29 January 2026
EMA/CHMP/3277/2026
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Rezurock

International non-proprietary name: belumosudil

Procedure No. EMEA/H/C/006421/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

7-PtR	7-point reduction
ADME	Absorption, distribution, metabolism, and excretion
API	Active pharmaceutical ingredient
AML	Acute myelogenous leukaemia
AMPK	Adenosine monophosphate-activated protein kinase
ATP	Adenosine triphosphate
ABC	Adenosine triphosphate-binding cassette transporter
ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine aminotransferase
α-SMA	Alpha-smooth muscle actin
AI	American Indian or Alaska native
Vz/F	Apparent volume of distribution based on the terminal phase calculated using aucinf after a single extravascular administration where F (fraction of dose bioavailable) is unknown
AUC	Area under the concentration-time curve
AUC_{inf}	Area under the concentration-time curve from pre-dose (time 0) extrapolated to infinity
$AUC_{(0\text{-last})}$	Area under the curve from time 0 to the time of last measurable concentration
$AUC_{0\text{-}24}$	Area under the plasma concentration-time curve from pre-dose (time 0) to 24 hours post-dose
A	Asia
AST	Aspartate aminotransferase
BAT	Best available therapy
BOR	Best overall response
BCS	Biopharmaceutics classification system
B	Black or African American
BP	Blood pressure
BMI	Body mass index
BCRP	Breast cancer resistance protein

BO	Bronchiolitis obliterans
CNIs	Calcineurin inhibitors
CAMK	Calcium/calmodulin-dependent protein kinase
CK	Casein kinase
CNS	Central nervous system
cGVHD	Chronic graft versus host disease
CSR	Clinical study report
CTR	Clinical trial register
CIA	Collagen-induced arthritis
CHMP	Committee for Medicinal Products for Human use
CTD	Common technical document
CTCAE	Common Terminology Criteria for Adverse Events
CR	Complete response
CI	Confidence interval
CTGF	Connective tissue growth factor
COVID-19	Coronavirus disease 2019
QTc	Corrected QT interval
CPP	Critical process parameter
CMQ	Customized MedDRA Query
CYP	Cytochrome P450
CMV	Cytomegalovirus
DSC	Differential scanning calorimetry
DDI	Drug-drug interaction
DO7-PtR	Duration of a 7-point reduction
DoR	Duration of response
ECG	Electrocardiogram
ESI-MS	Electrospray ionisation mass spectrometry
eGFR	Estimated glomerular filtration rate
EC	European Commission
EMA	European medicines agency

Ph. Eur.	European Pharmacopoeia
EBMT	European Society for Blood and Marrow Transplantation
EU	European Union
ER	Extraction ratio
FFS	Failure-free survival
1L	First line
Tfh	Follicular helper T
FDA	Food and Drug Administration
FT-IR	Fourier transform infrared spectroscopy
FTIR	Fourier transform infrared spectroscopy
QTcF	Fridericia QT correction method
GGT	Gamma-Glutamyl Transferase
GC-HS	Gas chromatography headspace
GC-MS	Gas chromatography mass spectrometry
GI	Gastrointestinal
GD	Gestation day
GSR	Global severity rating
GFR	Glomerular filtration rate
GCP	Good clinical practice
GLP	Good laboratory practice
GMP	Good manufacturing practice
GVHD	Graft-versus-host disease
IC_{50}	Half-maximal inhibitory concentration
HR	Heart rate
HCT	Hematopoietic cell transplantation
HDPE	High density polyethylene
HDPE	High density polyethylene
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
HLT	High-level term

hERG	Human ether-a-go-go related gene
HPBL	Human peripheral blood lymphocytes
HAS	Human serum albumin
HSA	Human serum albumin
HIF1α	Hypoxia-inducible factor-1 alpha
ICP-OES	Inductively coupled plasma optical emission spectroscopy
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety
IL	Interleukin
ICH	International Council for Harmonisation
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IP	Intraperitoneal
IV	Intravenous
IMP	Investigational medicinal product
IND	Investigational new drug
JAK	Janus kinase
jRCT	Japan Registry for Clinical Trials
K-M	Kaplan-meier
KF	Karl Fischer titration
AGC	Kinase containing PKA, PKG, PKC families
LR	Lack of response
LR-M	Lack of response - Mixed
LR-P	Lack of response - Progression
LR-U	Lack of response - Unchanged
LSS	Lee symptom scale
LOT	Line of therapy
LC-MS	Liquid chromatography mass spectrometry
LFT	Liver function tests
mTOR	Mammalian target of rapamycin

MARCO	Margin consolidated
MAH	Marketing authorisation holder
MA	Marketing authorization
Cmax	Maximum concentration
MTD	Maximum tolerated dose
mITT	Modified Intent-to-Treat
MATE	Multidrug and toxin extrusion protein
MMF	Mycophenolate mofetil
NCT	National clinical trial
NIH	National Institutes of Health
NADPH	Nicotinamide adenine dinucleotide phosphate
NOAEL	No observed adverse effect level
NOR	Normal operating range
NA	Not available; not applicable
NEC	Not elsewhere classified
NR	Not reached
NMR	Nuclear magnetic resonance
NMR	Nuclear magnetic resonance
tmax	Observed time to reach peak plasma concentration
QD	Once daily
OATP	Organic anion transporting polypeptide
O	Other
ORR	Overall response rate
OS	Overall survival
PR	Partial response
ppm	Parts per million
PROMIS	Patient-reported Outcomes Measurement Information System
PPS	Per protocol set
P-gp	P-glycoprotein
PD	Pharmacodynamic

PK	Pharmacokinetic
P2MLAG	Phase 2 multiple lines analysis group
ΔΔ	Placebo-corrected or placebo-adjusted change-from-baseline
PP	Polypropylene
PP	Polypropylene
popPK	Population pharmacokinetic
PT	Preferred term
PEP	Primary efficacy endpoint
PPI	Proton pump inhibitor
PAR	Proven acceptable range
QP	Qualified person
QC	Quality control
RCT	Randomised controlled trial
RD	Rate difference
RWE	Real-world evidence
REC	Recommendation
Treg	Regulatory T cell
RH	Relative humidity
RORγt	Retinoic acid-related orphan receptor γt
ROCK	Rho-associated coiled-coil containing protein kinase
ROCK	Rho-associated, coiled-coil containing protein kinase
RMP	Risk management plan
Ser/Thr	Serine/threonine
SAE	Serious adverse event
STAT	Signal transducer and activator of transcription
SD	Standard deviation
SMQ	Standardized meddra Query
SAP	Statistical analysis plan
SmPC	Summary of product characteristics
SOC	System organ class

SLE	Systemic lupus erythematosus
TCR	T cell receptor
Tfh	T follicular helper cells
TMLE	Targeted maximum likelihood estimation
t1/2	Terminal elimination half-life
Th17	T-helper 17 cells
TTNT	Time to next treatment
TTR	Time to response
CL/F	Total body clearance calculated after a single extravascular administration where F (fraction of dose bioavailable) is unknown
TK	Toxicokinetic
TGF-β	Transforming growth factor beta
TGF-β	Transforming growth factor beta
TEAE	Treatment-emergent adverse event
TFA	Ttrifluoroacetic acid
BID	Twice daily
TK (kinase)	Tyrosine kinase
TKL	Tyrosine kinase-like
UGT1A1	UDP-glucuronyltransferase 1A1
UK	United Kingdom
US	United states, united states
U	Unreported/unknown
W	White
WT	Wild type
XRPD	X-ray powder diffraction
AGP	A1-acid glycoprotein

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Sanofi Winthrop Industrie submitted on 13 September 2024 an application for marketing authorisation to the European Medicines Agency (EMA) for Rezurock, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 14 September 2023.

Rezurock, was designated as an orphan medicinal product EU/3/19/2205 on 17 October 2019, in the following condition: the treatment of graft-versus-host disease.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Rezurock as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website: https://www.ema.europa.eu/en/medicines/human/EPAR/Rezurock

The applicant initially applied for the following indication: Rezurock is indicated for the treatment of patients 12 years and older with chronic graft versus-host disease (cGVHD) after failure of at least two prior lines of systemic therapy.

The indication was later modified into the proposed indication as follows:

"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"

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0065/2024 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0065/2024 was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Applicant's request(s) for consideration

1.5.1. Conditional marketing authorisation

The applicant requested consideration of its application for a conditional marketing authorisation in accordance with Article 14-a of regulation (EC) n)726/2004.

1.5.2. New active Substance status

The applicant requested the active substance belumosudil mesylate contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.6. Protocol assistance

The applicant received the following Protocol assistance on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
17 October 2019	EMEA/H/SA/4227/1/2019/SME/III	Romaldas Mačiulaitis, Walter Janssens
25 June 2020	EMEA/H/SA/4227/1/FU/1/2020/PA/SME/II	Karin Janssen van Doorn, Romaldas Mačiulaitis
21 July 2022	EMA/SA/0000084848	Ole Weis Bjerrum, Hrefna Gudmundsdottir
30 March 2023	EMA/SA/0000105166	Karri Penttila, Mette Linnert Jensen
28 April 2023	EMA/SA/0000128686	Rosalía Ruano Camps, Mette Linnert Jensen
14 September 2023	EMA/SA/0000151065	Livia Puljak, Mette Linnert Jensen

The Protocol assistance pertained to the following quality, non-clinical, and clinical aspects:

- Acceptability of the drug substance starting materials, the proposed change in the drug substance

manufacturing process, the proposed control strategy for potential genotoxic impurities

- Acceptability of a waiver of formal mouse and rat non-clinical carcinogenicity studies

- Adequacy of the proposed evidence generation plan to support a CMA for the proposed indication, where the belumosudil cohort will be derived from the phase 2 program and a set of BAT cohorts will be derived from matched European and US real-world data sources. The proposal to supplement this by post-marketing data on belumosudil in European patients with a prospective comparative observational study. Design of the proposed Phase 3 study, including study population (inclusion/exclusion criteria and the definition of line of therapy), choice of active comparator arm, duration, choice of primary efficacy endpoint, choice of secondary endpoints, and statistical considerations including interim analysis.

1.7. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Johanna Lähteenvuo Co-Rapporteur: Beata Maria Jakline Ullrich

The application was received by the EMA on	13 September 2024
The procedure started on	3 October 2024
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	18 December 2024
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	n/a
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	6 January 2025
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	30 January 2025
The applicant submitted the responses to the List of Questions on	14 April 2025
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	26 May 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	05 June 2025
The CHMP agreed on a list of outstanding issues in an oral explanation to be sent to the applicant on	19 June 2025
The applicant submitted the responses to the CHMP List of Outstanding Issues on	18 August 2025
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	3 and 11 June 2025

The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	16 September 2025
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a negative opinion for granting a marketing authorisation to Rezurock on	16 October 2025
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product	16 October 2025

1.8. Steps taken for the re-examination procedure

The re-examination Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Peter Mol Co-Rapporteur: Filip Josephson

The Applicant submitted written notice to the EMA, to request a re-examination of Rezurock CHMP opinion of 16 October 2025, on	21 October 2025
The CHMP appointed a re-examination Rapporteur and Co-Rapporteur on	13 November 2025
The Applicant submitted the detailed grounds for the re-examination on	01 December 2025
The re-examination procedure started on	02 December 2025
The CHMP agreed on a list of questions to the Ad Hoc Expert Group (AHEG) on	11 December 2025
The CHMP Rapporteur's re-examination assessment report was circulated to all CHMP and PRAC members on	15 December 2025
The CHMP Co-Rapporteur's re-examination assessment report was circulated to all CHMP and PRAC members on	11 December 2025
AHEG was convened to address questions raised by the CHMP on	13 January 2026
The CHMP Rapporteurs circulated re-examination Joint Assessment Report containing AHEG minutes to all CHMP and PRAC members on	19 January 2026
The PRAC agreed on the PRAC Assessment Overview and Advice on	15 January 2026
The detailed grounds for re-examination were presented by the applicant during an oral explanation before the CHMP on	27 January 2026
The CHMP, in the light of the scientific data available and the scientific discussion within the Committee, re-examined its initial opinion and in its final opinion concluded that the application satisfied the criteria for authorisation and recommended the granting of the conditional marketing authorisation on	29 January 2026

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The Applicant is seeking following indication:

Rezurock is indicated for the treatment of patients 12 years and older with chronic graft versus-host disease (cGVHD) after failure of at least two prior lines of systemic therapy.

This proposed indication was later modified as follows:

"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"

2.1.2. Epidemiology

Allogeneic hematopoietic cell transplantation (HCT) is the only potentially curative therapy for many hematologic malignancies, immunodeficiencies, and bone marrow failure syndromes. In year 2022, a total of 19011 allogeneic HCTs were reported to the registry of European Blood and Marrow transplantation Society (EBMT) from 463 European centres for HCT (Passweg *et al.* Bone Marrow Transplant 2024). Despite significant advances in donor selection, conditioning regimens, and supportive care, chronic GVHD (cGVHD) remains the leading cause of late morbidity and mortality among HCT survivors. Chronic GVHD occurs in approximately 30% to 70% of adult transplant recipients. Although the incidence of cGVHD in the paediatric population is lower than in adults, in part due to the younger age of the recipients and the donors, it still affects between 6% to 33% of paediatric patients. Chronic GVHD, once established, is a heterogeneous and pleomorphic syndrome which treatment typically requires prolonged (median 2-3.5 years) use of immunosuppressive agents.

2.1.3. Aetiology and pathogenesis

Chronic GVHD is a result of complex mechanisms occurring in three phases: (1) early inflammation due to tissue injury, (2) thymic injury and T- and B-cell dysregulation, and (3) tissue repair and fibrosis (Hamilton BK, Haematology 2021). Currently available data point out the similarity in the pathophysiology of cGVHD between paediatric and adult patients.

The initial phase of cGVHD begins with damage of host tissues by pretransplant conditioning and the subsequent release of inflammatory cytokines. Damage to gut tissues and release of microbial contents result in the activation of antigen-presenting cells, and inflammatory cytokines stimulate the activation of donor alloreactive T cells, driving helper T (Th1)/T-cytotoxic 1 (Tc1), and Th17/Tc17 differentiation and expansion of effector T cells, causing further cytotoxicity to host target cells.

The second phase is characterized by thymic injury leading to the emergence of and selection of auto- and alloreactive T-cell populations. A loss of central and peripheral tolerance leads to impaired or deficient regulatory T (Treg) and B cells. Donor T follicular helper (Tfh) cells expand in the secondary lymphoid organs

and promote the survival, expansion, and differentiation of donor B cells into aberrant anti-host-immunoglobulin-producing plasma cells via cytokines such as IL-21 and B-cell activating factor. Chronic inflammation is thought to be maintained by Th17 cells that have escaped immune regulation.

The third phase is marked by aberrant tissue repair. Activated macrophages dependent on IL-17 and colony-stimulating factor play an important role in this process by producing transforming growth factor β and platelet-derived growth factor alpha. This leads to fibroblast activation, resulting in fibrotic manifestations of cGVHD such as scleroderma or bronchiolitis obliterans.

2.1.4. Clinical presentation, diagnosis and prognosis

The clinical manifestations are systemic, involving multiple organs, with profound impact upon quality of life and non-relapse mortality. The most frequently involved organs include skin, mouth, eyes, liver and joints. Patients who develop cGVHD after HCT face a multifaceted burden, including physical, functional, and psychosocial deficits, which negatively influence quality of life. Presence of fibrotic skin, limited motility of joints/fascia, and/or lung involvement have the greatest effect on physical capability and quality of life. Advanced fibrotic skin involvement of cGVHD mimics the clinical picture of systemic scleroderma.

The severity of cGVHD is assessed as defined by the 2014 NIH Consensus Development Project on Clinical Trials in cGVHD (Jagasia MH *et al*. Biol Blood Marrow Transplant 2015). Total severity scoring is divided into mild, moderate, or severe based on the number and severity of involved organs. Each individual organ system (skin, eyes, mouth, oesophagus, upper gastrointestinal [GI], lower GI, liver, lungs, joints/fascia, and genital tract) is assessed with scores 0-3. Total severity of cGVHD is defined by NIH as following:

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

Patients affected by cGVHD require prolonged immunosuppressive treatment for an average of 2 to 3 years from the initial diagnosis, with 15% of those surviving for at least 7 years still requiring immunosuppressive treatment. Chronic GVHD not responding to therapy ultimately leads to death.

2.1.5. Management

Chronic GVHD is a serious condition with an unmet medical need for safer and more effective treatment options. Approaches to treatment of cGVHD in adults and children are similar.

Current treatment options primarily affecting the inflammatory component of cGVHD are associated with limited efficacy and significant toxicities with an increased risk of infections, cytopenias, and secondary malignancies. The standard initial treatment for cGVHD requiring systemic therapy is corticosteroids, with or without calcineurin inhibitors (CNIs). However, corticosteroids are associated with significant side effects and unsatisfactory outcomes, particularly for patients with high-risk features of cGVHD. The limited activity of currently available cGVHD treatments in affecting the fibrotic changes of cGVHD results in patients cycling

through treatments. Approximately 50% to 75% of patients with cGVHD will require at least second line treatment (Flowers & Martin, Blood 2015).

In 2022, the oral selective JAK1/2 inhibitor ruxolitinib (Jakavi®) was approved in the EU for the treatment of patients aged 12 years and older with acute GVHD or cGVHD who have inadequate response to corticosteroids or other systemic therapies, and this is currently the only approved second-line therapy for cGVHD with a MA in the EU. However, only half of the patients maintained the response to ruxolitinib at 24 weeks after treatment (Zeiser *et al*. NEJM 2021). Ibrutinib (Imbruvica®), an oral BTK inhibitor, was approved by the FDA for the treatment of adult patients with cGVHD after failure of 1 or more lines of systemic therapy based on data from an open-label, a single-arm study of 42 subjects with cGVHD who had failed first line corticosteroid therapy and required additional therapy. Ibrutinib is not yet approved for cGVHD in the EU.

More than 47% of cGVHD patients progress to third or later lines of therapy primarily due to lack of efficacy and/or toxicity (Lee *et al*. Biol Blood Marrow Transplant 2018). In the long term, approximately one-third of patients with cGVHD have relapsed or died, one-third have discontinued therapy successfully and one third remain on long-term treatment for cGVHD. Of patients who remain on therapy long-term, half progress to fourth- or fifth-line therapy (Lee *et al.* Biol Blood Marrow Transplant 2018). Chronic GVHD not responding to therapy ultimately leads to death. Approximately 20% of patients stop cGVHD therapies due to toxicity. Of the cGVHD patients treated with ibrutinib, approximately 24% discontinued treatment due to toxicities. Of the patients treated with ruxolitinib, 18% discontinued the treatment due to adverse events (JAKAVI 2024).

There have been no new agents approved in the EU to address the unmet medical need for alternative treatments of cGVHD after patients failed two or more lines systemic treatments. The unmet medical need is further substantiated by the high demand of belumosudil for compassionate use in the EU more than 400 patients and around the world as of 17 July 2024. Recently, EBMT (Penack *et al.* Lancet Haematol 2024) has updated their recommendation on cGVHD treatment and considered belumosudil as a potential therapeutic option based on its efficacy data and a low drug induced toxicity.

2.2. About the product

Belumosudil is a ROCK2 selective small molecule kinase inhibitor. Rho-associated (coiled-coil containing) protein kinases (ROCKs) are members of the serine/threonine kinase family. ROCK signaling has a role in conditions including autoimmune disease aggravated or caused by a Th17-polarized T cell response and pulmonary fibrosis. Rho-GTPase-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. ROCK is also downstream of several major pro-fibrotic mediators. In addition, ROCK mediates stress fiber formation and regulates the transcription of pro-fibrotic genes.

During the immune response, ROCK signalling is critical in the coordination and balancing of T cell- mediated immune responses, including cellular movement, T-cell receptor (TCR) signalling and the acquisition of the appropriate T-cell effector program. Moreover, targeted ROCK2 inhibition decrease IL-17 production. Taken together, ROCK2 inhibition targets both inflammation and fibrosis.

Belumosudil is approved for the treatment of cGVHD in the US, Canada, Great Britain, Israel, United Arab Emirates, Hong Kong, Argentina, Saudi Arabia, Australia, China, Japan Mexico, South Korea, Kuwait, India, Taiwan, Turkey, Russia, Thailand, and Brazil (as of 16 Sep 2025).

In the EU, the proposed indication is:

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 medicinal products approved for use in cGVHD provide limited clinical benefit or are not suitable. The proposed dose regimen is 200 mg tablet QD.

2.3. Type of Application and aspects on development

The applicant requested consideration of its application for a Conditional Marketing Authorisation in accordance with Article 14-a of the above-mentioned Regulation, based on the following criteria:

- The benefit-risk balance is positive.

  The evidence of efficacy and safety of belumosudil demonstrates the positive benefit/risk balance in the treatment of cGVHD in patients who received at least 2 prior lines of systemic treatment. A total of 260 patients with cGVHD have been enrolled in four clinical studies (KD025-213 [DRI17633; registration trial], KD025-208 [ACT17631]), ME3208-2, and BN101-201) and received belumosudil. A total of 147 patients has been treated with a dose of 200 mg once daily (QD), including 140 patients who have received at least 2 prior lines of systemic treatment prior to enrolment in a study.

  Based on the intended indication (treatment of patients 12 years and older with cGVHD after failure of at least two prior lines of systemic therapy) and the similarity in the pathophysiology of cGVHD across age groups, the population included in the pivotal trial KD025-213 is considered representative for the intended indication.

  Although there is no standard primary endpoint established in clinical trials for the treatment of cGVHD, the overall response rate (ORR), the primary endpoint in study KD025-213, is considered clinically relevant and has been used in other registrational studies including the REACH3 study, which was the basis for the marketing authorisation (MA) approval of ruxolitinib in European Union (EU).

  The ORR (95% CI) for 77 adult patients who received belumosudil 200 mg QD (intended registration dose) in Study KD025-213 was 74% (62.8, 83.4), and the lower bound of the 95% CIs exceeded the pre-defined null hypothesis of 30%. Duration of Response (DOR) and time to response (TTR) demonstrated that the response to belumosudil is sustained. The median TTR and primary DOR (defined as the time from first response to the time of first documentation of deterioration from best response) was 4.4 weeks and 23.9 weeks, respectively. The efficacy profile has been further validated by other three independent clinical interventional studies (Studies KD025-208, ME3208-2 and BN101-201) and a supportive non-interventional RWE study AA_00117, which showed consistent results with what was reported in Study KD025-213.

  In terms of safety, the most commonly reported events were consistent with those seen in the patient population with cGVHD receiving systemic immunosuppression. Adverse events of special interest have been identified and characterized; none have been assessed as important identified risks at this time.

  Since the first marketing authorization was granted, events reported from post marketing experience and compassionate use including adolescent and paediatric patients, have been consistent with the known safety profile of belumosudil; no new risks or signals have been identified in the post marketing setting or from compassionate use.

No new signals were identified based on the totality of data from clinical studies and postmarketing experience. Belumosudil 200 mg QD has shown to have an acceptable safety profile consistent with that expected in cGVHD, a serious disease with limited therapeutic options. The overall benefit risk profile of belumosudil 200 mg QD is favourable.

The current body of evidence indicates a favourable risk/benefit profile for belumosudil in the treatment of cGVHD in patients who received at least 2 prior lines of systemic treatment.

Approval of belumosudil in cGVHD has been granted from several Health Authorities including US, Australia, Canada, Great Britain, Israel, China, United Arab Emirates, Japan, Hong Kong, Argentina, Saudi Arabia and Mexico, and all mentioned the favourable benefit/risk profile of belumosudil in their assessments.

In conclusion, in the opinion of the Applicant, belumosudil 200 mg QD has shown a favourable benefit/risk profile and the current data, in light of the serious nature of the disease and the limited therapeutic options, supports a conditional marketing authorization approval in the proposed indication.

- It is likely that the applicant will be able to provide comprehensive data.

  The applicant initially proposed an ongoing confirmatory study, study EFC17757, as specific obligation supporting the conditional marketing authorisation. The originally planned confirmatory study EFC17757 comparing belumosudil in combination with corticosteroid with placebo in combination with corticosteroid in patients with newly diagnosed moderate and severe cGVHD was terminated by the Applicant on 26 June 2025. Termination of the study was based on the DMC's recommendation based on the results of efficacy data from more than 100 participants during pre-planned futility analysis. For further details, please see section 5.7.3.

  The Applicant has conducted a survey among transplantation haematologists in the EU regarding feasibility of alternative study designs for another SOB. Based on the results of the survey, the Applicant proposes a new SOB, Phase 3 randomized controlled study to fulfil the specific obligation of the CMA.

  This phase 3, randomized, open-label, multi-centre study will investigate the efficacy and safety of belumosudil versus BAT in participants ≥12 years of age with cGVHD after at least 2 prior lines of systemic therapy including ruxolitinib unless it is inappropriate or inadequate at discretion of the investigator. More than 300 participants will be randomized 1:1 to receive either belumosudil or the BAT. The stratification factors include severity of cGVHD at baseline according to the NIH consensus diagnosis and staging criteria (2014) (moderate vs severe) and the number of prior lines of therapy (2 vs >2).

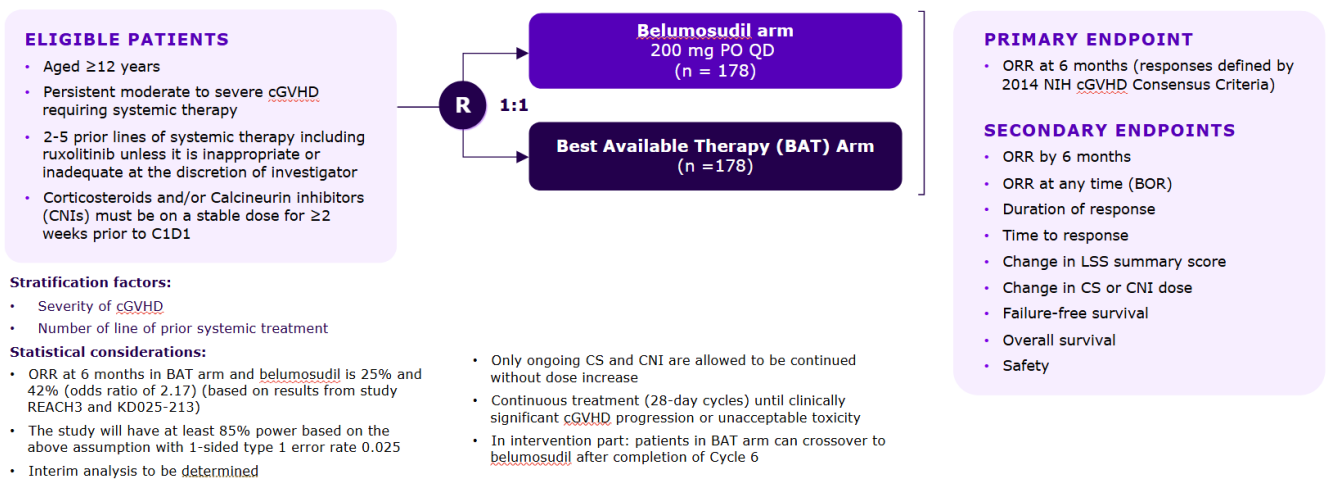


Figure 1: Study schema of the new proposed SOB

The Applicant commits to finalise the protocol for CHMP review on 18 Dec 2025. The study is planned to be initiated in Aug 2026, leading to the availability of CSR submission to EU in April 2030.

Randomised Control Trial (RCT) description:

Participants assigned to belumosudil arm will receive belumosudil at 200 mg once daily. Increasing the dosage of belumosudil to 200 mg twice daily when co-administered with proton pump inhibitors (PPIs) or strong CYP3A4 inducers is required.

Participant assigned to the BAT arm will receive one of the following options: extracorporeal photopheresis (ECP), mycophenolate mofetil (MMF), rituximab, mTOR inhibitors (sirolimus, everolimus), imatinib, ibrutinib, proteasome inhibitors, and pentostatin. No other types or combinations of BATs are permitted. The choice of BAT for each participant will be determined by the investigator and must be entered in the interactive response technology (IRT) prior to randomization. Dose and frequency for various BATs will depend on local prescribing information and institutional guidelines.

Participants can continue the study intervention (belumosudil or BAT) until cGVHD disease progression, intolerable toxicities, or other reasons to terminate study intervention. Each cycle will be 28 days in duration. Participants in the BAT arm will have the option to crossover to belumosudil arm after completion of Cycle 6 (time point for ORR at 6 months) if developing toxicity to BAT treatment, not achieving PR or CR or having cGVHD progression.

Concomitant use of systemic corticosteroids and calcineurin inhibitors (CNIs) only are allowed. Participants on systemic corticosteroids and/or CNIs must be on a stable dose for at least 2 weeks prior to C1D1. Concomitant systemic treatment for cGVHD other than corticosteroids and CNIs is prohibited until study intervention discontinuation. It is recommended that any participant receiving a CNI at study entry will remain on the same CNI during the study treatment period. Changes in doses of drugs to maintain therapeutic levels are not considered as a change in dose/schedule. Use of topical or organ specific therapies for cGVHD is permitted.

Endpoints and Statistical Assumption

The primary endpoint is the ORR (PR or CR) at 6 months based on ITT population from the RCT population.

Secondary efficacy endpoints include ORR by 6 months, ORR at any time, duration of response (DOR), time to response (TTR), failure free survival (FFS), modified Lee Symptom Scale (mLSS) improvement, change in corticosteroid and CNI doses, and overall survival. In addition, safety is also assessed as a secondary endpoint.

- **Unmet medical needs will be addressed**

The eligibility for a conditional marketing authorization is further justified by the high unmet medical need for effective therapies to treat cGVHD in the EU in patients who failed at least two previous lines of treatment.

Chronic GVHD is a serious condition with a significant unmet medical need for safer and more effective treatment options. The limited to no activity of currently available cGVHD treatment in affecting the fibrotic changes of cGVHD inevitably results in patients cycling through treatments quickly. It is estimated that approximately 50% to 75% of patients with cGVHD will require at least second line treatment (Flowers & Martin, 2015).

In 2022, the oral selective JAK1/2 inhibitor ruxolitinib (Jakavi®) was approved in the EU for the treatment of patients aged 12 years and older with acute GVHD or cGVHD who have inadequate response to corticosteroids or other systemic therapies, and this is currently the only approved second-line therapy for cGVHD with a marketing authorization in the EU. However, only 50% of patients maintained the response to ruxolitinib at 24 weeks after treatment, indicating the needs for subsequent therapy beyond second line treatment (Zeiser, et al., 2021). In addition, it has been reported that ~20% of patients stop cGVHD therapies due to toxicity (Lee, et al., 2018). In patients with cGVHD who received ruxolitinib, Grade 3 anaemia was reported in 14.8% of patients. Grade 3 and 4 neutropenia were reported in 9.5% and 6.7% of patients, respectively. Of the patients who received ruxolitinib 18.1% discontinued the treatment due to adverse events (Jakavi, EPAR 2024).

It has been reported that more than 47% of patients progress to third or more lines of therapy primarily due to lack of efficacy and/or toxicity leading to discontinuation with the potential for disease progression (Bachier, et al., 2021) (Lee, et al., 2018). In the long term, approximately one-third of patients with cGVHD have relapsed or died, one third have discontinued therapy successfully and one third remain on long-term treatment for cGVHD. Of patients who remain on therapy long-term, half progress to fourth- or fifth-line therapy (Lee, et al., 2018).

There have been no new agents approved in the EU in the past two years to address the unmet need for alternative treatments of cGVHD after patients failed two or more lines systemic treatments. The high unmet medical need is further substantiated by the high demand of belumosudil for compassionate use in the EU and around the world. The Applicant has implemented a compassionate use program in 2022 for belumosudil across the EU, allowing more than 500 patients from 19 different EU countries suffering from cGVHD with no other treatment alternatives to be treated as of 17 August 2024.

The limitation of available therapies has been fully recognized by the community. Recently, the European society for Blood and Marrow Transplantation (EBMT) has updated their recommendation on cGVHD treatment and considered belumosudil a potential therapeutic option based on its

compelling efficacy data and a low drug induced toxicity profile observed in non-randomized trials which are used as part of primary evidence in this dossier (Studies KD025-213 and KD025-208) (Penack, et al., 2020).

Altogether, there is a significant unmet medical need for efficacious and well-tolerated therapies for patients with cGVHD who have failed at least 2 prior lines of systemic therapy in the EU.

- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required.

  In the opinion of the Applicant, the benefit of the immediate availability of belumosudil to patients is greater than the risk inherent to the fact that additional data are still required considering that

  - Belumosudil offers a unique novel mechanism of action that addresses both the inflammation and the significant fibrosis seen in cGVHD. No approved treatments in the European Region provide such characteristics.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as film-coated tablet containing belumosudil mesylate equivalent to 200 mg belumosudil as active substance.

Other ingredients are:

Core tablet: microcrystalline cellulose, hypromellose, croscarmellose sodium, colloidal anhydrous silica, and magnesium stearate.

Film-coating: polyvinyl alcohol (E1203), macrogol (1521), talc (E553b), titanium dioxide (E171), and iron oxide yellow (E172).

The product is available in high density polyethylene (HDPE) bottles, each with a polypropylene (PP) child-resistant closure and a silica gel desiccant.

2.4.2. Active Substance

General information

The chemical name of belumosudil mesylate is 2-(3-(4-(1*H*-indazol-5-ylamino)quinazolin-2-yl)phenoxy)-*N*-isopropylacetamide methane sulfonic acid salt corresponding to the molecular formula $C_{26}H_{24}N_6O_2.CH_3SO_3H$. It has a molecular weight of 452.52 g/mol (free base) and 548.62 g/mol (mesylate) and the following structure:

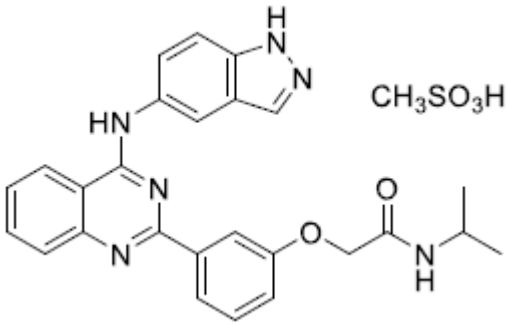


Figure 2: Active substance structure

The chemical structure of belumosudil mesylate was elucidated by a combination of Fourier transform infrared (FT-IR) spectrometry, nuclear magnetic resonance (NMR) spectrometry (^{1}H and ^{13}C NMR), electrospray ionization mass spectrometry and single crystal x-ray structure analysis. The solid state properties of the active substance were measured by x-ray powder diffraction (XRPD), differential scanning calorimetry, and thermogravimetric analysis.

The active substance is a slightly hygroscopic yellow crystalline solid. Only 1 polymorph was identified during development. It has low solubility across the physiological pH range, being slightly soluble at pH 2-3 and very slightly soluble at pH 6 but practically insoluble at pH 1.2 and 4-5. Belumosudil is achiral.

Manufacture, characterisation and process controls

Evidence of GMP compliance of the manufacturing sites has been provided in the QP declaration.

The manufacturing process has multiple chemical transformation steps from well-defined proposed starting materials followed by the salt formation. In the initial submission, the CHMP considered that one of the starting materials was not adequately justified as a starting material considering that limits for mutagenic impurities were too wide, some potential impurities had not been discussed, and that adequate demonstration of impurity purge had not been provided resulting in a major objection. In response, the applicant provided a comprehensive discussion of potential and actual mutagenic impurities, provided spike and purge data demonstrating that impurities are purged to acceptable levels during isolation of downstream intermediates, and tightened limits for relevant impurities in the starting material specification. That starting material was thus considered an acceptable starting material based on the revised control strategy and the major objection was resolved.

Initially, the risk assessment and proposed control strategy for mutagenic impurities was not considered acceptable. Several Class 2 or 3 impurities were discussed but the limit for multiple impurities was not considered and the justification for the proposed ICH M7 option 3 and 4 control strategy was inadequate, resulting in a major objection. In response, the applicant provided the results of extensive fate and purge studies demonstrating adequate purge of relevant impurities. Furthermore, limits for mutagenic impurities in several intermediates were tightened in line with batch data and to ensure adequate purge. A limit for multiple mutagenic impurities was proposed and justified. The overall control strategy is considered acceptable and the major objection resolved.

The specifications and control methods for intermediate products, starting materials and reagents have been presented. The initially proposed specification for a reagent used in the final step of the process was not considered adequate resulting in a major objection. In response, the applicant added a specific identification

test and tightened the assay limit. A justification for not including impurity limits based on batch data was accepted and the major objection was resolved.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program although the synthetic route has remained the same throughout. In the initial submission, the establishment of process parameters and definition of critical steps had not been adequately justified, resulting in a major objection. In response, the applicant explained that process development was conducted according to ICH principles including risk assessment and investigation of parameter settings and ranges in univariate and multivariate experiments. Normal operating ranges and set points were justified and it was clarified that a design space is not claimed. Critical process parameters (CPPs) were therefore defined. The definition of CPPs and control strategy have been adequately justified by development studies.

Adequate in-process controls are applied during the synthesis. The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process.

The primary contact materials comply with Commission Regulation (EU) 10/2011, as amended.

Specification

The active substance release and shelf-life specifications includes tests for description (visual), identity (FT-IR, HPLC), assay (HPLC), impurities (HPLC), methane sulfonic acid content (potentiometric titration), chloride content (ion chromatography), residual solvents (GC-HS), palladium content (ICP-OES), residue on ignition (Ph. Eur.), methyl methane sulfonate content (GC-MS) water content (KF), physical quality (DSC and XRPD) and particle size distribution (laser diffraction).

Impurities limits are set according to ICH guidelines. The omission of a limit for microbial quality has been adequately justified. The specifications comply with pharmacopoieal requirements.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards has been presented.

Batch analysis data from 6 batches of active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from 3 production scale batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 48 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. Photostability testing following the ICH guideline Q1B was performed on 1 batch. Batches were tested according to the shelf-life specifications. No significant changes to any of the measured parameters were observed. The active substance is photostable.

The analytical methods used were the same as for release and were stability indicating as demonstrated in forced degradation studies.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period of 48 months without specific storage conditions in the proposed container.

2.4.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The finished product is a conventional immediate-release film-coated tablet containing belumosudil mesylate equivalent to 200 mg belumosudil. The tablets are pale yellow to yellow, oval shaped tablet, debossed with "KDM" on one side and "200" on the other side, with dimensions of 7.4 x 14.8 mm.

The finished product is for oral administration and the choice of pharmaceutical form, and its strength adequately address the proposed dose regimen, *i.e.*, 200 mg (one tablet) once or twice daily.

Belumosudil mesylate is categorised as a BCS Class IV (low solubility, low permeability) substance. The maximum solubility of belumosudil mesylate within the physiological pH range is at pH 2.0-3.0 where it is slightly soluble. In addition, it has been adequately demonstrated that the crystal form of the active substance does not change during the manufacture and storage of the finished product.

The chosen excipients are commonly used in immediate-release tablets and described in the Ph. Eur. except the film-coating, which consists of pharmacopeial ingredients. The list of excipients is included in section 6.1 of the SmPC. The selection of each excipient at the proposed level has been adequately justified. Compatibility between excipients and the active substance has been demonstrated through binary compatibility studies and finished product stability studies. Control of functionality related characteristics of the excipients has been adequately justified.

Throughout development of the finished product, four different formulations were investigated. Initial phase I clinical trials used 10 mg and 100 mg hard capsules that contained only the active substance. Subsequently, additional phase I trials, along with phase II and III trials, were conducted using two tablet formulations of 200 mg strength, one of which is the intended commercial formulation. Overall, satisfactory information on all clinical batches used to date has been provided.

Overall, the development of the manufacturing process and the identification of both non-critical and critical process parameters have been thoroughly addressed, and the influence of the manufacturing process steps on the critical quality attributes of the finished product has been appropriately investigated. The final control strategy of the manufacturing process was provided, indicating defined process parameters and their targets or associated ranges.

The development of the dissolution method has been described in sufficient detail including demonstration of the discriminatory power of the method.

The medicinal product is indicated for children of 12 years and older. Adequate justification regarding the development of the medicinal product in accordance with the "Guideline on pharmaceutical development of medicines for paediatric use" has been provided. A study has been initiated to evaluate the feasibility of tablet crushing with subsequent oral administration for patients who have difficulty in swallowing tablets. This study is on-going, and the CHMP recommended that the applicant submit the results of the tablet crushing

study post-authorisation, once available. If the study confirms that tablet crushing is feasible, the product information should be updated accordingly to reflect these findings (REC).

The primary packaging is HDPE bottles, each with desiccant and closed by a child-resistant PP screw cap with an induction-sealed, aluminium-faced, closure-liner. The materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

Valid proof of GMP status has been provided for relevant sites.

The manufacturing process consists of multiple steps: weighing and screening, blending / processing of the API with the excipients, compression, film-coating and packaging. The process is considered to be a standard manufacturing process.

The manufacturing process has been adequately described including relevant process parameters, in-process controls and type of equipment.

Critical process parameters have been identified in line with the pharmaceutical development. All values and ranges of the critical and non-critical process parameters have been justified by pharmaceutical development and process validation.

A bulk hold time is justified by the provided stability data.

The manufacturing process has been validated on 3 consecutive commercial scale batches. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form according to ICH Q6A and Ph. Eur. monograph 0478 for tablets, including appearance (visual), identification (UV, HPLC), identification of pigment (Ph. Eur.), assay (HPLC), related substances (HPLC), uniformity of dosage units (Ph. Eur.), dissolution (Ph. Eur.), water content (Ph. Eur.) and microbial limits (Ph. Eur.).

The acceptance criteria are set according established based on regulatory and Ph. Eur. requirements, as well as batch analysis and stability data of both the active substance and the finished product. Two degradation products originating from the active substance are specified and the limits have been set at the identification and qualification limit considering the maximum daily dose of 400 mg.

In the initial dossier, the limits for the dissolution method had not been adequately justified and data was lacking resulting in a major objection. The applicant provided data from 10 batches used in clinical trials, but the CHMP considered that the proposed limit was not tight enough. In response, the applicant tightened the release specification, and the major objection was thus resolved.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification.

The initially submitted nitrosamines risk assessment was not considered adequate, resulting in a major objection. In response, the applicant submitted a risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed (as requested) considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Considering the presence of a secondary amine in the active substance structure (as mesylate salt), the potential presence of nitrite in the excipients, and the processing of belumosudil with the excipients, a risk of formation of *N*-nitrosobelumosudil was identified. To mitigate the risk, the applicant attempted to generate *N*-nitrosobelumosudil using various sets of forcing conditions, but none could be detected using a suitably sensitive analytical method. Testing also confirmed that nitrosamines potentially derived from solvents and reagents used in the API process were not detected. Therefore, it was accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards has been presented.

Batch analysis results are provided for 10 production scale batches (four of which used a slightly different ratio of active substance to filler) confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Stability data from 3 commercial scale batches of finished product stored for up to 24 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. Data was also provided for up to 24 months for batches stored at 2-8 ºC.

Samples were tested according to the shelf-life specifications. The analytical procedures used are stability indicating. No significant changes or trends were observed to any of the measured parameters.

In addition, 1 batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The finished product is photostable.

Based on available stability data, the proposed shelf-life of 3 years without specific storage conditions as stated in the SmPC (sections 6.3 and 6.4) is acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. 5 major objections were raised during the procedure by the CHMP in relation to the overall active substance control strategy, the mutagenic impurity control strategy in one of the starting materials, the specification of a reagent used in the final active substance step, the nitrosamines risk assessment and the dissolution method specification limit. All were resolved by provision of further justification or additional data.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.4.6. Recommendation for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- the applicant should submit the results of the tablet crushing with subsequent oral administration for patients who have difficulty in swallowing tablets and update the product information as appropriate.

2.5. Non-clinical aspects

2.5.1. Introduction

The nonclinical studies were conducted in compliance with the principles set forth in International Council for Harmonisation (ICH) M3 (R2) (Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals; 11 Jun 2009), its associated M3(R2) Q&A document (05 Mar 2012), and the other applicable ICH guidelines involving nonclinical studies. Components of the GLP nonclinical studies or nonclinical studies that were not in full compliance with GLP regulations were conducted in accordance with established Test Facility or Test Site standard operating procedures or processes. *In vivo* safety pharmacology studies were conducted in rats and dogs. Pivotal repeat-dose toxicity studies were conducted in rats and dogs. Embryo-foetal development studies were conducted in rats and rabbits.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

Table 1: summary of in vitro and in vivo primary pharmacodynamic studies with key findings (Note: KD025 = belumosudil mesylate).

Type of study	Test system	Method of adm.	Dose or conc.	No. per group and gender (M/F)	Noteworthy findings
ROCK1/ROCK2 Kinase activity	*in vitro*	NA	NA	NA	KD025 is a potent, competitive, and selective inhibitor of ROCK2 but not ROCK1
In vitro Immunomodulatory Pharmacodynamics	*in vitro*	NA	NA	NA	KD025 regulates IL-21 and IL-17 secretion in human CD4+ T cells. Treatment with KD025 under Th17 skewing conditions down-regulates the phosphorylation of STAT3 and leads to reduced levels of IRF4 and RORγt protein in a dose-dependent manner. The concurrent regulation of STAT3/STAT5 phosphorylation by KD025 is followed by a 2-fold increase in the percentage of Foxp3+ T cells and the ability of human Tregs to suppress target cell proliferation.
In vitro Anti-Fibrotic Pharmacodynamics	*in vitro*	NA	NA	NA	KD025 blocked the expression of collagen-1a1 mRNA and reduced pro-collagen 1a secretion. Treatment of cultured human lung fibroblasts with KD025 inhibited CTGF expression, suggesting that KD025 was able to disrupt profibrotic signaling of dysregulated matrix proteins and shut off the prolonged survival mechanism of myofibroblasts.
Effect of KD025 on Chronic Graft-versus- Host Disease in Mice	Mouse/ C57BL/6	IP	0 mg/kg 100 mg/kg (QD) x 28 days	8/group	KD025 significantly improved pulmonary function tests in cGVHD mice. KD025 has no effect on body weight curves and survival rates.
Effect of KD025 on chronic graft- versus-host disease in mice	Mouse/ C57BL/6	IP	0 mg/kg 30 mg/kg 100 mg/kg 150 mg/kg (QD) x 28 days	8/group	KD025 showed dose dependent positive effects on pulmonary function. KD025 has no deleterious effects on body weight curves and survival rates. KD025 treatment improved cGVHD endpoints, including lung fibrosis.

Type of study	Test system	Method of adm.	Dose or conc.	No. per group and gender (M/F)	Noteworthy findings
A study of KD025 in the treatment of pulmonary fibrosis induced by bleomycin in C57Bl/6 mice	Mouse/ C57BL/6	Oral	0 mg/kg 50 mg/kg 100 mg/kg 150 mg/kg (QD) x 14 days	12/group	KD025 demonstrates dose dependent anti-fibrotic effects in a model of pulmonary fibrosis, when treatment was administered after significant tissue fibrosis has been established.
Effects of KD025 in a semi-therapeutic SLE model in MRL/MpJ-Faslpr/J mice	Mouse/ MRL/MpJ -Faslpr/J	Oral	0 mg/kg 100 mg/kg 175 mg/kg (QD) x 6 weeks	15/group	KD025 treatment significantly improved clinical and histological scores in MRL/MpJ-Faslpr/J mice. KD025 reduced levels of dsDNA antibodies in a dose-dependent manner.
Effect of collagen - induced arthritis model in DBA1/J mice	Mouse/ DBA/1J	IP	0 mg/kg 100 mg/kg (QD) x 30 days	6/group	KD025 treatment markedly down-regulates the progression of inflammatory arthritis in a dose-dependent manner. KD025 reduces the robust infiltration of immune cells in joints. The anti-inflammatory effect of KD025 *in vivo* is mediated by targeting and reducing the percentage of IL-17 and IL-21 expressing CD4+ T cells in spleen.

Abbreviations: adm.: Administration; cGVHD: Chronic GVHD; conc. Concentration; CTGF: Connective tissue growth factor; dsDNA: Double-stranded deoxyribonucleic acid; F: female; IL: Interleukin; IRF4: Interferon regulatory factor 4; M: male; mRNA: Messenger ribonucleic acid; NA: not applicable; QD: once daily; ROCK: Rho-associated coiled-coil containing protein kinase; RORγt: Retinoic acid-related orphan receptor γT; SLE: Systemic lupus erythematosus STAT: Signal transducer and activator of transcription; Th17: T helper 17; Treg: Regulatory T cell

In vitro

Belumosudil and its metabolite KD025m1 were ATP competitive, and selective inhibitors of full length ROCK2 isolated from rat brain homogenate. Belumosudil's IC_{50} values for inhibition of ROCK2 were generally less than 100 nM. The metabolite KD025m2 was shown to be less effective with Ki of 6 times higher than that of KD25m1 for full length ROCK2 protein that was isolated from various tumour cell lines or tissues. Belumosudil was significantly less potent against ROCK1, with enzymatic activity inhibition IC_{50} values ranging from 3 µM to greater than 10 µM.

Immunomodulatory pharmacodynamics of belumosudil was studied in different *in vitro* models. The published experimental data demonstrate the role of ROCK2 in controlling IL-21 and IL-17 secretion in human T cells via regulation that involves Th17-specific transcription factors STAT3, IRF4 and RORγt. Treatment with belumosudil led to increased percentage of Foxp3+ T cells via a STAT5-dependent mechanism and positively regulated the suppressive function of human Tregs. This indicates that belumosudil may modulate immune homeostasis in man, shifting the Th17/Treg balance towards the Treg phenotype. Re-stimulation of peripheral blood mononuclear cells obtained from the subjects in a phase 1 clinical trial (KD025-101), demonstrated that oral administration of belumosudil to healthy human subjects down-regulated the ability of T cells to secrete Th17 cytokines, such as IL-21 and IL-17 by 90% and 60% respectively in response to T-cell receptor stimulation *in vitro*.

The pathogenesis of idiopathic pulmonary fibrosis is defined by abnormalities in multiple signaling pathways and cell types that are involved in the normal wound healing process. *In vitro* anti-fibrotic effects of belumosudil included inhibition of expression of collagen mRNA and decreased collagen secretion of human lung fibroblasts, and concentration-dependent suppression of expression of connective tissue growth factor (CTGF) and α-smooth muscle actin (α-SMA) in fibroblasts.

Overall, in *in vitro* primary pharmacodynamic studies belumosudil demonstrated selectivity on ROCK2 inhibition, an effect on the T helper 17 (Th17) and regulatory T cells (Tregs) immune responses as well as on the actin/myosin cytoskeletal network and collagen formation in human cells. All these pharmacodynamic effects contribute to pathogenesis of chronic graft versus host disease (cGVHD).

In vivo

Belumosudil showed efficacy in a number of *in vivo* models that are relevant to cGVHD pathogenesis. In cGVHD mouse model with bronchiolitis obliterans syndrome, belumosudil significantly improved results of pulmonary function tests. In line with the improvement in respiratory function, belumosudil reduced collagen and antibody deposition in the lungs of treated mice. In addition, belumosudil treatment significantly reduced the percentage of Tfh cells and plasma B cells while the percentage of Tregs was increased in the spleen. Beneficial pharmacological effects were also observed in chronic sclerodermatous cGVHD mouse model, in which, compared to vehicle-treated mice, belumosudil treatment decreased the GVHD score in mice. The anti-fibrotic therapeutic benefits of belumosudil were also examined in a commonly utilized model of pulmonary fibrosis induced with bleomycin in mice. In this model belumosudil at 100 mg/kg and 150 mg/kg significantly reduced mean lung wet weight and significantly reduced pulmonary fibrosis and inflammation in comparison to vehicle-control therapy. Thus, as in the cGVHD models described above, belumosudil demonstrated anti-fibrotic effects in animal models with significant tissue fibrosis.

Besides in *in vivo* models relevant to cGVHD pathogenesis belumosudil demonstrated efficacy in a mouse systemic lupus erythematous (SLE) model and collagen-induced arthritis (CIA) model further providing evidence of its immunomodulatory activity in murine models of autoimmunity and inflammation. In murine models belumosudil had dose-dependent activity, however a plateau effect was generally reached after a 100 mg/kg dose.

2.5.2.2. Secondary pharmacodynamic studies

Table 2: summary of secondary pharmacodynamic studies with key findings (Note: KD025 = belumosudil mesylate)

Type of study	Test system	Method of administration	Dose or concentration	No. per group and gender (M/F)	Noteworthy findings
Selectivity of KD025 beyond ROCK2	*in vitro*	NA	NA	NA	KD025 demonstrated limited off target activity when evaluated in a kinase and receptor\ion channel panels.
Selectivity of KD025 beyond ROCK2 – Follow-up (adenosine A2A and A3 receptors)	*in vitro*	NA	NA	NA	KD025 was not an agonist and did not demonstrate pharmacologically relevant antagonist activity (IC_{50} >10 µM) on adenosine A2A and A3 receptors.
Cytotoxicity screening for KD025 in HepG2 cells	*in vitro*	NA	NA	NA	In HepG2 cells, there was no significant KD025-induced cytotoxicity over the concentration range from 0.009 to 150 µM.
KD025 inhibits mTOR pathway in normal and transformed fibroblasts (mTOR activity and signaling)	*in vitro*	NA	NA	NA	KD025 inhibits the mTOR pathway and reduces the proliferation of NIH3T3 mouse fibroblasts in a concentration dependent manner.
mTOR activity/signaling and HIF1a expression	*in vitro*	NA	NA	NA	KD025 reduces mTORC1 activity through activation of the upstream inhibitory TSC complex in response to increased AMPK activity. KD025 at 10 µM decreased basal (normoxic) and hypoxia-induced HIF-1 α expression.

Abbreviations: AMPK: Adenosine monophosphate-activated protein kinase; F: female; HIF-1α: Hypoxia-inducible factor-1 alpha; IC50: Half-maximal inhibitory concentration; M: male; mTOR: Mammalian target of rapamycin; NA: not applicable; ROCK: Rho-associated coiled-coil containing protein kinase; TSC: Tuberous sclerosis complex

Belumosudil was evaluated in traditional secondary pharmacodynamics selectivity assays. Belumosudil demonstrated limited off-target activity when evaluated in commercial kinase and receptor\ion channel panels. With the exception of ROCK and CK2 (IC_{50} approximately 100 nM), belumosudil IC_{50} values were above 5 µM for all other interrogated ATP-dependent kinases. In follow up cell-based target engagement assays, belumosudil did not demonstrate pharmacologically relevant CK2 activity (IC_{50}>10 µM). Likely related to its role as an ATP competitive kinase inhibitor, belumosudil inhibited ligand binding to the adenosine A2A and A3 receptors with IC_{50} values of 0.66 µM and 0.13 µM, respectively. In follow-up cell-based function assays belumosudil was not an agonist and did not demonstrate pharmacologically relevant antagonist activity (IC_{50} >10 µM) on adenosine A2A and A3 receptors. In conclusion, belumosudil is not expected to have pharmacologically relevant activity on adenosine A2A and A3 receptors. Belumosudil inhibited the mTOR

pathway in a concentration dependent manner via an indirect mechanism that involves activation of adenosine monophosphate-activated protein kinase.

HIF-1alpha is an important regulator of IL-8 expression in human bone marrow stromal cells under hypoxic microenvironment. Under normoxic conditions 10 μM belumosudil and fasudil decreased HIF-1alpha levels significantly. HT-1 080 cells exposed to hypoxic conditions for 16 hr increased expression of HIF-1alpha by upwards of four folds. Differently from fasudil, belumosudil at 10 μM decreased the level of HIF-1 alpha under hypoxic condition.

Belumosudil demonstrated several other pharmacological activities including potent inhibition of proliferation of human umbilical vein endothelial cells (HUVEC) with IC_{50} ~0.3-1 μM *in vitro*, inhibition of IFN-y stimulated secretion of monocyte chemoattractant protein-1 (MCP-1) in a dose-responsive manner in both a differentiated macrophage THP-1 cell line and in primary human macrophages freshly isolated from blood. For comparison, dual ROCK1/2 inhibition by Y-27632 did not block IFN-y stimulated secretion of MCP-1. 3T3-Ll cells maintained under differentiating condition did not appear to differentiate in the presence of 10 μM belumosudil. The reduction in fat accumulation and the reduced levels of markers of adipocyte differentiation demonstrated the ability of belumosudil to block the differentiation of preadipocytes to mature adipocytes. Differently from fasudil, pretreatment with belumosudil attenuated the increase in serum ALT and AST during LPS-induced acute liver injury in male mice.

2.5.2.3. Safety pharmacology programme

Table 3: summary of safety pharmacology studies with noteworthy findings (Note: KD025= belumosudil mesylate)

Organ system evaluated	Test system	Method of adm.	Dose or conc.	No. per group and gender (M/F)	Noteworthy findings	GLP
Central nervous system						
	Rat	Oral	Single dose 0,50, 175, 350 mg/kg	6 M/6 F	All dose levels: No adverse test article-related clinical observations. 350 mg base/kg (Males): Non-adverse transiently lower motor activity 350 mg base/kg (Females): Non-adverse transiently lower body temperature	Yes

Organ system evaluated	Test system	Method of adm.	Dose or conc.	No. per group and gender (M/F)	Noteworthy findings	GLP
Cardiovascular (*in vitro*)						
	HEK293 cells	*In vitro*	0.3 to 10 µM	NA	Belumosidil and KD025m1 inhibited hERG channel activity in a concentration-dependent manner with estimated IC_{50} of 0.6 and 1.5 µM, respectively. KD025m2 had no inhibitory effect at concentrations up to 10 µM	Yes
Cardiovascular (*in vivo*)						
	Dog	Oral	0, 25, 75, 150 mg/kg	4 M/4 F	≤150 mg base/kg (Males): No test article-related effects ≤75 mg base/kg (Females): No test article-related effects 150 mg base/kg (Females): Non-adverse and low magnitude decrease in systolic BP (up to 15 mmHg), diastolic BP (up to 11 mmHg), and mean arterial pressure (up to 11 mmHg) from 1 to 18 hours post-dose	Yes
Respiratory						
Initial study	Rat	Oral	0, 50, 175, 350 mg/kg	8 M/8 F	50 mg base/kg: No test article related findings 175 mg base/kg: Test article related decrease in absolute minute volume in males (up to 12%) 350 mg base/kg: Test article related decrease in minute volume (up to 19%), respiratory frequency (11%) and tidal volume (11%) was noted in males Study repeated to evaluate the reproducibility of effects (See 8289751 below)	Yes
Confirmatory study	Rat	Oral	0, 50, 175, 350 mg/kg	8 M/8 F	All dose levels: No test article effect on mortality, clinical observations, or any component of respiratory function.	Yes

Formal stand-alone safety pharmacology studies were conducted with belumosudil, evaluating central nervous system (CNS) (rat), *in vitro* human ether-a-go-go related gene (hERG), *in vivo* cardiovascular (dog), and respiratory (rat) function. All studies were GLP compliant.

Central Nervous System:

In the rat CNS safety pharmacology study, except for a small, transient decrease in spontaneous locomotor activity at the highest dose level of 350 mg/kg, not clinically relevant and/or adverse changes were observed in the functional observational battery to male and female rats. No PK analysis was included in the study. However, in a single oral PK study in fasted rats (SLx-PK-113-213), at dose level 150 mg/kg plasma C_{max} values for belumosudil, m2 metabolite and m1 metabolite were 2662, 560 and 1238 ng/mL, respectively. These concentrations suggest that sufficient systemic exposure was achieved both at the NOEL dose of 175 mg/kg and NOAEL dose of 350 mg/kg.

Cardiovascular:

In vitro, belumosudil and KD025m1 (minor human metabolite) inhibited hERG channel activity modestly in a concentration-dependent manner with estimated IC_{50} of 0.6 µM [272 ng/mL free drug] and 1.5 µM [616 ng/ml free drug], respectively. Metabolite KD025m2 was without effect. In fed human volunteers dosed a single 200 mg dose, C_{max} in the plasma was 2120 ng/mL (4.6 µM). Considering unbound fraction (fu) of only 0.12% for belumosudil in human plasma (Study KDM/06), C_{max} in human plasma corresponds to 2.5 ng/mL (0.0055 µM) unbound compound, which is significantly below IC_{50} for hERG inhibition.

In the *in vivo* dog cardiovascular safety pharmacology study, no evidence of changes in electrocardiogram (ECG) waveforms (PR, QRS, RR, QT, QTcV and heart rate (HR)-derived) was detected. Belumosudil demonstrated low magnitude lowering of systolic BP, diastolic BP, and mean arterial pressure in female dogs at 150 mg/kg. Administration of 150 mg/kg belumosudil to female dogs resulted in lower systolic blood pressure (up to 15 mmHg lower), diastolic blood pressure (up to 11 mmHg lower), and mean arterial pressure (up to 11 mmHg lower) from 1 to 18 hours post-dose when compared to the control group change from baseline values. These changes in arterial pressure were not considered to be adverse due to the magnitude of change.

TK analysis was included in dog cardiovascular study. Oral administration of belumosudil to male and female dogs resulted in systemic exposure to belumosudil for all animals with 2 exceptions (both males), one of which was attributable to emesis that occurred shortly after dosing. Where belumosudil exposure was low, KD025m2 and KD025m1 exposure was also low and was not measurable for 3 of 4 males at 25 mg/kg, 2 males and 1 female at 75 mg/kg, and for 1 male at 150 mg/kg. In general, exposure increased with increasing dosage for all analytes, although several individual exceptions were observed. For a 6-fold increase in dosage, exposure to belumosudil , KD025m1, and KD025m2 increased by 5- to 29-fold in terms of AUC_{last} and by 2- to 10-fold in terms of C_{max} for females. For males, where samples contained measurable analyte, exposure to belumosudil at 150 mg/kg was much lower than at 25 mg/kg for 1 animal, and much higher than at 25 mg/kg for the other 2 animals (>200-fold in terms of AUC_{last}, >50-fold for C_{max}). For males, exposure to KD025m1 and KD025m2 could only be compared for 2 males between the 75 and 150 mg/kg dosages, where AUC_{last} increased by approximately 2- to 3-fold and C_{max} increased by nearly 2-fold or was similar between the 75 and 150 mg/kg dosages. For all analytes, inter-animal variability within a group was generally greater than variability between sexes, particularly for males, where systemic exposure was not observed for several animals. Mean exposure was generally slightly higher for females than males (up to 2-fold), in terms of AUC_{last} and C_{max}. Inter-animal variability in dogs precluded rigorous assessment of dose

proportionality. For all analytes, inter-animal variability within a group was generally greater than variability between genders, particularly for males, where systemic exposure was not observed for several animals.

Respiratory system:

Belumosudil (50, 175, or 350 mg/kg) was administered once orally to male and female Sprague Dawley rats and the effect on respiration rate and tidal volume was evaluated. Lower absolute minute volume was noted in males (up to 12% lower) and females (up to 17% lower) following administration of 175 mg/kg, when compared to the vehicle-control group. Lower minute volume was noted in males (up to 19% lower) and females (up to 25% lower) following administration of 350 mg/kg. The changes in absolute minute volume were reflected as a decrease in minute volume when adjusted for pre-dose baseline position in males, but no significant differences were observed in females. Of note, dyspnea has also been reported as a side effect in clinical trials with belumosudil. Given the small magnitude of the effect of belumosudil on minute volume that was considered adverse in male rats at 175 mg/kg, the entire study was repeated to evaluate the reproducibility of this effect, and to examine any respiratory effects of belumosudil in detail. In the new study, same doses and rat strain were used. The noted changes from the previous study were not apparent in the more recent study. Of note, in the first respiratory safety study (SLX-TX-0054) C_{max} of belumosudil at 350 mg/kg dose in male rats was 6354 ng/mL in the plasma while in the confirmatory study (8289751) C_{max} after a same dose in males was 3940 ng/mL. In females such a difference in C_{max} was not observed between these studies.

2.5.2.4. Pharmacodynamic drug interactions

No studies were conducted. The Applicant justified the lack pharmacodynamic interaction studies by expected pharmacology and patient population. In the Guideline on the investigation of drug interactions (CPMP/EWP/560/95/Rev. 1 Corr. 2**) it is stated that the needed pharmacodynamic interaction studies should be determined on a case-by-case basis. The potential for pharmacodynamic interactions should be considered for drugs which compete with each other at the pharmacological target and/or have similar or opposing pharmacodynamic (therapeutic or adverse) effects. If such drugs are likely to be used concomitantly, pharmacodynamic interaction studies should be considered.

2.5.3. Pharmacokinetics

For the measurement of belumosudil (KD025, SLx-2119), minor human metabolite (KD025m1, SLx-3047) and main human metabolite (KD025m2, SLx-2131) in mouse, rat, rabbit and dog the following bioanalytical methods have been developed and used: liquid chromatography with tandem mass spectrometry (LC-MS/MS) as well as Direct QRA, Liquid Scintillation Counting, HPLC-RAD-MS/MS and Quantitative Whole-Body Autoradiography for radiolabelled studies.

Table 4: summary of analytical methods, corresponding studies, analytes and samples

Report number / method	Corresponding studies	Analyte	Sample type
WIL-602032 LC-MS/MS	WIL 602030 WIL 602029	SLx-2119 Metabolite SLx-2131 Metabolite SLx-3047	Rat plasma Dog plasma
8291392 LC-MS/MS	Covance 8289751 MPI 2420-006 MPI 2420-008	KD025 KD025m1 KD025m2	Rat plasma
1173-054 LC-MS/MS	MPI 1173-028	SLx-2119 Metabolite SLx-2131 Metabolite SLx-3047	Rat plasma
031722 LC-MS/MS	Ricerca 029502	KD025 KD025m1 KD025m2	Dog plasma
8325599 LC-MS/MS	MPI 2420-007	KD025 KD025m1 KD025m2	Rabbit plasma
1173-040 LC-MS/MS	MPI 1173-029	SLx-2119 Metabolite SLx-2131 Metabolite SLx-3047	Dog (canine) plasma
031721 LC-MS/MS	Ricerca 029281	KD025 KD025m1 KD025m2	Dog plasma
8289747 LC-MS/MS	Covance 8289750	KD025 KD025m1 KD025m2	Dog plasma

SLx-2119 = KD025; Metabolite SLx-2131= KD025m1; Metabolite SLx-3047= KD025m2

The validation reports for each analytical method have been submitted and were available for assessment. The corresponding studies were GLP-compliant and analytical method validation was conducted in accordance with GLP standards. Assay range and stability duration were appropriate for the conducted studies. Analysis of study samples were performed in line with ICH Guideline M10 on bioanalytical method validation and study sample analysis (EMA/CHMP/ICH/172948/2019).

Absorption

The data suggests that belumosudil solubility decreases when pH increases, and calculated results of efflux ratio at 10 and 100 µM belumosudi indicate that it is a substrate of efflux transporter probably saturated at 100 µM, as the recorded apical-to-basolateral permeability in Caco-2 cells was low. However, calculated results at 1 µM of belumosudil are unreliable since measurements were BLQ.

In mouse and rat single-dose studies, clearance and volume of distribution were low.

The PK/TK analysis for belumosudil was performed in large number of single-dose and repeated-dose administration studies, including repeat-dose toxicology, DART studies, safety pharmacology studies and genotoxicity studies. As belumosudil is intended for a treatment of cGVHD, the long-term repeat dose studies

are evaluated to be the most relevant studies for the kinetics evaluation. Single-dose administration by IV (dose 1mg/kg) and oral routes was performed in fed mice (20-100 mg/kg), fasted rat (10-150 mg/kg) and in second fed rat study (only oral application 150 mg/kg). In latter, influence of gender and food was also investigated.

In addition to parent compound, belumosudil metabolites KD025m1 and KD025m2 were investigated in PK/TK studies. In general, exposure to the parent drug was greater than exposure to metabolites and general picture of absorption parameters for KD025m1 and KD025m2 did not differ from parent compound.

The absorption was rapid in fed and fasted mice and variable (fast to moderate) in rats and dogs in both single- and repeated-dose oral administration. Oral bioavailability increased from 15% to 85% from the lowest to the highest dose in rodents. Generally, increase in exposure was greater than dose-proportional in low doses and dose-proportional in high doses for belumosudil and both metabolites or less than dose-proportional to belumosudil in some experiments. No significant differences were recorded between exposures on day 1 and the last day. Accumulation increased with higher dosing. In rats, exposure of females was greater than males, however, in dogs no clear sex differences were recorded. Gender differences were not studied in mice and rabbits. In dogs T_{max} was recorded from 3 to 7 hours, increasing with food and dose. No difference in the exposure levels after single-dose administration of belumosudil ≥ 1000 mg/kg (up to 2000 mg/kg) suggest saturation of absorption and metabolism. In pregnant rabbits, the exposure was generally dose-proportional for all analytes on GD6 and G18 (C_{max}) and greater than dose-proportional for AUC_{0-24}, however, with high variability in the high dose group. No accumulation was recorded in pregnant rats or rabbits.

Distribution

Tissue distribution studies in albino and partially pigmented rats by quantitative whole-body autoradiography showed rapid distribution of belumosudil to liver, adrenal gland, kidney and bladder. In all analysed tissues radiolabelled belumosudil was still present 24 hours after dosing. Concentrations of radioactivity were below the limit of quantifications at 120h timepoint in all organs except fur and liver. No radioactivity was detected in sciatic nerve or uveal tract 72h after administration, however, spinal nerve showed radioactivity at 6 and 24h after belumosudil administration but not at later time points in albino rats. In partially pigmented rats, radioactivity in the uveal tract and pigmented skin was detected, indicating some affinity of belumosudil for melanin.

The data derived by equilibrium dialysis method suggest that the binding of belumosudil to mouse, rat, rabbit, dog, and human plasma proteins is high. In human plasma, the binding to albumin was preferred independently of concentration, whereas binding to α1-acid glycoprotein decreased with increased belumosudil concentration. The suggested protein binding is high, and it is uncertain if the assay sensitivity is sufficient for the precise determination of unbound fraction. However, as the default value (1%) of unbound fraction is used in the calculation of DDI potential in clinical PK assessment, this uncertainty is accepted.

Blood to plasma partition was evaluated in human, dog, rabbit, rat and mouse whole blood. This data suggested that belumosudil distributes in plasma in greater extent than to blood in all species but rabbit.

No placental transfer or excretion to milk were studied.

Metabolism

Belumosudil metabolism was studied in mouse, rat, rabbit, dog and human microsomes and hepatocytes. The *in vitro* clearance was high (>0.7) in rodents, dog and human and moderate (0.3-0.7) in rabbit. 32 metabolites were identified in liver microsomes and 28 in hepatocytes. In human samples, 2 metabolites

were identified (M21[glucuronidation] and M28/KD025m2) in >5% normalised peak area, KD025m2, proposed as the hydrolysis metabolite of the parent drug, present in all species and being the main metabolite in humans. KD025m1, de-alkylation metabolite, was identified in samples from all species and was considered as minor metabolite in humans. M21[glucuronidation] was detected in > 6% in human samples (microsomes/ hepatocytes) but only low percentage in rabbit samples (appr. 1%) and in very low percentage in dog and rat samples (≤0.12%) *in vitro*. In rats, unchanged belumosudil was the major component in plasma and faeces. In females, the percentage of unchanged belumosudil was markable higher than in males. Belumosudil was not detected in the urine. In plasma, 4 main metabolites were identified in males and 2 main metabolites in females. In faeces, 2 main metabolites were identified in males and 1 main metabolite in females. Main circulating metabolites KD025m1 (P6) and KD025m2 (P11) were only detected in male rats. These data suggest than males metabolise belumosudil more efficiently than females. Human metabolite M21[glucuronidation] was identified only in low levels in non-clinical species but >5% in human samples. The non-clinical characterisation of this metabolite remains limited; however, it is not foreseen as a toxicological concern based on the metabolic mechanism (glucuronidation) and considering the exposure is below 10%. Toxicological potential of reactive intermediates of all metabolites was not discussed. This is considered acceptable based on limited exposure.

Belumosudil was suggested to be mainly metabolised via CYP1A2, CYP2C8, CYP2D6, CYP3A4 and UGT1A9. Specifically, CYP3A4 may be involved in the formation of KD025m2 and CYP2C8 and CYP3A4 are involved in the formation of KD025m1. Incubations of KD025m2 with recombinant enzymes indicated that UGT1A1 may be involved in the further metabolism of KD025m2, with little to no contribution from CYP enzymes. The analysis of clinical samples (plasma and faeces) further confirmed that KD025m2 is the main metabolite in humans. Major contribution to metabolism of KD025 was recorded with CYP3A4/5 (41.9%), minor contribution with CYP2D6 (21.7%) and CYP2C8 (14.2%). *In vitro* data suggests some increase in mRNA levels of CYP1A1, CYP2B6 and CYP3A4 caused by belumosudil whereas KD025m2 had little or no effect on these parameters. Belumosudil directly inhibited CYP2C8, CYP2C9, CYP1A2, CYP2C19, CYP2D6 and CYP3A4/5. It is a competitive inhibitor of CYP2C8 and competitive/noncompetitive inhibitor of CYP2C9, and time- and NADPH-dependent inhibitor of CYP1A2, CYP2C19, CYP2D6 and CYP3A4/5. KD025m2 directly inhibited CYP1A2, CYP2C8, CYP2C9 and CYP3A4/5. It is metabolism-dependent inhibitor of CYP3A4/5 activities.

Excretion

The excretion study in rats show that belumosudil is predominantly excreted *via* the faecal route. No gender differences were observed.

No information is provided on excretion to milk.

PK drug interactions

Belumosudil is a substrate of P-gp and an inhibitor of P-gp, BCRP, OATP1B1, MATE and MATE2-K. Main metabolite KD025m2 is a substrate of a substrate of BSEP, OATP1B1, OATP1B3, OAT1, OAT3 and MATE2-K and an inhibitor of OATP1B1 (IC_{50} < 1µM) and less potent inhibitor of BCRP, BSEP, OATP1B3, OAT3, MATE1 and MATE2-K (IC_{50} > 1µM).

The inhibition effects for UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, UGT2B7, and UGT2B15 were recorded for belumosudil and for UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, UGT2B7, UGT2B15, and UGT2B17 for KD025m2.

2.5.4. Toxicology

2.5.4.1. Single dose toxicity

Table 5: single dose toxicity studies conducted and their respective findings

Study details Species Duration + recovery (weeks) Route GLP status (Study ID)	**No: Sex/ Group**	**Dose** (mg/kg/ day)	**Exposure**		**Major findings**
			sex	C_{max} *Belumosudil* *KD025m1* *KD025m2* ng/ml	
Single-dose toxicity studies (NOAEL /MTD in bold)					
Rat PO GLP Dosing D1, necropsy D5 (0500-05015)	5 M + 5 F	100[a]	M	4660 1387 604	600 mg/kg/day: Mortality of one F on D1, one M on D2, one F on day 5. Gasping, laboured breathing, dyspnoea, dehydration. Distended stomach/GI with test article-like contents and/or gas, enlarged adrenals, mottled red lungs.
			F	1606 615 267	
		200[a]	M	4525 2577 1394	
			F	4661 1141 596	
		200[b]	M	4887 874 380	
			F	5203 738 235	
		400[b]	**M**	**3964** **1296** **538**	
			F	**5837** **545** **213**	
		600[b]	M	2172 1149 538	
			F	2375 169 60	
Dog PO Termination 7 days after last dose Non-GLP (1173-023)	2 M + 2 F Dose-escalation 3 days washout between doses	**50[b]**		**NA**	200 mg/kg (F): Emesis 250 and 300 mg/kg: Emesis 400 mg/kg: Emesis and faecal changes
		200[b]		**NA**	
		250[b]		NA	
		300[b]		NA	
		400[b]		NA	

[a] Trifluoroacetic acid salt form (not belumosudil mesulate).
[b] Mono-hydrochloride salt form (not belumosudil mesulate).

2.5.4.2. Repeat dose toxicity

Repeat-dose toxicity of belumosudil was investigated in total of 6 GLP-compliant studies: 28-day and 3/6-month rat studies and 7-day, 28-day, 13-week and 9-month dog studies. The summary of all data is presented in **Table 6**.

