EU-RISK MANAGEMENT PLAN FOR REZUROCK® (BELUMOSUDIL MESYLATE)

Data Lock Point (DLP)	29-JAN-2024
RMP Version number	Version 1.4
Date of final sign-off	22-JAN-2026

Table 1 - RMP version to be assessed as part of this application

Rationale for submitting an updated RMP	The RMP version 1.3 has been revised to version 1.4 in order to address the requests from the Committee for Medicinal Products for Human Use (CHMP) and the Pharmacovigilance Risk Assessment Committee (PRAC) at during the initial marketing authorization application (MAA) evaluation for belumosudil (EMEA/H/C/006421).
Summary of significant changes in this RMP	Alignment with the summary of product characteristics (SmPC). Safety concerns and Pharmacovigilance Plan wordings are updated to meet the EMA requests. Part IV is modified to align with the CHMP comments.

CHMP: Committee for Medicinal Products for Human Use; EMA/EMEA: European Medicines Agency; MAA: Marketing Authorization Application; PRAC: Pharmacovigilance Risk Assessment Committee; RMP: Risk Management Plan; SmPC: Summary of Product Characteristics.

Table 2 - Other RMP versions under evaluation

RMP Version number	Submitted on	Submitted within
Not applicable	-	-

RMP: Risk Management Plan.

Table 3 - Details of the currently approved RMP

Version number	Not applicable (initial submission)
Approved with procedure	Not applicable (initial submission)
Date of approval (opinion date)	Not applicable (initial submission)

RMP: Risk Management Plan.

Table 4 - QPPV name and signature

Qualified Person Responsible for Pharmacovigilance (QPPV) name	[redacted][a]
QPPV signature	Electronic signature on file

a Deputy QPPV by delegation from Heike Schoepper, QPPV for Sanofi.
QPPV: Qualified Person Responsible for Pharmacovigilance.

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ABBREVIATIONS

A:	Asian
ADI:	Actual Dose Intensity
AE:	Adverse Event
AI:	American Indian/Alaskan Native
ALP:	Alkaline Phosphatase
ALT:	Alanine Transaminase
AML:	Acute Myeloid Leukemia
AST:	Aspartate Aminotransferase
ATC:	Anatomical Therapeutic Chemical
AUC:	Area Under the Plasma Concentration-Time Curve
B:	Black
BCRP:	Breast Cancer Resistance Protein
BID:	Twice Daily
BP:	Blood Pressure
cGVHD:	Chronic Graft Versus Host Disease
CHMP:	Committee for Medicinal Products for Human Use
CI:	Confidence Interval
CIBMTR:	Center for International Blood and Marrow Transplant Research
C_{max}:	Mean Maximum Plasma Concentration
CNI:	Calcineurin Inhibitors
CYP:	Cytochrome P450
DALA:	Drug Abuse Liability Assessment
dcSSc:	Diffuse Cutaneous Systemic Sclerosis
DDD:	Defined Daily Dose
DDI:	Drug-Drug Interactions
DILI:	Drug Induced Liver Injury
DLP:	Data Lock Point
EBMT:	European Society for Blood and Marrow Transplantation
ECG:	Electrocardiogram
eCTD:	Electronic Common Technical Document
EEA:	European Economic Area
EMEA:	European Medicines Agency
EPAR:	European Public Assessment Report
EU:	European Union
F:	Female
FDA:	Food and Drug Administration
GFR:	Glomerular Filtration Rate
GGT:	Gamma-Glutamyl Transferase
GOT:	Glutamic Oxaloacetic Transaminase
GVHD:	Graft-Versus-Host Disease
HCP:	Healthcare Professional
HCT:	Hematopoietic Cell Transplantation
hERG:	Human Ether-a-go-go Related Gene

HIV:	Human Immunodeficiency Virus
HLA:	Human Leukocyte Antigen
HLGT:	High Level Group Term
HLT:	High Level Term
HR:	Hazard Ratio
HSCT:	Hematopoietic Stem Cell Transplantation
IC_{50}:	Half-Maximal Inhibitory Concentration
IL:	Interleukin
INN:	International Nonproprietary Name
INR:	International Normalized Ratio
IPF:	Idiopathic Pulmonary Fibrosis
JAK:	Janus Kinase
LFT:	Liver Function Test
LTE:	Long-Term Extension
m:	Month
M:	Male
MA:	Marketing Authorization
MAA:	Marketing Authorization Application
MAH:	Marketing Authorization Holder
MARCO:	Margin Consolidated
MATE:	Multidrug And Toxin Extrusion
Max:	Maximum
MedDRA:	Medical Dictionary for Regulatory Activities
Min:	Minimum
mITT:	Modified Intent-To-Treat
mTOR:	Mammalian Target of Rapamycin
n:	Number of Applicable Subjects
N:	Number of Subjects Evaluated
NA:	Not Applicable
NCT:	National Clinical Trial
NEC:	Not Elsewhere Classified
NOAEL:	No-Observed-Adverse-Effect Level
NR:	Not Reported
NRM:	Non-Relapse Mortality
O:	Other
OATP:	Organic Anion Transporting Polypeptide
p:	Probability
PBRER:	Periodic Benefit Risk Evaluation Report
PD:	Pharmacodynamic
P-gp:	P-glycoprotein
PK:	Pharmacokinetics
PL:	Package Leaflet
PPI:	Proton Pump Inhibitor
PRAC:	Pharmacovigilance Risk Assessment Committee
PT:	Preferred Term
Q:	Quarter
QD:	Once Daily

QPPV:	Qualified Person Responsible for Pharmacovigilance
QTc:	Corrected QT
RDI:	Relative Dose Intensity
RMM:	Risk Minimization Measure
RMP:	Risk Management Plan
ROCK:	Rho-Associated Coiled-Coil Containing Protein Kinase
SD:	Standard Deviation
SmPC:	Summary of Product Characteristics
SMQ:	Standardized MedDRA Query
SOC:	System Organ Class
TEAE:	Treatment Emergent Adverse Event
Tfh:	T Follicular Helper
U:	Unknown/Unreported
UGT1A1:	UDP-Glucuronosyltransferase
UK:	United Kingdom
ULN:	Upper Limit of Normal
US:	United States
UV:	Ultraviolet
W:	White
WHO:	World Health Organization

RISK MANAGEMENT PLAN - PART I: PRODUCT (S) OVERVIEW

Table 5 - Product Overview

Active substance(s) **(International Nonproprietary Name [INN] or common name)**	Belumosudil mesylate, hereafter referred to as belumosudil
Pharmacotherapeutic group(s) **(Anatomical Therapeutic Chemical [ATC] Code)**	L04AA48
Marketing Authorization Holder (MAH)	Sanofi Winthrop Industrie
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Rezurock
Marketing authorization procedure	Centralized procedure
Brief description of the product	Chemical class: Kinase inhibitor.
	Summary of mode of action: Belumosudil is a selective Rho-associated, coiled-coil containing protein kinase-2 (ROCK2) inhibitor that mediates signaling in immune cellular function and fibrotic pathways. *In vivo*, belumosudil demonstrated activity in animal models of cGVHD.
	Important information about its composition: Each film-coated tablet contains belumosudil mesylate, equivalent to 200 mg belumosudil.
Hyperlink to the product information.	Refer to electronic common technical document (eCTD) sequence 0003, Module 1.3.1 English version of the proposed Product Information.
Indication(s) in the EEA	Current: *Rezurock is indicated for the treatment of adults and paediatric patients (12 years and older with a body weight of at least 40 kg) with chronic graft-versus-host disease (cGVHD) when other treatment options provide limited clinical benefit, are not suitable, or have been exhausted.*
	Proposed: Not applicable
Dosage in the EEA	Current: *The recommended dose is 200 mg given orally once daily at approximately the same time with a meal.* *Treatment is recommended until disease progression or unacceptable toxicity.*

	Paediatric Population *The safety and efficacy of Rezurock in paediatric patients aged less than 12 years and with a bodyweight of less than 40 kg have not been established. No data are available.*
	Proposed: Not applicable
Pharmaceutical form(s) and strength(s)	Current: Film-coated tablet (tablet) *Pale yellow to yellow, oval shaped tablet, with "KDM" on one side and "200" on the other side, with dimensions of 7.4 x 14.8 mm.*
	Proposed: Not applicable
Is/will the product (be) subject to additional monitoring in the European Union (EU)?	Yes

ATC: Anatomical Therapeutic Chemical; cGVHD: Chronic Graft-Versus-Host Disease; eCTD: Electronic Common Technical Document; EEA: European Economic Area; EU: European Union; INN: International Nonproprietary Name; MAH: Marketing Authorization Holder; RMP: Risk Management Plan; ROCK: Rho-Associated Coiled-Coil containing Protein Kinase.

RISK MANAGEMENT PLAN - PART II MODULE SI: EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

Rezurock is indicated for the treatment of adults and paediatric patients (12 years and older with a body weight of at least 40 kg) with chronic graft-versus-host disease (cGVHD) when other treatment options provide limited clinical benefit, are not suitable, or have been exhausted.

Chronic graft-versus-host disease is the most common long-term complication and a major cause of morbidity and mortality after allogeneic hematopoietic cell transplantation (HCT). (1) (2) It is a pleiotropic, multi-organ syndrome involving tissue inflammation and fibrosis that often results in permanent organ dysfunction. Chronic graft-versus-host disease is fundamentally caused by replacement of the host's immune system with donor cells, although the heterogeneity of clinical manifestations suggests that patient, donor, and transplant factors modulate the phenotype. (2)

The pathology of cGVHD involves both T cells and B cells and is characterized by an overproduction of pro-inflammatory cytokines interleukin (IL)-21 and IL-17 and over-activation of pro-inflammatory T follicular helper (Tfh) cells and B cells, leading to an overproduction of antibodies. (3) In addition, cGVHD is associated with fibrotic changes in multiple organs. (4)

The epidemiology of cGVHD in Europe does not seem to differ from the worldwide data provided below, based mainly on a large-scale international study conducted by the Center for International Blood and Marrow Transplant Research (CIBMTR) (5), involving more than 500 transplant centers worldwide and including data from the respective centers in Europe (including Switzerland and United Kingdom [UK]).

Where available or applicable, data specific to Europe are provided separately.

Belumosudil is indicated for the treatment of patients 12 years and older with cGVHD after failure of at least two prior lines of systemic therapy in the United States (US), Canada and United Arab Emirates.

Belumosudil is indicated for the treatment of patients aged 12 years and older with cGVHD who have received at least two prior lines of systemic therapy in Israel and UK.

In Australia, belumosudil is indicated for the treatment of patients with cGVHD aged 12 years and older who have an inadequate response to corticosteroids.

In China, belumosudil is indicated for the treatment of patients with cGVHD aged 12 years and older who have an inadequate response to corticosteroids or other systemic treatments.

Belumosudil was approved after the RMP DLP in Japan (26 March 2024) for the treatment of adult and pediatric patients 12 years and older with cGVHD after hematopoietic stem cell transplantation (HSCT), in Hong Kong (06 May 2024), Argentina (19 June 2024), Mexico (12 August 2024), South Korea (29 August 2024), Kuwait (17 November 2024), India (27 December 2024), Taiwan (10 February 2025) , Turkey (21 February 2025), Russia (18 March 2025), Thailand (16 August 2025) and Brazil (08 September 2025) for the treatment of patients 12 years and older with cGVHD after failure of at least two prior lines of systemic therapy, and in Saudi Arabia (10 July 2024) for

the treatment of patients aged 12 years and older with cGVHD who have received at least two prior lines of systemic therapy.

The epidemiology of the disease is summarized in the following table.

