash, and pruritis. And increased the incidence rates (>5%) for fatigue/asthenia, nausea, abdominal pain, dyspnea, and cough. FDA revised the selected laboratory abnormalities (LAs) table based on FDA safety review to provide additional LAs and severity grades. FDA removed (b) (4)
7. Drug Interactions	**7.1 Effect of Other Drugs on REZUROCK**	FDA revised this section to require dosage modifications for REZUROCK when administered with strong CYP3A inducers or with proton pump inhibitors.
8. Use in Specific Populations	**8.1 Pregnancy**	FDA revised the Risk Summary from "(b) (4)" to "adverse developmental outcomes, including alterations to growth, embryo-fetal mortality, and embryo-fetal malformations."

		FDA revised the Data, *Animal Data* subsections based on FDA Pharmacology/Toxicology review findings to support the labeling revisions to the Risk Summary.
8. Use in Specific Populations	**8.3 Females and Males of Reproductive Potential**	To the Infertility subsection, FDA added: "*Females* Based on findings from rats, REZUROCK may impair female fertility. The effect on fertility is reversible *[see Nonclinical Toxicology (13.1)]."* and revised the infertility information for males to provide reversibility information.
8. Use in Specific Populations	**8.4 Pediatric Use**	FDA added statements to clarify the evidence used to establish safety and effectiveness in pediatric patients 12 years and older.
11 Description	**…**	FDA revised the required pharmacological class from (b) (4) " to "kinase inhibitor" for consistency with the established pharmacologic class and other information in subsection 12.1 of this USPI.
12 Clinical Pharmacology	**12.1 Mechanism of Action**	FDA revised focus on pertinent information for the indicated population; to add details of the established mechanism(s) of action; and to remove (b) (4) .
12 Clinical Pharmacology	**12.2 Pharmacodynamics** (b) (4)	FDA removed this subsection based on inadequate data to support this statement.
12 Clinical Pharmacology	**12.3 Pharmacokinetics**	FDA revised the pharmacokinetic information for REZUROCK as follows: - Removed information (b) (4) - Revised the Tmax from "(b) (4)" to "1.26 to 2.53 hours"

		- Revised the (b) (4) provided to geometric Vd (184 L). - Added details to clearly define specific populations - Added details on drug interactions for moderate CYP3A inhibitors; CYP3A, CYP2C9, CYP2C8 substrates; and other CYP enzyme inhibition.
13.1 Nonclinical Toxicology	…	FDA added information related to adverse changes in male and female reproductive organs from general toxicology studies.
14. Clinical Studies	…	FDA revised this subsection to reflect patients (n=65) from the randomized trial who received the recommended dose of REZUROCK (200 mg once daily) and that failed the number of required lines of therapy specified in the indications and usage statement (at least two prior lines of therapy). To the demographic and baseline disease table: - FDA added: - median (range) number of prior lines of therapy - prior chronic GVHD treatment with ruxolitinib (n, %) - median (range) Lee Symptom Scale Score at baseline - FDA removed: (b) (4) FDA added the response criteria description used in the randomized trial (2014 NIH Response Criteria). FDA removed efficacy results for (b) (4)

		(b) (4) . FDA added efficacy results for: - partial response(PRs) (revised "achieved in majority of patients" to "n, %") - no death or new systemic therapies in patients who had responses for chronic GVHD for at least 12 months - exploratory analyses of the patient-reported symptom bother (≥ 7 point decrease in Lee Symptom Scale through Cycle 7, Day 1). FDA removed general statements that (b) (4)
17 Patient Counseling Information	…	FDA revised the Embryo-Fetal Toxicity information to standard advice used labeling for products with these risks FDA added counseling advice related to effective contraception, lactation, and infertility risks to males and females.

12 RISK EVALUATION AND MITIGATION STRATEGIES (REMS)

The FDA's Assessment:

The review team has not identified a need for a REMS.

13 POSTMARKETING REQUIREMENTS AND COMMITMENT

The FDA's Assessment:

PMR #1 Conduct a pharmacokinetics trial to compare the relative bioavailability of belumosudil pediatric formulation to belumosudil tablets and develop an age-appropriate pediatric formulation of belumosudil. Submit datasets and product quality information with the final report.

PMR #2 Conduct a clinical trial to determine the appropriate dose of belumosudil and to assess the safety, efficacy, and pharmacokinetics of belumosudil in pediatric patients with chronic graft-versus-host disease. Include at least 20 adolescents 12 to < 17 years old, 4 children 2 to < 12 years old, and 2 infants ≥ 3 months to < 2 years old. Submit the datasets with the final report.

PMR #3 Conduct an integrated safety analysis using data obtained from clinical trials to further characterize the safety of long-term treatment with belumosudil and determine the rate of infections, hypertension and other adverse events. The integrated safety analysis should include all adverse events, major safety events, dose-reductions, dose interruptions, withdrawals, and efficacy when all patients have completed at least three years of treatment with belumosudil or withdrew earlier. Submit the datasets with the final report.

PMR #4 Conduct a clinical pharmacokinetic trial evaluating the effect of repeat doses of belumosudil on the single-dose pharmacokinetics of a UGT1A1 substrate to assess the potential for excessive drug toxicity. This trial should be designed and conducted in accordance with the FDA Guidance for Industry titled, "Clinical Drug Interaction Studies – Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions." Submit the datasets with the final report

PMR #5 Conduct a clinical pharmacokinetic trial evaluating the effect of repeat doses of belumosudil on the single-dose pharmacokinetics of sensitive substrates (P-gp, BCRP and OATP1B1) to assess the potential for excessive drug toxicity. This trial should be designed and conducted in accordance with the FDA Guidance for Industry titled, "Clinical Drug Interaction Studies – Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions." Submit the datasets with the final report.

PMR #6 Conduct a clinical pharmacokinetic trial to determine a safe and appropriate dose of belumosudil in subjects with mild, moderate, and severe hepatic impairment. This trial should be designed and conducted in accordance with the FDA Guidance for Industry titled "Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling." The final report should include assessment of subjects with mild, moderate and severe hepatic impairment. Submit the datasets with the final report.

PMR #7 Conduct a thorough QT/QTc trial to evaluate the effect of repeat doses of belumosudil on the QT/QTc interval to address the potential for excessive drug toxicity. This trial should be designed and conducted in accordance with the FDA Guidances for Industry titled, E14 Clinical Evaluation of QT/QTc and E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs Questions and Answers (R3). Submit the datasets with the final report.

PMR #8 Conduct a clinical trial in a sufficient number of Black patients with chronic graft-versus-host-disease to assess the risk of cardiac toxicities and further characterize Grade 3 toxicities, including gastrointestinal and vascular disorders, associated with the use of belumosudil. This study should characterize the exposure (including PK data), safety, and efficacy of belumosudil. Submit the datasets with the final report.

PMR #9 Conduct a rodent carcinogenicity study in mice to evaluate the potential for carcinogenicity. Submit a carcinogenicity protocol for a Special Protocol Assessment (SPA) prior to initiating the study.

PMR #10 Conduct a rodent carcinogenicity study in rats to evaluate the potential for carcinogenicity. Submit a carcinogenicity protocol for a Special Protocol Assessment (SPA) prior to initiating the study.

PMR #11 Conduct an in vitro mechanism-based inhibition study (such as the two-step dilution method) estimating the inactivation parameters (k_{inact} and K_I) of CYP1A2, CYP2C19 and CYP2D6 enzymes and measuring nonspecific binding of belumosudil to assess the potential of drug interaction with belumosudil on these enzymes in accordance with the FDA Guidance for Industry titled "In Vitro Drug Interaction Studies – Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions."

PMC #1 Conduct a clinical trial to assess the pharmacokinetics of belumosudil among U.S. racial and ethnic groups. This study should characterize the exposure (including PK data), efficacy, and safety of belumosudil.

PMC #2 Development and validation of an optimal and discriminating dissolution method for the Quality Control (QC) testing of REZUROCK™ (belumosudil mesylate) Tablets, 200 mg. Submit a Prior Approval Supplement to update the NDA to include the method in the drug product specifications.

Dissolution acceptance criterion/criteria proposal, based on the data generated from the unexpired clinical and registration batches, and the first six commercial batches, using the new dissolution method. Submit a Prior Approval Supplement to update the NDA to update the dissolution acceptance criterion in the drug product specifications. (Note: if six commercial batches have not been manufactured at the time of final report submission, dissolution acceptance criterion will be based on the data generated from the unexpired clinical and registration batches and from all available commercial batches).

14 DIVISION DIRECTOR (DHM1)

15 OFFICE DIRECTOR

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

16 APPENDICES

16.1 References

The Applicant's References:

Arai S, Arora M, Want T, et al. Increasing incidence of chronic graft-versus-host disease in allogeneic transplantation: a report from the Center for International Blood and Marrow Transplant Research. Biol Blood Marrow Transplant. 2015;21(2):266-274.

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Thumkeo D, Keel J, Ishizaki T, et al. Targeted disruption of the mouse rho-associated kinase 2 gene results in intrauterine growth retardation and fetal death. Mol Cell Biol. 2003;23(14):5043-5055.

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Weiss JM, et al. ROCK2 signaling is required to induce a subset of T follicular helper cells through opposing effects on STATs in autoimmune settings. Sci. Signal. 2016;9(437):1-9.

The FDA's References:

FDA acknowledges the Applicant cited references and added the following references:

Cook KR, Luznik, L, Sarabtopoulos S, et al. The biology of chronic graft-versus-host disease. Biol Blood Marrow Transplant 2017;23:211-234.

Lee S, Cook EF, Soiffer R, Antin JH. Development and validation of ascale to measure symptoms of chronic graft-versus-host disease. Biol Blood Marrow Transplant. 2002;8:444-452.

Lee SJ, Wolff D, Kitko C, et al. Measuring therapeutic response in chronic graft-versus-host disease. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: IV. The 2014 Response Criteria Working Group Report. Biol Blood Marrow Transplant. 2015;21(6):984-999.

16.2 Financial Disclosure

The Applicant's Position:

The Applicant provided financial disclosures for 375 clinical investigators participating in Studies KD025-208 and KD025-213 (see Sections 8.1.1 and 8.1.2 for Study KD025-208 and Study KD025-213, respectively). Both Study KD025-208 and Study KD025-213 do not have any clinical investigators with disclosable financial arrangements.

Covered Clinical Study (Name and/or Number):*

Was a list of clinical investigators provided:	Yes ☐	No ☐ (Request list from Applicant)
Total number of investigators identified: _____		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): _____		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): _____		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in study: _____ Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

*The table above should be filled by the applicant, and confirmed/edited by the FDA.

The FDA's Assessment:

The Applicant has not filled the table above. FDA filled the following table based on information submitted by the Applicant on 9/30/2020. There were 120 investigators identified for the Study KD025-208, and 455 investigators identified for the Study KD025-213. In both Study KD025-208 and Study KD025-213, there was not any clinical investigator with disclosable financial arrangements.

Covered Clinical Study (Name and/or Number): Study KD025-208

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 120		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): No		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in study: _____ Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): Study KD025-213

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 455		

Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in study: _____ Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

16.3 Nonclinical Pharmacology/Toxicology

Data:

All relevant data presented in Section 5, Nonclinical Pharmacology/Toxicology.

The Applicant's Position:

None

The FDA's Assessment:

FDA concurs with the Applicant's statement.

16.4 OCP Appendices

The FDA's Assessment:

16.4.1 Physiologically Based Pharmacokinetic (PBPK) Modeling Analysis

Executive Summary

The objective of this review is to evaluate the adequacy of the Applicant's physiologically based pharmacokinetic (PBPK) analyses to evaluate the drug-drug interaction (DDI) potentials:

- as a victim of CYP3A moderate inhibitors and inducer
- as an inhibitor of CYP2C8, CYP2C9, CYP3A4, P-gp, OATP1B1, BCRP, and MATEs

The Division of Pharmacometrics has reviewed the PBPK report DEVELOPMENT OF A PBPK MODEL FOR KD025 FOR EVALUATION OF DDI LIABILITY AS A PERPETRATOR AND A VICTIM OF RELEVANT METABOLISM ENZYMES AND TRANSPORTERS, and the modeling supporting files, and concluded that

- The PBPK analyses are adequate to evaluate the effects of moderate CYP3A inhibitors and inducers on the PK of belumosudil and the effects of belumosudil on the substrates of CYP2C9 and CYP3A and CYP2C8 substrates that are not substrates of OATP1B. Drug interactions of belumosudil are expected to be
  - minimal with moderate CYP3A inhibitors, CYP2C9 substrates or CYP2C8 substrates that are not substrates of OATP1B
  - weak with the moderate CYP3A inducer efavirenz or CYP3A substrates.
- The analyses were inadequate to confirm a negative DDI effect of belumosudil on the exposure of substrates of P-gp, BCRP, OATP1B, and MATEs due to lack of quantitative *in vitro* to *in vivo* extrapolation for the *in vitro* transporter inhibition parameters and/or limitations identified in the PBPK models of these transporter substrates.

Background

Belumosudil (KD-025) is a rho-associated, coiled-coil containing protein kinase-2 (ROCK2) inhibitor and is being investigated for treatment of adult and pediatric patients 12 years and older with chronic graft-versus-host disease (chronic GVHD) after failure of at least two prior line of systemic therapy. The proposed dosing regimen is 200 mg (tablet) once daily taken orally with food. Following oral administration of single and multiple once daily doses of belumosudil (capsule) in healthy subjects, its AUC and C_{max} increased approximately dose proportional across the dose range of 40 to 500 mg. High fat breakfast increased belumosudil exposure (C_{max} and AUC) approximately 2-fold following a single dose of 200-mg tablet in healthy subjects. Following oral administration of a 200-mg tablet once daily with food, belumosudil AUC in cGVHD patients was approximately 2-fold higher compared to healthy subjects. The tablet and capsule formulations were bioequivalent.

Belumosudil is extensively metabolized through CYP3A4, CYP2C8, CYP2D6 and UGT1A9 (XT184069 and XT174009). In the human ADME study, approximately 4% and 85% of radioactivity were recovered in the urine (0% parent) and the feces (28% unchanged parent), respectively. M2 is the major oxidative metabolite of belumosudil and is further metabolized by UGT1A1. Belumosudil is a BCS Class IV compound and a P-gp substrate. M2 is a substrate of OATP1B1, OATP1B3, OAT1, OAT3, and MATE-2K. Belumosudil is determined in vitro to be a mechanism-based inhibitor of CYP3A4 with the k_{inact} and K_I values of 2.7 h^{-1} and 0.81 μM, respectively. In vitro inhibition of CYP enzymes and transporters by belumosudil and M2 is summarized in **Table 100**. Belumosudil induced concentration-dependent increases in CYP1A2, CYP2B6 and CYP3A4 mRNA up to 6.4-, 2.2-. and 4.5-fold, respectively, at 15 μM. Although mRNA increases of all these CYP enzymes were less than 20% of the positive controls, potential induction by belumosudil cannot be ruled out due to cell toxicity at higher concentrations. M2 is not an inducer of CYP1A2, CYP2B6 and CYP3A4. The applicant conducted clinical DDI studies with itraconazole and rifampin to evaluate some of the *in vitro* findings. Refer to the Clinical Pharmacology review section for detail information on belumosudil regarding ADME properties, *in vitro* and clinical studies used in PBPK modeling.