Table 6: summary of repeat-dose toxicity studies performed with belumosudil

Study details Species Duration + recovery (weeks) Route GLP status (Study ID)	**No: Sex/ Group**	**Dose** (mg/ kg/ day)	**Exposure**		**Major findings & NOAEL**
			C_{max}[a] ng/ml	AUC_{0-24}[a] ng*h/ml	
Repeat-dose toxicity studies (NOAELs in bold)					
Rat (Sprague-Dawley) 28 days + 14 days recovery for negative control and high dose group PO GLP (SLX-TX-0051)	M 10	50	1 950	14 400	**50 mg/kg/day:** ↑liver weight (non-adverse); Panlobular hepatocellular hypertrophy (non-adverse) **150 mg/kg/day:** Generally similar as above sometimes with increased severity; ↓ BW gain and/or FC (non-adverse); Mild ↓in red cell mass (non-adverse) **375 mg/kg/day:** Mortality (2 F); Clinical signs of intolerability (F); ↓BW gain and food consumption; ↑heart and liver weight; ↓pituitary, ovary, and uterus weight; panlobular hepatocellular hypertrophy with ↑GGT, ALP, Tbil, triglycerides, cholesterol, and HDL cholesterol. ↓red cell mass with bone marrow hyperplasia, ↑reticulocytes and platelets and some variable changes in PT time. Some findings still evident after the 2-week recovery period
	M 10	**150**	**5 750**	**68 500**	
	M 15	375	13 900	150 000	
	F 10	50	4 010	40 400	
	F 10	**150**	**9 640**	**98 000**	
	F 15	375	23 000	369 000	
Rat (Sprague-Dawley) 3/6 months (termination on D92 + recovery group termination on D120 / Termination on D183 + recovery group termination on D211) PO GLP (029502)	M25	50	3 640/ 2 980[b]	24 000/ 25 000[b]	**50 mg/kg/day:** ↓BW gain and food consumption (Non-adverse); ↑Organ weights (reversible): Adrenal glands, heart, kidneys, liver, thyroid/parathyroid, spleen; histological organ changes: Non-adverse in adrenal gland [hypertrophy], liver [hypertrophy], kidney [basophilia of tubules, protein droplets, and diffuse gold pigmentation of tubules], spleen [↑lymphocytes], thymus [lymphocyte depletion], and thyroid [↓colloid/hypertrophy], testes [degeneration]; Mild ↓in red cell mass and other clinical pathology changes (non-adverse); Majority of findings were reversible or partially reversible. Male NOAEL < 50 mg/kg/day. **125 mg/kg/day:** Generally similar as above sometimes with ↑severity; Non-adverse additional clinical pathology (↓serum cholinesterase and sodium, ↑albumin and TP)
	M25	125	10 400/ 7 100[b]	68 300/ 61 500[b]	
	M35	275	13 900/ 10 600[b]	162 000/ 112 000[b]	
	F25	50	8 670/ 7 390[b]	60 400/ 73 500[b]	
	F25	**125**	**15 800/ 14 900**[b]	**164 000/ 167 000**[b]	
	F35	275	29 600/ 29 500[b]	394 000/ 474 000[b]	

					↓RBC counts, mean haemoglobin concentration, mean haematocrit; ↑mean reticulocyte counts (adverse in F) **275 mg/kg/day**: Generally similar as above sometimes with ↑severity; Mortality (1 F, Day 85, enlarged liver, thymus multifocal congestion, hypertrophy of adrenal cortex, gold pigmentation of proximal tubules, diffuse depletion of lymphocytes of the thymic cortex). ↑GGT, ALP, and Tbil; ↑Organ weights: Adrenal glands, heart, kidneys, liver, thyroid/ parathyroid, spleen; Organ histological changes (Epididymis [degeneration], Cervix [hypoplasia], Ovaries [↓follicular development], Uterus [hypoplasia]) ↓RBC counts, mean haemoglobin concentration, mean haematocrit; ↑mean reticulocyte counts (adverse in F) **TK:** Belumosudil exposure ↑linearly, no sex differences. Moderate accumulation. KD025m1 and KD025m2 showed higher TK values in M than in F, moderate accumulation.
Dog 7 days[f] PO Non-GLP SLX-TX-0071	2M/ 2F	25	647[d]	3606[d]	**25 mg/kg/day:** Infrequent emesis **100 mg/kg/day:** Mild ↓in BW and food consumption, emesis; Mild ↓in red cell mass **200 mg/kg/day:** Mild ↓in BW and food consumption, emesis; faecal changes, mild ↓in red cell mass, and sporadic ↓in phosphorus (1 animal)
		100	3827[d]	28219[d]	
		200	**1847**[d]	**27911**[d]	
Dog 28 days[f] + 14 day recovery period PO GLP SLX-TX-0073	4M/4F 4M/4F 6M/6F	25	2690[d]	12800[d]	**25 mg/kg/day:** ↓thymus weight **75 mg/kg/day:** Infrequent emesis; Mild ↓in red cell mass (with ↑reticulocytes), ↓thymus weight. **200/125 mg/kg/day:** Severe BW Loss and intolerability; ↓red cell mass (with ↑reticulocytes); ↑ALP, GGT, Tbil, urine volume, and liver weights; ↓thymus weight, Liver histopathology [cholestasis sometimes with hepatocellular vacuolation, biliary hyperplasia, and ↑pigment in Kupffer cells].
		75	**5790**[d]	**41200**[d]	
		200/ 125[C]	7330[d]	60100[d]	
Dog 3 months[g] + 28 day recovery period PO GLP 029281	8M 8M 12M	35	4910	25200	**35 mg/kg/day:** ↓BW gain and food consumption (non-adverse); ↑liver weights (non-adverse); Mild ↓in red cell mass (with rebound reticulocytes); non-adverse histopathology in spleen [lymphocyte depletion], and thymus [lymphocyte depletion]; adverse histopathology in epididymides [degeneration] and testes [degeneration]; all findings reversible. Male NOAEL < 35 mg/kg/day. **70 mg/kg/day:** ↓BW Gain and food consumption (adverse); Mild ↓in red cell mass (with ↑platelets and rebound reticulocytes]; ↑liver weight; ↓spleen and thymus weight; histopathology in Liver [multifocal centrilobular biliary stasis and/or diffuse atrophy sometimes with increased ALT], Kidney [multifocal bilateral gold/brown pigment of renal proximal tubule epithelium], spleen [lymphocyte depletion], and thymus [lymphocyte depletion]; adverse histopathology in epididymides [degeneration] and testes [degeneration]; all
		70	6170	44800	
		125	NA[e]	NA[e]	
	8F 8F 12F	**35**	**4620**	**23300**	
		70	7250	50100	
		125	NA[e]	NA[e]	

					findings reversible except for liver and kidney. **125 mg/kg/day[h]:** Generally similar as above with higher severity Mortality \Morbidity (2 M, Day 21); not well tolerated. Severe ↓in BW and food consumption; Multiple organ macroscopic, weight, and histopathology findings. TK: Linear increase of exposure, no sex differences. Accumulation of belumosudil and main metabolites was recorded.
Dog 9 months[f] + 8 week recovery period PO GLP 8289750	8M 10M 12M	5	386	1180	**5 mg/kg/day:** None **20 mg/kg/day:** Infrequent emesis; ↑ALT and liver weights. Low magnitude liver histopathology (↑mononuclear cell infiltrates and degeneration/necrosis).. **40 mg/kg/day:** Generally similar as above with higher incidence and the addition of ↓BW gain and food consumption.
		20	**854**	**4040**	
		40	2060	15500	
	8F 10F 12F	5	249	833	
		20	**1480**	**8400**	
		40	3220	22500	
[a] Last dose exposures [b] 3/6 month exposures [c] Dose reduction: 200 mg/kg belumosudil on Days 1-14, no dosing D15-18, and 125 mg/kg on D19-28. [d] Gender combined exposure [e] Not tolerated; high dose cessation on Day 21; animals euthanized on Day 51 (limited histopathology and no TK conducted). [f] *Ad libitum* feeding [g] Animals offered food for 4 hours per day (starting 0.5-1h prior to dosing) [h] Not tolerated; high dose cessation on Day 21; animals euthanized on day 51(Limited histopathology and no TK conducted)					

2.5.4.3. Genotoxicity

The results of the genotoxicity studies are displayed in the table below.

Table 7: summary of genotoxicity studies performed with belumosudil

Type of test/study ID/GLP	**Test system**	**Concentrations/ Concentration range/ Metabolising system**	**Results positive/negative/equivocal**
Gene mutations in bacteria GLP SLX-TX-0068	Salmonella typhimurium strains TA98, TA100, TA1535 and TA1537 Escherichia coli strain WP2 uvrA instead of the TA102	TA1535: 15, 50, 150, 500, 1500 and 5000 µg per plate +/- S9 TA98, TA100, TA1537, WP2 uvrA: 50, 150, 500, 1500 and 5000 µg per plate +/- S9 +/- S9	**Negative** in the presence and absence of S9. No toxicity was observed.
Mammalian chromosome aberration test GLP SLX-TX-0069	Human peripheral blood lymphocytes (HPBL)	6.25 to 250 µg/mL +/- S9 4hr exposure group; 3.13 to 150 µg/mL- S9 20hr exposure group	**Negative**. Only 200 cells per concentration were evaluated instead of 300 (OECD GL 473).
Chromosomal aberrations *in vivo* GLP SLX-TX-0067	Rat erythrocyte micronucleus test	5M/5F rats: Control (24/48h), positive control (24h), or 500 (24h), 1000 (24h) or 2000 (24/48h) mg/kg belumosudil	No mortality, no life threatening clinical signs of toxicity. No significant increase of micronucleated polychromatic erythrocytes. **Negative** (C_{max} 12 403 ng/mL (males) / 11 120 ng/mL

			(females); AUC_{0-24} 174 789 h*ng/mL (males) / 181 366 h*ng/mL (females).

2.5.4.4. Carcinogenicity

The results of the carcinogenicity studies are displayed in the table below.

Table 8: summary of carcinogenicity studies performed with belumosudil

Study details Species Duration (weeks) Route GLP status (Study ID)	**No: Sex/ Group**	**Dose** (mg/kg/ day)	**Exposure** Plasma concentrations (ng/ml) 2h post-dose (D1/D180)		**Major findings**
				Carcinogenicity studies (NOAELs highlighted)	
Mouse (tg-rasH2) 26 weeks Oral GLP CAR0205 Positive control urethane (ip)	25 / M	0	-		No belumosudil-related effects on survival. Significant Harderian gland adenoma incidence increase across doses in females (not related to belumosudil). No belumosudil-related neoplastic or non-neoplastic findings. Urethane exhibited expected neoplastic changes, assay considered validated. **TK:** In general, increased exposure with increased dose for belumosudil and metabolites KD025m1 and KD025m2
		8	170.9/190.3		
		15	332.7/399.7		
		30	2101/2157		
	25 / F	0	-		
		4	93.43/66.33		
		8	197.3/342.7		
		15	465.7/714		
Rat (Sprague-Dawley)	*Ongoing*				

2.5.4.5. Reproductive and developmental toxicity

The results of the reproductive and developmental toxicity studies are displayed in the table below.

Table 9: summary of reproductive and developmental toxicity studies performed with belumosudil

Study details Species treatment period Route GLP status (Study ID)	**No: Sex/ Group**	**Dose** (mg/ kg/ day)	**Exposure**		**Major findings & NOAEL**
			C_{max} ng/ml	AUC_{0-24} ng/ml/h	
Fertility and early embryonic development studies (NOAELs in bold)					
Rat (Sprague-Dawley) 14 days prior to pairing + mating period to GD 7 PO GLP 2420-008	25F 25F 25F	**50** **150** **275**	3200 9860 14900	26 200 99 500 209 000	**50 mg/kg, general toxicity NOAEL:** Low magnitude decrease in body weight gain and food consumption (non-adverse) **150 mg/kg, embryo-foetal NOAEL:** Decreased body weight gain and food consumption (adverse) **275 mg/kg, fertility NOAEL:** Abnormal faeces and thin body condition (adverse), decreased BW gain and food consumption (adverse) Increased post-implantation loss (19.42% vs 3.55% in controls) and resorptions (2.8 vs 0.5 per animal in controls), decrease in viable embryos (10.3 vs 13.1 embryos in controls).
Rat (Sprague-Dawley) 70 days prior to pairing + mating period to GD 7 PO C-section GD13 GLP 2420-008	25M 25M 25M	**50** **150** 275	2480 10 100 20 400	21 600 70 100 191 000	**50 mg/kg, general toxicity NOAEL:** Low magnitude decrease in body weight gain and food consumption (non-adverse) **150 mg/kg/day, fertility NOAEL:** Decreased body weight gain and food consumption (adverse) **275 mg/kg:** Abnormal faeces and thin body condition (adverse), decreased body weight gain and food consumption (adverse), decreased fertility rate, decreased testes\epididymis size and organ weight, abnormal sperm parameters (low motility (59.3% vs 91.8% in control rats) and concentration; increased abnormal sperm morphology), testes/epididymis histopathology

Study details Species treatment period Route GLP status (Study ID)	**No: Sex/ Group**	**Dose** (mg/ kg/ day)	**Exposure**		**Major findings & NOAEL**
			C_{max} ng/ml	AUC_{0-24} ng/ml/h	
					(degeneration/atrophy in 16 out of 25 rats)
Embryo-foetal toxicity studies (NOAELs in bold)					
Rat (Sprague-Dawley) Exploratory GD6-GD17 (Dosing) C-Section GD20 PO Non-GLP 2420-004	5 (main) + 6 (TK) F	25	1 800	20 400	**25 mg/kg/day:** Slight reduction in maternal body weight gain and food consumption toxicity, slightly decreased foetal weight (female only) **50 mg/kg/day:** Slight reduction in maternal body weight gain and food consumption, increased foetal post-implantation loss (11.62% vs 4.41% in controls)\viable litter size (11.6 vs 12.8 in controls), foetal malformations (edematous, whole body or absent anus and tail) in 2 foetus **150 mg/kg/day**: Moderate decrease in maternal body weight gain and food consumption, decreased foetal weight, foetal malformations (omphalocele) in 1 foetus **300 mg/kg/day:** Excessive decrease in maternal body weight gain and food consumption, increased foetal post-implantation loss (24.51% vs 4.41 on controls)\viable litter size (10 vs 12.8 in controls), decreased foetal weight, foetal malformations (dome-shaped head) in 1 foetus.
		50	5 110	61 800	
		150	8 790	120 000	
		300	14 700	193 000	
Rat (Sprague-Dawley) GD6-GD17 (Dosing) C-Section GD20 PO GLP	25 (main) + 10 (TK) F	**15**	**1 320**	**11 900**	**15 mg/kg/day (Maternal NOAEL):** None **50 mg/kg/day (Embryo-foetal NOAEL):** Decreased body weight gain and food consumption **150 mg/kg/day:** Decreased body weight gain and food consumption; decreased foetal body weight (3.82 vs 4.12 in controls)
		50	**4 360**	**33 300**	
		150	7 800	88 300	

Study details Species treatment period Route GLP status (Study ID) 2420-006	**No: Sex/ Group**	**Dose** (mg/ kg/ day)	**Exposure**		**Major findings & NOAEL**
			C_{max} ng/ml	AUC_{0-24} ng/ml/h	
Rabbit (New Zealand White) Exploratory Phase A: 5 day dose range-finding study (non-pregnant rabbits), termination D20 Phase B: GD6-GD18 (Dosing) C-Section GD28 PO Non-GLP 2420-005	A:2 B:6 A:2 B:6 A:2 A:2 B:6 A:2 A:2 B:6 A:2 A:2 B: 4 (TK) in all dose groups	25	207	568	***Phase B*** **25 mg/kg/day:** None **50 mg/kg/day:** None **100 and 250 mg/kg/day:** Dose dependent decrease in maternal body weight gain/loss, decreased food consumption, clinical signs (inappetence, faecal abnormalities, thin appearance), and veterinary intervention (food enrichment).
		50	**621**	**2 480**	
		75	NA	NA	
		100	699	3 160	
		125	NA	NA	
		200	NA	NA	
		250	2100	15 600	
		300	NA	NA	
		400	NA	NA	
Rabbit (New Zealand White) GD6-GD18 (Dosing) C-Section GD28 PO GLP 2420-007	23 (main) + 5 (TK)	**50**	**437**	**1 590**	**50 mg/kg/day (Embryo-foetal and maternal NOAEL):** None **125 mg/kg/day:** Decreased body weight gain and food consumption, abortion (1 F, GD19), increased post-implantation loss (7.42% vs 4.07% in controls)/decreased viable litter size (8.0 vs 8.4 in controls and 8.64 in historical control data). **225 mg/kg/day:** Body weight loss and decreased food consumption, thin appearance, mortality (1 F, GD9), Abortion (1 F, GD19), increased post-implantation loss (17.72% vs 4.07% in controls)/decreased viable litter size (7.4 vs 8.4 in controls and 8.64 in historical
		125	1 670	9 290	
		225	2 380	23 500	

Study details Species treatment period Route GLP status (Study ID)	**No: Sex/ Group**	**Dose** (mg/ kg/ day)	**Exposure**		**Major findings & NOAEL**
			C_{max} ng/ml	AUC_{0-24} ng/ml/h	
					control data), decreased foetal body weights, malformations (short tail, thoracic cavity and thoracic vertebral malformations, such as ribs branched, fused or misshapen, sternebrae fused/extra, neural arches fused, misaligned, misshapen).

2.5.4.6. Toxicokinetic data

The results of the toxicokinetic studies are displayed in the table below.

Table 10: summary of the toxicokinetic studies performed with belumosudil

Study ID/ species	**Dose (mg/kg)**	**Study day / week**	**Animal AUC_{0-24} (ng*h/ml)**		**C_{max} (ng/ml)**	
			♂	♀	♂	♀
SLX-TX-0051 / Rat						
Belumosudil	50	Day 28	14400	40400	1950	4010
	150		**68500**	**98000**	**5750**	**9640**
	375		150000	369000	13900	12000
KD025m1	50		8140	6520	9930	6220
	150		20800	17500	20000	8890
	375		34200	46400	29100	16700
KD025m2	50		4350	3290	5430	3590
	150		11500	7950	11100	4320
	375		18000	24100	15800	8920
029502 /Rat						
Belumosudil	50	Day 179	25000	73500	2980	7390
	125		61500	**167000**	7100	**14900**
	275		112000	474000	10600	29500
KD025m1	50		8020	7920	710	865
	125		19700	23000	2100	2060
	275		31900	52700	2180	3090

KD025m2	50		5500	4390	662	412
	125		14400	11700	1430	1090
	275		17300	24400	1650	1250
SLX-TX-0073 / Dog (only combined exposure data for M + F available)						
Belumosudil	25	Day 28	12800		2690	
	75		**41200**		**5790**	
	200/125		60100		7330	
KD025m1	25		1350		278	
	75		8010		1000	
	200/125		14100		1590	
KD025m2	25		567		98.2	
	75		1150		129	
	200/125		1680		169	
029281 / Dog						
Belumosudil	**35**	Day 91	25200	**23300**	4910	**4620**
	70		44800	50100	6170	7250
	125		NA	NA	NA	NA
KD025m1	35		2290	2360	445	430
	70		6050	8840	761	1210
	125		NA	NA	NA	NA
KD025m2	35		979	969	151	150
	70		1610	1590	149	175
	125		NA	NA	NA	NA
8289750 / Dog						
Belumosudil	5	Week 39	1180	833	386	249
	20		**4040**	**8400**	**854**	**1480**
	40		15500	22500	2060	3220
KD025m1	5		NA	NA	NA	NA
	20		259	712	54.7	153
	40		1430	2710	239	379
KD025m2	5		NA	NA	NA	NA
	20		335	538	61.9	89.9
	40		1390	1520	141	175
SLX-TX-0067 / Rat						
Belumosudil	2000	Day 1	174789	18366	12403	11120

20332155 / Mouse						
Belumosudil	15	Day 28	2350	5200	870	1390
	75		**31500**	**48600**	**5340**	**6780**
	225		132000	275000	12900	21500
2420-008 / Rat						
Belumosudil	50	Day 70 (males) / Day 14 (females)	21600	26200	2480	3200
	150		**70100**	99500	**10100**	9860
	275		191000	**209500**	20400	**14900**
KD025m1	50		8460	3690	770	294
	150		16200	18200	1800	1260
	275		44200	37000	3350	2290
KD025m2	50		4080	1390	410	125
	150		9520	7110	1070	523
	275		28900	20700	1900	1480
2420-006 / Rat						
Belumosudil	**15**	GD17 (females)		**11900**		**1320**
	50			**33300**		**4360**
	150			88300		7800
KD025m1	15			572		55.6
	50			3580		350
	150			11100		972
KD025m2	15			978		93.3
	50			5040		434
	150			16400		1310
2420-007 / Rabbit						
Belumosudil	**50**	GD18 (females)		**1590**		**437**
	125			9290		1670
	225			23500		2580
KD025m1	**50**			**2470**		**1120**
	125			16700		3610
	225			41500		4620
KD025m2	**50**			**1220**		**569**
	125			2740		1350
	225			14800		1680

Table 11: safety exposure margins based on animal exposures

Study ID/ species	NOAEL (mg/kg/day)	Animal AUC (ng.h/ml)		Cmax (ng/ml)		Animal: Human Exposure Ratio (200 mg QD)	
		♂	♀	♂	♀	♂	♀
Rat Toxicology (3/6 months)	M 125/<*50** F 125	68300/ *25000**	164000/ 167000	10400/ *2980**	15800/ 14900	3.0/<*1.1**	7.2 / 7.4
Rat Embryo-foetal (GD6-17)	F 50		33300		4360		1.4
Rat Fertility 70 days (M) 14 days (F)	M 150 F275	70100	209000	10100	14900	3.0	9.2
Rabbit Embryo-foetal GD6-18	F 50		1590		437		0.08
Dog Toxicology 3 months	M <*35** F 35	*25200**	23300	*4910**	4620	<*1.1**	1.0
Dog Toxicology 39 weeks	M 20 F 20	4040	8400	854	1480	0.2	0.4

2.5.4.7. Tolerance

No separate local tolerance studies have been conducted.

2.5.4.8. Other toxicity studies

Studies on impurities

The *in silico* prediction resulted in identification of N-nitro or N-nitroso compound (cohort of concern), three known mutagenic carcinogens (ICH M7 Class 1 substances) and three known mutagens (ICH M7 Class 2 substances) were identified in the databases. No non-clinical studies have been performed to qualify impurities. The detailed impurity analysis and their control strategy was included in the Quality dossier and assessed in the Quality section.

Phototoxicity

The summary of the phototoxicity studies is presented in table below

Table 12: summary of the phototoxicity studies performed with belumosudil

Type	Concentration Levels Evaluated (mg/mL)	Positive/ Negative	Study Summary
UV and Visible Light In-Vitro absorption (OECD Method) Study 20082808 Non-GLP	Various	**Positive** Phototoxic Potential	Under the conditions of this study, belumosudil was concluded to have absorption between 290 and 370 nm with a peak MEC of 10 743 L mol^{-1} cm^{-1}
In Vitro Mouse 3T3 Neutral Red Uptake Assay (OECD Method) Study 20082809 GLP	Various	**Positive** Phototoxic Potential	Under the conditions of this study, belumosudil reduced the viability of 3T3 mouse fibroblasts in the presence of UV light compared to UV light alone.

Abbreviations: MEC: Molar extinction coefficient; OECD: Organization for Economic Cooperation and Development; UV : Ultraviolet

2.5.5. Ecotoxicity/environmental risk assessment

Summary of main study results

Substance (INN/Invented Name): belumosudil			
CAS-number: belumosudil free base: 911417-87-3 belumosudil mesylate: 2109704-99-4			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	Test method not known	3.5 at pH 6.5	Potential PBT: N
PBT-statement:	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater\ ,\ refined}$	0.008	µg/L	> 0.01 threshold:N
Other concerns (e.g. chemical class)			N

Octanol/Water Partition coefficient (Log K_{ow}, Log P_{ow}) of belumosudil was determined to be 3.5 at pH 6.5 indicating that there is no further need to screen the compound for persistence, bioaccumulation and toxicity.

The Applicant refined F_{pen} based on projected sales of belumosudil and epidemiology data for the medicinal product with Orphan Status in Europe. Using the refined F_{pen} PEC_{SW} was calculated to be 0.008 µg/L, which is less than threshold 0.01 µg/L requiring Phase II Risk assessment. The Applicant calculated belumosudil consumption (mg/year) based on prevalence 0,00008 for GVHD in EU. This consumption-based approach for refining Fpen is not mentioned in the updated ERA guideline anymore. According to EMEA/CHMP/SWP/4447/00 Rev. 1, for orphan drug submissions, Fpen can be refined based on the prevalence for which the medicinal orphan drug designation was based, as adopted by the Committee for Orphan Medicinal Products (COMP). Using the prevalence 8/100 000 $_{Fpen\text{-}refined}$ = 0.00008, the refined F_{pen} results in PEC_{SW} that is equal to the one calculated by the Applicant.

2.5.6. Discussion on non-clinical aspects

Pharmacology

In vitro primary pharmacodynamics

Belumosudil and its minor metabolite KD025m1 were ATP competitive, and selective inhibitors of full length ROCK2 isolated from rat brain homogenate. Belumosudil's IC_{50} values for inhibition of ROCK2 were generally less than 100 nM. The metabolite KD025m2 was less effective with Ki of 6 times higher than that of KD25m1 for full length ROCK2 protein that was isolated from various tumour cell lines or tissues. Belumosudil was significantly less potent against ROCK1, with enzymatic activity inhibition IC_{50} values ranging from 3 µM to greater than 10 µM.

Immunomodulatory pharmacodynamics of belumosudil was studied in different *in vitro* models. The published experimental data demonstrate the role of ROCK2 in controlling IL-21 and IL-17 secretion in human T cells via regulation that involves Th17-specific transcription factors STAT3, IRF4 and RORγt. Treatment with belumosudil led to increased percentage of Foxp3+ T cells via a STAT5-dependent mechanism and positively regulated the suppressive function of human Tregs. This indicates that belumosudil may modulate immune homeostasis in man, shifting the Th17/Treg balance towards the Treg phenotype. Re-stimulation of peripheral blood mononuclear cells obtained from the subjects in a phase 1 clinical trial (KD025-101),

demonstrated that oral administration of belumosudil to healthy human subjects down-regulated the ability of T cells to secrete Th17 cytokines, such as IL-21 and IL-17 by 90% and 60% respectively in response to T-cell receptor stimulation *in vitro*.

Fibrosis is characterized by excess accumulation of collagens and other matrix proteins, which disrupts tissue architectures and ultimately leads to organ failure. *In vitro* anti-fibrotic effects of belumosudil included inhibition of expression of collagen mRNA and decreased collagen secretion of human lung fibroblasts, and concentration-dependent suppression of expression of connective tissue growth factor (CTGF) and α-smooth muscle actin (α-SMA) in fibroblasts.

Overall, in *in vitro* pharmacological studies belumosudil demonstrated an effect on the T helper 17 (Th17) and regulatory T cells (Tregs) immune responses as well as on the actin/myosin cytoskeletal network and collagen formation in human cells. All these pharmacodynamic effects contribute to pathogenesis of cGVHD.

In vivo primary pharmacodynamics

Belumosudil showed efficacy in a number of *in vivo* models that are relevant to cGVHD pathogenesis. In cGVHD mouse model with bronchiolitis obliterans syndrome, belumosudil significantly improved results of pulmonary function tests. In line with the improvement in respiratory function, belumosudil reduced collagen and antibody deposition in the lungs of treated mice. In addition, belumosudil treatment significantly reduced the percentage of T follicular helper (Tfh) cells and plasma B cells while the percentage of Tregs was increased in the spleen.

Beneficial pharmacological effects were also observed in chronic sclerodermatous cGVHD mouse model, in which, compared to vehicle-treated mice, belumosudil treatment decreased the GVHD score in mice. The anti-fibrotic therapeutic benefits of belumosudil were also examined in a commonly utilized model of pulmonary fibrosis induced with bleomycin in mice. In this model belumosudil at 100 mg/kg and 150 mg/kg significantly reduced mean lung wet weight and significantly reduced pulmonary fibrosis and inflammation in comparison to vehicle-control therapy. Thus, as in the cGVHD models described above, belumosudil demonstrated anti-fibrotic effects in animal models with significant tissue fibrosis.

Besides in *in vivo* models relevant to cGVHD pathogenesis belumosudil demonstrated efficacy in a mouse SLE model and collagen-induced arthritis (CIA)-model further providing evidence of its immunomodulatory activity in murine models of autoimmunity and inflammation. In murine models belumosudil had dose-dependent activity, however a plateau effect was generally reached after a 100 mg/kg dose.

Secondary pharmacodynamics

Belumosudil was evaluated in traditional secondary pharmacodynamics selectivity assays. Belumosudil demonstrated limited off-target activity when evaluated in commercial kinase and receptor\ion channel panels. With the exception of ROCK and CK2 (IC_{50} approximately 100 nM), belumosudil IC_{50} values were above 5 µM for all other interrogated ATP-dependent kinases. In follow-up cell-based target engagement assays, belumosudil did not demonstrate pharmacologically relevant CK2 activity (IC_{50}>10 µM). The Applicant claimed that in cell-based function assays belumosudil was not an agonist and did not demonstrate pharmacologically relevant antagonist activity (IC_{50} >10 µM) on adenosine A2A and A3 receptors. However, in the follow-up cell based functional assays (TW04-0007414), belumosudil demonstrated an *in vitro* pharmacologically relevant antagonist activity on human adenosine A2A receptor. The IC_{50} of belumosudil was 0.350 µM (i.e. 158 ng/mL of free base). In cGVHD patients (200 mg daily, tablet, fed, no perpetrator), the maximum concentration (Cmax) in plasma at steady state was 2230 ng/mL. With 0.11% of belumosudil unbound fraction, the unbound concentration is 2.45 ng/mL, which is insufficient to efficiently antagonize the

adenosine A2A receptors in patients. If the adenosine A2A receptor antagonism was nevertheless achieved *in vivo*, effects could have been produced, in particular neurological or immune-related effects. However, belumosudil is not brain penetrant and demonstrates no central nervous system-related toxicities in safety pharmacology and toxicology studies, suggesting the brain adenosine A2A receptor could not be engaged by belumosudil. Regarding immune cells, the outcome of belumosudil (mainly reduced inflammation), indicates a potential A2A antagonism of belumosudil is likely insignificant, when immunosuppression is reached.

Belumosudil inhibited the mTOR pathway in a concentration dependent manner via an indirect mechanism that involves activation of adenosine monophosphate-activated protein kinase.

An *in vitro* study to evaluate the cytotoxicity of belumosudil in HepG2 cells was conducted. The IC_{50} for cytotoxicity in this assay was above the highest tested concentration of 150 µM, however compound precipitation was observed already at concentrations of 9.38 µM and higher.

Belumosudil demonstrated *in vitro* several other secondary pharmacological activities, however these effects are not directly related to pathogenesis of cGVHD and therefore, are not discussed here.

The conducted *in vitro* and *in vivo* pharmacodynamic studies are considered adequate to describe the mode of action of belumosudil and its pharmacological effects in relation to its therapeutic target in the intended clinical indication.

Safety pharmacology

Formal stand-alone safety pharmacology studies have been conducted with belumosudil, evaluating CNS (rat), *in vitro* hERG, *in vivo* cardiovascular (dog), and respiratory (rat) function. All these studies were GLP compliant.

Effects of belumosudil, KD025m1 and KD025m2 on cloned hERG potassium channels were assessed in HEK293. Belumosudil and KD025m1 inhibited hERG channel activity in a concentration-dependent manner with estimated IC_{50} of 0.6 (272 ng/mL free drug) and 1.5 µM (616 ng/ml free drug), respectively. The main human metabolite KD025m2 had no inhibitory effect in this assay at concentrations up to 10 µM. Hence, belumosudil and its minor metabolite KD025m1 show some potential for the Ikr repolarisation inhibition.

In the *in vivo* dog cardiovascular safety pharmacology study, no evidence of changes in electrocardiogram waveforms (PR, QRS, RR, QT, QTcV and heart rate (HR)-derived) was detected. Belumosudil demonstrated low magnitude lowering of systolic blood pressure (BP), diastolic BP and mean arterial pressure in female dogs at 150 mg/kg (the highest dose tested). The Applicant considered 150 mg/kg as the NOAEL for cardiovascular parameters (equivalent to C_{max} of 2019 ng belumosudil/mL in males and 4224 ng/mL in females), however due to lowering of BP and issues with achieving the sufficient systemic exposure probably due to post-dose emesis choice of 75 mg/kg as the NOAEL would have been appropriate. In TK analysis for all analytes, inter-animal variability within a group was generally greater than variability between genders, particularly for males, where systemic exposure was not observed for several animals. It is obvious that the reported large inter-animal variability and even absence of systemic exposure may have had impact on cardiovascular results and conclusions. The Applicant agreed that the collected TK data revealed inter-animal variability in exposure, lack/very low of systemic exposure (3 out 8 animals, low and mid dose groups), lack of dose proportionality, or potential gender difference in dogs. Caution should be taken in the interpretation of cardiovascular data collected.

Based on data collected from the QTc study in healthy humans (KD025-110), belumosudil had no clinically relevant effects on ECG parameters and based on the concentration-QTc analysis, an effect on ΔΔQTcF

exceeding 10 ms was excluded at up to concentrations of 12 080 ng/mL of belumosudil. This clinical data can be considered to provide primary evidence that there is no cardiovascular safety concern with belumosudil.

In a rat respiratory study, a small magnitude of the effect of belumosudil on minute volume was reported and considered adverse in male rats at 175 mg/kg. Therefore, the study was repeated to evaluate the reproducibility of this effect and examine any respiratory effects of belumosudil in more detail. In the repeated study, same doses and rat strain were used with no apparent respiratory adverse effects on minute volume. In the first respiratory safety study (SLX-TX-0054) C_{max} of belumosudil at 350 mg/kg dose in male rats was 6354 ng/mL in the plasma while in the confirmatory study (8289751) C_{max} after a same dose in males was 3940 ng/mL. In females such difference in C_{max} was not observed between these studies. Dyspnoea has also been reported as an adverse effect in clical trials with belumosudil. The main experimental condition that differentiates the 2 respiratory safety pharmacology studies is related to the fasted/fed status of the animals. Rats were fasted overnight in the initial study, whereas food was ad libitum in the second study (all animals were deprived of food when in the plethysmography chamber). This change in study design (fed/fasted) resulted in marked differences in PK parameters, especially the known impact of food on drug exposure. It is apparent that the 1.6-fold "higher" C_{max} found at 350 mg/kg dose in male fasted rats in the initial study should be considered as it is also associated with respiratory changes (lower respiratory frequency, lower tidal volume, lower minute volume). The CHMP agreed with the Applicant conclusion that, the C_{max} of 6354 ng/mL observed in rats is 2.8 -fold higher than the plasma C_{max} achieved in fed cGVHD patients at steady state (2230 ng/mL, 200 mg daily, tablet, fed conditions), suggesting that belumosudil at therapeutic dose should not affect the respiratory function in humans.

Modified Irwin test with locomotor activity assessment showed no clinically relevant or adverse changes in the functional observational battery after a single dose administration of 350 mg belumosudil/kg to male and female rats.

Pharmacodynamic drug interactions

Possible pharmacodynamic drug interactions with antihypertensive, antiarrythmic and immunosuppressant drugs were discussed by the Applicant. Overall, pooled analysis of the safety data did not identify any new safety concern consistent with a pharmacodynamic drug drug interaction. Continued pharmacovigilance surveillance activities will monitor for potential new signals of potential pharmacodynamic drug interactions. The Applicant justified the lack of the pharmacodynamic interaction studies by expected pharmacology and patient population. According to the Guideline on the investigation of drug interactions (CPMP/EWP/560/95/Rev. 1 Corr. 2**), the need for pharmacodynamicinteraction studies should be determined on a case-by-case basis. The potential for pharmacodynamic interactions should be considered for drugs which compete with each other at the pharmacological target and/or have similar or opposing pharmacodynamic (therapeutic or adverse) effects. If such drugs are likely to be used concomitantly, pharmacodynamic interaction studies should be considered.

The principal mode of action of belumosudil is a potent, competitive, and selective inhibition of ROCK2 kinase. ROCK-inhibitors are in clinical use as eye drops for the treatment of glaucoma. The Applicant agrees that concurrent eye instillation of ROCK inhibitor drugs for ophthalmologic therapeutic indication in combination with belumosudil may potentially exacerbate pharmacodynamic effect (low intraocular pressure) or compound-side effects (conjunctival hyperemia, blurred vision, instillation site pain, corneal verticillata, increased tearing, etc.). Since glaucoma disease requires to be regularly monitored by ophthalmologists there are no safety concerns locally in the ocular tissues including lacrimal gland for patients with glaucoma that may receive oral administration of belumosudil. Due to very low plasma concentrations following glaucoma

eye drops the risk of pharmacodynamic drug interaction is negligeable systemically in patient receiving belumosudil and glaucoma treatment concurrently.

In the SmPC section 4.4 Special warnings and precautions for use, a warning related to use of belumosudil concurrently with eye-instilled ROCK inhibitor treatments in patients with glaucoma should be added.

Pharmacokinetics

A comprehensive number of *in vitro* and *in vivo* PK studies were performed with belumosudil. The TK data was collected from the pivotal toxicology program: Repeat-dose toxicity studies, safety pharmacology studies, genotoxicity study and DART studies. The methods were accurate and adequately validated and considered suitable for accurate detection of relevant analytes in different matrixes.

To show capability of belumosudil to permeate through intestinal epithelial cells and study absorption mechanism intestinal mucosal bidirectional permeation experiment on monolayer Caco-2 cells was conducted at 1, 10, 100 µM concentrations. The data suggests that belumosudil solubility decreases when pH increases, and calculated results of efflux ratio at 10 and 100µM belumosudil indicate that it is a substrate of efflux transporter probably saturated at 100 µM, as the recorded apical-to-basolateral permeability in Caco-2 cells was low. The higher concentration (100 µM) was chosen to mimic high concentration of belumosudil in intestinal tract after administration However, calculated results at 1 µM of belumosudil are unreliable since measurements were BLQ.

The follow up study (ADME-KD-200630-Caco-2) was done in presence of 1% BSA and at 1, 3 and 10 µM. The results of the follow up study ascribe higher permeability of belusomide compared to results of the first study ADME-KAD-200410-CaCo-2. To conclude, the results indicate that belumosudil is a medium permeability compound and may be a substrate of efflux transporter. In the follow up study, thanks to the addition of 1% BSA in buffer, belumosudil was quantified and the permeability coefficient and the efflux ratio were determined at each concentration (1, 3 and 10 µM).

In the PK analysis, belumosudil and main metabolites KD025m1 and KD025m2 in animals were investigated. In general, exposure to the parent drug was greater than exposure to metabolites and general picture of absorption parameters for KD025m1 and KD025m2 did not differ from parent compound.

The absorption was rapid in fed and fasted mice and fast to moderate in rats and dogs in both single- and repeated-dose administration. Oral bioavailability increased from 15% to 85% from the lowest to the highest dose in rodents. In mouse and rat single-dose studies, clearance and volume of distribution of belumosudil were low. Generally, increase in exposure was greater than dose-proportional in low doses and dose-proportional in high doses for belumosudil and both metabolites or less than dose-proportional to belumosudil in some experiments. No significant differences were recorded between exposures on day 1 and the last day. Accumulation increased with higher dosing. In rats, exposure of females was greater than males, however, in dogs no clear sex differences were recorded. No difference in the exposure levels after single-dose administration of high doses of belumosudil (1000 mg/kg - 2000 mg/kg) suggest saturation of absorption and metabolism. In pregnant rabbits, the exposure was generally dose-proportional for all analytes on GD6 and G18 (C_{max}) and greater than dose-proportional for AUC_{0-24}, with high variability in the high dose group. No accumulation was recorded in pregnant rats or rabbits.

Tissue distribution studies in albino and partially pigmented rats by quantitative whole body autoradiography showed rapid distribution of belumosudil to liver, adrenal gland, kidney and bladder in albino rats, however, radioactivity was measured only in fur and liver at 120h timepoint. In partially pigmented rats, radioactivity in the uveal tract and pigmented skin was detected, indicating some affinity of belumosudil for melanin.

Binding of belumosudil to mouse, rat, rabbit, dog, and human plasma proteins is high. It is uncertain if the assay sensitivity is sufficient for the precise determination of unbound fraction. As the default value (1%) of unbound fraction is used in the calculation of DDI potential in clinical PK assessment, this uncertainty is accepted.

Belumosudil distributes in plasma in greater extent than to blood in all species but rabbit.

32 metabolites were identified in liver microsomes and 28 in hepatocytes. In human samples, 2 metabolites were identified (M21[glucuronidation] and M28/KD025m2) in >5% normalised peak area, KD025m2 being the main metabolite. KD025m1 was identified in samples from all species and was considered as minor metabolite in humans. In rats, unchanged belumosudil was the major component in plasma and faeces. In females, the percentage of unchanged belumosudil was markable higher than in males. Belumosudil was not detected in the urine. The data suggest that male rats metabolise belumosudil more efficiently than females.

The characterization of the human metabolites was performed by metabolic profiling within the human mass balance study that included 5 healthy participants (KD025-108). After the administration of ^{14}C-belumosudil, among the metabolites quantified *in vivo* in human plasma by radiodetection, two phase 1 and two phase 2 metabolites were identified.

Human metabolite M21[glucuronidation] was identified only in low levels in non-clinical species but >5% in human samples. Despite the limited characterisation of M21 and considering the low exposure below 10% is not foreseen as a toxicological concern based on the metabolic mechanism (glucuronidation).

Belumosudil was suggested to be mainly metabolised via CYP1A2, CYP2C8, CYP2D6, CYP3A4 and UGT1A9. Major contribution to metabolism of KD025 was recorded with CYP3A4/5 (41.9%), minor contribution with CYP2D6 (21.7%) and CYP2C8 (14.2%). The analysis of clinical samples (plasma and faeces) further confirmed that KD025m2 is the main metabolite in humans.

The excretion study in rats show that belumosudil is predominantly excreted via the faecal route. No information is provided on placental transfer or excretion to milk. A contraindication for breastfeeding was added, as requested by CHMP.

The possible PK drug interactions are discussed later in the Clinical section and adequately addressed in SmPC Sections 4.2, 4.5 and 5.2.

Toxicology

In general, the toxicological data package to belumosudil is comprehensive. All pivotal safety studies were GLP-compliant. Repeat-dose toxicity studies for belumosudil were conducted in rats and dogs, and in rats and rabbits for developmental and reproductive toxicity. The 6-month transgenic mouse model was used to investigate the carcinogenic properties of belumosudil. To support the long-term therapeutic use of belumosudil, studies were performed by oral dosing up to 6 months in rat and 9 months in dog.

The batch used in the non-clinical testing is foreseen as representative for clinical batch as the synthesis route of belumosudil has not been changed since the initiation of the non-clinical study program. Single dose studies, 28-days study in rats and 7-days study in dogs were conducted with HCl and TFA salts and not mesylate of belumosudil.

Single-dose toxicity of belumosudil was studied in rats and dogs. In rats, the NOAEL was 400 mg/kg, based on the deaths and clinical signs in the high dose group.

In female and male dogs, the MTD was 50 mg/kg and 200 mg/kg, respectively. The toxicity in dogs was limited to GI tract symptoms.

Overall, the acute toxicity of belumosudil was considered to be low.

In repeat-dose toxicity studies the main toxicological findings in rats and dogs were associated with decreased food consumption, resulting in decrease of body weight gain and signs of GI-tract toxicity (emesis, salivation, vomitus Other main target organs for toxicity were liver, kidneys, thymus, spleen, red cell mass, epididymes and testes. Mortalities were observed at higher doses in both species. Chronic toxicity was observed at relatively low doses, with exposures in the range of expected exposure in the clinical use. Decreased red blood cell mass with bone marrow hyperplasia, increased reticulocytes and platelets recorded in rat and dog studies suggest belumosudil-induced regenerated anaemia.

Histological changes in sexual organs (epididymis, testis, cervix, ovaries, uterus) were reported in rat and dog studies. Testicular/epididymal findings partially reversible in rats (decreased organ weights and degenerative histopathology) and reversible in dogs (degenerative histopathology) were considered to be adverse at ≥50 mg/kg/day or ≥35 mg/kg/day, respectively. In 3/6 month study high-dose female rats, effects in ovaries and uterus were also reported.

The repeat-dose toxicity of belumosudil is adequately characterised in rats and dogs. The general toxicity occurred approximately at exposures ≤ 1x in rats (males, 6-months) and dogs (both males and females, 9-months) of the recommended clinical dose (200 mg).

In the SmPC Section 4.6, the decrease on body weight and testicular findings are adequately reported with cross-reference to SmPC Section 5.3: "Belumosudil repeat dose toxicity studies in rats demonstrated adverse effects of general toxicity manifesting in low body weight that may lead to impairment of female fertility (see section 5.3). Based on testicular findings from rats and dogs, belumosudil may impair male fertility (see section 5.3)."

GLP compliant *in vitro* and *in vivo* genotoxicity studies with belumosudil suggested no genotoxicity. The use of negative and positive control in the *in vivo* rat study was acceptable and the sampling times acceptable. However, the E. coli WP2 uvrA was used instead of the TA102 in the Ames test. In order to detect cross-linking mutagens, it is preferable to include TA102 or to add a DNA repair proficient strain of E.coli [e.g. E.coli WP2 or E.coli WP2 (pKM101)]. The other two genotoxicity tests further confirmed that belumosudil was not a cross-linking genotoxicant. The TK analysis of *in vivo* studies suggested saturation of exposure in a high dosing, which is in line with the other studies.

A long-term rodent carcinogenicity study (6-month transgenic mice study) has been performed, and 2-year rat carcinogenicity study is currently ongoing. The study report is expected to be available for submission to authorities in June 2026.

In the 6-month mouse study, the TK analysis was considered adequate and the recorded toxicological profile in transgenic mice was in line with the repeat-dose toxicity studies in rats/dogs, however, no decrease in food consumption and body weight gain was observed with the relatively low dosing used in the carcinogenicity study. No pre-neoplastic or neoplastic changes nor increase in the incidence of hyperplastic changes were identified. Harderian gland adenoma observed in female mice that received 8 and 15 mg/kg belumosudil and not in female controls was not considered treatment related. This is agreed with and supported by the historical control incidence rate reported in the literature and for the specific testing facility. Other neoplastic and proliferative microscopic changes observed (e.g., subcapsular cell hyperplasia in the adrenal glands, haemangioma and hemangiosarcoma in multiple tissue, and cystic endometrial hyperplasia in

the uterus/cervix) were also considered to be of the nature commonly observed in mice of this age and strain and not treatment related.

A discussion on the carcinogenic potential of belumosudil following Treg stimulation/Tfh inhibition in humans based on the literature and existing safety data from clinical use showed controversial data on the role of Treg in cancer. However, the safety data collected from clinical use of belumosudil does not suggest causality between belumosudil administration and reported cancer cases. Additional PV activities are suggested to investigate this potential risk further in the post authorisation setting.

In female rat, no fertility effects were observed. The embryo-foetal toxicity (increase in post-implantation loss and resorptions and decrease in viable embryos) may be due to the maternal weight loss and worsened general condition observed in all treatment groups.

Belumosudil had effects on male fertility parameters such as fertility rate and sperm parameters. The fertility rate and testes/epididymis size and weight decreased in high dose group. Histopathologic findings in these organs were degeneration and atrophy, and the sperm parameters were abnormal, e.g., low sperm motility.

2 species (rats and rabbits) were used in the embryo-foetal toxicity studies. The general toxicity and GI-tract toxicity was observed similarly as with repeat-dose toxicity studies, and maternal NOAEL was 15 mg/kg for rats and 50 mg/kg for rabbits.

Increased post-implantation loss (early and late resorptions especially in high dosing), malformations, decreased foetal body weights and was seen in both species. Abortions, skeletal developmental effects and decreases in viable foetuses/litter size were observed in rabbits. It should be noted that skeletal and visceral variations were noted already in the low doses. The overall increase in incidence of visceral variations in rabbits is suggestive for dysmorphogenesis even at lower exposures. In both species, embryo-foetal NOAEL was 50 mg/kg/day, however, some effects - fused sternebrae were already observed at this dose in rabbits. For the observed malformations, there are no safety margins in comparison to expected clinical exposure (as at NOAEL the calculated safety margin is only 0.08). The embryo-foetal toxicity studies conducted in rats and rabbits confirm the developmental toxicity of belumosudil reported also in fertility and early embryonic development studies. As clearly positive results for the developmental toxicity were observed in one species, conducting these studies in second species would not have been necessary (ICH S5) and is- in respect with 3R principles.

No PPND studies were conducted. This is accepted. No juvenile toxicity studies have been conducted. This is in line with EMA Scientific advice (2019) stating that there may be no added value on performing juvenile toxicity studies as the hazard has already been identified in repeat-dose toxicity studies. Additionally, targeted ROCK2 receptor knockdown in homozygous knockout mice showed placental dysfunction, intrauterine growth retardation, and foetal death. Consequently, a PPND study is not considered necessary based on current knowledge.

In conclusion, a potential for male fertility effects and reproductive toxicity is identified in the fertility and early embryonic development studies. The risk to reproduction is appropriately reflected in SmPC sections 4.4. and 4.6. Pregnancy and breast feeding was, and on request, it was added as a contraindication to the SmPC Section 4.3. It is also noted that other Rock-inhibitor (netarsudil) PI also mention non-clinical findings (embryofoetal toxicity and malformations), suggesting potential class-effect for Rock-inhibitors concerning embryofoetal toxicity.

Overall, the exposure levels reached in pivotal non-clinical studies were adequate to allow the assessment of the belumosudil-related safety findings. In all tested species, adverse effects were noted after repeat-dose

administration at similar or lower levels as the expected exposure in clinical settings after 200 mg once daily administration. In the rabbit embryo-foetal toxicity study, the NOAEL resulted in safety margin of 0.08, and dog 9-month repeat dose toxicity study NOAELs resulted in safety margins of 0.2 and 0.4, when compared to the expected clinical exposure.

No separate local tolerance studies, antigenicity studies or toxicological studies for metabolites have been conducted. These studies are not required.

No separate immunotoxicity studies have been conducted, but the immunotoxicity endpoints have been assessed in the repeat-dose toxicity studies. It is agreed that no immunotoxicity is predicted based on available data and not further data is requested.

The *in silico* prediction on impurities resulted in identification of N-nitro or N-nitroso compound (cohort of concern), three known mutagenic carcinogens (ICH M7 Class 1 substances) and three known mutagens (ICH M7 Class 2 substances) were identified in the databases. No non-clinical studies have been performed to qualify impurities. This is accepted as the detailed impurity analysis and their control strategy was included in the Quality dossier and assessed in the Quality section.

Phototoxicity potential of belumosudil has been demonstrated *in vitro*. As no phototoxic reactions have been reported in clinical settings, the phototoxicity potential of belumosudil is considered low.

Belumosudil is expected to have low abuse potential based on its capability to cross the blood-brain-barrier, and therefore no drug abuse liability assessment has been performed. This is agreed with.

ERA

Belumosudil $PEC_{surfacewater}$ value was below the action limit of 0.01 µg/L and is not a PBT substance as log Kow did not exceed 4.5.

Therefore, belumosudil is not expected to pose a risk to the environment.

2.5.7. Conclusion on non-clinical aspects

Overall, the primary pharmacodynamic studies showing selectivity on ROCK2 inhibition, immunomodulating effects and anti-fibrotic activity support the development of belumosudil for treatment of cGVHD.

From the pharmacokinetic point of view the Applicant has performed a comprehensive number of *in vitro* and *in vivo* PK studies with belumosudil. As belumosudil is intended for a treatment of cGVHD, the long-term repeat dose studies are evaluated to be the most relevant studies for the ADME evaluation.

In general, the toxicological data package to belumosudil is adequate. All pivotal safety studies were GLP-compliant. The application is acceptable from the non-clinical perspective. The results of the non-clinical data are appropriately summarised in the SmPC section 5.3.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Table 13: tabular listing of clinical studies

Study identifier	Study design	Population (incl number of subjects, healthy vs patient and gender ratio)	Dosing regimen	Formulation
[SLx-2119-09-01]	Randomized, double-blind, placebo-controlled, single dose, dose-escalating study to evaluate the safety, tolerability, and PK study	Healthy male participants (n=6 participants/cohort) Placebo (n= 2 participants/cohort)	Single dose belumosudil on Day 1: 20, 40, 80, and 160 mg; 7-day washout between each escalation Placebo	Capsule
[KD025-101]	Randomized, double-blind, placebo-controlled, single and multiple dose, dose-escalating study to evaluate the safety, tolerability and PK study	Healthy male participants (n=6 participants/cohort) Placebo (n=2 participants/cohort)	Single dose belumosudil on Day 1: 40, 80, 120, 160, 240, 320, 400, and 500 mg followed by belumosudil QD for 7 days beginning on Day 8 Placebo	Capsule
[KD025-102]	Randomized, double-blind, multiple dose, dose- escalating, placebo-controlled study to evaluate the safety, tolerability, and PK study	Healthy male and post-menopausal female participants (n=6 particip nts/cohort) Placebo (n=2 participants/cohort)	Multiple dose belumosudil for 7 days: 500 mg QD, 800 mg QD, 500 mg BID, and 1000 mg QD Placebo	Capsule
[KD025-103]	Randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, PK, and exploratory PD	Healthy male and post-menopausal female participants (n=6 participants) Placebo (n=2 participants)	Multiple dose belumosudil for 4 weeks: 500 mg BID Placebo	Capsule
[KD025-105]	Randomized, open-label, single dose, two-period, crossover study to evaluate the safety, PK, and food effect x	Healthy male participants (n=6/cohort)	Single dose belumosudil on Day 1: 500 mg with food or fasted followed by 7-day washout; single dose belumosudil on Day 8 following crossover design	Capsule
[KD025-106]	Randomized, open-label, single dose, three-period,	Healthy male participants (n=8/cohort)	Single dose belumosudil on Day 1: 200 mg tablet (fasted), 200 mg tablet (fed), or	Capsule/Tablet

	crossover study to evaluate BA		200 mg (2x100 mg) capsule (fed) followed by 6-day washout; single dose belumosudil on Day 7 following crossover design	
[KD025-107]	Non-randomized, open-label, two-part, sequential study to evaluate the effect of itraconazole, rifampicin, rabeprazole and omeprazole on PK	Healthy male participants Part 1: (n=35) Part 2: (n=38)	**Part 1** Period 1: belumosudil 200 mg QD Period 2: itraconazole 200 mg QD, fed, for 7 days; belumosudil 200 mg QD + itraconazole 200 mg QD, fed, on Day 8; itraconazole 200 mg QD, fed, on Day 9 followed by 8-day washout Period 3: rabeprazole 20 mg BID, fed, for 3 days; belumosudil 200 mg QD, fed + rabeprazole 20 mg QD, fasted, on Day 4 followed by 4-day washout Period 4: rifampicin 600 mg QD, fasted, for 9 days; belumosudil 200 mg QD, fed, on Day 10 **Part 2** Period 1: belumosudil 200 mg BID, fed Period 2: Omeprazole 20 mg QD, fasted, for 3 days; belumosudil 200 mg BID, fed + omeprazole 20 mg QD, fasted, on Day 4	Tablet
[KD025-108]	Open-label, two-part study to assess the absolute bioavailability and determine the mass balance recovery, metabolite profile, and identification of metabolite structures Human metabolite identification 4.2.2.4 Metabolism [KDM/05]	Healthy male participants (n=5)	**Part 1:** Single oral dose belumosudil 200 mg followed by 15 min IV infusion of 100 µg [14C]-KD025 (Day 1, 1.75 h post-oral dose) containing NMT 37 kBq (1000 nCi) [14C], followed by 7-day washout **Part 2:** [14C]-KD025 capsule containing NMT 9.8 MBq (266 µCi) 14C, 200 mg	Tablet, IV infusion and Capsule ([^{14}C]-KD025)
[KD025-109]	Non-randomized, open-label, parallel-group study to	Participants with normal hepatic function and mild,	Single dose belumosudil 200 mg (fed)	Tablet

	determine effect of hepatic impairment on PK, safety, and tolerability of single oral doses	moderate, or severe hepatic impairment (n=36)		
[KD025-110]	Double-blind, randomised, balanced, placebo and positive-controlled crossover, single oral dose crossover study to investigate the effects of KD025 on QTc interval	Healthy participants (n=34)	Single dose belumosudil 200 mg (fed) Single dose belumosudil 1000 mg (fed) Single dose placebo Single dose moxifloxacin 400 mg	Tablet
[KD025-112]	A 3-part, sequential, non-randomized, open-label study designed to evaluate the effect of oral belumosudil on UGT1A1, P-gp, BCRP and OATP1B1 inhibition in the fed state	Healthy male participants	Part 1: D1 and D7: 400 mg of raltegravir (SD) D3 to D8: 200 mg QD belumosudil (n=19) Part 2: D1 and D9: SD of dabigatran 75 mg D5 to D12: 200 mg QD belumosudil (n=19) Part 3: D1 and D10 rosuvastatin 10 mg SD D6 to D13: belumosudil 200 mg QD (n=14)	Tablet
[ME3208-01]	A 2-part, randomized, placebo-controlled, double-blind (part 1) and randomized, open-label, 3-period crossover study (part 2) study of the safety, tolerability, and PK of belumosudil tablets after single and repeated oral administration and investigation of the effect of food on belumosudil tablets (commercial formulation).	Japanese healthy adult male participants Part 1: n= 48 with 6 in each cohort and 2 on placebo/cohort. Part 2: n=18 with 6 in each cohort	Part 1: Placebo, 200, 400, 800 mg after single dose (Cohorts 1-3) Placebo, 200 mg QD, 200 mg BID, or 400 mg QD for 7 days (Cohorts 4-6) Part 2: single 200 mg dose; fasted, 5 mins and 30 mins after meal.	Tablet
[BN101-101]	Placebo-controlled single ascending dose study of the safety, tolerability, and PK of belumosudil	Chinese healthy male and female participants (n=23)	Cohort 1: Placebo and 200 mg (n=11) Cohort 2: placebo and 400 mg (n=12)	Tablet
[KD025-208 Follow-up]	Open-label, dose-escalation study to evaluate safety,	Participants with cGVHD after 1-3 prior	Multiple dose belumosudil: 200 mg QD, 200 mg BID, or	Capsule (initially) and Tablet

	tolerability, and belumosudil activity	lines of systemic therapy (n=54)	400 mg QD, fed, in 28-day cycles until disease progression	
[KD025-213 Final]; [KD025-213 Synoptic for Adolescent] addendum; [KD025-213 Follow-up] synopsis	Randomized, multi-center, open-label study to evaluate efficacy and safety	Participants with cGVHD after at least 2 prior lines of systemic therapy (n=155)	Arm A: belumosudil 200 mg QD, fed Arm B: belumosudil 200 mg BID, fed Treatment received in 28-day cycles until clinically significant disease progression	Tablet
KD025-217 [Protocol amendment 1]	Open-label, long-term treatment and follow-up study to evaluate safety and efficacy Participants previously treated with belumosudil in Study KD025-208 or in Study KD025-213.	Participants with cGVHD (n=23)	Participants continue with the dose assigned in their previous study: KD025-208: belumosudil 200 mg QD, 200 mg BID, or 400 mg QD KD025-213: belumosudil 200 mg QD or 200 mg BID	Tablet
[BN101-201]	A Phase 2, Open-label, Multicenter Study to Evaluate the Efficacy and Safety of BN101/belumosudil	Chinese Subjects with Chronic Graft Versus Host Disease (cGVHD) After at Least 1 Prior Line of Systemic Therapy (n=30)	Belumosudil 200 mg QD. Followed for at least 6 months	Tablet
[ME3208-02]	Open-label, single-arm study to evaluate efficacy and safety	Japanese participants with steroid-dependent/resistent cGVHD (n=21)	Belumosudil 200 mg	Tablet
AA_00117	Non-interventional study (using targeted learning methods for causal) to evaluate the efficacy and safety of belumosudil versus best available therapy in patients with cGVHD who have failed 2–5 prior LOTs	Patients with cGVHD (n=196)	According to routine clinical practice	Tablet

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Pharmacokinetics of belumosudil have been investigated in healthy volunteers and in patients with cGVHD both after single dose and after multiple dose studies. In the early stage of development, the clinical studies were conducted with capsule formulation, which has subsequently been changed to tablet formulation. The tablet formulation is intended for commercial use.

Analytical methods

Three liquid chromatography - tandem mass spectrometry (LC-MS/MS) analytical methods were developed to quantify concentrations of belumosudil, belumosudil metabolite 1 (KD025m1, active minor metabolite), and belumosudil metabolite 2 (KD025m2, inactive main metabolite) in human plasma.

The analytical method applied for the majority of the clinical studies was validated at Covance Laboratories, Madison, USA, then transferred to Covance, Harrogate, UK, and amended at Quotient Sciences, UK. Comparability of the results between two sites (Covance, Harrogate, UK and Quotient Sciences, UK) were demonstrated with cross-validation.

Methods for the determination of total radioactivity and metabolites of [^{14}C]-belumosudil in human whole blood, plasma, urine, and faecal homogenates as well as for metabolite characterization and identification were adequate.

The analytical methods are acceptable and properly validated.

Population PK model

Data from five Phase 1 studies in healthy subjects (KD025-101, KD025-102, KD025-103, KD025-106, and KD025-107; total n=174 subjects) and two Phase 2 studies (KD025-208 and KD025-213, conducted in cGVHD subjects, total n=178 subjects) were utilized for adult population PK (popPK) model development. An updated, re-parameterized model was provided during the assessment upon the request of the CHMP.

Belumosudil PK was described by a 2-compartment structural model, the absorption phase was described through first order absorption constant, a lag-time and a relative bioavailabily parameters. Included covariates were as follows: formulation (capsule vs tablet) on both lag-time and absorption constant, feeding status on both bioavailability and lag-time, coadministration of proton pump inhibitors on the absorption constant and bioavailability, coadministration of CYP3A4 inhibitors on clearance, coadministration of CYP3A4 inducers on clearance and bioavailability, and subject's status (healthy participants vs patients) on the lag-time and bioavailability. Age (18-77 years), body weight (38.6-143 kg), race, sex, eGFR, and plasma liver function biomarkers (ALT, AST, bilirubin) at baseline were not statistically significant covariates for clearance or central volume of distribution and were not included in the final popPK model.

PBPK models

A total of three physiologically based PK (PBPK) modelling reports were presented by the Applicant.

An integrated parent-metabolite PBPK model based on *in vitro* and *in vivo* information on the metabolism and pharmacokinetics (PK) of belumosudil and main metabolite KD025m2 was constructed with the aim of predicting plasma concentration-time profiles of belumosudil and KD025m2 following single dose and/or repeat dosing in healthy subjects. As belumosudil has been shown *in vitro* to be metabolised by cytochrome P450 (CYP)3A4 (fmCYP3A4 value of 0.26,) and is also a time-dependent inhibitor of CYP3A4, autoinhibition was integrated within the belumosudil PBPK model. *In vitro* CYP2C8, UGT1A1 and OATP1B1 (both belumosudil and KD025m2), CYP2C9, CYP3A4, UGT1A9, P-glycoprotein (P-gp), breast cancer resistance protein (BCRP) and MATEs (belumosudil only) enzyme and transporter competitive inhibition constant for unbound drug (Ki,u) values, or IC_{50} values for transporters, were also incorporated into the PBPK model, as were time-dependent inhibition constants for CYP1A2, CYP2C19, and CYP3A4 (belumosudil only). Fraction unbound (fu) of belumosudil was set to 0.11%. The parent-metabolite model was essentially the same in all three PBPK reports, a few *in vitro* parameters were updated in the second and third reports.

A combination of *in vitro* data and clinical PK data following a single dose of 200 mg belumosudil tablet were used to develop the model for belumosudil and KD025m2. fmCYP3A4 values for belumosudil and KD025m2 were refined using observed peak concentration (C_{max}) and area under the curve (AUC) geometric mean ratios (GMRs) following a single dose of 200 mg belumosudil in the absence and presence of itraconazole and rifampicin (study KD025-107).

The developed models were used prospectively to evaluate the likely impact of coadministration of moderate CYP3A4 inhibitors and moderate CYP3A4 inducers on the PK of belumosudil and KD025m2. The simulations indicated that coadministration with moderate CYP3A4 inhibitors fluconazole and erythromycin does not result in clinically relevant interaction (belumosudil C_{max} and AUC increased by less than 25%). Simulations with a moderate CYP3A4 inducer efavirenz predicted a weak interaction (belumosudil AUC decreased by 33 %).

The PBPK models were also used prospectively to predict the extent of the DDI between belumosudil (as perpetrator) with sensitive substrates for CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP3A4, P-gp, BCRP, OATP1B1 and MATEs. Importantly, the effect of belumosudil as inhibitor of CYP enzymes has not been evaluated in a clinical DDI study. All simulations were performed under steady state conditions following belumosudil 200 mg once daily (QD) regimen and using the measured *in vitro* Ki,u (enzyme competitive inhibition constant) and K_{app} (enzyme inhibition constant for time-dependent inhibition) estimates for belumosudil. No clinically significant DDIs were predicted following coadministration belumosudil with sensitive substrates for CYP2C8 (repaglinide), CYP2C9 (*S*-Warfarin), CYP2C19 (omeprazole). Specifically, the predicted AUC and C_{max} ratios with and without coadministration of belumosudil were < 1.25 for these three CYP enzymes. A weak DDI potential was predicted with probe substrates of CYP1A2 (caffeine; AUC increased by 1.59-fold, C_{max} increased by 1.08-fold) and CYP3A4 (midazolam; AUC increased by 1.65-fold, C_{max} increased by 1.30-fold).

Initially performed simulations for substrates of P-gp (dabigatran etexilate), BCRP (sulfasalazine), OATP1B1 (pravastatin) and MATEs (metformin) indicated no effect by belumosudil on exposure to substrates of these transporters. In contrast, clinically significant effects of belumosudil on PK of dabigatran etexilate and rosuvastatin (BCRP and OATP1B1 substrate) were observed in a clinical DDI study: observed AUC and C_{max} increased by 2.4-fold and 2.1-fold for dabigatran and by 4.4-fold and 3.6-fold for rosuvastatin. Subsequently, simulations were conducted for dabigatran etexilate, rosuvastatin, and metformin. Using the *in vitro* measured IC_{50} values, dabigatran AUC and C_{max} were predicted to increase by <10%, which does not match the observed interaction. Belumosudil was predicted to increase exposure to rosuvastatin, but the PBPK model did not adequately capture the observed data (simulated AUC and C_{max} ratios were 2.84 and 5.36,

respectively). Simulations for metformin predicted no clinically significant interaction (<10% increase in metformin AUC and C_{max}).

Absorption

Absorption of belumosudil is fast, peak concentrations occur about 3 hours after dosing. Absolute bioavailability of belumosudil was estimated to be about 64 %.

Food affects bioavailability of belumosudil. Exposure of belumosudil increased to approximately 2-fold when belumosudil was administered in fed state and t_{max} was delayed by 0.5 hours after the tablet formulation; exposure increased similarly when tablet was taken after meal or 5 to 30 minutes before meal. Belumosudil should be taken with concomitant food.

Distribution

Belumosudil is extensively bound to proteins in human plasma (mean 99.88% to 99.89% bound, independent of concentration). [^{14}C]-belumosudil was preferentially bound to human serum albumin (99.91%) compared to α1-acid glycoprotein (98.64%). Metabolites KD025m1 and KD025m2 are also extensively bound to human plasma proteins (fraction bound >99%).

Elimination

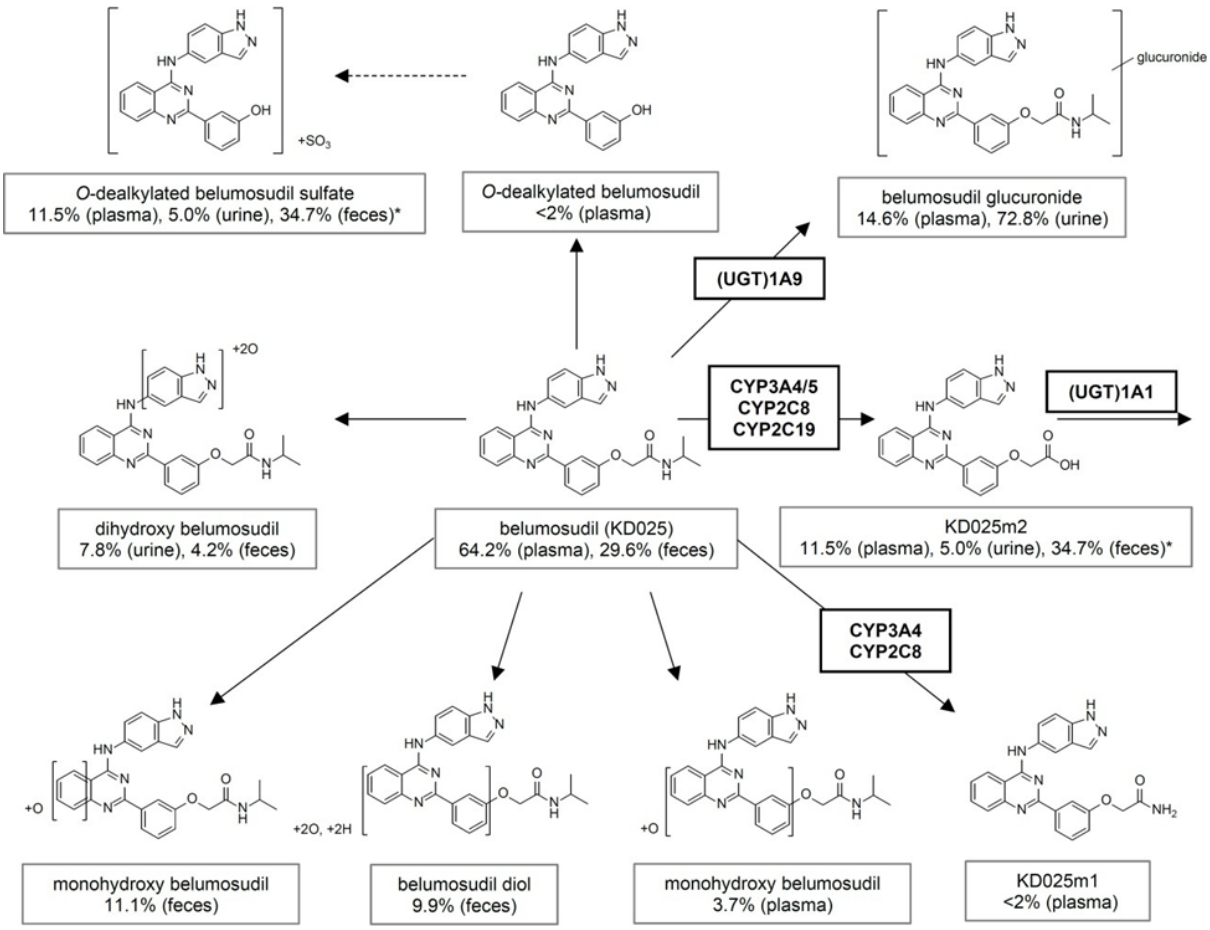
Excretion and metabolism of belumosudil have been investigated in a mass balance study. The majority of total radioactivity was recovered in feces (85%) and <5% was recovered in urine within 216 hours, suggesting there is minimal renal elimination and the predominant route of clearance of [^{14}C]-belumosudil and associated metabolites is biliary and/or intestinal. Half-life of belumosudil in healthy subjects was about 5-9 hours.

Metabolism

Based on *in vitro* assessment, CYP3A4 was the predominant CYP isoform responsible for the metabolism of belumosudil, although CYP2D6, CYP2C8, CYP1A2, CYP2C19, and UGT1A9 contribute to a lesser extent.

Two metabolites have been assayed in clinical studies, namely an active minor metabolite KD025m1 and a relatively less active main metabolite KD025m2.

Structural identification of other belumosudil metabolites was attempted on radioactive components representing 10% or more of the circulating radioactivity in plasma and accounting for greater than 10% of the dose in feces. No single radioactive component present in urine accounted for more than 10% of the dose. Of the total plasma radioactivity, belumosudil was 64%, KD025m2 and coeluting O-dealkylated belumosudil sulfate was 11.5%, and a belumosudil glucuronide was 15%. In feces, belumosudil was 30% and KD025m2 and *O*-dealkylated belumosudil sulfate accounted for a combined 35% of the total sample radioactivity. The belumosudil diol (belumosudil $^{+2}$O, $^{+2}$H) and monohydroxy belumosudil were 10% and 11% in feces, respectively.



*These two compounds co-elute and the percentage refers to the total contribution of both components.
Sources: Report XT174009, Report XT184060, Report KDM/05.

Figure 3: proposed biotransformation scheme for belumosudil in humans

Dose proportionality and time dependencies

Peak concentrations and AUC increase slightly more than dose-proportionally between doses 20 mg to 500 mg QD but less than dose-proportional with doses over 500 mg. In patients with cGVHD the increase between doses 200 mg and 400 mg is approximately dose proportional.

Special populations

PK in special populations was evaluated using population PK model for belumosudil. In addition, a separate study in subjects with hepatic impairment has been conducted.

Impaired renal function: In Study KD025-108, the majority of total radioactivity was recovered in feces (85%) and <5% was recovered in urine, suggesting there is minimal renal elimination. In the popPK analysis, there was no significant effect of eGFR or creatinine clearance on belumosudil CL/F.

Impaired hepatic function: Belumosudil is hepatically eliminated and about 85 % of the radioactive dose of belumosudil is recovered in feces. The Applicant has performed a single dose study with belumosudil in subjects with hepatic impairment. Geometric mean PK exposure of belumosudil was higher in participants with hepatic impairment compared to participants with normal hepatic function. Statistical analysis showed that the effect of mild and moderate hepatic impairment on belumosudil PK exposure was not statistically significant. The ratios of the GLSMs (90% CI) for $AUC_{0-\infty}$, AUC_{0-t} and C_{max} were 1.36 (0.831, 2.21), 1.48 (0.960, 2.28), and 1.20 (0.907, 1.58), respectively, for the mild hepatic impairment group, and 1.51 (0.975, 2.33), 1.50 (0.973, 2.31), and 0.944 (0.600, 1.48), respectively, for the moderate hepatic impairment group, with 90% CIs spanning unity. However, severe hepatic impairment significantly increased the $AUC_{0-\infty}$ and AUC_{0-t} of belumosudil but had no apparent effect on its C_{max}, with the ratios of the GLSMs (90% CI) of 4.21 (2.20, 8.06), 3.23 (1.53, 6.81), and 1.32 (0.896, 1.94), respectively. In addition, the unbound belumosudil $AUC_{0-\infty}$,u was higher (~16-fold) in participants with severe hepatic impairment than in healthy participants.

Weight, gender, race, age

Population PK analysis indicated no statistically significant effect of weight, gender, or race on belumosudil PK.

The mean age in the PK population was 44.4 (SD 15.3) years, mean weight was 81.5 (SD 15.6) kg, gender distribution was 77% males (271/352) and 23% females (81/352), race was predominantly white/Caucasian with n=267 (75.9%) followed by Black/African-American n=60 (17.0%), Asian n=7 (1.99%), Native American n=5 (1.42%), Other n=5 (1.42%), Unknown n=8 (2.27%). A total of 46 subjects in the population PK dataset were ≥65 years of age and 6 of them were ≥75 years of age.

Paediatric population

The proposed indication includes adolescent patients 12 years and older.

Simulations using the adult population PK model (with added fixed allometric exponents 0.75 and 1.0 for clearance and volume parameters, respectively) showed that the simulated exposure with 200 mg QD regimen is slightly higher in adolescents (age 12-17 years and weight ≥40 kg) compared with adults, but clearly below exposure in adults with 200 mg BID and 400 mg QD regimens that were investigated in clinical efficacy/safety studies KD025-208 and KD025-213 (figure below).

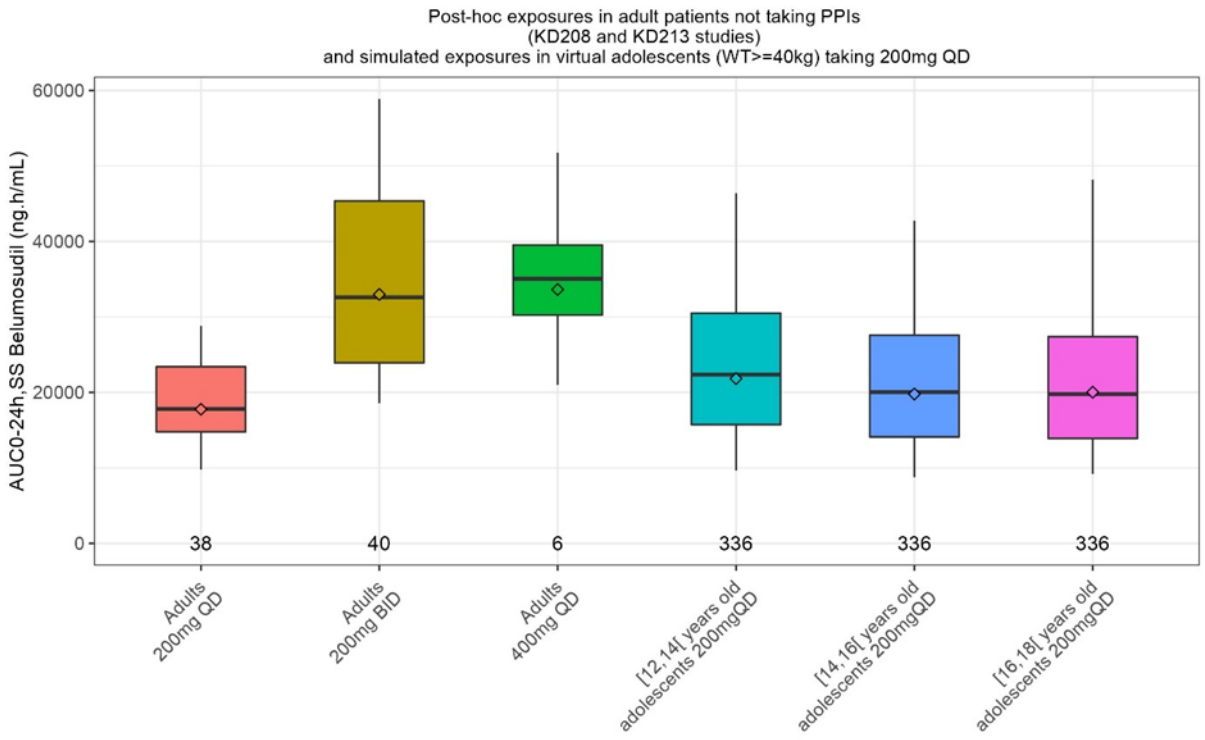


Figure 4: box plots of AUC_{0-24h}, at steady state in virtual adolescent patient population and adult patients from KD025-208 and KD025-213 studies

Pharmacokinetic interaction studies

Clinical study KD025-107: Strong CYP3A4 inhibitor itraconazole (200 mg QD for 7 days) increased belumosudil AUC and C_{max} 25% and 20%, respectively. Strong CYP3A inducer rifampicin (600 mg for 9 days) decreased belumosudil C_{max} and AUC approximately 60 % and 72 %, respectively, compared to situation when belumosudil was administered alone. A delay in absorption and a reduction in belumosudil exposure were also observed when belumosudil was administered with a strong proton pump inhibitor (PPI) rabeprazole or with a moderate PPI omeprazole (belumosudil AUC decreased 82% and 49% when co-administered with rabeprazole and omeprazole, respectively).