Table 6 - Epidemiology of chronic graft-versus-host disease

Indication	Chronic graft-versus-host disease
Incidence	Multicentre and registry statistics, mostly from the US and Canada, showed an aggregate cumulative incidence of 30% to 50%. (1)(2)(5)(6) The incidence of cGVHD has increased over the past three decades. In a large-scale analysis of data from the registry of the CIBMTR, including data from European registries, a clear increase in the incidence of cGVHD was identified, providing rates at 1 year of 28% for the 1995-1999 time period, 31% for 2000-2003, and 37% for 2004-2007. (5) This increase may be attributed to multiple factors, including general advances in transplantation practices, leading to improved (early) survival of transplant recipients by decreasing non-relapse mortality (NRM), increasing number of allogeneic HCT in elderly patients, and a wide use of peripheral blood stem cells. (5)
Prevalence	It is estimated that worldwide between 10% and 70% of patients who undergo HCT develop cGVHD, depending upon donor and transplant characteristics. Among those, around 10% of patients are afflicted with mild cGVHD, 59% with moderate cGVHD, and 31% with severe cGVHD. (7)
Demographics of the population in the authorized/proposed indication	The incidence of cGVHD is lower in children than adults treated with allogeneic HCT, but other risk factors remain similar. (8) **Risk factors** The risk factors for development of cGVHD include the following (2)(4)(5): • Preceding acute graft-versus-host disease (GVHD), • Use of peripheral blood stem cells from all categories of donor groups, • Use of bone marrow from a mismatched or unrelated donor, • Transplant of female donors to male recipients, • Absence of antithymocyte globulin in conditioning, • Older HCT recipients, • Older donor age (9), • Human leukocyte antigen (HLA) disparity. (10)
Main existing treatment options	Corticosteroids (eg, prednisone) with or without calcineurin inhibitors (CNI); (eg, cyclosporine, tacrolimus) remain the standard initial treatment for cGVHD. Corticosteroids are associated with significant adverse effects and unsatisfactory outcomes, particularly for patients with high-risk features of cGVHD. (11) Patients with cGVHD require prolonged immunosuppressive treatment for an average of 2 to 3 years from the initial diagnosis, with 10% of those surviving for at least 7 years still requiring immunosuppressive treatment (5)(12) at that time and beyond. Most patients with cGVHD are not adequately managed with first line corticosteroids (6), with more than 50% of patients requiring second-line therapy within 2 years of treatment (13), and beyond corticosteroids, effective treatment options are limited. (4) The most widely used options of second-line treatment for cGVHD, in addition to corticosteroids, are CNIs (cyclosporine, tacrolimus), extracorporeal photopheresis, ibrutinib (which is approved by the Food and Drug Administration [FDA]), ruxolitinib (a janus kinase [JAK] inhibitor), mycophenolate mofetil, rituximab, mammalian target of rapamycin (mTOR) inhibitors (sirolimus, everolimus), pentostatin, proteasome inhibitors (eg, bortezomib), and tyrosine kinase inhibitors (eg, imatinib). (14)(15)

Indication	Chronic graft-versus-host disease
	In Europe, the standard of care for second line is ruxolitinib, these is no standard of care for third line and beyond (15) Ruxolitinib is a JAK inhibitor approved in Europe since May-2022 for the treatment of patients aged 12 years and older with cGVHD who have inadequate response to corticosteroids or other systemic therapies. Ibrutinib is a small-molecule Bruton's tyrosine kinase inhibitor approved in the US and Canada but not in Europe for the treatment of cGVHD after failure of one or more lines of systemic therapy. Apart from ruxolitinib, for which Phase 3 trial data were recently reported (REACH-3 study) (16), none of the therapies are supported by evidence from randomized clinical trials. As a result, the latest consensus recommendations of the European Society for Blood and Marrow Transplantation (EBMT) (2020) advise that centers should follow their institutional guidelines and enroll participants in clinical trials whenever possible. (15) The approval of ruxolitinib means that the majority of patients may already have received ruxolitinib as standard of care before enrollment in a study; however, standard of care approaches are expected to remain variable due to local ruxolitinib access and patient/physician preference. Therefore, there continues to be an important need for safe and efficacious treatments for patients with cGVHD, and particularly for patients who have unsuccessfully undergone 2 prior lines of systemic therapy.
Natural history of the indicated condition in the untreated population including mortality and morbidity	Chronic GVHD has emerged as the major cause of NRM and morbidity in patients who have undergone allogeneic HCT. (2)(4) It poses a major burden on the patients' quality of life. (8) Patients affected by cGVHD require prolonged immunosuppressive treatment for an average of 2 to 3 years from the initial diagnosis, with 10% of those surviving for at least seven years still requiring immunosuppressive treatment. (5) Most cases of cGVHD are diagnosed within the first year after allogeneic HCT, but 5% to 10% of affected patients do not develop signs and symptoms until later. Approximately 30% of cGVHD was reported as de novo without any preceding acute GVHD. (5)(2) From other authors, the clinical patterns of onset of cGVHD include 9% de novo (without prior acute GVHD), 52% progressive (progressing directly from acute GVHD), and 39% quiescent onset (following complete resolution of acute GVHD). (10) Chronic GVHD typically manifests with multi-organ pathology. At onset, many patients have an inflammatory skin rash, oral sensitivity or dryness, or dry, irritated eyes. Transaminase elevations and eosinophilia are common. These early manifestations are relatively easy to control with standard corticosteroid-based immunosuppression but often recur with the same or new manifestations when immunosuppression is tapered. Other manifestations that are less common but much more difficult to control include skin sclerosis or fasciitis, bronchiolitis obliterans syndrome, oral ulcers unresponsive to local therapies, severely dry eyes, serositis, and gastrointestinal involvement. These manifestations respond poorly to standard immunosuppressive therapies, cause significant organ dysfunction, and are often persistent or permanent. (2) Arai et al. analyzed and reported data from the registry of the CIBMTR, evaluating the incidence and outcomes of cGVHD for patients who underwent a first allogeneic HCT between 1995 and 2007. (5) Non-relapse mortality for all transplanted patients has decreased over time. However, for patients who underwent a first allogeneic transplant between 2004 and 2007, the 3-year and 5-year NRM rates were 21% and 22%, respectively, for patients without cGVHD, while the 3-year and 5-year NRM rates for patients with cGVHD were 30% and 37%, respectively. The authors comment that newer transplantation practices have impacted early NRM in patients with cGVHD, but that 5-year NRM and overall survival have not significantly changed over time, suggesting an adverse impact of protracted immunological derangements associated with cGVHD. (5) Jiang et al. compared the NRM in younger (<60 years) and older (≥60 years) allogeneic HSCT patients with and without cGVHD from 1999 to 2018. Among the 1194 patients that were studied, 373 patients developed cGVHD. Regardless of age, patients with cGVHD were at

Indication	Chronic graft-versus-host disease
	higher risk of NRM compared to patients with no cGVHD (hazard ratio (HR): 1.52, 95% confidence interval [CI]: 1.16-1.99; probability [p] = 0.002). (17) In a retrospective analysis of 775 patients who underwent allogeneic stem cell transplantation between 2002 and 2008, 232 patients were diagnosed with cGVHD. The 3-year cumulative incidence of NRM was 22.8% and the study found that all GVHD subtypes were associated with significantly higher NRM compared to no GVHD. (18) DeFilipp et al. analyzed patient, transplant, and cGVHD-related variables, as well as risk factors and causes of NRM in 937 allogeneic HCT recipients with cGVHD between 2007 and 2019 through the Chronic GVHD Consortium. The study found an increase in NRM over time with the 1-year, 3-year, and 5-year cumulative incidence of NRM being 7%, 15%, and 22%, respectively. Predictive modelling displayed an upward trend in the cumulative incidence of NRM, reaching 40% at 12 years. cGVHD was the most common cause of NRM, accounting for 37.8% of deaths. The authors highlight that NRM associated with cGVHD does not plateau, but rather increases over time, suggesting the need for novel therapeutic solutions that do not predispose patients to infections. (19) In a prospective observational study of 250 adult patients who had previously undergone allogeneic transplantation, enrolled between 2007 and 2012, and subsequently received systemic treatment for cGVHD at Fred Hutchinson Cancer Research Centre (20) at 5 years after diagnosis, approximately: • One-third were alive, malignancy free and off immunosuppressive therapy, • One-third were still on immunosuppressive therapy (of whom half were on fourth or greater line of therapy, • One-third had died. A multicentre prospective study on 911 HCT recipients between 2011 and 2014 evaluated cGVHD after transplantation. The cumulative incidence of cGVHD was found to be 47% by 2 years post-HCT. Among the 428 patients diagnosed with cGVHD, NRM was 12% at 2 years. Further analysis showed that the 2-year NRM was 11% for mild cGVHD, 8% for moderate cGVHD, and 18% for severe cGVHD. The authors suggest the need for more effective GVHD treatment interventions to improve HCT success. (1) In a retrospective analysis of 581 patients who underwent allogeneic HCT, included between 2000-2004 and re-assessed between 2013-2017, 304 (52.3%) patients had cGVHD. (21) The frequency of several chronic health conditions was significantly higher in patients with a history of cGVHD than in those without cGVHD: oral (difficulty in tasting/swallowing/chewing) and/or ocular (dry eyes) conditions (54% versus 34%, p <0.0001), diabetes (17% versus 11%, p = 0.04), osteonecrosis (13% versus 5%, p = 0.002), neurological symptoms (tremors/decreased sense/prolonged pain: 33% versus 23%, p = 0.007), pulmonary complications (fibrosis/scarring/oxygen supplementation: 23% versus 12%, p = 0.0005), and gastrointestinal complications (esophageal strictures and rectal/ anal strictures: 13% versus 8%, p = 0.05). A frailty phenotype was constructed from responses provided by bone marrow transplantation survivors using modified Fried criteria. (21) The frequency of frailty was also higher in those with cGVHD versus those without cGVHD (17.1% versus 6.14%, p <0.0001). Overall, 45% of allogeneic bone marrow transplant recipients with cGVHD versus 25% of those without cGVHD had 2 or more chronic health conditions (p <0.0001). Moreover, patients with cGVHD are at risk of long-term adverse effects associated with chronic immunosuppressive therapy.
Important co-morbidities	Patients with hematologic cancer who underwent allogeneic HCT present with various co-morbidities, depending on the primary malignancy.

Indication	Chronic graft-versus-host disease

cGVHD: Chronic Graft-Versus-Host Disease; CI: Confidence Interval; CIBMTR: Center for International Blood and Marrow Transplant Research; CNI: Calcineurin Inhibitors; EBMT: European Society for Blood and Marrow Transplantation; FDA: Food and Drug Administration; GVHD: Graft-Versus-Host Disease; HCT: Hematopoietic Cell Transplantation; HLA: Human Leukocyte Antigen; HR: Hazard Ratio; HSCT: Hematopoietic Stem Cell Transplantation; JAK: Janus Kinase; mTOR: Mammalian Target of Rapamycin; NRM: Non-Relapse Mortality; p: Probability; US: United States.

RISK MANAGEMENT PLAN – PART II MODULE SII: NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Good Laboratory Practice-compliant general toxicology/toxicokinetic studies of acute, sub-chronic, and chronic duration have been conducted in rats and dogs. In addition, safety pharmacology studies evaluating human ether-a-go-go related gene (hERG), central nervous system, and respiratory and cardiovascular organ systems have been conducted.

Furthermore, belumosudil has been evaluated in a panel of studies evaluating drug genotoxicity and phototoxicity potential. Reproductive and developmental studies have also been conducted.

The overall description of the non-clinical program for belumosudil is provided in the eCTD Module 2.4 (Non-clinical Overview).

The primary non-clinical toxicology findings at/near clinically relevant exposures were limited to changes in the cardiovascular, hepatic, renal, gastrointestinal, and hematopoietic/immunologic systems. The key non-clinical findings are presented in the following table.

Table 7 - Key safety findings from non-clinical studies and relevance to human usage

Key Safety Findings	Relevance to human usage
Toxicity General toxicity	
• Gastrointestinal adverse effects: In rat and dog toxicology studies, significant effects were observed in food consumption which correlated with decreases in body weight gain and/or loss. Additionally, infrequent emesis was observed in dogs.	Gastrointestinal adverse events (AEs) were commonly reported in the clinical development program in subjects with cGVHD. Considering that cGVHD represents a confounding factor for gastrointestinal adverse effects, and a minimal clinical impact of these events on the intended target population, this risk is considered non-important for the RMP.
• Adverse effects on the hematopoietic/immunologic system: Mild anemia with regeneration, lymphoid depletion in the thymus, and lymphoid depletion in the spleen (dog).	Hematologic AEs were observed in the clinical development program for belumosudil in subjects with cGVHD. Considering the mild to moderate nature of reported events and the lack of directly attributable clinical outcomes, this potential risk is considered non-important for the RMP.
• Liver adverse effects: Mild to potentially significant increases in serum markers that can be indicative of liver injury occurred in animals (alanine transaminase [ALT], alkaline phosphatase [ALP], gamma-glutamyl transferase [GGT], and/or total bilirubin). In addition, minimal to mild cholestasis, moderate hepatocyte atrophy, mononuclear cell infiltration and/or increased liver and gall bladder weights occurred in animals. Low magnitude hepatocellular hypertrophy was also observed in rats.	Increases in Liver function tests (LFT) were observed in the clinical development program for belumosudil. Liver function tests elevation is considered as non-important risk in the RMP.

Key Safety Findings	Relevance to human usage
• Renal adverse effects: Mild elevations of serum urea nitrogen were observed in rats. In dogs and rats, a presence of gold/brown pigmentation in the kidneys was noted that, in rats, was further associated with multifocal basophilia of the tubules and minimal to moderate intracellular protein droplets in the epithelium. At higher exposure levels in rats and dogs, adverse renal changes were observed in a single rat (early death) in the 6-month toxicology study and a single moribund dog in the 1-month toxicology study.	The non-clinical findings were observed at exposure levels well above the human exposure at the recommended dose of 200 mg once daily (QD).
• Testicular adverse effects: Minimal to mild, multifocal, unilateral, or bilateral degeneration of spermatogenic elements of the seminiferous tubules were observed in dogs and rats, including the lowest dose tested, 50 mg/kg/day in rats and 35 mg/kg/day in dogs, respectively.	Testicular findings could be seen at clinically relevant exposures, reversible in dog and partially reversible in rats in a study setting with insufficient recovery-phase duration shorter than a spermatogenesis cycle time. Impaired male fertility is considered non-important potential risk for the RMP (see [Part II Module SVII]).
Reproductive/developmental toxicity studies	
• Embryofoetal toxicity and teratogenicity: In animal reproduction studies, administration of belumosudil to pregnant rats and rabbits during the organogenesis resulted in embryofoetal mortality, reduced fetal weight and/or fetal abnormalities. In rats, 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 dose of 200 mg once daily (QD) based on the area under the plasma concentration-time curve [AUC]). In rabbits, 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 dose of 200 mg QD based on AUC). Published studies of ROCK2-deficient mice showed placental dysfunction, intrauterine growth retardation, and fetal death. (22)(23) Because ROCKs are critical	Belumosudil has demonstrated a potential for embryofoetal toxicity and/or malformations at clinically relevant exposures. There are no human data on belumosudil use during pregnancy. The use in “Pregnancy and breastfeeding” is contraindicated for belumosudil. Thus, “Embryofetal toxicity and teratogenicity” does not represent an important potential risk of belumosudil (refer to [Part II Module SVII]).