Table 100. In vitro inhibition of belumosudil and KD025-M2 on CYP enzymes and transporters

Enzymes	Inhibition IC_{50} (μM)		Mechanism based inhibition		Transporters	Inhibition IC50 (μM)*	
	belumosudil	M2	belumosudil	M2		belumosudil	M2
CYP1A2	12	4.9	Yes	No	**P-gp**	0.198	<50%
CYP2B6	>25	>100	No	No	**BCRP**	0.031	7.73
CYP2C8	0.46 (K_i)	0.67 (K_i)	No	No	**OATP1B1**	0.235	0.39
CYP2C9	0.92 (K_i)	26	No	No	**OATP1B3**	<50%	1.55
CYP2C19	2.7	>100	Yes	No	**MATE1**	0.397	70.8
CYP2D6	24	>100	Yes	No	**MATE2K**	0.224	13.2
CYP3A4/5	3.4 (TEST)	86 (TEST)	Yes	Yes	**OAT1/OCT2**	<50%	<50%
CYP3A4/5	11 (MDZ)	>100 (MDZ)	Yes	Yes	**OAT3**	<50%	15.9
UGT1A1	0.06	0.63			**BSEP**	<50%	48.2
UGT1A9	0.86	11.2					

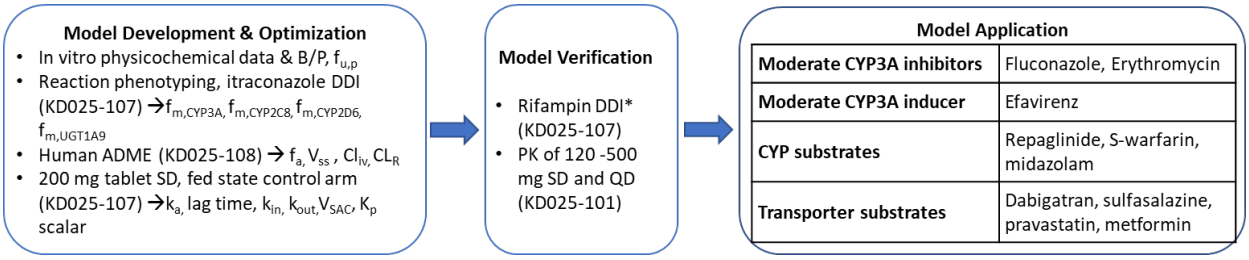
TEST= testosterone; MDZ= midazolam. *IC50 values were determined when transporter inhibition >50%
Source: XT178018, XT175017, and ADME-KAD-200630-UGT Inhibition

Methods

All simulations were performed using the PK/PD Profiles mode in the Simcyp® Simulator (Version 18 Certara, Sheffield, UK). Schemes of the PBPK simulation strategy are shown in **Figure 14,** which summarizes parameters optimized and the studies used for parameter optimization in model development, studies used in model verification, and model applications in DDI predictions. The belumosudil PBPK model consists of a minimal PBPK distribution model and first-order absorption and elimination models. M2 PBPK model consists of a minimal PBPK distribution model and a first-order elimination model. Simcyp library files of itraconazole fed capsule and hydroxy-itraconazole, fluconazole, erythromycin, efavirenz, repaglinide, S-warfarin,

midazolam, dabigatran, pravastatin, metformin, and a sulfasalazine research file were used for DDI simulations without any modification unless noted in the following review.

Figure 14. Modeling and simulation strategy



Source: This flow chart was generated by the reviewer.

Results

1. Can the PBPK model adequately describe the PK profiles of belumosudil and its metabolite M2?

The predicted and observed PK parameters of belumosudil and M2 following administration of single or multiple doses of belumosudil in healthy subjects under the fasted state were compared and are shown in **Table 101**. The PBPK models of belumosudil and M2 were optimized based on belumosudil and M2 PK of a single 200-mg belumosudil tablet in the absence and presence of itraconazole from the itraconazole DDI study. Despite the fact that belumosudil had linear PK and tablet and capsule formulations were bioequivalent, the PBPK models of belumosudil and M2 didn't capture the t_{max} of belumosudil and M2 and tended to under-predict the AUC of belumosudil and M2 at the doses greater than 160 mg following single and multiple doses of belumosudil.

Table 101. Predicted and observed PK parameters of belumosudil and its metabolites M2 following a single dose or 7 or 14 days of once daily doses of belumosudil (capsule) in healthy subjects under the fasted state

Dose (mg)		KD025 Day 1			KD025 Day 8			KD025 Day 14			M2 Day 1			M2 Day 8			M2 Day 14		
		C_{max} (ng/mL)	t_{max} (h)	$AUC_{0\text{-infinity}}$ (hr*ng/mL)	C_{max} (ng/mL)	t_{max} (h)	$AUC_{0\text{-infinity}}$ (hr*ng/mL)	C_{max} (ng/mL)	t_{max} (h)	$AUC_{0\text{-tau}}$ (hr*ng/mL)	C_{max} (ng/mL)	t_{max} (h)	$AUC_{0\text{-infinity}}$ (hr*ng/mL)	C_{max} (ng/mL)	t_{max} (h)	$AUC_{0\text{-infinity}}$ (hr*ng/mL)	C_{max} (ng/mL)	t_{max} (h)	$AUC_{0\text{-tau}}$ (hr*ng/mL)
120	Observed	771	4.02	4744	1010	4.02	4923	574	4.00	3644	84	4.04	501	109	4.02	708	107	4.00	548
	CV (%)	42	(4.00 - 4.05)	50	46	(2.00 - 6.02)	45	58	(0.98 - 5.98)	61	30	(4.02 - 6.00)	15	83	(2.00 - 4.03)	45	62	(4.00 - 5.98)	67
	Simulated	1048	2.22	4246	1100	2.21	4683	1100	2.21	4333	184	2.45	604	184	2.45	600	184	2.45	600
	CV (%)	58	(1.23 - 3.44)	35	56	(1.26 - 3.40)	37	56	(1.26 - 3.40)	36	44	(1.59 - 3.63)	40	43	(1.65 - 3.65)	41	43	(1.65 - 3.65)	41
	S/O	1.36	0.55	0.90	1.09	0.55	0.95	1.92	0.55	1.19	2.20	0.61	1.21	1.69	0.61	0.85	1.72	0.61	1.09
160	Observed	1115	6.98	8226	1115	6.98	8226	910	4.01	6467	229	6.00	1205	162	6.98	1230	112	4.03	654
	CV (%)	37	(3.98 - 7.98)	29	37	(3.98 - 7.98)	29	49	(1.00 - 6.00)	60	60	(4.00 - 8.12)	56	47	(3.98 - 7.98)	14	66	(1.00 - 6.00)	72
	Simulated	1413	2.22	5615	1413	2.23	5149.00	1488	2.20	5766	246	2.45	792	246	2.45	742	243	2.45	832
	CV (%)	69	(1.23 - 3.44)	38	69	(1.25 - 3.40)	40	67	(1.26 - 3.40)	39	44	(1.59 - 3.63)	39	44	(1.60 - 3.66)	40	42	(1.65 - 3.65)	40
	S/O	1.27	0.32	0.68	1.27	0.32	0.63	1.63	0.55	0.89	1.08	0.41	0.66	1.52	0.35	0.60	2.17	0.61	1.27
240	Observed	1894	5.00	12061	1810	4	11820	2194	4.02	14108	548	5.00	2093	480	4	2017	571	4.02	3077
	CV (%)	36	(4.00 - 8.02)	21	28	(4.00 - 6.03)	27	42	(4.00 - 8.00)	26	66	(4.00 - 8.02)	58	33	(4.00 - 6.03)	42	57	(4.00 - 8.00)	57
	Simulated	2122	2.22	8340	2121	2.23	8341	2240	2.20	8648	374	2.45	1191	374	2.45	1191	363	2.48	1171
	CV (%)	59	(1.23 - 3.44)	37	21	(1.26 - 3.45)	49	57	(1.25 - 3.45)	39	42	(1.59 - 3.63)	40	42	(1.61 - 3.65)	40	41	(1.65 - 3.65)	41
	S/O	1.12	0.44	0.69	1.17	0.56	0.71	1.02	0.55	0.61	0.68	0.49	0.57	0.78	0.61	0.59	0.64	0.62	0.38
320	Observed	2513	4.01	20222	2625	6	20817	2767	6.00	19295	548	5.00	2093	342	6	2105	416	6.01	2164
	CV (%)	33	(1.02 - 12.03)	30	39	(2.00 - 7.98)	37	38	(1.00 - 16.0)	38	66	(4.00 - 8.02)	58	84	(2.0 - 7.98)	52	75	(1.0 - 16.0)	52
	Simulated	3027	2.15	11495	3027	2.15	11496	3216	2.16	12089	519	2.40	1635	519	2.40	1541	494	2.45	1594
	CV (%)	66	(1.23 - 3.44)	38	66	(1.25 - 3.45)	38	67	(1.26 - 3.45)	41	47	(1.59 - 3.63)	41	47	(1.6 - 3.61)	41	43	(1.65 - 3.70)	40
	S/O	1.20	0.54	0.57	1.15	0.36	0.55	1.16	0.36	0.63	0.95	0.48	0.78	1.52	0.40	0.73	1.19	0.41	0.74
400	Observed	2122	5.00	16075	2334	6.97	18755	3185	5.01	21225	438	6.00	1743	325	6.965	2935	861	6.00	4112
	CV (%)	34	(1.10 - 12.00)	23	64	(4.0 - 8.0)	38	31	(4.0 - 7.98)	45	86	(1.10 - 12.00)	60	56	(4.03 - 8)	52	86	(4.0 - 8.0)	69
	Simulated	3886	2.15	14660	3885	2.15	14661	4151	2.15	15590	649	2.40	2043	649	2.40	1927	601	2.45	1959
	CV (%)	65	(1.31 - 3.23)	38	65	(1.30 - 3.25)	38	66	(1.30 - 3.21)	42	46	(1.61 - 3.44)	40	46	(1.60 - 3.46)	41	41	(1.65 - 3.50)	40
	S/O	1.83	0.43	0.91	1.66	0.31	0.78	1.30	0.43	0.73	1.48	0.40	1.17	2.00	0.34	0.66	0.70	0.41	0.48
500	Observed	3342	5.00	25656	3883	4	24872	3904	5.01	30192	438	6.00	1743	838	4	3756	1290	4.02	7332
	CV (%)	30	(2.00 - 8.00)	26	43	(4.0 - 6.0)	59	40	(4.0 - 7.95)	45	86	(1.10 - 12.00)	60	45	(4.0 - 6.0)	58	61	(4.0 - 6.0)	64
	Simulated	4542	2.23	17866	4861	2.16	17026	4875	2.25	19066	784	2.45	2508	810	2.40	2407	720	2.50	2395
	CV (%)	57	(1.24 - 3.43)	37	65	(1.30 - 3.25)	39	56	(1.26 - 3.45)	39	42	(1.60 - 3.63)	41	46	(1.61 - 3.45)	41	41	(1.65 - 3.70)	42
	S/O	1.36	0.45	0.70	1.25	0.54	0.68	1.25	0.45	0.63	1.79	0.41	1.44	0.97	0.60	0.64	0.56	0.62	0.33

Values are geometric mean except T_{max} (median, range)
Source: Tables 19-36 in the PBPK report.

2. Can PBPK analyses predict the effects of moderate CYP3A inhibitors and moderate CYP3A inducers on the PK of belumosudil?

Yes. The model could be used to predict the effects of moderate CYP3A inhibitors and inducers. The predicted effects of fluconazole and erythromycin on belumosudil exposure were similar to that observed in the itraconazole DDI study (**Table 102**). Because efavirenz is not expected to induce intestinal P-gp (Mouly S et al), this model could also be used to predict the induction effect of efavirenz, and efavirenz was predicted to be a weak inducer of belumosudil (**Table 102**).

Reviewer's comments:
To predict the effects of moderate CYP3A inhibitors and inducers on belumosudil PK, the fraction metabolized by CYP3A ($f_{m,CYP3A}$) is one of key parameters that need to be verified in the belumosudil PBPK model. In model development, the applicant used belumosudil PK data from the itraconazole DDI study to optimize the $f_{m,CYP3A}$ value. Belumosudil is a P-gp substrate and has low permeability, thus P-gp inhibition by itraconazole could potentially affect belumosudil exposure. To optimize belumosudil $f_{m,CYP3A}$ using itraconazole DDI data,

one has to assume, though never mentioned in the report, that P-gp inhibition by itraconazole has a minimal effect on belumosudil PK at 200-mg belumosudil. This assumption may be supported by 1) The results from the human ADME and absolute bioavailability studies showed that fraction absorbed is approximately 86%, indicating that enough belumosudil entered systemic circulation and P-gp may play a minor role in belumosudil absorption. 2) The optimized $f_{m,CYP3A}$ value (26%) using the itraconazole DDI data was similar to that (28.3%) estimated based on the human ADME and reaction phenotyping studies. Therefore, it is likely that P-gp was saturated at the 200-mg dose and P-gp inhibition by itraconazole had a minimal effect on belumosudil PK. Therefore, the optimized $f_{m,CYP3A}$ in belumosudil PBPK model is considered acceptable.

Table 102. Predicted and observed effects of CYP3A perpetrators on belumosudil PK following co-administration of multiple-dose CYP3A perpetrators with a single oral dose of 200-mg belumosudil

CYP3A inhibitors	Belumosudil dosing day	$C_{max,inh}$ (ng/mL)	$AUC_{0\text{-}inf,\ inh}$ (ng/mL.h)	C_{max} Ratio	$AUC_{0\text{-}inf}$ Ratio	
Itraconazole 200 mg capsule QD 9d, fed	D8	2130	11200	1.20	1.25	observed
Itraconazole 200 mg capsule QD 9d, fed	D8	2069	9473	1.13	1.29	simulated
Fluconazole 200 mg QD 28d	D10	1886	9660	1.09	1.22	predicted
Erythromycin 500 mg TID 28d	D8	1900	9850	1.10	1.25	predicted
Efavirenz 600 mg QD 15d	D8	1396	5141	0.68	0.65	predicted

Values are geometric mean
Source: Tables 37 and 38 in the PBPK report, CSR KD025-107, and 107-itra-model-fm3a4.xlsx

3. Can PBPK analyses be used to estimate the effects of belumosudil and its metabolite M2 on substrates of transporters and CYPs?

1) Effects of belumosudil and M2 on substrates of transporters

The applicant simulated drug interactions of belumosudil with transporter substrates to assess its effect on P-gp, BCRP, OATP1B and MATEs (**Table 103**). The applicant also conducted sensitivity analysis of calculated Ki (b) (4) Overall, these PBPK analyses are considered inadequate to estimate the effects of belumosudil on transporter substrates because the in vitro to in vivo extrapolation (IVIVE) of in vitro inhibition parameter K_i has not been established, and/or the ability of the PBPK models of transporter substrates to predict the effects of transporter inhibitors has not been demonstrated. Detail assessment of each interaction is as follows:

- (b) (4)

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA. The FDA's position is highlighted in gray.