Clinical study KD025-112: Belumosudil (200 mg QD) increased AUC and C_{max} of dabigatran (substrate of P-gp) by about 2.1-fold and 2.4-fold, respectively, and AUC and C_{max} of rosuvastatin (substrate of BCRP and OATP1B1) 4.6-fold and 3.6-fold, respectively. In addition, belumosudil decreased formation of the glucuronide metabolite of UGT1A1 sensitive substrate raltegravir (AUC of glucuronide metabolite decreased from 1420 to 859 ng.h/mL), but belumosudil had little effect on exposure to raltegravir (AUC and C_{max} of raltegravir decreased 5% and 13%, respectively).

Drug-drug interaction (DDI) risk assessment was conducted based on *in vitro* data for the effect of belumosudil as CYP450 enzyme inhibitor at the recommended dosage of 200 mg QD in cGVHD patients. The results are summarised in the table below.

Table 14: summary of DDI static assessment for belumosudil as CYP450 enzyme inhibitor

Enzyme	Substrate	Reversible inhibition Risk if R >0.02[a]	Reversible inhibition (gut level) Risk if R >10[a]	Time-dependent inhibition Risk if R >1.25[a]
CYP1A2	Phenacetin	0.003	-	**10.5**[b]
CYP2C8	Amodiaquine	0.0198	-	-
CYP2C9	Diclofenac	**0.022**[b]	-	-
CYP2C19	S-Mephenytoin	0.019	-	**2.51**[b]
CYP2D6	Dextromethorphan	0.001	-	-
CYP3A	Midazolam/ Testosterone	0.002/ 0.015	**583**[b]/ **4601**[b]	**16.5**[b] / -

Abbreviations: CYP: cytochrome P450; -: Not applicable
a Equation corresponding to R values are provided in ICH M12 (1)
b Risk identified

2.6.2.2. Pharmacodynamics

Mechanism of action

Belumosudil is a potent selective Rho-associated, coiled-coil protein kinase-2 (ROCK2) inhibitor. ROCK2 has been shown to be activated in Th17 skewed milieu, leading to the upregulation of signal transducer and activator of transcription 3 phosphorylation and the consequent increased expression of Th17 specific transcription factors. *In vivo*, belumosudil has demonstrated efficacy in a variety of clinically relevant animal models of disease including chronic GVHD. Available human PD data is very limited. It was demonstrated that administration of belumosudil to healthy human subjects down-regulates the ability of T cells to secrete Th17 cytokines, such as IL-21 and IL-17 *ex vivo,* which was further supported by down-regulation of relevant transsciption factors (phosphorylation of STAT3 and reduced levels of IRF4 and RORγt protein) in a dose-dependent manner. No data from cGVHD patients is currently available, but additional PD data were collected in the confirmatory study EFC17757 recently terminated.

Taken together, the data indicate that ROCK2 inhibition may be a valuable approach to treatment for cGVHD patients.

Primary and Secondary pharmacology

Thorough QTc study (study KD025-110)

The thorough QTc study was designed to exclude a threshold effect below which QTc changes were considered to have no clinical consequence, currently a placebo-corrected change-from-baseline (ΔΔ) QTc (ΔΔQTc) of approximately 5 msec as demonstrated by the upper bound of the 2-sided 90% confidence interval (CI) being below 10 msec (ie, a negative TQT study). Moxifloxacin was used as a positive control to determine the assay sensitivity of this study, with an expected peak QT effect (ΔΔQTc) of 10 to 15 msec.

All subjects received a single oral dose of each of the following treatments in a randomized order: A therapeutic dose of belumosudil (1 x 200-mg tablet); A supratherapeutic dose of belumosudil (5 x 200-mg

tablets; 1000 mg; taken 5 minutes after a meal to increase exposure); A 400-mg dose of moxifloxacin (1 x 400-mg tablet), open label; Placebo.

The concentration-QTc analysis predicted that an effect of belumosudil on ΔΔQTcF exceeding 10 ms can be excluded within the range of plasma concentrations of belumosudil up to ~12080 ng/mL.

Table 15: predicted ΔΔQTcF interval at geometric mean peak belumosudil concentration

Treatment	Geometric mean at C_{max} of Belumosudil (ng/mL)	ΔΔQTcF Estimate (ms) (90% CI)
Therapeutic Dose Belumosudil group	1765.2	-0.36 (-1.04, 0.31)
Supratherapeutic Dose Belumosudil group	5769.0	2.37 (0.81, 3.92)
10 ms Threshold	12080	6.67 (3.33, 10.00)

Based on a linear mixed-effects model with ΔQTcF as the dependent variable, time-matched belumosudil plasma concentration as an explanatory variate, centered baseline QTcF as an additional covariate, treatment (active = 1 or placebo = 0) and time as fixed effects, and a random intercept per subject.

Exposure-efficacy and exposure-safety analyses

Using the updated popPK model, steady-state individual post hoc AUC_{0-24} values were predicted for cGVHD subjects in KD025-208 and KD025-213 studies and were plotted against efficacy endpoint duration of response. The exposure-efficacy exploratory plots indicated no relationship between belumosudil exposure and response duration over the range of exposures observed in Studies KD025-208 and KD025-213.

2.6.3. Discussion on clinical pharmacology

Pharmacokinetics of belumosudil have been investigated in healthy volunteers and in patients with cGVHD both after single dose and after multiple dose studies. In the early stage of development, the studies were conducted with capsule formulation, which has subsequently been changed to tablet formulation. The tablet formulation is the intended commercial product. Relative bioavailability between the capsule and tablet formation has been assessed in healthy subjects. The rate and extent of absorption of belumosudil are similar between the tablet and capsule formulations (Study KD025-106).

Absorption of belumosudil is fast, with peak concentrations occurring about 3 hours after dosing. Absolute bioavailability of belumosudil based on $AUC_{inf\ oral}/AUC_{inf\ IV}$ was estimated to be about 64% following oral administration of 200 mg belumosudil tablet, in fed state (Study KD025-108). Peak concentrations and AUC increase slightly more than dose-proportionally between doses 20 mg to 500 mg QD but less than dose-proportional with doses over 500 mg (Studies SLx-2119-09-01, KD025-101, KD025-102). In patients with cGVHD, the exposure increase between doses 200 mg and 400 mg is approximately dose-proportional. Minor deviation from dose proportionality has no clinical significance with the proposed posology of 200 mg QD.

Food affects the bioavailability of belumosudil. Exposure of belumosudil increased to approximately 2-fold in fed state as compared to fasted state in healthy subjects and t_{max} was delayed by 0.5 hours (Study KD025-106). In the phase 2 studies the patients with cGVHD were instructed to take belumosudil with food. The SmPC also recommend taking belumosudil with concomitant food. Belumosudil is a BCS Class IV compound.

Belumosudil is extensively bound to proteins in human plasma (mean 99.88% to 99.89% bound, independent of concentration). [^{14}C]-belumosudil was preferentially bound to human serum albumin (99.91%) compared to α1-acid glycoprotein (98.64%). The two main metabolites, KD025m1 and KD025m2,

are also extensively bound to human plasma proteins (fraction bound >99%). Chronic GVHD involving the kidneys can lead to significant proteinuria, resulting in hypoalbuminaemia.

In the mass balance study (Study KD025-108), subjects received a single dose of 200 mg belumosudil tablet in fed state followed by an intravenous (IV) dose of [^{14}C]- belumosudil (100 µg) as a 15-minute IV infusion 1.75 hours after oral dose administration. The majority of total radioactivity was recovered in feces (85%) and <5% was recovered in urine within 216 hours, suggesting there is minimal renal elimination, and the predominant route of clearance of [^{14}C]-belumosudil and associated metabolites is biliary and/or intestinal. Exposure (AUC) of belumosudil and the metabolites KD025m2 and KD025m1 accounted for ~34% of the total circulating radioactivity based on AUC.

Structural identification of belumosudil metabolites was attempted on radioactive components representing 10% or more of the circulating radioactivity in plasma and accounting for greater than 10% of the dose in feces. No single radioactive component present in urine accounted for more than 10% of the dose. Of the total plasma radioactivity, belumosudil was 64%, KD025m2 and coeluting O-dealkylated belumosudil sulfate together was 11.5%, and a belumosudil glucuronide was 15%. In feces, belumosudil was 30% and KD025m2 and *O*-dealkylated belumosudil sulfate accounted for a combined 35% of the total sample radioactivity. The belumosudil diol (belumosudil $^{+2}$O, $^{+2}$H) and monohydroxy belumosudil were 10% and 11% in feces, respectively.

Based on *in vitro* assessment, 14 metabolites of belumosudil were detected in human liver microsomes (only KD025m2 >10%) and 19 metabolites of belumosudil were detected in human hepatocytes (only KD025m2 >10%). Additional metabolite identification was done on clinical samples from Study KD025-108. CYP3A4 was the predominant CYP isoform responsible for the metabolism of belumosudil, whereas CYP2D6, CYP2C8, CYP1A2, CYP2C19, and UGT1A9 contributed to a lesser extent. The metabolism of belumosudil to KD025m1 was CYP3A4 and CYP2C8 dependent. The metabolism of belumosudil to KD025m2 was CYP3A4-dependent with further metabolism of KD025m2 dependent on UGT1A1, with little to no contribution from CYP enzymes.

Belumosudil was a time-dependent inhibitor (TDI) of CYP1A2, CYP2C19, and CYP3A4/5. KD025m2 was also a TDI of CYP3A4/5.

Human plasma concentrations of metabolite KD025m1 were lower than those of metabolite KD025m2 and both were lower than belumosudil. Metabolites are not expected to contribute to clinical effects of belumosudil.

Population PK Model

The Applicant has fitted a population PK model to PK data from five Phase 1 studies (KD025-101, KD025-102, KD025-103, KD025-106, and KD025-107) and two Phase 2 studies (KD025-208 and KD025-213, conducted in cGVHD subjects). The new model, which was redeveloped during assessment as requested by the CHMP, did not have the problems of the prior popPK model (e.g., minimization not successful). The new final model is a two-compartment model, in which the absorption phase was described through first order absorption constant, a lag time and a relative bioavailabily parameters. The parameter estimates were consistent with the observed clinical data. Diagnostic plots and bootstrap indicated a reasonably good performance. The main elimination pathway(s) of belumosudil is metabolism by CYP enzymes, primarily by CYP3A4, which are expected to be mature by the age of 12 years. The lowest body weight in the popPK dataset was 38.6 kg. The popPK model was used by the Applicant to estimate effects of covariates on PK and to simulate exposure in adult and adolescent patients (≥12 years of age and ≥40 kg) following posology used in Phase 2 clinical studies. The model is fit for these purposes.

PBPK models

A total of three PBPK modelling reports were presented by the Applicant. The models for belumosudil and metabolite KD025m2 were based on *in vitro* data and calibrated based on clinical PK data over several dose levels following single and multiple doses, and in the presence and absence of CYP3A4 inhibitor itraconazole and CYP3A4 inducer rifampicin. The model for belumosudil is complex, with time-dependent autoinhibition of CYP3A4 affecting clearance. Fraction unbound (f_u) of belumosudil (0.11%) was justified by results of *in vitro* protein binding studies. Full validation reports of the protein binding studies were not provided, this was not pursued because the PBPK model was considered not fit for purpose.

The intended use of the PBPK modelling was to predict DDI scenarios involving several enzymes and transporters and also the interaction potential of a metabolite, for several aspects based on *in vitro* data only. The submitted PBPK models are not considered to be fit for purpose because of the following: The models consistently underpredicted belumosudil steady state AUC when compared to observed data, with simulated/observed belumosudil AUC ratios ranging between 55% and 95%. On the other hand, steady state C_{max} of belumosudil was consistently overpredicted by the PBPK model. Importantly, the model failed to predict the outcome of the performed clinical DDI studies with belumosudil as an inhibitor of transporter mediated interactions (P-gp and BCRP/OATP1B1). The effect of belumosudil as inhibitor of CYP enzymes has not been evaluated in a clinical DDI study, therefore, it is not known if the model can accurately predict this type of interaction.

Special populations

PK in special populations was evaluated using the popPK model for belumosudil. In addition, a dedicated PK study in subjects with hepatic impairment has been conducted.

Regarding renal impairment, the human mass balance study indicated minimal renal elimination (<5% total radioactivity recovered in urine). The population PK analysis found no significant effect of mild to moderate renal impairment on belumosudil CL/F. The SmPC includes a warning that patients with severe renal impairment or end-stage renal disease should be carefully monitored with regard to safety and efficacy during belumosudil treatment. This is appropriate and agreed by CHMP.

Regarding hepatic impairment, belumosudil is eliminated mainly via metabolism in the liver. PK of belumosudil has been studied in subjects with mild, moderate and severe hepatic impairment and healthy subjects have been also included in the study as recommended in the guideline (CPMP/EWP/2339/02). Belumosudil exposure increases in subjects with impaired hepatic function, clearance being almost three times lower and AUC three times higher in patients with severe hepatic impairment compared to healthy subjects. In addition, unbound belumosudil $AUC_{0-\infty,u}$ was markedly higher (~16-fold) in participants with severe hepatic impairment than in healthy participants. Belumosudil is contraindicated in patients with severe hepatic impairment (Child-Pugh C) without liver GVHD and use in patients with moderate hepatic impairment (Child-Pugh B) without liver GVHD is not recommended. Clearance of belumosudil decreased and the AUC increased slightly in subjects with mild hepatic impairment (Child-Pugh A), but no dose adjustment is recommended when administering belumosudil to these subjects. This is considered acceptable by CHMP.

Weight, gender, race, age: Population PK analysis showed that there was no significant effect of weight, gender, race, and age on belumosudil PK. In clinical efficacy/safety studies, no dose adjustment was done based on weight, gender, race, and age.

The population PK model was used to predict exposure in adolescents (age ≥12 years and weight ≥40 kg) to support an indication in adolescents. PK simulations indicated that steady-state AUC, C_{max} and C_{trough} values in adolescents (age ≥12 years and weight ≥40 kg) were in the exposure range for which adult efficacy and safety data are available. (please refer to efficacy section of this AR for more extensive discussion on the paediatric indication)

PK interactions

Belumosudil as a substrate

Belumosudil is extensively metabolized by several pathways, metabolism by CYP3A4 is estimated to be the major elimination route. In a clinical DDI study (KD025-107), the effect of CYP3A4 inhibition and induction on belumosudil were evaluated using itraconazole (strong CYP3A inhibitor) and rifampicin (strong CYP3A inducer). Itraconazole did not have a clinically meaningful effect on belumosudil PK (~20% increase in C_{max} and ~25% increase in AUC_{inf}). Based on the results of study KD025-107, no dose adjustment is required for administration of belumosudil with concomitant use of strong (or mild to moderate) CYP3A4 inhibitors. However, rifampicin decreased belumosudil C_{max} by 59% and AUC by 72%. If concomitant use of a strong CYP3A4 inducer and belumosudil cannot be avoided, it is recommended to increase the belumosudil dose to 200 mg twice daily (BID). The usual belumosudil dose (200 mg once daily) should be resumed within 1 day after the last administration of the strong CYP3A4 inducer. This is expected to result in temporarily decreased exposure to belumosudil and no overexposure. Moderate CYP3A4 inducers are expected to have a reduced effect on belumosudil as compared to strong CYP3A4 inducers, and dose adjustment is not recommended.

A reduction in belumosudil exposure was observed when belumosudil was administered with a strong PPI rabeprazole (80%-90% decrease) or with a moderate PPI omeprazole (50%-70% decrease) (Study KD025-107). It is believed that an increase in gastric pH leads to decreased solubility of belumosudil, thus resulting in decreased absorption. The dose of belumosudil should be increased to 200 mg BID when used together with a PPI, if concomitant use cannot be avoided.

H2 antagonists and antacids only temporarily increase the pH in the stomach. If these medicinal products are taken at the same time as belumosudil then the belumosudil absorption is expected to be significantly decreased. Therefore, it is recommended to take belumosudil 2 hours before or 12 hours after H2 antagonists and antacids.

Belumosudil as inhibitor of CYP and UGT enzymes

Belumosudil was *in vitro* a competitive and/or time-dependent inhibitor of CYP1A2, CYP2C19, and CYP3A4/5 and a borderline competitive inhibitor of CYP2C9. The clinical relevance of these *in vitro* signals is not known at present. The Applicant will conduct a clinical study to evaluate the clinical significance of these *in vitro* signals (**PAM**). A warning of potential inhibition of CYP1A2 and CYP3A4 is included in the SmPC, and warning of potential inhibition of CYP2C19 should be added (see comment in section 4.5 of the SmPC document). Finally, the risk of inhibition of CYP2C9 is considered to be so low that a warning in the SmPC is not warranted.

Belumosudil was *in vitro* an inhibitor of UGT1A1. In a clinical DDI study (KD025-112), belumosudil decreased the formation of the glucuronide metabolite of UGT1A1 sensitive substrate raltegravir by approximately 40% (KD025-112), which indicates that belumosudil (or its metabolite) inhibits UGT1A1. Co-administration of belumosudil with UGT1A1 substrates, for which minimal concentration changes may lead to serious toxicities, is not recommended.

Belumosudil as inhibitor of transporters

The impact of belumosudil on exposures of P-gp substrate dabigatran and BCRP and OATP1B1 substrate rosuvastatin was investigated in a clinical DDI study (KD025-112). A 2.1-fold increase in AUC of dabigatran and a 4.4-fold increase in AUC rosuvastatin was observed after multiple doses of belumosudil.

Tacrolimus and sirolimus

Belumosudil is an inhibitor of P-gp and CYP3A4. Tacrolimus and sirolimus are substrates of P-gp and CYP3A4, have narrow therapeutic index, and are commonly used in the target population. The section 4.5 of SmPC adequately reflects the concomitant use and recommends close therapeutic drug monitoring.

Exposure-response analyses

Exposure-response analysis using individual exposure estimates from the new, acceptable popPK model did not find a relationship between exposure (AUC_{0-24}) and efficacy (duration of response). The relationship between exposure and effect in dose range 200 mg to 400 mg per day has not been established, even though such a relationship may exist in a wider dose range. The proposed dose is not supported by formal exposure-response analyses. This was not pursued because the E-R analyses are not critically important for the overall evaluation of Benefit/Risk at the proposed clinical dose.

Cardiac safety / thorough QTc study

The Applicant has conducted a thorough QTc analysis with moxifloxacin as a positive control. The study was double-blind, with each subject receiving placebo, 200 mg belumosudil, 1000 mg belumosudil, and 400 mg moxifloxacin. The PK and ECG sampling was sufficiently dense around the T_{max}.

The 90% CI for ΔΔQTcF was clearly below 10 ms at the maximum belumosudil concentration resulting from 200 mg dose, or from 1000 mg supratherapeutic dose). This indicates that there is a sufficient safety threshold for belumosudil not causing clinically relevant QTc changes at the proposed clinical dose (200 mg once daily), even when accounting for a minor accumulation of belumosudil that is observed following repeated dosing. It can be assumed that the lack of QTc prolongation in healthy volunteers also generalizes to lack of QTc prolongation patients receiving belumosudil for the treatment of cGVHD.

2.6.4. Conclusions on clinical pharmacology

Clinical pharmacokinetics and pharmacodynamics of belumosudil have been investigated in sufficient detail for benefit/risk assessment. The Applicant will conduct a post-approval clinical study to evaluate positive *in vitro* signals of belumosudil as an inhibitor of CYP enzymes.

There are still requests regarding DDI information in sections 4.4 and 4.5 of the SmPC that have not been agreed.

2.6.5. Clinical efficacy

Studies included in belumosudil clinical development program for cGVHD to support the efficacy of belumosudil in the treatment of patients 12 years and older with cGVHD after failure of at least 2 prior lines of systemic therapy are presented in **Table 16**.

Three studies provide primary evidence of the efficacy of belumosudil:

- Study KD025-213, a Phase 2, open label, randomized, multicenter study conducted in the US
- Study KD025-208, a Phase 2a, dose-escalation open label study
- Study KD025-217, a long-term extension (LTE) study of eligible adult participants treated with belumosudil in Studies KD025-213 and KD025-208.

These three studies are included in the integrated analysis of efficacy.

Three studies provide supportive efficacy data:

- Study ME3208-2, a Phase 3, single-arm, open-label study in Japanese participants
- Study BN101-201, a phase 2, open-label study in Chinese participants
- Study AA_00117, a non-interventional study, comparing the efficacy and safety of belumosudil to best available therapy (BAT).

Table 16: overview of clinical studies designed to support the efficacy of belumosudil in proposed indication

Study No. NCT No. (Status)	Objectives	Phase study design	Dosing regimen and treatment duration	Study population	Prior lines of systemic therapy	Number of participants/ age
KD025-213 *Fout! Verwijzingsbron niet gevonden.* **NCT03640481 (Completed)**	Long-term efficacy, safety, and tolerability	Phase 2, open-label, randomized study	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	2-5 ≥2: 155 (100%)	155 ≥12
KD025-208 **NCT02841995 (Completed)**	Efficacy, safety, and tolerability	Phase 2a, open-label, dose-escalation study	200 mg QD 200 mg BID 400 mg QD Treatment until cGVHD progression or unacceptable toxicity	Participants with cGVHD	1-3 ≥2: 35 (68.9%)	54 ≥18
KD025-217 *Fout! Verwijzingsbron niet gevonden.* **NCT05305989 (Ongoing)**	Extended treatment and follow-up of adult participants treated with belumosudil in Study KD025-208 or Study KD025-213	Phase 2, open-label LTE study	Dose assigned in the parent study	Participants with cGVHD	2-5	23 *Fout! Verwijzingsbron niet gevonden.* ≥18
ME3208-2 **(Ongoing)**	To verify efficacy, using best ORR and evaluate safety	Phase 3, open label, single-arm	200 mg QD, tablet	Participant with steroid-dependent/	1-3 ≥2: 19 (90.5%)	20 planned, 21 analyzed/ ≥12

Study No. NCT No. (Status)	Objectives	Phase study design	Dosing regimen and treatment duration	Study population	Prior lines of systemic therapy	Number of participants/ age
				resistant cGVHD		
BN101-201 (Completed)	To evaluate the efficacy and safety of BN101/belumosudil in the treatment of patients with cGVHD who have received at least one line of systemic therapy	Phase 2, open label, single arm	200 mg QD, tablet	Participants with cGVHD	1-5 ≥2: 27 (90.0%)	30/ ≥18
AA_00117 (Completed)	To evaluate the efficacy and safety of belumosudil versus best available therapy in patients with cGVHD who have failed 2–5 prior LOTs.	Non-interventional study (using targeted learning methods for causal inference to emulate a hypothetical RCT)	According to routine clinical practice	Participants with cGVHD	2-5	196/ ≥12

Abbreviations: BID = twice daily; cGVHD = chronic graft versus host disease; LOT = line of therapy; LTE = long tern extension; NCT = national clinical trial; ORR = objective response rate; QD = once daily; RCT = randomized controlled trial.

a **Data cutoff date for Study KD025-208: 08 July 2022.**

b **Number of participants in modified intent-to-treat population included 152 adult participants and 3 adolescent participants; Database lock date for adult participants: 01 September 2022, data cutoff date for adolescent participants: 11 December 2023.**

c **Data cutoff date for Study AA_00117: 27 March 2024.**

d **Data cutoff date for ME3208-2: interim analysis: 10 August 2023.**

e **Data cutoff date for BN101-201: 10 December 2022.**

f **Data cutoff date for Study KD025-217: 29 January 2024.**

Table 17 presents the numbers of the patients in each study supporting the efficacy of belumosudil in the proposed indication (> 12 years, belumosudil 200 mg OQ, > 2 LOT).

Table 17: summary of clinical data that support the efficacy of belumosudil in cGVHD in the proposed indication

Level of evidence	Data Source	Study design/ Patient Population / No. of participants	Primary endpoint
Primary	KD025-213 (pivotal)	Phase 2 dose finding study/cGVHD after 2-5 LOT/ N=79 at 200 mg QD group[a]	ORR
	KD025-208	Phase 2A dose escalation study/ cGVHD after 1-3 LOT/N=17 at 200 mg QD group (≥2 LOT, N=15)[b]	ORR
	Integrated analysis	Integrated analysis of KD025-213 and KD025-208 and long-term data on 23 patients (KD025-217)	ORR
Supportive	ME3208-02	Phase 3 single arm study/ cGVHD after 1 to 3 LOT/ N=21 (≥2 LOT, N=19)	Best ORR at 24 weeks[c]
	BN101-201	Phase 2 single arm study/ cGVHD after 1 to 5 LOT; N=30 (≥2 LOT, N=27)	ORR
	AA_00117	Non-interventional comparative study/ cGVHD after 2-5 LOT/ ; 196 patients (113 Belumosudil , 83 BAT)	ORR at 6 months[d]

Abbreviations: LOT=line of therapy; BAT=best available therapy

a Total of 155 participants (152 adults and 3 adolescents) enrolled in Study KD025-213, of which 79 participants (77 adults and 2 adolescents) received 200 mg QD dose.

b Total of 54 participants enrolled in Study KD025-208. Seventeen participants received 200mg QD dose, including 15 participants with at least 2 prior lines of systemic therapy.

c Best ORR in Study ME3208-2 is defined as the proportion of participants who achieved CR or PR in the overall response at least once at any time point of assessment during the study drug treatment period. Best ORR at 24 weeks is calculated using all time points from baseline to 24 weeks, which is equivalent to ORR within 24 weeks defined in KD025-213 and KD025-208 studies.

d ORR at 6 months is defined as the proportion of LOT-episodes achieving one of the following, in this order: complete or partial response per 2014 NIH consensus criteria; if not available, complete or partial response based on physician assessment; if not available, corticosteroid dose reduction of at least 50% without evidence of disease progression. The algorithm for this endpoint is defined in 5.3.5.4 Study AA_00117 [Figure 6]. Death, relapse and initiation of new line of therapy were categorized as failures.

2.6.5.1. Dose-response studies

Study KD025-208 was a phase 2a, dose-escalation, open-label study designed to evaluate the safety, tolerability, and activity of belumosudil in subjects with steroid-dependent active cGVHD, who had previously received 1 to 3 prior lines of systemic cGVHD therapy. The notable difference compared to pivotal Study KD025-213 was the number of prior lines of treatment for cGVHD. Participants who had received only one prior line of therapy were allowed since there was no approved second line therapy at the time of study initiation.

Overall, 64 subjects were screened for the study, and 54 subjects were included in the mITT population (all subjects who received at least 1 dose of study drug) (**Figure 5**). Eligible subjects were allocated sequentially based on the safety assessment of the lower dosing group. Seventeen subjects were assigned to Cohort 1 (200mg QD), then sixteen subjects to Cohort 2 (200mg BID), then the last twenty-one subjects to Cohort 3 (400mg QD). The study drug was administered in 28-day cycles until disease progression or unacceptable toxicity. From Protocol Amendment 5.0 (29 May 2018) onward, participants with a response assessment of "lack of response (LR) - mixed (LR-M)" (CR or PR in at least 1 organ accompanied by progression in another

organ) were permitted to continue treatment with belumosudil and remain in the study if the Investigator considered continued treatment to be in the participant's best interest.

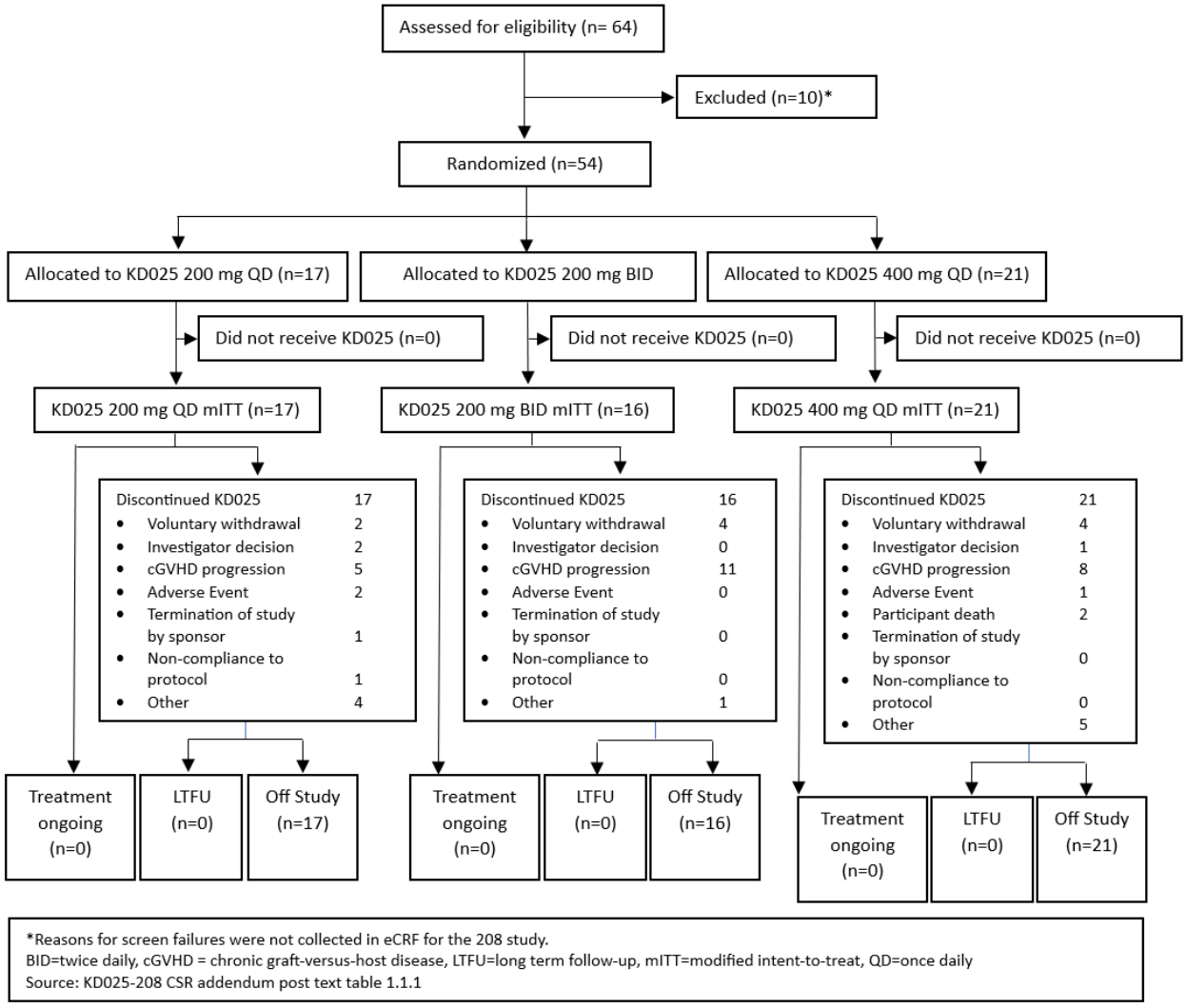


Figure 5: consort Diagram – All Informed Consent Subjects (KD025-208 CSR Addendum)

Belumosudil was supplied as 100 mg capsules or 200 mg tablets. The study was initiated using belumosudil capsules and later transitioned to belumosudil tablets (intended commercial formulation). In total, 28 out of 54 subjects were dosed with tablets.

Prior to the enrolment of subsequent cohorts, the safety data in each previous cohort were evaluated after 8 subjects had reached 2 months of treatment. It was planned that if ≥ 25% of subjects in a cohort experienced a Common Terminology Criteria for Adverse Events (CTCAE) v4.03 Grade 2 liver toxicity or a CTCAE v4.03 Grade 3 (or higher) AE in the same organ or body system, or if > 25% of subjects in a cohort were discontinued for toxicity that persisted for 14 days, then dose escalation to the next cohort would not have occurred, and all subjects in that dose cohort would have received a reduced dose. Subjects, who required pauses of more than 14 days or treatment-related Grade 2 or treatment-related Grade 3 toxicities persisted for 14 days, were discontinued from the study.

The overall median follow-up was 45.5 months (range from 0.7 months to 64.2 months). Forty-one (75.9%) subjects were in follow-up for ≥ 24 months.

Baseline characteristics

Median age of the subjects was 51.5 years. There were no notable differences in baseline characteristics across the cohorts. All subjects had received a previous allogeneic HCT. The overall median number of prior lines of systemic cGVHD therapy was 2.5 and 16 (29.6%) subjects had one prior line of therapy. In total, 35 (35/48; 72.9%) known subjects were refractory to the last systemic cGVHD treatment prior to enrollment in the study. Forty-two (77,8%) subjects suffered from severe cGVHD.

All 54 subjects had received prior systemic corticosteroid therapy. Forty-seven (87.0%) subjects had taken antineoplastic and immunomodulating agents of which most common were tacrolimus (26 subjects), sirolimus (24 subjects), rituximab (16 subjects), and mycophenolate mofetil (12 subjects); 15 had received ECP. The median number of organs involved at baseline was 3.5, which was similar across all cohorts.

Efficacy results

Primary efficacy endpoint, ORR (CR, PR, LR), was assessed as defined by the 2014 NIH Consensus Development Project on Clinical Trials in cGVHD (for details please see Section 3.3.1.1.5 in Clinical AR). **Table 18** summarizes ORR for the mITT Population presented in the original CSR, and the updated ORR based on the data cut-off date of 08 July 2022. The overall number of subjects who achieved ORR was 35 (64.8%) in the original CSR compared with 34 (63.0%) in the updated analysis. There were no notable differences in ORR according to cohort (dose level).

Table 18: Overall Response Rate – mITT Population

	Data Cut-off Date of 19 February 2020				Data Cut-off Date of 08 July 2022			
ORR	Cohort 1 200 mg QD N=17	Cohort 2 200 mg BID N=16	Cohort 3 400 mg QD N=21	Overall N=54	Cohort 1 200 mg QD N=17	Cohort 2 200 mg BID N=16	Cohort 3 400 mg QD N=21	Overall N=54
ORR (CR or PR) – n (%)	11 (64.7)	11 (68.8)	13 (61.9)	35 (64.8)	11 (64.7%)	11 (68.8%)	12 (57.1%)	34 (63.0%)
95% CI of ORR [1]	(38.3, 85.8)	(41.3, 89.0)	(38.4, 81.9)	(50.6, 77.3)	(38.3%, 85.8%)	(41.3%, 89.0%)	(34.0%, 78.2%)	(48.7%, 75.7%)

Statistical notes:
1. 95% CI (2-sided) were calculated using the Clopper-Pearson exact method.
BID = twice daily; CI = confidence interval; CR = complete response; mITT = modified Intent-to-Treat; n = number; ORR = Overall Response Rate; PR = partial response; QD = once daily.
Source: Post-text Table 5.1.1, the data cut-off date of 19 February 2020 and 08 July 2022.

Source: KD025-208 CSR Addendum

Table 19 summarizes the BoR for the mITT Population. All responses in 34 (64.8%) subjects were PRs; no subject had a CR.

Table 19: Best Overall Response – mITT Population

	Data Cut-off Date of 19 February 2020				Data Cut-off Date of 08 July 2022			
	Cohort 1 200 mg QD N=17 n (%)	Cohort 2 200 mg BID N=16 n (%)	Cohort 3 400 mg QD N=21 n (%)	Overall N=54 n (%)	Cohort 1 200 mg QD N=17 n (%)	Cohort 2 200 mg BID N=16 n (%)	Cohort 3 400 mg QD N=21 n (%)	Overall N=54 n (%)
Response								
CR	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
PR	11 (64.7)	11 (68.8)	13 (61.9)	35 (64.8)	11 (64.7)	11 (68.8)	12 (57.1%)	34 (63.0%)
LR								
LR-U	2 (11.8)	3 (18.8)	4 (19.0)	9 (16.7)	2 (11.8)	3 (18.8)	4 (19.0)	9 (16.7)
LR-M	3 (17.6)	1 (6.3)	0 (0)	4 (7.4)	2 (11.8)	1 (6.3)	0 (0)	3 (5.6)
LR-P	1 (5.9)	0 (0)	1 (4.8)	2 (3.7)	2 (11.8)	1 (6.3)	1 (4.8)	4 (7.4)
No response assessment	0 (0)	1 (6.3)	3 (14.3)	4 (7.4)	0 (0)	0	4 (19.0)	4 (7.4)

BID = twice daily; CR = complete response; LR = Lack of Response; LR-M = Lack of Response - Mixed; LR-P = Lack of Response - Progression; LR-U = Lack of Response - Unchanged; mITT = modified Intent-to-Treat; n = number; PR = partial response; QD = once daily.
Source: Post-text Table 5.1.2, data cut-off date of 19 February 2020 and 08 July 2022.

Safety results

In the original report, the median duration of treatment overall was 8.4 months. In total, 23 (42.6%) subjects had a treatment duration of more than 12 months.

Table 20 provides an overall summary of TEAEs. Overall, 53 subjects (98.1%) subjects experienced at least one TEAE and the number was similar across all cohorts.

In total, 33 (61.1%) subjects experienced at least 1 Grade ≥ 3 TEAE. In the updated analysis, 24 (44.4%) subjects experienced a serious TEAE, which occurred more often in Cohort 3 than in the other cohorts. In total, 19 (35.2%) subjects experienced a TEAE that led to discontinuation of treatment: 5 (29.4%) subjects in Cohort 1, 5 (31.3%) subjects in Cohort 2, and 9 (42.9%) subjects in Cohort 3; however, not all of these subjects were discontinued due to AE. No subjects in Cohorts 1 or 2 experienced a TEAE leading to death, and 4 (19.0%) subjects in Cohort 3 experienced a serious TEAE that led to death. None of these deaths was assessed as associated with the study treatment.

Overall, belumosudil was well tolerated with a safety profile consistent with that expected in a population of cGVHD subjects.

Table 20: Overall Summary of Treatment-Emergent Adverse Events (Safety Population)

	Data Cut-off Date of 19 February 2020				Data Cut-off Date of 08 July 2022			
	Cohort 1 200 mg QD N=17 n (%)	Cohort 2 200 mg BID N=16 n (%)	Cohort 3 400 mg QD N=21 n (%)	Overall N=54 n (%)	Cohort 1 200 mg QD N=17 n (%)	Cohort 2 200 mg BID N=16 n (%)	Cohort 3 400 mg QD N=21 n (%)	Overall N=54 n (%)
Subjects with at least 1 TEAE	17 (100)	16 (100)	20 (95.2)	53 (98.1)	17 (100)	16 (100)	20 (95.2)	53 (98.1)
Subjects with TEAEs by maximum severity								
Grade 1: mild	1 (5.9)	1 (6.3)	0 (0)	2 (3.7)	1 (5.9)	1 (6.3)	0 (0)	2 (3.7)
Grade 2: moderate	7 (41.2)	5 (31.3)	6 (28.6)	18 (33.3)	7 (41.2)	5 (31.3)	6 (28.6)	18 (33.3)
Grade 3: severe	8 (47.1)	8 (50.0)	6 (28.6)	22 (40.7)	8 (47.1)	8 (50.0)	6 (28.6)	22 (40.7)
Grade 4: life-threatening	1 (5.9)	2 (12.5)	4 (19.0)	7 (13.0)	1 (5.9)	2 (12.5)	4 (19.0)	7 (13.0)
Grade 5: fatal	0 (0)	0 (0)	4 (19.0)	4 (7.4)	0 (0)	0 (0)	4 (19.0)	4 (7.4)
Subjects with related TEAE	8 (47.1)	8 (50.0)	14 (66.7)	30 (55.6)	8 (47.1)	8 (50.0)	14 (66.7)	30 (55.6)
Subjects with serious TEAE	5 (29.4)	6 (37.5)	12 (57.1)	23 (42.6)	5 (29.4)	6 (37.5)	13 (61.9)	24 (44.4)
Subjects with related serious TEAE	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (4.8)	1 (1.9)
Subjects with Grade ≥3 TEAE	9 (52.9)	10 (62.5)	14 (66.7)	33 (61.1)	9 (52.9)	10 (62.5)	14 (66.7)	33 (61.1)
Subjects with related Grade ≥3 TEAE	1 (5.9)	3 (18.8)	2 (9.5)	6 (11.1)	1 (5.9)	3 (18.8)	2 (9.5)	6 (11.1)
Subjects with TEAE leading to dose reduction	0	0	2 (9.5)	2 (3.7)	0	0	2 (9.5)	2 (3.7)
Subjects with TEAE leading to dose held	4 (23.5)	8 (50.0)	8 (38.1)	20 (37.1)	4 (23.5)	8 (50.0)	8 (38.1)	20 (37.0)
Subjects with TEAE leading to dose discontinuation	6 (35.3)	5 (31.3)	7 (33.3)	18 (33.3)	5 (29.4)	5 (31.3)	9 (42.9)	19 (35.2)
Subjects with TEAE leading to death	0 (0)	0 (0)	4 (19.0)	4 (7.4)	0 (0)	0 (0)	4 (19.0)	4 (7.4)

Conclusions

Taken together, the results of Study KD025-208 show that belumosudil can improve cGVHD symptoms in a majority of subjects with an acceptable safety profile. Furthermore, the dosing regimen does not appear to notably affect responses. Given the potential safety signal observed for Cohort 3, the overall results support further investigations using dosing regiments of 200 mg QD and/or 200 mg BID.

2.6.5.2. Main study

Study KD025-213 (ROCKstar)

Methods

KD025-213 was a phase 2, randomized, multicenter study to evaluate the efficacy and safety of belumosudil (KD025) in subjects with cGVHD after at least 2 prior lines of systemic therapy.

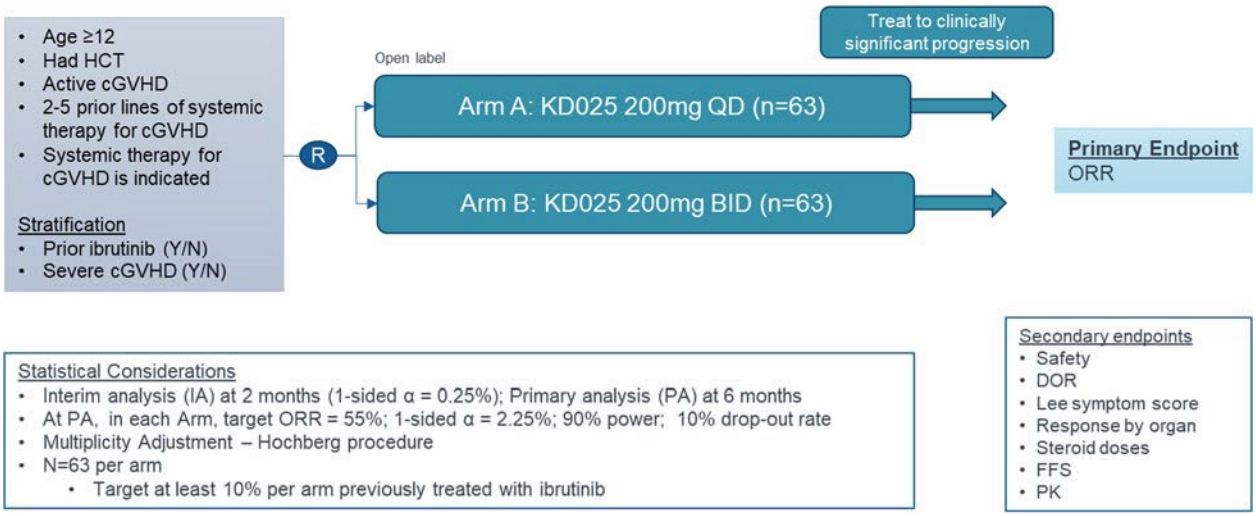


Figure 6: KD025-213 Study Schema

BID = twice daily; cGVHD = chronic graft versus host disease; DOR = Duration of Response; FFS = Failure-Free Survival; HCT = hematopoietic cell transplantation; IA = interim analysis; ORR = Overall Response Rate; PA = primary analysis; PK = pharmacokinetics; QD = once daily; R = randomization; Y/N = yes/no

Study Participants

Eligible subjects were required to have active cGVHD despite treatment with corticosteroids and after failure of at least 2 prior lines of systemic therapy. Topical agents were not considered as a line of therapy. A target of >10% of the enrolled population having previously received ibrutinib as a therapy for cGVHD was set/met.

Inclusion criteria

A subject had to meet all of the following criteria to be eligible for the study:

GVHD Criteria

1. Male and female subjects at least 12 years of age who had an allogeneic HCT;
2. Previously received at least 2 prior lines and no more than 5 lines of systemic therapy for cGVHD;
3. Received glucocorticoid therapy with a stable dose over the 2 weeks prior to screening;
4. Had persistent cGVHD manifestations and systemic therapy was indicated;
5. Karnofsky (if aged > 16 years)/Lansky (if aged <16 years) Performance Score of >60;

Laboratory Parameters

6. Absolute neutrophil count >1.5 x 10E9/L;
7. Platelet count >50 x 10E9/L;
8. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) <3 X upper limit of normal (ULN);
9. Total bilirubin <1.5 x ULN;
10. Glomerular filtration rate (GFR) ≥30 mL/min/1.73m3

General criteria

11. Female subjects of childbearing potential who had a negative urine pregnancy test at screening;
12. Sexually active females of childbearing potential enrolled in the study must have agreed to use 2 forms of accepted methods of contraception during the course of the study and for 3 months after their last dose of study drug;
13. For male subjects who were sexually active and who were partners of females of childbearing

potential: agreement to use 2 forms of contraception as in criterion 12 above and to not donate sperm during the treatment period and for at least 3 months after the last dose of study drug;
14. Subject (or the subject's legal authorized representative) was able to provide written informed consent/assent prior to the performance of any study-specific procedures;
15. Weight >40 kg; and
16. It was in the best interest of the subject to participate in the study.

Exclusion Criteria

A subject who met any of the following criteria was ineligible for the study:
1. Subject had not been on a stable dose/regimen of systemic cGVHD treatments for at least 2 weeks prior to screening;
2. Had histological relapse of the underlying cancer or post-transplant lymphoproliferative disease at the time of screening;
3. Had current treatment with ibrutinib. Prior treatment with ibrutinib was allowed with a washout of at least 28 days prior to randomization;
4. Female subjects who were pregnant or breastfeeding;
5. Had a history or other evidence of severe illness or any other conditions;
6. Had known active hepatitis B virus or hepatitis C virus or history of HIV;
7. Was diagnosed with another malignancy (other than malignancy for which transplant was performed) within 3 years of enrolment, with the exception of completely resected basal cell or squamous cell carcinoma of the skin, carcinoma in situ of the cervix, resected breast ductal carcinoma in situ, or prostate cancer with Gleason score <6 and stable prostate-specific antigen over 12 months)
8. Had previous exposure to KD025;
9. Had known allergy/sensitivity to belumosudil or any other ROCK2 inhibitor;
10. Subject had QTc(F) >480 ms;
11. Subject had a FEV1 of <39% or had lung score of 3;
12. Subject was considered unlikely to adhere to treatment and/or follow protocol in the opinion of the Investigator; or
13. Had treatment with any non-GVHD investigational agent, or any investigational device or procedures, within 28 days of enrolment.

There were no exclusions based on the type of prior systemic therapies which reflected the currently heterogeneous available treatment options. Subjects receiving SOC cGVHD therapies, such as CNIs (tacrolimus, cyclosporine), sirolimus, MMF, methotrexate, rituximab, or ECP, may have been enrolled if they had been on a stable dose. Changes in doses of drugs to maintain therapeutic levels were not considered as a change in dose/schedule.

Of the concomitant medications, concomitant use of investigational systemic immunosuppressant drugs (excluding ruxolitinib) for cGVHD as well as use of strong cytochrome P450 (CYP) and strong CYP3A4 inducers was prohibited.

Patients with more than 5 prior lines are excluded to maintain a relatively homogeneous population, particularly as their disease has likely become sclerotic with minimal likelihood to respond to a new treatment intervention.

Treatments

Eligible subjects were randomized to open-label treatment arms belumosudil 200 mg QD (arm A) or belumosudil 200 mg BID (arm B) in 1:1 ratio. The randomisation was stratified by prior ibrutinib therapy (yes/no) and cGVHD severity (severe/not severe) with a block size of 4.

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

Subjects who experienced cGVHD progression as defined by NIH criteria but for whom no new systemic therapy was planned may have continued to receive belumosudil and were assessed again at their next cycle. If progression per NIH criteria was not confirmed or no new systemic therapy was planned, subjects may have continued on belumosudil per Investigator discretion.

Subjects with a lack of response may have continued treatment with belumosudil and remained on the study if the Investigator considered continued treatment to be in the subject's best interest.

After a sustained response for 6 months and cessation of all other immunosuppressants for at least 3 months, belumosudil was tapered.

Subjects were withdrawn from the study if there had been no response after 12 cycles of belumosudil; or, if in the judgment of the Investigator, there had been no clinical benefit for the subject.

At study entry, according to inclusion criteria, subjects were receiving glucocorticoid therapy with a stable dose over the 2 weeks prior to screening. Corticosteroids may have been tapered at the discretion of the Investigator after ≥ 2 weeks of belumosudil administration. Transient increases in corticosteroid dosing (not exceeding 1 mg/kg/day prednisone equivalent) were permitted for the treatment of cGVHD flare, but the dose must have been reduced back to the pre-randomization dose within 6 weeks. If the dose remained elevated for more than 6 weeks, this was considered a belumosudil treatment failure. More than 2 episodes of cGVHD flare that required increased corticosteroid therapy in the first 6 months of belumosudil treatment was also considered a belumosudil treatment failure.

Objectives

The primary objective of this study was to evaluate the efficacy and safety of belumosudil, at dose levels of 200 mg once daily (QD) and 200 mg twice daily (BID), in subjects with cGVHD who had previously been treated with at least 2 prior lines of systemic therapy.

Outcomes/endpoints

The primary efficacy endpoint was the ORR, as defined by the 2014 NIH Consensus Development Project on Clinical Trials in cGVHD and as assessed by Investigators *(***Table 21** *and* **Table 22***).* Responders included subjects that achieved a response (PR+CR).

Table 21: Response Definitions by the 2014 NIH Consensus Development Project on Clinical Trials in cGVHD

Response	Definition
CR	Resolution of all manifestations of cGVHD in each organ or site
PR	Improvement in at least 1 organ or site without progression in any other organ or site
LR	
LR-M [1]	CR or PR in at least 1 organ accompanied by progression in another organ
LR-U	Outcomes that did not meet the criteria for CR, PR, LR-M, or LR-P
LR-P	Progression in at least 1 organ or site without a response in any other organ or site
Statistical note: 1. This response was considered progression for purposes of analysis. cGVHD = chronic graft versus host disease; CR = complete response; LR = Lack of Response; LR-M = Lack of Response-mixed; LR-P = Lack of Response-progression; LR-U = Lack of Response-unchanged; PR = partial response.	

Table 22: Response determination for chronic GVHD clinical trials based on clinician assessments

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

ULN indicates upper limit of normal.

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

The secondary efficacy endpoints were the following: DOR, TTR, Response rate by organ system, Change in cGVHD GSR based on the Clinician-Reported Global cGVHD Activity Assessment, Change in Lee Symptom Scale Score (LSS), FFS, TTNT, OS, change in the corticosteroid dose, change in NCI dose, and change in symptom activity based on the cGVHD Activity Assessment Patient Self-Report.

Sample size

The CSR reflects Amendment 1 of the protocol under which 126 subjects were planned for enrolment. For a single arm, assuming a true ORR of 55%, dropout rate of 10%, power of 90%, and 2-sided alpha of 0.045 to demonstrate ORR >30%, the sample size was calculated to be 63. With Amendment 2, the planned sample size was increased to 166 subjects.

Randomisation and blinding (masking)

Eligible subjects were randomized to open-label treatment arms belumosudil 200 mg QD (arm A) or belumosudil 200 mg BID (arm B) in 1:1 ratio. The randomisation was stratified by prior ibrutinib therapy (yes/no) and cGVHD severity (severe/not severe) with a block size of 4.

Chronic GVHD severity assessment was based on NIH Global Severity Scoring where severe cGVHD was defined as at least 1 organ with a score of 3, or a lung score of 2 or 3.

Statistical methods

The following populations were included in analyses:

mITT Population was defined as all randomized subjects who received at least 1 dose of study drug. The mITT Population was used for tables of demography, baseline characteristics, and efficacy**.** The Responder Population was defined as subjects in the mITT Population that achieved a PR or CR at any post-baseline response assessment**.** The Non-Responder Population was defined as any subject in the mITT Population that was not a responder**.** The Responder and Non-Responder Populations were used for some subgroup analyses.

The Safety Population was equivalent to the mITT Population.

Primary endpoint

Since the study had 2 belumosudil treatment arms, the Hochberg procedure was used for multiplicity adjustment for the primary endpoint. Point estimates, confidence intervals (CIs) (Clopper-Pearson [exact] method), and unadjusted and Hochberg adjusted p-values corresponding to the null hypothesis of ORR ≤30% versus the alternative hypothesis of ORR >30% by treatment arms were reported. Based on best overall response, the proportion reaching PR and CR were also reported.

Secondary endpoints

Duration of Response

Various definitions of duration of response were evaluated for the Responder Population with different criteria for terminus: The time from first documentation of response to the time of

1. first documentation of deterioration from best response (eg, CR to PR or PR to LR)
2. first documentation of LR
3. initiation of new systemic cGVHD therapy (which was reviewed and confirmed by a clinical team review).

Kaplan-Meier plots and descriptive statistics of DOR, with censoring rules applied; and landmark analyses: number and percentage of subjects with a response sustained for ≥12, ≥20, ≥24, ≥32, ≥36, and ≥48 weeks with (from Kaplan-Meier estimate) and without adjustment to censoring.

Table 23: Censoring Rules for Duration of Response

DOR	Events	Censoring
Primary	Deterioration from best response. Initiation of new systemic therapy for cGVHD. Death.	Last documented response assessment. If LR or initiation of new systemic therapy happened immediately after 2 or more missed response assessments, the event date was set as 4 weeks (1 cycle) after last documented response assessment prior to this event.
Secondary	Documented LR. Initiation of new systemic therapy for cGVHD. Death.	
Tertiary	Initiation of new systemic therapy for cGVHD. Death.	Last response assessment or Long-Term Follow-Up assessment, whichever was the latest and available.

cGVHD = chronic graft versus host disease; DOR = Duration of Response; LR = Lack of Response.

In response to Day 120 list of questions, sensitivity analyses were provided for the first and secondary definitions for DoR such that censoring is applied for administrative reasons only, while treatment discontinuation due to non-administrative reasons was considered as loss of response.

Time to Response

TTR was measured as the time from first treatment to the time of first documentation of response. Descriptive statistics and plots of cumulative number and percentage of responders over time (4, 8, 12, 16, 24, 32, 40, and ≥48 weeks) were provided. TTR analyses were only conducted for the Responder Population.

In response to Day 120 list of questions, distribution of cGvHD response status ranging from "complete response" to "lack of response – progression") was summarised by visit. In this summary, participants who had discontinued treatment were considered to have progression at subsequent time points.

Response by organ system

The best response (CR or PR) for the 9 individual organs (skin, eyes, mouth, esophagus, upper GI, lower GI, liver, lungs, and joints and fascia) plus GSR were summarized.

TTR at the organ level was also evaluated. Descriptive statistics and plots of cumulative number and percentage of responders over time (4, 8, 12, 16, 24, 32, 40, and ≥48 weeks) were provided. Two series of percentages are presented:

1. With the total number of subjects in the mITT Population with involvement of the given organ at baseline as denominator; and

2. With the number of subjects in the Responder Population with involvement of the given organ at baseline as denominator.

Change in Lee Symptom Scale Score

The LSS was assessed on the same schedule as response assessments. The questionnaire consisted of 30 items over 7 domains: skin, eyes and mouth, breathing, eating and digestion, muscles and joints, energy, and emotional distress. Each question was scored 0, 1, 2, 3, or 4.

A domain score was calculated for each domain by taking the mean of all items completed if more than 50% were answered and normalizing to a 0 to 100 scale. A summary score was calculated as average of all non-missing domain scores if more than 50% of them were non-missing. A higher score indicated more bothersome symptoms. A 7-point or greater reduction on the summary score of cGVHD Symptom Scale was considered to be clinically meaningful.

The following analyses were conducted on the mITT, Responder, and Non-Responder Populations:

- Descriptive statistics of absolute score and change from baseline score (summary score and domain scores) were summarized as continuous variables by treatment arm and visit;
- Number and percentage of subjects with a ≥7-point reduction (7-PtR) from baseline (C1D1);
- Number and percentage of subjects with a 7-PtR from baseline on 2 consecutive assessments; and
- Duration of a 7-PtR (DO7-PtR) (defined as time from documentation of the first ≥7-PtR to the first documentation of <7-PtR). If there were multiple episodes, then DO7-PtR was measured as the sum of DO7-PtR from all episodes.

Failure-Free Survival

FFS was defined as the time from the first dose of belumosudil to the time of the first event; events included the initiation of new systemic cGVHD therapy, non-relapse mortality, and recurrent malignancy (ie, underlying disease). FFS was censored by last response assessment or Long-Term Follow-Up assessment, whichever was the latest and available. Kaplan-Meier plots, descriptive statistics of FFS, and the landmark analyses at 6, 12, 18, and 24 months are provided. In addition, the number of events for each of the 3 components of FFS are provided.

Time to Next Treatment

TTNT was measured as the time from the first dose of belumosudil to the time of new systemic cGVHD treatment, censored by last response assessment or Long-Term Follow-Up assessment, whichever was the latest and available. TTNT was analyzed by the Kaplan-Meier survival method as well as with landmark analyses.

Overall Survival

OS was defined as time from the first dose of belumosudil to the date of death due to any cause. Kaplan-Meier plots, descriptive statistics of OS, and the landmark analyses at 6, 12, 18, and 24 months are provided.

Change in corticosteroid dose

Corticosteroid doses are presented as mg/kg/day prednisone equivalent dose. Descriptive statistics for the mITT, Responder, and Non-Responder Populations and subgroups defined by baseline corticosteroid dose level (upper and lower 50^{th} percentiles) are provided for the following:

- Systemic corticosteroid dose over time;
- Change and percent change from baseline (C1D1) to the greatest corticosteroid dose reduction during belumosudil treatment period;
- Number and percentage of subjects who reduced systemic corticosteroid dose during belumosudil treatment period; and
- Number and percentage of subjects who ever discontinued systemic corticosteroid usage during belumosudil treatment period.

If subjects were not using prednisone as the systemic corticosteroid, then the equivalent dose of 1 mg of prednisone was determined according to the following conversion ratios: 4 mg hydrocortisone, 0.8 mg methylprednisolone, 0.15 mg dexamethasone, 1 mg prednisolone, and 0.8 mg triamcinolone.

Transient increases in corticosteroid dosing (not exceeding 1 mg/kg/day prednisone equivalent, were permitted for the treatment of cGVHD flare, but the dose was reduced back to the pre-randomization dose within 6 weeks. If the dose remained elevated for more than 6 weeks, this was considered a belumosudil treatment failure. More than 2 episodes of cGVHD flare that required increased corticosteroid therapy in the first 6 months of belumosudil treatment was also considered a belumosudil treatment failure.

Change in CNI dose

CNIs included systemic tacrolimus and cyclosporine. Descriptive statistics are provided for the following:

- Number and percentage of subjects who reduced CNI dose during the belumosudil treatment period; and
- Number and percentage of subjects who ever discontinued CNI during the belumosudil treatment period.

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

Activities were assessed on D1 of C2 through C5, then on D1 of every other cycle thereafter and at the EOT visit. Symptoms were rated on a 0- to 10-point numeric rating scale, with a score of 0 indicating symptoms were "not present" and a score of 10 indicating symptoms were "as bad as you can imagine." Three Patient Global Ratings were also collected. The global rating was a 0- to 10-point numeric rating scale, with a score of 0 indicating "cGVHD symptoms not at all severe" and a score of 10 indicating "most severe cGVHD symptoms possible." The severity status reported by subjects was categorized as none, mild, moderate, or severe. The comparison of cGVHD symptoms to a month before completing the assessment was also reported by subject, ranging from -3 (very much worse) to +3 (very much better);

The summary of global ratings and the change from baseline in global ratings are presented by visit. The summary of the comparison of cGVHD to a month previous to the time of assessment are also presented. The number and percentage of subjects who reported none, mild, moderate, or severe cGVHD were summarized by visit.

Planned subgroup analyses

Subgroup analyses were conducted for the following subgroups: Prior ibrutinib (Yes / No), Severe cGVHD (Yes / No), Number of organs involved (<4 / ≥4), Number of prior lines of therapy (≤3 / >3), Duration of cGVHD before enrolment, Lung involvement (Yes / No), Concomitant treatment with a proton pump inhibitor (Yes / No), and Age (12-17, 18-64, ≥65).

Results

Participant flow

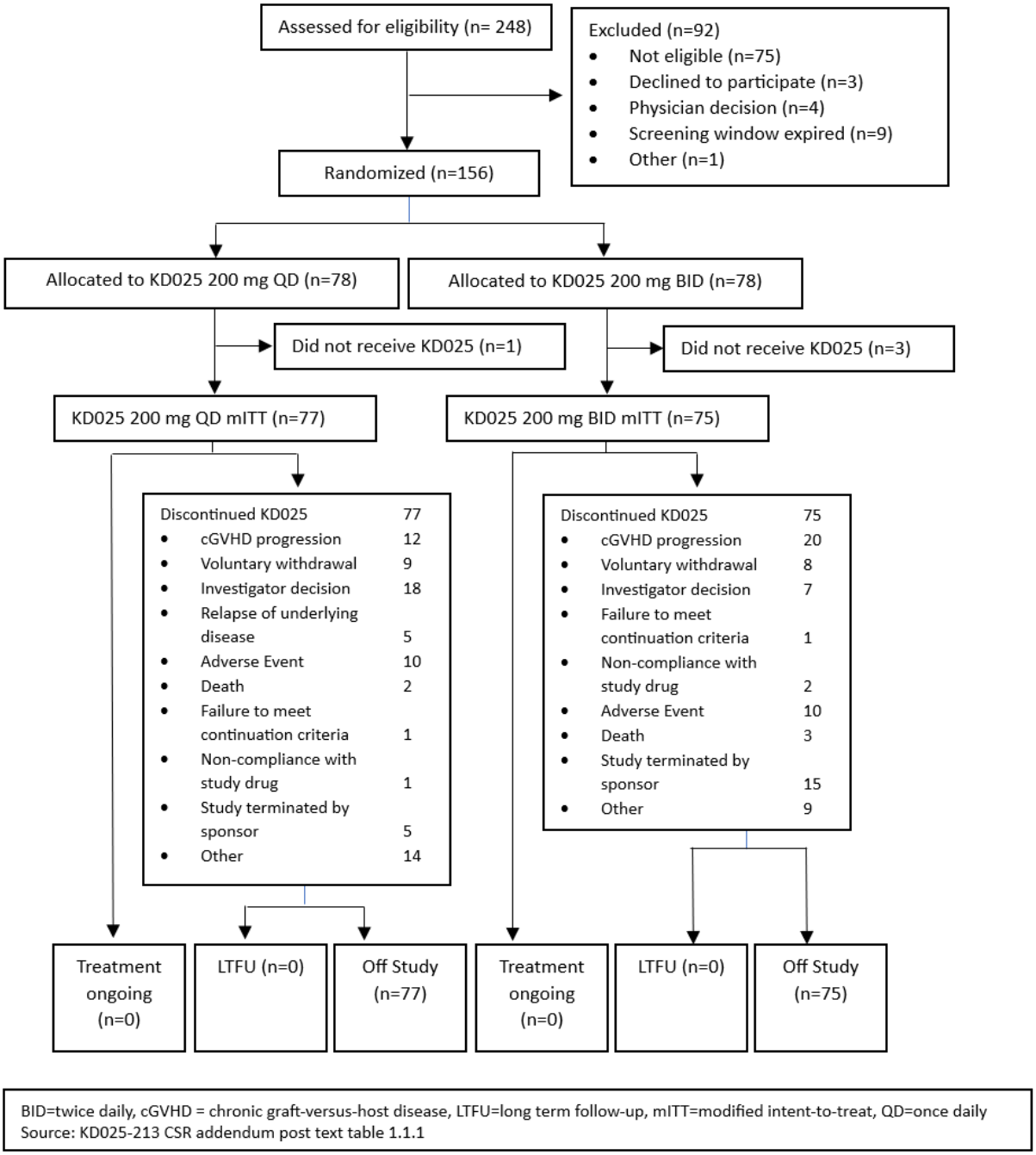


Figure 7: Consort Diagram – All Informed Consent Subjects (KD025-213 CSR Addendum)

The patient disposition of Study KD025-213 according to Study Addendum (01 September 2022) is shown in **Figure *7***. In total, 156 patients were randomized: Arm A 78 patients and Arm B 78 patients. One patient in

Arm A and three patients in Arm B were randomized but never dosed. Hence, mITT population included 152 patients: 77 patients in Arm A and 75 patients in Arm B.

In addition, after the original report three adolescent subjects were randomized, two in Arm A and one in Arm B.

In total, the median treatment duration was 10,5 months: 9,2 months for Arm A and 11,9 months for Arm B. Treatment was continued > 24 months in 38 (25,0%) subjects: in 19 (24,7%) in Arm A and in 19 (25,3%) in Arm B).

The median follow-up duration was 29.9 months (0.6-40.5): 28.2 months (0.6-40.5) in Arm A and 31.3 months (0.9-39.6) in Arm B.

All 152 (100%) subjects discontinued from treatment with belumosudil. The most common reasons for treatment discontinuation were progression of cGVHD (21% of the subjects) and physician decision (16% of the subjects).

As cut-off date 01 September 2022, all patients discontinued from the study. The most common reason for discontinuation was study termination by Sponsor in 71 (46.7%) subjects.

Protocol deviations

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

Five of the deviations were considered to be major and led to a change in analysis:
- Exclusion criterion #3: Receiving glucocorticoid therapy with a stable dose over the 2 weeks prior to screening:
    - Patient was on a stable dose of CS for 7 days prior to start of study drug. This patient was included in the mITT primary analysis, but was excluded from the PP population.
    - Patient was not on prednisone during screening, prior to C1D1, or within14 days of screening. Prednisone was started on C1D30 and this was considered the date of belumosudil treatment failure (when a new systemic cGVHD therapy was initiated). All responses for this patient were set to be NE.
- Patient received treatment with investigational systemic immunosuppressant drugs for cGVHD:
    - Patient was on ruxolitinib throughout screening and throughout dosing with study drug. This patient was included in the mITT primary analysis but was excluded from the PP population.
- Patient met discontinuation criteria and was not discontinued from study treatment:
    - Patient required increase in steroid dose above baseline level for >6 weeks. By protocol definition, this was considered a treatment failure at the time of steroid increase. All responses after steroid increase were set to NE.
    - Patient did not return to pre-randomization dose of corticosteroid. All responses after steroid increase were set to NE.

Recruitment

The initiation date of the Study KD025-213 was 11 October 2018. End date of the primary reporting period was 19 February 2020, and End Date of Reporting Period (Addendum) 01 September 2022.

Conduct of the study

The original protocol was dated 25 June 2018. Under this protocol 135 subjects were enrolled (135 subjects randomized and 132 dosed). There were 4 amendments to the original protocol: Amendment 1, dated 26 June 2019; Amendment 2, dated 01 June 2020; Amendment 3, dated 30 August 2021; Amendment 4, 21 April 2022. The key changes are summarized below.

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

• TTR and TTNT were added as secondary objectives and secondary efficacy endpoints
• The investigational plan was updated: The duration of treatment with belumosudil was updated to allow treatment until clinically significant disease progression, and was not limited to disease progression as defined by NIH criteria
• The inclusion criteria were updated: To include subjects who were ≥ 12 years of age instead of subjects who were ≥ 18 years of age; To include the Lansky scale for subjects 12 to 15 years of age; Addition of inclusion criterion #15 to state that subjects must have weighed >40 kg; Addition of inclusion criterion #16 to state that subjects could have been included in the study if it was in their best interest to participate in the study;
• The exclusion criteria were updated: To exclude subjects if they were not on a stable dose/regimen of systemic cGVHD treatment for at least 2 weeks prior to screening; To exclude subjects with QTcF >480 ms at baseline; To exclude treatment with any non-GVHD investigational agent, device, and/or procedure within 28 days (or 5 half-lives, whichever was greater)
• Permission was given for documented standard of care assessments performed within 14 days of C1D1 to be used as screening assessments
• The withdrawal criteria: Clarification for subjects with disease progression, whether NIH-defined or not, for continuing the study was added; The tapering schedule after sustained response for 6 months and cessation of all other immunosuppressants for at least 3 months was added; Specified that pregnant subjects would be discontinued from the study
• The dosage and administration procedures were updated: Specified that subjects may have returned to the clinic every other treatment cycle starting on C19D1; Tapering guidelines to reduce the dose to every 2 cycles instead of every 2 weeks were added for subjects who had sustained a response for 6 months and had discontinued/ceased all other immunosuppressants for at least 3 months and clarified for subjects whose cGVHD did not progress or respond to treatment;
• Concomitant medications and procedures were updated: Dietary/herbal/OTC supplements were considered to be concomitant medications; Correction of an error that listed rituximab as a prohibited cGVHD therapy; Doses of systemic therapies could have been tapered at the discretion of the Investigator after > 4 weeks of belumosudil; Strong CYP3A4 inducers were prohibited
• Safety was added as a secondary endpoint and the primary safety outcome was added as the percentage of subjects in each arm who experienced AEs
• The study stopping rules were updated: Enrolment was changed to be paused for an assessment of safety instead of the study arm being terminated early; Withdrawal due to study drug-related AEs within 3 months of randomization of >30% of subjects were replaced with withdrawal due to study drug-related AEs in >20% of subjects;
• A formal interim analysis with pre-specified timing and alpha spend was added. The sample size section was updated accordingly. Planned analyses included the following: An interim analysis would be conducted approximately 2 months after 126 subjects had been enrolled in the mITT Population; A primary analysis would be conducted approximately 6 months after 126 subjects had been enrolled in the mITT Population; A

follow-up analysis would be conducted approximately 12 months after 126 subjects had been enrolled in the mITT Population
• Concomitant treatment with PPI medication and age (categorical) were added to subgroup analyses.

The major changes in Amendment 2 (01 June 2020):
• The study enrolment period was revised from 12 to 24 months; The anticipated study close out was revised to occur approximately 4 years after the first subject enrolled
• The number of subjects to be enrolled was updated from 126 to 166. The additional 40 subjects to include 20 adolescents and 20 adults to be enrolled into a site-specific Companion Study
• The belumosudil tapering guidance was updated to state that subjects whose cGVHD had not progressed at the time of discontinuation of belumosudil treatment should have been tapered off belumosudil;
• Analyses were added to be conducted to include adolescent subjects and Companion Study subjects approximately 6 months after the completion of enrolment of the respective subjects
• The age category in the subgroup analyses was updated to 12 to 17 and 18 to 64 years of age

The major changes in Amendment 3 (30 August 2021):
• The time frame of the LTFU was revised to end after a FFS event occurred or until study close-out (whichever occurred first)
• Belumosudil treatment failures required discontinuation of study drug
• The expectation to end participation in the study for all subjects (excluding the 20 adolescent subjects) that received at least 6 months of belumosudil treatment or were in LTFU without having an FFS event
• Subjects were to be instructed to take belumosudil with food
• Clarification that cytochrome P450 (CYP)3A4 inducers decrease exposure to belumosudil. Statement concerning that CYP3A4 and CYP1A2 inducers needed to be used with caution or were prohibited was removed

The major changes in Amendment 4 (21 April 2022):
• An addendum for the adolescent cohort was added to the protocol appendices which included the following information: Remaining eligible adolescent subjects were enrolled into the study at belumosudil 200 mg once daily (QD) dose; No more randomization and stratification factors were applied; Any adolescent taking a proton-pump inhibitor (PPI) or a strong CYP3A4 inducer began C1D1 at an escalated dose of belumosudil 200 mg twice daily (BID).
• Subjects on strong CYP3A4 inducers or PPIs were permitted to dose modify to 200 mg BID if they were dosing at 200 mg QD
• Ruxolitinib was added to the list of prohibited concomitant medications

Baseline data

The Applicant has provided updated baseline characteristics of Study KD025-213 *(***Table 24***)* according to the CSR Addendum (data lock 01 September 2022) in ITT population. The updated baseline characteristics are in line with those reported in the First Study Report (data lock 19 February 2020).

Table 24: Demographics and Baseline Characteristics – ITT Population

Demographics and baseline characteristics
(ITT population)

	200 mg QD N = 78	200 mg BID N = 78	Overall N = 156
Age (Years)			
n	78	78	156
Mean	53.5	55.2	54.3
SD	13.7	13.8	13.7
Median	53.0	57.0	55.0
Min, Max	21, 77	18, 77	18, 77
Sex - n (%)			
Female	29 (37.2%)	40 (51.3%)	69 (44.2%)
Male	49 (62.8%)	38 (48.7%)	87 (55.8%)
Child-bearing potential - n (%)			
Yes	8 (27.6%)	11 (27.5%)	19 (27.5%)
No	21 (72.4%)	29 (72.5%)	50 (72.5%)
Ethnicity - n (%)			
Hispanic or Latino	7 (9.0%)	11 (14.1%)	18 (11.5%)
Not Hispanic or Latino	71 (91.0%)	63 (80.8%)	134 (85.9%)
Not reported	0	3 (3.8%)	3 (1.9%)
Unknown	0	1 (1.3%)	1 (0.6%)
Race - n (%)			
American Indian or Alaska Native	0	2 (2.6%)	2 (1.3%)
Black or African American	7 (9.0%)	1 (1.3%)	8 (5.1%)
Asian	2 (2.6%)	2 (2.6%)	4 (2.6%)
Asian Indian	1 (1.3%)	0	1 (0.6%)
Chinese	0	1 (1.3%)	1 (0.6%)
Filipino	0	0	0
Japanese	0	0	0
Korean	0	0	0
Vietnamese	0	0	0
Other Asian	1 (1.3%)	1 (1.3%)	2 (1.3%)
Native Hawaiian or Other Pacific Islander	0	0	0
White	66 (84.6%)	70 (89.7%)	136 (87.2%)
Unreported/unknown	3 (3.8%)	3 (3.8%)	6 (3.8%)
Multiple	0	0	0
Karnofsky performance status - n (%)			
60	3 (3.8%)	2 (2.6%)	5 (3.2%)
70	8 (10.3%)	18 (23.1%)	26 (16.7%)
80	38 (48.7%)	29 (37.2%)	67 (42.9%)
90	24 (30.8%)	22 (28.2%)	46 (29.5%)
100	4 (5.1%)	4 (5.1%)	8 (5.1%)
Missing	1 (1.3%)	3 (3.8%)	4 (2.6%)

Weight (kg)			
n	77	75	152
Mean	79.1	78.2	78.7
SD	17.9	17.2	17.5
Median	77.1	76.6	77.0
Min, Max	38.6, 133.3	51.3, 119.8	38.6, 133.3
Height (cm)			
n	72	61	133
Mean	173.0	168.9	171.1
SD	10.5	11.5	11.1
Median	173.0	168.0	171.0
Min, Max	154.9, 194.0	149.0, 193.0	149.0, 194.0
BMI (kg/m^2)			
n	72	64	136
Mean	26.7	27.4	27.0
SD	4.9	6.2	5.6
Median	26.5	26.3	26.3
Min, Max	14.5, 37.7	18.0, 47.4	14.5, 47.4

All subjects received a previous allogeneic haematopoietic stem cell transplantation. The most common indication for the most recent transplantation was acute myelogenous leukaemia (AML) (65 subjects, 42%). In the majority of the subjects, the conditioning regimen was myeloablative (102 subjects, 65%). Forty-seven (30%) were treated with total body irradiation. The graft was collected from an unrelated donor in 95 subjects (61%) and from a related donor in 61 subjects (39%). Majority of the subjects received a matched graft (141 subjects, 90%). Graft source was mainly peripheral blood stem cells (144 subjects, 92%). Gender-mismatch was documented in 71 subjects (46%). CMV serostatus (patient/donor) was negative/negative in 35 subjects (22%). The median time from most recent transplantation to enrolment was 40 months.

Table 25 summarizes GVHD history for the ITT Population. The NIH cGVHD severity at baseline was mild in 2 (1.3%) subjects, moderate in 44 (28%) subjects, and severe in 110 (71%) subjects.

Table 25: Graft Versus Host Disease History – ITT Population

	200 mg QD N = 78	200 mg BID N = 78	Overall N = 156
GVHD prophylaxis after transplant			
None	0	1 (1.3%)	1 (0.6%)
CNI Only	5 (6.4%)	7 (9.0%)	12 (7.7%)
CNI + methotrexate	34 (43.6%)	34 (43.6%)	68 (43.6%)
CNI + methotrexate + other	9 (11.5%)	6 (7.7%)	15 (9.6%)
CNI + MMF	7 (9.0%)	11 (14.1%)	18 (11.5%)
CNI + MMF + other	5 (6.4%)	4 (5.1%)	9 (5.8%)
CNI + MMF + ATG	0	1 (1.3%)	1 (0.6%)
CNI + sirolimus	6 (7.7%)	6 (7.7%)	12 (7.7%)
CNI + corticosteroids	2 (2.6%)	1 (1.3%)	3 (1.9%)
Other regimen	9 (11.5%)	7 (9.0%)	16 (10.3%)
Missing	1 (1.3%)	0	1 (0.6%)
Prior aGVHD			
Yes	51 (65.4%)	60 (76.9%)	111 (71.2%)
No	26 (33.3%)	18 (23.1%)	44 (28.2%)
Missing	1 (1.3%)	0	1 (0.6%)
Time from most recent transplant to cGVHD diagnosis (Months)			
n	77	75	152
Mean	9.93	10.59	10.26
SD	6.98	8.61	7.81
Median	7.06	7.00	7.03
Min, Max	1.0, 38.7	1.8, 48.8	1.0, 48.8
Time from cGVHD diagnosis to enrollment (Months)			
n	77	75	152
Mean	35.05	37.24	36.13
SD	31.48	29.24	30.31
Median	25.26	30.00	28.14
Min, Max	1.6, 162.4	3.7, 144.1	1.6, 162.4
Time from most recent transplant to enrollment (Months)			
n	78	78	156
Mean	44.79	47.00	45.89
SD	31.20	29.59	30.33
Median	36.91	40.48	40.10
Min, Max	7.2, 165.2	7.3, 151.2	7.2, 165.2
NIH cGVHD severity at screening - n (%)			
Mild	2 (2.6%)	0	2 (1.3%)
Moderate	19 (24.4%)	25 (32.1%)	44 (28.2%)
Severe	57 (73.1%)	53 (67.9%)	110 (70.5%)

Note:
- The percentages are calculated based on the number of ITT population.
- Time from most recent transplant to cGVHD diagnosis (Months) = (Date of cGVHD diagnosis
- Date of most recent Allogeneic Hematopoietic Cell Transplant +1)/365.25*12.
- Time from cGVHD diagnosis to enrollment (Months) = (Date of Informed Consent -
Date of cGVHD diagnosis +1)/365.25*12.
- Time from most recent transplant to enrollment (Months) = (Date of Informed Consent
- Date of most recent Allogeneic Hematopoietic Cell Transplant +1)/365.25*12.