Key Safety Findings	Relevance to human usage
for cardiovascular and central nervous system development, the embryonic lethality was noted in both ROCK1 and ROCK2 knockout mice, albeit showing different phenotypes of lethality. (23)(24) The clinical relevance/translatability of these non-clinical data to human subjects is unknown.	
• Impaired male fertility: Male rats treated with belumosudil at the highest dose evaluated (275 mg base/kg/day) for 70 days (when mated with 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 recovered males at 275 mg base/kg/day were comparable to concurrent controls at the end of recovery phase of 77 days indicating potential reversibility of these parameters. No adverse fertility changes were observed at lower dose levels.	Male fertility findings could be seen at clinically relevant exposures, functionally reversible but complete morphological reversibility has not been confirmed. Considering the seriousness of the condition intended to be treated by belumosudil (cGVHD in transplant recipients), this does not represent an important risk for the RMP (refer to Part II Module SVII.1.1).
Carcinogenicity	
• No formal in vivo carcinogenicity studies have been conducted with belumosudil within the initial development program, based on the intended patient population. The study in transgenic Tg(HRAS)2 mice is completed. The administration of belumosudil to mice by QD oral gavage for 26 weeks at dose levels of 0 (control article), 4, 8, and 15 mg/kg/day for females or 0 (control article), 8, 15, and 30 mg/kg/day for males did not result in any carcinogenic effect related to belumosudil.	Malignancy (secondary neoplasm and relapse of the underlying malignancy) is proposed as non-important potential risk in this RMP (refer to Part II Module SVII).
Genotoxicity	
Belumosudil is not considered genotoxic or mutagenic. There was no evidence of genotoxicity in the in vitro Bacterial Reverse Mutation Assay, the in vitro mammalian chromosome aberration test, or the in vivo mammalian erythrocyte micronucleus test mutagenicity assay.	The results of genotoxicity studies suggest that the risk of genotoxicity in humans is negligible.

Key Safety Findings	Relevance to human usage
Safety pharmacology	
The safety pharmacology data demonstrate a low potential for adverse and/or non-monitorable belumosudil-related central nervous system, respiratory, or cardiovascular effects at clinically relevant exposures.	
• Effects on blood pressure (BP): Belumosudil demonstrated low magnitude-lowering of systolic BP, diastolic BP, and mean arterial pressure in the dog safety pharmacology cardiovascular study.	Hypotension does not represent a risk for belumosudil, based on the experience with pan-ROCK inhibitors (25) of unknown relevance to belumosudil and no significant findings from the clinical development program.
• Effects on QT interval: No changes in electrocardiogram (ECG) parameters, including corrected QT interval (QTc), were observed. These cardiovascular effects were not considered adverse at exposures similar to those expected in human subjects at the highest anticipated dose exposure. No evidence for an increased risk of QTc interval prolongation with belumosudil has been observed during in vivo preclinical testing. In an in vitro human hERG assay, belumosudil and its minor human metabolite (KD025m1) inhibited hERG channel activity in a concentration-dependent manner with estimated half maximal inhibitory concentration (IC_{50}) of 0.6 μM (approximately 270 ng/mL) and 1.5 μM (approximately 600 ng/mL), respectively. The human metabolite (KD025m2) had no inhibitory effect in this assay at concentrations up to 10 μM. When interpreting in vitro hERG results, it is important to consider in vivo cardiovascular assessments in non-rodent species at belumosudil plasma concentrations similar to or greater than the hERG IC_{50}. At the highest dose evaluated (150 mg base/kg; mean maximum plasma concentration [C_{max}] of 3122 ng/mL [gender combined]) in the cardiovascular safety pharmacology study, no evidence of changes in ECG waveforms were detected in beagle dogs. In addition, in the 28-day repeat-dose general toxicology study in beagle dogs, a dose (200 [male]/125 [female] mg base/kg, mean C_{max} of 7330 ng/mL [gender combined]) above the no observed adverse effect level (NOAEL) had no ECG evidence of adverse cardiac effects or histopathology indicative of cardiotoxicity. In addition, generally reversible heart weight increases (possibly secondary to changes in body weight) have been observed in rat and dog toxicology	The potential of belumosudil to affect QTc was evaluated in the clinical program for belumosudil and based on the evaluation of collected data; no safety signal was identified. Moreover, the performed concentration-QT analysis ruled out an effect of belumosudil on QT at therapeutic and supratherapeutic doses. Additionally, the results of the Thorough QT/QTc study KD025-110 confirmed no clinically relevant effects on studied parameters. Based on the concentration-QTc analysis, an effect on ΔΔQTcF exceeding 10 ms can be excluded up to belumosudil plasma concentrations of approximately 12 080 ng/mL.

Key Safety Findings	Relevance to human usage
studies generally at levels above those expected in human subjects.	
Other toxicity-related information or data	
• Phototoxicity: Belumosudil non-clinical data suggest the potential for phototoxicity. Belumosudil has demonstrated photo-absorbance between 290 and 370 nm, some distribution into the skin and uveal tract, based on the rat quantitative whole body autoradiography studies with [^{14}C]-belumosudil, and positive phototoxic potential in the in vitro 3T3 Neutral Red Uptake Assay, where belumosudil reduced the viability of 3T3 mouse fibroblasts in the presence of ultraviolet (UV) light compared to UV light alone. [^{14}C]-belumosudil distribution in partial-pigmented rats demonstrated higher tissue retention in melanin-containing tissues (uveal tract and pigmented skin), indicating some affinity of belumosudil for melanin.	No phototoxic effects were observed in the clinical development program for belumosudil and considering the seriousness of the condition intended to be treated by belumosudil (cGVHD in transplant recipients), phototoxicity does not represent a risk for belumosudil.
• Drug-drug interactions: – Based on in vitro assessments, cytochrome P450 (CYP) 3A4 was the predominant CYP isoform responsible for the metabolism of belumosudil.	Co-administration of belumosudil with proton pump inhibitors (PPIs) and CYP3A4 inhibitors/inducers were of interest based on non-clinical data. Specifically, belumosudil has been found to have a pH dependent solubility and to be predominantly metabolized via hepatic CYP3A4. As such, co-administration with strong PPIs and CYP3A4 inhibitors/inducers have the potential to alter belumosudil exposure. The analyses of clinical data showed that the overall incidence of treatment emergent adverse event (TEAE) was similar between subjects taking PPIs and subjects not taking PPIs (98.1% and 100%, respectively). Similarly, the overall incidence of TEAEs was similar between subjects taking strong CYP3A inhibitors and subjects not taking strong CYP3A inhibitors (98.0% and 99.4%, respectively). As such, CYP3A-mediated inhibitory drug-drug interactions (DDI) do not represent a risk for belumosudil.
– Based on in vitro data, belumosudil is a potential reversible inhibitor of CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5 and a time-dependent inhibitor of CYP1A2, CYP2C19 and CYP3A4. Belumosudil is not an in vitro inducer of CYP1A2, CYP2B6, or CYP3A4.	Based on in vitro data and circulating levels of belumosudil at therapeutic dose, there is no clinically relevant risk identified for belumosudil to inhibit CYP2C8 and CYP2D6 enzymes at systemic level. Risk for significant clinical inhibition is unlikely for CYP2C9 but cannot be excluded for CYP1A2, CYP2C19 and CYP3A4 at systemic level and for CYP3A4 at gut level. As such, co-administration of belumosudil with CYP1A2, CYP2C19 and CYP3A4 sensitive substrates of these enzymes, for which small concentration changes may lead to serious toxicities, is not recommended. If co-administration cannot be avoided, the substrate dose(s) should be

Key Safety Findings	Relevance to human usage
	decreased in accordance with the respective product information.
– Belumosudil is an in vitro inhibitor of BCRP and P-glycoprotein (P-gp). In vitro assessments indicate low clinical risk of multidrug and toxin extrusion (MATE), MATE2-K, or organic anion transporting polypeptide (OATP) 1B1 inhibition. Belumosudil is a substrate of P-gp.	In a clinical DDI study with healthy volunteers, belumosudil increased the AUC of rosuvastatin by 4.4-fold, indicating an inhibition of the transporters OATP1B1 and breast cancer resistance protein (BCRP). A 2.4-fold increase was also observed in dabigatran AUC, indicating moderate inhibition of P-gp. Caution should be taken when administering belumosudil to patients taking rosuvastatin or low safety index P-gp substrate drugs such as dabigatran. In the same study, while no difference was observed in raltegravir pharmacokinetics (PK) \ after multiple doses of belumosudil, the concentrations of raltegravir glucuronide were decreased by 40%, indicating potential for some inhibition of UDP-Glucuronosyltransferase 1A1 (UGT1A1). As such, co-administration of belumosudil with sensitive UGT1A1 substrates, for which small concentration changes may lead to serious toxicities, is not recommended. If co-administration cannot be avoided, the UGT1A1 substrate dose(s) should be decreased in accordance with the respective product information. Drug-drug interactions do not represent an important risk for belumosudil (refer to Part II Module SVII).

AE: Adverse Event; ALP: Alkaline Phosphatase; ALT: Alanine Transaminase; AUC: Area Under the Plasma Concentration-Time Curve; BCRP: Breast Cancer Resistance Protein; BP: Blood Pressure; cGVHD: Chronic Graft-Versus-Host Disease; C_{max}: Mean Maximum Plasma Concentration; CYP: Cytochrome P450; DDI: Drug-Drug Interaction; ECG: Electrocardiogram; GGT: Gamma Glutamyl Transferase; hERG: Human Ether-A-Go-Go Related Gene; IC_{50}: Half Maximal Inhibitory Concentration; LFT: Liver Function Test; MATE: Multidrug And Toxin Extrusion; NOAEL: No-Observed-Adverse-Effect Level; OATP: Organic Anion Transporting Polypeptide; P-gp: P-glycoprotein; PK: Pharmacokinetics; PPI: Proton Pump Inhibitor; QD: Once Daily; QTc: Corrected QT; RMP: Risk Management Plan; ROCK: Rho-Associated Coiled-Coil containing Protein Kinase; TEAE: Treatment-Emergent Adverse Event; UGT1A1: UDP-Glucuronosyltransferase 1A1; UV: Ultraviolet.

RISK MANAGEMENT PLAN – PART II MODULE SIII: CLINICAL TRIAL EXPOSURE

The clinical development program for belumosudil includes Phase 1 and Phase 2 clinical studies in 4 indications, healthy volunteers, and subjects with varying degree of hepatic impairment:

- Chronic graft-versus-host disease
  - Studies KD025-208, KD025-213, KD025-217 (long-term extension [LTE] study of KD025-208 and KD025-213), KD025-218 and EFC17757
- Belumosudil has also been studied in other indications: idiopathic pulmonary fibrosis (IPF): total 76 patients in study KD025-207, 52 treated with belumosudil; psoriasis: total 156 patients in studies (KD025-205, KD025-206 and KD025-211), 138 treated with belumosudil; Diffuse cutaneous systemic sclerosis (dcSSc): total 45 patients in studies KD025-209, KD025-215, 33 treated with belumosudil. The development of these indications has been discontinued for reasons not related to safety.
- Healthy volunteers
  - Studies SLx-2119-09-01, KD025-101, KD025-102, KD025-103, KD025-105, KD025-106, KD025-107, KD025-108, KD025-110, KD025-111, KD025-112
- Subjects with varying degree of hepatic impairment
  - Study KD025-109.

In addition, 4 co-development partner sponsored clinical studies, including 2 Phase 1 studies performed in China (BN-101) and Japan (ME3208-01), and a Phase 3 study (ME3208-2) in Japan and a Phase 2 study (BN101-201) in China were conducted.

Cumulatively, 1033 subjects were enrolled in the clinical development program (all studies and indications), of which 830 were exposed to belumosudil.

A tabular summary of all completed and ongoing Phase 1 and 2 studies in the belumosudil clinical development program for cGVHD is provided in the table below Table 8).