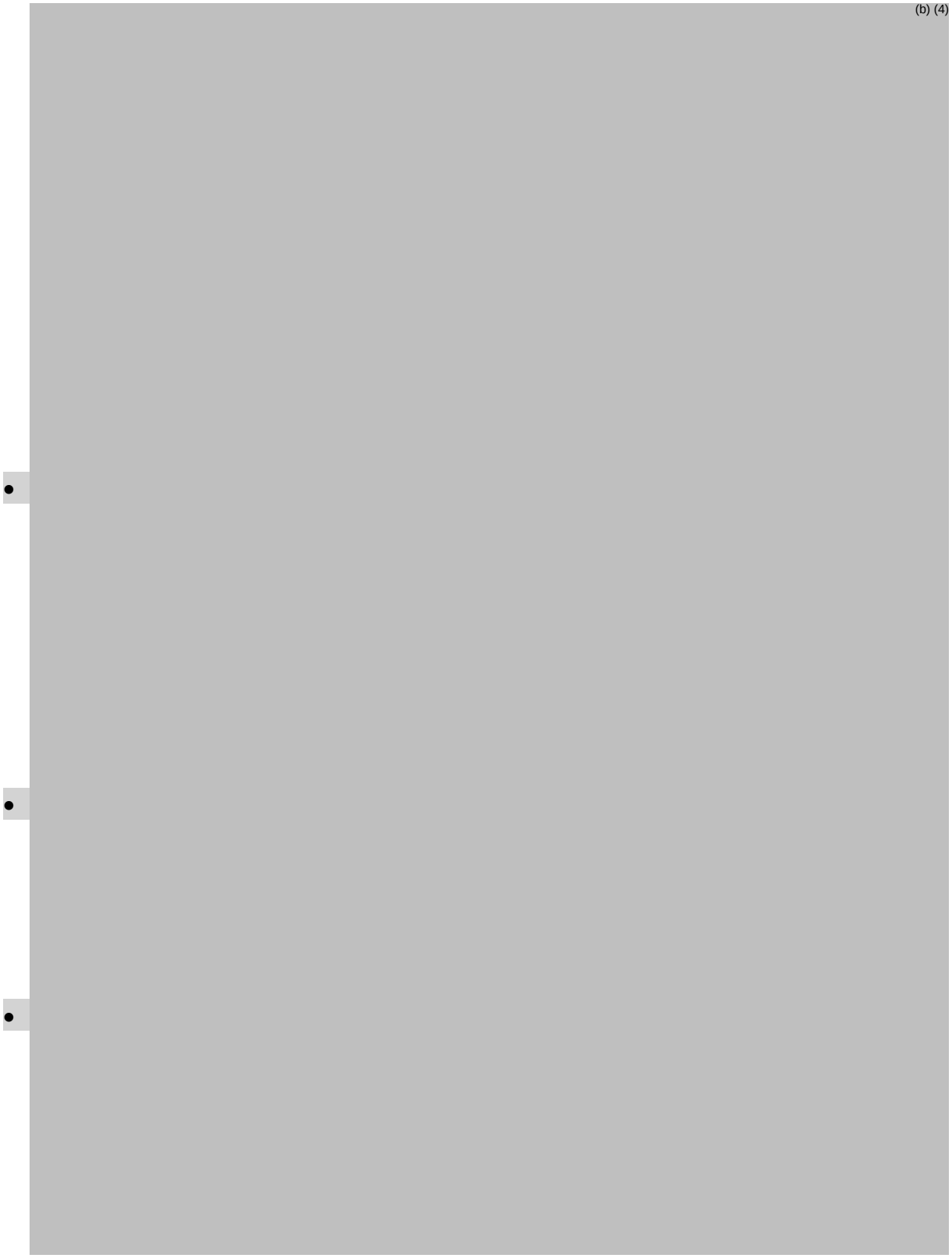


Table 103. Predicted inhibitory effects of belumosudil and M2 on the exposure of transporter substrates following twice daily dosing of 200-mg belumosudil for 14 days

Transporter Substrates	Belumosudil K_i value (μM)	Predicted C_{max} ratio	Predicted AUC ratio
Dabigatran (P-gp)	(b) (4)		
Pravastatin (OATP1B1)			
Sulfasalazine (BCRP)			
Metformin (MATE1/MATEs)			

Values are geometric means. Simulations were performed using the sim-Healthy Volunteer model (N=200).
*Reviewer's analysis.

Source: Tables 44 -51 in the PBPK report

2) Effects of belumosudil and M2 on CYP substrates

The PBPK analyses are adequate to predict the effect of belumosudil on CYP2C9, CYP3A and CYP2C8. but is inadequate to predict the effects of belumosudil on the repaglinide due to the uncertainty about the OATP1B1 Ki value.

- *Interaction with the CYP2C9 substrate warfarin*: Belumosudil was predicted to have little effects on CYP2C9 when the K_i values of belumosudil and M2 for CYP2C9 were reduced to 100-fold from the experimental K_i values.
- *Interaction with the CYP3A substrate midazolam*: Belumosudil is a time-dependent inhibitor of CYP3A. Its inactivation parameters k_{inact} and K_I cannot be verified by simulating belumosudil PK data from the single and multiple ascending dose studies in healthy subjects because belumosudil had a small $f_{m,CYP3A}$ and had a linear PK. However, because there are currently few examples that the extent of CYP3A interactions are underpredicted using experimentally generated k_{inact} and K_I values, the predicted effect is considered acceptable. The inhibitory effect of belumosudil on CYP3A was predicted to be weak at belumosudil exposure observed in patients.
- *Interaction with the CYP2C8 substrate repaglinide:* Repaglinide is a substrate of CYP2C8, CYP3A and OATP1B1, and belumosudil is an inhibitor of CYP2C8, CYP3A and OATP1B1 in vitro. The effect of belumosudil on repaglinide exposure is determined by the net effects of belumosudil on CYP2C8, CYP3A and OATP1B1. A preliminary analysis by the reviewer showed that, to reproduce the observed interactions of CYP2C8 reversible

inhibitors with CYP2C8 substrates (e.g. the predicted values are within the 0.80-1.25-fold of the clinical observations), the in vitro K_i values of CYP2C8 inhibitors need to be (b) (4)-fold. Taken together with the uncertainty about OATP1B1 Ki, the effects of belumosudil on repaglinide exposure cannot be confidently predicted. However, for CYP2C8 substrates that are not an OATP1B substrate, belumosudil was predicted to have minimal effects (Table 104).

Table 104. Predicted inhibitory effects of belumosudil and M2 on the exposure of CYP substrates following twice daily dosing of 200-mg belumosudil for 14 days

CYP Substrates	CYP K_i	OATP1B1/3 K_i	Applicant Predicted		
			AUC_{0-inf} Ratio	C_{max} Ratio	
S-warfarin 10 mg SD D9	Ki		1.00	1.00	
	Ki/100		1.23	1.02	*
Midazolam po 3 mg SD D9	TDI		1.47	1.26	
	TDI		1.55	1.28	*†
	TDI		2.20	1.55	*‡
Repaglinide 0.25 mg SD D9	(b) (4)				

Values are geometric means. Simulations were performed using the sim-Healthy Volunteer model (N=200). (b) (4) †Belumosudil was given 500 mg QD for 14 days. ‡Belumosudil was given 500 mg BID for 14 days. *Reviewer's analysis.

Source: Tables 40 -43 in the PBPK report

Additional comments:

- *The steady-state exposure of belumosudil is two-fold higher in the cGVHD patients compared to the healthy subjects following once daily dosing of 200-mg belumosudil with food. The mechanism for higher exposure in patients is unknown and cannot be explained simply by assuming potential increase in belumosudil absorption in patients. This may pose uncertainty about the predicted DDI effects.*
- *M2 is an inhibitor of multiple CYP enzymes and transporters (**Table 100**), yet its exposure in cGVHD patients is unclear due to limited data. In healthy subjects, at the exposure of belumosudil similar to that observed in cGVHD patients, the steady-state M2 exposure ranged from 11 to 19% of belumosudil exposure (**Table 101**). Based on the limited data,*

*M2 exposure in patients may be similar to or lower than that observed in healthy subjects (Response to Clin Pharm IR due on April 2, 2021). Considering M2 is less potent inhibitor and has lower exposure compared to the parent drug, the underpredicted exposure of M2 (**Table 101**) may have less effect on the overall predicted magnitude of interaction.*

- *To ensure sufficient exposures of parent drug for simulations of the effect of multiple doses of belumosudil on single dose PK of a CYP substrate, the steady-state exposure of belumosudil in cGVHD patients following once daily dosing of 200-mg belumosudil was simulated using 200-mg belumosudil twice daily dosing regimen in virtual healthy subjects (sim-healthy subject population) (Table 105).*

Table 105. Comparison of belumosudil steady-state exposure in healthy subjects with its exposure in patients following multiple doses of belumosudil with food

Population	Belumosudil Dosing regimen	$C_{max,ss}$ (ng/mL)	$AUC_{0\text{-}24h,\ ss}$ (ng*h/mL)	Sources
Patients with cGVHD	200 mg QD	2240	20000	popPK analysis
	200 mg BID	2740	39900	
Healthy subjects	200 mg QD	1570	11400	
	200 mg BID	1720	22800	
Healthy subjects	200 mg QD	2001	8033	*Simulated using the belumosudil PBPK model
	200 mg BID	2165	16371	
	500 mg QD	4713	21302	
	500 mg BID	5490	44849	

Median values were reported. * reviewer's analysis
Source: Table 3 in the popPK report

Conclusions

The PBPK analyses are adequate to evaluate the effects of CYP3A inhibitors and inducers on the PK of belumosudil and the effects of belumosudil on the substrates of CYP2C9 and CYP3A, and CYP2C8 substrates that are not substrates of OATP1B. The analyses were inadequate to evaluate effects of belumosudil on transporter substrates.

References

1. Mouly S, Lown KS, Kornhauser D, Joseph JL, Fiske WD, Benedek IH, and Watkins PB (2002) Hepatic but not intestinal CYP3A4 displays dose-dependent induction by efavirenz in humans. Clinical pharmacology and therapeutics 72:1-9.
2. (b) (4)
3.

(b) (4)

16.4.2 Pharmacometrics Review

A population pharmacokinetics (PPK) model was developed by the Applicant to characterize the PK of belumosudil in healthy subjects and Graft versus Host Disease (GVHD) patients. Intrinsic and extrinsic factors which influence the PK and PK variability of belumosudil were identified. The exposure-response (E-R) relationships for efficacy and safety were explored. In this review, FDA verified the Applicant's analyses, as well as conducted independent analyses to evaluate the Applicant's dose selection.

1. Population PK Analyses

Data from five Phase 1 studies (KD025-101, KD025-102, KD025-103, KD025-106, and KD025-107) including 174 healthy subjects and two Phase 2 studies (KD025-208 and KD025-213, conducted in cGVHD subjects) including 178 GVHD subjects were utilized for PPK model development. The demographic characteristics of subjects included in the final PPK model dataset are shown in **Table 106**.

Table 106. Summary of demographic characteristics for subjects included in the final PPK model dataset

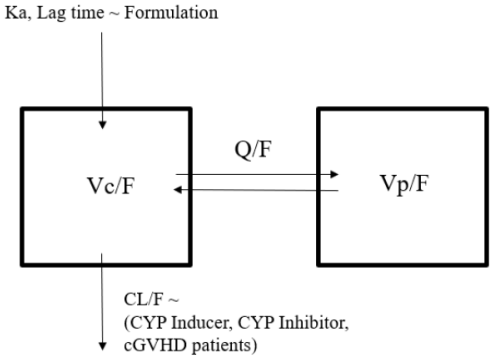
Characteristic	Statistic	KD025-101 (n=48)	KD025-102 (n=24)	KD025-103 (n=6)	KD025-106 (n=23)	KD025-107 (n=73)	KD025-208 (n=54)	KD025-213 (n=124)	All Subjects (n=352)
Age (years)	Mean (SD)	35.5 (8.89)	32.9 (9.54)	33.2 (9.33)	36.2 (11.5)	34.7 (11.4)	51.4 (13.8)	54.7 (13.3)	44.4 (15.3)
	Median (Min, Max)	35.5 (19.0, 55.0)	32.0 (20.0, 51.0)	34.0 (19.0, 46.0)	33.0 (20.0, 54.0)	31.0 (18.0, 55.0)	51.5 (20.0, 75.0)	55.5 (21.0, 77.0)	44.0 (18.0, 77.0)
Weight (kg)	Mean (SD)	83.3 (10.3)	75.6 (9.89)	75.4 (12.3)	81.2 (10.0)	84.6 (12.5)	83.0 (19.5)	79.7 (18.3)	81.5 (15.6)
	Median (Min, Max)	84.6 (59.8, 104)	75.9 (59.4, 99.8)	79.5 (58.2, 87.3)	83.6 (64.6, 97.4)	82.2 (57.1, 118)	80.7 (50.2, 143)	78.0 (38.6, 137)	80.7 (38.6, 143)
Sex: Male	N (%)	48 (100%)	20 (83.3%)	5 (83.3%)	23 (100%)	73 (100%)	34 (63.0%)	68 (54.8%)	271 (77.0%)
Sex: Female	N (%)	0 (0%)	4 (16.7%)	1 (16.7%)	0 (0%)	0 (0%)	20 (37.0%)	56 (45.2%)	81 (23.0%)
Race: White/Caucasian	N (%)	20 (41.7%)	10 (41.7%)	3 (50.0%)	20 (87.0%)	63 (86.3%)	47 (87.0%)	104 (83.9%)	267 (75.9%)
Race: Black/African-American	N (%)	26 (54.2%)	14 (58.3%)	3 (50.0%)	3 (13.0%)	5 (6.85%)	2 (3.70%)	7 (5.65%)	60 (17.0%)
Race: Asian	N (%)	1 (2.08%)	0 (0%)	0 (0%)	0 (0%)	3 (4.11%)	0 (0%)	3 (2.42%)	7 (1.99%)

Characteristic	Statistic	KD025-101 (n=48)	KD025-102 (n=24)	KD025-103 (n=6)	KD025-106 (n=23)	KD025-107 (n=73)	KD025-208 (n=54)	KD025-213 (n=124)	All Subjects (n=352)
Race: Native American	N (%)	1 (2.08%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (3.70%)	2 (1.61%)	5 (1.42%)
Race: Other	N (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (2.74%)	3 (5.56%)	0 (0%)	5 (1.42%)
Race: Unknown	N (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	8 (6.45%)	8 (2.27%)
Healthy	N (%)	48 (100%)	24 (100%)	6 (100%)	23 (100%)	73 (100%)	0 (0%)	0 (0%)	174 (49.4%)
cGVHD Patients	N (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	54 (100%)	124 (100%)	178 (50.6%)
Not Fasting	N (%)	0 (0%)	0 (0%)	0 (0%)	15 (65.2%)	73 (100%)	54 (100%)	124 (100%)	266 (75.6%)
Fasting	N (%)	48 (100%)	24 (100%)	6 (100%)	8 (34.8%)	0 (0%)	0 (0%)	0 (0%)	86 (24.4%)
Concomitant PPI	N (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	70 (95.9%)	36 (66.7%)	62 (50.0%)	168 (47.7%)
Concomitant 3A4 Inhibitor	N (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	35 (47.9%)	29 (53.7%)	73 (58.9%)	137 (38.9%)
Concomitant 3A4 Inducer	N (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	30 (41.1%)	1 (1.85%)	0 (0%)	31 (8.81%)

Source: Applicant's population PK/PD report Appendix Table 13

The final model structure is a 2-comparment model with first order absorption and a lag time, with a statistically significant effect of formulation on Ka and lag time (Figure 15). The parameter estimates of the final model are shown in **Table 107**.