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Table 26 summarizes prior systemic cGVHD therapy for the ITT Population. The overall median number of prior lines of systemic cGVHD therapy was three; for Arm A the median number prior lines was three 3 and for Arm B four, respectively. In total, 79 (51%) subjects had at least four prior lines of therapy. In total, 90 (73%) subjects with known status were refractory to the last systemic cGVHD treatment prior to enrolment in the study (stable/progressive cGVHD): 50 (81%) subjects in Arm A and 40 (65%) subjects in Arm B.

Table 26: Summary of Prior Systemic cGVHD Therapy – ITT Population

	200 mg QD N = 78	200 mg BID N = 78	Overall N = 156
Number of prior lines of systemic cGVHD therapy - n (%)			
1	0	0	0
2	26 (33.3%)	16 (20.5%)	42 (26.9%)
3	18 (23.1%)	20 (25.6%)	38 (24.4%)
4	18 (23.1%)	19 (24.4%)	37 (23.7%)
5	14 (17.9%)	21 (26.9%)	35 (22.4%)
>=6	2 (2.6%)	2 (2.6%)	4 (2.6%)
Median	3.0	4.0	3.0
Number of patients previously treated with ruxolitinib	29 (37.2%)	28 (35.9%)	57 (36.5%)
Prior therapies - n (%)			
PREDNISONE	77 (98.7%)	77 (98.7%)	154 (98.7%)
TACROLIMUS	50 (64.1%)	50 (64.1%)	100 (64.1%)
SIROLIMUS	35 (44.9%)	38 (48.7%)	73 (46.8%)
ALL OTHER THERAPEUTIC PRODUCTS*	34 (43.6%)	36 (46.2%)	70 (44.9%)
IBRUTINIB	26 (33.3%)	27 (34.6%)	53 (34.0%)
MYCOPHENOLATE MOFETIL	19 (24.4%)	19 (24.4%)	38 (24.4%)
RUXOLITINIB PHOSPHATE	17 (21.8%)	16 (20.5%)	33 (21.2%)
RITUXIMAB	15 (19.2%)	14 (17.9%)	29 (18.6%)
RUXOLITINIB	12 (15.4%)	12 (15.4%)	24 (15.4%)
METHOTREXATE	3 (3.8%)	3 (3.8%)	6 (3.8%)
METHYLPREDNISOLONE	3 (3.8%)	3 (3.8%)	6 (3.8%)
CICLOSPORIN	4 (5.1%)	1 (1.3%)	5 (3.2%)
BUDESONIDE	3 (3.8%)	1 (1.3%)	4 (2.6%)
INTERLEUKIN-2	2 (2.6%)	2 (2.6%)	4 (2.6%)
VEDOLIZUMAB	3 (3.8%)	1 (1.3%)	4 (2.6%)

INVESTIGATIONAL DRUG	0	3 (3.8%)	3 (1.9%)
BECLOMETASONE	1 (1.3%)	1 (1.3%)	2 (1.3%)
CYCLOPHOSPHAMIDE	1 (1.3%)	1 (1.3%)	2 (1.3%)
IMATINIB	2 (2.6%)	0	2 (1.3%)
IMATINIB MESILATE	1 (1.3%)	1 (1.3%)	2 (1.3%)
IXAZOMIB	1 (1.3%)	1 (1.3%)	2 (1.3%)
ARTEMETHER;LUMEFANTRINE	0	1 (1.3%)	1 (0.6%)
AZATHIOPRINE	0	1 (1.3%)	1 (0.6%)
CARFILZOMIB	0	1 (1.3%)	1 (0.6%)
DEXAMETHASONE	0	1 (1.3%)	1 (0.6%)
HYDROCORTISONE	1 (1.3%)	0	1 (0.6%)
HYDROXYCHLOROQUINE	1 (1.3%)	0	1 (0.6%)
IXAZOMIB CITRATE	0	1 (1.3%)	1 (0.6%)
MERCAPTOPURINE	1 (1.3%)	0	1 (0.6%)
METHYLPREDNISOLONE SODIUM SUCCINATE	0	1 (1.3%)	1 (0.6%)
MYCOPHENOLATE SODIUM	0	1 (1.3%)	1 (0.6%)
OFATUMUMAB	0	1 (1.3%)	1 (0.6%)
OTHER IMMUNOSUPPRESSANTS	0	1 (1.3%)	1 (0.6%)
SONIDEGIB	0	1 (1.3%)	1 (0.6%)
THALIDOMIDE	1 (1.3%)	0	1 (0.6%)
VISMODEGIB	0	1 (1.3%)	1 (0.6%)
Best response to the last systemic cGVHD treatment prior to enrollment to study - n (%)			
CR	0	1 (1.3%)	1 (0.6%)
PR	12 (15.4%)	21 (26.9%)	33 (21.2%)
SD	29 (37.2%)	20 (25.6%)	49 (31.4%)
PD	21 (26.9%)	20 (25.6%)	41 (26.3%)
Unknown	16 (20.5%)	16 (20.5%)	32 (20.5%)
Refractory to the last systemic cGVHD treatment prior to enrollment to study - n (%)			
SD or PD	50 (80.6%)	40 (64.5%)	90 (72.6%)

Note:
- The percentages are calculated based on the number of ITT population. The percentages of refractory are based on the number of ITT population whose best response to the last systemic cGVHD treatment prior to enrollment to study is CR or PR or SD or PD.
- Prior therapies are sorted in descending order of frequency in the overall column.
- *: ECP is coded as "ALL OTHER THERAPEUTIC PRODUCTS".

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The number of organs involved at baseline are shown in **Table 27**. The median number of organs involved was 4: 4 organs in Arm A and 3.5 organs in Arm B. Forty (510%) subjects in Arm A and 39 (51%) subjects in Arm B had $\geq$ 4 organ involvements at baseline.

Of note, one subject was randomized into Arm A with cGVHD involvements of the liver and the GI at screening for which corticosteroids were indicated. This subject neither had increased liver enzymes nor presented with GI symptoms at C1D1 and therefore did not have organ involvement per NIH criteria at baseline. The Investigator considered the possibility of cGVHD involvement because corticosteroid dose could not be reduced with a cGVHD flare.

Table 27: Number of Organs Involved at baseline and baseline score– ITT Population

	200 mg QD N = 78	200 mg BID N = 78	Overall N = 156
Number of organs involved at baseline			
0	2 (2.6%)	2 (2.6%)	4 (2.6%)
1	3 (3.8%)	0	3 (1.9%)
2	8 (10.3%)	14 (17.9%)	22 (14.1%)
3	25 (32.1%)	23 (29.5%)	48 (30.8%)
4	12 (15.4%)	18 (23.1%)	30 (19.2%)
5	14 (17.9%)	11 (14.1%)	25 (16.0%)
>= 6	14 (17.9%)	10 (12.8%)	24 (15.4%)
>= 4	40 (51.3%)	39 (50.0%)	79 (50.6%)
n	78	78	156
Mean	3.8	3.7	3.8
SD	1.6	1.5	1.5
Median	4.0	3.5	4.0
Min, Max	0, 7	0, 7	0, 7
Skin - n (%)			
Involvement at baseline	63 (80.8%)	64 (82.1%)	127 (81.4%)
Skin score			
0	0	0	0
1	19 (30.2%)	14 (21.9%)	33 (26.0%)
2	15 (23.8%)	31 (48.4%)	46 (36.2%)
3	29 (46.0%)	18 (28.1%)	47 (37.0%)
Skin Feature Score			
0	11 (17.5%)	13 (20.3%)	24 (18.9%)
2	10 (15.9%)	12 (18.8%)	22 (17.3%)
3	42 (66.7%)	38 (59.4%)	80 (63.0%)
NIH skin score			
0	0	0	0
1	8 (12.7%)	5 (7.8%)	13 (10.2%)
2	11 (17.5%)	17 (26.6%)	28 (22.0%)
3	44 (69.8%)	41 (64.1%)	85 (66.9%)

	200 mg QD N = 78	200 mg BID N = 78	Overall N = 156
No involvement at baseline	14 (17.9%)	12 (15.4%)	26 (16.7%)
Not assessed	1 (1.3%)	2 (2.6%)	3 (1.9%)
Eyes - n (%)			
Involvement at baseline	56 (71.8%)	52 (66.7%)	108 (69.2%)
NIH score			
0	0	0	0
1	22 (39.3%)	14 (26.9%)	36 (33.3%)
2	22 (39.3%)	19 (36.5%)	41 (38.0%)
3	12 (21.4%)	19 (36.5%)	31 (28.7%)
No involvement at baseline	21 (26.9%)	24 (30.8%)	45 (28.8%)
Not assessed	1 (1.3%)	2 (2.6%)	3 (1.9%)
Mouth - n (%)			
Involvement at baseline	41 (52.6%)	52 (66.7%)	93 (59.6%)
Total NIH Modified OMRS score			
0	0	2 (3.8%)	2 (2.2%)
1	11 (26.8%)	23 (44.2%)	34 (36.6%)
2	13 (31.7%)	11 (21.2%)	24 (25.8%)
3	8 (19.5%)	2 (3.8%)	10 (10.8%)
4	4 (9.8%)	5 (9.6%)	9 (9.7%)
5	2 (4.9%)	3 (5.8%)	5 (5.4%)
6	1 (2.4%)	0	1 (1.1%)
7	2 (4.9%)	3 (5.8%)	5 (5.4%)
8	0	0	0
9	0	0	0
10	0	0	0
11	0	2 (3.8%)	2 (2.2%)
12	0	0	0

	200 mg QD N = 78	200 mg BID N = 78	Overall N = 156
Erythema NIH Modified OMRS score			
0	10 (24.4%)	22 (42.3%)	32 (34.4%)
1	22 (53.7%)	22 (42.3%)	44 (47.3%)
2	9 (22.0%)	5 (9.6%)	14 (15.1%)
3	0	2 (3.8%)	2 (2.2%)
Lichenoid NIH Modified OMRS score			
0	6 (14.6%)	12 (23.1%)	18 (19.4%)
1	19 (46.3%)	25 (48.1%)	44 (47.3%)
2	12 (29.3%)	12 (23.1%)	24 (25.8%)
3	4 (9.8%)	2 (3.8%)	6 (6.5%)
Ulcers NIH Modified OMRS score			
0	37 (90.2%)	41 (78.8%)	78 (83.9%)
3	4 (9.8%)	8 (15.4%)	12 (12.9%)
6	0	2 (3.8%)	2 (2.2%)
No involvement at baseline	36 (46.2%)	24 (30.8%)	60 (38.5%)
Not assessed	1 (1.3%)	2 (2.6%)	3 (1.9%)
Esophagus - n (%)			
Involvement at baseline	23 (29.5%)	13 (16.7%)	36 (23.1%)
NIH score			
0	1 (4.3%)	0	1 (2.8%)
1	15 (65.2%)	10 (76.9%)	25 (69.4%)
2	7 (30.4%)	2 (15.4%)	9 (25.0%)
3	0	1 (7.7%)	1 (2.8%)
No involvement at baseline	54 (69.2%)	63 (80.8%)	117 (75.0%)
Not assessed	1 (1.3%)	2 (2.6%)	3 (1.9%)
Upper GI - n (%)			
Involvement at baseline	14 (17.9%)	10 (12.8%)	24 (15.4%)
NIH score			
0	0	0	0
1	9 (64.3%)	6 (60.0%)	15 (62.5%)

	200 mg QD N = 78	200 mg BID N = 78	Overall N = 156
2	3 (21.4%)	3 (30.0%)	6 (25.0%)
3	2 (14.3%)	1 (10.0%)	3 (12.5%)
No involvement at baseline	63 (80.8%)	66 (84.6%)	129 (82.7%)
Not assessed	1 (1.3%)	2 (2.6%)	3 (1.9%)
Lower GI - n (%)			
Involvement at baseline	7 (9.0%)	8 (10.3%)	15 (9.6%)
NIH score			
0	1 (14.3%)	0	1 (6.7%)
1	4 (57.1%)	5 (62.5%)	9 (60.0%)
2	1 (14.3%)	3 (37.5%)	4 (26.7%)
3	1 (14.3%)	0	1 (6.7%)
No involvement at baseline	70 (89.7%)	68 (87.2%)	138 (88.5%)
Not assessed	1 (1.3%)	2 (2.6%)	3 (1.9%)
Liver			
Involvement at baseline	10 (12.8%)	4 (5.1%)	14 (9.0%)
ALT			
<=1 x ULN	4 (40.0%)	0	4 (28.6%)
>1 x ULN to <=2 x ULN	3 (30.0%)	0	3 (21.4%)
>2 x ULN to <=3 x ULN	3 (30.0%)	3 (75.0%)	6 (42.9%)
>3 x ULN	0	0	0
ALT (U/L)			
n	10	3	13
Mean	58.4	99.3	67.8
SD	31.3	12.5	32.9
Median	54.5	99.0	59.0
Min, Max	21, 113	87, 112	21, 113
ALP			
<=1 x ULN	1 (10.0%)	2 (50.0%)	3 (21.4%)
>1 x ULN to <=2 x ULN	3 (30.0%)	1 (25.0%)	4 (28.6%)

	200 mg QD N = 78	200 mg BID N = 78	Overall N = 156
>2 x ULN to <=3 x ULN	3 (30.0%)	0	3 (21.4%)
>3 x ULN	3 (30.0%)	0	3 (21.4%)
ALP (U/L)			
n	10	3	13
Mean	302.4	105.3	256.9
SD	224.8	55.2	214.2
Median	280.0	84.0	168.0
Min, Max	107, 856	64, 168	64, 856
Total bilirubin			
<=1 x ULN	10 (100.0%)	3 (75.0%)	13 (92.9%)
>1 x ULN to <=1.5 x ULN	0	0	0
>1.5 x ULN	0	0	0
Total bilirubin (umol/L)			
n	10	3	13
Mean	10.13	8.07	9.65
SD	4.27	0.60	3.82
Median	10.20	8.00	8.00
Min, Max	4.6, 14.5	7.5, 8.7	4.6, 14.5
No involvement at baseline	67 (85.9%)	72 (92.3%)	139 (89.1%)
Not assessed	1 (1.3%)	2 (2.6%)	3 (1.9%)
Lung			
Involvement at baseline	27 (34.6%)	25 (32.1%)	52 (33.3%)
NIH score - n (%)			
0	1 (3.7%)	1 (4.0%)	2 (3.8%)
1	14 (51.9%)	13 (52.0%)	27 (51.9%)
2	12 (44.4%)	11 (44.0%)	23 (44.2%)
3	0	0	0
FEV1 (% Predicted)			
>=75	1 (3.7%)	2 (8.0%)	3 (5.8%)
>=65 to 75	6 (22.2%)	11 (44.0%)	17 (32.7%)

	200 mg QD N = 78	200 mg BID N = 78	Overall N = 156
>=55 to 65	7 (25.9%)	5 (20.0%)	12 (23.1%)
<55	13 (48.1%)	6 (24.0%)	19 (36.5%)
FEV1 (% Predicted)			
n	27	24	51
Mean	56.5	63.1	59.6
SD	9.7	12.6	11.5
Median	55.0	65.5	63.0
Min, Max	39, 76	29, 97	29, 97
No involvement at baseline	50 (64.1%)	51 (65.4%)	101 (64.7%)
Not assessed	1 (1.3%)	2 (2.6%)	3 (1.9%)
Joints and Fascia - n (%)			
Involvement at baseline	59 (75.6%)	58 (74.4%)	117 (75.0%)
NIH score			
0	1 (1.7%)	1 (1.7%)	2 (1.7%)
1	20 (33.9%)	20 (34.5%)	40 (34.2%)
2	28 (47.5%)	32 (55.2%)	60 (51.3%)
3	10 (16.9%)	4 (6.9%)	14 (12.0%)
Total P-ROM Score (summation of 4 individual| P-ROM scores)			
<= 10	2 (3.4%)	0	2 (1.7%)
11	0	0	0
12	0	2 (3.4%)	2 (1.7%)
13	3 (5.1%)	3 (5.2%)	6 (5.1%)
14	0	0	0
15	3 (5.1%)	1 (1.7%)	4 (3.4%)
16	6 (10.2%)	1 (1.7%)	7 (6.0%)
17	4 (6.8%)	3 (5.2%)	7 (6.0%)
18	5 (8.5%)	5 (8.6%)	10 (8.5%)
19	9 (15.3%)	3 (5.2%)	12 (10.3%)
20	1 (1.7%)	6 (10.3%)	7 (6.0%)
21	4 (6.8%)	5 (8.6%)	9 (7.7%)

	200 mg QD N = 78	200 mg BID N = 78	Overall N = 156
22	5 (8.5%)	8 (13.8%)	13 (11.1%)
23	5 (8.5%)	8 (13.8%)	13 (11.1%)
24	7 (11.9%)	6 (10.3%)	13 (11.1%)
25	4 (6.8%)	5 (8.6%)	9 (7.7%)
Shoulder P-ROM Score			
1	0	0	0
2	3 (5.1%)	0	3 (2.6%)
3	1 (1.7%)	1 (1.7%)	2 (1.7%)
4	6 (10.2%)	6 (10.3%)	12 (10.3%)
5	16 (27.1%)	10 (17.2%)	26 (22.2%)
6	12 (20.3%)	18 (31.0%)	30 (25.6%)
7	21 (35.6%)	21 (36.2%)	42 (35.9%)
Elbow P-ROM Score			
1	0	0	0
2	0	1 (1.7%)	1 (0.9%)
3	2 (3.4%)	0	2 (1.7%)
4	1 (1.7%)	4 (6.9%)	5 (4.3%)
5	16 (27.1%)	9 (15.5%)	25 (21.4%)
6	20 (33.9%)	18 (31.0%)	38 (32.5%)
7	20 (33.9%)	24 (41.4%)	44 (37.6%)
Wrist P-ROM Score			
1	3 (5.1%)	0	3 (2.6%)
2	6 (10.2%)	4 (6.9%)	10 (8.5%)
3	8 (13.6%)	4 (6.9%)	12 (10.3%)
4	2 (3.4%)	5 (8.6%)	7 (6.0%)
5	14 (23.7%)	12 (20.7%)	26 (22.2%)
6	13 (22.0%)	15 (25.9%)	28 (23.9%)
7	13 (22.0%)	16 (27.6%)	29 (24.8%)
Ankle P-ROM Score			
1	0	1 (1.7%)	1 (0.9%)
2	15 (25.4%)	10 (17.2%)	25 (21.4%)

	200 mg QD N = 78	200 mg BID N = 78	Overall N = 156
3	27 (45.8%)	28 (48.3%)	55 (47.0%)
4	16 (27.1%)	17 (29.3%)	33 (28.2%)
No involvement at baseline	18 (23.1%)	18 (23.1%)	36 (23.1%)
Not assessed	1 (1.3%)	2 (2.6%)	3 (1.9%)
Global Severity Rating			
0	1 (1.3%)	0	1 (0.6%)
1	0	0	0
2	2 (2.6%)	1 (1.3%)	3 (1.9%)
3	4 (5.1%)	2 (2.6%)	6 (3.8%)
4	8 (10.3%)	3 (3.8%)	11 (7.1%)
5	7 (9.0%)	10 (12.8%)	17 (10.9%)
6	15 (19.2%)	15 (19.2%)	30 (19.2%)
7	15 (19.2%)	25 (32.1%)	40 (25.6%)
8	21 (26.9%)	15 (19.2%)	36 (23.1%)
9	4 (5.1%)	3 (3.8%)	7 (4.5%)
10	0	1 (1.3%)	1 (0.6%)
n	77	75	152
Mean	6.3	6.6	6.4
SD	1.9	1.5	1.7
Median	7.0	7.0	7.0
Min, Max	0, 9	2, 10	0, 10

Note:
- Percentages of subjects of each baseline score or category are calculated based on the number of baseline involved subjects. All other percentages are calculated based on the number of ITT population.

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Concomitant systemic cGVHD therapies

Table 28 summarizes systemic cGVHD concomitant therapies by type of medication (≥10%) on Cycle 1 Day 1. All 152 (100%) subjects were taking a concomitant cGVHD medication. In 44 (28.9) subjects ECP treatments were performed.

Range of duration of most frequently used concomitant medications prior to study showed that over 80% of participants started their concomitant treatment 30 days or more prior to Cycle 1 Day 1 (C1D1) and more than 60% of participants started treatment more than 90 days prior to C1D1.

Table 28: Systemic concomitant cGVHD treatments (≥10%) on Cycle 1 Day1

Type of systemic cGVHD treatments	Belumosudil		
	200mg QD N=77 n (%)	200 mg BID N=75 n (%)	Overall N=152 n (%)
Corticosteroids	76 (98.7)	74 (98.7)	150 (98.7)
Calcineurin inhibitors			
Tacrolimus	30 (39.0)	26 (34.7)	56 (36.8)
Cyclosporin	1 (1.3)	0	1 (0.7)
Sirolimus	21 (27.3)	20 (26.7)	41 (27.0)
MMF	11 (14.3)	3 (4.0)	14 (9.2)
ECP	19 (24.7)	25 (33.3)	44 (28.9)

Source: 5.3.5.2, KD025-213 Study CSR Addendum [Table 3.1.3.1] and [Table 3.1.4.1].

Table 29: Duration of concomitant cGVHD systemic treatments prior to study

Duration of concomitant cGVHD treatments	Belumosudil		
	200mg QD N=77	200 mg BID N=75	Overall N=152
14-30 days prior to study start day, n (%)	6 (7.8)	12 (16.0)	18 (11.8)
31-60 days prior to study start date, n (%)	16 (20.8)	14 (18.7)	30 (19.7)
61-90 days prior to study start date, n (%)	9 (11.7)	9 (12.0)	18 (11.8)
>90 days prior to study start date, n (%)	54 (70.1)	43 (57.3)	97 (63.8)

Source: 5.3.5.3, KD025-213 Adhoc63 for EMA questions [Table 1.1.11.5].
Participants were counted more than once if they received multiple concomitant cGVHD systemic treatments.

Numbers analysed

Table 30: Numbers analysed in the Study KD025-213.

	Arm A 200 mg QD n (%)	Arm B 200 mg BID n (%)	Overall n (%)
Informed consent - n			248
Screen failed - n			92
Randomized - n	78	78	156
Randomized but never dosed - n	1	3	4
mITT Population	77 (100.0)	75 (100.0)	152 (100.0)
Responder Population	57 (74.0)	57 (76.0)	114 (75.0)
Non-Responder Population	20 (26.0)	18 (24.0)	38 (25.0)
Safety Population	77 (100.0)	75 (100.0)	152 (100.0)

Outcomes and estimation

Primary efficacy endpoint

Table 31 summarizes the Overall Response Rate (ORR) for the ITT Population. The ORR (95% CI) with belumosudil was 73.1% (65.4, 79.9): 73.1% (61.8, 82.5) in Arm A and 73.1% (61.8, 82.5) in Arm B. Across both arms, 6 (3.8%) subjects achieved a CR and 108 (69.2%) subjects achieved a PR.

Table 31: Overall Response Rate – ITT Population

	200 mg QD N = 78	200 mg BID N = 78	Overall N = 156
ORR (CR or PR) - n (%)	57 (73.1%)	57 (73.1%)	114 (73.1%)
CR - n (%)	4 (5.1%)	2 (2.6%)	6 (3.8%)
PR - n (%)	53 (67.9%)	55 (70.5%)	108 (69.2%)
Exact method			
95% CI of ORR	(61.8%, 82.5%)	(61.8%, 82.5%)	(65.4%, 79.9%)
97.5% CI of ORR	(60.3%, 83.6%)	(60.3%, 83.6%)	(64.3%, 80.7%)
One-sided exact p-value (null hypothesis: ORR<=30%)			
Unadjusted	<0.0001	<0.0001	<0.0001
Hochberg multiplicity adjusted*	<0.0001	<0.0001	

Note:
- The percentages are calculated based on the number of ITT population.
- CI = confidence interval (two-sided), exact CI is calculated using Clopper-Pearson method, normal distribution approximation CI is calculated using Wilson (score) method.
- *: Threshold to claim efficacy by adjusted p-value: interim analysis 0.0025; primary analysis 0.0225 (if one arm failed to pass interim analysis) or 0.025 (if both arms passed interim analysis).
- Interim p-value (exact method): <0.0001 (200 mg QD), <0.0001 (200 mg BID).
- Response assessment performed on or after initiation of new systemic therapy for cGVHD are excluded from analysis.

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There were 3 adolescent participants in Study KD025-213, two in Arm A and one in Arm B. One participant in Arm A and one in Arm B achieved a PR.

Table 32 summarizes the ORR for responses occurring within 6 months of treatment for the ITT Population. The ORR (95% CI) within 6 months of belumosudil treatment was 70.5% (62.7, 77.5): 70.5% (59.1, 80.3) in Arm A and 70.5% (59.1, 80.3) in Arm B. There were no notable differences in ORR within 6 months of treatment according to arm (dose level).

Table 32: Overall Response Rate for Responses Occurring Within 6 Months of Treatment – ITT Population

Overall response rate (ORR) for responses occurring within 6 months of treatment (ITT population)

	200 mg QD N = 78	200 mg BID N = 78	Overall N = 156
ORR (CR or PR) - n (%)	55 (70.5%)	55 (70.5%)	110 (70.5%)
CR - n (%)	2 (2.6%)	1 (1.3%)	3 (1.9%)
PR - n (%)	53 (67.9%)	54 (69.2%)	107 (68.6%)
Exact method			
95% CI of ORR	(59.1%, 80.3%)	(59.1%, 80.3%)	(62.7%, 77.5%)
97.5% CI of ORR	(57.5%, 81.5%)	(57.5%, 81.5%)	(61.6%, 78.4%)
One-sided exact p-value (null hypothesis: ORR<=30%)			
Unadjusted	<0.0001	<0.0001	<0.0001
Hochberg multiplicity adjusted	<0.0001	<0.0001	
Normal distribution approximation method			
95% CI of ORR	(59.6%, 79.5%)	(59.6%, 79.5%)	(62.9%, 77.1%)
97.5% CI of ORR	(58.0%, 80.6%)	(58.0%, 80.6%)	(61.8%, 78.0%)
One-sided asymptotic p-value (null hypothesis: ORR<=30%)			
Unadjusted	<0.0001	<0.0001	<0.0001
Hochberg multiplicity adjusted	<0.0001	<0.0001	

Note:
- The percentages are calculated based on the number of ITT population.
- CI = confidence interval (two-sided), exact CI is calculated using Clopper-Pearson method, normal distribution approximation CI is calculated using Wilson (score) method.
- Response assessment performed on or after initiation of new systemic therapy for cGVHD are excluded from analysis.

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Source: KD025-213 CSR Addendum, data lock 01 Sep 2022

Table 33 summarizes the best response for the ITT Population. In total, 114 (73%) subjects achieved a response: 6 (3.8%) subjects achieved a CR and 108 (69.2%) subjects achieved a PR. There were 33 (21.1%) subjects who were non-responders. Of these non-responders, 5 (3.23%) subjects achieved a Lack of Response-Mixed, indicating a response in at least 1 organ system.

Table 33: Best Response – ITT Population

	200 mg QD N = 78 n (%)	200 mg BID N = 78 n (%)	Overall N = 156 n (%)
Response			
Complete response (CR)	4 (5.1%)	2 (2.6%)	6 (3.8%)
Partial response (PR)	53 (67.9%)	55 (70.5%)	108 (69.2%)
Lack of response (LR)			
Unchanged (LR_U)	15 (19.2%)	10 (12.8%)	25 (16.0%)
Mixed (LR_M)	1 (1.3%)	4 (5.1%)	5 (3.2%)
Progression (LR_P)	1 (1.3%)	2 (2.6%)	3 (1.9%)
No response assessment	4 (5.1%)	5 (6.4%)	9 (5.8%)

Note:
- The percentages are calculated based on the number of ITT population.
- Response assessment performed on or after initiation of new systemic therapy for cGVHD are excluded from analysis.

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Source: KD025-213 CSR Addendum, data lock 01 Sep 2022

The response pattern at population level, the distribution of response status by visit in overall population is presented in **Figure 8**. According to the applicant, the results show that the overall responses are observed starting from 1 cycle treatment and continue to deepen and maintain overtime.

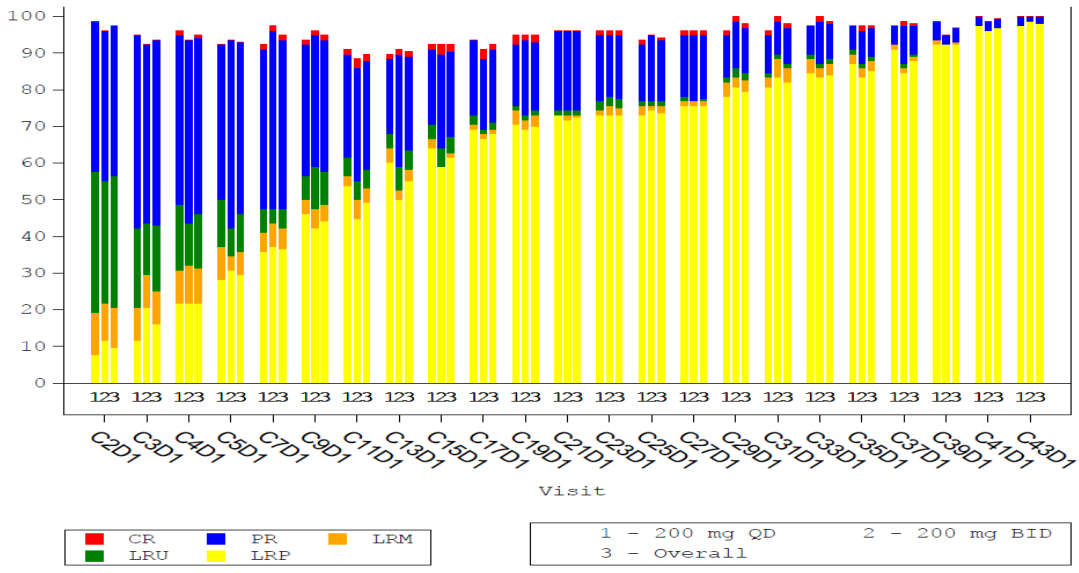

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Figure 8: Bar plot of overall response over time (ITT population)

Subgroup analysis of ORR by different duration of concomitant medication prior to initiation of belumosudil as shown in **Table 34** demonstrates comparably high ORR, regardless of the duration of concomitant treatment prior to C1D1.

Table 34: ORR (investigator assessment) by concomitant cGVHD treatment on C1D1 duration prior to study categories (ITT population)

	200 mg QD N = 78	200 mg BID N = 78	Overall N = 156
14 - 30 days prior to study start day - n (%)*	6 (7.7%)	12 (15.4%)	18 (11.5%)
ORR (CR or PR) - n (%)	5 (83.3%)	9 (75.0%)	14 (77.8%)
ORR (CR) - n (%)	1 (16.7%)	0	1 (5.6%)
ORR (PR) - n (%)	4 (66.7%)	9 (75.0%)	13 (72.2%)
95% CI of ORR	(35.9%, 99.6%)	(42.8%, 94.5%)	(52.4%, 93.6%)
31 - 60 days prior to study start day - n (%)*	16 (20.5%)	14 (17.9%)	30 (19.2%)
ORR (CR or PR) - n (%)	11 (68.8%)	13 (92.9%)	24 (80.0%)
ORR (CR) - n (%)	2 (12.5%)	0	2 (6.7%)
ORR (PR) - n (%)	9 (56.3%)	13 (92.9%)	22 (73.3%)
95% CI of ORR	(41.3%, 89.0%)	(66.1%, 99.8%)	(61.4%, 92.3%)

	200 mg QD N = 78	200 mg BID N = 78	Overall N = 156
61 - 90 days prior to study start day - n (%)*	9 (11.5%)	9 (11.5%)	18 (11.5%)
ORR (CR or PR) - n (%)	8 (88.9%)	9 (100.0%)	17 (94.4%)
ORR (CR) - n (%)	0	2 (22.2%)	2 (11.1%)
ORR (PR) - n (%)	8 (88.9%)	7 (77.8%)	15 (83.3%)
95% CI of ORR	(51.8%, 99.7%)	(66.4%, 100.0%)	(72.7%, 99.9%)
> 90 days prior to study start day - n (%)*	54 (69.2%)	43 (55.1%)	97 (62.2%)
ORR (CR or PR) - n (%)	39 (72.2%)	29 (67.4%)	68 (70.1%)
ORR (CR) - n (%)	2 (3.7%)	0	2 (2.1%)
ORR (PR) - n (%)	37 (68.5%)	29 (67.4%)	66 (68.0%)
95% CI of ORR	(58.4%, 83.5%)	(51.5%, 80.9%)	(60.0%, 79.0%)

Note:
- The percentages with * are calculated based on the number of ITT population. The other percentages are calculated based on the number of the specific subgroup in ITT population in each subgroup.
- CI = confidence interval, CI is calculated using Clopper-Pearson interval (exact) method.
- Response assessment performed on or after initiation of new systemic therapy for cGVHD are excluded from analysis.

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Subgroup results by most commonly used concomitant therapy for ORR and other key efficacy endpoints in overall population from KD025-213 study are presented in **Table 35**.

Table 35: Summary of efficacy endpoints for belumosudil (ITT population) by concomitant therapy subgroup

		Concomitant systemic treatment on C1D1				
Efficacy endpoints	Overall	Steroid only	Steroid + CNI	Steroid + mTOR or MMF	ECP	Others
n	152	29	26	19	44	34
ORR n (%)	114 (75.0%)	19 (65.5%)	18 (69.2%)	14 (73.7%)	36 (81.8%)	27 (79.4%)
95% CI	(67.3%, 81.7%)	(45.7%, 82.1%)	(48.2%, 85.7%)	(48.8%, 90.9%)	(67.3%, 91.8%)	(62.1%, 91.3%)
ORR at 6 months n (%)	73 (48.0%)	10 (34.5%)	13 (50.0%)	11 (57.9%)	20 (45.5%)	19 (55.9%)
95% CI	(39.9%, 56.3%)	(17.9%, 54.3%)	(29.9%, 70.1%)	(33.5%, 79.7%)	(30.4%, 61.2%)	(37.9%, 72.8%)
Median DOR (weeks)	26.0	32.0	36.1	36.1	14.3	32.3
mLSS improvement (%)	61.2%	55.2%	42.3%	68.4%	68.2%	67.6%

Note:
- The percentages are calculated based on the number of ITT population with concomitant treatment.
- CI = confidence interval.
- Response assessment performed on or after initiation of new systemic therapy for cGVHD are excluded from analysis.
- CNI including tacrolimus and ciclosporin, and mTOR including sirolimus and everolimus.
- Concomitant ECP group includes all patients who had ECP on C1D1 regardless if any other concomitant therapy for cGVHD were used or not.
- Others: patients with concomitant medication for cGVHD on C1D1.

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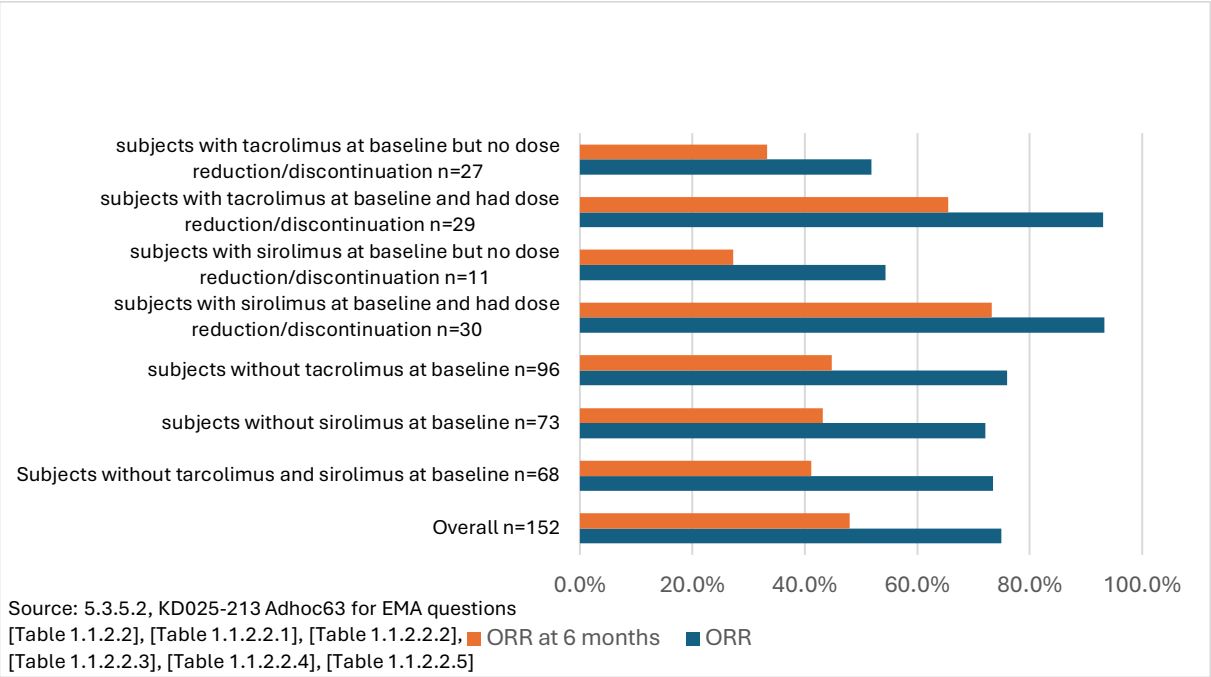
Figure 9 shows ORR by concomitant sirolimus and tacrolimus at baseline. Among participants who did not take tacrolimus or sirolimus at baseline, the ORR (and ORR at 6 months) are similar and comparable to overall participants enrolled in KD025-213 study. Among participants taking tacrolimus or sirolimus at baseline, the ORR (and ORR at 6 months) are higher in participants who had dose reduction or discontinuation compared to those of participants who had not. Although the reason for sirolimus and tacrolimus dose reduction was not collected, considering no significant difference in safety profile between participants with dose reduction and those without, the Applicant believes that the most likely reason for dose reduction is tapering after response achieved and therefore it demonstrates that belumosudil could reduce the need of other immunosuppressant drugs. The ORR (and ORR at 6 months) are similar in participants with sirolimus dose reduction/discontinuation and participants with tacrolimus dose reduction/discontinuation. The same was noted in participants who had not undergone dose reduction/discontinuation on either drug. According to the applicant, these data demonstrate that the response observed is attributable to belumosudil and no significant impact of belumosudil on tacrolimus and sirolimus is anticipated from efficacy perspective.



Source: 5.3.5.2, KD025-213 Adhoc63 for EMA questions [Table 1.1.2.2], [Table 1.1.2.2.1], [Table 1.1.2.2.2], [Table 1.1.2.2.3], [Table 1.1.2.2.4], [Table 1.1.2.2.5]

Figure 9: ORR by concomitant sirolimus and tacrolimus at baseline

An increased corticosteroid dose for a flare during the first 6 months of study treatment was reported in a total of 9 responders, 5 in the 200 mg QD arm, 4 in the 200 mg BID arm, and 2 non-responders, one in each arm. One responder in the 200 mg QD arm had increased corticosteroid for a flare incorrectly reported as starting on D-35. Six of the remaining 8 responders demonstrated a response to belumosudil treatment prior to the corticosteroid increase, indicating that the increased corticosteroid dose was not related to belumosudil treatment.

Total of 44 participants were having extracorporeal photopheresis (ECP) as concomitant procedure at baseline. The median duration of ECP prior to C1D1 was 135.5 and 150 days in overall group and 200 mg QD group, respectively. Among these participants, the majority (54.5% and 68.4% of participants in overall and 200 mg QD group) had started ECP more than 90 days prior to C1D1. The smallest time interval between start of ECP and C1D1 seen in study KD025-213 was 16 days.

Analysis of responses in participants with concomitant ECP at baseline demonstrates comparable ORR and ORR at 6 months, regardless of the duration of ECP treatment prior to C1D1, or as compared to participants that did not receive ECP treatment (**Table 36**). Specifically, participants with duration of ECP prior to C1D1 ≤ 50th percentile had an ORR of 78.3% and a 6-month ORR of 47.8%. Participants with duration of ECP prior to C1D1 > 50th percentile days had an ORR of 85.7% and a 6-month ORR of 42.9%. Participants that did not receive ECP had an ORR of 72.7% and a 6-month ORR of 49.1%. The Applicant concludes that responses seen after the start of belumosudil treatment were not associated with concomitant ECP treatment which had started prior to screening and prior to start of belumosudil treatment.

Table 36: ORR (investigator assessment) by concomitant ECP on C1D1 (ITT population).

	200 mg QD N = 78	200 mg BID N = 78	Overall N = 156
Concomitant ECP (No) - n (%)*	59 (75.6%)	53 (67.9%)	112 (71.8%)
ORR (CR or PR) - n (%)	41 (69.5%)	37 (69.8%)	78 (69.6%)
ORR (CR) - n (%)	3 (5.1%)	1 (1.9%)	4 (3.6%)
ORR (PR) - n (%)	38 (64.4%)	36 (67.9%)	74 (66.1%)
95% CI of ORR	(56.1%, 80.8%)	(55.7%, 81.7%)	(60.2%, 78.0%)
Concomitant ECP and treatment duration from start date until C1D1 is <= 90 days (Yes) - n (%)*	6 (7.7%)	14 (17.9%)	20 (12.8%)
ORR (CR or PR) - n (%)	6 (100.0%)	12 (85.7%)	18 (90.0%)
ORR (CR) - n (%)	1 (16.7%)	1 (7.1%)	2 (10.0%)
ORR (PR) - n (%)	5 (83.3%)	11 (78.6%)	16 (80.0%)
95% CI of ORR	(54.1%, 100.0%)	(57.2%, 98.2%)	(68.3%, 98.8%)
Concomitant ECP and treatment duration from start date until C1D1 is > 90 days (Yes) - n (%)*	13 (16.7%)	11 (14.1%)	24 (15.4%)
ORR (CR or PR) - n (%)	10 (76.9%)	8 (72.7%)	18 (75.0%)
ORR (CR) - n (%)	0	0	0
ORR (PR) - n (%)	10 (76.9%)	8 (72.7%)	18 (75.0%)
95% CI of ORR	(46.2%, 95.0%)	(39.0%, 94.0%)	(53.3%, 90.2%)
Concomitant ECP and treatment duration (Days) from start date until C1D1 > 50th percentile (Yes) - n (%)*	9 (11.5%)	12 (15.4%)	21 (13.5%)
ORR (CR or PR) - n (%)	8 (88.9%)	10 (83.3%)	18 (85.7%)
ORR (CR) - n (%)	1 (11.1%)	1 (8.3%)	2 (9.5%)
ORR (PR) - n (%)	7 (77.8%)	9 (75.0%)	16 (76.2%)
95% CI of ORR	(51.8%, 99.7%)	(51.6%, 97.9%)	(63.7%, 97.0%)
Concomitant ECP and treatment duration (Days) from start date until C1D1 <= 50th percentile (Yes) - n (%)*	10 (12.8%)	13 (16.7%)	23 (14.7%)
ORR (CR or PR) - n (%)	8 (80.0%)	10 (76.9%)	18 (78.3%)
ORR (CR) - n (%)	0	0	0
ORR (PR) - n (%)	8 (80.0%)	10 (76.9%)	18 (78.3%)
95% CI of ORR	(44.4%, 97.5%)	(46.2%, 95.0%)	(56.3%, 92.5%)

Note:
- The percentages with * are calculated based on the number of subjects of ITT population. The other percentages are calculated based on the number of the specific subgroup in ITT population.
- CI = confidence interval, CI is calculated using Clopper-Pearson interval (exact) method.
- Response assessment performed on or after initiation of new systemic therapy for cGVHD are excluded from analysis.
- The 50th percentile categories are based on participants within 200 mg QD and 200 mg BID, respectively.

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Secondary Efficacy Endpoints - Adults

Results for the secondary efficacy endpoints of DOR, TTR, response by organ system, LSS score, FFS, TTNT, OS, and change in corticosteroid dose are summarized in **Table 37**.

Table 37: Study KD025-213 secondary efficacy endpoints, iTT population, adults

	Belumosudil		
Variable	200 mg QD N = 78	200 mg BID N = 78	Overall N = 156
Duration of response (responders), n	57	57	114
K-M estimate, median (weeks)			
Primary (95% CI)	23.9 (11.43, 50.43)	32.0 (20.86, 53.14)	26.0 (19.86, 40.14)
Secondary (95% CI)	23.9 (11.43, 50.43)	32.0 (20.86, 60.29)	26.0 (19.86, 40.14)
Tertiary (95% CI)	101.1 (64.29, NA)	NA (59.29, NA)	109.6 (81.14, NA)
Time-to-response (weeks)	57	57	114
Median	4.43	4.43	4.43
Min, max	3.7, 80.1	3.7, 40.1	3.7, 80.1
Best Response by organ system, % (n/total)			
Skin	31.7 (20/63)	43.8 (28/64)	37.8 (48/127)
Eyes	42.9 (24/56)	50.0 (26/52)	46.3 (50/108)
Mouth	56.1 (23/41)	59.6 (31/52)	58.1 (54/93)
Esophagus	56.5 (13/23)	53.8 (7/13)	55.6 (20/36)
Upper GI	64.3 (9/14)	40.0 (4/10)	54.2 (13/24)
Lower GI	71.4 (5/7)	75.0 (6/8)	73.3 (11/15)
Liver	20.0 (2/10)	25.0 (1/4)	21.4 (3/14)
Lungs	33.3 (9/27)	24.0 (6/25)	28.8 (15/52)
Joints and fascia	71.2 (42/59)	67.2 (39/58)	69.2 (81/117)
GSR	44.9 (35/78)	57.7 (45/78)	51.3 (80/156)
Lee Symptom Scale score, n (%)			
Participants with a 7-PtR from baseline	45 (57.7%)	48 (61.5%)	93 (59.6%)
Participants with a 7-PtR from baseline on 2 consecutive assessments	36 (46.2%)	31 (39.7%)	67 (42.9%)
Failure-free survival (months)			
K-M estimate, median (95% CI)	16.3 (10.15, 26.48)	17.2 (11.27, NA)	16.6 (12.85, 24.18)
6 months (95% CI)	0.75 (0.63, 0.83)	0.79 (0.67, 0.86)	0.77 (0.69, 0.83)
12 months (95% CI)	0.58 (0.45, 0.68)	0.62 (0.50, 0.72)	0.60 (0.51, 0.67)
18 months (95% CI)	0.48 (0.36, 0.59)	0.49 (0.37, 0.60)	0.49 (0.40, 0.57)
24 months (95% CI)	0.43 (0.31, 0.54)	0.44 (0.32, 0.55)	0.43 (0.35, 0.52)
Time-to-next treatment (months)			
Number of patients who initiated a new systemic therapy for cGVHD, n (%)	34 (43.6%)	31 (39.7%)	65 (41.7%)
Median (95% CI)	24.2 (13.37, NA)	NA (14.55, NA)	27.3 (16.59, NA)

OS			
Number of deaths, n (%)	14 (17.9%)	14 (17.9%)	28 (17.9%)
Median (95% CI)	NA (NA, NA)	NA (NA, NA)	NA (NA, NA)
6 months (95% CI)	0.95 (0.87, 0.98)	0.97 (0.90, 0.99)	0.96 (0.91, 0.98)
12 months (95% CI)	0.91 (0.81, 0.95)	0.92 (0.83, 0.96)	0.91 (0.85, 0.95)
18 months (95% CI)	0.89 (0.79, 0.94)	0.85 (0.75, 0.92)	0.87 (0.80, 0.92)
24 months (95% CI)	0.86 (0.75, 0.92)	0.84 (0.73, 0.91)	0.85 (0.77, 0.90)
Corticosteroid dosing			
Median greatest reduction (%)	-50.00	-66.67	-53.14
Min, max	-100.0, 0.0	-100.0, 900.0	-100.0, 900.0
Participants who discontinued corticosteroid usage, n (%)	21 (26.9%)	23 (29.5%)	44 (28.2%)

Abbreviations: 7-PtR = 7-point reduction; BID = twice daily; cGVHD = chronic graft versus host disease; CI = confidence interval; CR = complete response; GI = gastrointestinal; GSR = global severity rating; K-M = Kaplan-Meier; max = maximum; min = minimum; OS = overall survival; PR = partial response; QD = once daily.
Note: Responder population was used for DOR and cumulative response rate. The ITT population was used for other endpoints.

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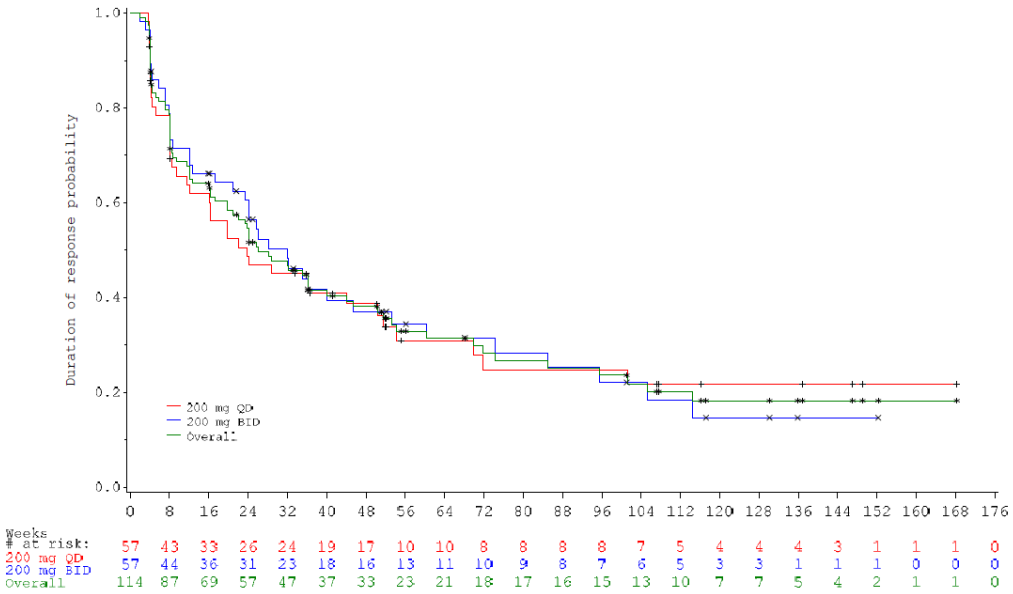
Source: Summary Clin Efficacy

Duration of response

Figure 10 and **Figure 11** show Kaplan-Meier plots of primary and tertiary DORs for the responder population.



= number; BID = twice daily; DOR = Duration of Response; QD = once daily.
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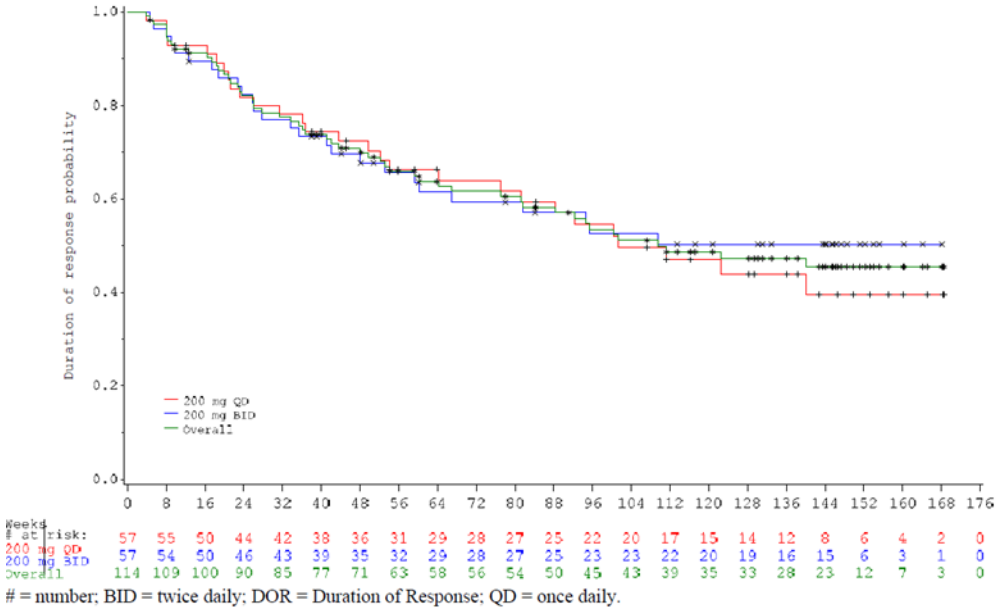
Figure 10: Kaplan-Meier Plot of Primary DOR – Responder Population



= number; BID = twice daily; DOR = Duration of Response; QD = once daily.

Figure 11: Kaplan-Meier Plot of Tertiary DOR – Responder Population

Source: KD025-213 CSR Addendum, data lock 01 Sep 2022

When considering treatment discontinuation as loss of response, in addition to the events listed, the estimated median (95% CI) DoR were 19.9 (8.43, 36.14) and 24.1(15.86, 35.00) months in Arm A and B, respectively.

Time to Response

Overall, the median Time to Response (TTR) was 4.43 weeks: 4.43 weeks in Arm A and 4.43 weeks in Arm B. In total, 95 (83.3%) of responders achieved a response by the 10-week assessment, 108 (94.7%) of responders achieved a response by the 24-week assessment, and 114 (100%) of responders achieved a response after at least 48 weeks of belumosudil treatment.

Response by organ system

Table 38 summarizes the best response by individual organ for the ITT Population.

Table 38: Best Response by Individual Organ – ITT Population

	200 mg QD N = 78	200 mg BID N = 78	Overall N = 156
Skin - n	63	64	127
Complete response (CR)	9 (14.3%)	13 (20.3%)	22 (17.3%)
Partial response (PR)	11 (17.5%)	15 (23.4%)	26 (20.5%)
Total (PR + CR)	20 (31.7%)	28 (43.8%)	48 (37.8%)
Eyes - n	56	52	108
Complete response (CR)	9 (16.1%)	6 (11.5%)	15 (13.9%)
Partial response (PR)	15 (26.8%)	20 (38.5%)	35 (32.4%)
Total (PR + CR)	24 (42.9%)	26 (50.0%)	50 (46.3%)
Mouth - n	41	52	93
Complete response (CR)	20 (48.8%)	25 (48.1%)	45 (48.4%)
Partial response (PR)	3 (7.3%)	6 (11.5%)	9 (9.7%)
Total (PR + CR)	23 (56.1%)	31 (59.6%)	54 (58.1%)
Esophagus - n	23	13	36
Complete response (CR)	13 (56.5%)	7 (53.8%)	20 (55.6%)
Partial response (PR)	0	0	0
Total (PR + CR)	13 (56.5%)	7 (53.8%)	20 (55.6%)
Upper GI - n	14	10	24
Complete response (CR)	8 (57.1%)	4 (40.0%)	12 (50.0%)
Partial response (PR)	1 (7.1%)	0	1 (4.2%)
Total (PR + CR)	9 (64.3%)	4 (40.0%)	13 (54.2%)
Lower GI - n	7	8	15
Complete response (CR)	5 (71.4%)	5 (62.5%)	10 (66.7%)
Partial response (PR)	0	1 (12.5%)	1 (6.7%)
Total (PR + CR)	5 (71.4%)	6 (75.0%)	11 (73.3%)
Liver - n	10	4	14
Complete response (CR)	1 (10.0%)	1 (25.0%)	2 (14.3%)
Partial response (PR)	1 (10.0%)	0	1 (7.1%)
Total (PR + CR)	2 (20.0%)	1 (25.0%)	3 (21.4%)
Lungs - n	27	25	52
Complete response (CR)	5 (18.5%)	3 (12.0%)	8 (15.4%)
Partial response (PR)	4 (14.8%)	3 (12.0%)	7 (13.5%)
Total (PR + CR)	9 (33.3%)	6 (24.0%)	15 (28.8%)
Joints and Fascia - n	59	58	117
Complete response (CR)	11 (18.6%)	12 (20.7%)	23 (19.7%)
Partial response (PR)	31 (52.5%)	27 (46.6%)	58 (49.6%)
Total (PR + CR)	42 (71.2%)	39 (67.2%)	81 (69.2%)
Global severity rating - n	78	78	156
Complete response (CR)	5 (6.4%)	3 (3.8%)	8 (5.1%)
Partial response (PR)	30 (38.5%)	42 (53.8%)	72 (46.2%)
Total (PR + CR)	35 (44.9%)	45 (57.7%)	80 (51.3%)

Note:
- n = number of ITT population for global severity rating, and number of specific organ involved at baseline for other organs.
- The percentages are calculated based on the corresponding n.
- Response assessment performed on or after initiation of new systemic therapy for cGVHD are excluded from analysis.

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Source: KD025-213 CSR Addendum

The most common baseline global severity rating (GSR) score was 6 or 7 (70 subjects): 30 subjects in Arm A and 40 subjects in Arm B. Of these subjects, 43 (61.4%) subjects had a response (CR or PR): 15 (50.0%) subjects in Arm A and 28 (70.0%) subjects in Arm B.

The organs that had the longest median TTR were the lungs (16.14 weeks) and mouth (11.86 weeks). The organ that had the shortest median TTR was lower gastrointestinal (4.14 weeks). Late organ responses that occurred after more than 24 weeks of belumosudil were seen in eyes (14 responses), skin (9 responses), lungs (7 responses), mouth (6 responses), joints and fascia (4 responses), oesophagus (2 responses), liver (1 response), and GSR (15 responses).

Lee Symptom Scale Score

In total, 93 (61.2%) subjects reported a clinically meaningful improvement (> 7-point reduction, 7-PtR, from baseline) at least once, as assessed by the LSSS: 45 (57.7%) subjects in Arm A and 48 (61.5%) subjects in Arm B. In total, 67 (42.9%) subjects reported a clinically meaningful improvement on 2 consecutive assessments: 36 (46.2%) subjects in Arm A and 31 (39.7%) subjects in Arm B. The median duration for a 7-PtR was 24.9 weeks: 24.9 weeks in Arm A and 24.7 weeks in Arm B. The longest duration for a 7-PtR was > 48 weeks (32 [20.5%] subjects): 16 (20.5%) subjects in Arm A and 16 (20.5%) subjects in Arm B.

Failure-Free Survival

The median Kaplan-Meier estimate of FFS (95% CI) was 16.6 (12.85, 24.18) months: 16.3 (10.15, 26.48) months for Arm A and 17.2 months for Arm B.

The most common failure event at 24 months was initiation of new systemic therapy for cGVHD in 61 participants (39.1%): in 31 participants (39.7%) in Arm A and in 30 participants (38.5%) in Arm B.

Figure 12 is a Kaplan-Meier plot for FFS for the mITT Population.

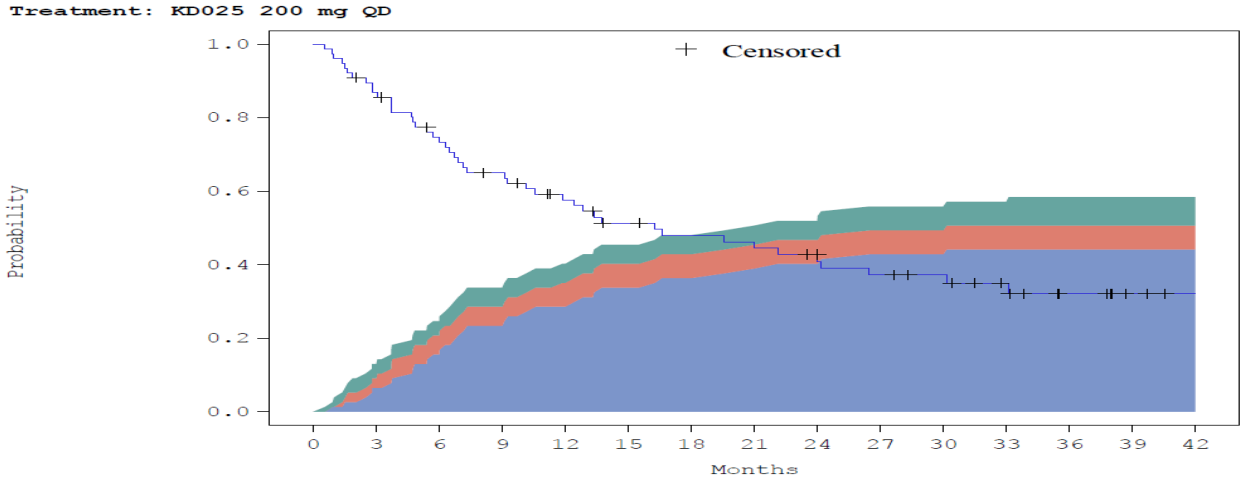

Figure 12: Kaplan-Meier Plot for FFS – ITT Population

Source: KD025-213 CSR Addendum, data lock 01 Sep 2022

Time to Next Treatment

The median Time to Next Treatment (TTNT) (95% CI) was 27.3 (16.59, not available) months: 24.2 (13.37, not available) months for Arm A and the estimate has not been reached for Arm B (**Table 39**)

Table 39: Descriptive Kaplan-Meier and landmark statistics for Time to New Treatment (TTNT) (ITT population)

	200 mg QD N = 78	200 mg BID N = 78	Overall N = 156
TTNT - n (%)			
Censored	43 (55.1%)	44 (56.4%)	87 (55.8%)
Study ongoing	0	0	0
Study discontinued	43 (55.1%)	44 (56.4%)	87 (55.8%)
Failure event: New cGVHD systemic therapy	34 (43.6%)	31 (39.7%)	65 (41.7%)
K-M estimate (Months)			
25th percentile	7.3	8.0	7.3
Median (95%CI)	24.2 (13.37, NA)	NA (14.55, NA)	27.3 (16.59, NA)
75th percentile	NA	NA	NA
K-M estimate of TTNT (95%CI)			
6 months	0.83 (0.72, 0.90)	0.80 (0.69, 0.87)	0.81 (0.74, 0.87)
12 months	0.68 (0.55, 0.78)	0.68 (0.56, 0.77)	0.68 (0.59, 0.75)
18 months	0.57 (0.44, 0.68)	0.59 (0.46, 0.70)	0.58 (0.49, 0.66)
24 months	0.51 (0.38, 0.63)	0.55 (0.42, 0.66)	0.53 (0.44, 0.61)

	200 mg QD N = 78	200 mg BID N = 78	Overall N = 156
Cumulative failure rate - n (%)			
New cGVHD systemic therapy			
6 months	12 (15.4%)	15 (19.2%)	27 (17.3%)
12 months	22 (28.2%)	23 (29.5%)	45 (28.8%)
18 months	28 (35.9%)	28 (35.9%)	56 (35.9%)
24 months	31 (39.7%)	30 (38.5%)	61 (39.1%)

Note:
- The percentages are calculated based on the number of ITT population.
- Time to next therapy (TTNT) is defined as the time from the first dose of KD025 to the start of additional systemic cGVHD therapy.

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Source: KD025-213 CSR Addendum, data lock 01 Sep 2022

Overall Survival

Table 40 presents the descriptive Kaplan-Meier and landmark statistics for OS for the ITT Population.

Table 40: Descriptive Kaplan-Meier and landmark statistics for Overall survival (OS) (ITT population)

	200 mg QD N = 78	200 mg BID N = 78	Overall N = 156
OS - n (%)			
Censored	63 (80.8%)	61 (78.2%)	124 (79.5%)
Alive	61 (78.2%)	61 (78.2%)	122 (78.2%)
Lost to follow up	2 (2.6%)	0	2 (1.3%)
Event: Death	14 (17.9%)	14 (17.9%)	28 (17.9%)
K-M estimate (Months)			
25th percentile	NA	NA	NA
Median (95%CI)	NA (NA, NA)	NA (NA, NA)	NA (NA, NA)
75th percentile	NA	NA	NA
K-M estimate of OS (95%CI)			
6 months	0.95 (0.87, 0.98)	0.97 (0.90, 0.99)	0.96 (0.91, 0.98)
12 months	0.91 (0.81, 0.95)	0.92 (0.83, 0.96)	0.91 (0.85, 0.95)
18 months	0.89 (0.79, 0.94)	0.85 (0.75, 0.92)	0.87 (0.80, 0.92)
24 months	0.86 (0.75, 0.92)	0.84 (0.73, 0.91)	0.85 (0.77, 0.90)

Note:
- OS = Overall survival, is defined as time from first dose of KD025 to the date of death due to any cause.
- The percentages are calculated based on the number of ITT population.

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Change in corticosteroid dose

The median baseline prednisone equivalent dose of corticosteroids was 0.186 mg/kg/day: 0.178 mg/kg/day for Arm A and 0.214 mg/kg/day for Arm B. A total of 105 (67.3%) subjects had a corticosteroid dose reduction during treatment with belumosudil: 50 (64.1%) subjects in Arm A and 55 (70.5%) subjects in Arm B. In total, 44 (28.2%) subjects discontinued corticosteroid usage: 21 (26.9%) subjects in Arm A and 23 (29.5%) subjects in Arm B. The median percent change from baseline to the greatest reduction was -53.14%: -50.00% for Arm A and -66.67% for Arm B.

Change in calcineurin inhibitor dose

In total, 58 (38.2%) subjects were taking a calcineurin inhibitor (CNI) at baseline. Of these subjects, 30 (51.7%) subjects reduced their CNI dose, and 16 (27.6%) subjects discontinued their CNI dose altogether.

Secondary endpoint analysis – Adolescents

None of the 3 adolescent participants had received prior treatment with ibrutinib.

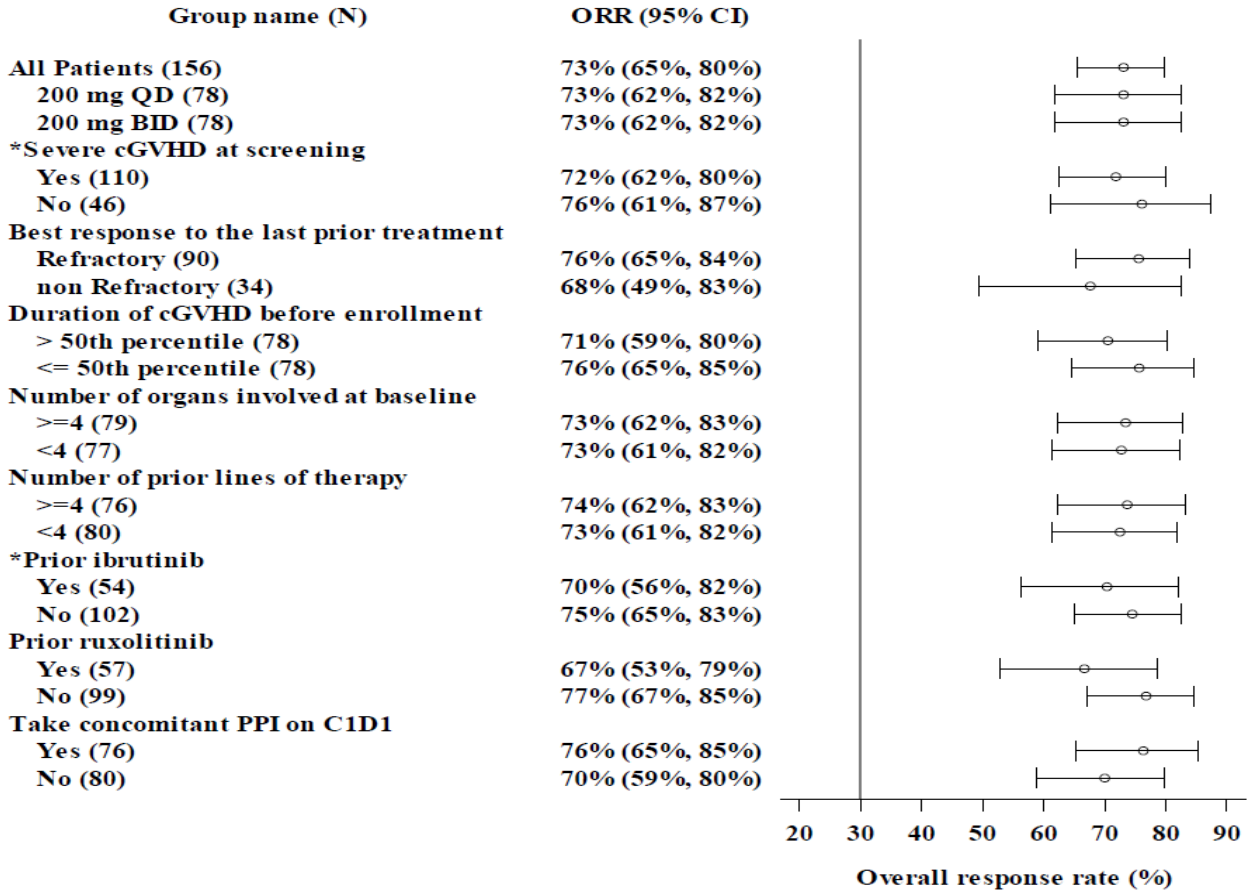
Duration of response was reported only for 2 (out of 3) participants who achieved a PR. One participant in Arm A showed primary/secondary DOR for 113 days each with documented LR. The same participant showed tertiary DOR for 820 days (censored due to study terminated by Sponsor). One participant in Arm B showed primary/secondary DOR for 29 days. One participant in Arm A showed a decrease in corticosteroid use (dose

reduction from 40.5 mg/day on C1D1 to 2.5 mg/day on C10D1). None of the participants in Arm A showed FFS events, and one participant showed PR for skin and mouth.

Subgroup analysis

ORR

In 200 mg QD dose group the ORR was consistently high and did not differ between low-and high-risk group categories. Responses were detected in all subgroups, with ORRs ranging from 82.9% (67.9, 92.8) (duration of cGVHD) to 65.5% (45.7, 82.1) (prior ruxolitinib treatment). In addition, the 95% CI for each subgroup pair overlapped extensively, providing no evidence that the subgroup variable such as prior treatment with ruxolitnib, severe cGVHD, >3 prior LOTs and duration of cGVHD, had an effect on ORR.



Note:

- *: Indicates stratification factors.
- ORR = Overall response rate; CI = confidence interval, CI is calculated using Clopper-Pearson interval (exact) method.
- Response assessment performed on or after initiation of new systemic therapy for cGVHD are excluded from analysis.

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Figure 13: Forest Plot for Subgroup Analyses of Overall Response Rate – ITT Population

Duration of response

In the 200 mg QD dose group, in the subgroup with prior ruxolitinib, primary DOR was 36.1 (8.14, NA) weeks versus 23.9 (12.14, 50.43) weeks with no prior ruxolitinib treatment. In the subgroup with severe cGVHD at baseline primary DOR was 36.1 (9.43, 71.1) weeks versus 19.9 (8.14, 28.71) weeks in the no severe cGVHD at baseline, subgroup. In terms of prior treatment, primary DOR in the ≤ 3 prior LOTs subgroup was 36.1 (16.14, 71.71) weeks versus 16.4 (5.14, 51.57) weeks in the > 3 prior LOTs subgroup. Finally, in the 200 mg QD dose group, primary DOR duration of cGVHD prior to enrolment was higher in the >50 percentile subgroup, versus ≤50 percentile, 50.4 (16.29, 69.86) versus 16.1 (8.14, 36.14), respectively.

Ancillary analyses

Not applicable.

2.6.5.3. Summary of main efficacy results

Table 41 summarises the efficacy results from the main studies supporting the present application.

Table 41: Summary of efficacy for trial KD025-213 (DRI17633)

Title: A Phase 2, Randomized, Multicenter Study to Evaluate the Efficacy and Safety in Subject with Chronic Graft Versus Host Disease (cGVHD) After at Least 2 Prior Lines of Systemic Therapy		
Study identifier	KD025-213 (DRI17633) NCT#03640481	
Design	Open-label, randomized, multicentre phase 2 study in patients with chronic Graft Versus Host Disease (cGVHD) who had received 2-5 prior lines of systemic therapy to evaluate the efficacy and safety of belumosudil. Enrolled patients were randomized at 1:1 ratio to receive belumosudil 200 mg daily or 200 mg twice daily until cGVHD progression.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	Median follow-up time: 29.86 months not applicable not applicable
Hypothesis	The primary endpoint was overall response rate (ORR). The primary efficacy objective is to demonstrate an ORR > 30%, i.e. that the lower bound of the CI of ORR is greater than 30%	
Treatments groups	Arm A belumosudil	200 mg daily (QD) until clinically significant progression of cGVHD 77 patients dosed
	Arm B belumosudil	200 mg twice daily (BID) until clinically significant progression of cGVHD 75 patients dosed

Endpoints and definitions	Primary endpoint	Overall response rate (ORR) defined as the proportion of participants who achieved partial response (PR) or complete response (CR) at any time in the absence of new systemic treatment for cGVHD. Responses are defined by the 2014 National Institutes of Health (NIH) Consensus Development Project on clinical trials in cGVHD, and are assessed by Investigators.	
	Secondary endpoint	Primary duration of response (DOR) defined as the time from first documentation of response to the time of first documentation of deterioration from best response (eg, CR to PR, or PR to Lack of Response [LR])	
	Secondary endpoint	The secondary DOR defined as the time from first documentation of response to the time of first documentation of lack of response	
	Secondary endpoint	The tertiary DOR defined as the time from first documentation of response to the time of initiation of new systemic cGVHD therapy	
	Secondary endpoint	Time to response (TTR) defined as the time from the first dose of belumosudil to the time of the first documentation of response.	
	Secondary endpoint	Time to next treatment (TTNT) defined as the time from the first dose of belumosudil to the time of starting new cGVHD systemic treatment.	
	Secondary endpoint	Change in Lee Symptom Scale (LSS) score defined as the proportion of participants who achieved at least 7-point reduction from baseline assessed by LSS.	
Database lock	Adult participant population : 01 September 2022 Adolescent participant population : 11 December 2023		
Results and Analysis			
Analysis description	**Primary Analysis in adult population**		
Analysis population and time point description	Adult population and adolescent population were analysed and reported separately. The primary analysis in adults was conducted on the Intent-to-Treat (ITT) population, defined as all participants analyzed in the groups to which they were randomly assigned. Efficacy assessments were assessed on Day 1 of Cycle 2-5 and then on Day 1 of every other cycle during treatment and at the end of treatment (EOT) visit. Changes in corticosteroid dose was evaluated throughout the study.		
Descriptive statistics and estimate variability	Treatment group	Arm A 200 mg QD	Arm B 200 mg BID
	Number of participants	78	78

	ORR n (%) 95% CI	 57 (73.1) 61.8, 82.5	 57 (73.1) 61.8, 82.5
	Primary DOR n median (weeks) 95% CI	 57 23.9 11.43, 50.43	 57 32.0 20.86, 53.14
	Secondary DOR n median(weeks) 95% CI	 57 23.9 11.43, 50.43	 57 32.0 20.86, 60,29
Descriptive statistics and estimate variability	Tertiary DOR n median (weeks)	 57 101.1	 57 Not reached (NR)
	TTR (weeks) N Median Min, Max	 57 4.43 3.7, 80.1	 57 4.43 3.7, 40.1
	TTNT (months) Median 95% CI	 24.2 13.37, NR	 NR 14.55, NR
	Change in LSS score, n (%) Participant with a 7-point reduction from baseline Participant with a 7-point reduction from baseline on 2 consecutive assessments	 45 (57.7) 36 (46.2)	 48 (61.5) 31 (39.7)
	Participants who discontinued corticosteroid usage n (%)	21 (26.9)	23 (29.5)

Notes	3 adolescent participants were enrolled in the study and reported separately. Two participants received 200 mg QD dose, and one participant received 200 mg BID dose. Two out of 3 participants achieved PR including one in the 200mg QD group and one in the 200 mg BID group. The responded participants in the 200 mg QD dose showed a TTR of 53 days, primary/secondary DOR of 113 days and tertiary DOR of 820 days., The responded participant in the 200 mg BID dose showed a TTR of 29 days, primary/secondary DOR of 29 days and tertiary DOR of 180 days. One participant showed reduction in systemic corticosteroid dose from 40.5 mg/day to 2.5 mg/day. Both participants in the 200 mg QD dose did not have any FFS event and they discontinued the study by the Investigator based on sustained response and the participant in the 200 mg BID dose had initiated a new systemic therapy for cGVHD on study Day 208.

2.6.5.4. Clinical studies in special populations

Table 42: Clinical studies in special populations

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
Controlled Trials	NA	NA	NA
Non Controlled trials	45/209	6/209	0/209

2.6.5.5. In vitro biomarker test for patient selection for efficacy

Not applicable.

2.6.5.6. Analysis performed across trials (pooled analyses and meta-analysis)

Integrated Analysis of Studies KD025-213, KD025-208, and KD025-217

Disposition of study participants

A total of 193 participants from Studies KD025-208, KD025-213, and KD025-217, were included in the mITT – P2MLAG analysis (all participants who had at least 2 prior lines of systemic therapy and received at least 1 dose of belumosudil): 94 participants in the 200 mg QD group, 85 participants in the 200 mg BID group, and 14 participants in the 400 mg QD group.