Table 8 - Overview of clinical studies designed to support the safety of belumosudil in cGVHD

Study Number **NCT Number** **Status**	**Objectives**	**Phase** **Study Design**	**Dosing Regimen and Treatment Duration**	**Study Population**	**Median Age** **Sex** **Race**
Primary studies providing evidence of safety in the proposed indication					
KD025-208/ ACT17631 NCT02841995 Completed	Efficacy, safety, and tolerability	Phase 2a Open-label, Dose-escalation study	200 mg QD 200 mg BID 400 mg QD Treatment until disease progression or unacceptable toxicity	Participants with cGVHD	51.5 years 34 M/20 F 47 W/2 B/ 2 AI/ 3 O

Study Number **NCT Number** **Status**	**Objectives**	**Phase** **Study Design**	**Dosing Regimen and Treatment Duration**	**Study Population**	**Median Age** **Sex** **Race**
KD025-213/ DRI17633 NCT03640481 Completed for the adult population Completed for the adolescent population	Efficacy, safety, and tolerability	Phase 2 Open-label, Randomized	200 mg QD 200 mg BID Treatment until clinically significant cGVHD progression requiring addition of systemic therapy for cGVHD, or unacceptable toxicity	Participants with cGVHD	54.1 years 86 M/66 F 132 W/ 6 U/ 8 B/4 A/ 2 AI 12.33 years 2 M/1 F 2 W/1 B/Hispanic or Latino
KD025-217/ LTS17660 NCT05305989 Completed	Long-term safety, efficacy, and tolerability	Phase 2a Open-label, dose-escalation	200 mg QD 200 mg BID 400 mg QD Treatment until disease progression or unacceptable toxicity	Participants with cGVHD	Study completed 60 years 16 M/7 F 22 W/1 NR
SLx-2119-09-01 NA Completed	PK, safety, and tolerability	Phase 1 Randomized, double-blind, placebo controlled, single-dose, dose escalating	20, 40, 80, and 160 mg and Placebo 1 day	Healthy male participants	27-43 years 32 M 15 W/16 B/ 1 A
KD025-101/ MAD17647 NA Completed	PK, safety, and tolerability	Phase 1, Randomized, placebo-controlled	40, 80, 120, 160, 240, 320, 400, and 500 mg and Placebo/ 1 day and 7 days multiple dose	Healthy male participants	30.0-41.5 years 64 M 37 B/24W/1A 1 A.I.
KD025-102 NA Completed	PK, safety, and tolerability	Phase 1, Randomized, double-blind, placebo-controlled	500, 800, and 1000 mg QD, 500 mg BID and Placebo/ 7 days	Healthy male and post-menopausal female participants	32.0 years 28 M/4 F 18 B/13 W/1 A.I.
KD025-103 NA Completed	PK, safety, and tolerability, and exploratory PD	Phase 1, Randomized, double-blind, placebo-controlled	500 mg BID and Placebo/ 28 days	Healthy male and post-menopausal female participants	29.5 years 7 M/1 F 4 B/4 W
KD025-105/ PKM17650 NA Completed	PK, safety, and food effect	Phase 1, Open-label, single-dose, two-period, crossover	500 mg/ 2 days	Healthy male participants	28.0 years 12 M 8 B/4 W

Study Number **NCT Number** **Status**	**Objectives**	**Phase** **Study Design**	**Dosing Regimen and Treatment Duration**	**Study Population**	**Median Age** **Sex** **Race**
KD025-106/ BEQ17651 NCT02557139 Completed	Capsules vs Tablets	Phase 1, Open-label, single-dose, three-period, crossover	200 mg tablet (fed and fasted), 200 mg capsule/ 3 days	Healthy male participants	33.0 Years 23 M 20 W/3 B
KD025-107/ INT17652 NCT03530995 Completed	DDI	Phase 1, Open-label, two-part, non-randomized	Part 1: Period 1: KD025 200 mg QD Period 2: itraconazole 200 mg QD and itraconazole 200 mg plus KD025 200 mg QD Period 3: rabeprazole 20 mg BID and rabeprazole 20 mg plus KD025 200 mg QD Period 4: rifampicin 600 mg QD and rifampicin 600 mg plus KD025 200 mg QD Part 2: Period 1: KD025 200 mg BID Period 2: omeprazole 20 mg QD, KD025 200 mg BID plus omeprazole 20 mg QD Part 1: 4 days Part 2: 2 days	Healthy male participants	Part 1: 34 years 35 M 28 W/4 B/2 A/1 O Part 2: 29.5 years 38 M 35 W/1 B/1 A/1 O
KD025-108/ BEX17653 NCT03907540 Completed	Bio-availability	Phase 1, Open-label, two-part	Part 1: Single oral dose of KD025 followed by an infusion of [14C]-KD025 Part 2: Single dose of [14C]-KD025 capsule/ 1 day	Healthy male participants	53.0 years 5 M 4 W/1 O
KD025-109/ POP17629 NCT04166942	PK, Hepatic impairment	Phase 1, Open-label	Single oral dose of KD025	Mild, moderate, or severe hepatic impairment, or	58.0 years 18 M/9 F 24 W/3 B

Study Number NCT Number Status	Objectives	Phase Study Design	Dosing Regimen and Treatment Duration	Study Population	Median Age Sex Race
Completed				normal hepatic function	
KD025-110 Not applicable Completed	QTc Interval	Phase 1, Double-blind, Placebo and Positive controlled, Parallel group	Single doses of: Belumosudil tablets 200 mg x 1 Belumosudil tablets 200 mg x 5 (1000 mg) Moxifloxacin tablets 200 mg x 2 (400 mg) Placebo	Healthy participants	36.5 years 33 M/1 F 13 W/21 B
KD025-111 NCT04735822 Completed	Taste profile, Bioavailability	Phase 1, Two-part	Part 1: Belumosudil oral suspension tasted (not ingested) over 1 day Part 2: Belumosudil 200 mg x 1 each of tablet, oral suspension regimens over 9 days	Healthy adult male participants	Part 1: 35.5 years 12 M/0 F 8 W/2 B/2 A Part 2: 39.5 years 18 M/0 F 11 W/1 B/6 A
KD025-112/ INT17676 Not applicable Completed	UGT1A1, P-gp, BCRP, OATP1B1 inhibition liability of oral belumosudil and the PK of belumosudil in the fed state	Phase 1, Single center, non-randomized, open-label, three-part, sequential-dosing, drug-drug interaction study	Part 1: 200 mg QD on Days 3 to 8 (overall treatment duration: 6 days) Part 2: 200 mg QD on Days 5 to 12 (overall treatment duration: 8 days) Part 3: 200 mg QD on Days 6 to 13 (overall treatment duration: 8 days)	Healthy adult male participant	Part 1: 35.0 19 M/0 F 17 W/2 B Part 2: 38.0 19 M/0 F 16 W/3 B Part 3: 41.0 14 M/0 F 12 W/2 B
Other studies providing supporting evidence of safety					
KD025-218/ SFY17661 NCT05567406 Ongoing	Safety and efficacy	Phase 2, Open-label, multicenter study	200 mg QD until progression of disease	Black or African American, American Indian, or Alaska Native, and Native Hawaiian or Other Pacific Islander participants	No participants enrolled

Study Number **NCT Number** **Status**	**Objectives**	**Phase** **Study Design**	**Dosing Regimen and Treatment Duration**	**Study Population**	**Median Age** **Sex** **Race**
EFC17757 NCT06143891 Terminated	Efficacy and safety in newly diagnosed cGVHD	Phase 3 Randomized, double-blind, multi-center study to evaluate efficacy and safety of belumosudil in combination with corticosteroids versus placebo in combination with corticosteroids	Belumosudil 200 mg QD Prednisone 1 mg/kg/day Placebo	Participants with cGVHD	Study terminated
ME3208-1 (Co-development partner sponsored study) jRCT2071200077 Completed	Safety, Tolerability, and PK	Phase 1 Part 1: Single center, randomized, placebo controlled, double blind study. Part 2: Single center, randomized, open-label, 3-period crossover study	Part 1: Cohorts 1-3: single doses of 200 mg, 400 mg (2 tablets), or 800 mg (4 tablets) of study drug Cohorts 4-6: 200 mg QD, 200 mg BID, or 400 mg (2 tablets) QD over 7 days Part 2: Group 1: 200 mg tablet fasted state (single dose) Group 2: 200 mg 5 minutes after meal (single dose) Group 3: 30 minutes after meal (single dose)	Healthy participants	Part 1: (6 male, Japanese participants per cohort or placebo group) Cohort 1: 27.0 Cohort 2: 24.5 Cohort 3: 25.5 Placebo: 23.0 Cohort 4: 28.0 Cohort 5: 23.5 Cohort 6: 32.0 Placebo: 21.5 Part 2: 6 male, Japanese participants per group) Group 1: 24.5 Group 2: 26.0 Group 3: 26.5
ME3208-2 (Co-development partner sponsored study) jRCT2011210041 Completed	Efficacy in participants with steroid-depended/ resistant cGVHD	Phase 3, multicenter, open-label, single-arm clinical study	200 mg QD for 48 weeks and every 12 weeks until completion of study or until treatment discontinuation criteria was met	Participants with steroid-depended/ resistant cGVHD	50.0 years 14 M/7 F All Japanese
BN101-101 (Co-development partner sponsored study) CTR:20202159 Completed	Tolerability, Safety, and PK	Phase 1, Randomized, placebo-controlled, single ascending-dose	Cohort 1: 200 mg (1 tablet, single dose) Cohort 2: 400 mg QD (two 200 mg tablets, single dose)	Healthy participants	Cohort 1: 36.5 6 M/2 F 8 Han Chinese Cohort 2: 33.0

Study Number NCT Number Status	Objectives	Phase Study Design	Dosing Regimen and Treatment Duration	Study Population	Median Age Sex Race
			Placebo 200 mg/400 mg		7 M/2 F 9 Han Chinese Placebo 200/400 mg: 29.5 4 M/2 F 6 Han Chinese
BN101-201 (Co-development partner sponsored study) NCT: 04930562 Completed	Efficacy and safety	Phase 2, Open-label, single-arm multicenter study	1 (200 mg) tablet QD Treatment continued until cGVHD progression, intolerable toxicity, start of new cGVHD therapies, hematologic neoplasm recurrence, participant's loss to follow-up, withdrawal of informed consent, or death (whichever occurred first).	Participants with cGVHD	29.5 21 M/9 F 29 Han Chinese/1 Other

A: Asian; AI: American Indian or Alaskan Native; B: Black; BCRP: Breast Cancer Resistance Protein; BID: Twice Daily; cGVHD: Chronic Graft-Versus- Host Disease; DDI: Drug-Drug Interactions; F: Female; M: Male; NA: Not Applicable; NCT: National Clinical Trial; NR: Not Reported; O: Other; OATP: Organic Anion Transporting Polypeptide; PD: Pharmacodynamic; P-gp: P-glycoprotein; PK: Pharmacokinetics; QD: Once Daily; QTc: Corrected QT; U: Unknown/Unreported; UGT1A1: UDP-Glucuronosyltransferase 1A1; W: White.

The primary safety data pertinent to this RMP and in support of the proposed indication for the belumosudil marketing authorization (MA) application is based on the sponsor's Phase 2/2A clinical studies (KD025-208 [ACT17631] and KD025-213 [DRI17633]) and the LTE of these parent studies (KD025-217 [LTS17660]) in participants with cGVHD. The parent studies were completed, and the LTE study was ongoing as of the cutoff date for the RMP (29 January 2024). The Phase 2 study BN101-201 in Chinese patients and the Phase 3 study ME3208-2 in Japanese patients with cGVHD provide supplementary data on the efficacy and safety of belumosudil in the treatment of cGVHD in patients who failed prior lines of cGVHD treatment.

Total of 209 patients with cGVHD who were enrolled in clinical studies and exposed to belumosudil are included in the safety set. The belumosudil exposure is present in the tables below (Tables 9 to 12), focusing on the parameters of interest for the RMP.

- Duration of exposure (Table 9)
- Exposure by age group and gender (Table 10)

- Exposure by dose (Table 11)
- Exposure by ethnic origin (Table 12)

The overall description of the clinical program for belumosudil pertinent to this RMP is provided in the eCTD Module 2.5 (Clinical Overview), Module 2.7.4 (Summary of Clinical Safety) and Integrated Summary of Safety. In order to complement the exposure information, the exposure data of the two supportive studies BN101-201 and ME3208-2 are added to this section (Table 13 and Table 14).

Table 9 - Duration of exposure (studies KD025-208, KD025-213 and KD025-217) (Safety Population)

Cumulative for cGVHD		
Duration of exposure (at least)	**Patients n (%)**	**Person-time (month)**
<1 m	8 (3.8)	5.49
1 to <3 m	33 (15.8)	69.45
3 to <6 m	36 (17.2)	163.58
≥6 m etc.	132 (63.2)	2956.42
Total person time		3194.94

Program Source: P:\01_OngoingProjects\G_100_HEM_KD025_CGVHD_IDB_SA\EMA\Programs\TFL\Original\ISS\t_1_eurmp .sas
cGVHD: Chronic Graft-Versus-Host Disease; m: Month; n: Number of Applicable Subjects.