Figure 15. **Belumosudil final PPK model structure**



CL/F- Clearance; KA- First order absorption rate constant; Q/F- Intercompartmental Clearance; Vc/F- Central volume of distribution; Vp/F-Peripheral volume of distribution

Source: Applicant's population PK/PD report

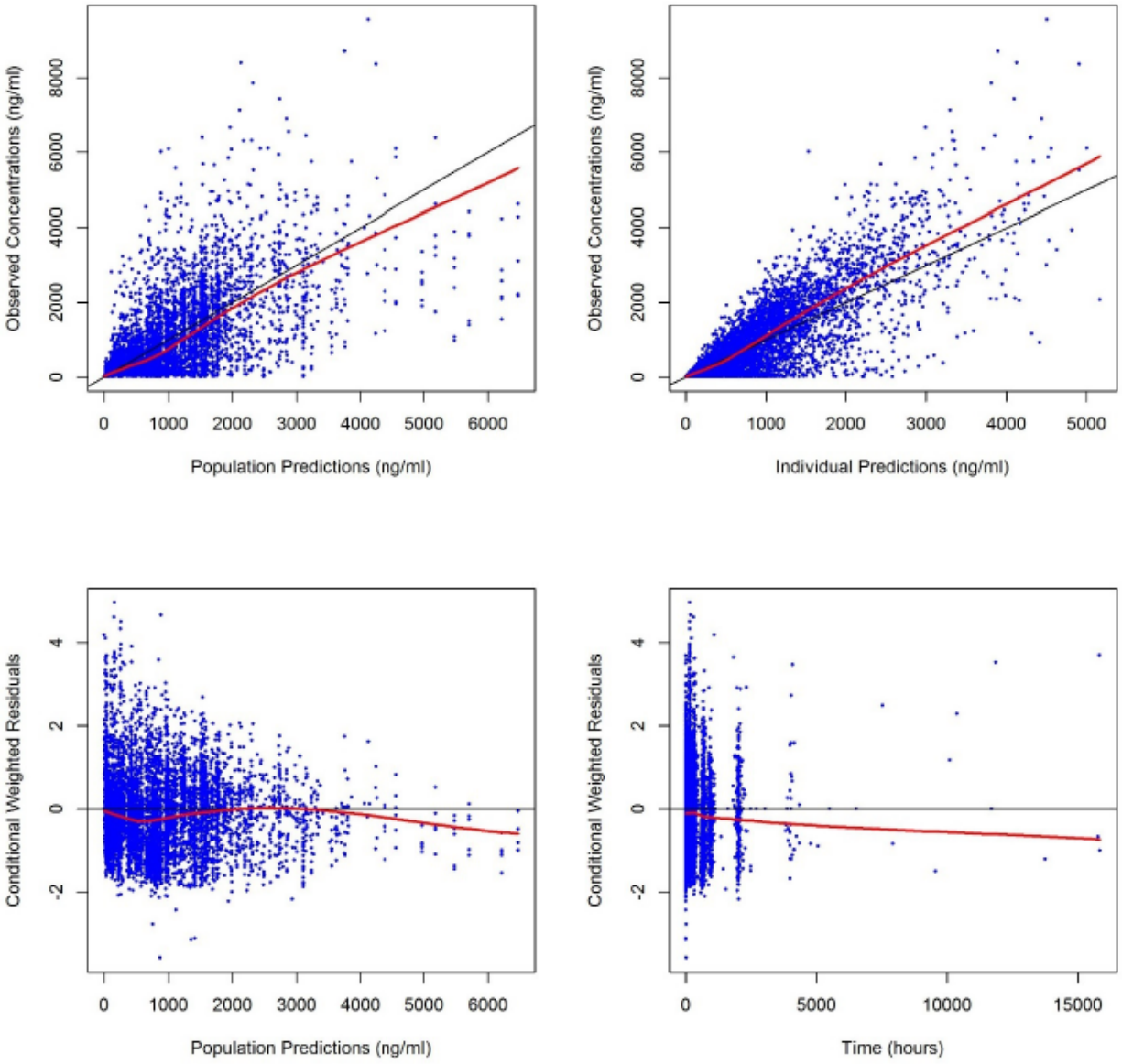
Table 107. Parameter estimates for the final PPK model of belumosudil

Parameter (units)	Estimate (RSE%)
CL/F (L/h)	21.1 (2.03)
CL/F in CYP3A4 Inhibition (L/h)	16.2 (2.94)
CYP3A4 induction effect on CL/F	2.88 (2.82)
GVHD effect on CL/F	0.466 (6.63)
V2/F (L)	29.7 (8.15)
V3/F (L)	78.8 (3.06)
Q/F (L/h)	5.13 (3.49)
Ka for capsule formulation (h^{-1})	0.291 (3.61)
Effect of tablet formulation Ka (h^{-1})	1.17 (3.71)
Lag time for capsule formulation (h)	0.609 (3.3)
Lag time for tablet formulation (h)	0.486 (0.121)
Bioavailability, Fasted (Phase 1 studies)	1 FIXED
Parameter (units)	**Estimate (RSE%)**
Relative Bioavailability, Fed (Phase 1 studies)	1.12 (1.91)
Relative Bioavailability, Fed (Phase 2 studies)	1.02 (4.55)
Relative Bioavailability, Concomitant PPIs	0.523 (0.859)
IIV on CL/F (%CV)	46.0 (2.99)
IIV on V2/F (%CV)	142.6 (2.99)
IIV on KA (%CV)	34.4 (1.08)
Additive error (SD, ng/mL)	3.46 (5.81)
Proportional Error (%CV)	63.4 (0.751)

%CV = percent coefficient of variation; IIV = inter-individual variability; PPI = proton pump inhibitor; RSE = relative standard error; SD = standard deviation
Source: Applicant's population PK/PD report

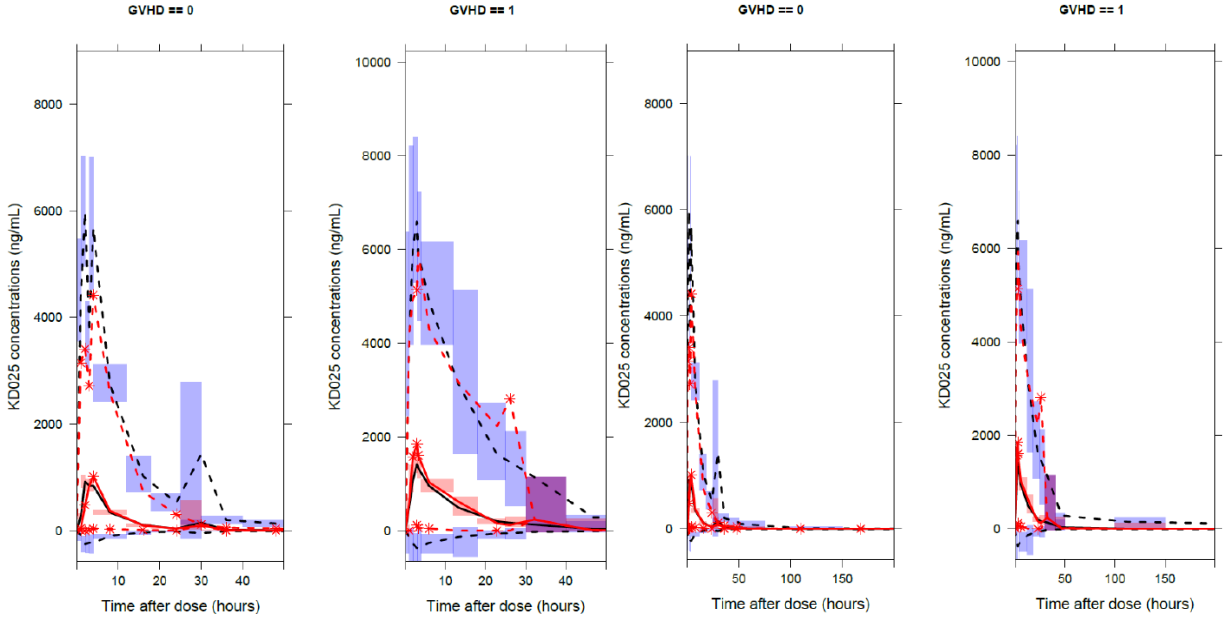
The goodness-of-fit (GOF) plots are shown in **Figure 16**. The time-after-dose Visual Predictive Check (VPC) plots stratified by disease status are shown in **Figure 17**.The time-after-dose VPC plots are also stratified by study shown in **Figure 18**. The time-after-first dose VPCs are shown in **Figure 19**.

Figure 16. Goodness of fit plots for the final PPK model for belumosudil



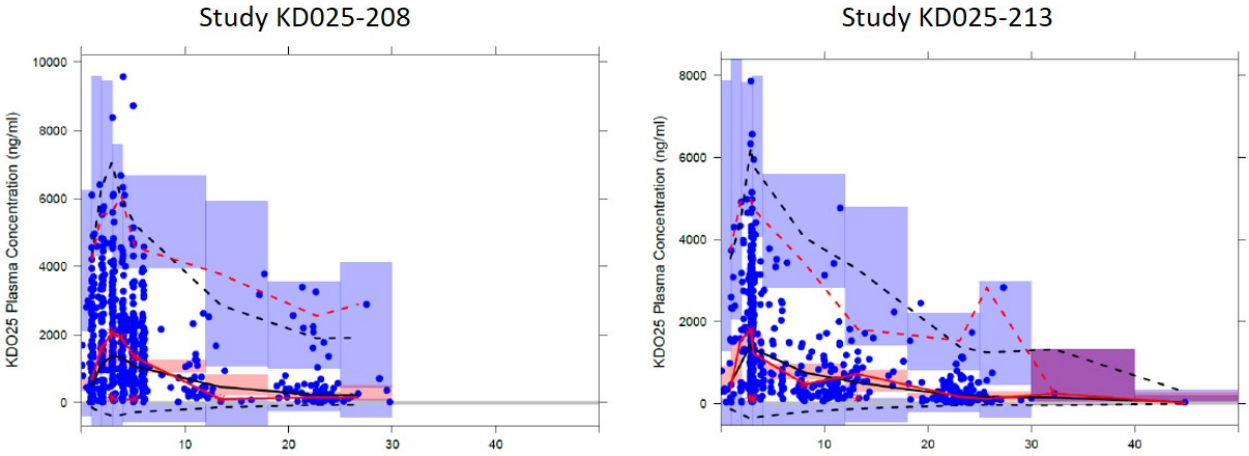
Source: Applicant's population PK/PD report

Figure 17. VPCs by time after dose and GVHD status for the final PPK model for belumosudil



0=Healthy-subjects; 1=cGVHD subjects
The red and black solid lines represent the median (50th percentile) of the observed data and model simulations, respectively. The lower red and black dashed lines represent the 2.5th percentile of the observed and model simulations, respectively. The upper red and black dashed lines represent the 97.5th percentile of the observed and model simulations, respectively. The red shaded area represents the 95% CI of the median of the model simulated data. The lower and upper blue areas represent the 95% CI of the 2.5th percentile and 97.5th percentile of the model simulated data, respectively.
Source: Applicant's population PK/PD report

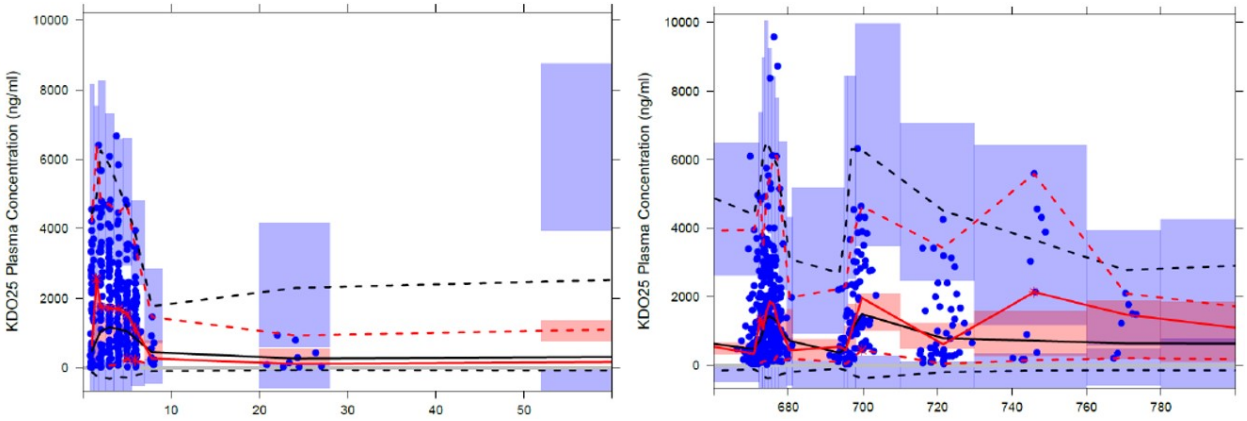
Figure 18. VPC by time after dose (hours) for Studies KD025-208 and KD025-213 for the final PPK model for belumosudil



The red and black solid lines represent the median (50th percentile) of the observed data and model simulations, respectively. The lower red and black dashed lines represent the 2.5th percentile of the observed and model simulations, respectively. The upper red and black dashed lines represent the 97.5th percentile of the observed and model simulations, respectively. The red shaded area represents the 95% CI of the median of the model

simulated data. The lower and upper blue areas represent the 95% CI of the 2.5th percentile and 97.5th percentile of the model simulated data, respectively.
Source: Adapted from the Applicant's population PK/PD report

Figure 19. VPC by time since first dose for combined Studies KD025-208 and KD025-213 for the final PPK model for belumosudil



The red and black solid lines represent the median (50th percentile) of the observed data and model simulations, respectively. The lower red and black dashed lines represent the 2.5th percentile of the observed and model simulations, respectively. The upper red and black dashed lines represent the 97.5th percentile of the observed and model simulations, respectively. The red shaded area represents the 95% CI of the median of the model simulated data. The lower and upper blue areas represent the 95% CI of the 2.5th percentile and 97.5th percentile of the model simulated data, respectively.
Source: Adapted from the Applicant's population PK/PD report

The PPK model estimated that the relative bioavailability was approximately 48% lower in concomitant PPI administration compared to no PPI administration. Concomitant administration of CYP3A4 inhibitors reduced belumosudil CL/F by approximately 23% in healthy subjects. The belumosudil CL/F with concomitant CYP3A4 inducers was 2.88 times of that without concomitant CYP3A4 inducers. In addition, an approximately 52% lower CL/F was estimated in cGVHD subjects compared to healthy subjects. No significant effects of hepatic and renal function were observed on the CL/F of belumosudil. The Applicant also predicted the exposure under 200 mg QD and 200 mg BID dosing regimens administered in healthy subjects and cGVHD patients as shown in **Table 108**.