As of the cutoff date for the Integrated Analysis of 29 January 2024, in the 200 mg QD dose group and overall group respectively, the median follows up duration was 29.9 (0.6, 83.7) months and 31.2 (0.6, 83.7) months and the cumulative duration of exposure was 122.11 and 247.94 patient-years, respectively. In the 200 mg QD group, the most common reason for discontinuation from treatment was progression of cGVHD (20 [21.3%] participants).

A higher percentage of participants in the 400 mg QD group had a primary reason of discontinuation from the study due to death (50% versus 20.2% 200 mg QD, respectively). None of these deaths were determined to be related to belumosudil administration; the increased incidence may be suggestive of the higher acuity of the patient population. Almost 50% of participants in the 400 mg QD group had baseline lung involvement with baseline FEV1 values lower than observed in other groups, suggesting a sicker population.

Table 43: Participant disposition, mITT population and Phase 2 multiple lines analysis group

	Belumosudil				
Category, n (%)	**200 mg QD N = 94**	**200 mg BID N = 85**	**Combined 200 mg N = 179**	**400 mg QD N = 14**	**Overall N = 193**
Treatment ongoing	5 (5.3)	1 (1.2)	6 (3.4)	0	6 (3.1)
Discontinued from treatment	89 (94.7)	84 (98.8)	173 (96.6)	14 (100.0)	187 (96.9)
Primary reason for discontinuation from treatment					
Adverse event	13 (13.8)	11 (12.9)	24 (13.4)	1 (7.1)	25 (13.0)
Death	2 (2.1)	3 (3.5)	5 (2.8)	2 (14.3)	7 (3.6)
Failure to meet continuation criteria	1 (1.1)	1 (1.2)	2 (1.1)	0	2 (1.0)
Investigator decision	1 (1.1)	2 (2.4)	3 (1.7)	0	3 (1.6)
Noncompliance to protocol	2 (2.1)	3 (3.5)	5 (2.8)	0	5 (2.6)
Physician decision	17 (18.1)	7 (8.2)	24 (13.4)	0	24 (12.4)
Progression of cGVHD	20 (21.3)	29 (34.1)	49 (27.4)	4 (28.6)	53 (27.5)
Progression of underlying disease	7 (7.4)	0	7 (3.9)	3 (21.4)	10 (5.2)
Study terminated by sponsor	6 (6.4)	12 (14.1)	18 (10.1)	0	18 (9.3)
Withdrawal by subject	11 (11.7)	9 (10.6)	20 (11.2)	3 (21.4)	23 (11.9)
Other	9 (9.6)	7 (8.2)	16 (8.9)	1 (7.1)	17 (8.8)
Study ongoing	7 (7.4)	2 (2.4)	9 (5.0)	0	9 (4.7)
Discontinued from study	87 (92.6)	83 (97.6)	170 (95.0)	14 (100.0)	184 (95.3)
Primary reason for discontinuation from study					
Adverse event	1 (1.1)	0	1 (0.6)	0	1 (0.5)
Complete follow up	4 (4.3)	5 (5.9)	9 (5.0)	4 (28.6)	13 (6.7)
Death	19 (20.2)	16 (18.8)	35 (19.6)	7 (50.0)	42 (21.8)
Lost to follow-up	4 (4.3)	2 (2.4)	6 (3.4)	0	6 (3.1)
Progression of disease under study (cGVHD)	3 (3.2)	1 (1.2)	4 (2.2)	0	4 (2.1)
Site terminated by sponsor	1 (1.1)	3 (3.5)	4 (2.2)	0	4 (2.1)
Study terminated by sponsor	29 (30.9)	38 (44.7)	67 (37.4)	0	67 (34.7)
Withdrawal by subject	6 (6.4)	6 (7.1)	12 (6.7)	1 (7.1)	13 (6.7)

Table 44: Participant disposition, mITT population and Phase 2 multiple lines analysis group - continued

	Belumosudil				
Category, n (%)	200 mg QD N = 94	200 mg BID N = 85	Combined 200 mg N = 179	400 mg QD N = 14	Overall N = 193
Other	19 (20.2)	11 (12.9)	30 (16.8)	2 (14.3)	32 (16.6)
Missing	1 (1.1)	1 (1.2)	2 (1.1)	0	2 (1.0)
Duration of treatment (months), n	94	85	179	14	193
Median	9.2	11.7	10.3	8.3	10.2
Min, max	0.5, 83.7	0.4, 55.3	0.4, 83.7	0.7, 49.2	0.4, 83.7
Duration of follow-up (months), n	94	85	179	14	193
Median	29.9	31.8	30.4	39.6	31.2
Min, max	0.6, 83.7	0.9, 60.7	0.6, 83.7	0.7, 52.6	0.6, 83.7

Abbreviations: BID = twice daily; cGVHD = chronic graft versus host disease; max = maximum; min = minimum; mITT = modified intent-to-treat; QD = once daily.
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Demographic and baseline characteristics

Demographic and baseline characteristics were consistent with those expected in a real-world cGVHD population and similar across treatment groups. Median age among participants in the 200 mg QD group and overall was 52.5 (12, 77) years and 54.0 (12, 77) years, respectively. Most participants in the 200 mg QD group had a baseline KPS score of 80 (46.8%) or 90 (30.9%), as did all belumosudil-treated participants (41.4% and 31.1%, respectively).

Transplantation and cGVHD history

Overall, there were no meaningful differences in either cGVHD or transplantation history across treatment groups. History of GVHD was balanced between the 200 mg QD and all treated participants. Participants were treated most often prophylactically with CNI + methotrexate (81, [42.0%] participants). Most participants had received one previous allogeneic HCT (184 [95.3%] participants). Median time from the most recent transplantation to the diagnosis of cGVHD was 7.06 (1.0, 48.3) months and 7.29 (1.0, 48.3) months, overall and in the 200 mg QD group, respectively. The median time from the diagnosis of cGVHD to enrolment was 27.43 (1.6, 162.4) months and 26.6 (1.6, 162.4) months, overall and 200 mg QD dose group, respectively.

Prior cGVHD therapy

Participants were heavily pretreated, as the median number of prior lines of systemic cGVHD therapy was 3 both in the 200 mg QD group and overall. In the 200 mg QD group and in all belumosudil-treated group, the best response to the last systemic cGVHD treatment before study enrolment was PR in 17 (17.7%) and 47 (22.5%) participants, respectively. In the 200 mg QD group and overall, 62 (78.5%) participants and 125 (72.3%) participants, respectively, were refractory to the last systemic cGVHD treatment received before enrolment into the study.

Among participants in the 200 mg QD group, the most common prior cGVHD therapy was prednisone in 94 (97.9%) participants. The other prior treatments were following tacrolimus 58 (60.4%), sirolimus 44

(45.8%), ECP 39 (41.5%), ruxolitinib 30 (31.3%), ibrutinib 27 (28.7%), MMF 22 (23.4%) and rituximab 23 (24.5%) participants.

Organ involvement

Among participants in the 200 mg QD group and in all belumosudil-treated participants, the median number of organs involved at baseline was 4. Over half of participants in each dose group had involvement of the skin, eyes, mouth, and joints and fascia. The median GSR was 7 in all dose groups. Most participants in the 200 mg QD (67 [71.3%] participants) and in all belumosudil-treated participants (136 [70.5%], participants) had severe cGVHD at screening. There were no meaningful differences in organ involvement across treatment groups.

Concomitant systemic cGVHD medication

All participants were taking a systemic cGVHD medication on C1D1 of the study. Among participants in the 200 mg QD group, the most common systemic medications were corticosteroids (prednisone 74 [78.7%] participants), followed by tacrolimus (36 [38.3%] participants), sirolimus (21 [22.3%] participants), and MMF (11 [11.7%] participants). All belumosudil-treated participants had a similar exposure to systemic medications. There were 22 (23.2%) participants and 53 (27.5%) participants, respectively, in the 200 mg QD and in all belumosudil-treated participants who were receiving ECP on C1D1.

Efficacy results of Integrated Analysis

Primary efficacy endpoint:

Overall response rate

Best overall response and ORR for the mITT - P2MLAG population are summarized. For participants in the 200 mg QD and all belumosudil-treated participants, ORR was 72.3% and 72.0%, respectively. The lower bound of the 95% CIs for the 200 mg QD and for all participants exceeded 60%.

Among participants in the 200 mg QD group, best responses of CR and PR were achieved by 6 (6.4%) participants and 62 (66.0%) participants, respectively. Overall, best responses were similar to those in the 200 mg QD group: CR and PR were achieved by 8 (4.1%) participants and 131 (67.9%) participants, respectively.

Table 45: Best overall response on treatment, mITT population, Phase 2 multiple lines analysis group

	Belumosudil				
Variable	200 mg QD N = 94	200 mg BID N = 85	Combined 200 mg N = 179	400 mg QD N = 14	Overall N = 193
ORR (CR or PR), n (%)	68 (72.3)	63 (74.1)	131 (73.2)	8 (57.1)	139 (72.0)
95% CI of ORR	(62.2, 81.1)	(63.5, 83.0)	(66.1, 79.5)	(28.9, 82.3)	(65.1, 78.2)
One-sided p-value	<0.0001	<0.0001	<0.0001	0.0315	<0.0001
Best overall response					
Complete response	6 (6.4)	2 (2.4)	8 (4.5)	0	8 (4.1)
Partial response	62 (66.0)	61 (71.8)	123 (68.7)	8 (57.1)	131 (67.9)
Lack of response					
Unchanged	18 (19.1)	12 (14.1)	30 (16.8)	2 (14.3)	32 (16.6)
Mixed	2 (2.1)	4 (4.7)	6 (3.4)	0	6 (3.1)
Progression	3 (3.2)	3 (3.5)	6 (3.4)	1 (7.1)	7 (3.6)
No response assessment	3 (3.2)	3 (3.5)	6 (3.4)	3 (21.4)	9 (4.7)
ORR (CR or PR) within 6 months of treatment, n (%)	61 (64.9)	59 (69.4)	120 (67.0)	7 (50.0)	127 (65.8)
Complete response	2 (2.1)	1 (1.2)	3 (1.7)	0	3 (1.6)
Partial response	59 (62.8)	58 (68.2)	117 (65.4)	7 (50.0)	124 (64.2)
95% CI of ORR	(54.4, 74.5)	(58.5, 79.0)	(59.6, 73.9)	(23.0, 77.0)	(58.6, 72.5)
One-sided p-value	<0.0001	<0.0001	<0.0001	0.0933	<0.0001
ORR (CR or PR) within 12 months of treatment, n (%)	64 (68.1)	63 (74.1)	127 (70.9)	8 (57.1)	135 (69.9)
Complete response	3 (3.2)	2 (2.4)	5 (2.8)	0	5 (2.6)
Partial response	61 (64.9)	61 (71.8)	122 (68.2)	8 (57.1)	130 (67.4)
95% CI of ORR	(57.7, 77.3)	(63.5, 83.0)	(63.7, 77.5)	(28.9, 82.3)	(62.9, 76.3)
One-sided p-value	<0.0001	<0.0001	<0.0001	0.0315	<0.0001

Abbreviations: BID = twice daily; CI = confidence interval; CR = complete response; mITT = modified intent-to-treat; ORR = overall response rate; PR = partial response; QD = once daily.
Notes: Response assessments performed on or after initiation of new systemic therapy for cGVHD are excluded from the analysis.
Program Source: P:\01_OngoingProjects\G_100_HEM_KD025_CGVHD_IDB_SA\EMA\Programs\TFL\Original\ISE\t_26.sas

Source: Summary of Clinical Efficacy

Secondary efficacy endpoints:

Duration of response

The primary and the secondary methods of analysis are similar, but the primary method counts a CR to PR change as a loss of response while the secondary method does not. As there were a limited number of CRs, the differences between the 2 methods of analysis are minimal. A Kaplan-Meier plot of primary DOR in the responder population is presented in **Figure 14**.

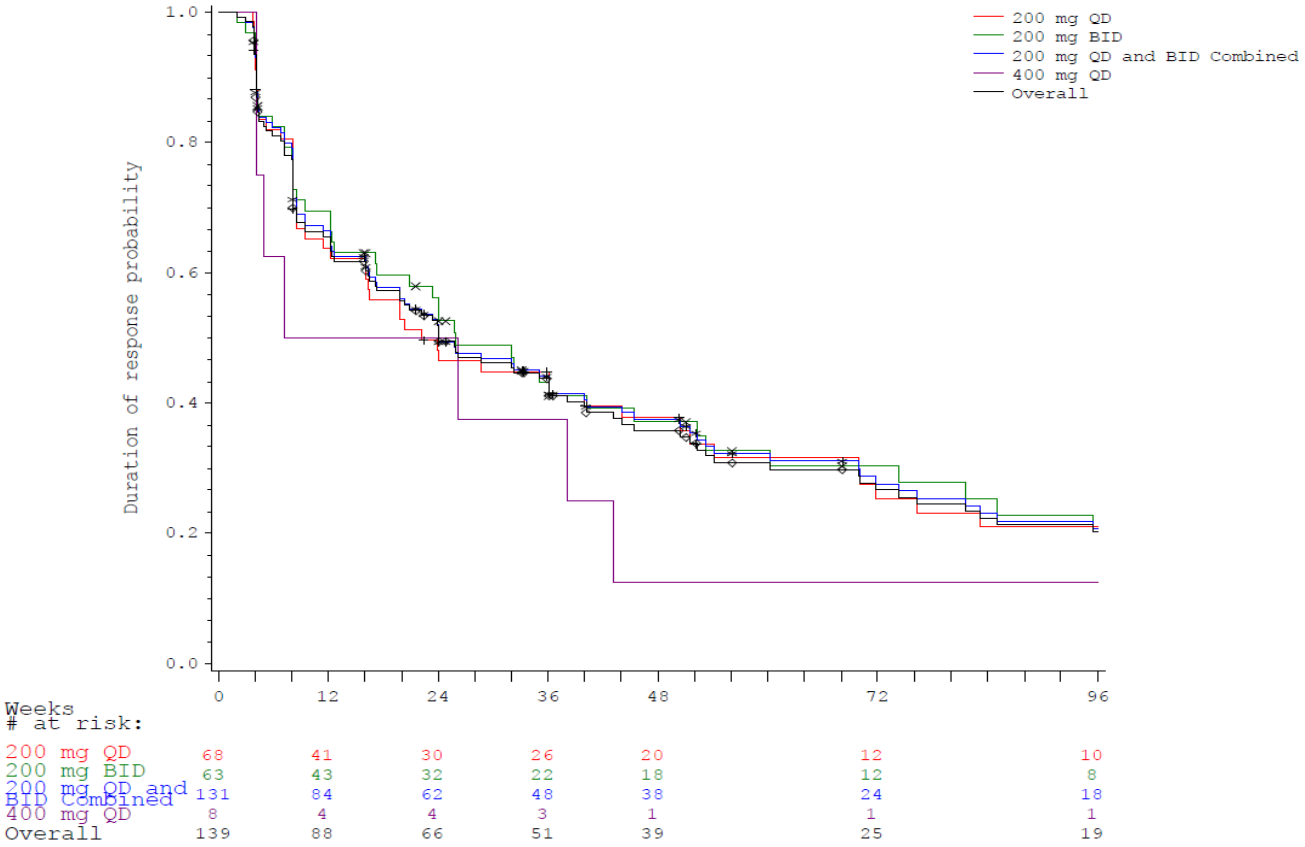

Figure 14: Kaplan-Meier plot of primary duration of response - responder population, Phase 2 multiple lines analysis group

Source: Summary of Clinical Efficacy

In this follow-up analysis, median primary DOR among participants in the 200 mg QD was 22.1 (12.14, 44.14) weeks. At the time of the data cutoff, 41 (60.3%) participants in the 200 mg QD group had a sustained response to treatment at ≥ 12 weeks; 30 (44.1%) at ≥24 weeks; and 20 (29.4%) participants at ≥ 48 weeks.

A Kaplan-Meier plot of tertiary DOR is graphically presented in **Figure 15**. Median tertiary DOR was 111.1 weeks (95% CI: 76.86, not reported [NR]) in the 200 mg QD group.

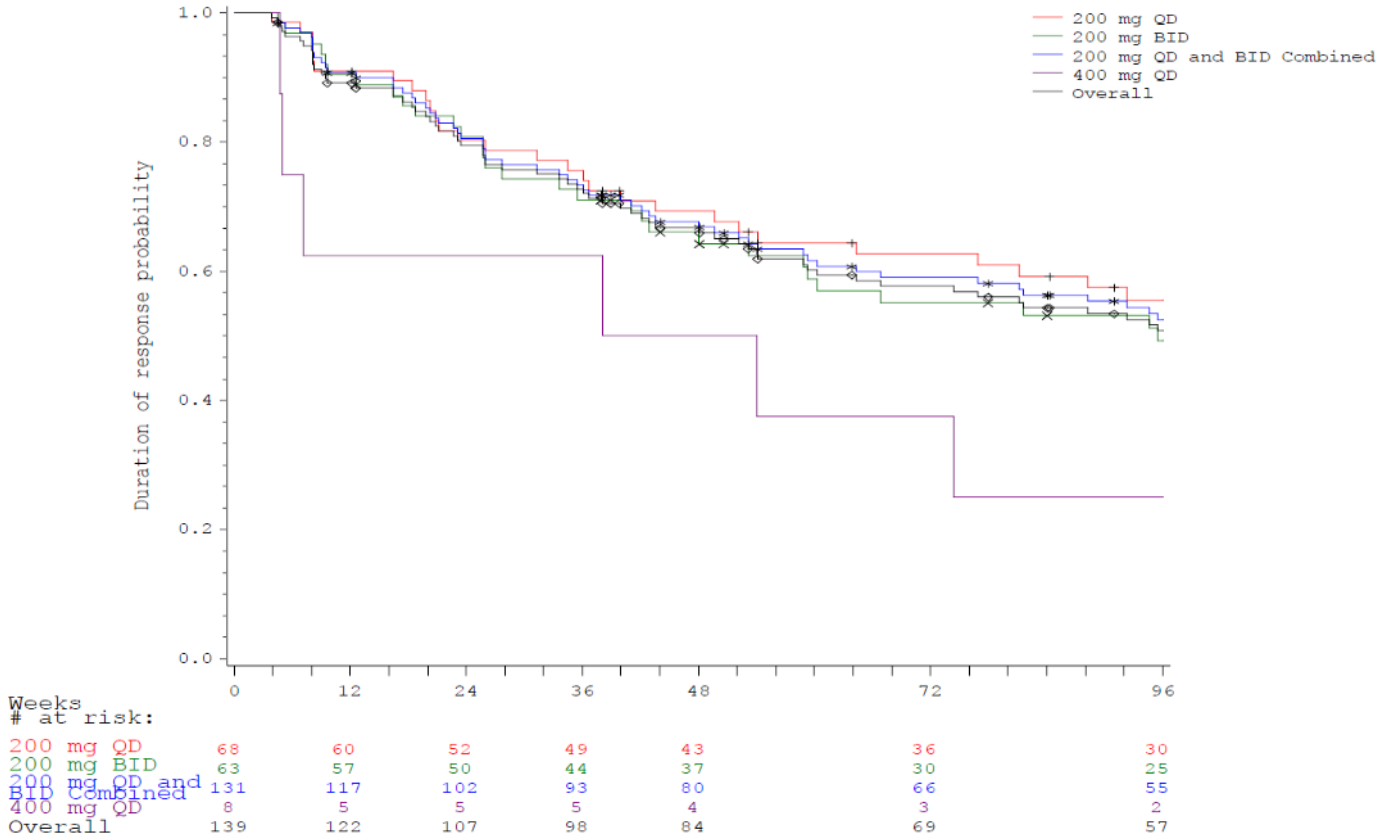

Figure 15: Kaplan-Meier plot of tertiary duration of response - Responder population, Phase 2 multiple lines analysis group

Source: Summary of Clinical Efficacy

Time to response

The median TTR for the 200 mg QD group in the responder population-P2MLAG was 7.71 weeks (3.7, 80.1).

Response by organ system

Complete responses were seen in all organs and were consistent with that reported in Study KD025-213. Upper (11/16 subjects, 68.8%), and lower (5/8 subjects, 62.5%) GI tract was the organ with the higher responses observed followed by joints/fascia (48/70 subjects, 68.6%), mouth (29/53, 54.7%) and oesophagus (14/25, 56%).

Lee Symptom Scale Score

As assessed by LSS, 53 (56.4%) participants in the 200 mg QD group and 110 (57.0%) participants overall experienced a clinically meaningful improvement in DO7-PtR at least once. There were 40 (42.6%) participants in the 200 mg QD group and 77 (39.9%) participants in the all belumosudil-treated group who experienced a clinically meaningful improvement on at least 2 consecutive assessments up to and including Cycle 7 Day 1.

In the 200 mg QD group the median duration of a 7-point reduction (DO7-PtR) was 8.4 weeks (0, 22 weeks), and 29 (30.9%) participants had a DO7-PtR ≥8 weeks.

As assessed by LSS, 45 (66.2%) responders in the 200 mg QD group experienced clinically meaningful improvement at least once, up to and including C7D1. There were 34 (50.0%) responders in the 200 mg QD group who experienced a clinically meaningful improvement on at least 2 consecutive assessments. The median DO7-PtR was 8.4 (0, 22) weeks in responders in the 200 mg QD group. Twenty-five (36.8%) responders in the 200 mg QD group had a DO7-PtR ≥8 weeks. Of the non-responders in the 200 mg QD group, 8 (30.8%) subjects experienced meaningful improvement at least once and six (23.1%) subjects on at least 2 consecutive assessments. Four (15.4%) non-responders had a DO7-PtR ≥8 weeks.

Failure free survival

The median FFS among participants in the 200 mg QD was 16.3 (10.15, 24.18) months. Kaplan-Meier estimates of FFS at 6, 12, 18, and 24 months in the 200 mg QD group was 75%, 56%, 48%, and 42%, respectively.

Time to next treatment

The Kaplan-Meier estimates of median TTNT among participants in the 200 mg QD group was 22.1 (13.73, NA) months.

Overall survival

For participants in the 200 mg QD group median OS was not reached (NR) at the time of the data cutoff.

Corticosteroid dose

Median baseline corticosteroid dose in the mITT population-P2MLAG among participants in the 200 mg QD group and all belumosudil-treated groups was 0.187 and 0.195 mg/kg/day, respectively. In the 200 mg QD group and overall, 63 (67.0%) and 133 (68.9%) participants, respectively, were able to reduce their corticosteroid dose during the study. Among participants in the 200 mg QD and overall, median percentage change from baseline to the greatest reduction in dose was in both -50.0% (-100, 0.00). Twenty-six (27.7%) and 51 (26.4%) participants, in the 200 mg QD and overall, respectively, were able to discontinue the use of corticosteroids during treatment with belumosudil.

In the responder population, 50 (73.5%) participants in the 200 mg QD dose group, and 108 (77.7%) participants overall were able to reduce the corticosteroid dose during the study, whereas ≤50% of non-responders achieved this goal. In total, 46 (33.1%) of responders and 5 (9.3%) of non-responders were able to discontinue use of corticosteroids.

Subgroup analysis of ORR and DOR

The best ORR and primary DOR, in studies tested, were generally similar across demographic subgroups, disease profile, previous LOT received, although in some cases sample size was small.

Responses were consistently demonstrated across key subgroups including in participants who had ≥2 prior LOT, in participants with ≥4 organs involved at baseline, in participants with severe cGVHD, and in participants who had cGVHD refractory to the prior line of treatment (including ibrutinib and ruxolitinib).

Forest Plot for subgroup analysis is presented in **Figure 16**.

Primary DOR, in the 200 mg QD dose group, with the prior ruxolitinib was 19.9 (8.1, 83.1) weeks and 23.9 (12.1, 44.1) weeks in those without prior ruxolitinib. In terms of cGVHD severity, median DOR in the 200 mg QD dose group was 36.1 (11.4, 69.9) weeks versus 18.0 (8.1, 28.7) weeks in the severe versus no severe

subgroups. For number of organs involved (<4 versus ≥4) median primary DOR was 20.3 (8.1, 40.0) weeks and 28.7 (12.1, 83.1), respectively.

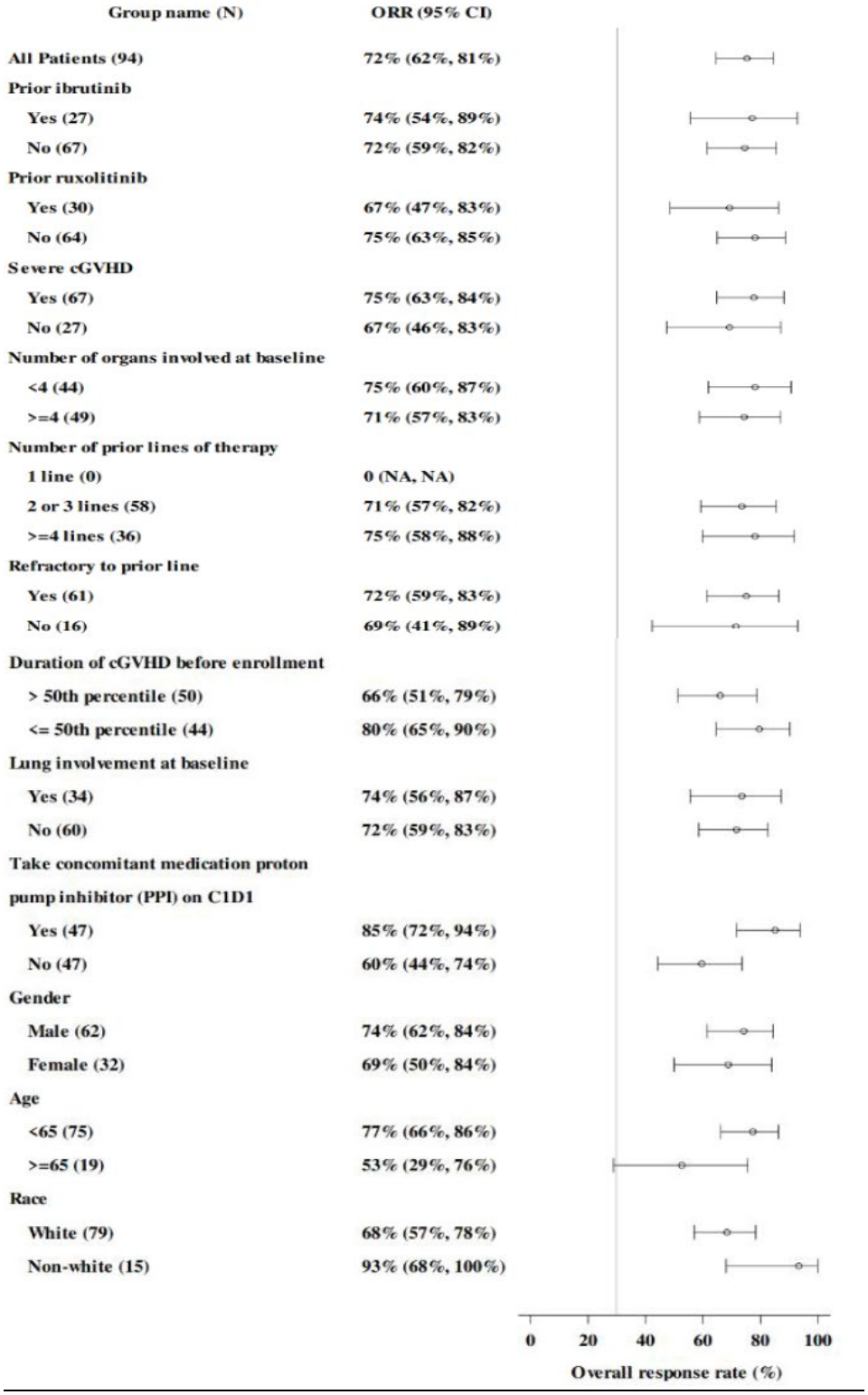

Figure 16: Forest plot of overall response rate by subgroup - 200 mg QD dose, mITT population, Phase 2 multiple lines analysis group

Source: Summary of Clinical Efficacy

2.6.5.7. Supportive studies

ME3208-2

ME3208-2 is a Phase 3 multicenter, open-label, single-arm study. The primary objective was to verify the efficacy of belumosudil in patients in Japan with steroid-dependent or -resistant cGVHD. The study is ongoing and the enrolment was completed with 21 participants enrolled. The median follow-up time is 13.80 (4.3, 19.5) months. The eligibility criteria of Study ME3208-2 were similar to those of Studies KD025-213 and KD025-208. The notable difference was the number of prior lines of treatment for cGVHD. Participants who had received 1 prior line of therapy were allowed since there had not been any approved second line therapy in Japan at the time of study initiation.

Participants received belumosudil 200 mg QD only. Treatment could be continued until 6 months after the date of belumosudil approval in Japan, at maximum.

The primary efficacy endpoint of Study ME3208-2 was the best ORR at 24 weeks after enrolment of the last study participant. The proportion of participants who achieved CR or PR in the overall response at least once at any time point of assessment during the study drug treatment period is defined as the best ORR. The secondary endpoints of the Study ME3208-2 were similar to those of the Study KD025-213.

Demographic and Other Baseline Characteristics

Twenty-five patients were screened of whom 4 subjects were screen failures. Hence, 21 subjects participated to the study.

The median age was 50.0 years. One adolescent subject, aged 13 years, was included in the study. Eighteen subjects (85.7%) were steroid-dependent, 1 subject (4.8%) was steroid-resistant, and 2 subjects (9.5%) were both steroid-dependent and resistant. Chronic GVHD was moderate in 12 subjects (57.1%) and severe in 9 subjects (42.9%). The median number of prior treatments was 2.0; two subjects (9.5%) had one prior LOT. Three subjects (14.3%) had a history of the use of ibrutinib. No subjects had used ruxolitinib priorly. The median dose of corticosteroids at baseline was 0.220 mg/kg/day. Five subjects (23.8%) had > 4 involved organs. Common organ involvements were mouth (18 subjects), eyes (15 subjects) and skin (11 subjects).

Efficacy results - Adults

Primary efficacy endpoint: Objective response rate

The best ORR (95% CI) at 24 weeks (by 24 weeks CR or PR at least once at any evaluation time) after enrolment of the last participant was 85.7% (63.66, 96.95). All responses were PR.

Secondary efficacy analysis

The median primary/secondary DOR was 68.10 (22.10, NA) weeks).

The median TTR was 4.10 (3.9, 8.10) weeks in the 200 mg QD group.

The median FFS was NA, and Kaplan-Meier estimates were 0.95 (0.71, 0.99) and 0.72 (0.37, 0.89) at 12 and 18 months, respectively.

Efficacy results – Adolescents

One 13-year-old adolescent subject responded (PR) 2 weeks after the start of treatment, and the response was maintained up to 28 weeks after the start of treatment, but subsequently the condition was assessed as progressive disease (PD) in the lower GI tract from 32 weeks after the start of treatment.

BN101-201

BN101-201 was a Phase 2, multicenter, single-arm, open-label study. The primary objective of the study was to evaluate the efficacy and safety of belumosudil in patients in China with cGVHD who had received at least 1 line of systemic therapy. The study enrolled 30 participants and was completed with a study end date of 10 December 2022. The median follow-up time was 12.94 (1.7, 18.4) months.

Study design

Participants received belumosudil 200 mg QD in 28-day cycles until cGVHD progression, intolerable toxicity, the start of new therapy for cGVHD, hematologic malignancy recurrence, the participant's loss to follow-up, withdrawal of informed consent or death.

Concomitant use of other cGVHD therapies (eg, corticosteroids, calcineurin inhibitor, mycophenolate mofetil, sirolimus, and ECP) taken/performed prior to screening with unchanged dose/regimen were allowed during the study. However, treatment failure would be determined if a new systemic therapy for cGVHD was initiated.

The eligibility criteria of Study BN101-201 were similar to those of Studies KD025-213 and KD025-208. The notable difference was the number of prior lines of treatment for cGVHD. Participants who had received 1 prior line of therapy were allowed since there had not been any approved therapy for second line in China at the time of study initiation.

Efficacy evaluation measures

The primary efficacy endpoint was the overall response rate (ORR, including complete response [CR] and partial response [PR]), assessed according to the NIH Consensus Criteria.

The secondary efficacy endpoints included median duration of response (DOR), time to response (TTR), change in Lee Symptom Scale score, system organ response rate, change in corticosteroid dose, change in calcineurin inhibitor dose, failure-free survival (FFS), time to new systemic therapy (TTNT), overall survival (OS), change in cGVHD severity assessed based on physician-reported cGVHD activity, and change in symptom activity based on patient-reported cGVHD activity.

DOR was presented as first/second/third definition of DOR, which is aligned with the definitions of primary/secondary/tertiary DOR in other studies.

Baseline characteristics

The mean age of the 30 subjects was 30.6 (18-50) years. The median number of involved organs was 4.0 (1-6) in all subjects, 16 (53.3%) subjects had ≥ 4 involved organs, and the most common involved organs were mouth and eye (22 subjects, 73.3% each). There were 20 (66.7%) subjects with severe cGVHD. The median number of prior cGVHD treatment lines was 3, and 13 (43.3%) subjects had received ≥ 4 lines of treatment. All subjects had previously received corticosteroid therapy. The best response to the last line of treatment before the study was LR in 23 (76.7%) subjects. Prior to enrolment, 16 (53.3%) subjects had received ruxolitinib and 4 (13.3%) subjects ibrutinib.

Efficacy results

Primary efficacy analysis: ORR

The ORR (95% CI) of the 30 participants included in the mITT set was 73.3% (54.1%-87.7%), and the best response achieved among all these participants was PR. The ORR (95% CI) over the 6-month treatment period was 66.7% (47.2%-82.7%).

Among 30 participants, 90% (27/30) participants had previously received ≥2 lines of systemic therapy for cGVHD. The ORR result of these 27 participants was 70.4% (49.8, 86.2) consistent with that in the mITT population.

Secondary efficacy analysis

In the responder population, the median DOR of the first and second definitions (95% CI) were both 20.2 (9.71-NA) weeks.The median DOR of the third definition was not reached.

The median TTR was 4.29 (3.9, 48.1) weeks, with 17 (77.3%) participants achieving a response by Week 10, 18 (81.8%) participants achieving a response by Week 12, and all 22 participants achieving a response at 24 weeks.

In the overall population, 15 (50.0%) participants reported a clinically significant improvement in the LSS score [a reduction of ≥ 7 points from baseline (7-PtR)] and 10 (33.3%) participants reported a clinically significant improvement in the LSS score at two consecutive visits, with a median 7-PtR duration of 16.0 (4, 69) weeks. More participants reported a clinically significant improvement in the LSS score in the responder population (12 [54.5%] participants) than in the non-responder population (3 participants, 37.5%).

ROCKreal Study (AA_00117)

AA_00117 is a retrospective non-interventional study to evaluate the efficacy of belumosudil compared with BAT for treating patients with cGVHD who have failed 2–5 prior lines of therapy (LOTs). The study was designed to emulate a phase 3 randomized controlled trial (RCT). The study population was drawn from patients treated for cGVHD in real-world clinical settings throughout the United States (US) and Europe (EU) between March 1, 2015 and March 27, 2024.

Key patient selection criteria include:

- cGVHD with age ≥12 years at time of cGVHD diagnosis
- Received 2–5 prior lines of therapy (LOT) (i.e. initiated 3rd
    - to 6th LOT)
- No prior exposure to belumosudil
- No prior relapse of underlying malignancy from the date of allogenic hematopoietic stem cell transplant (alloHCT)

Data from patient medical records were entered in an electronic data capture (EDC) system by the sites between August 20, 2023 and March 27, 2024 and extracted for analysis on April 4, 2024. Unlike the target trial in which patients are randomized to treatment with study drug belumosudil or BAT and followed-up for a specified time, in the AA_00117 study treatment decisions were made by clinicians. In addition, real-world patients were observed longitudinally, and some initiated multiple LOTs over time. Each LOT, as defined by the LOT algorithm, for which the patient met eligibility requirements at its initiation was included in the dataset, and is hereafter referred to as an LOT-episode. Thus, some patients contributed multiple BAT LOT

episodes, and some patients who received belumosudil also contributed one or more earlier BAT LOT-episodes.

The summary measure for the primary analysis is the causal (adjusted) difference in the proportion of successful outcomes at 6 months (OR = 1) when patients are treated with belumosudil versus treated with BAT. The proportion of successes, referred to as the overall response rate (ORR), is the average response over all LOT-episodes.

Targeted maximum likelihood estimation (TMLE), an efficient double robust estimator, was used to estimate the causal effect. TMLE utilized machine learning-based estimates of the outcome regression, the propensity score, and the outcome missingness mechanism to estimate the RD.

Primary endpoint

OR was observed at 6-months for 324 LOT-episodes (90.5%) and was missing for remaining 34 (9.5%). Among the 324 LOT-episodes where OR was observed, success or failure was determined via the NIH and/or Physician Response in 150 (43.2%), via treatment switch in 101 (31.2%), and via steroid dose taper in 51 (15.7%). Causal effect estimation indicated that belumosudil has a statistically significant effect on improving ORR as compared with BAT. Treating patients with Belumosudil and BAT results in a 6-month ORR of 38.7% and 26.8%, respectively. The ratio of ORR for belumosudil versus BAT was 1.442 indicating a 44.2% improvement. The rate difference (belumosudil minus BAT) was 11.9%. Confidence intervals for both these measures excluded the null, and p-values were well below the 0.05 threshold.

Study EFC17757

Study EFC17757 was the originally planned confirmatory study, which is a randomized, double-blind, multicentre phase 3 study in newly diagnosed patients with moderate to severe cGVHD to evaluate the efficacy and safety of belumosudil in combination with corticosteroids versus placebo in combination with corticosteroids in participants at least 12 years of age after allogeneic HCT. A total of approximately 260 participants were planned to be randomized in a 1:1 ratio. The primary endpoint is EFS and secondary endpoint ORR.

In total, 211 out of planned 260 patients had been enrolled in the study. On 26 June 2025, the Applicant decided to terminate the study due to the DMC's recommendation based on the results of pre-planned futility interim analysis from first 70 enrolled patients and on additional analysis of efficacy data from more than 100 participants.

No difference in EFS between the treatment arms could be shown. Median EFS in ITT population was 5 months (95% CI 2.9, 6.6) in the belumosudil + prednisone arm vs. 5 months (95% CI 3.8, 7.6) in the placebo + prednisone arm, HR 1.1 (95% CI 0.71, 1.72). ORR by 24 weeks (CR/PR) in belumosudil + prednisone arm and in placebo + prednisone arm was 44 (71%) and 54 (88.5%), respectively. There was no difference in CR rates between the treatment arms. Among those reaching response, median time to response was comparable (4.3 weeks vs. 4.4 weeks), corresponding to the timing of first response assessment. Duration of response was comparable.

No new safety concerns were identified.

2.6.6. Discussion on clinical efficacy

Belumosudil is a selective Rho-associated, coiled-coil protein kinase-2 (ROCK2) inhibitor which acts on both inflammation and fibrosis. It rebalances T-cell mediated immune response by downregulating IL-17 and IL-21 secretion thus leading to downregulation of proinflammatory Th17 cells and by increasing T regulatory cells (Treg). ROCK regulates multiple profibrotic processes. ROCK2 inhibitor belumosudil disrupts profibrotic signals and inhibits collagen expression in human lung fibroblasts.

Chronic GVHD is a major complication of allogeneic hematopoietic cell transplantation (HCT) involving multiple organs. The pathology of cGVHD is marked by both inflammatory and fibrotic changes in multiple organs. It involves both T cells and B cells and is characterized by overproduction of proinflammatory cytokines IL-21 and IL-17 and over-activation of pro-inflammatory T follicular helper cells (Tfh) and B cells, leading to overproduction of antibodies. Patients with cGVHD suffer from a multifaceted burden, including physical, functional, and psychosocial deficits, which negatively influence quality of life and increase non-relapse mortality. Presence of fibrotic skin, joint/fascia, and/or lung involvement have the greatest effect on function and quality of life. Patients affected by cGVHD require prolonged immunosuppressive treatment for an average of 2 to 3 years from the initial diagnosis, with 15% of those surviving for at least 7 years still requiring immunosuppressive treatment. Chronic GVHD not responding to therapy ultimately leads to death. Chronic GVHD is a serious condition with an unmet medical need for more effective and safer treatment options.

Dose selection

The Applicant has selected three target doses based on results from previous studies, mainly from healthy volunteers (not from patients with cGVHD) using single and multiple doses from 20 mg to 1000 mg belumosudil free base in capsule or film-coated tablet presentations. It was not justified how the doses 200 mg QD, 200 mg BID and 400 mg QD used in Study KD025-208 (called as dose escalation study in cGVHD patients) were concluded from the HV studies. Dose finding has not been performed targeting dose limiting toxicities and as such no traditional dose escalation study has been performed.

Based on the safety and efficacy results in the Study KD025-208, the Applicant decided to continue further investigations using dosing regimens of 200 mg QD and/or 200 mg BID. However, no clear differences in efficacy were observed comparing these doses in KD025-213, and dose selection was therefore driven by differences observed in safety profile of the two dose levels.

Design and conduct of clinical studies

The pivotal study supporting the targeted indication is based on the results of Phase 2 non-controlled, randomized, open-label study KD025-213 (Rockstar) conducted in the US. In addition, Integrated Analysis of the studies KD025-213, KD025-208 and KD025-217 (long-term follow-up of Studies KD025-213 and KD025-208) provided pooled data for efficacy assessment.

The study population represents a "last line" setting with high unmet medical need. Single arm study design is therefore considered to be acceptable in principle. However, interpretation of the results is complicated due to heterogeneity of the patient population, various previous and concomitant treatments, and the definition of the primary efficacy endpoint. These concerns were discussed in scientific advice (EMEA/H/SA/4227/1/2019/SME/III and EMEA/H/SA/4227/1/FU/1/2020/PA/SME/II).

Study KD025-213

Study KD025-213 included patients aged 12 years and older who suffered from cGVHD after allogeneic haematopoietic stem cell transplantation and who had received at least 2 but not more than 5 prior lines of treatment for cGVHD. Despite the given treatments, cGVHD was active requiring systemic therapy. Before enrolment corticosteroid dose had to be stable for at least two weeks.

The applied inclusion and exclusion criteria are appropriate. The inclusion criteria of the Karnofsky performance score > 60 reflects the performance score of the cGVHD population in clinical practise. The patients with lower performance score most likely suffer from advanced cGVHD with progressive fibrotic process and these patients would unlikely benefit from any treatment. Hence, the patient population was adequately selected. Although there were no specific requirements, except corticosteroids, for prior treatments, patients with 2 to 5 prior lines of systemic therapy are expected to have exhausted available treatment options. Key safety inclusion criteria were liver enzyme, renal function and ANC threshold values at baseline.

The primary objective of the study was to evaluate the efficacy and safety of belumosudil at dose of 200 mg once daily (QD) (Arm A) and 200 mg twice daily (BID) (Arm B) based on the results of Study KD025-208. The population in Arm A is in line with the proposed indication. Due to open-label nature of the study, no blinding was possible. Belumosudil was started as $\geq$ 3rd line treatment for patients with active cGVHD despite treatment with corticosteroids.

Various concomitant treatments were allowed. The study subjects may have been receiving SOC cGVHD therapies, such as CNIs (tacrolimus, cyclosporine), sirolimus, MMF, methotrexate, rituximab, or ECP if they had been on a stable dose for at least 2 weeks prior to screening. Concomitant ibrutinib treatment was prohibited, and in the protocol amendment 4, also ruxolitinib was added to the list of prohibited medications in order to limit any confounding effects that cotreatment with belumosudil might have on study analysis. Prior ruxolitinib treatment is not expected to play a role in observed responses. Wash-out period of 5 half-lives was required, and the minimum time period between the treatments was 10 days in the pivotal study. Initiation of a new systemic cGVHD treatment was defined as a treatment failure. Two episodes of transient increase in corticosteroid dosing (< 1 mg/kg/day prednisone equivalent) for 6 weeks each within first 6 months of belumosudil therapy were permitted for cGVHD flares. The permitted corticosteroid dose is significant, but an increased corticosteroid dose for a flare during the first 6 months of study treatment was reported in only of 8 of the responders, and 6 of them had a reported response before the flare. ECP was reported as a concomitant treatment in 44 participants. Responses with ECP appear with latency, and the treatments of cGVHD in stable phase may be continued for three months, before treatment failure can be stated. The clinical need for initiating combination therapy with belumosudil is not questioned, but isolation of the treatment effect with belumosudil is challenging in a SAT setting. The Applicant has added information concerning allowed concomitant cGVHD therapies in the SmPC section 5.1.

In the study, belumosudil was allowed to be tapered after a sustained response for 6 months and cessation of all other immunosuppressants for at least 3 months, at the Investigator's discretion. No recommendation to stop the treatment in patients who have achieved a sustained response, or tapering instructions, has been provided in the SmPC. However, this is considered acceptable, as only three participants in the belumosudil 200 mg QD arm had belumosudil dose tapered, and hence, the small number of participants does not allow to draw any conclusions regarding the benefit of tapering belumosudil treatment in participants that met protocol-specified belumosudil taper criteria.

Endpoints

Assessment of the primary efficacy endpoint, ORR (CR, PR, LR), is based on the guideline "the 2014 NIH Consensus Development Project on Clinical Trials in cGVHD" which is an accepted guideline for the response evaluation in cGVHD. ORR based on BOR in the current study is used as a direct measure of clinical benefit, i.e., symptomatic improvement of a chronic condition, rather than as a surrogate of a long-term benefit. It should be noted that the used ORR definition is not in line with the general requirements for an endpoint used in a single arm trial, as individual outcomes cannot be without a doubt considered to represent a clinically relevant drug effect. Assessment of response is, at least to some extent, subjective and hence, includes uncertainties regarding efficacy assessments in the context of single-arm trial. Importantly, response was defined as any improvement at any time during the treatment. Thus, any improvement in a single organ score in a single timepoint may categorise the patient as a responder despite persistent symptoms in other organs, and therefore random variability in how organs are scored on the ordinal scale could generate response allocation without true clinical improvement. Therefore, although the selected endpoint is acceptable considering the condition and target population, interpretation of the results in single arm setting is challenging and requires careful consideration on the magnitude of the benefit, clinical relevance of the observed responses, and impact of patient selection and concomitant treatments.

Although there are regulatory precedents where ORR has been accepted as the primary endpoint for GvHD, there are differences in timepoints and statistical methods utilized in different studies. Most importantly, the endpoint has been used as the basis of regulatory approval only in RCT setting and not in a SAT. ORR at 24 weeks has been used in the RCT REACH3 (ruxolitinib vs. BAT), which was the basis of the marketing authorization approval of ruxolitinib in EU for the treatment of cGVHD (Jakavi® EPAR).

The Applicant has not included gynaecological cGVHD among the assessed organ systems. This is acceptable, because in the assessment guidance of the 2014 National Institutes of Health (NIH) Consensus Development Project on Clinical Trials in cGVHD, it is noted that measures of genital response are considered exploratory since they may be under-reported or caused by conditions other than cGVHD, and proper evaluation requires an examination by a specialist.

The secondary endpoints are considered appropriate and relevant.

The primary DoR was defined as the time from first documentation of response to the time of first documentation of deterioration from best response (eg, CR to PR or PR to LR)] or to starting new systemic cGvHD therapies or death while having the best response. As per CHMP's request, primary and secondary DoR were also summarised considering treatment discontinuation due to non-administrative reasons (reasons other than site/study terminated by sponsor) also as an end of response. Since this sensitivity analysis definition led to only slightly shorter median DoR as compared with the predefined DoR, this issue will not be discussed further. The data were summarised using Kaplan-Meier estimate with right-censoring applied when follow-up of responses ended without observing an event considered as end of response.

As to the third DoR definition, the time from first documentation of response to the time of initiation of new systemic cGVHD therapy or death (before initiation of new systemic cGVHD therapy), it is noted that these were to be assessed 28 days after discontinuing treatment and as part of long-term follow-up. Provided that new cGvHD therapies were successfully captured as part of those post-treatment follow-ups for those withdrawn from the study, only administrative censoring is expected and, in fact, observed.

The description of time-to-response is restricted to those with an observed response. Hence there are no censored observations, and the descriptive analysis is uncontroversial.

Regarding analysis populations, generally analyses using the ITT population are requested. Although in this case the difference between ITT and mITT populations is minor, the Applicant was requested to present the

efficacy results based on the ITT population. The Applicant has provided efficacy results based on ITT population. Since certain endpoints, such as DoR, could only be quantified for responders, it is a pragmatic to present some of the results for Responder Population and Non-responder Population separately.

Efficacy data and additional analyses

ITT population (data lock point 01 Sep 2022) included 156 adult patients: Arm A 78 patients and Arm B 78 patients. One patient in Arm A and 3 patients in Arm B were randomized but never dosed. The Applicant has not provided reasons for not dosing these 4 patients, but this issue was not further pursued by the CHMP. In addition, the study included three adolescents: two in Arm A and one in Arm B. As there is no reason to deviate from the ITT principle, the Applicant provided upon request efficacy results based on the ITT population according to the data lock point of the Study KD025-213 CSR Addendum, 01 Sep 2022. Additionally, the Applicant provided a detailed list of concomitant systemic and local cGVHD medications.

As off the cut-off date 01 Sep 2022, the median follow-up duration was 28 months in Arm A and 31 months in Arm B. The most common reason for treatment discontinuation in both arms was progression of cGVHD (21% in the Arm A and 25% in the Arm B). The Applicant was asked to provide the reason(s) behind discontinuations of treatment due to withdrawal by patients and due to physician's decision in Study KD025-213. However, this additional information was not collected. This is considered acceptable, as this is not expected to have an impact on overall conclusions. All patients discontinued from the study. The most common reason for study discontinuation was termination of the study by the Sponsor.

The baseline patient characteristics were in line with characteristics of cGVHD patients treated with third or later line treatments in general cGVHD population. In Arm A, majority of the subjects (97%) suffered from moderate or severe cGVHD and the median number of prior treatment lines was three. Skin, eyes and joints/fascia were the most affected organs. The number of patients with lung involvement (27/78, 35%) is higher than expected. However, in clinical practise, lung involvement is an underdiagnosed problem if routinely performed pulmonary function tests are not scheduled appropriately.

In Arm A, 99% of the subjects used systemic corticosteroids. Other concomitant cGVHD treatments are widely used in corticosteroid dependent or resistant cGVHD. A significant proportion of the subjects (19 subjects, 24.7%) was treated with ECP, that reflects the severity of cGVHD in the study population. In addition, 39% of the subjects were on tacrolimus, 27% received systemic sirolimus and 14% MMF.

Primary endpoint

The KD025-213study included 156 randomized patients, 78 in Arm A and 78 in Arm B. Both arms met the objective of excluding a 30% ORR as reported by the investigator at the primary analyses, and the study was concluded to be positive. For assessment of efficacy, the analysis was limited to the patients in the cohort receiving belumosudil 200 mg daily (Arm A). Overall response rate of 57 out of 78 subjects (73%) in cohort A is clinically relevant. Four (5.1%) subjects achieved CR and 53 (67.9%) subjects PR.

From clinical perspective, the presented data has several strengths. The enrolled population is considered to adequately reflect a "last line" patient population that has exhausted available treatment options. Majority of the patients (81%) were documented to be refractory to the last systemic cGVHD treatment prior to enrolment in the study, and the responses to prior treatments were poor: for 64% of the subjects the best response to previous systemic therapy was SD (29 out of 78 patients, 37%) or PD (21 out of 78 patients, 27%). Thus, it is not considered plausible that the observed responses would be solely due to concomitant treatments or spontaneous fluctuation in clinical condition. Responses were observed in objectively measured outcomes such as liver function and pulmonary function, and in difficult to treat disease manifestations such

as fascia/joint involvement and lung involvement. Thus, it is considered that the responses observed could only occur in negligible extent (in number of subjects or size of the effect) without effective treatment.

One of the key issues is the isolation of treatment effect in relation to various concomitant treatments received. It is agreed that in daily practice

e, additional treatment is started on the top of the existing concomitant treatments, if treatment response is inadequate and clinical condition requires additional therapy. It has to be noted, that in a clinical condition such as steroid-refractory cGVHD, it is not possible to postpone the start of a new systemic treatment for several months due to the risk of immune activation not responding to any treatment anymore (circulus vitiosus).

The Applicant states that the median time to response for common cGVHD medications is around 4 weeks which is agreed. The KD025-213 Study protocol required the minimum duration of two weeks of the concomitant medications with stable doses before enrolment. Therefore, responses to concomitant treatments cannot be excluded based on study design. However, data is sufficient to conclude that recently started concomitant medications are not likely a key driver for the ORR. Over 80% of participants had started their concomitant treatment 30 days or more prior to C1D1 and more than 60% of participants had started treatment more than 90 days prior to C1D1. An analysis of ORR and ORR at 6 months according to the duration of the concomitant medication prior C1D1 (14-30 days, 31-60 days, 61-90 days, > 90 days), shows comparably high ORR and ORR at 6 months. Hence, the treatment effect seems not to be associated with the duration of prior concomitant medications.

The provided data also show that ORR and ORR at 6 months was not associated with the type of concomitant medications (steroid only vs. steroid + CNI vs. steroid + mTOR/MMF vs. ECP vs. others).

Concomitant sirolimus and tacrolimus treatments are of interest due to identified PK interaction. The available data is considered sufficient to conclude that this interaction is not a key driver for ORR. Among participants without tacrolimus/sirolimus treatment at baseline (n = 68), the ORR and ORR at 6 months are similar and comparable to overall participants enrolled in the KD025-213 study. It is not plausible that belumosudil response rate in sirolimus/tacrolimus treated population would have been lower than in overall population, but the observed comparable ORR would have been driven by increased sirolimus/tacrolimus blood concentrations. Moreover, the ORR and ORR at 6 months are higher in participants who had tacrolimus/sirolimus dose reduction or discontinuation as compared to those of participants who had not. This does not support the assumption that responses would be due to increased sirolimus/tacrolimus concentrations. This may reflect tapering after achieved response, but because the reasons for sirolimus and tacrolimus dose reductions were not collected, it could also be speculated that reasons for dose reductions were due to high blood concentrations of tacro/sirolimus, possibly caused by belumosudil that is an inhibitor of P-gp and CYP3A4. This would be in line with clinical practice, as after allo-HCT, blood concentrations of immunosuppressive medications are regularly followed to adjust the doses to target levels to avoid renal toxicity.

It is important to note that supratherapeutic blood concentrations of these two medicinal products increase the risk of adverse events but do not improve efficacy and, therefore, it is unlikely that higher responses would be caused by supratherapeutic blood concentrations of tacro/sirolimus.

Of the other concomitant medications, increased corticosteroids for flare is not considered to have had effect on treatment responses with belumosudil. In the belumosudil 200 mg QD arm, an increased corticosteroid dose for a flare was started in 5 (8.8%) responders and in one (5.0%) non-responder. Of the responders, two participants were treated with an increased corticosteroid dose prior response. However, in one of them

the start date of the increased corticosteroid treatment was reported erroneously, and the other participant had a long time interval between the increase in corticosteroid dose and response (390 days). Hence, even though the study protocol allowed increases in corticosteroid dose for flare within 6 months and majority of the responses appeared within that time period, effect of increased corticosteroid treatment on treatment responses can be excluded.

Combination treatment of belumosudil and ruxolitinib was used only by two patients; in one of them, the combination treatment lasted only for 12 days. It can be concluded that ruxolitinib treatment did not contribute to observed ORR, and no conclusions can be made on tolerability of the combination. As expected, concomitant ECP treatment may have contributed to observed clinical responses. ECP treatments should be continued for 3 months before the treatment can be assessed as ineffective. In the belumosudil 200 mg QD arm, 19 participants were treated with ECP at baseline with the median duration prior to C1D1 of 150 days (16-806 days). Six (31%) participants had been treated with ECP $\leq$ 90 days prior to C1D1. However, ORR and ORR at 6 months in participants receiving concomitant ECP at baseline, regardless of the duration of ECP treatment prior to C1D1, and in those who did not receive ECP, were comparable. In a SAT setting, it is no possible with certainty to exclude treatment responses of concomitant ECP treatments. However, based on the provided data, the effect of concomitant ECP treatments may be assessed as limited.

To further isolate the treatment effect of belumosudil, the Applicant provided response data of the non-interventional study AA_00117 showing that the ORR at 6 months in 19 participants with belumosudil monotherapy was higher than in 79 participants treated with belumosudil combinations (47.4% and 36.7%, respectively). However, due to methodological weaknesses no comparative conclusions should be made, and it can only be concluded that observed responses have been documented with belumosudil monotherapy.

There were no significant differences in ORR between clinically relevant subgroups, including patients with prior treatment with ibrutinib or ruxolitinib.

Secondary endpoints

The efficacy results of secondary endpoints were clinically relevant supporting efficacy of belumosudil.

Primary DoR defined as time from first documentation of response to the time of first documentation of deterioration from best response was 23.9 weeks. In subgroup analysis, primary DoR was longer in the patients with prior ruxolitinib, in the patients with severe cGVHD and in the patients with $\leq$ 3 LOTs (36.1 weeks). However, the number of patients in these subgroups are small and no firm conclusions can be drawn. Time to new immunosuppressive treatment, tertiary DoR, was 101.1 weeks, which is clinically relevant.

The response rates of different organ involvements varied between 20%-71%. The highest response rate (42/55 patients, 71%) was reported in joint/fascia involvement, which frequently responds poorly to any treatment. In clinical practise, pulmonary involvement of cGVHD (bronchiolitis obliterans), a very serious complication after allogeneic HCT, is usually resistant to any available therapy. Even though the low number of patients, nine out of 27 patients (33.3%) with pulmonary involvement achieved overall lung response with belumosudil treatment. Of note, five of the lung responses were CRs.

In LSS assessing symptom burden, 36 (46.2%) subjects reported a clinically meaningful improvement on 2 consecutive assessments and in 16 (20.8%) subjects, the improvement lasted $\geq$ 48 weeks.

In clinical practice, decline or cessation of corticosteroid treatment is essential to prevent side-effects associated with long-term steroid use. In target population with belumosudil dosing 200 mg QD, approximately a quarter of the patients were able to discontinue corticosteroid treatment. The decrease of

steroid dose as mg/kg/day was not notable, because the baseline corticosteroid dose was low, 0.18 mg/kg/day. It should be also noted that evaluating corticosteroid dose change at 6 months after treatment start, it might be expected that average reduction is observed among those who are still on treatment given that rules were in place to discontinue from the study patients with corticosteroid dose increase.

For discussion concerning improvement of LSS and changes in corticosteroid doses according to treatment response please see discussion of pooled analysis below.

In conclusion, although a single arm study can be considered acceptable in a population that has exhausted available treatment options, a drug effect is difficult to isolate in the Study KD025-213. However, based on the additional data provided by the Applicant, the impact of concomitant medications on treatment responses with belumosudil appears to be limited. Although the response rate observed is high in a difficult to treat population, clinical relevance of the observed responses is difficult to contextualise. Assessment of treatment responses is, at least to some extent, subjective and hence, includes uncertainties regarding efficacy assessments in the context of single-arm trial. Importantly, response was defined as any improvement at any time during the treatment in absence of concurrent worsening in other organs and starting a new systemic cGVHD therapy. However, clinically relevant response rate was consistently observed also in landmark analyses at 6 and 12 months, and a clear majority of the patients had a response in more than one organ system. Of the 73 responders at 6 months, 66 (90.4%) demonstrated response in multiple (≥2) organs at any time point based on best response per organ. The duration of observed responses was clinically relevant. Therefore, it can be concluded that belumosudil treatment has contributed to patients achieving a response. However, the magnitude of the effect of belumosudil treatment cannot be accurately estimated in the SAT.

Integrated Analysis of Studies KD025-213, KD025-208, and KD025-217

Efficacy data

In the provided integrated analysis, 94 patients (79 patients in Study KD025-213 and 15 patients in Study KD025-208) comprised the target population with proposed belumosudil dosing of 200 mg QD.

The results of the primary and secondary endpoints are in line with the results of the pivotal study, which included the majority of the patients in the pooled analysis. Instead of ITT-population, the Applicant has provided the treatment results in mITT-population, as commented previously.

Responses were in line with those of the pivotal study, because integrated analysis included only 15 additional patients. ORR of 72% in the target population with belumosudil 200 mg QD is considered clinically relevant. Six (6.4%) patients achieved CR and 62 (66%) PR. Responses were demonstrated across the key subgroups including participants who had ≥2 prior LOTs, participants with ≥4 organ involvements, participants with severe cGVHD, participants who had cGVHD refractory to the prior LOT and patients with prior treatment with ibrutinib or ruxolitinib.

Duration of the responses were sustainable, also considering the severity of cGVHD and the refractoriness to the prior therapies. The median duration of primary response was 22 weeks. Tertiary DoR, time to new systemic immunosuppressive treatment, was 111 weeks. This is clinically relevant in a situation where no effective treatment options are available.

Improvement in LSS was seen more frequently in responders than in non-responders (50% vs. 23%, respectively). Patient-reported symptom scores are difficult to interpret in open label single arm studies, and the data is of limited value. The data also demonstrates that clinically relevant reduction in symptom score can be independent of treatment response, and therefore the improvement does not reliably reflect drug effect.

Approximately 70% of the responders were able to reduce corticosteroid dose. However, the change of steroid dose as mg/kg/day was not notable, because the baseline corticosteroid dose was low, 0.19 mg/kg/day. However, approximately a third of the responders were able to stop corticosteroid treatment, which is an important outcome clinically. Only two of the non-responders could stop corticosteroid treatment.

In conclusion, the results of the integrated analysis are in line with the pivotal study.

ROCKreal Study (AA_00117)

The Applicant has included the results from the RWD study in SmPC Section 5.1 including a claim of superiority of belumosudil over Best Available Therapy. This claim cannot be supported, and the results are not considered sufficiently reliable due to multiple reasons. First of all, use of RWD for a causal claim is always more challenging than an RCT and in this setting an RCT could have easily been conducted. There is some evidence of data quality issues in the RWD, for example missing data and implausible values. The Applicant claims to have followed Target Trial emulation but it appears that this approach has not been systematically followed through the design, analysis and reporting, for example related to a precise definition of the treatment received. The clinical relevance of the primary endpoint has not been discussed.

The Applicant has used a novel causal inference methodology called TMLE+SL for the analysis and for several reasons it can be questioned whether this methodology is suitable for regulatory decision making. The Applicant has also not discussed how this methodology may deviate from current regulatory practice and guidelines. Further, there are some serious study conduct issues such as discrepancies and ambiguity in the definition of the primary endpoint between the protocol and the SAP. Reporting of the results is not sufficiently detailed to provide a sound basis for regulatory decision making and some basic tables such as distribution of actual treatment received in the BAT and belumosudil arms are missing. Furthermore, the fully unadjusted, complete case analysis provides the same results than the causal inference method defined for the primary analysis (TMLE+SL). As it is well known that fully unadjusted analyses of observational data do not provide appropriate, unbiased estimates in terms of both precision and accuracy, it would have been beneficial to better understand this result considering the novelty of the TMLE+SL and its unprecedented use in regulatory decision making. For all the above-mentioned reasons, the results are not considered sufficiently reliable to support B/R assessment of belumosudil in the sought indication and for inclusion in SmPC section 5.1.

Study EFC17757

Study EFC17757 was initially proposed as the Specific obligation for the CMA. However, the study was discontinued during the marketing authorisation assessment due to lack of efficacy. The study failed to demonstrate any clinical benefit in 1st line (1L) cGvHD. Based on preliminary DMC analysis,EFS was comparable as compared to placebo arm (HR 1.1) and ORR by 24 weeks was lower as compared to placebo arm (71% vs. 88.5% respectively). There was no difference in CR rates, time to response or duration of response.

The patient population of the originally planned confirmatory trial EFC17757 comparing belumosudil in combination with corticosteroid with placebo in combination with corticosteroid in patients with newly diagnosed moderate and severe cGVHD was different from the patient population of the study KD025-213 (first line vs. last line treatment). However, the confirmatory study was considered to be acceptable, and if the study had been positive, it would have been a clear signal that belumosudil also plays a clear role in (early) inflammatory component of cGvHD. The initially planned SOB was a high-risk study, as many trials have failed in the first line. It is plausible that disease pathophysiology is different, inflammation playing a more central role in early stages vs. fibrotic changes in later stages of the disease. Demonstrating add-on

efficacy to corticosteroid treatment is challenging, as response rate to corticosteroids is high in the first line treatment. Regardless, the study had been proposed by the Applicant as an adequate SOB to address the remaining uncertainties, and it did not provide any demonstration of drug activity. There is no clinical data to support the hypothesis that belumosudil would provide clinical benefit only in last line cGvHD setting due to differences in disease pahthophysiology, and therefore the lack of clinical benefit in 1L would not have an impact on B/R in last line. Therefore, the negative study adds to identified uncertainties from the pivotal study and based on the currently available evidence, the concept that belumosudil might be more beneficial in late line treatment setting, preventing or reversing fibrotic damage to vital organs, remains only hypothetical.

Additional expert consultation

No additional expert consultation was carried out.

Assessment of paediatric data on clinical efficacy

Only three adolescents were included in the pivotal trial, and two of them in Arm A. One of the two adolescents achieved a PR. Pathogenesis of cGVHD and the physiological basis of belumosudil mechanism of action may be considered to be similar in both adults and children. Based on simulations using an updated, acceptable PPK model, exposure to belumosudil in adolescent patients (age ≥12 years and bodyweight ≥40 kg) following dose regimen 200 mg QD taken with a meal is expected to be within the range of adult exposures for which safety is acceptable.

Among AEs in adults, overall, no specific concern has been reported with the use of belumosudil (see safety section for details). When considering AEs of particular concern to adolescent patients (infections and diarrhoea), belumosudil presents, so far, a favourable safety profile. Belumosudil has no overt impact on growth and development in animals, and it is not expected to have any impact on CNS development.

PK, efficacy, and safety results from studies ACT18369, EFC17757, and prior data from adolescent participants with cGVHD from studies KD025-213 and ME3208-2, will provide complementary data in adolescents to confirm the allometric scaled popPK model. The failed confirmatory study EFC17757 will provide additional safety and PK data. As there were no major uncertainties on these aspects, the role of this data will be very limited. The Rapp agrees with the Applicant that the rationale developed for the confirmation of the extrapolation concept in adolescents is still valid despite EFC17757 study termination. Altogether, PK data will be available in 12 adolescents and efficacy readouts in 10 adolescents. In addition, adolescents will be enrolled in the planned PK/efficacy/safety study DFI17893, which is currently approved as part of the paediatric investigation plan in EU (PIP Study 3) targeting pediatric patients (from 1 year to less than 18 years).

In general, treatments of cGVHD in adolescents are mostly extrapolated from the experience and efficacy results reported in adult patients. Hence, the currently presented PK, efficacy and safety data support an indication in adolescents aged 12 to under 18 years with a bodyweight ≥ 40 kg, and the Applicant agreed on to limit the paediatric indication to patients 12 years and older with a bodyweight ≥ 40 kg. It is considered acceptable not to set a weight limit to adult patients since there are no specific concerns on efficacy or safety beyond the weight range of the adult study population. No statistically significant weight effect on PK parameters was found in the updated population PK model over a wide range of body weight starting from 38.6 and up to 143 kg in adult participants and no observed difference in safety profile in four adult patients

weighing < 40 kg in clinical trials could be seen. Adult patients with body weight significantly under 40 kg are expected to be very rare, whereas the weight limit is highly relevant for adolescents (40 kg is approximately the 50th percentile for 12-year-old children).

Additional efficacy data needed in the context of a conditional MA

The demonstration of efficacy relies on one pivotal single arm study. This introduces well- known limitations with regards to interpretation of data, in particular with regards to assessment of time to event endpoints.

The originally planned confirmatory study EFC17757 comparing belumosudil in combination with corticosteroid with placebo in combination with corticosteroid in patients with newly diagnosed moderate and severe cGVHD was terminated by the Applicant on 26 June 2025. Termination of the study was based on the DMC's recommendation based on the results of pre-planned futility IA from first 70 patients enrolled in the trial, and on additional analysis of efficacy data from more than 100 participants. No difference in ORR and EFS between the treatment arms could be shown.

Based on the survey conducted among European transplantation haematologists concerning feasibility of alternative study designs for SOB, the Applicant proposes a new confirmatory trial to fulfil the specific obligation of the CMA. This phase 3, randomized, open-label, multi-centre study will investigate the efficacy and safety of belumosudil versus BAT in participants ≥12 years of age with cGVHD after at least 2 prior lines of systemic therapy including ruxolitinib unless it is inappropriate or inadequate at discretion of the investigator. A total of approximately 356 participants will be randomized 1:1 to receive either belumosudil or the BAT. The stratification factors include severity of cGVHD at baseline according to the NIH consensus diagnosis and staging criteria (2014) (moderate vs severe) and the number of prior lines of therapy (2 vs >2).

Participant assigned to the BAT arm will receive one of the following options: ECP, MMF, rituximab, mTOR inhibitors (sirolimus, everolimus), imatinib, ibrutinib, proteasome inhibitors, and pentostatin. No other types or combinations of BATs are permitted. The choice of BAT for each participant will be determined by the Investigator and must be entered in the interactive response technology (IRT) prior to randomization. Dose and frequency for various BATs will depend on local prescribing information and institutional guidelines.

Participants can continue the study intervention (belumosudil or BAT) until cGVHD disease progression, intolerable toxicities, or other reasons to terminate study intervention. Participants in the BAT arm will have the option to crossover to belumosudil arm after completion of Cycle 6 (time point for ORR at 6 months) if developing toxicity to BAT treatment, not achieving PR or CR or having cGVHD progression.

Concomitant use of systemic corticosteroids and calcineurin inhibitors (CNIs) only are allowed. Participants on systemic corticosteroids and/or CNIs must be on a stable dose for at least 2 weeks prior to C1D1. Concomitant systemic treatment for cGVHD other than corticosteroids and CNIs is prohibited until study intervention discontinuation. It is recommended that any participant receiving a CNI at study entry will remain on the same CNI during the study treatment period. Changes in doses of drugs to maintain therapeutic levels are not considered as a change in dose/schedule. Use of topical or organ specific therapies for cGVHD is permitted.

The Applicant commits to provide a final study protocol for CHMP review on 18 Dec 2025. Estimated data delivery of the proposed SOB will be in April 2030.

The proposed study population is largely in line with the currently applied indication and would therefore be fully suitable to confirm the B/R. Prior ruxolitinib use is required unless it is inappropriate or inadequate, reflecting the current clinical landscape. BAT as comparator is considered to be acceptable and reflects the

current heterogeneous clinical practice. The selection of BAT options is also acceptable. It is expected that for a majority of the patients, ECP would be the most appropriate treatment option. Option to cross over at 6 months limits the interpretation of any long term data but would not be considered to be with a major problem for addressing the key uncertainties at the moment. Compared to the pivotal study, fewer concomitant medications (corticosteroids and CNIs only) are allowed, and hence, isolation of the drug effect will be easier in a RCT setting.

The primary endpoint is ORR (PR or CR) at 6 months based on ITT population from the RCT population. The selected endpoint is acceptable, and in line with the regulatory precedent. Although time-to-event endpoints are suited for randomised studies, use of ORR would avoid the problems associated with the complex definition of EFS used in the study EFC17757.

Overall, the proposed study would have been far more suited to support the MAA as compared to the current pivotal SAT and would have been far more suited to serve as a SOB in the first place. The evaluation that the study would be feasible to conduct now, after belumosudil has been proved in various other countries globally, demonstrates that this study would have been feasible when the pivotal study ROCKstar was performed

An important concern is the timeline proposed for conducting, completing the study and ultimately submiting study results. Estimated data delivery of the proposed SOB will be in 2030. Accepting a SOB in early planning stages poses a high risk in a setting where isolation of drug effect is challenging in the pivotal study, the magnitude of treatment benefit cannot be reliably estimated, and one randomized study has already failed to demonstrate clinical benefit.

The survey conducted and feasibility analysis performed by the Applicant is appreciated, as during scientific advice procedures, and earlier stages of the MAA assessment, the Applicant has argued that conducting an RCT in the target population would not be feasible. The Applicant has not discussed the impact of availability of belumosudil on the market after if a CMA is granted in the predicted patient enrolment. In prior discussions, widespread managed access use of belumosudil was also considered to block the possibility of conducting an RCT in Europe. Therefore, it is not evident that the enrolment predictions would be realistic when the study has not been started, and it is not possible to predict if conducting the trial would actually be feasible in the evolving treatment landscape. Even if the study could be conducted as estimated, the first patient would be enrolled in the trial in Aug 2026, and it would take approximately 4,5 years before the efficacy data would be available (study report estimated in 2030). This would mean that a considerable number of patients would be exposed to belumosudil with uncertain clinical benefit in post marketing setting before the confirmation of B/R is available.

In conclusion, the identified uncertainties on clinical benefit from the pivotal study, and the added uncertainty due to one failed randomised controlled study are considered to be too great to accept a confirmatory study with uncertain timelines for data delivery. It is therefore concluded that it cannot be ascertained that the Applicant would be able to deliver comprehensive data to confirm the B/R within a reasonable timeframe. The criteria for a CMA are therefore not fulfilled (**MO**).

2.6.7. Conclusions on clinical efficacy

The observed response rates were high and could be considered clinically relevant in last line cGVHD population and demonstrate potential to address an unmet medical need. Based on available data, it can be concluded that belumosudil treatment has contributed to patients achieving a response. However, the magnitude of the effect of belumosudil treatment cannot be accurately estimated in the SAT. Assessment of response is, at least to some extent, subjective in chronic graft versus host disease (cGvHD) and includes

uncertainties regarding efficacy assessments in the context of single-arm trial (EMA/CHMP/458061/2024). Isolation of treatment effect is further complicated because various concomitant systemic treatments were permitted. Importantly, response was defined as any improvement at any time during the treatment. Hence, magnitude of clinical benefit is uncertain.

Importantly, the originally proposed specific obligation to the conditional marketing authorisation, randomised controlled trial in the first-line treatment of cGvHD (EFC17757), aiming at confirming positive B/R in the applied indication, failed to demonstrate any clinical benefit or even drug activity of belumosudil. Acknowledging the different patient population studied in a first line setting, this result further increases the uncertainty on the demonstration of efficacy of belumosudil.

In summary considering all available evidence, it is considered that the clinical benefit is uncertain and has not been sufficiently demonstrated.

There are also concerns regarding the study design and feasibility of the proposed new confirmatory trial.

Therefore, the CHMP considers (i) that a positive risk-benefit balance cannot be established for Rezurock in light of the uncertain clinical benefits based on the presented scientific evidence, and (ii) that it is unlikely that the applicant will be able to provide comprehensive data confirming that the risk-benefit balance is positive. (**MO**)

The B/R is therefore negative.

2.6.8. Clinical safety

The main safety data for belumosudil 200 mg QD for the treatment of cGVHD in patients with at least 2 prior lines of systemic therapy (LOT) derives from three open-label studies: the pivotal Phase 2 study KD025-213, the Phase 2a dose-escalation study KD025-208, and the ongoing long-term extension of these studies, the study KD025-217. The parent studies have been completed. The KD025-217 long-term extension study was ongoing as of the cutoff date, 29 January 2024. The pooled safety analysis included data from these three studies. The final CSR of the long-term extension study was submitted at D120. All relevant safety tables and figures were updated at D120 to include the additional and updated data of the final study report of the long-term extension study KD025-217. No new or unexpected safety concerns were evident from these novel data. The Applicant also discussed long-term clinical safety data beyond Month 12 of both the pooled safety data set (studies KD025-213, KD025-208 and KD025-217 updated) and individually for the pivotal study KD025-213. No new safety concerns arose from these data.

Supportive data for the safety are provided by the Phase 3 single-arm study ME3208-2 conducted in Japan and the Phase 2 single-arm study BN101-201 conducted in China. Further safety data are provided by the non-interventional real-world evidence (RWE) study AA_00117, which compared treatment with belumosudil versus best available treatment (BAT) in patients with cGVHD who failed at least 2 prior lines of systemic therapy.

Finally, additional supportive safety data are provided by 10 company sponsored Phase 1 trials that have been conducted in healthy participants and one in participants with varying degrees of hepatic impairment. Furthermore, Phase 1 studies have been conducted in China and Japan.

A summary of all clinical studies contributing to the safety data is presented in the efficacy section.

Definition of the clinical study populations

The pooled data (Safety Population) includes all initial safety data from patients with cGVHD after failure of 1 to 5 lines of therapy as of the cutoff date, studies KD025-213, KD025-208, and KD025-217 and were analysed according to doses administered: 200 mg QD, 200 mg BID, and 400 mg QD. The Safety Population for the pooled analysis included all participants who received at least 1 dose of study medication. All analyses are based on the Safety Population unless otherwise specified.

Outcomes assessed include the following: Participant disposition, TEAEs: defined as any AE that occurred or worsened in severity after the first administration of study medication until 28 days after the end of treatment, including: All TEAEs and treatment-related AEs, Treatment-emergent serious adverse events (SAEs) and related SAEs, TEAEs leading to dose reduction, dose interruption, and discontinuation (all and related), TEAEs of Grade ≥3 in severity, Adverse events of special interest (AESIs), including hepatic events/increased liver enzymes, infections, hematologic events (anaemia, leukopenia, neutropenia, and thrombocytopenia), malignancies/neoplasms (relapse of underlying malignancy and secondary neoplasm), impaired wound healing, and hypotension, Clinical laboratory evaluations, Vital signs and electrocardiograms (ECGs).

The collection of the safety data appears comply with guidance and is suitable for the intended purpose. The proposed pooling is not fully meaningful as it includes three different doses levels: 200 mg QD, 200 mg BID, and 400 mg QD and patients with other than the targeted LOTs. However, as the results are presented separately by each of the dosing regimens (and in addition for the all-inclusive cohort), this is acceptable.