Table 10 - Exposure by age group and gender (studies KD025-208, KD025-213 and KD025-217) (Safety Population)

Cumulative for cGVHD				
Age group	**Patients n (%)**		**Person-time (month)**	
	M	**F**	**M**	**F**
Adolescents (12 to 17 years)	2 (1.6)	1 (1.1)	31.24	8.05
Adults (18 to 64 years)	97 (79.5)	58 (66.7)	1728.53	742.47
Elderly people	23 (18.9)	28 (32.2)	267.14	417.51
Elderly people (65-74 years)	20 (16.4	25 (28.7)	224.79	353.48
Elderly people (75-84 years	3 (2.5)	3 (3.4)	42.35	64.03
Elderly people (85 years and more)	0	0		
Total	122 (100.0)	87 (100.0)	2026.91	1168.03

Program Source: P:\01_OngoingProjects\G_100_HEM_KD025_CGVHD_IDB_SA\EMA\Programs\TFL\Original\ISS\t_3_eurmp .sas
cGVHD: Chronic Graft-Versus-Host Disease; F: Female; M: Male; n: Number of Applicable Subjects.

Table 11 - Exposure by dose (studies KD025-208, KD025-213 and KD025-217) (Safety Population)

Cumulative for cGVHD		
Dose of exposure	**Patients n (%)**	**Person-time (month)**
KD025 200 mg QD	96 (45.9)	1503.05
KD025 200 mg BID	92 (44.0)	1398.64
KD025 400 mg QD	21 (10.0)	293.26
Total	209 (100.0)	3194.94

Program Source: P:\01_OngoingProjects\G_100_HEM_KD025_CGVHD_IDB_SA\EMA\Programs\TFL\Original\ISS\t_5_eurmp .sas
BID: Twice Daily; cGVHD: Chronic Graft-Versus-Host Disease; n: Number of Applicable Subjects; QD: Once Daily.

Table 12 - Exposure by ethnic origin (studies KD025-208, KD025-213 and KD025-217) (Safety Population)

Cumulative for cGVHD		
Ethnic origin	**Patients n (%)**	**Person-time (month)**
HISPANIC OR LATINO	26 (12.4)	513.38
NOT HISPANIC OR LATINO	179 (85.6)	2627.45
NOT REPORTED	3 (1.4)	45.14
UNKNOWN	1 (0.5)	8.97
Total	209 (100.0)	3194.94

Program Source: P:\01_OngoingProjects\G_100_HEM_KD025_CGVHD_IDB_SA\EMA\Programs\TFL\Original\ISS\t_7_eurmp .sas
cGVHD: Chronic Graft-Versus-Host Disease; n: Number of Applicable Subjects.

Supportive studies:

The exposure data of the two supportive studies BN101-201 and ME3208-2 are presented in Table 13 and Table 14.

Table 13 - Drug exposure and compliance for study BN101-201

	Overall (N = 30)
Drug exposure duration (months)	
n	30
Mean (standard deviation)	9.86 (5.52)
Median	10.25
Min, max	0.5, 18.4
Classification of drug exposure duration, n (%)	
0-3 months	5 (16.7%)
3-6 months	4 (13.3%)
6-9 months	4 (13.3%)

	Overall (N = 30)
Cumulative exposure (person-years)	24.64
Follow-up duration (months)	
n	30
Mean (standard deviation)	13.22 (3.66)
Median	12.94
Min, max	1.7, 18.4
Classification of follow-up duration (months)	
0-3 months	1 (3.3%)
3-6 months	0
6-9 months	2 (6.7%)
> 9 months	27 (90.0%)
Actual cumulative dose (mg)	
n	30
Mean (standard deviation)	59 377 (33 437)
Median	61 300
Min, max	3200, 110 800
Actual dose intensity (ADI) (mg/day)	
n	30
Mean (standard deviation)	197.76 (3.87)
Median	198.90
Min, max	182.1, 200.0
Relative dose intensity (RDI) (%)	
n	30
Mean (standard deviation)	98.88 (1.93)
Median	99.45
Min, max	91.1, 100.0
Classification of relative dose intensity (RDI), n (%)	
>95%	28 (93.3%)
≤95%	2 (6.7%)

The percentages were calculated using the number of subjects in the mITT population as the denominator.
ADI: Actual Dose Intensity; Max: Maximum; Min: Minimum; mITT: Modified Intent-To-Treat; N: Number of Subjects Evaluated; n: Number of Applicable Subjects; RDI: Relative Dose Intensity.

Table 14 - Drug exposure in study ME3208-2

	200 mg QD N = 21
Treatment duration (months)	
n	21
Mean	12.96
SD	3.59
Median	13.80
Q1, Q3	11.10, 16.40
Min, Max	3.5, 19.5
Treatment duration categories- n (%)	
0 to 6 months	1 (4.8)
6 to 12 months	7 (33.3)
12 to 18 months	12 (57.1)
18 to 24 months	1 (4.8)
≥ 24 months	0
Treatment ongoing - n (%)	15 (71.4)
Cumulative duration (patient-years)	22.7
Duration of follow up (months)	
n	21
Mean	13.60
SD	3.30
Median	13.80
Q1, Q3	11.30, 16.50
Min, Max	4.3, 19.5
Duration of follow up categories- n (%)	
0 to 6 months	1 (4.8)
6 to 12 months	6 (28.6)
12 to 18 months	13 (61.9)
18 to 24 months	1 (4.8)
≥ 24 months	0
Study ongoing - n (%)	19 (90.5)
Actual cumulative dose (mg)	
n	21
Mean	7 7933.3
SD	2 1769.1
Median	8 0000.0

	200 mg QD **N = 21**
Q1, Q3	6 7400.0, 97200.0
Min, Max	2 1200, 11 8600
Actual dose intensity (mg/day)	
n	21
Mean	197.41
SD	2.80
Median	198.10
Q1, Q3	196.70, 199.50
Min, Max	190.0, 200.0
Relative dose intensity (%)	
n	21
Mean	98.71
SD	1.41
Median	99.10
Q1, Q3	98.30, 99.80
Min, Max	95.0, 100.0
Relative dose intensity - n (%)	
> 95%	20 (95.2)
≤ 95%	1 (4.8)

(Data cut-off date: 10 Aug 2023), mITT population
% = n/N × 100
mITT: Modified Intent-To-Treat; N: Number of Subjects Evaluated; n: Number of Applicable Subjects; Q: Quarter; QD: Once Daily; SD: Standard Deviation.

RISK MANAGEMENT PLAN - PART II MODULE SIV: POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 EXCLUSION CRITERIA IN PIVOTAL CLINICAL STUDIES WITHIN THE DEVELOPMENT PROGRAM

The key exclusion criteria presented below are based on the exclusion/inclusion criteria used in studies KD025-208, KD025-213, KD025-217 and KD025-218 conducted in subjects with cGVHD.

Table 15 - Important exclusion criteria in pivotal studies in the development program

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Patients with hepatic impairment (ALT or aspartate aminotransferase (AST) >3 × upper limit of normal (ULN) and total bilirubin >1.5 × ULN)	This exclusion criterion was established to minimize the potential confounding factors for evaluation of the efficacy and safety of belumosudil. Metabolism is likely the main path of elimination of belumosudil clearance with more than 85% of total radioactivity excreted in feces in human mass balance study (unchanged compound contributing for 30% and the sum of identified metabolites for 60%).	No	A Phase 1, open-label, non-randomized, parallel-group study to determine the effect of hepatic impairment on the PK, safety, and tolerability of a single oral dose of KD025 compared to matched healthy subjects with normal hepatic function, conducted in 36 subjects, showed a statistically significant increase in belumosudil exposure (based on AUCs) in subjects with severe hepatic impairment compared with subjects with normal hepatic function. Use in patients with severe hepatic impairment (Child-Pugh C) without liver GVHD is contraindicated. Use in patients with moderate hepatic impairment (Child-Pugh B) without liver GVHD is not recommended. No dose adjustment is recommended when administering belumosudil to patients with mild hepatic impairment (Child-Pugh A).
Patients with severe renal impairment (glomerular filtration rate [GFR] <30 mL/min/1.73 m^2)	This exclusion criterion was established to minimize the potential confounding factors for evaluation of the efficacy and safety of belumosudil.	No	Belumosudil is only minimally excreted via the kidney (<10%). A population PK analysis of belumosudil in 186 subjects including 33 subjects with moderate

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
			renal impairment and 87 subjects with mild renal impairment showed that mild to moderate renal impairment did not have meaningful effects on the PK of belumosudil. Considering the minimal role of kidneys in the excretion of belumosudil, the safety profile of belumosudil is not expected to differ in patients with renal impairment, including severe impairment.
Patients with platelets <50 × 10^9/L and/or absolute neutrophil count <1.5 × 10^9/L	These exclusion criteria were established to minimize the potential confounding factors for evaluation of the efficacy and safety of belumosudil.	No	The safety profile of belumosudil is not expected to differ in this patient sub-population compared to the general safety profile seen in the belumosudil development program.
Patients with QT interval corrected for heart rate using Fridericia's formula >480 ms	These exclusion criteria were established to minimize the potential confounding factors for evaluation of the efficacy and safety of belumosudil.	No	Clinical and non-clinical studies, including the Thorough QT/QTc study KD025-110, confirmed no clinically relevant effects on studied parameters.
Patients who have a forced expiratory volume (in the first second) $\leq$39% or a lung score of 3	These exclusion criteria were established to minimize the potential confounding factors for evaluation of the efficacy and safety of belumosudil.	No	The safety profile of belumosudil is not expected to differ in this patient sub population compared to the general safety profile seen in the belumosudil development program.
Patients diagnosed with another malignancy (other than the malignancy for which allogeneic HCT was performed) within 3 years prior to enrolment	These exclusion criteria were established to minimize the potential confounding factors for evaluation of the efficacy and safety of belumosudil.	No	The safety profile of belumosudil is not expected to differ in this patient sub population compared to the general safety profile seen in the belumosudil development program.
Patients with known active hepatitis B or hepatitis C viral infection or a history of human immunodeficiency virus (HIV)	These exclusion criteria were established to minimize the potential confounding factors for evaluation of the efficacy and safety of belumosudil.	No	The safety profile of belumosudil is not expected to differ in this patient sub population compared to the general safety profile seen in the belumosudil development program.

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Pregnant or breastfeeding women	These criteria represent standard ethical measures. In addition, belumosudil showed teratogenic and embryotoxic effects in the non-clinical studies (refer to [Part II Module SVII]), a finding of unknown relevance to human use, however, supported by the literature about ROCK inhibitors. (22)(23)(24)	No	As per the Section 4.3 of the SmPC, the use in "pregnancy and breastfeeding" is contraindicated. As per Section 4.4 of the SmPC, women of childbearing potential must have their pregnancy status verified prior to initiating treatment with belumosudil and must use highly effective contraception during treatment with belumosudil and for at least one week after the last dose of belumosudil. In case pregnancy should occur during treatment, a risk/benefit evaluation must be carried out on an individual basis with careful counselling regarding potential risks to the fetus. Patient must be informed of the potential hazard to the fetus. Breast-feeding should be discontinued during treatment and for at least one week after the last dose of belumosudil.

ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; AUC: Area Under the Plasma Concentration-Time Curve; GFR: Glomerular Filtration Rate; GVHD: Graft Versus Host Disease; HCT: Hematopoietic Cell Transplantation; HIV: Human Immunodeficiency Virus; PK: Pharmacokinetics; QTc: Corrected QT; ROCK: Rho-Associated Coiled-Coil containing Protein Kinase; SmPC: Summary of Product Characteristics; ULN: Upper Limit of Normal.

SIV.2 LIMITATIONS TO DETECT ADVERSE REACTIONS IN CLINICAL TRIAL DEVELOPMENT PROGRAMS

Due to the low prevalence of cGVHD, which led to an orphan drug designation for belumosudil in the US, the clinical development program for belumosudil included a limited number of subjects. As such, it is unlikely that infrequent adverse reactions will be detected during the clinical development program. Furthermore, it is unlikely that certain types of adverse reactions such as rare or very rare adverse reactions, adverse reactions with a long latency, or adverse reactions caused by prolonged or cumulative exposure are detected.