Table 108. Predicted belumosudil pharmacokinetic parameters for 200 mg QD and BID dose regimens administered in healthy subjects and cGVHD patients in a fed state

Parameter (Units)	200 mg QD		200 mg BID	
	Median	Mean (SD)	Median	Mean (SD)
cGVHD Patients				
Single Dose AUC0-24 (ng*hr/mL)	16000	16700 (5720)	28800	29700 (10000)
Steady State AUC0-24 (ng*hr/mL)	20000	22700 (10900)	39900	45400 (21800)
Single Dose Cmax (ng/mL)	1900	2060 (986)	2250	2420 (1010)
Steady State Cmax (ng/mL)	2240	2390 (1040)	2740	2970 (1230)
Elimination t½ (h)	17.2	19.0 (7.48)	17.2	19.0 (7.48)
Distribution t½ (h)	1.28	1.85 (1.71)	1.28	1.85 (1.71)
Accumulation Ratio (AUC0-24)	1.23	1.35 (0.479)	1.54	1.84 (1.18)
Healthy Subjects				
Single Dose AUC0-24 (ng*hr/mL)	9250	10000 (3940)	17300	18600 (7140)
Steady State AUC0-24 (ng*hr/mL)	10100	11400 (5270)	20200	22800 (10500)
Single Dose Cmax (ng/mL)	1520	1650 (817)	1620	1800 (832)
Steady State Cmax (ng/mL)	1570	1740 (837)	1720	1940 (885)
Elimination t½ (h)	13.4	14.2 (5.44)	13.4	14.2 (5.44)
Distribution t½ (h)	0.748	1.13 (1.3)	0.748	1.13 (1.3)
Accumulation Ratio (AUC0-24)	1.09	1.14 (0.379)	1.24	1.37 (0.961)

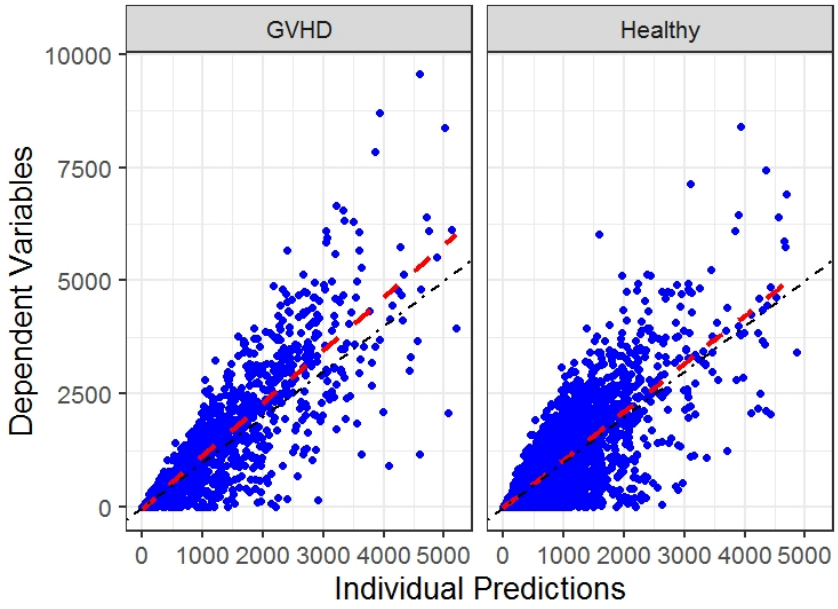
SD = standard deviation
Source: Applicant's population PK/PD report

Reviewer's comment:
*The Applicant's final PPK model is generally acceptable for describing the PK of belumosudil in the healthy subjects and GVHD subjects. Based on the VPCs stratified by healthy or GVHD subjects (*Figure 17*), there was a slight underprediction around the Cmax in GVHD subjects. Based on the Reviewer's GOF plots stratified by disease status, this underprediction is slightly more obvious in GVHD patients compared to healthy subjects (**Figure 20**). This underprediction of Cmax appears to be more evident for study KD025-208 (*Figure 18*) and a few hours after the first dose (*Figure 19*) in the GVHD patients. The Applicant stated that the lack of availability of accurate dosing information on non-clinic visit days for Study KD025-208 could have contributed*

to the more pronounced bias evident compared to the Study KD025-213 where accurate dosing history was present even on non-clinic visit days.

As the Applicant stated in the Summary of Clinical Pharmacology, the exposure of belumosudil appears to be slightly greater than dose-proportional over the 20 to 500 mg QD dose range in healthy subjects. This may potentially explain the underprediction around the Cmax. The model predicted Cmax,ss was then used in the exposure-response (E-R) analysis discussed in the following sections.

Figure 20. IPRED vs. DV plots stratified by disease status



Source: Reviewer's analysis

Out of the 352 subjects included in the PPK analysis, there were 138 subjects with mild renal impairment (RI), 33 subjects with moderate RI and 181 subjects with normal renal function. No severe RI subjects were included. The data from subjects in mild/moderate RI categories are considered adequate to estimate the effect on PK. In addition, the excretion route of belumosudil through renal is minimal. Thus, FDA agrees with the Applicant that no dose adjustment is necessary for patients with mild/moderate RI. The effect of severe RI is unknown. No significant effect of liver enzymes (AST, ALT and bilirubin) on PK of belumosudil was identified. The Applicant re-evaluated the effect of hepatic impairment (HI) using classification of hepatic function (normal, mild, moderate, or severe) as a categorical variable defined based on NIC organ dysfunction working group (NCI-ODWG) criteria upon FDA's request. Based on the updated analysis, out of 352 subjects in the PPK dataset, 303 had normal hepatic function and 49 had mild HI. None of the subjects had moderate or severe HI. The result shows that mild HI has no statistically significant effect. Thus, we agree with the Applicant that no dose adjustment is needed for GVHD subjects with mild HI. The effect of moderate/severe HI is unknown.

Based on PPK model predicted exposures following dosing regimens of 200 mg QD and 200 mg BID, no significant accumulation is expected for 200 mg BID dosing at steady-state compared to 200 mg QD dosing.

Based on a dedicated drug-drug interaction (DDI) study, belumosudil Cmax and AUC decreased approximately 87% and 80%, respectively with the concomitant administration of strong proton pump inhibitors (PPIs), including rabeprazole and esmoprazole (See details in section 6.3.2). However, it was unclear that in the popPK or E-R analysis, how many subjects were in the 200 mg QD belumosudil arm with the concomitant administration of the strong PPIs, and whether the efficacy was compromised in this subpopulation. Thus, the FDA Reviewer sent an information request (IR) to the Applicant. Based on the Applicant submitted data (ncaparm.xpt) in the response to the IR, there were only 5 subjects with concomitant use of strong PPIs following the proposed 200 mg QD belumosudil. The belumosudil exposures following different belumosudil regimens without or with mild/moderate/strong PPIs are shown in Table 109. *Within the same belumosudil dosing regimen, the exposure in subjects who were on concomitant PPIs usage was overall lower than that in subjects without PPIs. To further evaluate the appropriateness of 200 mg QD in subjects with concomitant use of PPIs, the Reviewer performed independent analyses, refer to section 3. The dose adjustment for concomitant use of PPI will be discussed in section 3.*

Table 109. Summary of exposure estimates stratified by PPI strength in different doses

Dose	PPI strength	Statistic	Cmax (ng/mL)[a]	Cmax,ss (ng/mL)	AUC24,ss (ng*h/mL)
200 mg QD	No PPI (N=36)	Mean (SD) GM (GMSD) Median [Min, Max]	2180 (671) 2070 (1.40) 2100 [794, 3720]	2390 (739) 2280 (1.38) 2320 [941, 4300]	18100 (6510) 17000 (1.46) 17300 [6560, 34800]
	Weak (N=18)	Mean (SD) GM (GMSD) Median [Min, Max]	1240 (700) 941 (2.73) 1100 [31.0, 2590]	1660 (926) 1330 (2.20) 1690 [146, 3450]	16200 (10700) 13000 (2.07) 13900 [2730, 42200]
	Moderate (N=17)	Mean (SD) GM (GMSD) Median [Min, Max]	1210 (513) 1100 (1.58) 1080 [510, 2100]	1390 (630) 1270 (1.56) 1260 [556, 3050]	11700 (7070) 10300 (1.63) 9700 [4780, 34600]
	Strong (N=5)	Mean (SD) GM (GMSD) Median [Min, Max]	1520 (639) 1410(1.51) 1290 [910, 2740]	1700 (844) 1570 (1.21) 1390 [1060, 3160]	13600 (9990) 11500 (1.38) 9380 [7690, 31200]
200 mg BID	No PPI (N=39)	Mean (SD) GM (GMSD) Median [Min, Max]	2200 (568) 2120 (1.34) 2170 [659, 3870]	2870 (806) 2760 (1.34) 2810 [1110, 5560]	36400 (8120) 33200 (1.53) 33600 [13140, 85000]
	Weak (N=18)	Mean (SD) GM (GMSD) Median [Min, Max]	991 (613) 834 (1.90) 836 [138, 2510]	1470 (844) 1280 (1.74) 1260 [354, 3590]	20400 (5450) 17780 (1.71) 16480 [6260, 43200]
	Moderate (N=24)	Mean (SD) GM (GMSD) Median [Min, Max]	1090 (516) 989 (1.60) 924 [257, 2410]	1480 (805) 1310 (1.65) 1270 [355, 3890]	19720 (5240) 17440 (1.65) 17860 [5620, 45800]

Dose	PPI strength	Statistic	Cmax (ng/mL)[a]	Cmax,ss (ng/mL)	AUC24,ss (ng*h/mL)
400 mg QD	No PPI (N=4)	Mean (SD) GM (GMSD) Median [Min, Max]	3740 (1010) 3620 (1.36) 3970 [2320, 4680]	4420 (1460) 4200 (1.48) 4870 [2380, 5580]	42100 (23000) 36700 (1.91) 41100 [15000, 71200]
	Weak (N=6)	Mean (SD) GM (GMSD) Median [Min, Max]	2700 (935) 2520 (1.55) 2910 [1110, 3780]	3070 (802) 2990 (1.28) 3050 [2210, 4480]	22900 (10000) 21200 (1.52) 19500 [13500, 38700]
	Moderate (N=7)	Mean (SD) GM (GMSD) Median [Min, Max]	2290 (1460) 1770 (2.39) 2470 [438, 4730]	3240 (1220) 3050 (1.48) 3160 [1660, 5400]	37000 (9450) 36000 (1.30) 39200 [23200, 52800]
	Strong (N=4)	Mean (SD) GM (GMSD) Median [Min, Max]	1900 (887) 1750 (1.62) 1800 [958, 3070]	2620 (1120) 2430 (1.60) 2630 [1330, 3880]	29900 (16600) 26200 (1.82) 28300 [14800, 48100]

[a] Single dose
Source: adapted from the Applicant's response to a clinical pharmacology IR

2. Exposure-Response of Belumosudil

Using the final PPK model, the Applicant conducted exposure-response (E-R) analyses for efficacy and safety based on the steady-state post hoc Cmax and AUC0-24 for subjects in Studies KD025-208 and KD025-213.

2.1 E-R Analyses for Efficacy

For E-R analyses for efficacy, the endpoints evaluated are duration of response, partial or complete response, Lee symptom scale score reduction and global severity rating decrease. The exposure metrics used in the analyses are total daily dose, AUC and Cmax. The Applicant's analyses showed that all the E-R relationships explored between the belumosudil exposure and the efficacy endpoint were flat over the range of exposures observed in Studies KD025-208 and KD025-213.

Reviewer's comment:

The Applicant explored the E-R relationships for efficacy and identified that the total daily dose and exposure between the binary efficacy endpoints were comparable, indicating the flat E-R relationships for these efficacy endpoints. The E-R finding is consistent with the observed dose-response relationships in Studies KD025-208 and KD025-213. To further confirm this, FDA conducted independent analyses to evaluate whether there was any imbalance in baseline demographic and disease characteristics across belumosudil exposure quartiles. Overall, there appears to be no imbalance of baseline patient characteristics across the AUC quartiles in cGVHD patients from the two studies (KD025-208 and KD025-213) except the GvHD organ involvement. Slightly higher proportions of patients with no involvement of liver, lower GI or upper GI were in the higher exposure quartiles compared to those in lower exposure quartiles, indicating that more severe patients were in the lower exposure quartiles without loss of efficacy. This further suggests that a change in belumosudil exposure is unlikely to be relevant to efficacy within the observed exposure range at the studied dose levels.