These three clinical trials are considered as the main studies of this MAA on the basis of which the benefit risk analyses will be performed. Thus, the safety sample population is to include patients with the sought indication and sought LOT and the sought dosing regimen of 200 mg QD. All relevant safety tables were also provided separately for this target population.

Not including any of the other supportive data in the safety pool can be considered acceptable as these data will not yield any additional, coherent data, considering that the major differences in the study design and target populations. For the assessment of causality of the TEAE i.e. ADRs, the most comprehensive patient cohort of the safety population with the target indication, LOT and target dosing regimen of belumosudil 200 mg QD must be used.

3.3.7.1. Patient exposure

A summary of the extent of exposure is presented in the table below.

Table 46: Patient exposure (cut-off date 31 January 2025)

	Patients enrolled*	Patients exposed**	Patients exposed to the proposed dose range	Patients with long term*** safety data
Blinded studies (placebo-controlled)	None			
Blinded studies (active -controlled)	None			
Open studies	307	193	94	121 (6 months) 82 (12 months)
Post marketing	Not applicable	>9500	>9500	Unknown
Compassionate use	Not applicable	976	Unknown	Unknown

Note: numbers reported in this table do not include study ME3208-2 and BN101-201. For study ME3208-2, 21 participants enrolled and 21 of them were treated (interim data cut-off date 10 Aug 2023). For study BN101-201, 45 participants signed informed consent, and 30 participants were treated (CSR date 23 Feb., 2023).
* Patients enrolled including all patients who signed informed consent (screen failed were also included).
** Received at least 1 dose of active treatment
*** In general, this refers to 6 months and 12 months continuous exposure data, or intermittent exposure.

As of the cutoff date, the Safety Population for the integrated analysis comprised 209 participants, including 94 participants treated with belumosudil 200 mg QD, 92 participants with 200 mg BID, and 21 participants with 400 mg QD.

The overall median duration of treatment with belumosudil was 10.22 months (range 0.39 to 83.75 months); the cumulative duration of exposure in the 200 mg QD group was 125.25 patient-years and in the all belumosudiltreated participants 266.25 patient-years. Forty-three participants (20.6%) were treated with belumosudil for ≥6 to 12 months and 89 participants (42.6%) were treated for ≥12 months. The median duration of treatment was similar across all dose groups at 9.18, 11.09, and 9.00 months in the 200 mg QD, 200 mg BID, and 400 mg QD treatment groups, respectively. As expected, based on the dosing frequency, the mean overall exposure was lower in the 200 mg QD group (85,382 mg) than in the 200 mg BID group (169,809 mg) and the 400 mg QD group (149,790 mg).

Demographic and baseline characteristics of participants with cGVHD in the integrated Safety Population were reflective of the disease under study and generally well-balanced across the belumosudil dose groups

analysed. The detailed description of the design and conduct of the main studies and the key baseline patient and disease characteristics are found in the efficacy section.

3.3.7.2. Adverse events

An overall summary of the incidence of TEAEs for the cGVHD pooled safety population is presented in the table below.

Table 47: Overall summary of cumulative treatment-emergent adverse events (safety population)

Parameter	200 mg QD N = 96 n (%)	200 mg BID N = 92 n (%)	400 mg QD N = 21 n (%)	All Belumosudil N = 209 n (%)
Participants with at least 1 TEAE	95 (99.0)	92 (100.0)	20 (95.2)	207 (99.0)
Participants with serious TEAE	44 (45.8)	37 (40.2)	13 (61.9)	94 (45.0)
Participants with Grade ≥3 TEAE	64 (66.7)	54 (58.7)	14 (66.7)	132 (63.2)
Participants with TEAE leading to dose reduction	3 (3.1)	5 (5.4)	2 (9.5)	10 (4.8)
Participants with TEAE leading to dose interruption	33 (34.4)	29 (31.5)	8 (38.1)	70 (33.5)
Participants with TEAE leading to drug discontinuations	21 (21.9)	20 (21.7)	9 (42.9)	50 (23.9)
Participants with TEAEs by maximum severity				
Grade 1: Mild	4 (4.2)	3 (3.3)	0	7 (3.3)
Grade 2: Moderate	27 (28.1)	35 (38.0)	6 (28.6)	68 (32.5)
Grade 3: Severe	54 (56.3)	42 (45.7)	6 (28.6)	102 (48.8)
Grade 4: Life threatening	5 (5.2)	7 (7.6)	4 (19.0)	16 (7.7)
Grade 5: Fatal	5 (5.2)	5 (5.4)	4 (19.0)	14 (6.7)
Participants with related TEAE	68 (70.8)	59 (64.1)	14 (66.7)	141 (67.5)
Participants with related serious TEAE	9 (9.4)	5 (5.4)	1 (4.8)	15 (7.2)
Participants with related Grade ≥3 TEAE	20 (20.8)	18 (19.6)	2 (9.5)	40 (19.1)
Participants with related TEAE leading to dose reduction	3 (3.1)	4 (4.3)	2 (9.5)	9 (4.3)
Participants with related TEAE leading to dose interruption	14 (14.6)	6 (6.5)	4 (19.0)	24 (11.5)
Participants with related TEAE leading to drug discontinuation	12 (12.5)	7 (7.6)	1 (4.8)	20 (9.6)
Grade 1: Mild	13 (13.5)	17 (18.5)	5 (23.8)	35 (16.7)
Grade 2: Moderate	35 (36.5)	24 (26.1)	7 (33.3)	66 (31.6)
Grade 3: Severe	17 (17.7)	17 (18.5)	1 (4.8)	35 (16.7)

Parameter	200 mg QD N = 96 n (%)	200 mg BID N = 92 n (%)	400 mg QD N = 21 n (%)	All Belumosudil N = 209 n (%)
Grade 4: Life threatening	2 (2.1)	0	1 (4.8)	3 (1.4)
Grade 5: Fatal	1 (1.0)	1 (1.1)	0	2 (1.0)

Abbreviations: BID=twice daily; BSC=best supportive care, cGVHD=chronic graft versus host disease; QD=once daily, TEAE=treatment-emergent adverse events. Program Source: P:\01_OngoingProjects\G_100_HEM_KD025_CGVHD_IDB_SA\EMA\Programs\TFL \Original\ISS\t_3.sas

Common adverse events

The most commonly reported TEAEs (≥10% of belumosudil-treated participants) are summarized by system organ class (SOC) and preferred term (PT) in **Table 48**.

Table 48: Cumulative most common (≥10%) treatment-emergent adverse events by system organ class and preferred term (safety population)

SOC Preferred Term	**200 mg QD N = 96 n (%)**	**200 mg BID N = 92 n (%)**	**400 mg QD N = 21 n (%)**	**All Belumosudil N = 209 n (%)**
Participants with at least 1 TEAE	95 (99.0)	92 (100.0)	20 (95.2)	207 (99.0)
Gastrointestinal disorders	69 (71.9)	68 (73.9)	17 (81.0)	154 (73.7)
Diarrhoea	41 (42.7)	29 (31.5)	7 (33.3)	77 (36.8)
Nausea	32 (33.3)	26 (28.3)	9 (42.9)	67 (32.1)
Vomiting	25 (26.0)	15 (16.3)	4 (19.0)	44 (21.1)
Abdominal pain	16 (16.7)	12 (13.0)	4 (19.0)	32 (15.3)
Dysphagia	15 (15.6)	8 (8.7)	2 (9.5)	25 (12.0)
Constipation	10 (10.4)	10 (10.9)	3 (14.3)	23 (11.0)
Infections and infestations	62 (64.6)	64 (69.6)	15 (71.4)	141 (67.5)
Upper respiratory tract infection	29 (30.2)	31 (33.7)	7 (33.3)	67 (32.1)
Pneumonia	11 (11.5)	15 (16.3)	1 (4.8)	27 (12.9)
General disorders and administration site conditions	64 (66.7)	50 (54.3)	15 (71.4)	129 (61.7)
Fatigue	40 (41.7)	26 (28.3)	10 (47.6)	76 (36.4)
Oedema peripheral	25 (26.0)	23 (25.0)	6 (28.6)	54 (25.8)
Pyrexia	19 (19.8)	14 (15.2)	3 (14.3)	36 (17.2)

SOC Preferred Term	200 mg QD N = 96 n (%)	200 mg BID N = 92 n (%)	400 mg QD N = 21 n (%)	All Belumosudil N = 209 n (%)
Respiratory, thoracic and mediastinal disorders	60 (62.5)	53 (57.6)	15 (71.4)	128 (61.2)
Dyspnoea	30 (31.3)	23 (25.0)	7 (33.3)	60 (28.7)
Cough	24 (25.0)	24 (26.1)	7 (33.3)	55 (26.3)
Nasal congestion	12 (12.5)	11 (12.0)	1 (4.8)	24 (11.5)
Productive cough	11 (11.5)	9 (9.8)	1 (4.8)	21 (10.0)
Musculoskeletal and connective tissue disorders	52 (54.2)	49 (53.3)	14 (66.7)	115 (55.0)
Arthralgia	20 (20.8)	15 (16.3)	5 (23.8)	40 (19.1)
Muscle spasms	15 (15.6)	15 (16.3)	6 (28.6)	36 (17.2)
Pain in extremity	15 (15.6)	16 (17.4)	4 (19.0)	35 (16.7)
Back pain	9 (9.4)	12 (13.0)	1 (4.8)	22 (10.5)
Investigations	48 (50.0)	54 (58.7)	12 (57.1)	114 (54.5)
AST increased	13 (13.5)	18 (19.6)	1 (4.8)	32 (15.3)
ALT increased	12 (12.5)	16 (17.4)	2 (9.5)	30 (14.4)
GGT increased	11 (11.5)	15 (16.3)	0	26 (12.4)
Metabolism and nutrition disorders	50 (52.1)	45 (48.9)	11 (52.4)	106 (50.7)
Hyperglycaemia	16 (16.7)	14 (15.2)	3 (14.3)	33 (15.8)
Decreased appetite	15 (15.6)	9 (9.8)	4 (19.0)	28 (13.4)
Skin and subcutaneous tissue disorders	44 (45.8)	46 (50.0)	8 (38.1)	98 (46.9)
Pruritus	10 (10.4)	15 (16.3)	0	25 (12.0)
Nervous system disorders	43 (44.8)	43 (46.7)	9 (42.9)	95 (45.5)
Headache	27 (28.1)	26 (28.3)	6 (28.6)	59 (28.2)
Dizziness	8 (8.3)	11 (12.0)	2 (9.5)	21 (10.0)
Injury, poisoning and procedural complications	40 (41.7)	37 (40.2)	6 (28.6)	83 (39.7)
Fall	12 (12.5)	15 (16.3)	1 (4.8)	28 (13.4)
Contusion	11 (11.5)	8 (8.7)	3 (14.3)	22 (10.5)
Vascular disorders	34 (35.4)	35 (38.0)	5 (23.8)	74 (35.4)

SOC Preferred Term	200 mg QD N = 96 n (%)	200 mg BID N = 92 n (%)	400 mg QD N = 21 n (%)	All Belumosudil N = 209 n (%)
Hypertension	19 (19.8)	18 (19.6)	4 (19.0)	41 (19.6)
Eye disorders	29 (30.2)	25 (27.2)	7 (33.3)	61 (29.2)
Dry eye	10 (10.4)	9 (9.8)	2 (9.5)	21 (10.0)
Blood and lymphatic system disorders	19 (19.8)	21 (22.8)	4 (19.0)	44 (21.1)
Anaemia	12 (12.5)	16 (17.4)	0	28 (13.4)

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; BID=twice daily; GGT=gamma glutamyltransferase; QD=once daily; SOC=system organ class; TEAE=treatment-emergent adverse events. Program Source: P:\01_OngoingProjects\ G_100_HEM_KD025_ CGVHD_IDB_SA\EMA\ Programs\TFL\Original\ISS\t_4.sas

Time to onset of treatment-emergent adverse events

The frequency of TEAEs did not significantly increase over time from the 0 to <1 month onset period to the 9 to <12-month onset period, indicating no cumulative toxicity with longer treatment. The incidence of the first occurrence of TEAE was similar between participants in the 200 mg QD group and all belumosudil-treated participants.

The incidence of fatigue in the 200 mg QD group during Month 1 (17.7%) of treatment with belumosudil decreased to 3.1% between 1 to <2 months and 9 to <12 months: at 1 to <2 months, 2 to <3 months, 3 to <6 months, and 6 to <9 months the incidence of fatigue was 9.0%, 5.9%, 8.5%, and 5.1%, respectively. The rate of fatigue in all belumosudil-treated participants followed a similar pattern: 18.7% during Month 1, 5.5% from 1 to <2 months, and then 4.8%, 6.5%, 2.2%, and 5.3%, from 2 to <3 months, 3 to <6 months, 6 to <9 months, and 9 to <12 months, respectively.

Adverse events by severity

In the pooled analysis (**Table 49**), 64 (66.7%) participants in the 200 mg QD group and 132 (63.2%) of all 209 belumosudil-treated participants experienced 1 or more Grade ≥3 TEAEs.

Table 49: Cumulative Grade ≥3 treatment-emergent adverse events reported in ≥2 participants in all belumosudil-treated participants by system organ class and preferred term (safety population)

	Belumosudil			
System Organ Class Preferred Term	200 mg QD N = 96 n (%)	200 mg BID N = 92 n (%)	400 mg QD N = 21 n (%)	All N = 209 n (%)
Participants with at least one Grade ≥3 TEAE	64 (66.7)	54 (58.7)	14 (66.7)	132 (63.2)
Infections and infestations	20 (20.8)	23 (25.0)	6 (28.6)	49 (23.4)
Pneumonia	9 (9.4)	10 (10.9)	0	19 (9.1)
Rhinovirus infection	3 (3.1)	3 (3.3)	0	6 (2.9)
Cellulitis	2 (2.1)	2 (2.2)	0	4 (1.9)
Gastroenteritis	2 (2.1)	1 (1.1)	0	3 (1.4)

	Belumosudil			
System Organ Class **Preferred Term**	**200 mg QD** **N = 96** **n (%)**	**200 mg BID** **N = 92** **n (%)**	**400 mg QD** **N = 21** **n (%)**	**All** **N = 209** **n (%)**
Lung infection	0	1 (1.1)	2 (9.5)	3 (1.4)
Sepsis	2 (2.1)	1 (1.1)	0	3 (1.4)
Appendicitis	1 (1.0)	1 (1.1)	0	2 (1.0)
COVID-19	0	2 (2.2)	0	2 (1.0)
Coronavirus infection	0	2 (2.2)	0	2 (1.0)
Device related infection	1 (1.0)	1 (1.1)	0	2 (1.0)
Influenza	0	2 (2.2)	0	2 (1.0)
Urinary tract infection	0	2 (2.2)	0	2 (1.0)
Metabolism and nutrition disorders	18 (18.8)	11 (12.0)	3 (14.3)	32 (15.3)
Hyperglycaemia	6 (6.3)	4 (4.3)	2 (9.5)	12 (5.7)
Hypertriglyceridaemia	2 (2.1)	2 (2.2)	0	4 (1.9)
Hyponatraemia	3 (3.1)	0	1 (4.8)	4 (1.9)
Dehydration	1 (1.0)	1 (1.1)	0	2 (1.0)
Hypocalcaemia	1 (1.0)	1 (1.1)	0	2 (1.0)
Hypokalaemia	0	2 (2.2)	0	2 (1.0)
Gastrointestinal disorders	18 (18.8)	10 (10.9)	2 (9.5)	30 (14.4)
Diarrhoea	5 (5.2)	1 (1.1)	0	6 (2.9)
Nausea	2 (2.1)	2 (2.2)	0	4 (1.9)
Vomiting	2 (2.1)	1 (1.1)	0	3 (1.4)
Abdominal pain	1 (1.0)	1 (1.1)	0	2 (1.0)
Rectal haemorrhage	1 (1.0)	1 (1.1)	0	2 (1.0)
Small intestinal obstruction	1 (1.0)	0	1 (4.8)	2 (1.0)
Respiratory, thoracic and mediastinal disorders	15 (15.6)	8 (8.7)	7 (33.3)	30 (14.4)
Dyspnoea	5 (5.2)	4 (4.3)	4 (19.0)	13 (6.2)
Hypoxia	5 (5.2)	2 (2.2)	2 (9.5)	9 (4.3)
Pulmonary embolism	2 (2.1)	1 (1.1)	0	3 (1.4)
Pleural effusion	0	0	2 (9.5)	2 (1.0)
Respiratory failure	1 (1.0)	1 (1.1)	0	2 (1.0)
Vascular disorders	13 (13.5)	9 (9.8)	1 (4.8)	23 (11.0)
Hypertension	7 (7.3)	5 (5.4)	0	12 (5.7)
Deep vein thrombosis	3 (3.1)	1 (1.1)	0	4 (1.9)
Hypotension	2 (2.1)	1 (1.1)	1 (4.8)	4 (1.9)
Haematoma	2 (2.1)	0	0	2 (1.0)

	Belumosudil			
System Organ Class Preferred Term	**200 mg QD N = 96 n (%)**	**200 mg BID N = 92 n (%)**	**400 mg QD N = 21 n (%)**	**All N = 209 n (%)**
Investigations	11 (11.5)	9 (9.8)	2 (9.5)	22 (10.5)
GGT increased	5 (5.2)	3 (3.3)	0	8 (3.8)
AST increased	1 (1.0)	3 (3.3)	0	4 (1.9)
ALT increased	1 (1.0)	2 (2.2)	0	3 (1.4)
Platelet count decreased	3 (3.1)	0	0	3 (1.4)
Blood cholesterol increased	2 (2.1)	0	0	2 (1.0)
Neutrophil count decreased	0	1 (1.1)	1 (4.8)	2 (1.0)
White blood cell count decreased	2 (2.1)	0	0	2 (1.0)
General disorders and administration site conditions	9 (9.4)	7 (7.6)	2 (9.5)	18 (8.6)
Fatigue	2 (2.1)	4 (4.3)	1 (4.8)	7 (3.3)
Asthenia	1 (1.0)	2 (2.2)	0	3 (1.4)
Multiple organ dysfunction	2 (2.1)	0	0	2 (1.0)
Non-cardiac chest pain	1 (1.0)	1 (1.1)	0	2 (1.0)
Blood and lymphatic system disorders	6 (6.3)	6 (6.5)	2 (9.5)	14 (6.7)
Anaemia	4 (4.2)	4 (4.3)	0	8 (3.8)
Neutropenia	1 (1.0)	1 (1.1)	0	2 (1.0)
Cardiac disorders	5 (5.2)	7 (7.6)	2 (9.5)	14 (6.7)
Cardiac arrest	0	2 (2.2)	1 (4.8)	3 (1.4)
Tachycardia	1 (1.0)	2 (2.2)	0	3 (1.4)
Myocardial infarction	2 (2.1)	0	0	2 (1.0)
Pericardial effusion	0	1 (1.1)	1 (4.8)	2 (1.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	7 (7.3)	1 (1.1)	5 (23.8)	13 (6.2)
AML recurrent	2 (2.1)	0	1 (4.8)	3 (1.4)
ALL recurrent	1 (1.0)	0	1 (4.8)	2 (1.0)
Myelodysplastic syndrome	1 (1.0)	0	1 (4.8)	2 (1.0)
Musculoskeletal and connective tissue disorders	5 (5.2)	5 (5.4)	1 (4.8)	11 (5.3)
Back pain	2 (2.1)	3 (3.3)	0	5 (2.4)
Arthralgia	3 (3.1)	1 (1.1)	0	4 (1.9)
Muscular weakness	1 (1.0)	1 (1.1)	0	2 (1.0)
Osteonecrosis	2 (2.1)	0	0	2 (1.0)
Pain in extremity	1 (1.0)	1 (1.1)	0	2 (1.0)

	Belumosudil			
System Organ Class Preferred Term	**200 mg QD N = 96 n (%)**	**200 mg BID N = 92 n (%)**	**400 mg QD N = 21 n (%)**	**All N = 209 n (%)**
Nervous system disorders	5 (5.2)	5 (5.4)	1 (4.8)	11 (5.3)
Syncope	3 (3.1)	2 (2.2)	1 (4.8)	6 (2.9)
Headache	0	3 (3.3)	0	3 (1.4)
Renal and urinary disorders	3 (3.1)	3 (3.3)	0	6 (2.9)
Acute kidney injury	2 (2.1)	1 (1.1)	0	3 (1.4)
Chronic kidney disease	0	2 (2.2)	0	2 (1.0)
Injury, poisoning and procedural complications	3 (3.1)	2 (2.2)	0	5 (2.4)
Fall	2 (2.1)	1 (1.1)	0	3 (1.4)
Psychiatric disorders	2 (2.1)	3 (3.3)	0	5 (2.4)
Depression	1 (1.0)	1 (1.1)	0	2 (1.0)

Abbreviations: ALT=alanine aminotransferase; ALL=acute lymphocytic leukaemia; AML=acute myeloid leukaemia; AST=aspartate aminotransferase; BID=twice daily; COVID-19=Coronavirus Disease 2019; GGT=gamma-glutamyl transferase; QD=once daily; TEAE=treatment emergent adverse events.
Program Source: P:\01_OngoingProjects\ G_100_HEM_KD025_CGVHD_IDB_SA\EMA\Programs\TFL\ Original\ISS\t_6.sas

Adverse drug reactions

Adverse drug reactions (ADRs) were reported in 70.8% of participants in the 200 mg QD group and in 67.5% of all belumosudil-treated participants *(***Table 50***)*.

Table 50: Cumulative treatment-related treatment-emergent adverse events (≥2 of all belumosudil-treated participants by system organ class and preferred term (safety population)

	Belumosudil			
System Organ Class Preferred Term	200 mg QD N = 96 n (%)	200 mg BID N = 92 n (%)	400 mg QD N = 21 n (%)	All N = 209 n (%)
Participants with at least one related TEAE	68 (70.8)	59 (64.1)	14 (66.7)	141 (67.5)
Gastrointestinal disorders	27 (28.1)	23 (25.0)	6 (28.6)	56 (26.8)
Nausea	11 (11.5)	10 (10.9)	4 (19.0)	25 (12.0)
Diarrhoea	12 (12.5)	10 (10.9)	0	22 (10.5)
Vomiting	8 (8.3)	3 (3.3)	1 (4.8)	12 (5.7)
Constipation	5 (5.2)	3 (3.3)	0	8 (3.8)
Abdominal pain	2 (2.1)	3 (3.3)	1 (4.8)	6 (2.9)
Gastrooesophageal reflux disease	0	2 (2.2)	2 (9.5)	4 (1.9)
Abdominal distension	2 (2.1)	1 (1.1)	0	3 (1.4)
Abdominal discomfort	2 (2.1)	0	0	2 (1.0)
Dry mouth	1 (1.0)	1 (1.1)	0	2 (1.0)
Investigations	23 (24.0)	25 (27.2)	3 (14.3)	51 (24.4)
AST increased	7 (7.3)	15 (16.3)	0	22 (10.5)
ALT increased	5 (5.2)	11 (12.0)	1 (4.8)	17 (8.1)
GGT increased	5 (5.2)	5 (5.4)	0	10 (4.8)
Weight decreased	3 (3.1)	5 (5.4)	1 (4.8)	9 (4.3)
Blood alkaline phosphatase increased	3 (3.1)	5 (5.4)	0	8 (3.8)
Blood creatine phosphokinase increased	3 (3.1)	3 (3.3)	0	6 (2.9)
Platelet count decreased	2 (2.1)	3 (3.3)	0	5 (2.4)
Blood creatinine increased	2 (2.1)	2 (2.2)	0	4 (1.9)
Blood lactate dehydrogenase increased	0	4 (4.3)	0	4 (1.9)
Lymphocyte count decreased	2 (2.1)	2 (2.2)	0	4 (1.9)
White blood cell count decreased	2 (2.1)	1 (1.1)	0	3 (1.4)
Blood phosphorus decreased	0	2 (2.2)	0	2 (1.0)
Blood uric acid increased	1 (1.0)	1 (1.1)	0	2 (1.0)
Transaminases increased	2 (2.1)	0	0	2 (1.0)
General disorders and administration site conditions	23 (24.0)	24 (26.1)	3 (14.3)	50 (23.9)
Fatigue	19 (19.8)	17 (18.5)	3 (14.3)	39 (18.7)
Oedema peripheral	3 (3.1)	7 (7.6)	0	10 (4.8)
Pyrexia	2 (2.1)	4 (4.3)	0	6 (2.9)

	Belumosudil			
System Organ Class **Preferred Term**	**200 mg QD** **N = 96** **n (%)**	**200 mg BID** **N = 92** **n (%)**	**400 mg QD** **N = 21** **n (%)**	**All** **N = 209** **n (%)**
Asthenia	0	4 (4.3)	0	4 (1.9)
Malaise	1 (1.0)	2 (2.2)	0	3 (1.4)
Nervous system disorders	17 (17.7)	20 (21.7)	4 (19.0)	41 (19.6)
Headache	10 (10.4)	9 (9.8)	4 (19.0)	23 (11.0)
Neuropathy peripheral	4 (4.2)	2 (2.2)	0	6 (2.9)
Dizziness	2 (2.1)	3 (3.3)	0	5 (2.4)
Dysgeusia	1 (1.0)	2 (2.2)	0	3 (1.4)
Paraesthesia	2 (2.1)	1 (1.1)	0	3 (1.4)
Muscle spasticity	1 (1.0)	0	1 (4.8)	2 (1.0)
Neuralgia	0	2 (2.2)	0	2 (1.0)
Infections and infestations	14 (14.6)	18 (19.6)	1 (4.8)	33 (15.8)
Upper respiratory tract infection	4 (4.2)	5 (5.4)	1 (4.8)	10 (4.8)
Pneumonia	2 (2.1)	2 (2.2)	1 (4.8)	5 (2.4)
Nasopharyngitis	1 (1.0)	2 (2.2)	0	3 (1.4)
Cellulitis	2 (2.1)	0	0	2 (1.0)
Coronavirus infection	0	2 (2.2)	0	2 (1.0)
Gastroenteritis	1 (1.0)	1 (1.1)	0	2 (1.0)
Sinusitis	1 (1.0)	1 (1.1)	0	2 (1.0)
Metabolism and nutrition disorders	18 (18.8)	12 (13.0)	2 (9.5)	32 (15.3)
Decreased appetite	6 (6.3)	2 (2.2)	0	8 (3.8)
Hyperglycaemia	4 (4.2)	2 (2.2)	1 (4.8)	7 (3.3)
Hyperkalaemia	1 (1.0)	6 (6.5)	0	7 (3.3)
Hypophosphataemia	2 (2.1)	3 (3.3)	0	5 (2.4)
Hypocalcaemia	1 (1.0)	3 (3.3)	0	4 (1.9)
Hypoalbuminaemia	1 (1.0)	2 (2.2)	0	3 (1.4)
Dehydration	1 (1.0)	1 (1.1)	0	2 (1.0)
Hyperlipidaemia	2 (2.1)	0	0	2 (1.0)
Hyperuricaemia	0	1 (1.1)	1 (4.8)	2 (1.0)
Hyponatraemia	0	2 (2.2)	0	2 (1.0)
Respiratory, thoracic and mediastinal disorders	13 (13.5)	9 (9.8)	2 (9.5)	24 (11.5)
Dyspnoea	6 (6.3)	4 (4.3)	0	10 (4.8)
Cough	2 (2.1)	5 (5.4)	1 (4.8)	8 (3.8)
Dyspnoea exertional	0	3 (3.3)	0	3 (1.4)

System Organ Class Preferred Term	Belumosudil 200 mg QD N = 96 n (%)	 200 mg BID N = 92 n (%)	 400 mg QD N = 21 n (%)	 All N = 209 n (%)
Hypoxia	2 (2.1)	0	0	2 (1.0)
Nasal congestion	1 (1.0)	1 (1.1)	0	2 (1.0)
Productive cough	0	2 (2.2)	0	2 (1.0)
Pulmonary embolism	2 (2.1)	0	0	2 (1.0)
Musculoskeletal and connective tissue disorders	11 (11.5)	6 (6.5)	4 (19.0)	21 (10.0)
Muscle spasms	2 (2.1)	4 (4.3)	3 (14.3)	9 (4.3)
Arthralgia	2 (2.1)	4 (4.3)	2 (9.5)	8 (3.8)
Back pain	3 (3.1)	1 (1.1)	0	4 (1.9)
Pain in extremity	1 (1.0)	2 (2.2)	1 (4.8)	4 (1.9)
Muscular weakness	1 (1.0)	1 (1.1)	0	2 (1.0)
Myalgia	1 (1.0)	1 (1.1)	0	2 (1.0)
Vascular disorders	4 (4.2)	11 (12.0)	0	15 (7.2)
Hypertension	2 (2.1)	8 (8.7)	0	10 (4.8)
Deep vein thrombosis	1 (1.0)	1 (1.1)	0	2 (1.0)
Blood and lymphatic system disorders	4 (4.2)	7 (7.6)	0	11 (5.3)
Anaemia	3 (3.1)	5 (5.4)	0	8 (3.8)
Neutropenia	1 (1.0)	1 (1.1)	0	2 (1.0)
Thrombocytopenia	0	2 (2.2)	0	2 (1.0)
Skin and subcutaneous tissue disorders	2 (2.1)	8 (8.7)	0	10 (4.8)
Pruritus	1 (1.0)	6 (6.5)	0	7 (3.3)
Rash	1 (1.0)	1 (1.1)	0	2 (1.0)
Psychiatric disorders	2 (2.1)	5 (5.4)	0	7 (3.3)
Insomnia	1 (1.0)	3 (3.3)	0	4 (1.9)
Cardiac disorders	4 (4.2)	2 (2.2)	0	6 (2.9)
Tachycardia	1 (1.0)	1 (1.1)	0	2 (1.0)
Renal and urinary disorders	1 (1.0)	5 (5.4)	0	6 (2.9)
Acute kidney injury	0	2 (2.2)	0	2 (1.0)
Endocrine disorders	2 (2.1)	0	2 (9.5)	4 (1.9)
Hypothyroidism	2 (2.1)	0	1 (4.8)	3 (1.4)

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; BID=twice daily; GGT=gamma glutamyl transferase; QD=once daily; TEAE=treatment-emergent adverse events. Program Source: P:\01_OngoingProjects\G_100_HEM_KD025_CGVHD_IDB_SA\EMA\Programs\TFL\Original\ISS\t_6.sas

The safety analyses and especially establishing the causality of the identified events in the current setting is not without uncertainties. Adverse effects of disease under study, previous and concurrent treatments and

adverse events predicted on the basis of the mode of action of belumosudil are overlapping, and it is understandable that only rough estimates for frequencies of these events can be made in this heterogeneous patient population. Causality assessment is nonetheless central.

On request, the Applicant provided a sufficiently detailed description of the method of the causality assessment of the adverse drug reactions, for the proposed labeling, and provided clarification on how the causality was defined and justified, and exactly on what basis safety information was reflected in the SmPC. The Applicant's current approach is now acceptable and appears to comply with guidance. The separate attached PI was revised and updated as requested regarding safety and is now acceptable.

3.3.7.3. AEs of special interest, Serious adverse events, deaths, and other significant events

3.3.7.3.1 AEs of special interest

AESIs were selected based on the mechanism of action, nonclinical toxicology profile, and emerging clinical data. The identified AESI terms included hepatic events/increased liver enzymes, infections, hematologic events (anemia, leukopenia, neutropenia, and thrombocytopenia), malignancy/neoplasms (relapse of underlying malignancy and secondary neoplasm), hypotension, and impaired wound healing.

a) Hepatic adverse events and increased liver enzymes

Drug-induced liver injury is a potential risk associated with belumosudil based on nonclinical safety findings and emergent clinical data. In the pooled analysis, AEs within Liver related investigations, signs and symptoms were reported in 24.0% of participants in the 200 mg QD group and 28.2% of all belumosudil treated participants. The most common TEAEs within the Drug related hepatic disorders were AST increased [n, (%)] 32 (15.3%), ALT increased 30 (14.4%), and GGT) increased 26 (12.4%), all Grade ≤3 in severity. One participant in the 200 mg BID group had a Grade 4 TEAE of elevated LFTs evaluated as serious, and the patient recovered without a dose change. Grade 4 GGT increased was reported in a second participant within the same group resulting in dose interruption. Neither event was considered related to the study drug.

There were 5 (5.2%) patients in the 200 mg QD group and 13 (6.2%) patients in all treated patients with at least 1 Grade ≥3 TEAE of Drug related hepatic disorders. One patient had concurrent Grade 3 events of ALT increased and AST increased assessed as possibly related to the study drug. A second patient reported ascites and died shortly afterwards due to leukemia relapse.

In the first month of treatment, the incidences of AST increased, ALT increased, and GGT increased in the 200 mg QD group were low (5.2%, 7.3%, and 5.2%, respectively). In the second month of treatment, the incidences decreased to 1.1%, 2.3%, and 3.4%, respectively, and declined further thereafter. A similar pattern was noted for all belumosudil treated patients.

In the pooled cGVHD analysis, 24.0% of patients in the 200 mg QD group and 28.2% of all belumosudil-treated group experienced events in this category which primarily included reports of AST increased (13.5% 200 mg QD and 15.3% all belumosudil) and ALT increased (12.5% 200 mg QD and 14.4% all belumosudil). The incidence of AEs was 28.2% overall. One participant in the 200 mg BID group with reported PTs of Grade 3 ALT and AST increased assessed as possibly related to the study drug, led to permanent discontinuation of the study drug. Of the 59 participants with events in the HLGT Hepatobiliary investigations, 9 events (excluding GGT increased) were associated with a recurrence of the underlying malignancy in 6 participants.

Concomitant medications were reviewed as a possible contributing factor affecting LFTs. As of the cutoff date, 5 (8.5%) participants were taking rivaroxaban at the time of the LFT elevation (excluding GGT increased).

Shifts in ALT from baseline Grade ≤2 to the highest-grade post-baseline, Grade 3, were observed in 2 participants in the 200 mg QD group and 6 participants in the all-belumosudil group. The majority of the shifts were from baseline Grade 0 to the highest-grade post-baseline, Grade 1. There were no on-treatment shifts to Grade 4 for ALT. One participant in the 200 mg QD group and 5 participants in the all-belumosudil group had a shift in AST from Grade ≤2 to 3. A shift in AST from Grade ≤2 to 4 was observed for 1 participant in the 200 mg BID group. A shift in bilirubin from baseline Grade ≤2 to 3 was observed for 2 participants in the 200 mg BID group.

a) Infections

An increase in infection rates is a potential risk associated with belumosudil based on the mechanism of action. Infection events are provided as well as frequencies for specific categories of infections. Cumulative treatment-emergent adverse events are found in **Table 51** and Cumulative treatment-emergent adverse events of Grade ≥3 infections in **Table 52**.

Table 51: Cumulative treatment-emergent adverse events (≥2 participants) by preferred term for all infections (safety population)

	Belumosudil			
Category/ Preferred Term	**200 mg QD N = 96 n (%)**	**200 mg BID N = 92 n (%)**	**400 mg QD N = 21 n (%)**	**All N = 209 n (%)**
Participants with at least one TEAE of infection events	62 (64.6)	64 (69.6)	14 (66.7)	140 (67.0)
Upper respiratory tract infection	29 (30.2)	31 (33.7)	7 (33.3)	67 (32.1)
Pneumonia	11 (11.5)	15 (16.3)	1 (4.8)	27 (12.9)
Conjunctivitis	6 (6.3)	5 (5.4)	3 (14.3)	14 (6.7)
Influenza	4 (4.2)	7 (7.6)	2 (9.5)	13 (6.2)
Coronavirus infection	3 (3.1)	9 (9.8)	0	12 (5.7)
Rhinovirus infection	6 (6.3)	5 (5.4)	1 (4.8)	12 (5.7)
Sinusitis	4 (4.2)	5 (5.4)	1 (4.8)	10 (4.8)
Gastroenteritis	5 (5.2)	3 (3.3)	1 (4.8)	9 (4.3)
Cellulitis	5 (5.2)	3 (3.3)	0	8 (3.8)
Urinary tract infection	3 (3.1)	5 (5.4)	0	8 (3.8)
Bronchitis	3 (3.1)	3 (3.3)	1 (4.8)	7 (3.3)
Candida infection	5 (5.2)	1 (1.1)	1 (4.8)	7 (3.3)
Oral candidiasis	5 (5.2)	2 (2.2)	0	7 (3.3)
Skin infection	2 (2.1)	4 (4.3)	0	6 (2.9)
COVID-19	2 (2.1)	3 (3.3)	0	5 (2.4)
Nasopharyngitis	2 (2.1)	3 (3.3)	0	5 (2.4)
Ear infection	3 (3.1)	1 (1.1)	0	4 (1.9)
Hordeolum	2 (2.1)	1 (1.1)	1 (4.8)	4 (1.9)
Respiratory tract infection	4 (4.2)	0	0	4 (1.9)
Otitis externa	2 (2.1)	1 (1.1)	0	3 (1.4)
Pharyngitis	0	2 (2.2)	1 (4.8)	3 (1.4)
Pseudomonas infection	1 (1.0)	2 (2.2)	0	3 (1.4)
Respiratory syncytial virus infection	0	1 (1.1)	2 (9.5)	3 (1.4)

	Belumosudil			
Category/ Preferred Term	200 mg QD N = 96 n (%)	200 mg BID N = 92 n (%)	400 mg QD N = 21 n (%)	All N = 209 n (%)
Sepsis	2 (2.1)	1 (1.1)	0	3 (1.4)
Acute sinusitis	1 (1.0)	1 (1.1)	0	2 (1.0)
Appendicitis	1 (1.0)	1 (1.1)	0	2 (1.0)
Bacteraemia	0	2 (2.2)	0	2 (1.0)
Corneal infection	0	2 (2.2)	0	2 (1.0)
Cytomegalovirus infection reactivation	0	2 (2.2)	0	2 (1.0)
Device related infection	1 (1.0)	1 (1.1)	0	2 (1.0)
Folliculitis	1 (1.0)	0	1 (4.8)	2 (1.0)
Fungal infection	2 (2.1)	0	0	2 (1.0)
Fungal skin infection	1 (1.0)	1 (1.1)	0	2 (1.0)
Gastroenteritis viral	2 (2.1)	0	0	2 (1.0)
Helicobacter infection	2 (2.1)	0	0	2 (1.0)
Herpes zoster	1 (1.0)	1 (1.1)	0	2 (1.0)
Localised infection	1 (1.0)	1 (1.1)	0	2 (1.0)
Parainfluenzae virus infection	1 (1.0)	1 (1.1)	0	2 (1.0)
Paronychia	1 (1.0)	1 (1.1)	0	2 (1.0)
Pneumonia viral	0	1 (1.1)	1 (4.8)	2 (1.0)
Staphylococcal bacteraemia	2 (2.1)	0	0	2 (1.0)
Tinea pedis	1 (1.0)	1 (1.1)	0	2 (1.0)
Tooth infection	1 (1.0)	0	1 (4.8)	2 (1.0)
Varicella zoster virus infection	1 (1.0)	0	1 (4.8)	2 (1.0)
Viral upper respiratory tract infection	1 (1.0)	1 (1.1)	0	2 (1.0)
Wound infection	1 (1.0)	0	1 (4.8)	2 (1.0)

Abbreviations: BID=twice daily, HLGT=high level group term; QD=once daily; TEAE=treatment-emergent adverse events.
Program Source: P:\01_OngoingProjects\G_100_HEM_KD025_CGVHD_IDB_SA\EMA\Programs\TFL\Original\ISS\t_17.sas

Table 52: Cumulative treatment-emergent adverse events of Grade ≥3 infections (≥2 participants) by preferred term (safety population)

	Belumosudil			
Category Preferred Term	200 mg QD N = 96 n (%)	200 mg BID N = 92 n (%)	400 mg QD N = 21 n (%)	All N = 209 n (%)
Infections and infestations	20 (20.8)	23 (25.0)	6 (28.6)	49 (23.4)
Pneumonia	9 (9.4)	10 (10.9)	0	19 (9.1)
Rhinovirus infection	3 (3.1)	3 (3.3)	0	6 (2.9)
Cellulitis	2 (2.1)	2 (2.2)	0	4 (1.9)
Gastroenteritis	2 (2.1)	1 (1.1)	0	3 (1.4)
Lung infection	0	1 (1.1)	2 (9.5)	3 (1.4)
Sepsis	2 (2.1)	1 (1.1)	0	3 (1.4)
Appendicitis	1 (1.0)	1 (1.1)	0	2 (1.0)
COVID-19	0	2 (2.2)	0	2 (1.0)

Category Preferred Term	Belumosudil 200 mg QD N = 96 n (%)	 200 mg BID N = 92 n (%)	 400 mg QD N = 21 n (%)	 All N = 209 n (%)
Coronavirus infection	0	2 (2.2)	0	2 (1.0)
Device related infection	1 (1.0)	1 (1.1)	0	2 (1.0)
Influenza	0	2 (2.2)	0	2 (1.0)
Urinary tract infection	0	2 (2.2)	0	2 (1.0)

Abbreviations: BID=twice daily; QD=once daily. Program Source: P:\01_OngoingProjects\G_100_HEM_KD025_CGVHD_IDB_SA\EMA \Programs\TFL\Original\ISS\t_18.sas

In total, 18.8% of participants in the 200 mg QD group and 14.8% of all belumosudil-treated participants had at least 1 TEAE within Bacterial infectious disorders. Grade ≥3 bacterial infectious disorders (HLGT) were uncommon, occurring in 5.2% of participants in the 200 mg QD group and 4.3% of all belumosudil-treated participants. One participant had a Grade 3 event of cellulitis orbital assessed as serious and not related to the study drug but related to the underlying disease. The study drug was interrupted, and the participant recovered from the event. One participant experienced a fatal event of pneumonia.

In the pooled analysis, 21.9% of participants in the 200 mg QD group and 26.8% of all belumosudil-treated participants had at least 1 TEAE within the HLGT Viral infectious disorders and coronavirus infection was reported in 3.1% and 5.7% respectively. The incidence of COVID-19 was 2.1% and 2.4% in the 2 groups, respectively. One patient died of COVID-19 approximately 1.5 months after the last dose of the study drug. The event was evaluated as serious and not related to the study drug or the underlying disease. The majority of coronavirus and COVID-19 infections in other participants were of Grade 1 or 2 and assessed as unrelated to the study drug. In 3 cases, the Investigator evaluated the infection as possibly related to the study drug: Grade 3 COVID-19 in 1 participant considered serious, Grade 1 COVID-19 in a second participant, which resolved, and Grade 2 COVID-19 in a third participant, all resolved. Coronavirus infection and COVID-19 PTs seem to refer for partly overlapping condition(s). Applicant, on request, provided the definition of both PTs and, and justifiable, these data were pooled to exclude any possible dilution in the relevant AEs frequencies.

In the pooled analysis, 53.1% of participants from the 200 mg QD group and 56.9% of all belumosudil-treated participants had at least 1 TEAE within the HLGT Infections - pathogen unspecified, including 34 (16.3%) belumosudil-treated participants with at least 1 pathogen unspecified infection of Grade ≥3. All other Grade ≥3 infections in this category occurred with an incidence of <2% of all belumosudil-treated participants, excepting pneumonia, which occurred in 9.1%.

Cytomegalovirus (CMV) reactivation was observed in two patients in the pooled data. Both events were considered not related to belumosudil treatment and remained unresolved. One of the concerned patients discontinued from the study due to a Listeria brain abscess.

Other categories of infections

The overall incidence of TEAEs for other infectious disorders of interest including Infections - pathogen unspecified (HLGT), sepsis (HLT Sepsis, bacteremia, viremia, fungaemia NEC, and SMQ Sepsis), Respiratory tract infections (HLGT), Lower respiratory tract infections NEC (HLT), Infective pneumonia (SMQ), and Opportunistic infections (CMQ) were generally low in participants with cGVHD with the exception of respiratory infections.

The majority of TEAEs for other infectious disorders were of mild or moderate severity. Grade ≥3 respiratory infections and infective pneumonia were reported in approximately 10% of participants in the 200 mg QD group and all belumosudil-treated participants (range from 9.4% to 12.9%). The incidence of Grade ≥3 events in the Opportunistic infections and the Sepsis was <3% overall.

One participant experienced a fatal event of septic shock 4 days after the last dose of the study drug. The event was assessed as serious and unlikely related to the study drug or the underlying disease.

b) Hematologic events

As shown in **Table 53**, 16.7% of participants in the 200 mg QD group and 20.1% of participants in the all-belumosudil group in the pooled cGVHD analysis had at least 1 TEAE of cytopenia (anaemia, thrombocytopenia, neutropenia, or leukopenia, or cytopaenias affecting more than 1 cell line).

Table 53: Summary of cumulative hematologic events (safety population)

	Belumosudil			
Category/ Preferred Term	**200 mg QD N = 96 n (%)**	**200 mg BID N = 92 n (%)**	**400 mg QD N = 21 n (%)**	**All N = 209 n (%)**
Participants met the search criteria of hematological events	16 (16.7)	23 (25.0)	3 (14.3)	42 (20.1)
Anaemia	12 (12.5)	16 (17.4)	0	28 (13.4)
Platelet count decreased	4 (4.2)	5 (5.4)	0	9 (4.3)
Lymphocyte count decreased	2 (2.1)	5 (5.4)	0	7 (3.3)
White blood cell count decreased	3 (3.1)	2 (2.2)	1 (4.8)	6 (2.9)
Neutrophil count decreased	1 (1.0)	3 (3.3)	1 (4.8)	5 (2.4)
Thrombocytopenia	0	3 (3.3)	1 (4.8)	4 (1.9)
Haematocrit decreased	0	1 (1.1)	1 (4.8)	2 (1.0)
Myelodysplastic syndrome	1 (1.0)	0	1 (4.8)	2 (1.0)
Neutropenia	1 (1.0)	1 (1.1)	0	2 (1.0)
Febrile neutropenia	0	0	1 (4.8)	1 (0.5)
Leukopenia	0	1 (1.1)	0	1 (0.5)
Red blood cell count decreased	0	1 (1.1)	0	1 (0.5)

Abbreviations: BID=twice daily; QD=once daily; TEAE=treatment-emergent adverse events. Program Source: P:\01_OngoingProjects\G_100_ HEM_KD025_CGVHD_IDB_SA\EMA\Programs\TFL\Original\ISS\t_17.sas

A total of 12 (12.5%) participants in the 200 mg QD group and 29 (13.9%) of all belumosudil-treated participants in the pooled cGVHD analysis experienced an event within the Haematopoietic erythropaenia including anaemia (12.5% 200 mg QD and 13.4% all belumosudil), haematocrit decreased (none in 200 mg

QD and 1.0% all belumosudil), and red blood cell count decreased (none in 200 mg QD and 0.5% all belumosudil). In 4 participants, anaemia was associated with a relapse of the underlying disease. Anaemia (PT) Grade ≥3 events were reported in 4 (4.2%) participants in the 200 mg QD group and 8 (3.8%) of all belumosudil-treated participants. There were no Grades 4 or 5 events. TEAEs of anaemia as possibly related in 3 (3.1%) participants in the 200 mg QD group and 8 (3.8%) participants overall. All events were of Grade 1 or Grade 2 severity with the exception of 2 TEAEs of anaemia (Grade 2 and Grade 3) experienced by one participant in the 200 mg BID group. None of these related TEAEs were serious.

No participant experienced at least 1 Grade ≥3 anaemia result based on laboratory data; and 4.2% of participants in the 200 mg QD group and 3.8% of all belumosudil-treated participants had at least 1 Grade ≥3 TEAE or Grade ≥3 anaemia on laboratory tests.

Two participants each had a serious TEAE of anaemia assessed as unlikely related and not related to the study medication, respectively. One participant, a 65–84-year-old male receiving belumosudil 200 mg BID, was hospitalized 18 days after the initiation of study treatment for upper GI hemorrhage, anaemia, pleural effusion, dyspnea, and upper extremity anaemia. The events were assessed by the Investigator as not related to the study drug. Approximately one week later, the patient experienced a fatal cardiac arrest. There were no consistent differences in the time to first occurrence of anaemia across dose groups in the pooled analysis. The highest incidence of anaemia was between 3 and <6 months (5.3% in the 200 mg QD group and 4.5% in the all-belumosudil group) from study start.

Thrombocytopenia

In the pooled cGVHD analysis, 4 (4.2%) participants in the 200 mg QD group and 12 (5.7%) of all belumosudil-treated participants experienced an event within Haematopoietic thrombocytopenia, including platelet count decreased (4.2% 200 mg QD and 4.3% all belumosudil) and thrombocytopenia (none 200 mg QD and 1.9% all belumosudil). Two participants in the 200 mg BID group each had a Grade 1 TEAE of thrombocytopenia considered possibly related to the study drug. The TEAEs were not serious, and the patients recovered without dosing interruption. Grade ≥3 TEAEs were reported in 3.1% of participants in the 200 mg QD group and 1.4% of all belumosudil-treated participants, all of which were platelet count decreased. There was no clear timing as to when participants had their first event of thrombocytopenia with respect to the start of treatment in the pooled cGVHD.

The highest incidence of platelet count decreased was between 0 and <1 month (2.1% 200 mg QD and 2.4% all belumosudil); there were no thrombocytopenia events reported in the 200 mg QD group and the incidence of thrombocytopenia in the all-belumosudil group was <1%. Shifts in platelets from Grade ≤2 to Grade 3 occurred in 3 participants in the 200 mg QD group and 5 of all belumosudil-treated participants. One participant in the 200 mg QD group experienced an on-treatment shift from Grade 1 to 4.

Leukopenia

A total of 6.3% of participants in the 200 mg QD group and 8.1% of all belumosudil-treated participants experienced a TEAE within the SMQ Haematopoietic leukopenia, most commonly lymphocyte count decreased (2.1% 200 mg QD and 3.3% all belumosudil), white blood cell count decreased (3.1% 200 mg QD and 2.9% all belumosudil), neutrophil count decreased (1.0% 200 mg QD and 2.4% all belumosudil), and neutropenia (1.0% 200 mg QD and 1.0% all belumosudil). Grade ≥3 TEAEs of leukopenia were reported in 3.1% of participants in the 200 mg QD group and 3.3% of all belumosudil-treated participants. Three Grade 4 TEAEs are described below: There were no consistent differences in the incidence of the first occurrence of events of leukopenia in belumosudil-treated participants in the pooled cGVHD analysis. An event of febrile neutropenia occurred after 12 months of treatment with belumosudil. Shifts in leukocytes from Grade ≤2 to 3 were not

observed in any participants in the 200 mg QD group but were observed in 1 of all belumosudil-treated participants. Two participants in the 200 mg QD group experienced on-treatment shifts from Grade 0 to 4.

Neutropenia

One (1.0%) participant in the 200 mg QD group and 3 (1.4%) participants in the belumosudil-treated group experienced an event of neutropenia (HLT) in the pooled cGVHD analysis. Grade ≥3 events in this category were reported in 1.0% of participants in the 200 mg QD group and 1.4% of all belumosudil-treated participants, neutropenia in 2 (1.0%) participants and febrile neutropenia in 1 (0.5%) participant overall. The 2 events of neutropenia occurred during the following time periods: between 6 and <9 months of treatment (200 mg QD) and between 0 and <1 month (200 mg BID). The event of febrile neutropenia occurred after 12 months of treatment with belumosudil. Shifts in neutrophils from normal at baseline to minimum value post-baseline of low occurred in 6 (6.3%) participants in the 200 mg QD group and in 17 (8.1%) of all belumosudil-treated participants in the pooled cGVHD analysis.

c) Malignancy/neoplasms

In the pooled cGVHD analysis, malignant or unspecified tumors were reported in 10.4% of participants in the 200 mg QD group and 9.6% of all belumosudil-treated participants. The most commonly reported (≥2 participants) events within this category included AML recurrent (2.1% 200 mg QD and 1.4% all belumosudil), acute lymphocytic leukemia recurrent (1.0% 200 mg QD and 1.0% all belumosudil), leukemia recurrent (1.0% 200 mg QD and 1.0% all belumosudil), plasma cell myeloma (1.0% 200 mg QD and 1.0% all belumosudil), and squamous cell carcinoma of the skin (0% 200 mg QD and 1.0% all belumosudil). Grade ≥3 events of malignant or unspecified tumors were reported in 6.3% of participants in the 200 mg QD group and 5.3% of all belumosudil-treated participants.

d) Hypotension

Based on the on-target effect of pan-Rho-associated, coiled-coil containing protein kinase (ROCK) inhibitors and the observed lowering of blood pressure in nonclinical studies, hypotension initially was considered a potential risk. The pooled analysis identified 4 (4.2%) participants in the 200 mg QD group and 11 (5.3%) belumosudil-treated participants overall with TEAEs in this category including hypotension in 4.2% and 5.3% of participants and orthostatic hypotension in 1.0% and 0.5% in the 200 mg QD group and all belumosudil-treated population, respectively. Nine of the 11 participants with TEAEs of hypotension were listed as recovered. Two participants in the 200 mg QD group had a dose interruption due to the event. The majority of TEAEs were of Grade 1 or 2 severity and occurred in 1 participant each with the exception of 1 participant who reported two Grade 2 TEAEs of orthostatic hypotension and hypotension. In 2 other participants the TEAE was assessed as serious, of Grade 3 severity and considered not or unlikely related to the study medication. One nonserious Grade 3 event was considered possibly related by the Investigator. A review of decreases from baseline in systolic and diastolic blood pressure in participants with cGVHD did not reveal substantial changes.

e) Impaired wound healing

Impaired wound healing is a potential risk due to the antifibrotic mechanism of action of belumosudil. The pooled analysis identified 1 (0.5%) participant with cGVHD with an event in this category; the event of impaired wound healing occurred in the first month of treatment with belumosudil 200 mg QD.

3.3.7.3.2. Serious adverse events

In the pooled cGVHD analysis, SAEs were reported in 45.8% of participants in the 200 mg QD group and in 45.0% of all belumosudil-treated participants (**Table 54**).

Table 54: Cumulative serious treatment-emergent adverse events ≥2 participants by system organ class and preferred term (safety population)

	Belumosudil			
System Organ Class Preferred Term	**200 mg QD N = 96 n (%)**	**200 mg BID N = 92 n (%)**	**400 mg QD N = 21 n (%)**	**All N = 209 n (%)**
Participants with at least one serious TEAE	44 (45.8)	37 (40.2)	13 (61.9)	94 (45.0)
Infections and infestations	17 (17.7)	25 (27.2)	5 (23.8)	47 (22.5)
Pneumonia	9 (9.4)	7 (7.6)	1 (4.8)	17 (8.1)
Cellulitis	2 (2.1)	2 (2.2)	0	4 (1.9)
Rhinovirus infection	2 (2.1)	2 (2.2)	0	4 (1.9)
Coronavirus infection	0	3 (3.3)	0	3 (1.4)
Lung infection	0	1 (1.1)	2 (9.5)	3 (1.4)
Sepsis	2 (2.1)	1 (1.1)	0	3 (1.4)
Urinary tract infection	0	3 (3.3)	0	3 (1.4)
Appendicitis	1 (1.0)	1 (1.1)	0	2 (1.0)
Bacteraemia	0	2 (2.2)	0	2 (1.0)
COVID-19	0	2 (2.2)	0	2 (1.0)
Device related infection	1 (1.0)	1 (1.1)	0	2 (1.0)
Staphylococcal bacteraemia	2 (2.1)	0	0	2 (1.0)
Upper respiratory tract infection	1 (1.0)	1 (1.1)	0	2 (1.0)
Respiratory, thoracic and mediastinal disorders	10 (10.4)	7 (7.6)	4 (19.0)	21 (10.0)
Dyspnoea	1 (1.0)	3 (3.3)	3 (14.3)	7 (3.3)
Hypoxia	1 (1.0)	1 (1.1)	2 (9.5)	4 (1.9)
Pulmonary embolism	2 (2.1)	1 (1.1)	0	3 (1.4)
Acute respiratory failure	1 (1.0)	1 (1.1)	0	2 (1.0)
Pleural effusion	0	1 (1.1)	1 (4.8)	2 (1.0)
Gastrointestinal disorders	7 (7.3)	6 (6.5)	2 (9.5)	15 (7.2)
Diarrhoea	2 (2.1)	1 (1.1)	0	3 (1.4)
Abdominal pain	0	2 (2.2)	0	2 (1.0)
Colitis	1 (1.0)	1 (1.1)	0	2 (1.0)
Nausea	1 (1.0)	1 (1.1)	0	2 (1.0)

	Belumosudil			
System Organ Class **Preferred Term**	**200 mg QD** **N = 96** **n (%)**	**200 mg BID** **N = 92** **n (%)**	**400 mg QD** **N = 21** **n (%)**	**All** **N = 209** **n (%)**
Small intestinal obstruction	1 (1.0)	0	1 (4.8)	2 (1.0)
Vomiting	1 (1.0)	1 (1.1)	0	2 (1.0)
General disorders and administration site conditions	8 (8.3)	3 (3.3)	2 (9.5)	13 (6.2)
Pyrexia	3 (3.1)	1 (1.1)	0	4 (1.9)
Face oedema	2 (2.1)	0	0	2 (1.0)
Influenza like illness	0	0	2 (9.5)	2 (1.0)
Multiple organ dysfunction syndrome	2 (2.1)	0	0	2 (1.0)
Cardiac disorders	4 (4.2)	6 (6.5)	2 (9.5)	12 (5.7)
Cardiac arrest	0	2 (2.2)	1 (4.8)	3 (1.4)
Myocardial infarction	2 (2.1)	0	0	2 (1.0)
Pericardial effusion	0	1 (1.1)	1 (4.8)	2 (1.0)
Vascular disorders	4 (4.2)	3 (3.3)	0	7 (3.3)
Hypotension	1 (1.0)	1 (1.1)	0	2 (1.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (3.1)	0	3 (14.3)	6 (2.9)
AML recurrent	2 (2.1)	0	0	2 (1.0)
Injury, poisoning and procedural complications	2 (2.1)	3 (3.3)	0	5 (2.4)
Fall	1 (1.0)	1 (1.1)	0	2 (1.0)
Renal and urinary disorders	3 (3.1)	1 (1.1)	1 (4.8)	5 (2.4)
Acute kidney injury	2 (2.1)	1 (1.1)	0	3 (1.4)
Blood and lymphatic system disorders	0	3 (3.3)	1 (4.8)	4 (1.9)
Anaemia	0	2 (2.2)	0	2 (1.0)
Musculoskeletal and connective tissue disorders	1 (1.0)	3 (3.3)	0	4 (1.9)
Back pain	0	2 (2.2)	0	2 (1.0)
Psychiatric disorders	1 (1.0)	2 (2.2)	0	3 (1.4)
Confusional state	1 (1.0)	1 (1.1)	0	2 (1.0)

Abbreviations: AML=acute myeloid leukaemia; BID=twice daily; QD=once daily; TEAE=treatment-emergent adverse events.
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No safety concerns were raised on these data.

3.3.7.3.3 Deaths

Table 55: Summary of participants who died within 28 days of ending study drug during the update period (safety population)

Participant's Treatment Group	Treatment Duration (Months)	Reason for Ending Treatment	Primary Cause of Death (Preferred Term)	Relationship to Study Drug as Assessed by Investigator	Time from Last Dose (Days)	Comments	Source
Deaths Occurring During the Safety Update Period							
Belumosudil 200 mg BID	9.6	Withdrawal by participant	Infection [due to cGVHD]	Possibly related	20	Male (65 to 84 years old) with a history of myelodysplastic syndrome, hypertension and Parkinson's disease experienced infection related to cGVHD.	Study KD025-213
Belumosudil 200 mg BID	9.0	Death	Cardiac arrest	Unlikely related	1	Male (18 to 64 years old) with a history of hyperglycaemia and hypertension experienced a cardiac arrest.	Study KD025-213
Belumosudil 200 mg BID	7.8	Death	Respiratory arrest	Unlikely related	1	Female (18 to 64 years old) with AML, type 2 diabetes mellitus, type IIa hyperlipidaemia, essential hypertension, and syncope experienced a respiratory arrest	Study KD025-213

Participant's Treatment Group	Treatment Duration (Months)	Reason for Ending Treatment	Primary Cause of Death (Preferred Term)	Relationship to Study Drug as Assessed by Investigator	Time from Last Dose (Days)	Comments	Source
Belumosudil 200 mg QD	33.0	Death	Multiple organ dysfunction	Not related	7	Male (65 to 85 years old) with AML and ongoing Type II diabetes mellitus, hyperlipidaemia, hypertension, dyspnoea, obliterative bronchiolitis, and gastroesophageal reflux disease who experienced multiple organ dysfunction.	Study KD025-213
Belumosudil 200 mg QD	1.0	Death	Hemothorax	Not related	5	Male (18 to 64 years old) hospitalized for pneumatosis of colon related to cGVHD died from haemothorax.	Study KD025-213
Belumosudil 200 mg QD	1.5	Adverse event	Aspiration Respiratory failure	Not related Not related	12	Male (65 to 84 years old) with recurrent aspiration events, left sided pneumothorax requiring chest tube placement, and non ST elevation myocardial infarction due to demand ischemia.	Study KD025-213
Belumosudil 200 mg QD	0.5	Death	Septic shock Multi organ dysfunction syndrome	Unlikely related Possibly related	4	Male (65 to 84 years old) died of AML complicated by neutropenic shock secondary to acute pneumonia.	Study KD025-213
Belumosudil 200 mg QD	1.3	Disease relapse	Acute myeloid leukaemia recurrent	Not related	17	Male (18 to 64 years old) had relapse of AML.	No qualifying narrative.

Participant's Treatment Group	Treatment Duration (Months)	Reason for Ending Treatment	Primary Cause of Death (Preferred Term)	Relationship to Study Drug as Assessed by Investigator	Time from Last Dose (Days)	Comments	Source
Belumosudil 200 mg BID	0.4	Death	Cardiac arrest	Unlikely related	15	Male (65 to 84 years old) experienced upper GI haemorrhage, anaemia, pleural effusion, dyspnoea and oedema right arm; died from cardiac arrest after 'do not resuscitate' order instituted.	Study KD025-213
Belumosudil 400 mg QD	0.7	Disease relapse	Leukaemia recurrent	Not related	5	Female (65 to 84 years old) had relapse of AML study Day 8	No qualifying narrative.
Belumosudil-400 mg QD	2.2	Death	Pneumonia	Not related	1	Female (18 to 64 years old), with cGVHD involving lung, hospitalized with suspected pneumonia and skin infection, and required repeated intubations due to hypoxia.	Study KD025-208
Belumosudil 400 mg QD	0.7	Death	Cardiac arrest	Not related	1	Male (18 to 64 years old) found unresponsive at home of suspected cardiac arrest.	Study KD025-208.
Belumosudil 400 mg QD	14.1	Progressive disease	GVHD in lung	Not related	2	Male (18 to 64 years old) with progression of cGVHD.	No qualifying narrative.

There were overall 13 deaths in the safety population. Two cases were without qualifying narratives. The incidence of treatment-related fatal cases was overall low. Five patients died in the 200 mg QD treatment group of which two deaths were deemed related to treatment with belumosudil. However, on the basis of the provided narratives, there was some uncertainty in the investigator´s assessment of causality for several subjects, who eventually died due to an event or within the event. However, considering the gravity of the clinical status of the patients and the plethora confounding factors, it is unlikely that any further delving into the available data would clarify the uncertainties inherent to the causality assessment of the deaths.

3.3.7.3.4 *Other significant events*

Cardiac safety Among the 209 belumosudil-treated patients, there were no events of Torsade de pointes, sudden death, ventricular tachycardia, ventricular fibrillation, ventricular flutter, or seizures. In the pooled cGVHD analysis, 3 participants suffered from a fatal cardiac arrest (2 participants 200 mg BID and 1 participant 400 mg QD), none of which were assessed as related to the study drug and with no evidence that the events were related to QTc prolongation. Cumulatively, 4 patients reported ECG QT prolongation and 6 reported syncope. None were assessed as related. Except for the fatal events of cardiac arrests and the single events of tachycardia and atrial flutter, all other events were nonserious, most participants recovered, and the study medication was not changed. Across all 209 patients, none with on-treatment QTcF of >480 reported a TEAE associated with a clinical event. The thorough QT study showed no association between belumosudil and QTc prolongation.

Renal safety Events of Acute renal failure were identified in a total of 12.5% of participants in the 200 mg QD group and 17.2% of all belumosudil treated participants in the pooled analysis. The most frequently reported TEAEs in this category in the 200 mg QD and all treated participants, respectively, included blood creatinine increased (7.3% and 9.1%) and acute kidney injury (4.2% and 5.7%). The majority of renal events were mild or moderate in severity. Grade ≥3 events were reported in a total of 4 (1.9%) participants. Acute kidney injury was reported in 3 (1.4%) participants overall: 2 (2.1%) in the 200 mg QD group, and 1 (1.1%) in the 200 mg BID group and Grade ≥3 proteinuria was reported in 1 (1.1%) patient (200 mg QD group) evaluated as related to the underlying disease. All Grade ≥3 events were reported as SAE and all were assessed as unlikely related or not related to treatment with the study drug. In 4 patients TEAEs of blood creatinine increased were assessed as possibly related. One of these patents had 6 TEAEs of blood creatinine increased, including 1 event concurrent with blood urea increased, also considered possibly related to the study drug. The participant recovered from all events without a dose change. The majority of events of renal failure occurred either in the first month of treatment or between 1 and <2 months of treatment.

3.3.7.4. Safety relationship with dose, dose regimen, and treatment duration

Review of the pooled analyses revealed no consistent differences in the incidence of the most commonly reported TEAEs for participants in the belumosudil 200 mg QD group compared to the 200 mg BID group, to the 400 mg QD group, or to all belumosudil-treated participants (see tables above). The frequency of TEAEs did not significantly increase over time from the 0 to <1 month onset period to the 9 to <12-month onset period, indicating no cumulative toxicity with longer treatment. The incidence of the first occurrence of events was similar between participants in the 200 mg QD group and all belumosudil-treated participants.

3.3.7.5. Laboratory findings

Haematology parameters

Results of shift analyses for platelet count, hemoglobin concentrations, neutrophil counts, and leukocyte counts are shown and discussed with the corresponding AESIs. Lymphocyte values were consistent over the course of treatment for all participants with cGVHD; results were similar across treatment/dosing groups. Among patients whose starting dose was 200 mg QD, shifts in lymphocytes from Grade ≤ 2 to maximum Grade 3 were observed for 1 (1.0%) participant; no patients had a shift from baseline Grade ≤ 2 to a maximum post-baseline Grade 4. Among the 209 participants with cGVHD, shifts in lymphocytes from Grade ≤2 to maximum Grade 3 were observed for 1 (1.0%) participant in the 200 mg QD group.

Clinical chemistry parameters

There were no clinically meaningful changes from baseline in mean serum chemistry parameters. These data including the liver function tests (LFT) and on-treatment shifts from baseline to worst CTCAE grade for LFT are found and discussed with the corresponding AESIs. It is noted that no patients met the criteria for Hy's Law.

These data including haematology parameters and the liver function tests (LFT) and on-treatment shifts from baseline to worst CTCAE grade for LFT, are found and discussed with the corresponding AESIs. Overall, the laboratory results were largely as expected for this type of study, considering the grave characteristics of the target cGVHD patient population, and the treatments under study.

In vitro biomarker test for patient selection for safety

N/A

3.3.7.6. Safety in special populations/subgroup analysis

Intrinsic factors

An analysis of TEAEs by age was performed with subgroups defined as ≥65 years and <65 years of age. The majority of participants in the pooled analyses were adults <65 years of age including 3 adolescents (158 of 209; 75.6%), and 51 participants (24.4%) were ≥65 years of age. The overall incidence of TEAEs was similar in younger and older participants (99.4% and 98.0%, for those <65 years and ≥65 years, respectively). Preferred terms that met the criteria for a >10 percentage point difference between age groups <65 versus ≥65, respectively were nausea (36.1% versus 19.6%), dysphagia (14.6% versus 3.9%), nasal congestion (14.6% versus 2.0%), and headache (32.3% versus 15.7%).

The overall incidence of TEAEs was similar in male and female (by gender) participants (100.0% and 97.7%, respectively). The most commonly reported TEAEs for both male and female participants were in the SOCs Gastrointestinal disorders (71.3% versus 77.0%, respectively) and Infections and infestations (61.5% versus 75.9%, respectively). Treatment-emergent AEs with a >10% difference in incidence in the all-belumosudil group between male and female participants included muscular weakness (13.1% versus 2.3%, respectively), neuropathy peripheral (2.5 versus 12.6, respectively), and anaemia (9.0% versus 19.5%, respectively).

An analysis of TEAEs by race was performed for White or Caucasian participants versus participants of "Other" race. In the pooled analysis, the majority of participants were White or Caucasian (182 of 209 [87.1%)]). Given the difference in sample size, any differences in incidence across the race subgroups should be evaluated with caution.

An analysis of TEAEs by BMI group was performed with subgroups defined as <25 kg/m^2, 25 to <30 kg/m^2, and ≥30 kg/m^2. The overall number of participants in the pooled analysis with cGVHD in the BMI categories of <25 kg/m^2, 25 to <30 kg/m^2, and ≥30 kg/m^2 was 70 (37.6%), 68 (36.6%), and 48 (25.8%) (note, baseline height data were collected for 186 participants). The overall incidence of TEAEs was similar across the BMI categories of <25 kg/m^2, 25 to <30 kg/m^2, and ≥30 kg/m^2 at 100%, 100%, and 97.9%, respectively. The most commonly reported TEAEs with >10% difference in incidence between BMI subgroups were abdominal pain (8.6%, 11.8%, and 20.8%), upper respiratory tract infection (28.6%, 33.8%, and 43.8%), pneumonia (5.7%, 13.2%, and 20.8%), back pain (2.9%, 19.1%, and 12.5%), fatigue (27.1%, 48.5%, and 27.1%), oedema peripheral (20.0%, 35.3%, and 16.7%), fall (12.9%, 7.4%, and 18.8%), ALT

increased (24.3%, 8.8%, and 4.2%), AST increased (25.7%, 8.8%, and 4.2%), and headache (22.9%, 32.4%, and 20.8%).

An analysis of TEAEs by baseline hepatic impairment was performed for participants with normal hepatic function versus participants with hepatic function >ULN (defined as AST>ULN or ALT>ULN or total bilirubin>ULN). The majority of all treated participants in the pooled analysis had normal hepatic function (142 [68.3%]), and 66 (31.7%) participants had hepatic function >ULN (note, baseline data are collected for 208 participants). Given the difference in sample size, any differences in incidence across the subgroups should be evaluated with caution. The overall incidence of TEAEs was similar between participants with normal hepatic function compared to those with >ULN hepatic function (98.6% and 100.0%, respectively). Overall, there were no consistent differences across treatment groups in the incidence of the most commonly reported TEAEs for participants with normal hepatic function compared to those with >ULN hepatic function.

The most commonly reported TEAEs in all treated participants with normal versus >ULN hepatic function were in the SOC Gastrointestinal disorders SOC (74.6% versus 71.2%, respectively). For normal hepatic function compared to hepatic impairment, differences of >10 percentage points were seen in nausea, AST increased, GGT increased, dyspnea, and cough.

An analysis of TEAEs by baseline renal impairment was performed for participants with normal renal function (glomerular filtration rate [GFR] >90), participants with mild renal impairment (GFR 60-90), and participants with moderate real impairment (GFR <60). Most participants had mild renal impairment at study entry; 71 participants (34.5%) had normal renal function, 97 participants (47.0%) had mild impairment, and 38 (18.4%) had moderate to severe impairment (note, baseline data were collected for 206 participants). Treatment-emergent AEs with a >10 percentage point difference between subgroups are summarized in **Table 56**.

Table 56: Treatment-emergent adverse events (>10 percentage point differences between subgroups) by renal impairment (safety population)

	All Belumosudil		
System Organ Class Preferred Term	**Normal GFR >90 N=71 n (%)**	**Mild GFR 60 to 90 N=98 n (%)**	**Moderate GFR <60 N=39 n (%)**
Participants with at least one TEAE	71 (100.0)	97 (99.0)	38 (97.4)
Gastrointestinal disorders	49 (69.0)	70 (71.4)	34 (87.2)
Diarrhoea	27 (38.0)	30 (30.6)	19 (48.7)
Nausea	17 (23.9)	34 (34.7)	16 (41.0)
Abdominal pain	11 (15.5)	11 (11.2)	10 (25.6)
General disorders and administration site conditions	41 (57.7)	61 (62.2)	27 (69.2)
Oedema peripheral	15 (21.1)	26 (26.5)	13 (33.3)
Metabolism and nutrition disorders	33 (46.5)	46 (46.9)	26 (66.7)
Hyperglycaemia	10 (14.1)	11 (11.2)	11 (28.2)
Dehydration	2 (2.8)	8 (8.2)	6 (15.4)
Hypomagnesaemia	2 (2.8)	3 (3.1)	5 (12.8)

	All Belumosudil		
System Organ Class Preferred Term	Normal GFR >90 N=71 n (%)	Mild GFR 60 to 90 N=98 n (%)	Moderate GFR <60 N=39 n (%)
Respiratory, thoracic and mediastinal disorders	43 (60.6)	58 (59.2)	26 (66.7)
Dyspnoea	21 (29.6)	23 (23.5)	15 (38.5)
Hypoxia	2 (2.8)	7 (7.1)	6 (15.4)
Nasal congestion	14 (19.7)	7 (7.1)	3 (7.7)
Vascular disorders	19 (26.8)	35 (35.7)	20 (51.3)
Hypertension	11 (15.5)	17 (17.3)	13 (33.3)
Deep vein thrombosis	1 (1.4)	2 (2.0)	5 (12.8)
Injury, poisoning and procedural complications	28 (39.4)	35 (35.7)	19 (48.7)
Fall	6 (8.5)	13 (13.3)	8 (20.5)
Investigations	42 (59.2)	52 (53.1)	19 (48.7)
Blood creatinine increased	2 (2.8)	9 (9.2)	8 (20.5)
Weight decreased	5 (7.0)	8 (8.2)	7 (17.9)
Blood urea increased	-	1 (1.0)	4 (10.3)
Renal and urinary disorders	12 (16.9)	18 (18.4)	14 (35.9)
Acute kidney injury	2 (2.8)	5 (5.1)	5 (12.8)
Chronic kidney disease	-	3 (3.1)	4 (10.3)
Blood and lymphatic system disorders	12 (16.9)	20 (20.4)	12 (30.8)
Anaemia	7 (9.9)	12 (12.2)	9 (23.1)

Abbreviations: TEAE=treatment-emergent adverse events.
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An analysis of TEAEs by severity of cGVHD, defined as at least one organ with a score of 3 or a lung score of 2 or 3 at screening was performed with subgroups defined as severe or not severe. The majority of participants overall had severe cGVHD at screening (149 of 209 [71.3%]); 60 (28.7%) participants did not have severe cGVHD at screening.

The overall incidence of TEAEs was similar between participants with severe and non-severe cGVHD at screening (98.7% and 100%, respectively). The incidence of TEAEs was generally higher in participants with non-severe diseases. The most commonly reported TEAEs overall in participants with severe and non-severe cGVHD were in the SOC Gastrointestinal disorders (72.5% versus 76.7%, respectively). TEAEs with a >10% difference in incidence between participants with severe and non-severe cGVHD in the all- belumosudil group included diarrhoea (32.9% versus 46.7%), vomiting (17.4% versus 30.0%), pyrexia (14.1% versus 25.0%), and nasal congestion (7.4% versus 21.7%).

An analysis of TEAEs by duration of cGVHD before enrollment was performed with subgroups defined as >50th percentile from the median and ≤50th percentile from the median; the calculated median for time from the diagnosis of cGVHD to enrollment was 25.17 months overall. In both subgroups, 99.0% of all-treated participants had a TEAE. There were no consistent differences across treatment groups in the incidence of the most commonly reported TEAEs for participants based on duration of cGVHD before

enrollment. Treatment-emergent AEs reported with a >10% difference in incidence between participants in the >50th percentile and ≤50th percentile in the all-belumosuincludingp included diarrhea (28.8% versus 44.8% participants, respectively).

Extrinsic factors

An analysis of TEAEs by number of prior lines of therapy was performed with subgroups defined as ≤3 and >3 prior lines of therapy. The majority of participants with cGVHD had received ≤3 lines of prior therapy (132 of 209, [63.2%]); overall, 77 (36.8%) participants had received >3 prior lines of therapy. The incidence of TEAEs in the all-treated group was similar in participants who had received ≤3 and >3 prior lines of therapy (99.2% and 98.7%, respectively). Overall, there were no consistent differences across subgroups in the incidence of the most commonly reported TEAEs. The highest incidence of TEAEs was observed in the SOC Gastrointestinal disorders with the overall incidence of TEAEs being similar between prior lines of therapy subgroups (72.0% in ≤3 prior lines of therapy and 76.6% in >3 prior lines of therapy). The only event with a >10% difference in incidence between subgroups in the all-belumosudil group was fatigue (31.1% in ≤3 prior lines versus 45.5% in >3 prior lines), likely indicating the severity of the disease in participants having received a greater number of prior lines of therapy.

3.3.7.7. Immunological events

N/A

3.3.7.8. Safety related to drug-drug interactions and other interactions

Review of the pooled analyses of drug-drug interaction for the belumosudil 200 mg QD group revealed no consistent differences in the incidence of the most commonly reported TEAEs for participants taking or not taking a proton pump inhibitor or a strong CYP3A inhibitor. Belumosudil has the following effects on UGT1A1, P-gp, and BCRP/OATP1B1:

-Data indicate that belumosudil may inhibit glucuronidation via UGT1A1. While there were no changes in raltegravir exposure, there was a 40% decrease in exposure of the glucuronide metabolite.