SIV.3 LIMITATIONS IN RESPECT TO POPULATIONS TYPICALLY UNDER-REPRESENTED IN CLINICAL TRIAL DEVELOPMENT PROGRAMS

Table 16 - Exposure of special populations included or not in clinical trial development programs

Type of special population	Exposure
Pregnant women	Not included in the clinical development program.
Breastfeeding women	Not included in the clinical development program.
Patients with relevant comorbidities • Patients with hepatic impairment	Patients with hepatic impairment (defined as ALT and AST >3 × ULN and total bilirubin >1.5 × ULN) were excluded from the clinical development program. The majority of subjects with cGVHD had a normal hepatic function (142 of 209; 67.9%); 66 subjects (31.6%) had a hepatic function above the ULN. Given the difference in sample size, any apparent differences in incidence across the subgroups should be evaluated with caution.
• Patients with renal impairment	Patients with severe renal impairment (GFR <30 mL/min/1.73 m^2) were excluded from the clinical development program. A population PK analysis of belumosudil in 209 subjects with cGVHD included 39 subjects with moderate renal impairment and 98 subjects with mild renal impairment.
• Patients with a disease severity different from inclusion criteria in clinical trials	Not applicable The majority of subjects with cGVHD had severe cGVHD at screening (149 of 209; 71.3%).
Population with relevant different ethnic origin	The majority of subjects with cGVHD were White or Caucasian (182 of 209; 87.1%); 27 subjects (12.9%) were non-White/Caucasian (including 11 Black Americans, 4 American Indians, 4 Asians, 7 unreported and 1 other). In addition, 110 subjects of Asian race were also enrolled (subjects with cGVHD and healthy volunteers) in studies ME3208-01, ME3208-2, BN101-101 and BN101-201. Given the difference in sample size, any apparent differences in incidence across the race subgroups should be evaluated with caution.
Sub-populations carrying relevant genetic polymorphism	Not applicable
Other: • **Children between 1 and 12 years of age** • **Elderly patients**	A limited number of children below 12 years of age (21 subjects) has been exposed to belumosudil post-approval in the postmarketing setting and under compassionate use at the DLP. A clinical study, DFI17893, is planned to start in quarter 1 2025 and will include patients between 1 and 12 years. Fifty-one of 209 subjects in total included in the clinical studies were elderly; 24.4% are ≥65 years of age, of which 6 patients were ≥75 years of age.

ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; cGVHD: Chronic Graft-Versus-Host Disease; DLP: Data Lock Point; GFR: Glomerular Filtration Rate; PK: Pharmacokinetics; ULN: Upper Limit of Normal.

No data are available concerning the use of belumosudil in pregnant or breastfeeding women. However, pregnant and breastfeeding women are not part of the target population, considering the teratogenic and embryotoxic effects of belumosudil noted in non-clinical studies.

To date, there is no information to suggest that patients of specific racial or ethnic origins are adversely affected by belumosudil.

The clinical study KD025-218 is currently ongoing and will provide information about the efficacy and safety in populations with different ethnic origins.

RISK MANAGEMENT PLAN - PART II MODULE SV: POST-AUTHORIZATION EXPERIENCE

SV.1 POST-AUTHORIZATION EXPOSURE

The MAH is currently utilizing the Margin Consolidated (MARCO) application for reporting sales data from postmarketing experience for the period from 01 April 2022 through 31 January 2024. No sales data were reported before 01 April 2022. The MARCO application collects data monthly, and as a result, the data may not correspond precisely to the current reporting interval.

SV.1.1 Method used to calculate exposure

- The World Health Organization (WHO) defined daily dose (DDD) is not available for belumosudil therefore, the MAH considered a mean daily dose of one tablet [1] for belumosudil.
- Total number of tablets sold were divided by the mean daily dose to calculate total treatment days (ie, the total treatment days are equivalent to the sales of tablets).

SV.1.2 Exposure

Exposure from the cumulative postmarketing experience is available for the period from 01 November 2021[2] through 31 January 2024.

The cumulative exposure to belumosudil was estimated to be 1 370 312 treatment days [3] [4]. There were no sales in [redacted] up until 31 January 2024. No sales data from partner Meiji was available as the product was not marketed in the partner territory. In addition, no sales data was available from partner BioNova during the reporting period.

Detailed usage data are not available therefore presentation of patient exposure by age, sex, and indication is not possible. Consequently, it is only presented by country and formulation.

[1] The number is an approximation assuming patients are taking one 200 mg tablet of belumosudil QD since there is currently no WHO DDD for this product. There could be a possibility of variation in the dosing of belumosudil (200 mg QD or 200 mg BID as per the product information).

[2] No sales were reported before 01 November 2021.

[3] There are compassionate use programs in Austria, Bulgaria, Croatia, Czech Republic, Finland, Greece, Hungary, Italy, Lithuania, Netherlands, Poland, and Sweden, but exposure numbers are not available as they are distributed by an external vendor.

[4] There are compassionate use programs in Hong Kong, Réunion (French Overseas department and territories), France, and Spain which are included in the MARCO database.

RISK MANAGEMENT PLAN - PART II MODULE SVI: ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

SVI.1 Potential for misuse for illegal purposes

The properties of belumosudil do not indicate a potential for misuse for illegal purposes.

A drug abuse liability assessment (DALA) study was not performed with belumosudil as the compound has no or only a limited ability to cross the blood-brain barrier with negligible exposure in the brain, and belumosudil has shown no propensity for eliciting any neurological effects in toxicology studies. The potential for misuse of belumosudil for illegal purposes is considered low as this product is not known to have attributes such as known pharmacological addictive effects that make it a candidate for intentional overdose, abuse, or illegal use.

Based on the mechanism of action, the potential for misuse for illegal purposes is considered negligible.

RISK MANAGEMENT PLAN - PART II MODULE SVII: IDENTIFIED AND POTENTIAL RISKS

SVII.1 IDENTIFICATION OF SAFETY CONCERNS IN THE INITIAL RMP SUBMISSION

Following the evaluation of the RMP v1.0, RMP v1.1 and RMP v1.2 by CHMP and PRAC (procedure EMEA/H/C/006421), the List of Safety Concerns has been revised, as described in sections [SVII.1.1], [SVII.1.2] and [SVII.2].

The following safety topics will be discussed in this section and will be presented in Section SVII.1.1 as risks or safety topics that are not considered important for inclusion in the list of safety concerns in the RMP:

- Liver function tests elevations,
- Gastrointestinal effects,
- Hematologic events (anemia, neutropenia, leukopenia, and thrombocytopenia),
- Impaired male fertility,
- Impaired wound healing,
- Potential harm for overdose,
- Potential for risks resulting from medication errors,
- Potential for transmission of infectious agent,
- Potential for off label use,
- Pharmacological class effect,
- Important risks related to identified or potential PK and pharmacodynamic interactions,
- Risks associated with the disposal of the used product,
- Risks related to the administration procedure,
- Paediatric safety issues,
- Infections,
- Embryofoetal toxicity and teratogenicity,
- Malignancy (secondary neoplasm and /or relapse of the underlying malignancy).

The following safety topics will be discussed in this section and will be presented in Section SVII.1.2 as the risks are considered important for inclusion in the list of safety concerns in the RMP:

- Important identified risk:
  - None
- Important potential risk:

- None Missing Information:
  - None

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Reason(s) for not including an identified or potential risk in the list of safety concerns in the RMP

- Risks considered acceptable (in relation to the severity of the indication treated) or which do not impact the benefit-risk profile:
  - **Liver function tests elevations**

    Liver function test elevations, including elevations in ALT, AST, GGT, blood ALP, and increased bilirubin levels were frequently reported in the belumosudil clinical development program. As such, increased LFTs represent a non-important identified risk of belumosudil.

    Since the majority of events were asymptomatic, mild, and transient increases in LFTs in the belumosudil clinical development program and their causative link to belumosudil has not been established due to the presence of confounding factors (eg, underlying cGVHD affecting the liver, concomitant medication), these effects represent a non-important risk of belumosudil. A search of the global pharmacovigilance database for postmarketing reports received since the first MA for belumosudil (16 July 2021) until the DLP (29 January 2024) was performed utilizing the Medical Dictionary for Regulatory Activities (MedDRA) (version 26.1) Standardized MedDRA Query (SMQ) Liver related investigations, signs and symptoms.

    Cumulatively, 113 events of increased liver enzymes were reported, 19 were serious.

    The most frequently reported events by preferred term (PT) were Hepatic enzyme increased (42 events), LFT increased (14 events), Hepatic enzyme abnormal (9 events), AST increased (8 events), Blood bilirubin increased, and Blood ALP increased (7 events each), and Hepatic function abnormal, ALT increased, and LFT abnormal (6 events each).

    The outcome of the events in most cases is unknown (67 events).

    The increase of LFTs could be indicative of a liver injury. “Drug-induced liver injury” is assessed through routine pharmacovigilance practices including the use of signal detection methods and reporting in Periodic Benefit Risk Evaluation Report (PBRER)s, if applicable, which are valuable methods for safety monitoring. The use of follow-up questionnaire, if applicable, for reports of “drug induced liver injury” will complement this evaluation. The proposed label includes a table with recommended dose modification in Section 4.2 and mentions hepatotoxicity in Section 4.4 of the SmPC; this might provide an adequate level of minimization through routine minimization measures. Furthermore, monitoring of LFTs represents a standard clinical practice in HCT recipients. LFTs should be obtained prior to the initiation of treatment with belumosudil in order to establish the patient’s baseline values. Total bilirubin, AST, and ALT should be monitored during treatment with belumosudil at least at one-month intervals. If Grade 3 ALT or AST increase (defined as >5 to 20 × ULN) or Grade 2

bilirubin increase (defined as >1.5 to 3 × ULN) occur, belumosudil treatment should be interrupted until recovered to Grade ≤1. Treatment with belumosudil should be permanently discontinued in case of Grade 4 ALT or AST increases (>20 × ULN), or Grade ≥3 bilirubin increase (>3 × ULN).

Consequently, Drug Induced Liver Injury (DILI) is considered sufficiently characterized through postmarketing evaluation and clinical studies. The robust, ongoing routine pharmacovigilance program will continue to adequately to assess this risk, without the need for further additional pharmacovigilance.

"Liver function tests elevations" is retained as a non-important risk (Section SVII.1.1),

- **Gastrointestinal effects**

Various treatment-related gastrointestinal TEAEs were commonly reported in subjects with cGVHD included in the belumosudil clinical program.

In study participants with cGVHD (N=209), the most commonly reported gastrointestinal events (≥10% of all belumosudil-treated subjects) included diarrhea (36.8%; 77/209), nausea (32.1%; 67/209), vomiting (21.1%; 44/209), abdominal pain (15.3%; 32/209), dysphagia (12.0%; 25/209), and constipation (11.0%; 23/209). The reported events were mainly Grade 1 or 2 in severity.

Treatment-related TEAEs of diarrhea, nausea, and vomiting led to treatment interruption in 1.9% subjects each (4/209) and only nausea led to discontinuation of belumosudil in more than 1 subject (1.0%; 2/209) of all belumosudil-treated subjects with cGVHD.

In rat and dog toxicology studies, adverse findings included decreased food consumption which correlated with decreases in body weight gain and/or loss. Additionally, infrequent emesis was observed in dogs (refer to [Part II Module SII]).

A search of the global pharmacovigilance database for postmarketing reports received since the first MA for belumosudil (16 July 2021) until the DLP (29 January 2024) was performed utilizing the MedDRA (version 26.1) SMQs "Gastrointestinal nonspecific inflammation and dysfunctional conditions" (broad) and "Gastrointestinal perforation, ulceration, hemorrhage or obstruction" (broad).

Cumulatively, 49 events were reported in 44 cases, most of which were non-serious (36 events) and reported by consumers (25 cases).

The most frequently reported events were Nausea (15), Diarrhea (8), Gastrointestinal hemorrhage (6), and Abdominal pain/ Abdominal pain upper (4 and 2 events, respectively).

The outcome of the event in most cases is unknown (35 events) and was fatal in two cases. Of the two fatal cases, one case had limited information provided and reported gastrointestinal hemorrhage, however, the cause of death was not reported. In the second case the patient reported hematemesis, the cause of death was reported as pneumonia, aspergilloma, pulmonary infarction.

Considering the underlying disease, which represents a main confounding factor for gastrointestinal findings and a minimal impact of these events on the intended target population, this risk is considered non-important for the RMP.

This risk is monitored via routine pharmacovigilance activities.

- **Hematologic events (anemia, neutropenia, leukopenia, and thrombocytopenia)**

  Mild anemia with regeneration, lymphoid depletion in the thymus, and lymphoid depletion (dog) were observed in the non-clinical program at belumosudil exposure levels in the range of those anticipated at the highest clinical dose/exposure (refer to [Part II Module SII]).

  Hematologic AEs, including anemia, neutropenia, leukopenia, and thrombocytopenia, were commonly reported in the belumosudil clinical development program in subjects with cGVHD. The incidence of hematologic TEAEs was 20.1% (42 of 209) in all belumosudil-treated subjects. The majority of events were anemia reported in 28 subjects of 209 (13.4% in the in all belumosudil-treated subjects).

  The majority of hematologic events were mild or moderate with a limited number of Grade ≥3 events. There were no Grade 5 events.

  The causative link between hematologic events and infections, which were also observed in the belumosudil clinical development program, has not been established and no clinical outcomes of hematologic AEs potentially associated with belumosudil were observed.

  A search of the global pharmacovigilance database for postmarketing reports received since the first MA for belumosudil (16 July 2021) until the DLP (29 January 2024) was performed utilizing the MedDRA (version 26.1) SMQ “Hematopoietic cytopenias” (broad).

  Cumulatively, 150 events were reported in 118 cases, the majority being non-serious (104 events).

  The most frequently reported events by PT are Hemoglobin decreased (28 events), Platelet count decreased (26 events), White blood cell count decreased (19 events), Cytopenia (18 events), and anemia (13 events).

  The outcome of the event in most cases is unknown (81); 3 patients died but the cause of in none of these cases was related to events included in the SMQ.