Table 110. Demographic characteristics and disease status across belumosudil AUC0-24 quartiles in patients with cGVHD from Studies KD025-208 and KD025-213

		AUCQ1	AUCQ2	AUCQ3	AUCQ4
AGE (yrs)	Mean (SD) Median; Min-Max	55.7 (13.0) 57; 21-74	52.8 (13.0) 53; 20-77	53.2 (14.1) 53; 21-77	53.1 (14.2) 52; 26-75
Gender	Female, n (%) Male, n (%)	18/44 (40.9%) 26/44 (59.1%)	15/44 (34.1%) 29/44 (65.9%)	19/45 (42.2%) 26/45 (57.8%)	24/45 (53.3%) 21/45 (46.7%)
Race	White, n/N (%) Black, n/N (%) Asian, n/N (%) Others, n/N (%)	40/44 (90.9%) 2/44 (4.5%) 0/44 (0%) 2/44 (4.5%)	36/44 (81.8%) 4/44 (9.1%) 1/44 (2.3%) 3/44 (6.8%)	37/ 45 (82.2%) 2/45 (4.4%) 1/45 (2.2%) 5/45 (11.1%)	38/45 (84.4%) 1/45 (2.2%) 1/45 (2.2%) 5/45 (11.1%)
Weight	Mean (SD) Median; Min-Max	81.2 (22.2) 80.6; 50.2-143	80.1 (17.3) 77.2; 48.4-128	80.2 (19.0) 78.7; 38.6-127	80.8 (16.9) 77.6; 51.3-115
BMI	Mean (SD) Median; Min-Max	27.7 (5.8) 26.8; 19.5-47.9	27.0 (5.7) 26.3; 18.9, 42.7	26.7 (4.8) 26.2; 14.5-35.5	29.0 (6.8) 27.4; 18.2-47.4
BSA	Mean (SD) Median; Min-Max	1.95 (0.28) 1.92; 1.50-2.56	1.92 (0.23) 1.99; 1.50-2.56	1.92 (0.25) 1.90; 1.48-2.47	1.90 (0.22) 1.89; 1.57-2.23
EGFR	Mean (SD) Median; Min-Max	84.4 (29.9) 76.4; 43.2-192	91.1 (30.6) 82.55; 51.0-180	89.5 (53.6) 78.2; 36.2-368	81.2 (33.3) 73.3; 33.9-190
ALB	Mean (SD) Median; Min-Max	4.0 (0.4) 4.0; 3.3-4.8	4.0 (0.3) 4.0; 3.3-4.6	3.9 (0.4) 4.0; 3.1-4.8	4.0 (0.4) 3.9; 2.5-4.7
BILI	Mean (SD) Median; Min-Max	0.43 (0.19) 0.37; 0.20-0.85	0.41 (0.19) 0.35; 0.20-1.05	0.45 (0.17) 0.40; 0.20-0.87	0.43 (0.22) 0.37; 0.13-1.30
ALT	Mean (SD) Median; Min-Max	36.1 (22.9) 30.0; 12.0-113	31.6 (17.9) 26.5; 12.0-95.0	34.4 (20.7) 27.0; 13.0-114	30.1 (17.1) 26.0; 5.0-83.0
AST	Mean (SD) Median; Min-Max	29.0 (14.6) 25; 9-73	26.4 (11.5) 23; 13-76	27.0 (10.0) 25; 14-51	24.7 (8.9) 22; 11-48

		AUCQ1	AUCQ2	AUCQ3	AUCQ4
Organ Involvement[a]	0, n/N (%) 1, n/N (%) 2, n/N (%) 3, n/N (%) 4, n/N (%) 5, n/N (%) 6, n/N (%) 7, n/N (%)	29/44 (65.9%) 6/44 (13.6%) 1/44 (2.3%) 5/44 (11.4%) 0/44 (0%) 0/44 (0%) 3/44 (6.8%) 0/44 (0%)	34/44 (77.3%) 1/44 (2.3%) 3/44 (6.8%) 4/44 (9.1%) 1/44 (2.3%) 0/44 (0%) 0/44 (0%) 0/44 (0%)	32/45 (71.1%) 2/45 (4.4%) 2/45 (4.4%) 7/45 (15.6%) 0/45 (0%) 0/45 (0%) 2/45 (4.4%) 0/45 (0%)	38/45 (84.4%) 1/45 (2.2%) 1/45 (2.2%) 3/45 (6.7%) 0/45 (0%) 0/45 (0%) 2/45 (4.4%) 0/45 (0%)
No. of Prior Lines of Therapy	Mean (SD) Median; Min-Max	3.3 (1.3) 3; 1-6	2.9 (1.1) 3; 1-6	2.9 (1.2) 3; 1-5	3.3 (1.4) 3; 1-6

[a]GVHD Organ Involvement; 0 = No involvement of liver, lower GI, or upper GI; 1 = Only liver involvement; 2 = Only lower GI involvement; 3 = Only upper GI involvement; 4 = Liver and lower GI involvement; 5 = Liver and upper GI involvement; 6 = Upper GI and lower GI involvement; 7 = Liver, lower GI, and upper GI involvement
Source: Reviewer's independent analysis

2.2 E-R Analyses for Safety

The Applicant explored E-R relationships for the following safety endpoints: the responses of eye, skin, mouth, esophagus, upper GI, lower GI, lung, joint and fascia, liver; headache, fatigue, abnormal liver function, nausea, and diarrhea. No relationships between belumosudil exposure and adverse events were observed with the dose levels of 200 mg QD, 200 mg BID and 400 mg QD. However, a significant increase of proportion of subjects with serious TEAE, Grade 4 and above TEAEs by maximum severity in the arm who received 400 mg QD (n=21) compared to the arms who received 200 mg QD or BID from patients with cGVHD (**Table 111**).

Table 111. Summary of TEAE profiles by Dose in patients with cGVHD

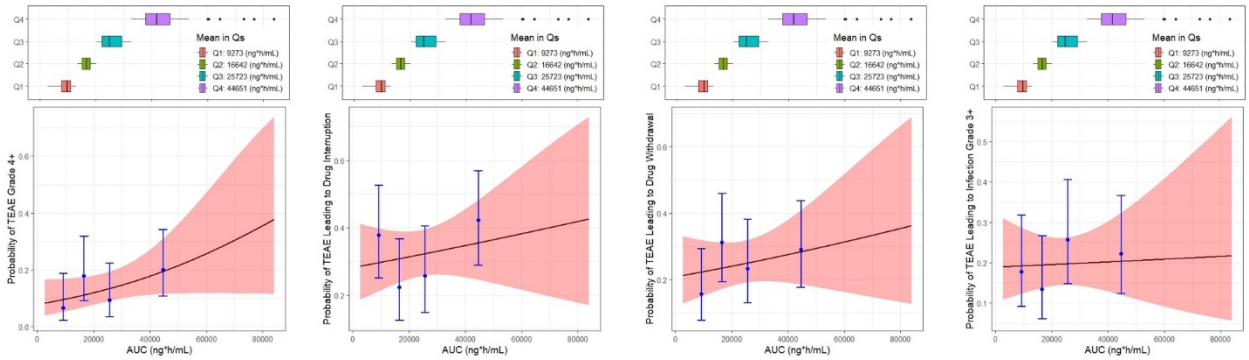
	200 mg QD (N=83)	200 mg BID (N=82)	400 mg QD (N=21)	All KD025 (N=186)
Subjects with TEAE	82 (98.8%)	81 (98.8%)	20 (95.2%)	183 (98.4%)
Subjects with Serious TEAE	**32 (38.6%)**	**24 (29.3%)**	**12 (57.1%)**	68 (36.6%)
Subjects with Grade >=3 TEAE	44 (53.0%)	40 (48.8%)	14 (66.7%)	98 (52.7%)
Subjects with TEAE Leading to Dose Reduction	2 (2.4%)	4 (4.9%)	2 (9.5%)	8 (4.3%)
Subjects with TEAE Leading to Dose Interruption	24 (28.9%)	24 (29.3%)	8 (38.1%)	56 (30.1%)
Subjects with TEAE Leading to Drug Withdrawl	21 (25.3%)	15 (18.3%)	8 (38.1%)	44 (23.7%)
Subjects with TEAEs by Maximum Severity				
Grade 1: Mild	6 (7.2%)	5 (6.1%)	0	11 (5.9%)
Grade 2: Moderate	32 (38.6%)	36 (43.9%)	6 (28.6%)	74 (39.8%)

	200 mg QD (N=83)	200 mg BID (N=82)	400 mg QD (N=21)	All KD025 (N=186)
Grade 3: Severe	37 (44.6%)	34 (41.5%)	6 (28.6%)	77 (41.4%)
Grade 4: Life Threatening	**3 (3.6%)**	**5 (6.1%)**	**4 (19.0%)**	12 (6.5%)
Grade 5: Fatal	4 (4.8%)	1 (1.2%)	4 (19.0%)	9 (4.8%)

Source: adapted from appendix 2 in Summary of Safety 1.

Reviewer's comment:
Given the significant increase of grade 4 and above TEAE observed in 400 mg QD group compared to 200 mg QD or BID group, FDA conducted independent E-R analyses for additional safety endpoints using logistic regression. As shown in Figure 21, there are positive trends in probability of TEAE Grade 4+ versus AUC , and probability of TEAE leading to drug withdrawal versus AUC. As discussed before, no major imbalance was identified across the exposure quartiles. Thus, the proposed dosing regimen of 200 mg QD for general population is acceptable from safety consideration.

Figure 21. **Exposure-response for safety endpoints based on AUC (top) and Cmax (bottom)**



Source: Reviewer's independent analysis

3. Reviewer's Analyses on PPI Effect

Based on the dedicated drug-drug interaction study and population PK analysis, the concomitant use of PPIs substantially decreased belumosudil exposure (Table 109, detail refers to section 6.3.2). To understand the clinical significance of this effect in GVHD patients, FDA conducted independent analyses to compare the efficacy endpoints across the subgroups stratified by PPI strength based on the data from Studies KD025-208 and KD025-213. As shown in **Figure 22**, overall the duration of response was comparable across all the belumosudil dosing regimens with or without PPIs. Within the same belumosudil dosing regimen, no clinical meaningful difference of dose duration across the groups of subjects who did not take or took mild/moderate/strong PPIs was observed. **Table 112** summarizes the rates of complete or partial response (ORR), Lee symptom score reduction (defined as 7-point reduction in Lee symptom scale score on two consecutive assessments at any point in the trial) and global severity rating decrease (defined as at least a 2-point reduction in global severity rating at any

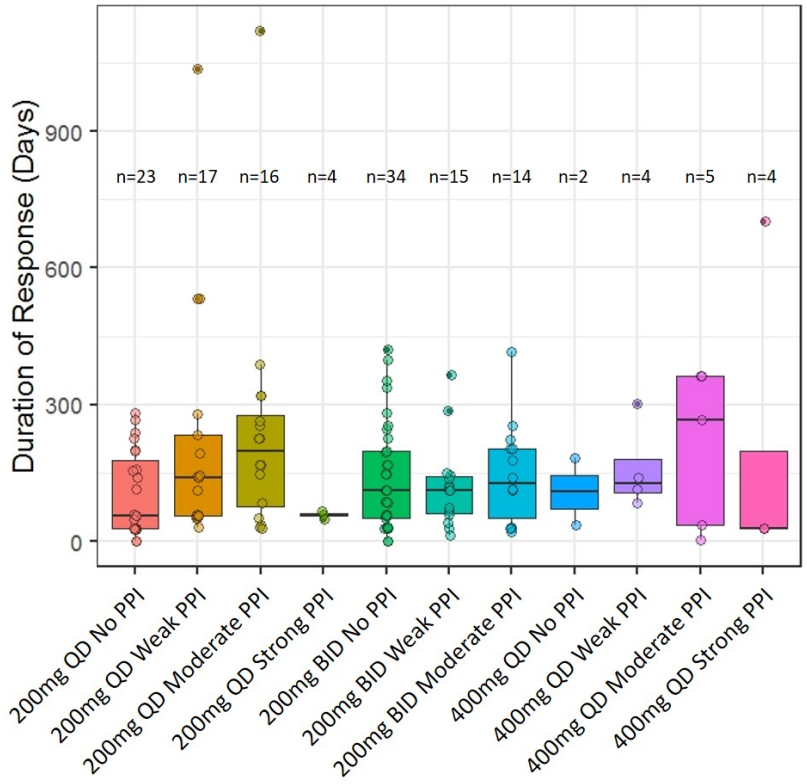
point in the trial). Overall, the result did not show a significant decrease of the efficacy with the concomitant use of weak/moderate/strong PPIs compared to that without concomitant administration of PPIs within the same belumosudil regimen. However, the number of subjects in the 200 mg QD belumosudil arm with the concomitant use of strong PPI was very limited (n=5). Given that 200 mg QD is the lowest dose studied and the significant reduction of belumosudil exposure expected with co-administration of strong PPI, there is a potential for compromised efficacy following the 200 mg QD belumosudil and co-administration of strong PPI.

To reduce the risk of lower efficacy in patients with the extremely low exposures with coadministration of strong PPIs, higher dosing regimen was considered. Due to lack of definition of weak/moderate/strong PPIs in the clinical practice, dose adjustment only for strong PPIs concomitant use is not practical. The dose adjustment was determined based on the pooled exposure from the mixed weak/moderate/strong PPIs usage. With the concomitant use of PPIs, the dosing regimen of 200 mg BID is expected to provide closer AUC24,ss compared to that following 200 mg QD without concomitant PPIs use, while the AUC24,ss following 400 mg QD with concomitant use of PPIs would be much higher than that following 200 mg QD without concomitant PPIs use (Table 109**Figure 23**). Considering the positive E-R for safety and significant increase of Grade 4 and above TEAEs in 400 mg QD arm compared to 200 mg QD and BID arms, the higher AUC24,ss following 400 mg QD arm with concomitant use of PPI is less optimal from safety perspective.

Due to potential confounding effect of different formulation used in studies KD025-208 and KD025-213, the comparison of AUC24,ss was also plotted using data from Study KD025-208 only (
Figure 24). Similar result was observed. The baseline demographic and disease characteristics were further evaluated to check potential imbalance between the subjects with and without PPI concomitant groups. As shown in

Table 113, no major imbalance appears between the groups with or without PPIs in each belumosudil dosing regimen.

Figure 22. Duration of response for all dosing regimens of belumosudil stratified by PPI strength in patients with cGVHD from Studies KD025-208 and KD025-213



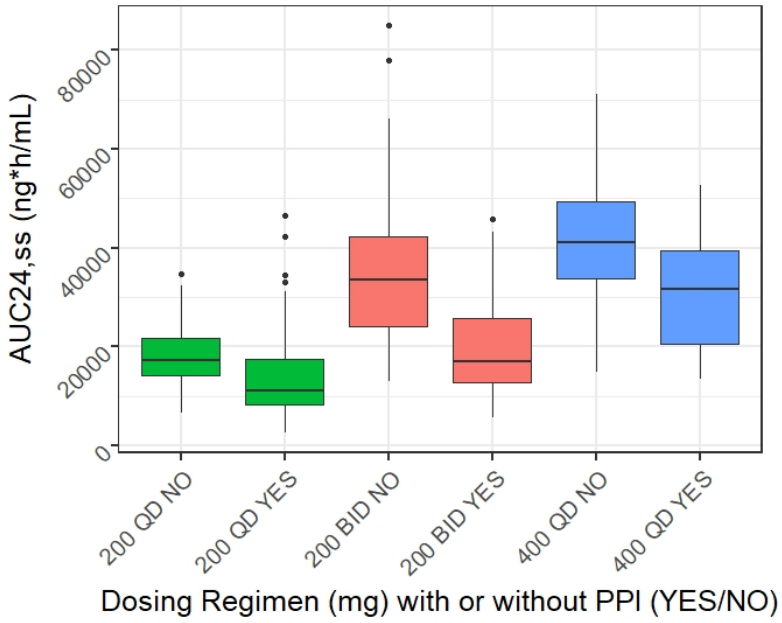
Source: Reviewer's independent analysis

Table 112. Partial or complete response, Lee symptom score reduction and global severity rating decrease for all dosing regimens of belumosudil stratified by PPI strength

Belumosudil regimen with or without PPI	Partial or Complete Response, n/N (%)	Lee Symptom Score Reduction, n/N (%)	Global Severity Rating Decrease, n/N (%)
200 mg QD NO PPI	23/36 (63.9%)	12/36 (33.3%)	12/36 (33.3%)
200 mg QD WEAK	15/18 (83.3%)	8/18 (44.4%)	9/18 (50.0%)
200 mg QD MODERATE	15/17 (88.2%)	10/17 (58.8%)	10/17 (58.8%)
200 mg QD STRONG	3/5 (60.0%)	0/5 (0%)	3/5 (60.0%)
200 mg BID NO PPI	34/39 (87.2%)	11/39 (28.2%)	22/39 (56.4%)
200 mg BID WEAK	15/18 (83.3%)	7/18 (38.9%)	12/18 (66.7%)
200 mg BID MODERATE	12/24 (50.0%)	8/24 (33.3%)	9/24 (37.5%)
400 mg QD NO PPI	2/4 (50.0%)	2/4 (50.0%)	1/4 (25.0%)
400 mg QD WEAK	4/6 (66.7%)	3/6 (50.0%)	4/6 (66.7%)
400 mg QD MODERATE	4/7 (57.1%)	2/7 (28.6%)	3/7 (42.8%)
400 mg QD STRONG	3/4 (75.0%)	2/4 (50.0%)	2/4 (50.0%)