0Data indicate that belumosudil may inhibit P-gp. Belumosudil increased unconjugated dabigratan Cmax by 2.4-fold, and AUC by 2.1-fold, while Tmax and T1/2 remained unchanged. Data indicate that belumosudil inhibits either one or both transporters OATP1B1 and BCRP. Belumosudil co-administration increased rosuvastatin Cmax by 3.6-fold and AUC exposure by 4.6-fold. Additionally, belumosudil co-administration resulted in an earlier Tmax (from 6 to 2.5 hours), and shorter T1/2 (from 4.1 to 2.7 hours), albeit with just 5 reliable estimates on Day 1.

Review of demographic factors in the pooled analyses found no evidence of notable differences in the TEAE profile of the belumosudil 200 mg QD group related to age, sex, race, region, body mass index, hepatic impairment, renal impairment, or on-treatment QTcF value or by region.

Review of disease factors in the pooled analyses found no evidence of unexpected differences in the TEAE profile of the belumosudil 200 mg QD group related to cGVHD severity, duration of cGVHD duration, or number of lines of prior therapy.

3.3.7.9. Discontinuation due to adverse events

In the pooled cGVHD analysis, discontinuation of belumosudil due to TEAEs was reported in 21.9% of participants in the 200 mg QD group and 23.9% of all belumosudil-treated participants. It should be noted that more than 23.8% (5/21) of participants in the 400 mg QD group discontinued study drug due to a malignancy.

The incidence of treatment-related TEAEs leading to study drug withdrawal was low (12.5% of participants in the 200 mg QD group and in 9.6% of all belumosudil-treated participants) and occurred most often due to fatigue (3 [1.4%] participants), and nausea, AST increased, and headache (2 [1.0%] participants each).

In the pooled cGVHD analysis, TEAEs leading to study drug interruption were reported in 33 (34.4%) of the 200 mg QD treated participants and 70 (33.5%) of all belumosudil-treated participants most frequently due to pneumonia (6 [6.3%] and 11 [5.3%] participants, respectively), diarrhoea (3 [3.1%] and 4 [1.9%] participants, respectively), nausea (2 [2.1%] and 4 [1.9%] participants, respectively), and vomiting (1 [1.0%] and 4 [1.9%] participants, respectively).

Treatment-related TEAEs leading to study drug interruption were reported in 14 (14.6%) of the 200 mg QD treated participants and 24 (11.5%) of the 209 belumosudil-treated participants, which included fatigue, diarrhoea, vomiting, and ALT increased in 2 (1.0%) participants each and nausea in 3 (1.4%) participants. All other events occurred in 1 participant each. The overall incidence of treatment-related TEAEs leading to study drug interruption was generally lower in participants with 200 mg QD (14.6%) and 200 mg BID (6.5%) dosing than in participants whose starting dose was 400 mg QD (19.0%).

Dose reductions due to TEAEs were uncommon in the pooled cGVHD analysis and were reported in 3 (3.1%) participants in the 200 mg QD group and 10 (4.8%) of all belumosudil-treated participants. Participants reduced their dose due to fatigue (3 [1.4%] participants) followed by neuropathy peripheral (2 [1.0%] participants). In 9 of the 10 belumosudil-treated participants with a dose reduction, the Investigator assessed the responsible TEAEs as related to the study drug.

Adverse events (fatigue and neuropathy) leading to dose reduction were rare, three cases in the belumosudil 200 mg treatment group. The dose interruptions were relatively high 34%, even for this type of study considering the seriousness of the patient status and overall, the treatment setting. Study drug withdrawals were on the other hand rarer, possibly indicating that they are at least partly be manageable.

Overall, no specific pattern or clustering of any discontinuations that would raise concern was clearly evident, even after the Applicant's clarification. Overall, no dose dependency was apparent.

3.3.7.10. Post marketing experience

Belumosudil received the first marketing authorization in the United States by the FDA on 16 July 2021 for the treatment of adult and adolescent patients 12 years and older with cGVHD after failure of at least 2 prior lines of systemic therapy, and since in Canada, Great Britain, Israel, United Arab Emirates, and Japan. Furthermore, belumosudil has been approved for the treatment of patients with cGVHD aged 12 years and older who have an inadequate response to corticosteroids in Australia on 12 November 2021 and in China on 01 August 2023. The approved pharmaceutical strength of belumosudil is 200 mg tablets.

Exposure from the cumulative post-marketing experience following the marketing authorisation in the US, Canada, Great Britain, and Israel is available from frpost-marketing experience for the period from 01 April 2022 through 31 January 2024. No sales data were reported before 01 April 2022.

Post marketing safety data was presented from USA and Britain and nine non-EU sources in four separate Periodic Benefit Risk Evaluation Reports extending just over two years from 12.11.2021 to 15.01.2024. An update of the post marketing data on the whole, to date, was on request provided by the Applicant. No new or unexpected safety concerns were evident from these data.

There are compassionate use programs in Hong Kong, France, Spain Austria, Bulgaria, Czech Republic, Greece, Italy, Hungary, Lithuania, Poland, Finland, Sweden, and Netherlands. Exposure data is only available from the first three countries the In addition, there are sales in Russian Federation from unsolicited requests processed through charity funds.

The cumulative exposure to belumosudil from post-marketing experience and compassionate use programs was estimated to be 1 324 857 treatment days. In total, approximately 6000 patients received belumosudil in the post-marketing setting since first launch and more than 300 patients under compassionate use. Of those, 2422 patients reported safety information (6994 events); the majority of events were nonserious (5654 [80.8%] nonserious versus 1559 [22.3%] serious). The majority of the reported events (>500) were classified in the following SOCs: General disorders and administration site conditions (1362 events, 19.6%), Injury, poisoning and procedural complications (999 events, 14.3%), Gastrointestinal disorders (868 events, 12.4%), Investigations (617 events, 8.8%), and Infections and infestations (548 events, 7.8%).

The most frequently reported events by PT (≥2%) were Fatigue (303 events, 4.3%), Inappropriate schedule of product administration (235 events; 3.3%); Drug ineffective (191, 2.7%), Product use in unapproved indication (170 events, 2.4%), Nausea (170 events, 2.4%), Diarrhoea (161 events, 2.3%), Off label use (151 events, 2.1%), and Dyspnoea (144 events, 2.1%).

In all, 69 patients were less than 18 years of age and received treatment with belumosudil in the post-marketing setting or during compassionate use. Forty-eight patients were adolescents (12 to 17 years) and 21 were paediatric patients (1 to 11 years). The majority of the reported events (≥20) were classified in the following SOCs: Injury, poisoning and procedural complications (42 events, 0.6%), Infections and infestations (25 events, 0.4%), Gastrointestinal disorders (22 events, 0.3%), General disorders and administration site conditions (21 events, 0.3%), and Investigations (20 events, 0.3%). The most frequently reported events by PT (≥5 events) were Product use in unapproved indication, Nausea, and Product use issue (7 events each), Inappropriate schedule of product administration (7 events), Off label use, Death, Headache and Product administered to patient of inappropriate age (5 events each). No actions were taken for safety reasons during the period covered by the four reports and the benefit-risk balance of belumosudil in the treatment of patients with chronic graft versus host disease remained positive in the currently approved indications.

3.3.7.11 Supportive studies

Study ME3208-2 (Japan) A multicenter, open-label, single-arm, phase 3 clinical study of belumosudil in patients with steroid-dependent/resistant cGVHD who have received one to three lines of systemic therapy

All 21 subjects who received the study drug were included in the safety analysis set (mITT population). The median duration of treatment was 13.80 months and compliance 99.10%. Twenty subjects (95.2%) received the study drug for ≥ 6 months, and 13 subjects (61.9%) received it for ≥ 12 months.
AEs occurred in 19 of 21 subjects (90.5%) and were assessed as ADRs in 8 of these subjects (38.1%). The AEs that occurred in 2 or more subjects were cataract in 5 subjects (23.8%), COVID-19 and diarrhoea in 4

subjects each (19.0%), herpes zoster and muscle spasms in 3 subjects each (14.3%), and sepsis, back pain, keratitis, constipation, large intestine polyp, rash, urticaria, hypokalaemia, oedema, and headache in 2 subjects each (9.5%). The ADRs that occurred in 2 or more subjects were herpes zoster, muscle spasms, and headache in 2 subjects each (9.5%). Grade ≥ 3 AEs occurred in 9 of 21 subjects (42.9%). Of these, Grade 3 AEs were COVID-19 and cataract in 2 subjects each (9.5%) and bronchitis, bronchopulmonary aspergillosis, pneumonia, skin infection, glaucoma, gastrointestinal polyp, pulmonary embolism, headache, and malignant mediastinal neoplasm in 1 subject each (4.8%). Grade 4 AEs were sepsis in 2 subjects (9.5%) and brain abscess, pneumonia aspiration, cataract, ileus, and cardiac failure in 1 subject each (4.8%). Grade 5 AE was acute myeloid leukaemia recurrent in 1 subject (4.8%). Grade ≥ 3 ADRs occurred in 2 of 21 subjects (9.5%), and were Grade 3 pneumonia and headache in 1 subject each (4.8%). The incidence of AEs and ADRs did not tend to increase over time. The incidence of AEs did not differ greatly by age (< 18 years/ ≥ 18 to < 65 years/ ≥ 65 years) and gender (male/female).
No AEs related to cytopenia, hypotension, impaired wound healing, and arrhythmia were reported. AEs related to hepatic function occurred in 2 of 21 subjects (9.5%). These events were liver disorder and blood bilirubin increased in 1 subject each (4.8%), and both were Grade 1. Neither event was considered related to the study drug. AEs related to infection occurred in 12 of 21 subjects (57.1%). Infection-related Grade ≥ 3 AEs occurred in 7 subjects (33.3%). The only infection-related Grade ≥ 3 ADR was Grade 3 pneumonia in 1 subject (4.8%). AEs related to secondary malignancy occurred in 1 of 21 subjects (4.8%). This subject had Grade 3 malignant mediastinal neoplasm and Grade 5 acute myeloid leukaemia recurrent, which led to discontinuation of treatment with the study drug. Neither event was considered related to the study drug. AEs related to hypersensitivity occurred in 6 of 21 subjects (28.6%).
Two subjects died during the study (myeloid leukaemia). The relationship of these events to the study drug were ruled out. Serious AEs occurred in 9 of 21 subjects (42.9%). These events were sepsis, COVID-19, and cataract in 2 subjects each (9.5%) and brain abscess, bronchitis, bronchopulmonary aspergillosis, pneumonia, pneumonia aspiration, skin infection, glaucoma, ileus, gastrointestinal polyp, cardiac failure, acute myeloid leukaemia recurrent, malignant mediastinal neoplasm, headache, and pulmonary embolism in 1 subject each (4.8%). Of these, pneumonia and headache in 1 subject each (4.8%) were judged related. Both events resolved following appropriate therapy, and the study treatment was continued. AEs leading to discontinuation of treatment occurred in 2 of 21 subjects (9.5%), skin infection and acute myeloid leukaemia recurrent and malignant mediastinal neoplasm. Neither event was considered related. Most subjects showed no clinically significant changes in laboratory values, vital signs, and body weight. No Grade ≥ 3 AEs related to laboratory values, vital signs, or body weight were observed, and no serious events were observed. No subjects had QTcF of > 450 msec or increase by > 30 msec from baseline during the treatment with the study drug.

Study BN101-201 (China) *A multicenter, open-label, single-arm, phase 2 study to evaluate the efficacy and safety of belumosudil in the treatment of patients with cGVHD who have received at least one line of systemic therapy*

Safety Results

A total of 30 subjects received treatment with the investigational drug (safety set). The median duration (range) of drug exposure in the 30 subjects was 10.25 (0.5-18.4) months, dose intensity (RDI) in these subjects was 99.45% (91.1%-100%), and the relative dose intensity in 28 (93.3%) subjects was > 95%.

In all, 29 (96.7%) subjects reported at least one TEAE. The most frequently reported (≥ 10%) TEAEs were upper respiratory tract infection (12, 40.0%), sinus tachycardia (11, 36.7%), pneumonia (7, 23.3%), hyperuricemia (5, 16.7%), liver injury (5, 16.7%), respiratory tract infection, hypoalbuminemia, hypoproteinaemia, ALT increased, blood creatinine increased, blood glucose increased, vomiting, nausea, and hypertension (3 subjects, 10.0%; in each). Eleven (36.7%) subjects reported at least one CTCAE Grade ≥ 3 TEAE. The most frequently reported (in ≥ 5% of subjects) CTCAE Grade ≥ 3 TEAE was pneumonia (5, 16.7%).

A total of 19 (63.3%) patients reported TEAEs related to investigational drug. The most frequently reported (in ≥ 5%) TEAEs were sinus tachycardia (9, 30.0%), upper respiratory tract infection (4, 13.3%), ALT (2, 6.7%), liver injury (2, 6.7%), blood pressure increased (2, 6.7%), and hypertension (2, 6.7%). CTCAE Grade ≥ 3 related TEAEs were reported in 4 (13.3%) subjects, with ALT increased, lymphocyte count decreased, pneumonia, skin bacterial infection, and muscle spasms each reported in 1 (3.3%) patient, respectively.

A total of 5 deaths occurred in the 30 subjects at the end of treatment (fulminant myocarditis, lung infection, sepsis and multiorgan failure, pneumonia, lung infection with respiratory failure, and leukaemia). These were mostly assessed as unlikely/unrelated and pneumonia as possibly related.
A total of 11 (36.7%) patients experienced SAEs, of which pneumonia occurred in 5 (16.7%) subjects, while other SAEs occurred in only 1 (3.3%) and included upper respiratory tract infection, neutrophil count decreased, oral infection, mouth ulceration, myocarditis, white blood cell count decreased, leukaemia recurrence, skin bacterial infection, bacterial pneumonia, muscle spasms, gastroenteritis, platelet count decreased, myasthenia gravis, and tooth impacted. Four (13.3%) patients experienced SAEs related to the investigational drug, including: pneumonia, skin bacterial infection, bacterial pneumonia, and muscle spasms, all of which were assessed as possibly related. All other SAEs were unrelated to the investigational drug.

In this study, one (3.3%) subject experienced a TEAE leading to a dose reduction of the investigational drug, i.e., ALT increased (possibly related). Two (6.7%) subjects experienced a TEAE leading to suspension of the investigational drug treatment, with the PTs being ALT increased (possibly related) and gastroenteritis (1, 3.3% each) judged as unrelated to the IMP. Five (16.7%) subjects experienced a TEAE leading to termination of the investigational drug treatment, with the PTs being pneumonia (2, 6.7%), myocarditis, leukaemia recurrence, and skin bacterial infection (1, 3.3% each), of which pneumonia and skin bacterial infection (1 subject, 3.3% each) occurring in 2 (6.7%) subjects were assessed as possibly related to the investigational drug, and the remaining ones were assessed as unlikely related or definitely unrelated to the investigational drug.

In all three (10.0%) subjects experienced at least one event of liver enzyme increased and hepatic adverse events in a total at least one event: ALT (3 subjects, 10.0%), AST (2 subjects, 6.7%), and gamma-glutamyltransferase increased (1 subject, 3.3%). A broader search showed that a total of 6 (20.0%) subjects experienced at least one event, and the preferred terms included hypoalbuminemia (3 subjects, 10.0%) and blood alkaline phosphatase increased (1 subject, 3.3%) in addition to the above terms. A comprehensive search (narrow) using drug-related liver diseases showed that a total of 12 (40.0%) subjects experienced the related events. The TEAEs included liver injury (5 subjects, 16.7%), ALT (3 subjects, 10.0%), hypoalbuminemia (3 subjects, 10.0%), AST (2 subjects, 6.7%), GGT increased (1 subject, 3.3%), drug-induced liver injury (1 subject, 3.3%), blood alkaline phosphatase increased (1 subject, 3.3%), and jaundice (1 subject, 3.3%). The results for CTCAE Grade ≥ 3 TEAEs were consistent, i.e., one (3.3%) subject experienced a CTCAE Grade ≥ 3 TEAE of ALT increased. In all, 21 (70.0%) subjects experienced AEs in the SOC of infections and infestations.

The most frequently reported (in ≥ 5% of subjects) TEAEs were: upper respiratory tract infection (12 subjects, 40.0%), pneumonia (7 subjects, 23.3%), respiratory tract infection (3 subjects, 10.0%), otitis media (2 subjects, 6.7%), oral infection (2 subjects, 6.7%), urinary tract infection (2 subjects, 6.7%), gastroenteritis (2 subjects, 6.7%), and nasopharyngitis (2 subjects, 6.7%). Seven (23.3%) subjects reported Grade ≥ 3 diseases in the SOC of infections and infestations: pneumonia (5 subjects, 16.7%), upper respiratory tract infection (1 subject, 3.3%), oral infection (1 subject, 3.3%), skin bacterial infection (1 subject, 3.3%), and gastroenteritis (1 subject, 3.3%). In addition, two (6.7%) subjects experienced TEAEs of bacterial infection, which involved the PTs of skin bacterial infection and bacterial pneumonia. One (3.3%) subject experienced a fungal infection, and one subject experienced a TEAE of viral infection, which involved the PTs of oral candidiasis, BK virus infection, and cytomegalovirus infection (1 subject, 3.3% each). One (3.3%) subject reported a Grade ≥ 3 TEAE of bacterial infection involving the PT of skin bacterial infection, while no subject reported a Grade ≥ 3 TEAE of CMQ fungal or viral infection.

A total of 2 (6.7%) subjects experienced the TEAE of cytopenia, neutrophil count decreased, lymphocyte count decreased, white blood cell count decreased, and platelet count decreased (1 subject, 3.3% each), all of which were CTCAE Grade ≥ 3. The lymphocyte count decreased was assessed as possibly related with an outcome of recovery. The remaining cytopenia events were assessed as unlikely related or definitely unrelated.

No subjects reported adverse events of secondary malignancy. Leukemia recurrence was reported in one (3.3%) subject, which was the main cause of death in this subject, judged as definitely unrelated. There were no reports of poor wound healing or hypotension.

In laboratory tests, very few subjects had CTCAE Grade ≥ 3 abnormal post-baseline haematology parameters: Grade 4 lymphocyte count decreased (2 subjects, 6.7%), Grade 3 lymphocyte count decreased, Grade 3 haemoglobin decreased, Grade 4 platelet count decreased, Grade 4 white blood cell count decreased, Grade 3 lymphocyte count increased, Grade 3 neutrophil count decreased, and Grade 4 neutrophil count decreased (1 subject, 3.3% each); very few subjects had CTCAE Grade ≥ 3 abnormal post-baseline blood chemistry parameters: Grade 3 ALT increased (2 subjects, 6.7%), Grade 3 GGT increased, and Grade 3 hypokalaemia (1 subject, 3.3% each), while the highest CTCAE Grade for the remaining post-baseline haematology and blood chemistry parameters was Grade 1 or Grade 2.

After receiving the investigational drug, the vast majority (29 subjects, 96.7%) of subjects had a post-treatment QTcF value ≤ 450 ms, and 1 (3.8%) subject had a maximum post-treatment QTcF value > 500 ms. The ECG abnormalities reported as clinically significant were mostly mild sinus tachycardia. One subject reported a CTCAE Grade 1 adverse event of palpitations, which was assessed as possibly related with the patient recovering. Fluctuations in vital signs were observed in individual subjects, but no trends of changes in vital signs were noted.

3.3.7.12 Real-world evidence study AA_00117

*Efficacy And Safety of Belumosudil as Compared with Physician's Choice of Best Available Therapy for the Treatment of Chronic Graft Versus Host Disease (*study initiation/completion dates: 0 August 2023/ 27 March 2024

The AA_000117 study was a retrospective, non-interventional study, based on real-world data (RWD), that compared belumosudil versus physician's choice of best available treatment (BAT) for the treatment of cGVHD, and where safety events were the additional (third) secondary endpoint. Data were collected through

a standardized case report form across sites in the US. The data source for evaluation of safety is shown in **Figure 16**. For further study details, including study design, baseline characteristics etc., see efficacy section.

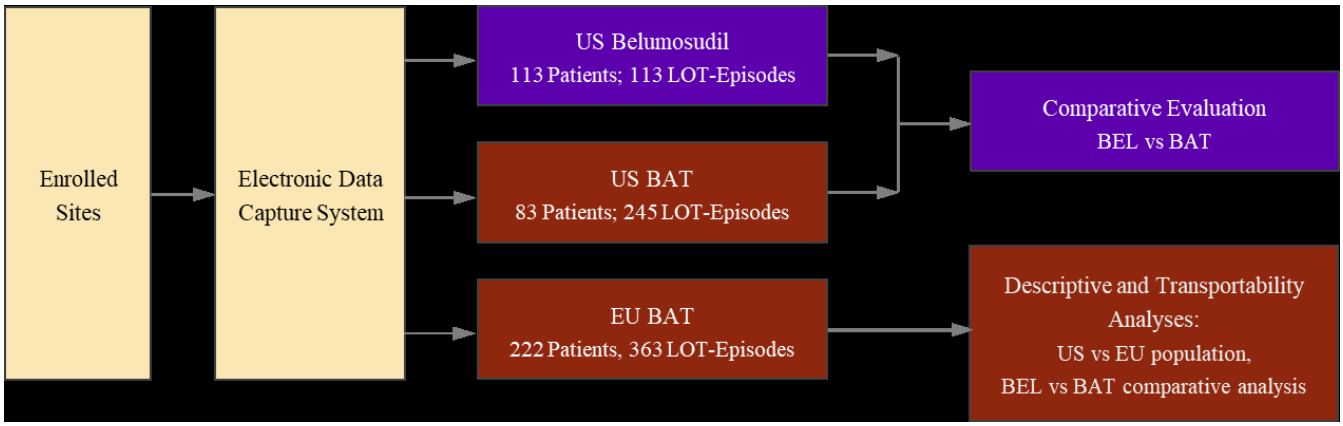

Figure 16: Data source for evaluation of efficacy and safety

Safety endpoints of interest were Serious infections (pneumonia, sepsis), Hepatotoxicity (lab: GGT, blood alkaline phosphatase, ALT, AST), Infections and infestations, Gastrointestinal disorders, Blood cell and lymphatic disorders, Hypotension, Hypertension (peripheral oedema), Renal toxicity (kidney disorders, renal failure), Lung disorders (upper respiratory tract infection, cough, dyspnoea, pneumonia), Hyperglycaemia, Fatigue, Muscle spasms, Malignancy, Embryofoetal toxicity/ teratogenicity, Fertility.

Paediatric population

The analysis of secondary and safety endpoints was not planned due to the low expected number of individuals.

Adult population

Safety endpoints were summarized descriptively as the observed rates per 100 episode-years in the belumosudil and BAT arms without adjusting for differences in prior comorbidities or other baseline characteristics. A safety endpoint analysis adjusting for potential confounders was not performed as it was considered that the study was unlikely to be adequately powered with the available sample size. Only descriptive statistics are presented because there were many heterogeneous safety endpoints and few events. Inferences were only made for safety events with a total count of ≥10 events.

Results

In the US, 196 patients (113 belumosudil arm and 83 BAT arm) satisfied screening and met all eligibility requirements. Patients contributed multiple line of therapy episodes to the analysis (113 belumosudil LOT episodes and 245 BAT episodes).

Adverse events (AEs) were reported in 33% of LOT-episodes (27% belumosudil, 36% BAT). AEs that occurred which lists the counts and incidence rate per 100 episode-years. The incidence rate per 100 episode-years may be understood as the expected number of episodes in which an AE would be observed during 1-year post treatment-initiation if 100 episodes were followed up.

The following was observed for AEs with a total count of ≥10 events: Respiratory-related AEs were more common in belumosudil LOT-episodes (8.713 belumosudil versus 4.106 BAT, per 100 episode-years), while

gastrointestinal (1.584 versus 2.346), hematologic (0 versus 4.106), cardiovascular (0.792 versus 3.226), thrombosis (0.792 versus 3.226), infection (15.049 versus 20.528), and other AEs (2.376 versus 3.519) were more common in the BAT LOT-episodes.

The safety endpoints in the adult population of the real-world evidence (RWE) study AA_00117 were summarized descriptively without adjusting for differences in prior comorbidities or other baseline characteristics. It was, however, also stated that 'Inferences were only made for safety events with a total count of ≥10 events'. The reason for this is not entirely clear, as it would appear that any applied threshold would be arbitrary. This approach could be acceptable for data presentation, but not for making any inferences. In the analysis of safety data, inferences are to be made on the basis of the whole safety database so that even the possible rarer TEAEs are taken into account and can undergo causality assessment to the investigative medicinal product.

This issue is, however, not pursued further for the following reason: the results of this RWE overall are not considered sufficiently reliable to support B/R assessment of belumosudil in the sought indication or for inclusion in SmPC section 5.1. Therefore, the Applicant was requested to delete all safety and efficacy data concerning this study from the SmPC.

2.6.9. Discussion on clinical safety

The safety data for belumosudil 200 mg QD in the proposed indication derive mainly from the pivotal Phase 2 study KD025-213, the Phase 2a, the so-called dose-escalation study, KD025-208, and the on-going joint long-term extension of these studies, study KD025-217. Of note, dose-escalation was not performed targeting dose limiting toxicities and, as such, the study is not a traditional dose escalation study.

The KD025-217 long-term extension study, ongoing as of the cutoff date, 29 January 2024 has been completed and the final clinical study report provided at D120. All pooled safety data (the safety population) were analysed according to doses administered: 200 mg QD, 200 mg BID, and 400 mg QD. The Safety Population included all patients who received at least 1 dose of study medication.

The pooling strategy is not entirely meaningful, as it includes doses not presently sought for, but can be, for now, acceptable as the results are also presented by different dosing regimens. All relevant tables containing the pooled results solely from the sought dosing regimen i.e. 200 mg QD, were requested and provided;Not including any of the other supportive data in the safety pool is acceptable, as these studies (see below) would not yield coherent enough data, considering the major differences in the study design, conduct and target populations.

Additional supportive safety data are provided by the Phase 3 single-arm study ME3208-2 conducted in Japan and the Phase 2 study BN101-201 conducted in China. Further, the retrospective, non-interventional real-world evidence (RWE) study AA_00117 provided data, which compared treatment with belumosudil with best available treatment (BAT) in patients with cGVHD who failed at least 2 prior lines of systemic therapy. These data are supplemented by safety data arising from 13 company sponsored Phase 1 trials that have been conducted in healthy participants and one in patients with different degree of liver injury. Post marketing safety data was presented from USA and Britain and nine non-EU sources in four separate PSUR reports extending just over two years from 12.11.2021 to 15.01.2024. An update of these data was provided at D120. No new or unexpected safety findings arose from these data.

To support the paediatric part of the claimed indication, paediatric safety data are available from the main clinical trials (safety population) from four patients, with scarce PK data from 3 patients. In the post-

marketing setting or during compassionate use a further 69 patients including 48 adolescents 12 to 17 years of age and 21 paediatric patients 1 to 11 years of age are included. These data were later updated with a total of 112 adolescent patients in the post marketing setting. The RWE accrued one adolescent paediatric patient.

Exposure

As of the cutoff date, the Safety Population for the pooled analysis comprised of 209 patients, including 94 patients treated with belumosudil 200 mg QD, 92 participants with 200 mg BID, and 21 patients with 400 mg QD.

The overall median duration of treatment with belumosudil was 10.22 months (range 0.39 to 83.75 months); the cumulative duration of exposure in the 200 mg QD group was 125.25 patient-years and in the all belumosudil-treated patients 266.25 patient-years.

Forty-three patients (20.6%) were treated with belumosudil for ≥6 to 12 months and 89 patients (42.6%) treated for ≥12 months. The median duration of treatment was similar across all dose groups at 9.18, 11.09, and 9.00 months in the 200 mg QD, 200 mg BID, and 400 mg QD treatment groups, respectively. As expected, based on the dosing frequency, the mean overall exposure was lower in the 200 mg QD group (85,382 mg) than in the 200 mg BID group (169,809 mg) and the 400 mg QD group (149,790 mg).

RWD, in the sought indication, was accrued in 196 patients with 113 in belumosudil and 83 in BAT arms. Post marketing data from USA, Britain and nine other non-EU countries comprise 2 years of data with a cumulative exposure to belumosudil estimated to be 1 324 857 treatment days. In total, approximately 6000 patients received belumosudil in the post-marketing setting and more than 300 patients under compassionate use. Of those, 2422 patients reported safety information (6994 events).

Although the presented exposure is limited in size and the design of the studies, and will ultimately have its inherent uncertainties, it could, nevertheless, be considered to provide sufficient evidence to support a safety evaluation of belumosudil 200 mg QD treatment in the target indication, (orphan condition) in , the setting of a SAT and the conditional MA eligibility. To address the missing safety data in the context of a CMA, the Applicant had a confirmatory phase 3 study ongoing. However, the originally planned confirmatory study EFC17757 was terminated by the Applicant on 26 June 2025.

Due to the rarity of cGVHD, which led to an orphan drug designation for belumosudil in the US and EU, the clinical development program for belumosudil includes a limited number of patients. 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. The single arm trial setting further complicates the interpretation of the safety data.

Safety population (belumosudil 200 mg QD in studies KD025-213, KD025-208 and KD025-217)

As expected, considering the clinical setting and the gravity of the disease under study, almost all cGVHD patients receiving belumosudil 200 mg QD experienced at least one TEAEs (99%).

The most common TEAEs as per SOC were Gastrointestinal disorders (71.9%), followed by Infections and infestations (64.6%), General disorders and administration site conditions (66.7%), and Respiratory, thoracic, and mediastinal disorders (62.5%).

By PT, the most common (>25%) TEAEs were diarrhoea (42.7%), fatigue (41.7%), nausea (33.3%), upper respiratory tract infection (30.2%), dyspnoea (31.3%), headache (28.1%), and peripheral oedema (26.0%) and cough (25.0%).

The exposure-adjusted event rate was 0.76 patients experiencing at least 1 event per patient year of exposure in the 200 mg QD group and 0.78 in all belumosudil-treated patients. The frequency of TEAEs did not appear to significantly increase over time from the 0 to <1 month onset period to the 9 to <12-month onset period, possibly indicating low cumulative toxicity with longer treatment.

Treatment-related TEAEs were reported in 70.8% patients and included ADRs in gastrointestinal disorders (28.1%), investigations (24.0%), and general disorders and administration site conditions (24.0%) SOC domains. On individual PT level, the most common TEAEs considered related to the study drug with ≥10% incidences were fatigue (19.8%), headache10 (10.4%) and diarrhoea 12 (12.5%) and nausea 11 (11.5%), followed by AST increased (7.3%).

The most common Grade 3 or 4 adverse reactions pneumonia (9.4%), hypertension (7.3%), musculoskeletal pain (6.3%), hyperglycaemia (6.3%) and dyspnoea (5.2%) were generally consistent with those expected considering the patient population under study and the treatments, including corticosteroids and other immunosuppressants, and were generally consistent with those expected in a population of patients with advanced cGVHD being treated with corticosteroids and other immunosuppressants.

The most frequent reasons for discontinuation included progression of disease under study (17.7%) and progression of underlying disease (8.3%) in patients with cGVHD treated with 200 mg once daily. The most common adverse reaction leading to discontinuation of treatment was nausea (2.1%). Adverse reactions leading to dose interruption occurred in 34.4% of patients and were pneumonia (6.3%) and diarrhoea (3.1%), followed by sepsis, nausea, fatigue, pyrexia, face oedema, hypotension (2.1% each). The Applicant further clarified these data by tabulating them.

SAEs were reported in 45.8% of the patients. The most commonly reported SAEs in >3 patients were pneumonia (9.4%), pyrexia (3.1%), cellulitis (2.1%), rhinovirus infection, followed by pulmonary embolism, diarrhoea, face oedema, multiple organ dysfunction syndrome, myocardial infarction, acute myeloid leukaemia recurrent, acute kidney injury (2.1% each), hypoxia (1.0%), and dyspnoea (1.0%). A total of 9 (9.4 %) SAEs were considered treatment related. The most commonly reported PT pneumonia, (1.9%), fatigue (1.4%), and both nausea and AST increase (1.0%, each).

The incidence of treatment-related fatal cases was overall low. In all, 13 (6.2%) patients with cGVHD died within 28 days of completing the study drug treatment. Five patients died in the 200 mg QD treatment group of which two deaths were deemed related to treatment with belumosudil. Most frequent event was disease progression.

Cardiac safety: No cardiac events were noted even at the supratherapeutic dose of 1000 mg. No signs or symptoms of QT prolongation including syncope, ventricular fibrillation/flutter, ventricular tachycardia were observed. Furthermore, belumosudil at the studied doses did not have a clinically relevant effect on HR or cardiac conduction (PR interval and the QRS complex).

Renal safety: Events of Acute renal failure (broad query) were identified in a total of 12.5% of participants in the 200 mg QD group. The most frequently reported TEAEs in this included blood creatinine increased (7.3%) and acute kidney injury (4.2%). The majority of events were mild or moderate in severity. All Grade ≥ 3

events were reported as SAEs and all were assessed as unlikely related or not related to treatment with the study drug. So far, overall, no signal for detrimental renal safety was clearly evident.

Hypotension: Hypotension was initially considered a potential risk. On analysis, there were no consistent differences in the incidence of the first occurrence of hypotension in belumosudil-treated patients in the pooled cGVHD analysis. Given the confounding effects of cGVHD, the low incidence in other populations investigated in clinical studies, and the lack of evidence for causality, it can be agreed that hypotension is no longer considered a potential risk based on data to date.

AEs of special interest (AESI)

AESIs were selected *a priori* by the Applicant based on the mechanism of action, nonclinical toxicology profile, and emerging clinical data and were as follows:

Hepatic events/increased liver enzymes: The nonclinical studies showed mild to potentially significant increases in serum markers that can be indicative of liver injury (i.e., ALT, ALP, 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 at exposure levels generally in the range of those expected at the highest anticipated human dose/exposure. Low magnitude hepatocellular hypertrophy was also observed in rats exposure levels less than or similar to that expected in human subjects.

To date, mainly asymptomatic, mild, and transient increases in LFTs were observed in the belumosudil clinical development program in the patients with cGVHD. Initial onset occurred early in treatment, and the number of subjects discontinuing treatment due to hepatic events was low, possibly indicating that the events appeared manageable and could be monitored by routine clinical follow-up. Overall, there were no cases of severe hepatoxicity, such as hepatitis, in subjects treated with belumosudil, and there have been no findings in belumosudil-treated patients that meet the criteria of Hy's Law. The CHMP recommended that the use of belumosudil should be contraindicated in patients with severe hepatic impairment with reference to the large increase in AUC in the dedicated PK study.

Infections: Infections are a potential risk due to the mechanism of action of belumosudil as an immune modulator. The risk is confounded by the underlying malignancy, transplantation, cGVHD, and use of immunosuppressive standard of care treatment in the patient population with cGVHD. Adverse effects on the hematopoietic/immunologic system were noted in the non-clinical program as well as in the clinical development program for belumosudil, where hematologic AEs and events of infections were reported. The most frequently reported infections were respiratory infections which are common in the population with cGVHD. Pneumonia and death from pneumonia have been considered related to the belumosudil treatment both in the main and supportive studies. Pneumonia is reported in SmPC section 4.8.C. In addition, it was clarified that cytomegalovirus (CMV) reactivation observed in two patients in Study KD025-213, were considered to be related to belumosudil.

Malignancies (secondary neoplasm and/or relapse of the underlying malignancy): Belumosudil is an immunomodulator and as such may increase the risk of malignancy, either recurrent or secondary, in treated patients. It is agreed that the reported neoplasm events were confounded by the primary malignancy of the patients, requiring haematopoietic cell transplantation (HCT), the performed allogeneic HCT and the long-term immunosuppression of the patients. HCT recipients are in general also at an increased risk of secondary malignancies in comparison to the general population, and recurrence of the underlying malignancy is common. Additionally, the systemic treatments for cGVHD, sirolimus, tacrolimus, and mycophenolate mofetil, include warnings in their product information regarding secondary cancers. These confound the evaluation of

malignancies in this population. The data so far do not indicate a risk of increased recurrence of malignancy or secondary neoplasm occurrence, recognising the lack of longer term follow-up. This is adequately reflected in the SmPC.

Pregnancy, breastfeeding and fertility: The nonclinical program showed that administration of belumosudil to pregnant rats and rabbits during the period of organogenesis resulted in embryofoetal mortality, reduced foetal weight and/or foetal abnormalities at maternal exposures ≥3.9 (rat) and ≥0.4 (rabbit) times the human exposure at the recommended dose. According to the Applicant, published literature links the teratogenic/embryotoxic effects directly to ROCK inhibition.

Considering the non-clinical findings and the gravity of the current clinical setting and the patient population, contraindicating pregnancy and breastfeeding was considered justified andis agreed. The Applicant also provided updated data on all currently available, pre- and post-marketing, data on pregnancy, breast-feeding and fertility in patients on belumosudil treatment, confirming and concluding that, to date, no human data is available.

Impaired wound healing: Impaired wound healing was considered a potential risk due to the antifibrotic mechanism of action of belumosudil. Overall, only few events of impaired wound healing were reported, it is agreed that it is not, to date, sufficient for a safety concern.

Drug interactions and subgroup analysis

Review of the pooled analyses for the belumosudil 200 mg QD group revealed no consistent differences in the incidence of the most commonly reported TEAEs for patients taking or not taking a proton pump inhibitor or a strong CYP3A inhibitorSubgroup analysis by age (younger vs. 65 ≤ years of age), sex, race, region, body mass index, hepatic impairment, renal impairment, or on-treatment QTcF value or by region did not reveal significant differences. Review of disease factors related to cGVHD severity, duration, or number of lines of prior therapy found no evidence of unexpected differences. The respective table for the clinical AR of the subgroup analyses was appropriately completed.

Laboratory results

Overall, the laboratory results were largely as expected for this type of study, considering the characteristics of the target cGVHD patient population, and the treatment under study.

Paediatric population

The number of paediatric patients in the main studies is overtly small (4), complemented with some post marketing data (48 patients in the 12 to 17 year old group and 21 in the 1 to 11 year old on belumosudil 200 mg QD) and RWE data (one patient on belumosudil treatment and two on BAT), so that any proposed claims on this target population will have to be based mainly on extrapolation of safety and efficacy data from the adult source population.

Post-marketing data

Since the first marketing authorisation for belumosudil was granted in the United States in the year 2021, post marketing safety data has been accrued in the USA, Britain and nine non-EU countries, the safety events reported from post marketing experience and compassionate use (including data from both adolescent and paediatric patients). Currently the available post marketing safety data are available for just over 2 years. Acknowledging the heterogeneity of these data, the safety profile has been in general consistent with the safety profile of belumosudil and the disease observed during clinical trials, with so far, no new or unexpected safety signals identified.

Additional supportive data

RWD study: Supportive real-world evidence (RWE) from routine clinical practice was derived from a non-interventional, retrospective RWD study comparing belumosudil 200 mg QD (the sought dose) and 200 mg BID treatment to the best available therapy (BAT) in the sought indication. In short, respiratory-related safety events were more common in the belumosudil arm, while gastrointestinal, hematologic, and cardiovascular events, thrombosis, infection, and other safety events were more common in the BAT arm. Acknowledging the methodological limitations of these data, the safety data appear to be in general similar with the established safety profile of belumosudil, with no new or unexpected findings evident.

However, the results of this RWE overall are not considered sufficiently reliable to support B/R assessment of belumosudil in the sought indication and for inclusion in SmPC section 5.1.

No significant new or unexpected safety data arose from the additional supportive Phase 2 single-arm *studies conducted in Japan and in China*. Interpretation of these data are limited by the difference in study design, the study population and the treatment setting. The studies show an earlier treatment setting and ethnic differences in both the patients and the treatment modes. Thus, the relevance of these results is of limited value and only supportive.

The safety profile in the supportive studies overall appeared similar to that of the main studies and any discrepancies in incidences of safety events appeared explainable by differences in the study populations, dosing regimens and study design.

Interactions

Review of the pooled analyses for the belumosudil 200 mg QD group revealed no consistent differences in the incidence of the most commonly reported TEAEs for participants taking or not taking a proton pump inhibitor or a strong CYP3A inhibitor. Subgroup analysis by age, sex, race, region, body mass index, hepatic impairment, renal impairment, or on-treatment QTcF value or by region did not reveal significant differences. Review of disease factors related to cGVHD severity, cGVHD duration, or number of lines of prior therapy found no evidence of unexpected differences.

The applicant was recommended to perform a DDI.

Adverse drug reactions for the product information

On the background of heterogeneity in disease manifestation, previous and concurrent therapies, and in the current setting of single arm trials, entailing the absence of randomisation, uncontrolled conditions, non-standardised treatments and uncertainties regarding data quality and completeness, the causality assessment of the TEAEs is key and was clarified upon CHMP request allowing assessment of safety information to be inserted in the SmPC.

In conclusion, although the safety profile of *belumosudil* was not completely innocuous, throughout the entire company safety database incidences of TEAEs leading to permanent discontinuation, and SAEs and the AESI were what could be expected for this this type of study. Importantly, of the reported treatment emergent deaths only a few were considered related to the study drug.

Acknowledging the limitations and uncertainties of the setting and the gravity of the characteristics of the cGVDH patient sample, the safety profile of belumosudil in these previously heavily treated cGVHD patients could be considered overall favourable in the later LOT in the proposed setting of a CMA. Safety was in general in accordance with what is expected for this type of medicinal product involving the specific ROCK2

kinase inhibition pathway and to what has been previously reported for this type of cGVHD patient populations under belumosudil therapy.

However, despite the uncertainties related to safety, in the context of a CMA the safety of belumosudil could be approvable.

Additional expert consultation

N/A

Assessment of paediatric data on clinical safety

Safety data from adolescents treated in clinical trials data, arise from various clinical trials and are low in numbers (n=8). (Four adolescent received belumosudil in completed clinical studies; 3 in the pivotal SAT study D025-213; and 1 in study ME3208-02 performed in Japan.) One adolescent has been recruited in the ongoing Phase 3 study EFC17757 in newly diagnosed cGVHD (no AEs reported so far) and 3 adolescents in the ongoing Phase 4 study ACT18369 in Chinese adolescents with cGVHD who have had an inadequate response to glucocorticoids or other systemic therapies). Overall, no specific safety concerns have been reported with the use of belumosudil in treatment of the few adolescents' patients with cGVHD in the clinical trial setting.

The post-marketing data includes safety data on 112 adolescent patients collected from different sources of variable quality, thus heterogeous. for example, the administered dose of belumosudil for the 28 patients treated in the compassionate use setting is not known. Further, the duration of exposure over 12 months is also not known for either the post-marketing or compassionate use setting. Thus, overall, the currently available data on the target adolescent patient population has its inherent limitations and uncertainties remain.

Further, based on the toxicology studies in adolescent/adult animals, at clinically relevant exposures, belumosudil had no overt impact on growth and development. Belumosudil does not penetrate CNS and hence, it is not expected to have any potential impact on CNS development in the proposed adolescent population. Impact on male fertility was observed under treatment, but male rat functional fertility impairment was reversible after drug free period even though histopathological testicular findings were still present.

Nonetheless, acknowledging these limitations, it can be agreed that so far the available post marketing safety data concerns appears similar to the safety profile of adult GVHD patients.

However, despite the risks and the uncertainties, the safety of belumosudil also in adolescents could be approvable.

Additional safety data needed in the context of a conditional MA

The safety database is based on single-arm trials entailing lack of randomisation, uncontrolled conditions, non-standardised treatments and uncertainties regarding data quality and completeness. These data are complemented by a SAT each in Japanese and Chinese cGVHD patients, by a study with RWE and by two years of post-marketing data from non-EU settings. On this background the assessment of the submitted safety data will have its inherent limitations and uncertainties.

The following measures are necessary to address the additional safety data needed in the context of a conditional MA: provide further safety data from a confirmatory trial as part of a specific obligation in a reasonable timeframe.

As mentioned earlier the newly proposed plan for a new SOB cannot be endorsed (see efficacy section for details).

2.6.10. Conclusions on clinical safety

The safety data for belumosudil 200 mg QD in 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 medicinal products approved for use in cGVHD provide limited clinical benefit or are not suitable. derive mainly from the analyses of the two pooled SAT studies and from their joint long-term extension study. These data are supplemented with supportive data from SAT studies performed in Chinese and Japanese patient populations, and data from post-marketing and compassionate use programmes. The main studies include adults and four paediatric patients. In the post marketing setting 112 adolescents received belumosudil.

Acknowledging the limitations and uncertainties of the provided data, the safety profile of belumosudil in a selected and previously heavily pre- and concurrently treated cGVHD patients could be considered overall acceptable. It was in general, in accordance with what is expected for this type of medicinal product involving the specific kinase inhibition pathway and to what has been previously reported for this type heavily pretreated cGVHD patient populations.

In conclusion, despite the risks and the uncertainties in the context of a CMA the safety of belumosudil is considered acceptable.

2.7. Risk Management Plan

2.7.1. Safety concerns

Summary of safety concerns

The applicant proposed the following summary of safety concerns in the RMP:

Summary of safety concerns	
Important identified risks	None
Important potential risks	Malignancy (secondary neoplasm and relapse of the underlying malignancy)
Missing information	None

2.7.1.1. Discussion and conclusion on safety specification

Assessment of the non-clinical and clinical data has not identified a need to add to the proposed safety specification. The safety data on children aged 12-17 is limited, but given the existing data, largely from the

post-marketing setting, which appears consistent with the safety profile in adolescents not differing from the safety profile of belumosudil in adults, it is not considered missing information.

The PRAC agree that it is appropriate to consider Malignancy (secondary neoplasm and relapse of the underlying malignancy) as a safety concern to be discussed in the PSURs.

2.7.2. Pharmacovigilance plan

The routine phamacovigilance activities (FUQ for malignancy) proposed by the applicant is considered not needed given the multiple risk factors for malignancy in belimosudil treated patients. The Applicant is asked to remove it from the RMP.

2.7.2.1. Summary of planned additional PhV activities from RMP

There is no additional pharmacovigilance activity in place for belumosudil.

2.7.3. Risk minimisation measures

Table 57: Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Malignancy (secondary neoplasm and relapse of the underlying malignancy)	**Routine risk communication:** None **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** **Legal status:** Prescription only medicine.

Routine risk minimization activities are considered sufficient to manage the safety concerns of the medicinal product. No additional risks minimization measures are proposed for belumosudil.

2.7.4. Conclusion on the RMP

The CHMP, having considered the data submitted in the application was of the opinion that due to the concerns identified with this application, the risk management plan cannot be agreed at this stage.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the

requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

Not applicable

Product information

In light of the negative opinion, a satisfactory summary of product characteristics, labelling and package leaflet cannot be agreed at this stage.

2.8.3. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.8.4. Additional monitoring

Not applicable due to the negative opinion.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Chronic GVHD is a result of complex mechanisms occurring in three phases: (1) early inflammation due to tissue injury, (2) thymic injury and T- and B-cell dysregulation, and (3) tissue repair and fibrosis (Hamilton BK, Haematology 2021). Currently available data point out the similarity in the pathophysiology of cGVHD between paediatric and adult patients.

The clinical manifestations are systemic, involving multiple organs, with profound impact upon quality of life and non-relapse mortality. The most frequently involved organs include skin, mouth, eyes, liver and joints. Patients who develop cGVHD after HCT face a multifaceted burden, including physical, functional, and psychosocial deficits, which negatively influence quality of life. Presence of fibrotic skin, limited motility of joints/fascia, and/or lung involvement have the greatest effect on physical capability and quality of life. Advanced fibrotic skin involvement of cGVHD mimics the clinical picture of systemic scleroderma.

The severity of cGVHD is assessed as defined by the 2014 NIH Consensus Development Project on Clinical Trials in cGVHD (Jagasia MH *et al*. Biol Blood Marrow Transplant 2015).

The Applicant submited a Marketing Authorisation Application for consideration of conditional approval of Rezurock (belumosudil). The Applicant agreed with the indication wording proposed by the CHMP:

"Rezurock is indicated for the treatment of adult 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".

Belumosudil is a selective Rho-associated, coiled-coil protein kinase-2 (ROCK2) inhibitor which acts on both inflammation and fibrosis. It rebalances T-cell mediated immune response by downregulating IL-17 and IL-21 secretion thus leading to downregulation of proinflammatory Th17 cells and by increasing T regulatory cells (Treg). ROCK2 inhibitor belumosudil disrupts profibrotic signals and inhibits collagen expression in human lung fibroblasts.

3.1.2. Available therapies and unmet medical need

Allogeneic HCT is the only potentially curative therapy for many haematologic malignancies, immunodeficiencies, and bone marrow failure syndromes. Despite significant advances in transplantation protocols, cGVHD remains the leading cause of late morbidity and mortality among HCT survivors. Among transplant recipients, cGVHD occurs in approximately 30% to 70% of adults and in 6% to 33% of children. Chronic GVHD is a heterogeneous syndrome which treatment typically requires prolonged (median 2-3.5 years) use of immunosuppressive agents.

The standard initial treatment for cGVHD requiring systemic therapy is corticosteroids, with or without calcineurin inhibitors (CNIs). However, corticosteroids are associated with significant side effects and unsatisfactory outcomes. The limited activity of currently available cGVHD treatments results in patients cycling through treatments. Approximately 50% to 75% of patients with cGVHD will require at least second line treatment. Approximately half of the patients progress to third or later lines of therapy. In the long term, approximately one-third of patients with cGVHD have relapsed or died, one-third have discontinued therapy successfully and one third remain on long-term treatment for cGVHD. Of patients who remain on therapy

long-term, half progress to fourth- or fifth-line therapy. Chronic GVHD not responding to therapy ultimately leads to death.

In 2022, ruxolitinib (Jakavi®) was approved in the EU for the second-line therapy for cGVHD. In the EU no new agents have been approved to address the unmet medical need for alternative treatments for patients failed two or more lines systemic treatments.

3.1.3. Main clinical studies

The main evidence of efficacy submitted is derived from study KD025-213, which was a single phase 2, non-controlled, randomized, multicenter study to evaluate the efficacy and safety of belumosudil (KD025) in subjects with cGVHD after at least 2 prior lines of systemic therapy. Eligible subjects were randomized to open-label treatment arms belumosudil 200 mg QD (arm A) or belumosudil 200 mg BID (arm B) in 1:1 ratio. Arm A included 77 adults and 2 adolescents, Arm B 75 adults and one adolescent. Hence, the pivotal study is a single arm trial.

3.2. Favourable effects

- The ORR (95% CI) with belumosudil was 73.0% (95% CI 61.8, 82.5) in Arm A. Four (5.1%) subjects achieved a complete response (CR) and 53 (67.9%) subjects achieved a partial response (PR).
- ORR at 6 months was 44.2% (95% CI 32.8, 55.9).
- K-M estimate of median primary DoR defined as time from first documentation of response to the time of first documentation of deterioration from best response was 23.9 weeks (95% CI 11.43, 50.43).
- K-M estimate of median tertiary DoR (time to new systemic immunosuppressive treatment) was 101.1 weeks (95% CI 64.29, NR)
- Time to Response (TTR) (med) was 4.43 weeks (95% CI 3.7, 80.1)

3.3. Uncertainties and limitations about favourable effects

Although a single-arm study can be considered acceptable in a population that has exhausted available treatment options, the main issue is that the drug effect is difficult to isolate in Study KD025-213. Given the concomitant use of other anti-GvHD therapies and the lack of control arm, the true contribution of belumosudil to the treatment outcome cannot be estimated. However, based on available data, it can be concluded that belumosudil treatment has contributed to patients achieving a response as the observed responses were not linked to any specific concomitant medication(s) or duration of concomitant treatments. Although the majority of the observed responses in patients cannot be reasonably associated with concomitant treatments, in a small proportion of cases the role of concomitant treatments cannot be excluded.

Further, the definition of the primary efficacy endpoint as any response at any time inflates the observed response rate. Although the majority of participants had a response in two or more organs which supports clinical relevance of the responses, some transient single organ responses are included. While this leads to an uncertainty in magnitude of clinical benefit, additional analyses such as ORR landmark analyses and detailed response data by organ system, visit etc. support the conclusion that the response rate is clinically relevant in both magnitude and duration.

Due to the above-mentioned uncertainties, the magnitude of treatment effect cannot be established based on Study KD025-213. It can only be concluded that the response rate is clearly beyond of what would be

expected in the target population without additional treatment. The results therefore only demonstrate potential to address an unmet medical need, rather than demonstrating the efficacy, as required to conclude positively on the benefit/risk balance in the context of granting a CMA.

Study EFC17757 comparing belumosudil in combination with corticosteroid with placebo in combination with corticosteroid in patients with newly diagnosed moderate and severe cGVHD was considered to be a suitable SOB to confirm efficacy in a context of a CMA. However, the study failed to demonstrate any clinical benefit, or even drug activity. Despite differences in patient population, treatment combination and disease pathophysiology in early vs. late stage of disease, the negative study adds to above uncertainties on clinical benefit of belumosudil treatment.

No clear dose-response relationship for efficacy has been demonstrated for belumosudil.

Benefit in adolescent patients is based on PK matching extrapolation, similarity of clinical condition and treatment options in this population, very limited clinical data from 8 adolescents from the clinical trials (3 in the pivotal trial) and safety data from compassionate use and post marketing data (n=122). Due to limited clinical data from clinical trials, additional data would be required in the post marketing setting of an approval under CMA in this population.

Of note, the Applicant had conducted a comparative (Best Available Therapy vs belumosudil), non-interventional study based on RWD to support benefit-risk assessment because no randomized controlled clinical trials are included in the submission. However, the results of this study cannot be considered sufficiently reliable to support regulatory decision making.

3.4. Unfavourable effects

The safety data derive mainly from study KD025-213 and study KD025-208 and their long-term extension study KD025-217. These data are complemented by real world evidence, and by two years of post-marketing data and by compassionate use data.

In all, 99% of the cGVHD patients receiving belumosudil 200 mg QD experienced at least one TEAEs. The most common TEAEs per SOC were Gastrointestinal disorders (71.9%), followed by Infections and infestations (64.6%), General disorders and administration site conditions (66.7%), and Respiratory, thoracic, and mediastinal disorders (62.5%).

By PT, the most common (>25%) TEAEs were diarrhea (42.7%), fatigue (41.7%), nausea (33.3%), upper respiratory tract infection (30.2%), dyspnea (31.3%), headache (28.1%), and peripheral oedema (26.0%) and cough (25.0%).

In belumosudil 200 mg QD in studies KD025-213, KD025-208 and KD025-217, treatment-related TEAEs were reported in 70.8% patients and included ADRs in Gastrointestinal disorders (28.1%), Investigations (24.0%), and General disorders and administration site conditions (24.0%) SOC domains. On an individual PT level, the most common TEAEs considered related to the study drug with ≥10% incidences were fatigue (19.8%), headache (10.4%) and diarrhoea (12.5%) and nausea (11.5%), followed by AST increased (7.3%).

The most common Grade 3 or 4 adverse reactions were pneumonia (9.4%), hypertension (7.3%), musculoskeletal pain (6.3%) and hyperglycaemia (6.3%) and dyspnoea (5.2%).

SAEs were reported in 45.8% of the patients. The most commonly reported SAEs in >3 patients were pneumonia (9.4%), pyrexia (3.1%), cellulitis (2.1%). A total of 9 (9.4 %) SAEs were considered treatment related.

Discontinuation of belumosudil due to TEAEs was reported in 21.9% of the patients in the 200 mg QD group. The most common adverse reaction leading to discontinuation of treatment was nausea (2.1%). Adverse reactions leading to dose interruption occurred in 34.4% of patients, and the most common reasons were pneumonia (6.3%) and diarrhoea (3.1%), followed by sepsis, nausea, fatigue, pyrexia, face oedema, hypotension (2.1% each).

In all, 13 (6.2%) patients with cGVHD died within 28 days of completing the study drug treatment. Most events were related to the underlying disease. In 2 cases the cause of death was assessed as possibly related to belumosudil.

3.5. Uncertainties and limitations about unfavourable effects

The safety database is based on single-arm trials (SAT) entailing lack of randomisation, uncontrolled conditions, non-standardised treatments and uncertainties regarding data quality and completeness. The single arm trial study setting impairs the causality assessment of the unfavourable effects. Adverse effects of the disease under study, previous and concurrent treatments and adverse events predicted on the basis of the mode of action and structure of belumosudil are overlapping, and only rough estimates for frequencies of these events can be made in this heterogeneous patient population.

From the safety perspective, in the context of a conditional MA (CMA), the main uncertainties pertain to the current setting of SATs, of the novel mechanism of action of belumosudil, the first in its class medicinal product under study.

However, despite the risks and the uncertainties in the context of a CMA the safety of belumosudil could be approvable if clinical benefit was demonstrated.

3.6. Effects Table

Table 58: Effects Table for Rezurock for the treatment of patients 12 years and older with chronic graft-versus-host disease (cGVHD) (data cut-off 01 Sep 2022).

Effect	Short Description	Unit	Belumosudil (KD025-213)	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
ORR	Overall response rate	% (95%CI)	73 (61.8, 82.5)	N/A	likely over-estimates the clinically relevant treatment effect	
ORR at 6 months	Overall response rate at 6 months	% (95%CI)	44.2 (32.8, 55.9)			

Effect	Short Description	Unit	Belumosudil (KD025-213)	Control	Uncertainties/ Strength of evidence	References
Primary DoR	Duration of response, time from first documentation of response to the time of first documentation of deterioration from best response	Median in weeks (95% CI)	23.9 (11.43, 50,43)	N/A		
Tertiary DoR	Duration of response, time from first documentation of response to the time of initiation of new systemic cGVHD therapy	Median in weeks (95% CI)	101.1 (54.29, NR)	N/A		
TTR	Time to response, time from first treatment to the time of first documentation of response	Median in weeks (95% CI)	4.43 (3.7-80.1)	N/A		
Unfavourable Effects (safety population)						
TEAEs, at least one		N (%)	95 (99.0)	N/A		
TEAEs per SOC	Gastrointestinal disorders	n (%)	69 (71.9)	N/A		
	General disorders and administration site conditions	n (%)	64 (66.7)	N/A		
TEAEs per PT, most common	diarrhoea	n (%)	41 (42.7)	N/A		
	fatigue	n (%)	40 (41.7)	N/A		
	nausea	n (%)	32 (33.3)	N/A		
TEAEs, ≥ Grade 3	pneumonia	n (%)	9 (9.4)	N/A		
SAE	In all	n (%)	44 (45.8)	N/A		
	pneumonia	n (%)	9 (9.4)	N/A		
Discontinuations	in all	n (%)	21 (21.9)	N/A		
Deaths	Possibly related	n (%)	2 (2,0)	N/A		

Abbreviations: SOC; System organ class; PT, Preferred Term

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

For the patients with corticosteroid resistant or dependent cGVHD authorised treatment options are few. In the EU, ruxolitinib has been the only authorized second-line therapy since 2022. However, approximately half of cGVHD patients progress to third or later lines of therapy primarily due to lack of efficacy and/or toxicity. Chronic GVHD not responding to treatment is ultimately fatal. Hence, there is unmet medical need for authorized treatments in later lines.

In the pivotal study KD025-213, ORR was high (73%), and relevant proportion of patients were responders also in landmark analyses at 6 and 12 months (48% and 33%, respectively). The responses were durable as median primary DoR, defined as time from first documentation of response to the time of first documentation of deterioration from best response, was 23.9 weeks and tertiary DoR (time to start of new systemic immunosuppressant) of 101.1 weeks. In the majority of cases, response was reported based on improvement in two or more organs. These results are considered clinically relevant in a patient population of cGVHD treated with at least two prior lines of therapy and demonstrate potential to address an unmet medical need.

It is acknowledged that while various concomitant treatments were allowed, the impact of these concomitant treatments on responses observed with belumosudil can be concluded to be limited. However, there is uncertainty about the clinical efficacy which cannot be clearly isolated and its magnitude, and this cannot be resolved based on data derived from a SAT. More importantly, the definition of the primary endpoint as any response at any time during the treatment inflates the response rate although analyses such as ORR landmark analyses support the conclusion that the response rate is clinically relevant in both magnitude and duration. Overall, due to major uncertainties (SAT, absence of control arm, definition of responder in the primary EP), it is considered that demonstration of efficacy has not been established; as required for establishing a positive benefit risk in the context of granting a CMA.

The uncertainties are further increased by the failed RCT EFC17757 in 1L setting, initially proposed as a SOB to the CMA. Lack of any clinical benefit or even drug activity cannot be overlooked despite differences in treatment setting and potential differences in disease pathophysiology.

In terms of safety, the number of patients exposed to belumosudil is limited, but it was initially considered that it could be sufficient to characterise the safety profile in the current last line and CMA setting. In addition to clinical trial data, available post-marketing data are in general consistent with the known safety profile of belumosudil, with no new or unexpected safety signals identified.

3.7.2. Balance of benefits and risks

The pivotal study results demonstrate a potential to address an unmet medical need in last line cGvHD population, as the observed response rate and duration of responses would be clinically relevant in last line cGvHD setting. However, there is a greater uncertainty about the demonstration of clinical efficacy which cannot be isolated and its magnitude, and this cannot be resolved based on data derived from a SAT. Importantly, in addition, a randomised placebo-controlled study in 1L cGvHD failed to demonstrate clinical efficacy or even drug activity as add-on treatment to corticosteroids exacerbating the uncertainty about the demonstration true treatment's effect.

In terms of safety, the number of patients exposed to belumosudil is limited, but is considered sufficient to characterise the safety profile in last line cGvHD population. In addition to clinical trial data, available post-marketing data are in general consistent with the known safety profile of belumosudil, with no new or unexpected safety signals identified. Despite the risks and the uncertainties in the context of a CMA the safety of belumosudil could be approvable if treatment benefit was sufficiently demonstrated.

The dataset is not considered to be comprehensive, and the criteria for a CMA are currently not fulfilled. Uncertainties on clinical benefit of belumosudil treatment are too great to conclude on positive B/R, and the proposed plan for a new SOB is not considered sufficient to address the uncertainties.

3.7.3. Additional considerations on the benefit-risk balance

Indication wording

Weight restriction:

The currently presented PK, efficacy and safety data are considered sufficient to support an indication in adolescents aged 12-18 years with a body weight of ≥40 kg. There is no basis for extrapolation for paediatric patients weighing less than 40 kg, which is approximately the 50th percentile for 12-year-old children. Therefore, the Applicant agreed to limit the paediatric indication to patients 12 years and older and with a body weight ≥ 40 kg.

It was agreed that weight limit is not needed for adult patients. This is acceptable, since it is not common to set weight limits based on study population weight range unless there are specific concerns on efficacy or safety beyond the weight range of the study population. No statistically significant weight effect on PK parameters was found in the updated population PK model over a wide range of body weight starting from 38.6 and up to 143 kg in adult participants and no observed difference in safety profile in four adult patients weighing < 40 kg in clinical trials could be seen. Adult patients with body weight significantly under 40 kg are expected to be very rare, whereas the weight limit is highly relevant for adolescents (40 kg is approximately the 50th percentile for 12-year-old children).

"Last line" wording:

The indication was requested to be limited to last line treatment of cGvHD due to 1) lack of demonstrated major therapeutic advantage over other authorised medicinal products (speficially, ruxolitinib in 2L+), and 2) to reflect the major uncertainties in demonstration of clinical benefit. Although prior ruxolitib treatment was not required in the pivotal trial, limiting the treatment to post-ruxolitinib setting is considered to be supported by available data. There were no significant differences in ORR between patients with prior treatment with ruxolitinib vs. ruxolitinib-naïve patients. Based on mode of action, there is no concern that efficacy or safety of belumosudil would be different in patients treated with prior ruxolitinib as compared to overall population.

The Applicant's request to include phrase "other medicinal products *approved for use* in cGVHD" was not agreed. It is acknowledged that beyond corticosteroid treatment in first line, and ruxolitinib approved for 2L+, there is no established standard of care. Majority of treatment options used in clinical practice are off-label, and use is based on variable level of evidence on clinical benefit. However, "approved for use" is not normally specified in the EU indication wordings. In this specific case, this exceptional solution to specify could even be misleading. Some corticosteroids, considered to be standard of care first line therapy, are not specifically authorized for treatment of cGvHD. Moreover, this would not reflect the pivotal study population:

patients in the ROCKstar trial had received various prior treatments, and received various concomitant treatments, that are off label in the EU.

Therefore, the indication was revised as follows:

"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"

Although only a few patients with mild cGVHD were included in the trial, the therapeutic indication does not need to be restricted by disease severity. Although majority of patients are expected to have moderate or severe disease stage at the time new systemic treatment is initiated, early treatment initiation may be beneficial in patients with a flare/disease re-activation, and treatment decision is best guided by clinical decision-making rather than restriction of the indication.

Extrapolation of indication to adolescent paediatric patients from 12 years to under 18 years of age and with a body weight of ≥ 40 kg

Pharmacokinetics

PK simulations using an acceptable population PK model indicated that with the 200 mg QD regimen exposure to belumosudil at steady state is expected to be slightly higher in adolescent patients (age ≥ 12 years and body weight ≥40 kg) compared to adult patients, but markedly less than exposure in adults treated with 200 mg BID and 400 mg QD regimens that were investigated in Phase 2 studies. Elimination of belumosudil is mainly by metabolism via several pathways, which are expected to be mature by the age of 12 years.

Extrapolation of efficacy to adolescents

The aetiology, pathomechanism and risk factors for outcomes of cGVHD are similar in adolescents and in adults. As for the second-line treatment of cGVHD only ruxolitinib is available in the EU, there is an unmet medical need in the adolescent patients suffering from corticosteroid resistant cGVHD. As the immune system of adolescents is relatively mature and comparable to adults, the treatment of cGVHD in adolescents is mostly extrapolated from the experience in adults. The Applicant has provided plans to confirm extrapolation in adolescents. PK, efficacy, and safety results from studies ACT18369, EFC17757, DFI17893 and along with prior data from adolescent participants with cGVHD from studies KD025-213 and ME3208-2, will provide complementary data in adolescents to confirm the allometric scaled popPK model.

Extrapolation of safety to adolescents

Safety data from adolescents treated in clinical trials data, arise from various clinical trials and is low in numbers (n=8). Overall, no specific safety concerns have been reported with the use of belumosudil in treatment of the few adolescent patients with cGVHD in the clinical trial setting.

The post-marketing data includes safety data on 112 adolescent patients. The quality of the accrued data are heterogenous and duration of exposure in the post marketing or compassionate use unknown. Nonetheless, acknowledging these limitations, it was agreed with the Applicant that the post-marketing data did not identify any new or unexpected safety concerns that would differ markedly from the known safety profile of belumosudil in treatment of adult GVHD patients.

Further, based on the toxicology studies in adolescent/adult animals, at clinically relevant exposures, belumosudil had no overt impact on growth and development.

Despite the risks and the uncertainties, the safety of belumosudil also in adolescents could be approvable.

Conditional marketing authorisation

As comprehensive data on the product are not available, a conditional marketing authorisation was requested by the applicant in the initial submission.

The CHMP considers that the product cannot be recommended for a conditional marketing authorisation as the benefit-risk balance is negative (as discussed). In addition, the applicant is unlikely to be able to provide comprehensive data after authorisation, and the benefits to public health of the immediate availability do not outweigh the risks inherent in the fact that additional data are still required. The pharmacological rationale of belumosudil is clear and adequately supported by non-clinical data. *In vitro* and *in vivo* results demonstrate a dose-dependent effect on key aspects of the disease process such as interleukin secretion, T cell regulation and fibrosis, but there are no suitable pharmacodynamic endpoints to support benefit in clinical setting.

This application is based on a single arm trial which was questioned for the purpose of MAA in scientific advice. The evidence for efficacy generated in a single arm trial is less robust and subject to different types of bias. Time-to-event endpoints are considered important for demonstration of clinical benefit but cannot be reliable assessed in a SAT setting. The broadly used primary efficacy endpoint ORR by NIH score is also difficult to interpret in a SAT, and the magnitude of treatment effect is uncertain.

Although there are regulatory precedents where ORR has been accepted as the primary endpoint for GvHD, there are differences in timepoints, and statistical methods utilized in different studies. The main issue is that the drug effect is difficult to isolate in Study KD025-213. Further to the clarification from the applicant (upon CHMP request), on the impact of concomitant medications, it can be concluded that in the SAT, the observed responses with belumosudil were not associated with any specific concomitant treatment or duration of concomitant treatment. Further it is noted that treatment responses have been observed in RW setting also with belumosudil monotherapy. Although the response rate is high, due to partially subjective nature of the endpoint and broad definition of the endpoint (any response at any time during the treatment), the isolation of the true effect remains unsolved, and the magnitude of the treatment effect is difficult to estimate. However, it can be concluded that the proportion of responders is relevant at the time of landmark analyses at 6 and 12 months (48% and 33%, respectively). The majority of responders at 6 months had, at any time during treatment, response in 2 or more organs (based on best response per organ).

Due to the multiple uncertainties, the available efficacy data is not considered to be comprehensive.

The pivotal study results demonstrate potential to address an unmet medical need in last line cGvHD population, as the observed response rate and duration of responses would be clinically relevant in last line cGvHD setting. However, a randomised placebo-controlled study in 1L cGvHD failed to demonstrate clinical benefit or even drug activity as add-on treatment to corticosteroids. This increases the uncertainty about the clinical benefit of belumosudil treatment.

As comprehensive data on the product are not available as discussed above, a conditional marketing authorisation was requested by the applicant in the initial submission.

The product falls within the scope of Article 14-a of Regulation (EC) No 726/2004 concerning conditional marketing authorisations, as it aims at the treatment of a life-threatening disease. In addition, the product is designated as an orphan medicinal product.

The product is not currently considered to fulfil the requirements for a conditional marketing authorisation:

- The positive benefit-risk has not been established, as Major Objections have been raised and considered not being addressed satisfactorily. The available efficacy data is not considered to be sufficiently robust to conclude on positive benefit/risk. While the pivotal SAT demonstrated potential to address an unmet medical need in last line cGvHD population, failed randomised controlled trial in first line cGvHD setting increases the uncertainty.

  Study EFC17757 was performed in newly diagnosed patients with cGVHD, and therefore in a considerably different patient population as compared to study KD025-213. The disease pathophysiology may be different, inflammation playing a more central role in early stages vs. fibrotic changes in later stages of the disease. Despite differences in patient population, treatment history and disease process, lack of any clinical benefit observed in the RCT study EFC17757, and even any drug activity as add-on treatment to corticosteroids, is concerning and adds to uncertainties identified based on pivotal study.

  In terms of safety, the number of patients exposed to belumosudil is limited but it was considered that it could be sufficient to characterize the safety profile in the setting of a CMA. In addition to clinical trial data, available post-marketing data are in general consistent with the known safety profile of belumosudil, with no new or unexpected safety signals identified.

- It is uncertain whether the Applicant is able to provide comprehensive data within a reasonable timeframe.

  During the initial assessment of marketing application of belumosudil, CHMP concurred that the Phase 3 study EFC17757 comparing belumosudil in combination with corticosteroid with placebo in combination with corticosteroid in patients with newly diagnosed moderate and severe cGVHD could serve as a Specific Obligation (SOB) for the applied CMA in the treatment of cGVHD after two prior lines of systemic therapy and provide confirmatory data on the efficacy and safety of belumosudil in both adult and adolescent cGVHD patients. A total of approximately 260 participants were planned to be randomized in a 1:1 ratio to receive either belumosudil in combination with prednisone or placebo in combination with prednisone. The primary endpoint is EFS, and ORR is included as a secondary endpoint.

  However, on 21 May 2025, at the time of pre-planned futility Analysis, the EFC17757 study DMC recommended to temporarily pause accrual to the study based on the efficacy data from the first 70 participants and safety data from 166 participants. As reported by the Applicant, no major safety concerns were noted. On 25 June 2025, based on the review of the efficacy data at the time of a futility analysis from more than 100 participants, the DMC recommended to discontinue both accrual to the study and dosing in currently enrolled participants. On 30 June 2025, the DMC clarified that patients with sustained CR or PR can continue treatment provided both the physician and the patient are in agreement. The Applicant made the decision to terminate the study EFC17757 on 26 June 2025. The Applicant will further collect data, analyse and publish the results subsequently. Thus, this study will not be able to confirm positive B/R.

  Due to the termination of the study EFC17757 the Applicant proposes a new SOB, Phase 3 randomized controlled study to fulfil the specific obligation of the CMA. A short outline of the planned study has been provided during D180 and CHMP Oral Explanation on 16 September 2025.

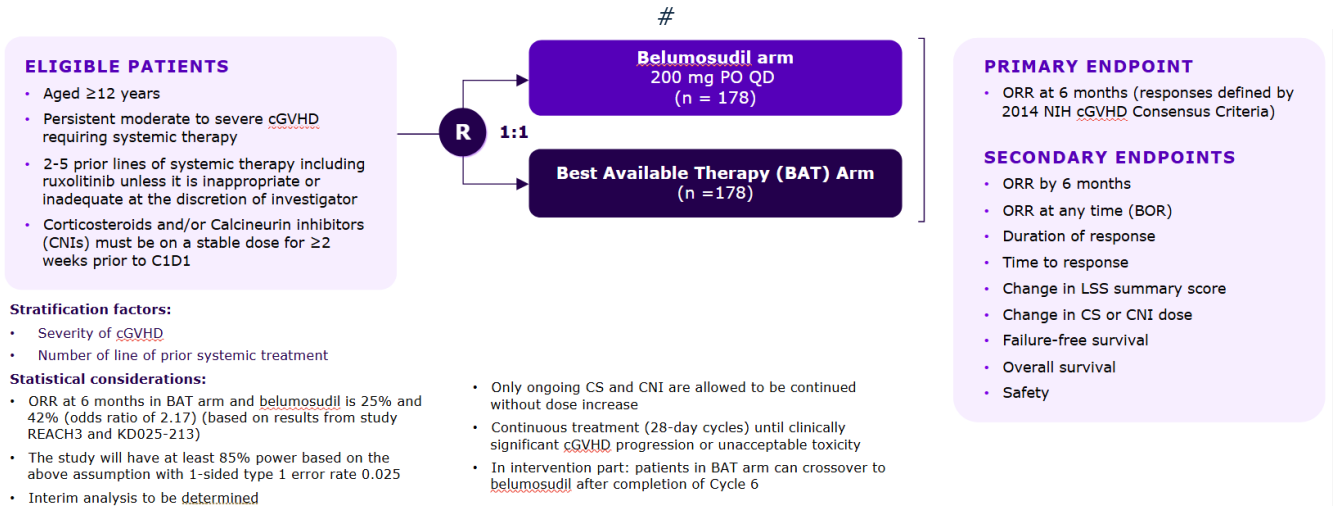

Figure 17: Study schema of the new proposed SOB.

This phase 3, randomized, open-label, multi-centre study will investigate the efficacy and safety of belumosudil versus BAT in participants ≥12 years of age with cGVHD after at least 2 prior lines of systemic therapy including ruxolitinib unless it is inappropriate or inadequate at discretion of the investigator. A total of approximately more than 300 participants will be randomized 1:1 to receive either belumosudil or the BAT. The stratification factors include severity of cGVHD at baseline according to the NIH consensus diagnosis and staging criteria (2014) (moderate vs severe) and the number of prior lines of therapy (2 vs > 2). For further details, please see section 2.6.7 Discussion on clinical efficacy.

The Applicant commits to provide a study protocol on 18 Dec 2025. Estimated data delivery of the proposed SOB will be in 2030.

The proposed study population is largely in line with the currently applied indication and would therefore be fully suitable to confirm the B/R. Prior ruxolitinib use is required unless it is inappropriate or inadequate, reflecting the current clinical landscape. BAT as comparator is considered to be acceptable and reflects the current heterogeneous clinical practice. It is expected that for a majority of the patients, ECP would be the most appropriate treatment option. Option to cross over at 6 months limits the interpretation of any long-term data but would not be considered to be with a major problem for addressing the key uncertainties at the moment. Compared to the pivotal study, fewer concomitant medications (corticosteroids and CNIs only) are allowed, and hence, isolation of the drug effect will be easier in a RCT setting.

The primary endpoint is ORR (PR or CR) at 6 months based on ITT population from the RCT population. The selected endpoint is acceptable, and in line with the regulatory precedent. Although time-to-event endpoints are suited for randomised studies, use of ORR would avoid the problems associated with the complex definition of EFS used in the study EFC17757.

Overall, the proposed study would have been far more suited to support the MAA as compared to the current pivotal SAT and would have been far more suited to serve as a SOB in the first place. The evaluation that the study would be feasible to conduct now, after belumosudil has been proved in many jurisdictions globally, demonstrates that this study would have been feasible when the pivotal study ROCKstar was performed.

An important concern is the timeline. Estimated data delivery of the proposed SOB will be in April 2030. Accepting a SOB in early planning stages poses a high risk in a setting where isolation of drug effect is challenging in the pivotal study, the magnitude of treatment benefit cannot be reliably estimated, and one randomized placebo-controlled study has already failed to demonstrate clinical benefit.

The survey conducted and feasibility analysis performed by the Applicant is appreciated, as during scientific advice procedures, and earlier stages of the MAA assessment, the Applicant has argued that conducting an RCT in the target population would not be feasible. The Applicant has not discussed the impact of availability of belumosudil on the market after if a CMA is granted in the predicted patient enrolment. In prior discussions, widespread managed access use of belumosudil was also considered to block the possibility of conducting an RCT in Europe, and a global trial was not considered feasible due to regulatory approvals in many jurisdictions. Therefore, it is not evident that the enrolment predictions would be realistic when the study has not been started, and it is not possible to predict if conducting the trial would actually be feasible in the evolving treatment landscape. Even if the study could be conducted as estimated, it would take approximately 4,5 years before the efficacy data would be available. This would mean that a considerable number of patients would be exposed to belumosudil in post marketing setting before the confirmation of B/R is available.

In conclusion, the identified uncertainties on clinical efficacy from the pivotal study, and the added uncertainty due to one failed randomised placebo-controlled study are considered to be too great to accept a confirmatory study with uncertain timelines for data delivery, in particular as the Applicant has previously continuously argued that such a study is not feasible. With estimated data delivery in april 2030, a considerable number of patients would be exposed to the treatment with uncertain clinical benefit. The availability of belumosudil on the market under a CMA increases the uncertainty in the predicted patient enrolment. It is therefore concluded that it cannot be ascertained that the Applicant would be able to deliver comprehensive data to confirm the B/R within a reasonable timeframe. The criteria for a CMA are therefore not fulfilled.