  Considering the presence of multiple confounding factors and the minimal impact of reported events on the intended target population for belumosudil, this risk is considered non-important for the RMP and is monitored via routine pharmacovigilance activities.

- **Impaired male fertility**

  In the non-clinical program, belumosudil-related testicular adverse effects at clinically relevant exposures were observed in the 3-month dog toxicity study at doses of ≥35 mg/kg/day and in the 6-month rat toxicity study at doses ≥50 mg/kg/day. Findings consisted of minimal to mild, multifocal, unilateral, or bilateral degeneration of spermatogenic elements of the seminiferous tubules, reversible in dog and partially reversible in rats in a study setting with an insufficient recovery-phase duration, which was shorter than a spermatogenesis cycle.

  The fertility study in rats, which was of a shorter treatment duration (70 days), showed that belumosudil administered to male rats resulted in impaired male fertility only at the highest dose tested (275 mg base/kg). Reversibility of all functional parameters during a

recovery-phase of a 1.4-fold duration of the spermatogenic cycle was determined, but complete morphological reversibility has not been confirmed (refer to [Part II Module SII]).

A search of the global pharmacovigilance database for postmarketing reports received since the first MA for belumosudil (16 July 2021) until the DLP (29 January 2024) was performed utilizing the MedDRA (version 26.1) SMQ Fertility disorders.

No cases of impaired male fertility were reported from postmarketing experience.

Considering the potential reversibility of these effects, the intended target population and multiple factors that may impact fertility, this risk is considered non-important for the RMP and is monitored via routine pharmacovigilance activities.

- **Impaired wound healing**

Impaired would healing represents a potential risk based on the role of ROCK inhibition in collagen production. (26)

Few events with the MedDRA high level term (HLT) Healing abnormal not elsewhere classified (NEC) were reported in the clinical program for belumosudil, including 1 (0.5%) subject with cGVHD who reported a Grade 1 event of impaired healing within the first month of treatment with belumosudil (200 mg QD), assessed as not related to belumosudil.

A search of the global pharmacovigilance database for postmarketing reports received since the first MA for belumosudil (16 July 2021) until the DLP (29 January 2024) was performed utilizing the MedDRA (version 26.1) HLT healing abnormal NEC.

Cumulatively, 5 events of Impaired healing (PT) were reported, 4 of which were serious. In 2 cases limited information was provided, the other 3 cases were confounded by a medical history of impaired wound healing, cancer treatment, high international normalized ratio (INR), or previous surgery.

Considering the minimal impact of this risk on the intended target population for belumosudil in view of confounding factors for impaired wound healing (eg, underlying cGVHD, corticosteroid use), this risk is considered non-important for the RMP and is monitored via routine pharmacovigilance activities.

- **Infections**

In subjects with cGVHD (N = 209), the most frequently reported infections in all belumosudil-treated subjects were respiratory infections, common in patients with cGVHD, including upper respiratory tract infection (67 subjects; 32.1%), pneumonia (27 subjects; 12.9%) and influenza (14 subjects; 6.7%). Overall, the reported infections were mainly mild to moderate in severity with Grade ≥3 events reported in 22.0% of subjects. The majority was assessed as not related to belumosudil, resolved with appropriate treatment, and did not frequently lead to treatment discontinuation.

No infection safety signals are reported to have been raised from the postmarketing safety data.

Infections represent a major cause of morbidity and mortality in patients after allogeneic HCT. (27) Infections in an immunosuppressed patient population can be life threatening, potentially leading to fatal outcomes if not recognized early and appropriately treated.

Belumosudil is a small molecular kinase inhibitor with immune modulating properties. Since belumosudil is not a typical immunosuppressive drug, its contribution to the incidence of infections in the treated population remains unknown and the current impact on the benefit-risk balance of belumosudil is considered acceptable. The target patient population presents with multiple confounding factors for the development of infections, including long-term corticosteroid therapy or the use of other immunosuppressants, including tacrolimus.

A causative link between belumosudil treatment and/or an increased incidence of infections has not been established, considering the presence of confounding factors for the development of infections in patients with cGVHD, including the use of corticosteroids and other immunosuppressants.

The current impact on the benefit-risk balance of belumosudil is considered acceptable. Patients with cGVHD treated with multiple immunosuppressive drugs are at higher risk of infections in general.

The assessment of infections is ensured through routine pharmacovigilance practices including the use of signal detection methods, reporting in PBRERs and adverse reactions of special interest in clinical trials. These methods are demonstrated to be valuable for the safety monitoring. It is considered that additional Pharmacovigilance activities would not be of added value to characterize infections.

The clinicians treating this patient population are aware about the risk of infections and patients are routinely monitored. Prophylactic (antibiotic, antifungal, antiviral) treatment and vaccinations are administered according to standard practice in transplant recipients. The routine minimization consisting of labeling measures are considered sufficient to mitigate the risk of infection.

The potential risk “infections” is considered sufficiently characterized through postmarketing and clinical studies. The robust, ongoing routine pharmacovigilance program will continue to adequately assess this risk, without the need for further additional pharmacovigilance. The routine minimization measures through labeling are appropriate to mitigate this risk. This aligns with the definitions of the Guidelines on GVP Module V - Risk management systems (Rev 2).

- **Embryofoetal toxicity and teratogenicity:**

In the nonclinical program, belumosudil has demonstrated a potential for embryofoetal toxicity and/or malformations at clinically relevant exposures. In humans, no pregnancies have been reported in clinical studies or during postmarketing experience. In the absence of comprehensive data, it is not possible to ascertain the actual level of impact on the benefit risk balance of belumosudil, which is currently considered acceptable, taking into account the severity of the target disease.

This risk is adequately minimized through routine minimization measures. The applicant has updated the SmPC with the addition of a contraindication for “pregnancy and breastfeeding”.

As per Section 4.4 of the SmPC, women of childbearing potential must have their pregnancy status verified prior to initiating treatment with belumosudil and must use

highly effective contraception during treatment with belumosudil and for at least one week after the last dose of belumosudil.

In case pregnancy should occur during treatment with belumosudil, a risk/benefit evaluation must be carried out on an individual basis with careful counselling regarding potential risks to the fetus (see Section 4.6). Patients must be informed of the potential hazard to the fetus. Breast-feeding should be discontinued during treatment and for at least one week after the last dose of belumosudil.

- **Malignancy (secondary neoplasm and /or relapse of the underlying malignancy):**

In patients with cGVHD (N = 209), 31 (14.8%) reported events within the SOC Neoplasms benign, malignant and unspecified. This SOC was used to identify secondary neoplasms. Neoplasms occurred sporadically over time, suggesting no cumulative toxicity of belumosudil. 14 (45.2%) of the 31 events are of Grade ≥3 severity.

Postmarketing experience:

A search of the global pharmacovigilance database for postmarketing reports received since the first MA for belumosudil (16 July 2021) until the DLP (29 January 2024) was performed utilizing the MedDRA (version 26.1) SOC Neoplasms benign, malignant and unspecified (incl cysts and polyps).

Cumulatively, 59 events were reported in 50 cases. The most frequently reported events were from the High Level Group Term (HLGT) Skin neoplasms malignant and unspecified (17 events), followed by HLGTs Leukemias (15 events), Gastrointestinal neoplasms malignant and unspecified (9 events), and Miscellaneous and site unspecified neoplasms malignant and unspecified (7 events).

The most frequently reported malignancy by PT within the HLGT Skin neoplasms malignant and unspecified were Skin cancer (7 events), and Basal cell carcinoma (5 events). Two events respectively of Squamous cell carcinoma of skin and Neoplasm skin were reported.

Within the HLGT Leukemias, 8 events of recurrence (Leukemia recurrent/ Acute lymphocytic leukemia recurrent/ Acute Myeloid Leukemia (AML) recurrent) were reported, the remaining 7 events were AML/ Leukemia/ Myelodysplastic syndrome/ Acute leukemia.

Within the HLGT Gastrointestinal neoplasms malignant and unspecified, the most frequently reported events (3 events both) were Esophageal carcinoma and Lip squamous cell carcinoma.

Within the HLGT Miscellaneous and site unspecified neoplasms malignant and unspecified, 3 events of Squamous cell carcinoma were most frequently reported.

With the exception of Squamous cell carcinoma of skin, Neoplasm skin and Neoplasm malignant (3 events reported for each malignancy), other malignancies were single events. The outcome of the majority of events is unknown; 4 events had a fatal outcome.

One fatal case was reported in the literature report and is also presented in the postmarketing section of drug-induced liver injury. It concerned a [redacted]

[redacted] with AML who had undergone HSCT 30 months before presentation. [redacted] developed multisystem cGVHD refractory to systemic glucocorticoids and 9 months of ruxolitinib. Ten months before presentation, [redacted] started belumosudil 200 mg daily. Seven months after [redacted] had started taking belumosudil, [redacted] underwent Mohs excision at a local clinic for cutaneous squamous-cell carcinoma of the mid-parietal scalp. Within 3 months, the lesion had recurred. A course of treatment with low dose cemiplimab (an anti-PD1 drug) was initiated. Because of the known risk of cemiplimab exacerbating GVHD, [redacted] continued to take belumosudil and started a prednisone taper. Three weeks later, [redacted] was admitted for liver failure caused by immunotherapy-induced liver injury or a GVHD flare. Despite receiving treatment with belumosudil and high dose prednisone, [redacted] died 2 weeks later from sequelae of liver failure. (28)

Two patients died due to Leukemia recurrent, one patient due to AML, but insufficient clinical details were provided. No safety signals of secondary malignancies have been identified from the postmarketing safety data.

Belumosudil as a small molecular kinase inhibitor with immune modulating properties may increase the risk of malignancies, either recurrent or secondary, in treated patients. Patients with cGVHD included in the clinical program for belumosudil reported neoplasms confounded by their primary malignancy requiring HCT and long-term immunosuppression. HCT recipients are in general at an increased risk of secondary malignancies in comparison with the general population (29) (30) (31), and the recurrence of the underlying malignancy is common. (32)

The relevance of the findings related to belumosudil treatment remains to be elucidated. However, there is currently no evidence that could link belumosudil treatment to the onset of malignancies, either secondary neoplasms or recurrence of the primary malignancy.

Chronic GVHD has also shown an association with the development of secondary malignancies, particularly squamous cell carcinomas, specifically in the head and neck region. In individuals with weakened immune systems, oncogenic viruses like human papillomavirus may contribute to the occurrence of squamous cell cancers in the skin and buccal mucosa. The underlying causes of the increased risk of squamous cell cancers in the buccal cavity and skin are not fully understood, but it could be attributed to the interaction between chronic lichen planus-like erosions, ionizing radiation, immunodeficiency, and possibly factors such as smoking or alcohol consumption. (33)

The current impact on the benefit-risk balance of belumosudil in a selected and previously heavily pre- and concurrently treated cGVHD is considered acceptable.

Additional Pharmacovigilance activities are thus not considered possible to characterize the risk “malignancy (secondary neoplasm and /or relapse of the underlying malignancy)”.

The following safety topics are not considered identified or potential risks for belumosudil:

- **Potential harm for overdose:**

  No instance of asymptomatic or symptomatic overdose has been observed in clinical studies. There is no specific experience in the management of an overdose of belumosudil in patients, and there is no known antidote. Single doses up to 1000 mg

have been administered to healthy volunteers with an acceptable tolerability. Thus, potential harm for overdose is not considered a risk for belumosudil.

No case of overdose is reported in the postmarketing setting.

- **Potential for risks resulting from medication error:**

  There are reports of medication errors of "Product use in unapproved indication" and "Inappropriate schedule of product administration" in the postmarketing setting

  Although belumosudil is indicated for the treatment of cGVHD, the indications for use reported in many cases are hematologic malignancies such as acute or chronic myeloid or lymphocytic leukemia, myelodysplastic syndrome, complications of bone marrow transplant, stem cell transplant and others, without providing information about the presence of cGVHD.

  Concerning the inappropriate schedule of product administration, patients report the use of belumosudil 200 mg BID or 400 mg QD without providing information on the concomitant use of strong CYP3A inducers or PPIs as per the reference product information. There also reports of patients taking 100 mg QD.

  There are no relevant safety findings on patterns of medication errors identified which would require specific risk minimization measures (RMMs) or additional pharmacovigilance activities. The available information does not change the overall benefit-risk evaluation of belumosudil. Medication errors are not considered a risk for belumosudil.

- **Potential for transmission of infectious agent:**

  As per the manufacturing process, which is carried out in accordance with the "EU Guidelines for Good Manufacturing Practice for Medicinal product for Human Use, Annex 1", there is no risk for transmission of infectious agents identified for belumosudil.

- **Potential for off-label use:**

  Reports of off-label use (product use in unapproved indication or unapproved age group) have been received. No relevant safety findings or patterns were identified which would require specific RMMs at this time.