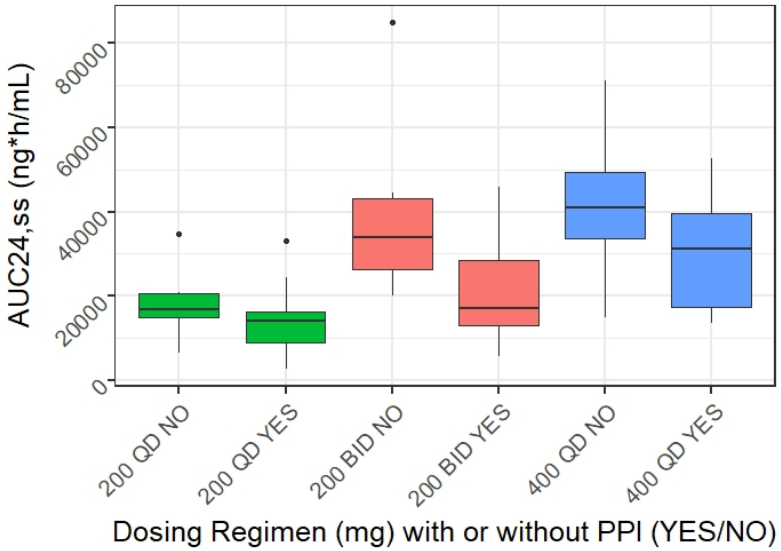
Source: Reviewer's independent analysis

Figure 23. Comparison of AUC24 at steady-state in each belumosudil dosing regimen with or without concomitant use of PPIs



Source: Reviewer's analysis based on ncaparam.xpt

Figure 24. Comparison of AUC24 at steady-state in each belumosudil dosing regimen with or without concomitant use of PPIs for Study KD025-208



Source: Reviewer's analysis based on ncaparam.xpt

Table 113. Baseline characteristics and disease status comparison across different belumosudil dosing regimens with or without PPIs

Belumosudil regimen with or without PPI	Age (years) Mean (SD)	Body weight (kg) Mean (SD)	Hepatic Impairment n/N (%)	GvHD Organ Involvement n/N (%)
200 mg QD No	52.44 (14.51)	78.57 (18.90)	Normal: 29/36 (80.6%) Mild: 7/36 (19.4%)	0: 28/36 (77.8%) 1: 8/36 (22.2%) 2: 0/36 (0%) 3: 0/36 (0%)
200 mg QD Yes	52.05 (12.95)	80.81 (17.95)	Normal: 32/40 (80%) Mild: 8/40 (20%)	0: 29/40 (72.5%) 1: 8/40 (20%) 2: 3/40 (7.5%) 3: 0/40 (0%)
200 mg BID No	54.46 (12.88)	81.68 (19.61)	Normal: 29/39 (74.4%) Mild: 10/39 (25.6%)	0: 31/39 (79.5%) 1: 6/39 (15.4%) 2: 2/39 (5.1%) 3: 0/39 (0%)
200 mg BID Yes	57.40 (12.56)	79.72 (19.23)	Normal: 33/42 (78.6%) Mild: 9/42 (21.4%)	0: 27/42 (64.3%) 1: 13/42 (30.9%) 2: 2/42 (4.8%) 3: 0/42 (0%)
400 mg QD No	57.00 (6.05)	81.25 (16.19)	Normal: 4/4 (100%) Mild: 0/4 (0%)	0: 3/3 (100%) 1: 0/3 (0%) 2: 0/3 (0%) 3: 0/3 (0%)
400 mg QD Yes	48.35 (16.36)	83.83 (20.34)	Normal 13/17 (76.5%) Mild 4/17 (23.5%)	0: 15/17 (88.2%) 1: 1/17 (5.9%) 2: 1/17 (5.9%) 3: 0/17 (0%)

GvHD Organ involvement: 0 = No involvement of liver, lower GI, or upper GI; 1 = Only liver or lower GI or upper GI involvement; 2 = Liver and lower GI, or liver and upper GI, or upper GI and lower GI involvement; 3 = Liver, lower GI, and upper GI involvement
Source: Reviewer's analysis

Based on both efficacy and safety considerations, the review team recommends dose adjustment to 200 mg BID for patients with concomitant use of PPIs.

Furthermore, the findings of PPI were applied to support dosing for concomitant use of strong CYP3A4 inducer. There was only one cGVHD patient with one concentration value available from Studies KD025-208 and KD025-213, although strong CYP3A4 inducer is estimated to decrease 59% of Cmax and 72% of AUC in the dedicated DDI study (refer to section 6.3.2).

Whether the efficacy of 200 mg QD belumosudil dose with the concomitant use of strong CYP3A4 inducer would be compromised is unknown. Given the similar effect on exposure of belumosudil generated by strong CYP3A4 inducer compared to PPIs, and the reasons discussed above, the higher dose of 200 mg BID is also recommended for subjects who are co-administrated with strong CYP3A4 inducer.

In conclusion, the review team recommends 200 mg BID with food for concomitant use of PPIs, and concomitant use of strong CYP3A inducers.

16.5 Additional Safety Analyses Conducted by FDA

The FDA's Assessment:

16.5.1 Grouped Terms Use for Safety Analyses

Table 114. Grouped Terms Used for FDA Analyses of Adverse Events

Grouped Term	Basis for Grouped Term
Abdominal pain	HLT Gastrointestinal and abdominal pains (excl oral and throat) Note - esophageal pain terms excluded
Asthenia	HLT Asthenic conditions
Bacterial infection	HLGT Bacterial infectious disorders
Confusional state	HLT Confusion and disorientation
Cough	HLT Coughing and associated symptoms
Diarrhoea	HLT Colitis (excl infective); HLT Diarrhoea (excl infective)
Drug hypersensitivity	PTs Anaphylactic reaction, Dermatitis allergic. Drug eruption. Drug hypersensitivity, Erythema multiforme, Urticaria
Dyspnoea	HLT Breathing abnormalities
Fungal infection	HLGT Fungal infectious disorders
Haemorrhage	Haemorrhage terms (excl laboratory terms) (SMQ) Note - Traumaitc bleeding terms excluded
Headache	HLGT Headaches
Hypertension	Hypertension (SMQ)
Hypotension	HLT Vascular hypotensive disorders
Infection	HLGT Infections - pathogen unspecified
Liver function test abnormal	HLT Liver function analyses
Musculoskeletal pain	HLT Musculoskeletal and connective tissue pain and discomfort
Nausea	HLT Nausea and vomiting symptoms
Oedema	HLT Oedema NEC
Pruritus	HLT Pruritus NEC
Rash	HLT Rashes, eruptions and exanthems NEC; HLT Exfoliative conditions
Renal failure	HLT Renal failure and impairment; HLT Renal function analyses
Stomatitis	HLT Stomatitis and ulceration
Syncope	PTs Loss of consciousness, Presyncope, Syncope
Tachycardia	PTs Atrial fibrillation, Sinus tachycardia, Supraventricular tachycardia, Tachycardia
Thrombosis	Embolic and thrombotic events (SMQ)
Viral infection	HLGT Viral infectious disorders
Visual impairment	HLT Visual disorders NEC

16.5.2 The Applicant's Shift Tables for Selected Laboratory Abnormalities.

The tables below are reproduced Shift Tables for Selected Laboratory Abnormalities based on the Applicant's tables submitted on 03/25/2020.

Table 115 summarizes the Applicant's analysis of shifts from baseline to minimum value post-baseline of neutrophils in KD025-213 study (Safety population). CTC grade is not calculated for laboratory test neutrophils of KD025-213 study, since the lower limit of normal is conflict with CTCAE criterion.

Table 116 summarizes the proportions of patients with shifts from Grades 0-1 to Grades 2-4 or Grades 3-4 in key laboratory parameters [**except neutrophil data for KD025-213**], based on the Applicant's IR response and tables submitted on 03/25/2020. The table shows number of patients with grade 0-1 abnormality at baseline, number (percentage) with shift from baseline grades 0-1 to maximum grades 2-4 on study, and number (percentage) with shift from baseline grades 0-1 to maximum grade 3-4 on study in key laboratory parameters.

Table 115. The Applicant's Analysis of Shifts from baseline to minimum value post-baseline of neutrophils in KD025-213 study (Safety population)

		200 mg QD (N=66) n (%)			**200 mg BID (N=66) n (%)**		
		>= 1.0 Baseline	0.5<= <1.0	<0.5	>= 1.0 Baseline	0.5<= <1.0	<0.5
Parameter	**Direction**	**Nx**	**n (%)**	**n (%)**	Nx	n (%)	n (%)
Neutrophils (10e9/L)	Low	66	1 (1.5%)	3 (3.0%)	66	0	0

Source: Reproduced from Applicant's Table adh_t_5_5_2_1a submitted on 03/25/2020.
The Applicant's note:
- Percentage is calculated by n/Nx*100%.
- CTC grade is not calculated for laboratory test neutrophils of KD025-213 study, since the lower limit of normal is conflict with CTCAE criterion.

Table 116. The Applicant's Analysis of Shifts in CTC grade from baseline to maximum post-baseline (Safety population, analysis group 1)

		200mg QD (N=83) n (%)			200mg BID (N=82) n (%)			400mg QD (N=21) n (%)		
		Grade 0-1 Baseline	Grade 2-4 Max Post	Grade 3-4 Max Post	Grade 0-1 Baseline	Grade 2-4 Max Post	Grade 3-4 Max Post	Grade 0-1 Baseline	Grade 2-4 Max Post	Grade 3-4 Max Post
Parameter	Direction	Nx	n (%)	n (%)	Nx	n (%)	n (%)	Nx	n (%)	n (%)
Albumin (g/L)	Low	82	5 (6.1%)	0	82	5 (6.1%)	1 (1.2%)	21	2 (9.5%)	0
Alkaline Phosphatase (U/L)	High	80	7 (8.8%)	0	80	2 (2.5%)	0	21	2 (9.5%)	0
Alanine Aminotransferase (U/L)	High	83	6 (7.2%)	2 (2.4%)	82	2 (2.4%)	1 (1.2%)	21	5 (23.8%)	0
Aspartate Aminotransferase (U/L)	High	83	1 (1.2%)	1 (1.2%)	82	6 (7.3%)	1 (1.2%)	21	0	0
Direct Bilirubin (umol/L)	High	83	0	0	82	0	0	21	0	0
Bilirubin (umol/L)	High	83	0	0	82	1 (1.2%)	1 (1.2%)	21	1 (4.8%)	0

		200mg QD (N=83) n (%)			200mg BID (N=82) n (%)			400mg QD (N=21) n (%)		
		Grade 0-1 Baseline	Grade 2-4 Max Post	Grade 3-4 Max Post	Grade 0-1 Baseline	Grade 2-4 Max Post	Grade 3-4 Max Post	Grade 0-1 Baseline	Grade 2-4 Max Post	Grade 3-4 Max Post
Parameter	Direction	Nx	n (%)	n (%)	Nx	n (%)	n (%)	Nx	n (%)	n (%)
Calcium (mmol/L)	High	83	0	0	82	0	0	21	0	0
	Low	82	10 (12.2%)	1 (1.2%)	82	15 (18.3%)	5 (6.1%)	21	2 (9.5%)	2 (9.5%)
Creatine Kinase (U/L)	High	83	1 (1.2%)	1 (1.2%)	81	4 (4.9%)	1 (1.2%)	21	0	0
Creatinine (umol/L)	High	83	3 (3.6%)	0	82	4 (4.9%)	0	21	1 (4.8%)	0
Glomerular Filtration Rate (mL/min/1.73m2)	Low	70	24 (34.3%)	0	63	30 (47.6%)	0	16	9 (56.3%)	0
Gamma Glutamyl Transferase (U/L)	High	47	10 (21.3%)	5 (10.6%)	56	15 (26.8%)	3 (5.4%)	17	4 (23.5%)	2 (11.8%)

		200mg QD (N=83) n (%)			200mg BID (N=82) n (%)			400mg QD (N=21) n (%)		
		Grade 0-1 Baseline	Grade 2-4 Max Post	Grade 3-4 Max Post	Grade 0-1 Baseline	Grade 2-4 Max Post	Grade 3-4 Max Post	Grade 0-1 Baseline	Grade 2-4 Max Post	Grade 3-4 Max Post
Parameter	Direction	Nx	n (%)	n (%)	Nx	n (%)	n (%)	Nx	n (%)	n (%)
Glucose (mmol/L)	High	63	24 (38.1%)	7 (11.1%)	71	25 (35.2%)	7 (9.9%)	18	6 (33.3%)	0
	Low	83	3 (3.6%)	1 (1.2%)	82	4 (4.9%)	1 (1.2%)	21	2 (9.5%)	0
Potassium (mmol/L)	High	82	6 (7.3%)	1 (1.2%)	81	5 (6.2%)	1 (1.2%)	21	3 (14.3%)	0
	Low	83	0	0	82	1 (1.2%)	1 (1.2%)	21	2 (9.5%)	2 (9.5%)
Lactate Dehydrogenase (U/L)	High	81	0	0	81	0	0	17	0	0
Magnesium (mmol/L)	High	83	0	0	82	2 (2.4%)	2 (2.4%)	21	0	0

Parameter	Direction	200mg QD (N=83) n (%)			200mg BID (N=82) n (%)			400mg QD (N=21) n (%)		
		Grade 0-1 Baseline Nx	Grade 2-4 Max Post n (%)	Grade 3-4 Max Post n (%)	Grade 0-1 Baseline Nx	Grade 2-4 Max Post n (%)	Grade 3-4 Max Post n (%)	Grade 0-1 Baseline Nx	Grade 2-4 Max Post n (%)	Grade 3-4 Max Post n (%)
Magnesium (mmol/L)	Low	83	2 (2.4%)	0	82	1 (1.2%)	0	21	0	0
Phosphate (mmol/L)	Low	76	21 (27.6%)	5 (6.6%)	75	18 (24.0%)	5 (6.7%)	19	4 (21.1%)	2 (10.5%)
Sodium (mmol/L)	High	83	0	0	82	0	0	21	0	0
	Low	81	7 (8.6%)	7 (8.6%)	82	2 (2.4%)	2 (2.4%)	21	1 (4.8%)	1 (4.8%)
Urate (umol/L)	High	83	0	0	82	0	0	21	0	0
Eosinophils (10^9/L)	High	83	0	0	82	0	0	21	0	0