- **Pharmacological class effect:**

  Rho-associated coiled coil containing protein kinases are members of the serine/threonine kinase family, often studied for their role in cell morphology, motility, and shape through effects on the cytoskeleton. Two ROCK isoforms have been identified, ROCK1 and ROCK2. (22) (34) (35) (36) While both are involved in Rho-mediated changes in the actin/myosin cytoskeletal network, ROCK1 and ROCK2 are not redundant signalling molecules and may serve different functions within cells. (37) (38) (39) Recent research has uncovered additional roles for ROCK signalling in conditions including autoimmune disease aggravated or caused by a Th17 polarized T cell response (27) and pulmonary fibrosis. (29) Rho guanosine triphosphate (GTP)ase-mediated signalling pathways play a central role in coordinating and balancing T cell mediated immune responses, including T cell receptor mediated signalling, cytoskeletal reorganization, and the acquisition of the appropriate T cell effector program. (40)

Besides belumosudil, 3 other approved ROCK inhibitors are approved.

Eril® (fasudil hydrochloride hydrate) (not approved in the EU) is a Rho-kinase inhibitor used to treat cerebral vasospasm and delayed cerebral ischemic symptoms after subarachnoid hemorrhage. The most common AEs (>5%) include myalgia, headache, insomnia, constipation, abnormal hepatic function, glutamic oxaloacetic transaminase (GOT) increased, sugar blood level increased, triglyceride increased, common cold syndrome, anemia, urinary occult blood positive, urinary tract infection, and fever. (36)

Glatetec® (ripasudil) (not approved in the EU) is a Rho-kinase inhibitor indicated for the treatment of ocular hypertension and open-angle glaucoma. The most common AEs (≥5%) are conjunctival hyperemia, conjunctivitis, blepharitis, and eye irritation. Other AEs (<5% and ≥0.1%) include corneal epithelial disorder, eye pruritus, abnormal sensation in eye, eye discharge, eye pain, conjunctival follicles, and intraocular pressure increased. (37)

Rhopressa®/Rhokiinsa® (netarsudil) (approved in the EU) is a Rho-kinase inhibitor indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension. The most common AEs are conjunctival hyperemia (53%), corneal verticillate, instillation site pain, and conjunctival hemorrhage. (38)

Important risks related to identified or potential PK and pharmacodynamic interactions:

- Co-administration of belumosudil with strong CYP3A inducers decreases belumosudil exposure, which may reduce the efficacy of belumosudil. Routine minimization measures (labeling) provide the appropriate recommendation to increase the dose of belumosudil when co-administered with strong CYP3A inducers. The co-administration of belumosudil with strong CYP3A4 inducers does not constitute a risk for belumosudil.
- Co-administration of belumosudil with PPIs decreases belumosudil exposure, which may reduce the efficacy of belumosudil. Routine minimization measures (labeling) provide the appropriate recommendation to increase the dose of belumosudil when co-administered with PPIs. The co-administration of belumosudil with PPIs does not constitute a risk for belumosudil.
- Co-administration of belumosudil with drugs transported by OATP1B1 and BCRP can lead to an increase in exposure of these concomitant drugs (eg, rosuvastatin), which may increase the risk of toxicities related to these substrates. Routine minimization measures (labeling) provide the appropriate recommendation to monitor patients closely for signs and symptoms of excessive exposure to the drugs that are substrates of OATP1B1 and BCRP. The labelling information includes a recommendation to avoid co-administration of belumosudil with substrates of these transporters. This interaction does not constitute a risk for belumosudil.
- Co-administration of belumosudil with drugs transported by P-gp with a narrow safety index can lead to an increase in exposure of these concomitant drugs (eg, dabigatran), which may increase the risk of toxicities related to P-gp substrates. Routine minimization measures (labeling) provide the appropriate recommendation to monitor patients closely for signs and symptoms of excessive exposure to drugs

that are substrates of P-gp with a narrow safety index. This interaction does not constitute a risk for belumosudil.

- Co-administration of belumosudil with CYP1A2, CYP2C19 CYP3A4 and UGT1A1 sensitive substrates of these enzymes could lead to an increase in exposure of these concomitant drugs. Co-administration of CYP1A2, CYP2C19,CYP3A4 and UGT1A1 sensitive substrates for which small concentration changes may lead to serious toxicities, is not recommended. If co-administration cannot be avoided, the substrate dose(s) should be decreased in accordance with the respective product information. This interaction does not constitute a risk for belumosudil.

Risks associated with the disposal of the used product:

This is not considered a risk, taking into account the mode of administration of belumosudil.

Risks related to the administration procedure:

This is not considered a risk, taking into account the mode of administration of belumosudil.

Pediatric safety issues:

The clinical efficacy of belumosudil 200 mg QD has been demonstrated in the treatment of cGVHD after failing 2 or more prior lines of therapy in adolescent and adult patients, and belumosudil is approved for the treatment of adult and adolescent patients ≥12 years with cGVHD after failing two lines of therapy. Considering the similarities in the pathophysiology of cGVHD, approaches to treatment and responses to therapy between adults and pediatric patients (15) (41), it is likely that belumosudil will also be efficacious in pediatric patients.

Reports of belumosudil use in pediatric patients younger than 18 years of age are available in the global pharmacovigilance database from postmarketing experience. Until the DLP of this RMP, 69 patients below 18 years of age received treatment with belumosudil in the postmarketing setting or during compassionate use.
Forty-eight patients were adolescents (12-17 years) and 21 were pediatric patients (1-11 years). The majority of the reported events (≥20) were classified in the following system organ class (SOCs): Injury, poisoning and procedural complications (46 events - 0.6%), Infections and infestations (25 events - 0.35%), Gastrointestinal disorders (23 events - 0.32%), General disorders and administration site conditions (22 events - 0.3%), and Investigations (20 events - 0.28%).

The most frequently reported events by PT (≥5 events) were Product use in unapproved indication, Nausea, and Product use issue (8 events each), Inappropriate schedule of product administration (7 events), Off label use (6 events), and Death, Headache and Product administered to patient of inappropriate age (5 events each). No new signals have been identified. Thus, pediatric safety in patients ≥12 years of age is not considered a risk for belumosudil. An open-label single-arm Phase 1/2 study (DFI 17893) of belumosudil in children aged 1 to <18 years with moderate to severe cGVHD after at least two lines of prior systemic therapy is planned to evaluate the PK, safety, and efficacy of belumosudil in children from 1 year to less than 18 years of age.

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

Not applicable

SVII.2 NEW SAFETY CONCERNS AND RECLASSIFICATION WITH A SUBMISSION OF AN UPDATED RMP

Following the evaluation of RMP v1.0, RMP v1.1 and RMP v1.2 by CHMP and PRAC (procedure EMEA/H/C/006421/0000), the List of Safety Concerns has been revised. The safety topics listed below have been removed from the List of Safety Concerns in the updated RMP version 1.3 (See Section SVII.1.1)

- Drug-induced liver injury:

  Drug induced liver injury is considered sufficiently characterized through clinical studies and postmarketing evaluation. The robust, ongoing routine pharmacovigilance program will continue to adequately to assess this risk, without the need for further additional pharmacovigilance.

  “Liver function test elevations” is retained as a non-important risk (Section SVII.1.1) in the updated RMP v1.1 and in the RMP v1.2.

- Infections:

  The potential risk “infections” is considered sufficiently characterized through clinical studies and postmarketing evaluation.

  The robust, ongoing routine pharmacovigilance program will continue to adequately to assess this risk, without the need for further additional pharmacovigilance.

  The routine minimization measures through labeling are appropriate to mitigate this risk. The clinicians treating this patient population are aware about the risk of infections and patients are routinely monitored. Prophylactic (antibiotic, antifungal, antiviral) treatment and vaccinations are administered according to standard practice in transplant recipients.

- Embryofoetal toxicity and teratogenicity:

  This risk is adequately minimized through routine minimization measures. The SmPC has been updated with the addition of a contraindication for “pregnancy and breastfeeding”.

  As per Section 4.4 of the SmPC, women of childbearing potential must have their pregnancy status verified prior to initiating treatment with belumosudil and must use highly effective contraception during treatment with belumosudil and for at least one week after the last dose of belumosudil.

- Malignancy (secondary neoplasm and /or relapse of the underlying malignancy):

  Additional Pharmacovigilance activities have not been considered feasible to characterize the risk.

SVII.3 DETAILS OF IMPORTANT IDENTIFIED RISKS, IMPORTANT POTENTIAL RISKS, AND MISSING INFORMATION

The following risks have been identified for belumosudil:

- Important identified risk:
  - None
- Important potential risk:
  - None
- Missing Information:
  - None

SVII.3.1 Presentation of important identified risks and important potential risks

There are no important identified or potential risks characterized for belumosudil.

SVII.3.2 Presentation of the missing information

Not applicable since there is no proposed missing information for belumosudil.

RISK MANAGEMENT PLAN - PART II MODULE SVIII: SUMMARY OF THE SAFETY CONCERNS

Summary of the safety concerns

Important identified risk	None
Important potential risk	None
Missing information	None

RISK MANAGEMENT PLAN - PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORIZATION SAFETY STUDIES)

III.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

No routine pharmacovigilance activities beyond adverse reactions reporting and signal detection are deemed necessary to monitor the risks of belumosudil.

The safety profile of belumosudil will continue to be further characterized in clinical conditions of use through postmarketing safety surveillance, encompassing analysis of spontaneous reporting of adverse drug reactions in periodic safety reports, product technical complaints (PTCs) relating to adverse events, and signal detection.

III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Not applicable since no additional pharmacovigilance activities are planned for this product.

III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Not applicable since no additional pharmacovigilance activities are ongoing or planned for belumosudil.

No effectiveness evaluation is set up since there are no risk minimization activities in place beyond routine.

RISK MANAGEMENT PLAN - PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

Table 17 - Planned and on-going post-authorization efficacy studies that are conditions of the marketing authorization

Study Status	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due date
Not applicable	-	-	-	-

Table 18 - Planned and on-going post-authorization efficacy studies that are specific obligations in the context of a conditional marketing authorization

Study Status	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due date
Study EFC22965 Planned	To confirm the efficacy and safety of Rezurock in adult and paediatric patients (12 years and older with a body weight of at least 40 kg) with cGVHD when other medicinal products approved for use in cGVHD provide limited clinical benefit or are not suitable.	Belumosudil superiority over BAT will be tested in planned phase 3 randomized controlled trial (ORR at 24 weeks).	• Protocol submission • Yearly recruitment updates • Final results	Jan-2026 Feb-2027, Feb-2028, Feb-2029 Q4 2029

BAT: Best Available Therapy; cGVHD: Chronic Graft-Versus-Host Disease; ORR: Overall Response Rate; Q: Quarter.

RISK MANAGEMENT PLAN - PART V: RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

V.1 ROUTINE RISK MINIMIZATION MEASURES

Routine risk minimization measures are in place for the safety risks of this medicinal product as conveyed in the labeling information. Because none of the safety risks are relevant for the RMP of belumosudil and in line with the GVP Module V (Rev 2.0), RMP part V.1 is empty.

V.2 ADDITIONAL RISK MINIMIZATION MEASURES

Routine risk minimization activities as described in [Part V.1] are considered sufficient to manage the safety concerns of the medicinal product. No additional risks minimization measures are proposed for belumosudil.

V.3 SUMMARY OF RISK MINIMIZATION MEASURES

Not applicable.

RISK MANAGEMENT PLAN - PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Rezurock (belumosudil)

This is a summary of the RMP for Rezurock. The RMP details important risks of Rezurock, how these risks can be minimized, and how more information will be obtained about Rezurock's risks and uncertainties (missing information).

Rezurock's SmPC and its package leaflet (PL) give essential information to healthcare professionals (HCPs) and patients on how Rezurock should be used.

This summary of the RMP for Rezurock should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Rezurock's RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

Rezurock is indicated for the treatment of adults and paediatric patients (12 years and older with a body weight of at least 40 kg) with chronic graft-versus-host disease (cGVHD) when other treatment options provide limited clinical benefit, are not suitable, or have been exhausted (see SmPC for the full indication). It contains belumosudil as the active substance and is given by oral route.

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS

Important risks of Rezurock, together with measures to minimize such risks and the proposed studies for learning more about Rezurock's risks, are outlined in the next sections.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and HCPs;
- Important advice on the medicine's packaging;
- The authorized pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status - the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine RMMs.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

II.A List of important risks and missing information

Important risks of Rezurock are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Rezurock. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine);

Table 19 - List of important risks and missing information

Important identified risk	None
Important potential risk	None
Missing information	None

II.B Summary of important risks

There are no important risks for belumosudil.

II.C Post-authorization development plan

II.C.I Studies which are conditions of the marketing authorization

Table 20 - Studies which are conditions of the marketing authorization

Study EFC22965
Purpose of the study: To confirm the efficacy and safety of Rezurock in adult and paediatric patients (12 years and older with a body weight of at least 40 kg) with cGVHD when other medicinal products approved for use in cGVHD provide limited clinical benefit or are not suitable.

cGVHD: Chronic Graft-Versus-Host Disease.

II.C.II Other studies in post-authorization development plan

There are no studies required for belumosudil.

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RISK MANAGEMENT PLAN - PART VII: ANNEXES

ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

NOT APPLICABLE

ANNEX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMIZATION ACTIVITIES

NOT APPLICABLE