Parameter	Direction	200mg QD (N=83) n (%)			200mg BID (N=82) n (%)			400mg QD (N=21) n (%)		
		Grade 0-1 Baseline Nx	Grade 2-4 Max Post n (%)	Grade 3-4 Max Post n (%)	Grade 0-1 Baseline Nx	Grade 2-4 Max Post n (%)	Grade 3-4 Max Post n (%)	Grade 0-1 Baseline Nx	Grade 2-4 Max Post n (%)	Grade 3-4 Max Post n (%)
Hemoglobin (g/L)	High	83	0	0	82	0	0	21	0	0
	Low	79	9 (11.4%)	1 (1.3%)	75	14 (18.7%)	1 (1.3%)	19	2 (10.5%)	1 (5.3%)
Lymphocytes (10^9/L)	High	80	7 (8.8%)	1 (1.3%)	79	9 (11.4%)	0	18	1 (5.6%)	0
	Low	62	18 (29.0%)	8 (12.9%)	67	21 (31.3%)	3 (4.5%)	18	7 (38.9%)	4 (22.2%)
Neutrophils* (10^9/L)	Low	17	0	0	16	1 (6.3%)	0	21	2 (9.5%)	2 (9.5%)
Platelets (10^9/L)	Low	82	8 (9.8%)	4 (4.9%)	82	1 (1.2%)	0	17	3 (17.6%)	2 (11.8%)

Parameter	Direction	200mg QD (N=83) n (%)			200mg BID (N=82) n (%)			400mg QD (N=21) n (%)		
		Grade 0-1 Baseline Nx	Grade 2-4 Max Post n (%)	Grade 3-4 Max Post n (%)	Grade 0-1 Baseline Nx	Grade 2-4 Max Post n (%)	Grade 3-4 Max Post n (%)	Grade 0-1 Baseline Nx	Grade 2-4 Max Post n (%)	Grade 3-4 Max Post n (%)
Leukocytes (10^9/L)	Low	83	6 (7.2%)	2 (2.4%)	82	3 (3.7%)	0	21	2 (9.5%)	2 (9.5%)

Source: Reproduced from Applicant's Table adh_t_5_5_2a submitted on 03/25/2020.
The Applicant's notes:
- Analysis Group 1 includes all subjects from cGVHD studies (KD025-208 and KD025-213).
- Percentage is calculated by n/Nx*100%.
- *Neutrophil data for KD025-208 study only.

16.5.3 List of Infections

The table below summarized the incidence of infections in the cGVHD Safety Population.

Table 117. cGVHD Safety Population: Infection Events

HLT	PT	Belumosudil		
		200 mg QD (N=83)	200 mg BID (N=82)	400 mg QD (N=21)
Bacterial infections				
Bacterial infections NEC	Catheter site cellulitis	1	0	0
Bacterial infections NEC	Cellulitis	4	4	0
Bacterial infections NEC	Citrobacter infection	0	1	0
Bacterial infections NEC	Stenotrophomonas infection	0	1	0
Bacterial infections NEC	Urinary tract infection bacterial	1	0	0
Clostridia infections	Clostridium difficile colitis	1	0	0
Escherichia infections	Escherichia urinary tract infection	1	0	0
Escherichia infections	Gastroenteritis Escherichia coli	1	0	0
Helicobacter infections	Helicobacter infection	4	0	0
Klebsiella infections	Klebsiella bacteraemia	0	0	5
Listeria infections	Listeriosis	0	1	0
Pseudomonal infections	Pseudomonal sepsis	0	0	5
Pseudomonal infections	Pseudomonas infection	1	2	0
Pseudomonal infections	Urinary tract infection pseudomonal	0	1	0
Staphylococcal infections	Staphylococcal bacteraemia	2	0	0
Staphylococcal infections	Staphylococcal infection	0	1	0
Streptococcal infections	Pharyngitis streptococcal	0	0	5
Fungal infections				
Aspergillus infections	Aspergillus infection	0	1	0
Candida infections	Candida infection	2	1	5
Candida infections	Genital candidiasis	0	1	0
Candida infections	Oral candidiasis	4	2	0
Fungal infections NEC	Fungal infection	1	0	0
Fungal infections NEC	Fungal skin infection	1	1	0
Fungal infections NEC	Respiratory tract infection fungal	1	0	0
Fungal infections NEC	Vulvovaginal mycotic infection	1	0	0
Tinea infections	Tinea pedis	1	1	0
Infections (not specified)				
Abdominal and gastrointestinal infections	Appendicitis	0	1	0
Abdominal and gastrointestinal infections	Gastroenteritis	2	1	5
Abdominal and gastrointestinal infections	Gastrointestinal infection	1	0	0

Table 117. cGVHD Safety Population: Infection Events

HLT	PT	Belumosudil		
		200 mg QD (N=83)	200 mg BID (N=82)	400 mg QD (N=21)
Abdominal and gastrointestinal infections	Infectious colitis	1	0	0
Central nervous system and spinal infections	Brain abscess	0	1	0
Dental and oral soft tissue infections	Tooth abscess	0	1	0
Dental and oral soft tissue infections	Tooth infection	1	0	5
Ear infections	Ear infection	2	1	0
Ear infections	Otitis externa	0	1	0
Eye and eyelid infections	Conjunctivitis	5	2	14
Eye and eyelid infections	Corneal infection	0	2	0
Eye and eyelid infections	Hordeolum	2	0	5
Infections NEC	Catheter site infection	0	1	0
Infections NEC	Device related infection	1	0	0
Infections NEC	Respiratory tract infection	4	0	0
Infections NEC	Wound infection	1	0	0
Lower respiratory tract and lung infections	Bronchitis	2	4	5
Lower respiratory tract and lung infections	Lower respiratory tract infection	0	1	0
Lower respiratory tract and lung infections	Lung infection	2	5	10
Lower respiratory tract and lung infections	Pneumonia	11	11	5
Sepsis, bacteraemia, viraemia and fungaemia NEC	Bacteraemia	0	1	0
Sepsis, bacteraemia, viraemia and fungaemia NEC	Sepsis	2	1	0
Sepsis, bacteraemia, viraemia and fungaemia NEC	Septic shock	1	0	0
Skin structures and soft tissue infections	Folliculitis	1	0	5
Skin structures and soft tissue infections	Nail infection	0	1	0
Skin structures and soft tissue infections	Rash pustular	0	1	0

Table 117. cGVHD Safety Population: Infection Events

HLT	PT	Belumosudil		
		200 mg QD (N=83)	200 mg BID (N=82)	400 mg QD (N=21)
Skin structures and soft tissue infections	Skin infection	1	2	0
Upper respiratory tract infections	Acute sinusitis	1	1	0
Upper respiratory tract infections	Pharyngitis	0	1	5
Upper respiratory tract infections	Sinusitis	5	5	5
Upper respiratory tract infections	Upper respiratory tract infection	31	33	33
Urinary tract infections	Urinary tract infection	1	5	0
Viral infections				
Cytomegaloviral infections	Cytomegalovirus infection	0	1	0
Epstein-Barr viral infections	Epstein-Barr viraemia	1	0	0
Epstein-Barr viral infections	Epstein-Barr virus infection	1	0	0
Herpes viral infections	Herpes zoster	0	1	0
Herpes viral infections	Varicella zoster virus infection	1	0	5
Influenza viral infections	Influenza	5	9	10
Parainfluenzae viral infections	Parainfluenzae virus infection	1	0	0
Respiratory syncytial viral infections	Pneumonia respiratory syncytial viral	0	1	0
Respiratory syncytial viral infections	Respiratory syncytial virus infection	0	1	10
Rhinoviral infections	Rhinovirus infection	5	4	5
Viral infections NEC	Bronchitis viral	1	0	0
Viral infections NEC	Corona virus infection	0	2	0
Viral infections NEC	Gastroenteritis viral	2	0	0
Viral infections NEC	Pneumonia viral	0	1	5
Viral infections NEC	Viral infection	1	0	0
Viral infections NEC	Viral pharyngitis	0	1	0
Viral infections NEC	Viral upper respiratory tract infection	2	1	0

Source: FDA analysis

NDA Multidisciplinary Review and Evaluation
NDA 214783
Rezurock (belumosudil)

DISCIPLINE	REVIEWER	OFFICE/ DIVISION	SECTIONS	AUTHORED/ APPROVED
PBPK Reviewer	Ying-Hong Wang, PhD	OOD/DHOT	Sections: 6, 16	X Authored Approved
	Signature: Ying-hong Wang -S Digitally signed by Ying-hong Wang -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Ying-hong Wang -S, 0.9.2342.19200300.100.1.1=2002939330 Date: 2021.07.13 09:42:58 -04'00'			
PBPK Team Leader	Yuching Yang, PhD	OOD/DHOT	Sections: 6, 16	Authored X Approved
	Signature: Yuching Yang -S Digitally signed by Yuching Yang -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Yuching Yang -S, 0.9.2342.19200300.100.1.1=2000846164 Date: 2021.07.13 10:23:10 -04'00'			

NDA Multidisciplinary Review and Evaluation
NDA 214783
Rezurock (belumosudil)

DISCIPLINE	REVIEWER	OFFICE/ DIVISION	SECTIONS	AUTHORED/ APPROVED
Nonclinical Reviewer	Ramadevi Gudi, PhD	OOD/DHOT	Sections: 5, 16.3	X Authored Approved
	Signature: Ramadevi Gudi -S	Digitally signed by Ramadevi Gudi -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Ramadevi Gudi -S, 0.9.2342.19200300.100.1.1=2000462985 Date: 2021.06.16 08:44:56 -04'00'		
Nonclinical Supervisor	Brenda Gehrke, PhD	OOD/DHOT	Sections: 5, 16.3	Authored X Approved
	Signature: Brenda Gehrke -S	Digitally signed by Brenda Gehrke -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Brenda Gehrke -S, 0.9.2342.19200300.100.1.1=0012062023 Date: 2021.06.16 09:53:03 -04'00'		
Nonclinical Deputy Director	Haleh Saber, PhD	OOD/DHOT	Sections: 5, 16.3	Authored X Approved
	Signature: Haleh Saber -S	Digitally signed by Haleh Saber -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Haleh Saber -S, 0 9.2342.19200300.100.1.1=1300212858 Date: 2021.06.16 10:38:14 -04'00'		
Clinical Pharmacology Reviewer	John Kadavil, PhD	OCP/DCPI	Sections: 6, 16.4	X Authored Approved
	Signature: John A. Kadavil -S	Digitally signed by John A. Kadavil -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300217653, cn=John A. Kadavil -S Date: 2021.06.17 09:45:13 -04'00'		
Clinical Pharmacology Team Leader	Olanrewaju Okusanya, PharmD, MS	OCP/DCPI	Sections: 6, 16.4	Authored X Approved
	Signature: Olanrewaju Okusanya -S	Digitally signed by Olanrewaju Okusanya -S Date: 2021.06.16 16:31:51 -04'00'		
Clinical Pharmacology Division Director	Brian Booth, PhD	OCP/DCPI	Sections: 6, 16.4	Authored X Approved
	Signature: Brian P. Booth -S	Digitally signed by Brian P. Booth -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Brian P. Booth -S, 0 9.2342.19200300.100.1.1=1300137436 Date: 2021 06.25 15:42:14 -04'00'		
Pharmacometrics Reviewer	Ruojing Li, PhD	OCP/DPM	Sections: 6, 16.4	X Authored Approved
	Signature: Ruojing Li -S (Affiliate)	Digitally signed by Ruojing Li -S (Affiliate) DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2002080834, cn=Ruojing Li -S (Affiliate) Date: 2021.06.16 10:50:59 -04'00'		
Pharmacometrics Team Leader	Lian Ma, PhD	OCP/DPM	Sections: 6, 16.4	Authored X Approved
	Signature: Lian Ma -S	Digitally signed by Lian Ma -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Lian Ma -S, 0.9.2342.19200300.100.1.1=2000825336 Date: 2021.06.16 11:45:29 -04'00'		

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Rezurock (belumosudil)

DISCIPLINE	REVIEWER	OFFICE/ DIVISION	SECTIONS	AUTHORED/ APPROVED
Statistical Reviewer	Alexei Ionan, PhD	OOD/DBIX	Sections: 8.1, 8.2, 8.4, 8.5	X Authored Approved
	Signature: Alexei C. Ionan -S Digitally signed by Alexei C. Ionan -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2002349747, cn=Alexei C. Ionan -S Date: 2021.06.30 11:30:09 -04'00'			
Statistical Team Leader	Jonathan Vallejo, PhD	OB/DBIX	Sections: 8.1, 8.2, 8.4, 8.5	Authored X Approved
	Signature: Jonathon J. Vallejo -S Digitally signed by Jonathon J. Vallejo -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2002146299, cn=Jonathon J. Vallejo -S Date: 2021.06.30 13:02:51 -04'00'			
Division Director (OB)	Thomas Gwise, PhD	OB/DBIX	Sections: 8.1, 8.2, 8.4, 8.5	Authored X Approved
	Signature: Thomas E. Gwise -S Digitally signed by Thomas E. Gwise -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300369224, cn=Thomas E. Gwise -S Date: 2021.07.12 08:00:22 -04'00'			
Clinical Reviewer	Robert Le, MD, PhD	OOD/DHMI	Sections: 2, 3.1, 7, 8, 9, 10, 16.5	X Authored Approved
	Signature: Robert Q. Le -S Digitally signed by Robert Q. Le -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Robert Q. Le -S, 0.9.2342.19200300.100.1.1=0012233511 Date: 2021.07.09 14:36:49 -04'00'			
Clinical Team Leader	Donna Przepiorka, MD, PhD	OOD/DHMI	Sections: 2, 3, 7, 8, 9, 10, 16.5	Authored X Approved
	Signature: Donna Przepiorka -S 2021.07.12 21:30:15 -04'00' *{See appended electronic signature page}*			
Associate Director for Labeling	William Pierce, PharmD, MPH	OOD	Sections: 11	X Authored Approved
	Signature: William F. Pierce -S5 Digitally signed by William F. Pierce -S5 DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300235575, cn=William F. Pierce -S5 Date: 2021.06.17 16:22:14 -04'00'			
Cross-Discipline Team Leader	Donna Przepiorka, MD, PhD	OOD/DHMI	Sections: 1, 4, 12, 13	X Authored Approved
	Signature: *{See appended electronic signature page}*			
Division Director (Clinical)	R. Angelo de Claro, MD	OOD/DHMI	Sections: All	Authored X Approved
	Signature: *{See appended electronic signature page}*			

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NDA 214783
Rezurock (belumosudil)

DISCIPLINE	REVIEWER	OFFICE/ DIVISION	SECTIONS	AUTHORED/ APPROVED
Office Director or designee	Marc Theoret, MD	OOD	Sections: All	Authored X Approved
	Signature: *{See appended electronic signature page}*			

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DONNA PRZEPIORKA
07/16/2021 08:28:30 AM

ROMEO A DE CLARO
07/16/2021 08:29:29 AM

MARC R THEORET
07/16/2021 12:42:22 PM
My signature indicates that I have considered the FDA assessments and recommendations included in this Review in determining the regulatory action.