- Demonstration of fulfilment of unmet medical needs is considered sufficient in last line population.

  Belumosudil will provide a novel option for the treatment of subjects with cGVHD, with a mechanism of action that is unique to all other approved therapies.

  However, there are authorised treatments of cGVHD in the EU, and products reviewed by the Applicant have overlapping indications with the proposed indication with belumosudil. In 2022, the oral selective JAK1/2 inhibitor ruxolitinib (JAKAVI) was approved in the EU for the treatment of patients aged 12 years and older with acute GVHD or cGVHD who have inadequate response to corticosteroids or other systemic therapies, and this is currently the only approved second-line therapy for cGVHD with a marketing authorization in the EU.

  Improved efficacy over ruxolitinib cannot be demonstrated. It can be concluded that efficacy appears to be similar as compared to ruxolitinib, despite differences in patient populations enrolled in the pivotal trials.

  Demonstration of MTA based on safety is not considered to be sufficient. It is not agreed that decreased toxicity on the bone-marrow alone would be sufficient to demonstrate MTA. This difference is relevant from clinical perspective, as it limits the use of ruxolitinib treatment in clinical practice and leads to treatment discontinuations. However, this difference is most relevant for patients who are ineligible for ruxolitinib at baseline. Many relevant adverse events, for example GI-related AEs, appeared to be more frequent in belumosudil vs. ruxolitinib-treated patients. It is acknowledged that

this was not reflected in the tolerability of the treatment, as both AEs leading to dose reduction/interruption and AEs leading to drug withdrawal were slightly less common in belumosudil treated patients as compared to ruxolitinib treatment. Overall, demonstration of MTA based on improved safety cannot be agreed on. Therefore, the indication needs to be limited to last line patient population.

- The benefits to public health of the immediate availability do not currently outweigh the risks inherent in the fact that additional data are still required. Although a new therapeutic option for cGVHD patients who have failed at least 2 prior lines is considered beneficial, the B/R is currently negative due to major uncertainties in demonstration of efficacy. Currently, there is no on-going trial that would be suitable for confirming clinical benefit of the treatment, and one randomised controlled trial, considered by both the Applicant and the CHMP to be suitable for confirming the B/R, has failed to demonstrate clinical benefit or drug activity. There is no clinical data to support the hypothesis that belumosudil would provide clinical benefit only in last line cGvHD setting due to differences in disease pathophysiology, and therefore the lack of clinical benefit in 1L would not have an impact on B/R in last line. Initiating a conducting a new confirmatory trial would take a considerable time, and the uncertainties are currently of such magnitude that the risk associated with exposure to a treatment with uncertain clinical benefit for a long period of time before additional data would be available is not justified.

3.8. Conclusions

The overall benefit /risk balance of Rezurock is negative.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy for Rezurock in 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, the CHMP considers by consensus that the efficacy of the above-mentioned medicinal product is not sufficiently demonstrated, and, therefore recommends the refusal of the granting of the conditional marketing authorisation for the above-mentioned medicinal product. The CHMP considers that:

- While the numerical outcomes of the pivotal SAT (KD025-213) indicated a potential to address an unmet medical need in last line cGvHD population, important uncertainties remained. Particularly, given the partially subjective nature of the endpoint, and the presence of co-treating agents, it is not evident that a single arm study in this setting isolates the effect of the experimental treatment or is capable of establishing its true magnitude.

  This concern is aggravated by the fact that the originally proposed specific obligation to the conditional marketing authorisation, a confirmatory randomised controlled trial in the first-line treatment of cGvHD (EFC17757), failed to demonstrate any clinical benefit or pharmacological activity of belumosudil. Notwithstanding the different patient population studied in a first line setting this outcome further increases the uncertainty of the demonstration of efficacy. Hence, the efficacy of belumosudil treatment has not been demonstrated.

- The Applicant's ability to provide comprehensive data post authorisation in a reasonable timeframe in the context of a conditional marketing authorisation is uncertain. The new proposed confirmatory study has not been started, and its feasibility is uncertain. The estimated data delivery is in April 2030 by then a considerable number of patients may be exposed to belumosudil in the post-marketing setting before a clinical benefit could be confirmed.

Due to the aforementioned concerns a satisfactory summary of product characteristics, labelling, package leaflet, pharmacovigilance system, risk management plan and post-authorisation measures to address other concerns as outlined in the list of outstanding issues cannot be agreed at this stage.

Furthermore, following review of the available data in the context of the applicant's claim of new active substance status, the CHMP position at the time of this report is reflected in the Appendix.

5. Re-examination of the CHMP opinion of 16 October 2025

Following the CHMP conclusion that Rezurock was not approvable based on clinical grounds above described the applicant submitted detailed documentation for the re-examination of the grounds for refusal.

5.1. Detailed grounds for re-examination submitted by the applicant

5.1.1. Introduction

The Applicant respectfully considered that, given the high unmet medical needs of last line cGVHD patients and the CHMP's findings in the D210 Assessment Report of "high", "durable" and "clinically relevant" response rates of belumosudil, and its sufficiently characterised and acceptable safety profile, the requirements for granting a CMA are met. The doubts expressed in the Grounds for refusal concern the *isolation* and *magnitude* of the acknowledged treatment effects, not their existence or clinical relevance. The Applicant welcomed the opportunity for an AHEG to provide its views on the isolation and magnitude of the treatment effects in light of the specificities of the multidimensional, multifactorial disease cGVHD, and on the Applicant's view that uncertainties regarding the isolation and magnitude are particularly suited to be addressed by the proposed Specific Obligations (SOB). The benefits of immediate availability are clear given the lack of effective alternative treatments, and the acknowledged safety profile after treatment of 17479 patients worldwide with belumosudil.

In the Applicant's view, prior assessments may not have fully captured these disease specific considerations, which may have contributed to residual uncertainty or potential misinterpretation of the efficacy profile in the cGVHD context and the interpretation of treatment effects in the presence of background therapy adjustments. An AHEG would therefore provide an appropriate forum to align the evidentiary framework with the realities of cGVHD and to support the targeted resolution of residual uncertainties through well-defined Specific Obligations.

Accordingly, the Applicant respectfully diverged from the CHMP opinion and explained in this document how the comprehensive scientific and clinical evidence presented to the CHMP supports the granting of a CMA for Rezurock pursuant to the requirements of Regulation (EC) No 726/2004 and of Regulation (EC) No 507/2006. The Applicant urged careful re-evaluation of key considerations that appear to have been underappreciated, including:

- The background to the benefit-risk assessment for this CMA application, i.e. urgent unmet medical need in patients who have exhausted all approved treatment options, and the toxicity and minimal efficacy associated with several of the off-label "best available therapy" (BAT) treatments which are currently provided to the belumosudil target population, and will continue to be provided, if no CMA is granted.
- The consistent and clinically meaningful benefit demonstrated across four prospective clinical studies in late-stage chronic graft-versus-host disease (cGVHD), including, in particular, the overall response rate of belumosudil (73.1%), which the CHMP found in D210 AR to be "high", "durable", and "clinically relevant", and "not associated with any specific concomitant treatment or duration of concomitant treatment". The CHMP also concluded that the efficacy of belumosudil "appears to be similar" as compared to the authorized medicinal product ruxolitinib.
- This evidence remains valid and unaltered by the early termination of the initially proposed first-line confirmatory study (EFC17757), performed in a patient population with material differences in biology.
- The high likelihood that the applicant will provide comprehensive data post-authorization, by mean of SOBs, in particular a randomised clinical trial (RCT) which the CHMP has already considered to be fully suitable to address the uncertainties raised by the CHMP regarding the isolation and magnitude of the treatment effect.
- In conclusion, for a product submitted for a CMA, where the unmet medical need is high and urgent, safety is acceptable, and the response rates are acknowledged to be high, durable and clinically relevant, the appropriate regulatory conclusion is to impose SOBs to gather comprehensive evidence confirming and quantifying the magnitude of the treatment effect – and to enable patient access through a CMA.
- As noted, the benefits of immediate availability deserve thoughtful consideration.

Before presenting the comprehensive body of scientific and clinical evidence that forms the basis for the grounds for re-examination and the granting of a CMA for Rezurock, and highlighting the issues on which the views of the AHEG would be particularly welcome, the Applicant would like to highlight key regulatory, clinical, and scientific considerations that frame the interpretation of the data and the overall assessment. These considerations underscore that, in the indication subject to this CMA re-examination, i.e. *adults and pediatric 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,* the benefit of immediate access to belumosudil clearly outweighs the risks of approving the product before comprehensive confirmatory data are available.

cGVHD is a progressive, debilitating, life-threatening disease with limited treatment options

Chronic GVHD is a major late complication after allogeneic hematopoietic stem cell transplantation (HSCT), affecting 30–50% of long-term survivors. Patients with cGVHD have already undergone a challenging journey including a diagnosis of a life-threatening haematological condition, a search for a compatible stem cell donor, intensive chemotherapy, and an allogeneic HSCT leading to a very complex immune reconstitution, only to face a new challenge with debilitating morbidity and major impact on quality of life. cGVHD causes inflammation in multiple host tissues (skin, eyes, salivary/lacrimal gland, upper and lower gastrointestinal (GI) tract, lung, liver, joints, genital tract) in a variable manner with features resembling chronic systemic

autoimmune diseases. cGVHD is considered one of the main causes of morbidity and late non-relapsed mortality after allogeneic HSCT.

The consequences for patients in the target population for belumosudil are profound and multifaceted. Physically, patients experience progressive multi-organ damage that may lead to irreversible fibrosis in affected tissues. Functionally and socially, patients face marked inability to maintain employment, attend school, or participate in family life while families face increasing caregiver burden, and across all domains, patients experience a steadily deteriorating quality of life.

Recent quality of life studies conducted jointly by patient advocacy groups and physicians in France and Spain have revealed the severe impact of chronic Graft-versus-Host Disease (cGVHD) on patients' lives. Spain's Fundación Josep Carreras patient advocacy group characterizes cGVHD as "not just a medical complication, but a condition with profound and lasting effects across all areas of life."

This pattern is reflected across Europe. The cGVHD Eurograft Initiative, in collaboration with the Lymphoma Coalition, convened a European patient advisory board, with findings published in *The Lancet*. Patient advisors described GVHD as a condition that profoundly disrupts daily life across physical, emotional, and practical dimensions—revealing widespread unmet needs including information, dedicated care, and psychosocial support.

Patient advocacy groups, local scientific societies, and individual stakeholders in Spain and France have recognized these unmet needs and mobilized to call for improved care frameworks for this rare and devastating disease .The Spanish manifesto explicitly highlights the urgent need for new treatments: “Although effective treatments have been developed in recent years for patients diagnosed with chronic GVHD (cGvHD), there are still unmet needs in the management of these patients, particularly in certain clinical manifestations that respond less to treatment, such as fibrosis in various organs. Therefore, the development and approval of new treatments capable of modifying the course of the disease—and thereby improving survival and quality of life for patients with chronic GVHD—remains necessary.”

Current first-line treatment with systemic corticosteroids ± calcineurin inhibitors (CNIs) provides incomplete and only temporary control while carrying a substantial side-effect burden including but not limited to hyperglycaemia, immunosuppression, GI ulcers, cardiomyopathy, osteoporosis, cataract and skin atrophy.

In 2022, the oral selective JAK1/2inhibitor ruxolitinib (Jakavi) was approved in the EU for the treatment of patients aged 12 years and older with acute GVHD or cGVHD who have inadequate response to corticosteroids or other systemic therapies, and this is currently the only approved second-line therapy for cGVHD with a marketing authorization in the EU). However, only 50% of patients had a response to ruxolitinib at 24 weeks after treatment, indicating the needs for subsequent therapy beyond second-line treatment). In addition, it has been reported that ~20% of patients who received ruxolitinib discontinued the treatment due to adverse events due to toxicity. Approximately half of cGVHD patients fail their first two lines of treatment and desperately need additional treatment options. Most patients develop steroid-refractory or steroid-dependent disease, where available therapies are limited, inconsistently effective, and often toxic. There is an immediate and substantial unmet medical need in the specific indication as proposed by CHMP.

Indeed, after failure of corticosteroids and ruxolitinib, the only EU-approved medicinal product for cGVHD, physicians are left with no authorized treatment options. They are forced to rely on off-label therapies that lack an established benefit-risk profile in cGVHD, often carry clinically significant toxicities, and show inconsistent efficacy. In the recent French quantity survey-based study including 80 patients who received ≥2 lines of systemic treatment for cGVHD, approximately 65% of patients considered cGVHD treatments as burdensome.

These consistent patient experiences, supported by scientific societies, underscore a clear reality: for patients who have exhausted approved therapies, the need for effective, authorized treatment is immediate, critical, and unaddressed by current options.

According to publicly available data in clinicaltrial.gov, the number of ongoing clinical trials in late-line therapy remains limited. The current clinical trial landscape is predominantly composed of Phase II studies, which are characterized by small sample sizes and a restricted number of participating centers in Europe. Furthermore, the only Phase III comparative study (NCT06682169) currently underway is conducted exclusively in China. Given this limited research landscape, without the approval of belumosudil, European patients may remain without valuable therapeutic solutions in late-line therapy, leaving a significant unmet medical need unaddressed.

The urgent unmet need for belumosudil is strikingly illustrated by data from the Managed Access Program (MAP) which recorded more than 600 European patients requesting access within a single 12-month period averaging 51 patients per month. These are patients who have exhausted all approved treatment options, leaving physicians with no viable alternatives. Across the EU, more than 1,300 patients in 19 countries have already accessed belumosudil through MAPs by 17 November 2025, underscoring the substantial and growing demand for this therapy. Importantly, the MAP captures only a fraction of the true patient population in need, highlighting the critical unmet medical need that belumosudil is uniquely positioned to address. These real-world experiences not only illustrate the critical unmet treatment needs but also confirm the value of belumosudil for patients receiving advanced lines of therapy, as will be further detailed in this document.

Access via managed access programs is inherently limited and unsustainable; 12 out of 19 participating EU countries will be required to discontinue these programs under local regulations if a CMA is not granted, further exacerbating the treatment gap and leaving patients without any viable therapeutic options. Granting a CMA is therefore essential to ensure timely, equitable, and continued safe administration and access to patients who have no approved alternatives and are facing debilitating complications.

Belumosudil: consistent and durable efficacy with well characterized and acceptable safety profile, independent of co-treatments

Belumosudil's inhibition of the ROCK2 enzyme represents a novel and differentiated mechanism of action that modulates both pro-inflammatory and pro-fibrotic pathways, key pathogenic drivers of cGVHD. This dual-targeted approach is mechanistically aligned with the complex, multisystemic nature of late-stage disease, addressing both immune dysregulation and tissue fibrosis simultaneously.

The pivotal study KD025-213 demonstrated a clinically meaningful overall response rate (ORR) of 73.1% in patients with heavily pre-treated, refractory cGVHD. This overall response rate is based on disease assessments in all affected organs through validated 2014 National Institutes of Health (NIH) Consensus response criteria.

These responses were:

- Durable and able to delay need for any further cGVHD treatment (median time to next treatment of 2 years)
- Consistent across all affected organs
- Independent of prior therapies, including ruxolitinib
- Independent of concomitant medications (the contribution of these existing concomitant medications to the efficacy after belumosudil was added is negligible)

- Associated with meaningful steroid-sparing effects (26.9% of patients discontinued corticosteroids)
- Associated with quality-of-life improvements

The onset of clinical benefit was typically rapid, with a median time-to-response of just 4.4 weeks, allowing for prompt assessment of treatment effect. This quick response time is particularly valuable in a late-line setting where patients cannot afford lengthy trial periods with ineffective therapies.

These findings have been replicated in several supportive prospective interventional studies across different geographies (US, Japan, China), creating a compelling totality of evidence. The consistency of these results, with ORRs ranging from 65% to 86%, and with consistent observations on durability of responses, on the ability to discontinue steroids, and on improvement in quality-of-life, strongly support a genuine treatment effect.

In addition, direct comparison versus best available therapy in the real-world study ROCKreal (AA_00117) has provided statistically significant evidence of the benefit of belumosudil over existing therapies. This comparative benefit is further supported by intra-patient comparison of treatment outcomes on belumosudil vs prior therapies in study KD025-213, and by indirect comparison of outcomes of belumosudil and of best available therapy in different pivotal studies.

As will be shown below and established by a newly submitted meta-analysis, four prospective studies and supportive RWE, generated across different geographies, all point in the same direction of belumosudil's strong efficacy and sustained ORR. The likelihood that the high consistency between the outcome would be due to coincidence is remote. Rather, the only reasonable scientific explanation for all the consistently positive outcomes is a true treatment effect.

The pivotal study KD025-213 and the supportive clinical study data have been reviewed and recognized as robust with clinically meaningful results by 20 Health Authority jurisdictions including the United States, United Kingdom, Canada, Japan and China. They ultimately concluded on a favorable benefit/risk in cGVHD patients who failed at least one or 2 prior lines of therapies. This has enabled 17 479 cGVHD patients worldwide to benefit from Rezurock, as of November 2025.

In addition to an extensive Health Authority recognition, belumosudil has been broadly integrated in the clinical practice and treatment guidelines making it a reference for cGVHD late-line treatment such as National Comprehensive Cancer Network (NCCN) and European Society for Blood and Marrow Transplantation (EBMT). Additionally, belumosudil has been added in local EU guidelines including GITMO (Italy) and GETH (Spain) and been recommended by Medicines and Healthcare products Regulatory Agency (MHRA) and National Institute for Health and Care Excellence (NICE) in UK.

As acknowledged by CHMP in its initial opinion, belumosudil has a well-characterized and acceptable safety profile. There are no new safety concerns emerging from extensive post-marketing experience in 20 countries since its first registration in 2021. This combination of robust, consistent, and durable efficacy with a well-understood safety profile underscores belumosudil's value for patients with heavily pre-treated cGVHD.

Early termination of EFC17757 does not affect the established benefit–risk in later line of therapy

Why first line futility does not inform last line efficacy: Newly diagnosed cGVHD is biologically distinct (predominantly inflammatory and steroid responsive), whereas later line disease is fibrotic/immune dysregulated, aligning with ROCK2 inhibition. EFC17757 tested add-on to high dose corticosteroids with a complex EFS primary endpoint. On the other hand, the last line programme evaluates monotherapy and uses ORR as the primary endpoint. The DMC acknowledged no major safety concern at futility. Multiple agents

which are efficacious in last- line have failed to add benefit alongside corticosteroids in first-line. Therefore, first-line futility is not probative of last line efficacy and cannot undermine a CMA targeted to last line.

The Applicant initially proposed study EFC17757 as the confirmatory trial for this CMA, comparing belumosudil plus corticosteroids versus placebo plus corticosteroids in patients with newly diagnosed moderate or severe cGVHD.

The study demonstrated excellent enrollment progress, outperforming initial projections; however, it was terminated on 26 June 2025 following a Data Monitoring Committee (DMC) recommendation based on the results of the pre-planned futility analysis.

While the Applicant acknowledges EMA's concerns regarding the early termination of this study, it is critical to underscore that the EFC17757 outcome should not negatively influence the assessment of belumosudil benefit for the proposed later-line indication for the following reasons that are further developed.

1. **Distinct disease biology between early and late-line cGVHD:**

As the CHMP has acknowledged (D210 AR pp. 16), chronic GVHD is a result of complex mechanisms occurring in three different phases. The pathophysiology of newly diagnosed cGVHD differs fundamentally from that of established, treatment-refractory disease. Early-stage cGVHD is predominantly driven by acute inflammatory mechanisms responsive to corticosteroids, whereas late-stage disease involves fibrotic and immune dysregulation pathways, the biological domains in which belumosudil's ROCK2 inhibition exerts its most pronounced therapeutic effect. Thus, lack of additive benefit in the first-line setting is not informative for efficacy in refractory cGVHD.

2. **Established precedent of divergent efficacy in combination with high-dose corticosteroids across cGVHD disease stages:**

Numerous agents across various drug classes recommended for treatment in later-line cGVHD, including JAK- and BTK-inhibitors and MMF (mycophenolate mofetil), have failed to demonstrate benefit when combined with high-dose corticosteroids in the first-line setting. This reflects inherent biological and clinical differences across disease stages and underscores the importance of evaluating treatment effect within the appropriate therapeutic context.

3. **Regulatory consistency and continued confidence in benefit–risk:**

Following notification of the first-line study termination, none of the 20 global health authorities that previously approved belumosudil in cGVHD patients (who failed at least one or 2 prior lines of therapies) raised any concerns regarding the established benefit–risk profile in the approved indication. This international regulatory consensus further supports that the EFC17757 outcome does not affect the positive benefit–risk assessment for belumosudil in later-line cGVHD patients.

In summary, the EFC17757 study was appropriately designed to explore efficacy in an entirely distinct disease stage and treatment context. The study's early termination for futility in the first-line setting should therefore be interpreted within that framework. Importantly, this outcome does not diminish the robust, clinically meaningful, and reproducible efficacy and safety evidence supporting belumosudil's use in heavily pre-treated patients with late-stage cGVHD.

It is likely that the Applicant will be able to provide comprehensive data post-authorisation as per Article 14-a(1)(b) of Regulation

As an alternative to the initial SOB, the Applicant proposes to conduct a confirmatory phase 3, randomized, open-label, multi-centre study designed to evaluate the efficacy and safety of belumosudil versus Best Available Therapy (BAT) in participants aged ≥12 years with chronic graft-versus-host disease (cGVHD) who have received at least two prior lines of systemic therapy, including ruxolitinib unless contraindicated or deemed inadequate or inappropriate at the investigator's discretion. Participants in the BAT arm will have the option to crossover to belumosudil arm if developing toxicity to BAT treatment, not achieving response or having cGVHD progression after completion of first 6 months treatment. The study design of the proposed phase 3 study was reviewed and agreed by CHMP in the D210 assessment report.

Recognizing the evolving treatment landscape and lessons learned from prior studies, the Applicant has introduced strategic design adjustments and leveraged recent advances in feasibility planning to enhance the operational viability of this later-line cGVHD trial. A comprehensive feasibility assessment was conducted, leading to a robust and data-driven implementation plan, supported by:

1. A pan-European feasibility survey, performed specifically in the context of CMA granted prior to study conduct, and involving 38 transplant centres across 11 countries.
2. Evidence-based enrolment projections, informed by historical recruitment metrics and current patient demographics, and accounting for the dynamics of gradual belumosudil reimbursement following CMA.
3. Investigator roundtable and patient representative interviews to optimize protocol and to identify/remove barriers for recruitment.
4. A detailed operational roadmap, encompassing site selection, activation timelines, and proactive monitoring strategies.
5. Integration of AI-enabled enrolment tracking tools to ensure real-time oversight and adherence to projected milestones.
6. A comprehensive risk mitigation strategy, anticipating potential recruitment and operational contingencies.

Further details are provided in Section 5.3.1.

The proposed data submission timeline is consistent with regulatory precedents for other CMAs and is proportionate to both the rarity of cGVHD and the complexity of the proposed phase 3 study.

In conclusion, the Applicant has demonstrated that that the generation of comprehensive data post-authorization is "likely" within the meaning of Article 14-a(1)(b) of Regulation (EC) No 726/2004. The proposed confirmatory trial represents a credible, feasible, and timely approach to fulfilling the outstanding specific obligation and ensuring the continued scientific and regulatory robustness of the conditional approval. The applicant also notes that the time to first results is shorter than the CHMP considered in the D210 AR.

Key considerations:

Given the serious, debilitating and life-threatening nature of cGVHD, the absence of approved therapeutic alternatives, and the consistent efficacy with an acceptable safety profile demonstrated across multiple independent studies, the benefit of immediate availability of belumosudil clearly outweighs the risks associated with awaiting additional data. This application fully aligns with the objectives of the CMA framework, which seeks to balance urgent patient need with structured, ongoing evidence generation.

The Applicant firmly believes that belumosudil meets all four CMA criteria:

1. Addresses a significant unmet medical need in a population with no approved alternatives.
2. Demonstrates a positive benefit–risk balance within the conditional approval framework.
3. Has a high likelihood of generating comprehensive data through the proposed confirmatory study.
4. Provides a clear public health benefit that outweighs the risks associated with the fact that comprehensive confirmatory clinical data still needs to be collected

Re-examination of the totality of evidence, acknowledging the distinct pathophysiology of late-stage cGVHD, the reproducible efficacy across diverse datasets, and the absence of effective alternatives supports a positive CHMP opinion. Belumosudil delivers meaningful clinical benefit with an established, acceptable safety profile and is already available to patients in 20 countries worldwide.

Granting a CMA would enable immediate and equitable access to a mechanism-based, life-changing therapy, while ensuring continued evidence generation under a scientifically rigorous and controlled framework. Any alternative regulatory pathway would fail to address the urgent and unmet therapeutic needs of patients with cGVHD in the European Union.

The Applicant therefore respectfully requests that the CHMP grant a CMA for belumosudil (Rezurock), ensuring timely access for European patients who currently have no viable treatment options.

5.2. Applicant position on *Ground 1*

Ground 1

While the numerical outcomes of the pivotal SAT (KD025-213) indicated a potential to address an unmet medical need in last line cGvHD population, important uncertainties remained. Particularly, given the partially subjective nature of the endpoint, and the presence of co-treating agents, it is not evident that a single arm study in this setting isolates the effect of the experimental treatment or is capable of establishing its true magnitude.

This concern is aggravated by the fact that the originally proposed specific obligation to the conditional marketing authorisation, a confirmatory randomised controlled trial in the first-line treatment of cGvHD (EFC17757), failed to demonstrate any clinical benefit or pharmacological activity of belumosudil. Notwithstanding the different patient population studied in a first line setting this outcome further increases the uncertainty of the demonstration of efficacy. Hence, the efficacy of belumosudil treatment has not been demonstrated.

5.2.1. Belumosudil demonstrates a favourable benefit - risk profile in the proposed indication

5.2.1.1. Description of development program

Studies included in belumosudil clinical development program for cGVHD to support the efficacy of belumosudil in the treatment of *adults and pediatric 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* are presented.

The treatment effect of belumosudil has not been investigated in a randomized study but has been established in a number of studies with consistent observations of benefit across territories.

Three studies provide primary evidence of the efficacy of belumosudil which are included in the integrated analysis of efficacy: Study KD025-213, KD025-208 and KD025-217.

Table 59: Overview of clinical studies designed to support the efficacy of belumosudil

Study No. NCT No. (Status)	Country/Region	Objectives	Phase study design	Dosing regimen and treatment duration	Study population	Prior lines of systemic therapy	Number of treated participants/ age
KD025-213 **NCT03640481 (Completed)**	US	Long-term efficacy, safety, and tolerability	Phase 2, open-label, randomized study	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	2-5 ≥2: 155 (100%)	155 ≥12
KD025-208 **NCT02841995 (Completed)**	US	Efficacy, safety, and tolerability	Phase 2a, open-label, dose-escalation study	200 mg QD 200 mg BID 400 mg QD Treatment until cGVHD progression or unacceptable toxicity	Participants with cGVHD	1-3 ≥2: 35 (68.9%)	54 ≥18
KD025-217 **NCT05305989 (Completed)**	US	Extended treatment and follow-up of adult participants treated with belumosudil in Study KD025-208 or Study KD025-213	Phase 2, open-label LTE study	Dose assigned in the parent study	Participants with cGVHD	2-5	23 ≥18
ME3208-2 **(Completed)**	Japan	To verify efficacy, using best ORR and evaluate safety	Phase 3, open label, single arm	200 mg QD, tablet	Participant with steroid-dependent/ resistant cGVHD	1-3 ≥2: 19 (90.5%)	20 planned, 21 analysed/ ≥12
BN101-201 (Completed)	China	To evaluate the efficacy and safety of BN101/belumosudil in the treatment of patients with cGVHD who have received at least one line of systemic therapy	Phase 2, open label, single arm	200 mg QD, tablet	Participants with cGVHD	1-5 ≥2: 27 (90.0%)	30/ ≥18
AA_00117 **(Completed)**	US and EU	To evaluate the efficacy and safety of belumosudil versus best available therapy in patients with cGVHD who have failed 2–5 prior LOTs.	Non-interventional study using target-trial emulation	According to routine clinical practice	Participants with cGVHD	2-5	196/ ≥12

Study No. NCT No. (Status)	Country/Region	Objectives	Phase study design	Dosing regimen and treatment duration	Study population	Prior lines of systemic therapy	Number of treated participants/ age

Abbreviations: BID = twice daily; cGVHD = chronic graft versus host disease; LOT = line of therapy; LTE = long tern extension; NCT = national clinical trial; ORR = overall response rate; QD = once daily; RCT = randomized controlled trial.

g **Number of participants in modified intent-to-treat population included 152 adult participants and 3 adolescent participants; Database lock date for adult participants: 01 September 2022, data cutoff date for adolescent participants: 11 December 2023.**

h **Data cutoff date for Study KD025-208: 08 July 2022.**

i **Data cutoff date for Study KD025-217: 06 June 2024.**

j **Data cutoff date for ME3208-2: 15 April 2024**

k **Data cutoff date for BN101-201: 10 December 2022.**

l **Data cutoff date for Study AA_00117: 27 March 2024.**

5.2.1.2. Treatment effect of belumosudil in pivotal study KD025-213

The Applicant summarised efficacy results for pivotal study KD025-213 on page 23-24 of the "*Detailed grounds for the request of re-examination of the CHMP opinion dated 16 October 2025'* document. Main results pertain:

Treatment group	Arm A 200 mg QD	Arm B 200 mg BID
Number of participants	78	78
ORR n (%) 95% CI	 57 (73.1) 61.8, 82.5	 57 (73.1) 61.8, 82.5
ORR at 6 months n (%) 95% CI	 34 (43.6) 32.4, 55.3	 39 (50.0) 38.5, 61.5
ORR at 12 months n (%) 95% CI	 21 (26.9) 17.5, 38.2	 29 (37.2) 26.5, 48.9
Primary DOR n median (weeks) 95% CI	 57 23.9 11.43, 50.43	 57 32.0 20.86, 53.14
Secondary DOR n median (weeks) 95% CI	 57 23.9 11.43, 50.43	 57 32.0 20.86, 60,29

Clinical relevance of the primary endpoint

The Applicant acknowledged the concern raised regarding the partially subjective nature of the primary endpoint and appreciates the opportunity to clarify the rationale and clinical relevance of the selected endpoint of overall response rate (ORR).

Responses were assessed by Investigators using criteria established by the 2014 National Institutes of Health (NIH) Consensus Development Project on Clinical Trials in cGVHD.

The Applicant recognizes that in certain organ systems, such as the esophagus and gastrointestinal tract, response assessments may rely on clinical symptomatology or physical examination, which could introduce inter-assessor variability. However, this potential variability is considered limited due to the use of a widely

accepted instrument with semi-quantified scale and the consistent application of evaluation procedures by the same group of investigators at the same clinical site throughout the study. In addition, cGVHD can affect multiple organs, and responses on belumosudil were consistently observed in organs such as lung or liver with objectively measurable disease parameters such as liver function and pulmonary function tests.

Furthermore, regulatory precedent supports the use of ORR as a clinically meaningful endpoint in cGVHD.

In conclusion, the Applicant respectfully maintains that ORR, as defined and assessed in this study, represents a clinically relevant and regulatory-acceptable endpoint for evaluating treatment benefit in cGVHD.

High and durable response in heavily pre-treated patients

Both belumosudil treatment arms in study KD025-213 met the objective of excluding a 30% ORR at the primary analyses, and the study was concluded to be positive. The overall responses were observed starting from 1st cycle of treatment, continued to deepen and were maintained over time. This time course, in particular the durability of the responses in this refractory population, and the consistency across organ responses argue against an important impact of subjective outcome reporting. The CHMP requested and reviewed DOR sensitivity analyses counting non-administrative discontinuations as events. The median DoR was only slightly shorter, addressing concerns that discontinuations were inflating durability. Median time to new immunosuppressive treatment, tertiary DOR, was 101.1 weeks (~23.3 months), which is clinically very relevant. The durability of response is supported by the results of failure-free survival (FFS) and time to next treatment (TTNT) as well.

The enrolled population is considered to adequately reflect a "last line" patient population that has exhausted available treatment options. In 200 mg QDarm, majority of the patients (81%) were documented to be refractory to the last systemic cGVHD treatment prior to enrolment in the study, and the responses to prior treatments were poor: for 64% of the participants the best response to previous systemic therapy was stable disease (SD) (37%) or progressive disease (PD) (27%). Consistently, the median duration of the last systemic cGVHD treatment is 4.39 months. In this population, only 15% had a treatment response (all PR) on their last prior cGVHD treatment, and in the patients previously treated with ruxolitinib, the only EU approved agent for cGVHD, only 23% had a treatment response. Thus, based on the course of disease and prior treatment responsiveness in the enrolled population it is not considered plausible that the observed responses would be solely due to concomitant treatments or spontaneous fluctuation in clinical condition. Responses to belumosudil were also observed in objectively measured outcomes such as liver function and pulmonary function, and in difficult to treat disease manifestations such as fascia/joint involvement and lung involvement. Thus, it is considered that the responses observed could only occur to a negligible extent (in number of participants or size of the effect) without effective treatment.

Treatment effect of belumosudil is not associated with the type of prior systemic therapy

Subgroup results for ORR 200 mg QD cohort from KD025-213 study show that the treatment effect of belumosudil is not associated with the type of prior systemic therapy. Belumosudil was also effective in participants who had previously failed ruxolitinib and the 3 most commonly selected second-line agents from the BAT arm of the ruxolitinib registrational REACH3 trial in terms of ORR and ORR at 6 months, namely ruxolitinib (65.5% and 41.4%), ibrutinib (73.1% and 46.2%), ECP (76.5% and 44.1%) and MMF (77.8% and 38.9%) in the 200 mg QD, respectively.

Treatment effect of belumosudil is not associated with the duration of concomitant medications prior to belumosudil treatment

Various concomitant treatments were allowed as per standard practice. The most frequently used systemic concomitant treatments that the patients were taking on Cycle 1 Day 1 in KD025-213 Study were corticosteroids, CNIs (tacrolimus or cyclosporin), sirolimus, MMF, and ECP. Meanwhile, since the minimal duration of concomitant medication is 2 weeks per protocol eligibility criteria, further analysis of range of duration of most frequently used concomitant medications prior to study showed that over 80% of participants were already receiving this concomitant treatment 30 days or more prior to Cycle 1 Day 1 (C1D1) and more than 60% of participants were already receiving this concomitant treatment more than 90 days. If a new immunosuppressive therapy was started during the study, this was considered a treatment failure and subsequent efficacy assessments would not be taken into account for belumosudil response determination.

Subgroup analysis of ORR and ORR at 6 months by different duration of concomitant medication prior to initiation of belumosudil demonstrates comparably high ORR and ORR at 6 months, regardless of the duration of concomitant treatment prior to C1D1.

Treatment effect of belumosudil is not associated with the type of concomitant medication

Subgroup results by most commonly used concomitant therapy for ORR and other key efficacy endpoints in overall population from KD025-213 study show that the efficacy of belumosudil was comparable across all subgroups regardless of the type of concomitant medication, indicating that the treatment effect of belumosudil is not associated with the type of concomitant medication.

In conclusion, the Applicant would like to reiterate that the CHMP agreed, in the D210 assessment report, that the treatment effect was not associated with the type of concomitant medications based on analyses presented above.

Consistent benefit within the proposed indication

Given ruxolitinib is the only authorized medicinal product in cGVHD in EU since 2022, the Applicant conducted an ad hoc analysis in a sub-population of participants who had received at least 2 prior lines of systemic therapy including ruxolitinib as a second-line of treatment to further support the benefit assessment of belumosudil. The subgroup reflects the currently proposed indication under condition and demonstrates a consistent and meaningful treatment benefit with belumosudil, reinforcing its clinical values in patients when other treatment options provide limited clinical benefit, are not suitable, or have been exhausted.

Among 29 participants treated at 200 mg QD dose, 83% of participants had severe cGVHD with a median of 4 organs involved at baseline. The median number of prior lines of systemic treatment was 4, and the majority of the participants (83%) were documented to be refractory to the last systemic cGVHD treatment prior to enrolment in the study, and the responses to prior treatments were poor: for 66% of the participants the best response to previous systemic therapy was stable disease (SD) (38%) or progressive disease (PD) (28%). In addition to ruxolitinib, the most common prior therapies received by the participants (>10%) were prednisone (100%), followed by tacrolimus (69%), ECP (52%), ibrutinib (45%), sirolimus (41%), MMF (24%), and rituximab (21%). Belumosudil demonstrated robust and consistent efficacy in this 'last line' patient population as shown below.

Table 64: Overall response rate in subgroup of participant who had received at least 2 LOTs including ruxolitinib (ITT population)

Variable/Category	200 mg QD N = 29	200 mg BID N = 28	Overall N = 57
ORR (CR or PR), n (%)	19 (65.5%)	19 (67.9%)	38 (66.7%)
95% CI	(45.7, 82.1)	(47.6, 84.1)	(52.9, 78.6)
Best overall response			
CR	0	0	0
PR	19 (65.5%)	19 (67.9%)	38 (66.7%)
ORR (CR or PR) within 6 months, n (%)	19 (65.5%)	19 (67.9%)	38 (66.7%)
CR	0	0	0
PR	19 (65.5%)	19 (67.9%)	38 (66.7%)
95% CI	(45.7, 82.1)	(47.6, 84.1)	(52.9, 78.6)
ORR (CR or PR) at 6 months, n (%)	12 (41.4%)	14 (50.0%)	26 (45.6%)
CR	0	0	0
PR	12 (41.4%)	14 (50.0%)	26 (45.6%)
95% CI	(23.5, 61.1)	(30.6, 69.4)	(32.4, 59.3)
ORR (CR or PR) at 12 months, n (%)	7 (24.1%)	8 (28.6%)	15 (26.3%)
CR	0	0	0
PR	7 (24.1%)	8 (28.6%)	15 (26.3%)
95% CI	(10.3, 43.5)	(13.2, 48.7)	(15.5, 39.7)

Abbreviations: BID = twice daily; CI = confidence interval; CR = complete response; ITT = Intent-to-Treat; ORR = Overall Response Rate; PR = partial response; QD = once daily.
Notes: 2-sided, exact CI was calculated using the Clopper Pearson method.

5.2.1.3. Translational research data support the clinical benefit of belumosudil

Pharmacodynamic effects on the immune microenvironment, consistent with the mechanism of action of belumosudil and predominantly seen in patients responding to belumosudil treatment, support the biologic plausibility that the observed treatment benefit is induced by belumosudil.

5.2.1.4. Consistent benefit reproduced in other supportive clinical studies

As established by the 2014 NIH Consensus Development Project response criteria and discussed above, ORR is a clinically meaningful outcome measure in participants with cGVHD. Therefore, ORR was used as the primary endpoint in all belumosudil clinical trials in cGVHD.

The efficacy of belumosudil is replicated in the supportive clinical trials (KD025-208, ME3208-2 and BN101-201). Across the four company-sponsored studies in previously treated cGVHD in different territories (US, Japan, China), the overall response rate of belumosudil 200 mg QD was between approximately 65% and 86%, consistent with the observation of a 73% ORR in the pivotal KD025-213 study. For studies with predefined hypotheses (KD025-213 and ME3208-2), both study results were statistically significant. In addition, meta-analysis combining the results from the 4 studies (KD025-213, KD025-208, ME3208-2 and BN101-201) shows that the observed differences between study results are not statistically significant.

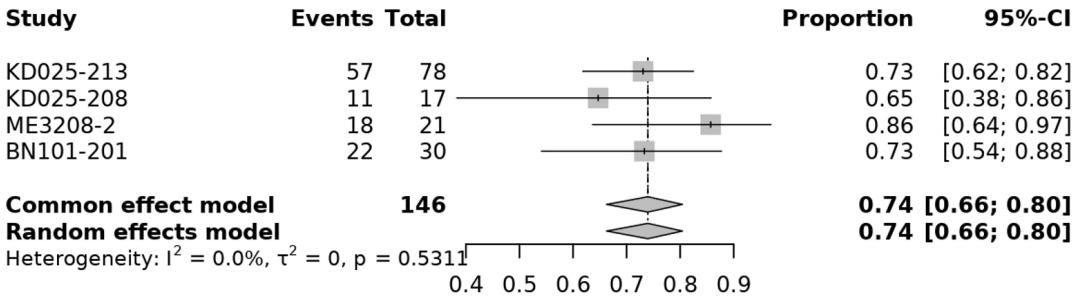

Figure 18: Meta analysis: Overall response rate (ORR) for 200 mg QD dose in all interventional clinical trials (ITT population and ≥ 2 prior LOT including ruxolitinib)

In each of the studies, consistent observations were made on the durability of the responses, the potential to discontinue all corticosteroid therapy, and the improvements in Lee Symptom Score.

Importantly for the considered indication, both the US KD025-213 study and the China BN101-201 study included patients previously treated with ruxolitinib as shown. A consistent response rate of 74.0% and 68.8% was observed. Also, consistency in the other efficacy endpoints of primary duration of response (36.1 weeks and 44.0 weeks), of frequency of steroid discontinuation (17.2% and 18.8%) and of improvement in LSS on 2 consecutive assessments (34.5% and 43.8%) was observed in the ruxolitinib-pretreated subgroups.

5.2.1.5. Major therapeutic advantages over existing best available therapy (BAT)

Direct comparison with BAT in non-interventional study using target trial emulation

To evaluate the effectiveness and safety of belumosudil compared to best available therapy (BAT) for the treatment of chronic graft-versus-host disease (cGVHD) in a real-world setting, a non-interventional study (ROCKreal; AA 00117) was conducted. In this study, the adjusted ORR at 6 months was 38.7% (95% confidence interval (CI): [27.1%, 50.4%]) for belumosudil and 26.8% (95% confidence interval (CI): [20.3%, 33.4%]) for BAT. The relative risk at 6 months post-LOT initiation was 1.442 (95% CI: [1.044, ∞); p-value = 0.031), indicating a 44.2% improvement with belumosudil.

The ROCKreal findings are consistent with other published studies and generalizable to the European populations.

Belumosudil effectiveness observed in ROCKreal is not driven by concomitant therapies (Additional analysis from AA_00117)

As CHMP indicated that concomitant medication use with belumosudil complicates interpretation of the primary analysis results from ROCKreal (AA_00117), an additional analysis was conducted to evaluate the effectiveness of belumosudil among patients only receiving concomitant background therapy (CS or CNI) without other BAT. In AA_00117, 32 belumosudil patients received belumosudil concomitantly with CS or CNI (excluding other BAT) during the line of therapy out of the 113 belumosudil-treated patients in the overall study. In an unadjusted analysis (without adjusting for baseline characteristics or right informative censoring), the ORR at 6 months among patients with concomitant background therapy (CS or CNI) was 37.9%, similar to the adjusted ORR at 6 months of 38.7% (95% confidence interval (CI): [27.1%, 50.4%]) in the pre-specified primary analysis result from AA_00117.

The consistency between these findings as well as alignment KD025-213 and other published real-world evidence studies on belumosudil support that belumosudil is driving the treatment efficacy in these hard-to-treat cGVHD patients. Patient level data were previously shared in the raw data pilot.

Effectiveness of belumosudil is similar in the proposed indication (Additional Analysis from ROCKreal AA_00117)

An analysis was conducted in patients from AA_00117 by restricting to cGVHD patients with 2-5 prior LOT with prior exposure to ruxolitinib for treatment of cGVHD. There were 77 belumosudil-treated patients (first eligible LOT) with prior ruxolitinib and 23 BAT patients with prior ruxolitinib (first eligible LOT). Among patients previously treated with ruxolitinib the ORR at 6 months was 36.8% in the belumosudil cohort and 25% in the BAT cohort. These results are consistent with closely mimic the adjusted results from the primary results from ROCKreal suggesting that belumosudil effectiveness is superior to BAT in cGVHD patients with 2-5 prior LOT after receiving ruxolitinib.

Intra-patient direct comparison of efficacy of belumosudil versus ruxolitinib and other prior therapies within study KD025-213

To further investigate the treatment effect of belumosudil versus ruxolitinib and other available therapies, the Applicant conducted a post-hoc analysis of the cGVHD response and time to next treatment, on belumosudil treatment in KD025-213 study versus what was reported for the same study participants as outcomes of their last prior systemic therapy line (regardless of type of therapy given) and, for those participants previously treated with ruxolitinib (regardless of which therapy line given), as outcomes of their prior ruxolitinib therapy.

The results suggest that belumosudil may have higher response rate and prolonged time to next treatment to what was reported by the investigator as the treatment effect of ruxolitinib, and of last line of prior treatment in the same participants. The same conclusion also applies to the comparison with prior ECP outcomes. This further demonstrates the major therapeutic advantage over existing therapies within the same patient population.

Side by side comparisons of interventional study results against BAT demonstrate improved efficacy

Data of BAT arm from REACH3 study is used to represent the efficacy of existing non-approved BAT.

The patient populations from REACH3 and KD025-213 differ. The baseline data indicate that participants enrolled in KD025-213 study had higher disease burden and were more heavily pre-treated.

Belumosudil has higher response rates (better efficacy) when compared to BAT. In addition, belumosudil has similar response rates when compared to ruxolitinib, the only EU approved therapy in cGVHD, despite being studied in a population with more extensive and more heavily pretreated cGVHD. Clinically this suggests that belumosudil is a better alternative to BATs and at least comparable to ruxolitinib.

Table 60: Summary of ORR for BAT from REACH3 and belumosudil from KD025-213 study (ITT population)

	Ruxolitinib N=165	Belumosudil 200mg QD N=78	BAT N=164
Overall response at 6 months– n (%)[1,2]	82 (49.7)	34 (43.6)	42 (25.6)
95% CI	41.8, 57.6	32.4, 55.3	19.1, 33.0
Overall response – n (%)[1,3]	126 (76.4)	57 (73.1)	99 (60.4)
95% CI	NR	61.8, 82.5	Not Reported

In conclusion, supportive comparative evidence, consisting of target trial emulation, intra-patient comparisons and side by side BAT benchmarks from REACH3 independently converges on a consistent treatment benefit with belumosudil in the last line population.

Within the different BATs used in REACH3, the most commonly used investigator choice BATs were extracorporeal photopheresis (ECP) (34.8%), mycophenolate mofetil (MMF) (22.2%), and ibrutinib (17.1%). The ORR at 24 weeks/6 months of belumosudil (43.6%) in KD025-213 is higher than any of the REACH3 BATs (ORR at 24 weeks ranges from 16.7% to 30.0%) even when participants from KD025-213 had higher disease burden and in later lines of treatment.

5.2.1.6. Consistent benefit of belumosudil is observed in real world

To identify available evidence on belumosudil's effectiveness in the real-world setting, a comprehensive targeted literature review was conducted. Out of 126 studies initially identified, 27 studies were identified as either assessing the efficacy and/or safety parameters.

Among the 16 studies reporting best Overall Response Rate (ORR), seven studies (44%) were conducted in European countries and the UK, with sample sizes ranging from 17 to 113 patients. Overall, high heterogeneity was observed in studies in terms of the patient characteristic and endpoint evaluation which likely accounts for the variation in the magnitude of observed benefit. On average patients had received 3 to 5 prior lines of treatment before initiating belumosudil therapy with most experiencing severe cGVHD. Across all 16 studies spanning 11 geographic regions, the cumulative best ORR was 56.5% among 657 belumosudil-treated patients (calculated by dividing the total number of responding patients by the total number of treated patients). Focusing specifically on European data, the seven real-world evidence studies evaluated 377 belumosudil-treated patients and demonstrated a pooled best ORR of 55.2%. The pooled ORR at 6 months across 11 studies was 54%.

Results of FFS measurement were reported in 14 studies (52%), of which six were conducted in Europe. Overall, the FFS rate ranged between 58–89% at 6 months (nine studies) and 61–86% at 12 months (nine studies). Two studies in the US reported a median FFS of 11 months and 20 months, respectively. Taken together, the consistent reporting of favorable outcomes across diverse settings strongly supports belumosudil's effectiveness in managing cGVHD. Safety outcomes related to the use of belumosudil showed that the use of belumosudil was generally safe in cGVHD patients, and the reported adverse events were mostly mild.

A recently published systematic literature review and meta-analysis evaluated efficacy, safety and organ-specific response of belumosudil in patients with cGVHD synthesizing data from 16 studies (real world studies and prospective clinical trials) comprising 651 patients. The publication highlighted variability in response rates across different study design, organ involvement, and patient characteristics. The pooled ORR was 60% highlighting the effectiveness of belumosudil in treating heavily pretreated cGVHD patients. Subgroup analysis showed higher response rate in prospective than retrospective studies (73% versus 54%). Overall, this literature review demonstrated clinically meaningful efficacy and a favorable safety profile in refractory cGVHD.

The sponsor is currently undertaking two initiatives to collect real-world effectiveness data on patients treated with Belumosudil in Europe, either as part of compassionate use program (Spain, France and Italy) or approved label (UK).

STARmania is a comparative, noninterventional retrospective study aiming to assess the effectiveness and safety of belumosudil (prescribed as part of compassionate use authorization) compared to best available therapy in France. ROCKreal II is single arm retrospective study to assess outcomes in patients treated with belumosudil in Spain, Italy (as part of compassionate use program) and UK (as part of approved label). Both STARmania and ROCKreal II will add to the existing body of evidence on belumosudil.

5.2.1.7. Well Established Safety Profile

The CHMP concluded on Day 210 that the safety profile of belumosudil is adequately characterized in the context of a CMA, with no new or unexpected signals from updated long-term extension or post-marketing data.

Belumosudil has a favorable safety profile and represents a potential therapeutic option to help patients with cGVHD decrease their reliance on long-term corticosteroid use.

Belumosudil has also demonstrated a more tolerable and manageable safety profile compared to ruxolitinib, which is standard-of-care in second-line cGVHD. In addition, there are some distinctly different adverse events that are more prevalent in ruxolitinib than belumosudil, which in the Applicant's opinion allows for a favorable benefit-risk profile for belumosudil. The main advantage in safety of belumosudil is related to its low impact on hematopoiesis. This contrasts with the significant myelosuppression with the use of ruxolitinib. The JAKs collectively are vital for normal hematopoietic function, thus the inhibition of this by ruxolitinib may be significant. Interruptions to the therapeutic regimen of ruxolitinib may lead to a potential of reduced efficacy.

In the document '*Detailed grounds for the request of re-examination of the CHMP opinion dated 16 October 2025'* an overall overview of safety based on REACH3 for ruxolitinib and the integrated analysis of phase 2 studies in patients with cGVHD for belumosudil (safety analyzed within 24 weeks for every treatment) is presented.

In the overall safety profile within 24 weeks, a consistent trend towards lower rates of grade 3 or higher TEAEs (57% ruxolitinib, 42.7% belumosudil), of SAEs (33.3% ruxolitinib, 30.2% belumosudil) and of AEs leading to dose interruptions (37.6% ruxolitinib, 25% belumosudil) were observed for belumosudil. Consistently, when comparing long-term follow-up results, lower rates of SAEs (52.1% ruxolitinib, 46.8% belumosudil), grade 3 or higher AEs (74.5% ruxolitinib, 66% belumosudil), and AEs leading to dose reduction/interruption (50.3% ruxolitinib, 38.3% belumosudil) were observed in the belumosudil cohort.

In REACH3 study long-term follow-up, notable differences were observed between belumosudil and ruxolitinib especially for CTCAE grade 3 or higher hematologic toxicities. For ruxolitinib CTCAE grade 3 anemia was reported in 17.6% of patients, while for belumosudil in the integrated analysis CTCAE grade 3 anemia was reported in 4.2% of patients. As to thrombocytopenia CTCAE grade 3 or higher was reported in 15.2% of patients with ruxolitinib. As for neutropenia CTCAE grade 3 or higher was reported in 13.3 % of patients for ruxolitinib. For belumosudil in the integrated analysis, neutropenia was observed in only one case in the belumosudil 200mg daily arm.

Potential risks for belumosudil include drug-induced liver injury, infections, and second malignancies including early recurrence of underlying malignancy. However, belumosudil presents a more manageable safety profile compared to ruxolitinib with lower observed rates of events such as pneumonia and ALT increase. With regards to secondary malignancies, in the integrated analysis of phase 2 studies for belumosudil, there were no safety concerns noted for secondary malignancy. There was only one case considered related to study treatment which was a case of prostate carcinoma – a diagnosis not traditionally associated with the post-transplant population.

5.2.1.8. Improved contribution to patient care

Belumosudil also offers improved contribution to patient care, particularly in its administration and monitoring requirements. Belumosudil is administered as a single 200 mg per tablet once daily (twice daily only when co-administered with proton pump inhibitors or strong CYP3A4 inducers), while ruxolitinib is available in four strengths at 5, 10, 15 and 20 mg and the recommended beginning dose in cGVHD is 10 mg twice a day. The once-daily convenient dosing of belumosudil is intended to maximize patient adherence.

Required monitoring for belumosudil is limited to monthly check of liver function tests as per the proposed EU SmPC. Dose adjustments are primarily based on liver function and drug interactions. In contrast, ruxolitinib requires more frequent dose adjustments based on platelet counts and other hematologic parameters. This reduced frequency of lab tests with belumosudil can lessen the burden on patients and healthcare providers, making it a more manageable option for long-term treatment of cGVHD.

In addition, belumosudil offers improved ease of use over BATs. Existing BATs require either close monitoring of plasma concentration (tacrolimus, sirolimus) or complicated administration or procedure (ECP, MMF). This ease of administration and difference in intensity of patient follow-up is an additional advantage of belumosudil over BATs.

5.2.1.9. Favourable benefit-risk assessment endorsed by 20 health Authorities

There is concluded on a favourable B/R assessment in 20 countries. The marketing authorisation of belumosudil in these 20 countries had led to the treatment of estimated 17479 patients with commercial belumosudil since the initial FDA approval in July 2021. As of November 2025, 8100 patients in USA and 450 patients in UK have been treated with commercial belumosudil. Average duration of treatment in USA has been 14 months, which further supports the long-term disease control and tolerability of belumosudil. Similar duration data are not available for UK.

5.2.1.10. Discontinued study in newly diagnosed cGVHD does not negate the benefit of belumosudil in the proposed last line indication

Having demonstrated the meaningful clinical benefit in the last line treatment of cGVHD, the Applicant will address the CHMP's second concern. While we acknowledge the CHMP's position, we will present comprehensive evidence demonstrating why the first-line study results should not impact the benefit-risk assessment in the last line setting.

Newly diagnosed cGVHD has different biology than late-line cGVHD

Although broadly grouped under "cGVHD," it is critical to distinguish between newly diagnosed cGVHD, and the treatment-defined entities of steroid-refractory (SR) cGVHD and steroid-dependent (SD) cGVHD. Recognizing these distinctions is essential for both biological understanding and therapeutic optimization.

Newly diagnosed cGVHD

Chronic GVHD develops in the post-transplant course after immune reconstitution and immunosuppression tapering, which can occur as classic chronic GVHD (without acute GVHD features) or chronic overlap GVHD (with acute GVHD features). Risk factors include gender/parity mismatches, use of myeloablative conditioning regimen, donor buffy-coat infusion, CMV infection/reactivation early post-allotransplant, and preceding low-grade acute GVHD. Clinically, cGVHD is a multisystem syndrome with features resembling autoimmune disease and with variable involvement of multiple tissues (skin, salivary/lacrimal gland, upper and lower GI tract, lung, liver, joint/fascia, genital). Because it reflects disease initiation, early recognition and standard management with corticosteroids can lead to initial disease control. Systemic treatment typically begins with prednisone at 0.5 to 1 mg/kg per day, followed by a taper to reach an alternate-day regimen, with or without cyclosporine or CNI.

Steroid-refractory vs. steroid-dependent cGvHD

In contrast, steroid-refractory and steroid-dependent cGVHD represent treatment-response phenotypes, reflecting disease evolution and therapeutic challenge rather than the mode of onset.

Steroid-Refractory (SR) cGVHD is defined by progression of cGVHD despite adequate steroid therapy. The biology often involves persistent allo/autoimmune activation, fibrotic tissue remodelling, and a reduced responsiveness to glucocorticoid immunomodulation. Recent reviews show that SR-cGVHD is associated with poor outcomes and lack of standardized second-line therapy (53).

Steroid-Dependent (SD) cGVHD refers to patients who respond to steroids but cannot successfully reduce or discontinue them without disease recurrence/flare. A multicentred retrospective study of 120 patients found that those requiring corticosteroid dependency beyond one year had significantly worse 5-year overall survival and higher rates of re-admission than those who could taper earlier (54).

Therapeutically, these distinctions matter. Treatment naïve cGVHD may be managed with first-line corticosteroids plus CNIs and monitored closely. But once the disease becomes refractory or dependent on steroids, the paradigm shifts to more focused therapeutic intervention: targeted therapies including JAK1 inhibitors, ROCK2 inhibitors, BTK inhibitors and CSF-1R inhibitors.

To further elucidate the immunological and molecular differences in treatment naive/ de novo vs steroid refractory/ steroid dependent cGVHD, new preclinical and translational data have demonstrated phenotypic differences.

Contemporary data from a paediatric cohort demonstrates immunological phenotypes that correspond to corticosteroid responsiveness and elucidated three distinct immune profiles within the de novo pediatric cGVHD population (55). This heterogeneity in immune cell phenotypes and correlation to response of corticosteroids underscores the challenge of treating patients in treatment naive setting, as this group of patients is unselected group with various pathologies. Aside from varying initial response to steroids based on phenotype in the treatment naive setting, the therapeutic pressure of treatment with corticosteroids may shift the immune and molecular profiles of steroid-refractory cGVHD patients. This phenomenon was captured in contemporary data in the acute GVHD setting, where both immune and molecular phenotypes were shifted under the therapeutic pressure of corticosteroids. These data showed lymphocytes are significantly reduced in the blood of steroid-refractory aGVHD patients compared with steroid-responsive aGVHD and myeloperoxidase (MPO) positive cells are increased in both lesions and blood of steroid-refractory aGVHD patients (56). Moreover, these immunological changes were complemented by molecular signaling pathway changes, specifically, corticosteroid therapeutic pressure drove molecular shifts in aGVHD, with ROCK signaling emerging as a dominant pathway (56). As the molecular landscape shifts from treatment naive aGVHD to steroid refractory aGVHD, ROCK1/2 is enriched in both murine models and humans with steroid-refractory aGVHD, with strong upregulation of ROCK1. (55, 56).

Pathophysiologically cGVHD is primarily thought to be a Th2-mediated T-effector cell response with a relative deficiency of regulatory T cells (Tregs). The early phase cGVHD is related to acute inflammation and tissue injury. The conditioning-related tissue damage has led to activation of donor T-cells on contact with antigen presenting cells. In addition, this epithelial damage from the conditioning has stimulated the release of soluble inflammatory mediators. Reduced Treg numbers or impaired suppressive function may have failed to control allo-reactive T-cells, contributing to the inflammation and tissue damage (57).

In second phase of cGVHD, hallmarks are chronic inflammation and dysregulated immunity. The tissue injury from the first phase has caused expansion of allo-reactive T cells to proliferate into type-1, type-2 and Type-17 helper T cells (57). In steroid-refractory cGVHD, Th17 cells are more prominent and associated with tissue fibrosis and chronic inflammation (58). Their resistance to steroids and ability to sustain inflammation make them key drivers of refractory disease (59). Again, this observation suggests that treatment naive and steroid refractory disease are inherently different from a pathophysiology perspective and require different treatment approaches.

Consistent with the different immune environment between treatment-naive and steroid-refractory or steroid-dependent cGVHD, numerous randomized clinical trials have failed to demonstrate a benefit from adding adjunctive agents to corticosteroids as first-line therapy for chronic GVHD. This applies to all drug classes which are approved for use in later line cGVHD (BTK inhibitors, JAK inhibitors) or are used as non-approved immunosuppressive agents in cGVHD (MMF, CNIs, mTOR inhibitors, thalidomide, azathioprine). Recent and notable examples are the iNTEGRATE trial (60), comparing corticosteroids combined with placebo versus corticosteroids combined with ibrutinib (dual inhibitor of BTK in B cells and ITK in a subset of T cells), and Gravitas-309 trial (61), comparing corticosteroids alone versus corticosteroids combined with itacitinib (JAK-1 inhibitor).

Collectively, these negative trials underscore the inherent challenges of evaluating established therapeutically active agents in combination with corticosteroids for first-line treatment. First-line cGVHD trials are typically enriched for steroid-responsive patients with predominantly inflammatory disease phenotypes, in contrast to steroid-refractory or steroid-dependent patients whose disease biology is more fibrotic, immune-evasive, and less amenable to corticosteroid modulation. Moreover, the prolonged and often high-dose corticosteroid

regimens required in first-line trial protocols may further obscure the independent effects of investigational agents, complicating the interpretation of efficacy signals.

Available 1L ph3 data does not preclude the benefit of belumosudil in later line

Study EFC17757 was a randomized, double-blind, multicentre phase 3 study in newly diagnosed patients with moderate to severe cGVHD to evaluate the efficacy and safety of belumosudil in combination with corticosteroids versus placebo in combination with corticosteroids in participants at least 12 years of age after allogeneic HCT. A total of approximately 260 participants were planned to be randomized in a 1:1 ratio.

In total, 211 out of planned 260 patients had been enrolled in the study. On 26 June 2025, the Applicant decided to terminate the study due to the DMC's recommendation based on the results of pre-planned futility interim analysis of ORR by 24 weeks from first 70 enrolled patients and on additional analysis of efficacy data from more than 100 participants. No major safety concerns were identified. While further recruitment and randomization were halted, the DMC recommended that, after unblinding, study participants on belumosudil arm who are in sustained complete or partial response can continue treatment provided both the physician and the patient are in agreement. As of 31 Oct 2025, there are 33 participants still under belumosudil treatment.

With the aim of understanding the potential reasons why study EFC17757 failed to demonstrate the superiority of belumosudil in combination with corticosteroid to placebo in combination with corticosteroid, the Applicant provides the detailed efficacy data based on ITT population in the *'Detailed grounds for the request of re-examination of the CHMP opinion dated 16 October 2025'*.

In short, the efficacy profiles between two treatment arms are generally comparable. No significant difference in the primary endpoint of EFS was shown.

No significant difference in ORR by 24 weeks was observed between the treatment arms.

The Applicant would like to reiterate that corticosteroids are efficacious anti-inflammatory agents and that therefore the initial response rates tend to be high in newly diagnosed cGVHD. Delaying disease progression may be more clinically relevant than increasing initial response, which was the rationale for the introduction of the novel composite endpoint of EFS.

Major differences between newly diagnosed setting and pre-treated setting

The biological differences between newly diagnosed cGVHD patients and later line patients are also reflected in disease characteristics observed in EFC17757 and KD025-213 studies, respectively. Later line patients had a longer disease history, more severe disease, a higher number of involved organs, and distinct pattern of organ involvement. Notably, in KD025-213, a greater proportion of patients had eye involvement, higher skin feature score, lower FEV1%, or elevated Joint and Fascia NIH score, indicators of fibrotic manifestation, compared to those in EFC17757 study. These findings support that the underlying biology differs between newly diagnosed and later-line patients and therefore results in differences disease presentation and evolution, duration and eventually response to treatment. The failure of study in newly diagnosed setting did not impact the B/R assessment in 20 countries where Rezurock holds a valid marketing authorization

Following the early termination of the first-line trial in newly diagnosed chronic graft-versus-host disease (cGVHD), health agencies worldwide were notified of the Data Monitoring Committee (DMC) outcome as per local regulations. Notably, none of the countries where Rezurock holds valid marketing authorization questioned the benefit-risk balance in the approved indications, and all existing marketing authorizations

remain active to date. No additional queries or concerns have been raised by any health agency regarding the product's safety or efficacy profile in approved setting.

Following the first-line study termination, two additional marketing authorizations for Rezurock were granted in September 2025 in Brazil and Thailand for 3rd line treatment. It is particularly noteworthy that Brazil participated in the first-line study and was notified of the termination of the first-line study before granting approval for the third-line indication. In conclusion, the first-line study outcome did not negatively influence the evaluation of the product in the approved indication and does not undermine the established positive benefit-risk profile in the already authorized indications.

Applicant's Summary of Benefit-Risk

In conclusion, in the opinion of the Applicant, belumosudil provides meaningful clinical benefit in the proposed indication based on a robust benefit-risk profile and a clear improvement in patient care. This conclusion is supported by consistent observations of belumosudil treatment effect in four prospective clinical studies in different territories, and by consistent observations in real-world use of belumosudil in different territories. It is further supported by a positive indirect comparison of treatment effect with outcomes of other cGVHD treatments across studies and by a positive direct comparison of treatment effect with outcomes of prior cGVHD treatments within the same participants in study KD025-213. The comprehensive package is sufficient to isolate the effect of belumosudil and is capable of establishing its true magnitude. Belumosudil offers a favourable safety profile over standard cGVHD therapies (in particular with ruxolitinib and chronic corticosteroids) with convenient dosing and handling instructions.

The positive benefit-risk assessment has been acknowledged by marketing authorisations in 20 countries in North- and South America, Asia, the Middle East, UK and Russia. The Applicant would like to reiterate that, despite current absence of EU approval, belumosudil has been acknowledged by EBMT treatment guidelines as recommended therapy in cGVHD (14) and, by European Respiratory Society (ERS)/EBMT clinical practice guidelines on treatment of pulmonary cGVHD in adults (62). Additionally, belumosudil has been added in local EU guidelines including GITMO (Italy) (63) and GETH (Spain) and been recommended by National Institute for Health and Care Excellence in UK (8).

These treatment guideline recommendations explain the increasing requests for belumosudil in both adolescent and adult patients through the Applicant's compassionate use program, particularly among European countries where belumosudil is currently not available.

Given the distinct pathophysiology and microenvironment in newly diagnosed cGVHD (acute inflammation and tissue injury) versus pre-treated steroid refractory or dependent cGVHD (chronic inflammation and fibrosis), data from study EFC17757 in patients with newly diagnosed should be independent of the benefit-risk assessment for the proposed indication.

Therefore, the Applicant believes belumosudil provides an efficacious and safe treatment with a robust benefit-risk profile for patients with cGVHD in proposed indication-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.

5.3. Applicant position on Ground 2

The Applicant's ability to provide comprehensive data post authorisation in a reasonable timeframe in the context of a conditional marketing authorisation is uncertain. The new proposed confirmatory study has not

been started, and its feasibility is uncertain. The estimated data delivery is in April 2030 by then a considerable number of patients may be exposed to belumosudil in the post-marketing setting before a clinical benefit could be confirmed.

5.3.1. Confirmatory phase 3 study within approved indication will be feasible under CMA

We understand the CHMP's concerns about both the feasibility of the proposed study and the timeline for delivering confirmatory data. In response, we present information that addresses these concerns, including:

Timeline with key results delivery by December 2029 - achieved through optimized site activation and enrollment strategies

Strong feasibility indicators from a comprehensive EU survey - 38 bone marrow transplant sites across 11 EU countries showing 67% interest in the RCT design and 70% likelihood of enrolling patients in the BAT arm

Proven operational capabilities and risk mitigation strategies - leveraging successful experience from EFC17757 study, AI-powered enrollment monitoring, and established relationships with 83% of planned study sites.

5.3.1.1. Study design

This Phase 3, randomized, open-label, multi-center study will investigate the efficacy and safety of belumosudil versus BAT in participants ≥12 years of age with cGVHD after at least 2 prior lines of systemic therapy. The primary endpoint is ORR at 6 months.

More than 300 participants will be randomized 1:1 to receive either belumosudil or BAT. Belumosudil or BAT may be used as add-on therapy alongside CS and/or CNIs. The choice of BAT will be decided by the Investigator before randomization in this study. The stratification factors include use of concomitant CS and/or CNI (ie, tacrolimus and cyclosporine) at baseline (Yes versus No), severity of cGVHD at baseline according to NIH consensus diagnosis and staging criteria (2014) (moderate versus severe), and the number of prior lines of therapy (2 versus more than 2). Participants randomized to the BAT arm will have the option to cross-over to open-label belumosudil treatment upon meeting predefined criteria for initiating a new systemic therapy for cGVHD and must have completed the Week 24 disease response.

The study design of the proposed phase 3 study was reviewed and agreed by CHMP in the D210 assessment report. The full protocol will be finalized at the time of positive re-examination.

5.3.1.2. Study feasibility considerations

The feasibility of the proposed phase 3 study as planned now differs from what was discussed as part of the *2022 Joint Scientific Consultation.*

First, the currently proposed study would allow for cross over to belumosudil after 6 months for BAT patients, avoiding an early crossover which had raised a concern on introducing potential bias, and would ensure prior exposure to ruxolitinib (unless inappropriate). Second, the increasing incorporation of belumosudil in treatment guidelines and the favorable experience with belumosudil in our MAP make EU physicians more convinced that a randomized study allowing belumosudil treatment in all study participants (due to cross over

potential) who have been previously treated with the EU approved agent ruxolitinib is an appropriate and feasible proposal to study candidates. And third, the observed high demand for belumosudil within the European MAP, which would be terminated by the start of the phase 3 study to avoid recruitment competition, and the results of the study feasibility survey and the operational planning detailed below, point towards the feasibility of the phase 3 study within a context of CMA.

Feasibility Survey indicates high interest for phase 3 randomized controlled trial (RCT)The feasibility is supported by the results of a survey performed in July 2025 in which the Applicant approached clinicians from more than 50 EU sites to collect feedback on their interest and overall feasibility of alternative study designs and to assess the possible enrollment challenges in recruiting patients in the best available therapy (BAT) arm accordingly.

The feasibility survey was performed specifically in the context of CMA granted prior to study conduct indicates high interest for phase 3 randomized controlled trial (RCT) including a Best Available Treatment (BAT) arm.

A total of 38 (76%) respondents provided their feedback. 67% indicated interest in a randomized controlled study; single arm trial was the next best option, 70% of the respondents found moderate to high likelihood of enrolling patients in the BAT arm, 76% of the respondents found crossover will make being assigned to the BAT arm acceptable.

The feasibility survey provided four possible study designs to serve as alternative confirmatory study

- Prospective non-interventional study- a European multi-country observational study comparing belumosudil versus BAT in cGVHD patients with 2-5 prior treatments.
- Single arm trial - a European multi-country clinical trial enrolling patients with moderate or severe cGVHD who received at least two prior lines of treatment including ruxolitinib unless inappropriate. This study would essentially mirror KD025-213 (conducted only in the United States) but would restrict concomitant medications to stable dose of corticosteroids and/or CNIs. While not randomized, this study would inform the true benefit of belumosudil addressing the issue of isolation of effect.
- RCT with hybrid control arm. Hybrid study consisting of RCT part where the trial population between belumosudil and BAT arms is randomly assigned at a ratio of 5:2 and BAT external control arm part. This would be a randomized study but designed in a way that the BAT arm consists of patients partially from the clinical trial and partially from a prospectively collected observational cohort.

Conventional RCT. This is a standard RCT, where the assignment between the belumosudil and BAT arms are at a 1:1 ratio. This study would include a higher number of patients and would allow for a robust estimate of the treatment effect. Design assumes the highest standard in evidence generation in clinical trial setting while the potential risks of enrollment or retention remains.First, the respondents were asked to rank the four study designs according to their level of interest. Based on the experience of the Applicant, investigator interest in the scientific question is the most important determinant of study engagement and continued recruitment of patients in the study. The survey showed investigators expressed a high level of interest on SAT (46%), followed by conventional RCT (38%) and then by hybrid study (16%). No investigators ranked NIS first. It is important to note that among the respondents who ranked RCT lower, competing trial in same population was the main reason for lower interest on the two RCT studies. Approximately 60% of the respondents ranked the two RCT designs as their second and third choices. To date, the other competing trial has been terminated, thus leaving the planned study as the only phase 3 study in later line moderate to severe cGVHD.

Based on the level of interest, clinical trials are of high interest to investigators. And since the Agency indicated the importance of RCT in the meeting held with the rapporteur on July 17, 2025, we focused the subsequent assessments on the RCT study design.

Second, the Applicant assessed the feasibility of enrolling patients in the BAT arm. A concern in running an open label RCT is that patients may participate more in a RCT if they are in preference of receiving the novel treatment, in this case belumosudil. However as shown 70% of the respondents found moderate to high likelihood of enrolling patients in the BAT arm. Based on these findings, both RCT designs seem to have the same likelihood of enrolling patients in the BAT arm.

Third, the Applicant assessed whether allowing BAT recipients crossover to the belumosudil arm after 6 cycles of treatment would make the study more acceptable. Approximately 75% of the respondents (moderate or high) think that ability to crossover will make being assigned to the BAT arm acceptable. Based on these findings, both RCT designs seem to indicate that allowing crossover after 6 cycles of treatment will render both designs equally acceptable to have patients be assigned to the BAT arm.

5.3.1.3. Study timeline assessment

As shown in **Table 63**, timelines could allow for the Applicant to provide the key results of the RCT by end 2029 (assuming CMA in 2026, this is within 4 years). The timelines for delivery of data were calculated based on assumptions explained below.

The estimated data delivery date for all options is mapped out based on previous experience from EFC17757 (also an RCT), the information on axatilimab's phase 3 study and the results of the feasibility survey.

Enrolment assumptions in a context of an approved CMA - based on experience from successfully enrolling study EFC17757

In EFC17757 study, a total of 73 EU sites were included (many more sites were interested but were refused due to proportional assignment across regions given the global nature of the study) with a recruitment rate of approximately 0.1 patient/site/month. Considering that the incidence rate of patients with cGVHD who received at least 2 to 5 prior lines of treatment is collectively higher than patients with newly diagnosed cGVHD, the enrollment rate for alternative confirmatory study could be higher than that of EFC17757. For study timeline planning purposes, we conservatively applied the same rate of 0.1 patient/site/month instead of increasing it. We also evaluated the enrollment assumptions in the axatilimab phase 3 RCT in a similar population. Based on published information, the study uses an enrollment rate assumption of 0.07 patient/site/month across 131 EU sites, of which 52 (40%) sites also participated in the EFC17757 study. After taking the results of the feasibility survey into account, as well as information from competing trials, assumes an average recruitment rate of 0.10 patient/site/month. While this is slightly higher than the computed enrollment rate of the axatilimab study (NCT06821542), it is important to note that belumosudil is an oral drug administered once a day while axatilimab is an intravenous drug given every two weeks. The logistical challenge of having patients come in more frequently may account for the lower enrollment rate assumption in the axatilimab study. Frequent visits were a strong concern among investigators during the planning of EFC17757. Taking into account all of the above, the Applicant believes the enrollment rate assumption being applied in the proposed study is achievable.

The Applicant has the operational capabilities and relationships that are essential to enrollment planning of a successful phase 3 study. The methods the Applicant is employing have been applied in the 1L study, which had an extremely successful enrollment.

Our enrollment assumptions are based on realistic numbers. Within a 12-month period, more than 600 patients in 3L+ requested access to belumosudil in Europe through the MAP, which is a monthly average of 51 EU patients with cGVHD after 2 prior lines. We used this as base number as possible sampling pool. We then assumed that only 15% of these patients will participate in the study, at an enrollment rate of 0.1 patients per site per month. This is the same rate we had in the 1L study, even if the collective patients pool in 3L+ is higher than 1L.

Using the same MAP numbers, we identified that the top 5 countries accounted for 85% of the population; we therefore selected 60% of our target sites from these countries, then identified sites with competing studies from these countries, and deliberately only picked 25% overlap with our selected sites – these are large centres with high patient volume. However, we just recently found out that the other competing study is being discontinued for strategic reasons. Therefore, this allows us to maximize further the use of these 5 countries.

Furthermore, the numbers we estimated from these 5 countries assumed for a higher enrollment rate within the first 2 years from first participant in (FPI), and a lower enrollment rate after 2 years, to account for when belumosudil reimbursement would be widely available following the CMA.

Site activation acceleration and maximization of number of sites

The applicant intended to accelerate the site initiations within 3 months. In the initiation stage of the study, we will focus on EU site activation. The centralized nature of the protocol approval in EU will allow for all sites to be activated at the same time.

To account for potential impact of increasing belumosudil reimbursement under CMA, the Applicant plans to include other EU and non-EU European countries to help sustain the enrolment in the later part of the study. In addition, the Applicant will evaluate the inclusion of non-European countries with similar healthcare systems for incorporation in the study.

EBMT accredited sites will be selected; this will be a global study with the majority of sites in the EU region. The Large majority of the sites will have previous experience with the applicant. The expectation is that each site will contribute more than two patients over the entire enrolment period.

Lastly, as applied in our 1L study, the Applicant will have a robust monitoring plan with interventions to mitigate fluctuation in patient enrllment.

As shown in **Table 61** assuming a positive opinion from the CHMP on 29 January 2026 followed by an EC decision, the Applicant commits to finalise the protocol and assumes availability of key study results to be shared with the Agency in Dec 2029.

Table 61: Detailed timeline for conventional Randomised Controlled Trial (RCT)

Key Milestone	Estimated Timeline
CHMP CMA opinion	29 Jan 2026
Protocol final for CHMP review	30 Jan 2026
Key results shared with EMA	Dec 2029

The applicant has prepared a detailed site activation and cumulative enrolment projection. This forecast, which will be further modified prior to study start, will be used to monitor the enrolment performance of the study and will be presented to EMA annually as part of annual renewal of CMA. In addition to the standard methods used in study monitoring, the Applicant will use artificial intelligence (AI)-driven software called PLAI to monitor in real-time enrolment performance by sites and countries. The actual enrolment data will be fitted against the original forecast and used by the study team to assess enrolment in a real-time fashion. The software is also able to establish trends and alerts the team when remedies or mitigation should be implemented to address enrolment issues. The Applicant has successfully used this in several RCTs including EFC17757 in which the enrolment was excellent and beyond the initial assumptions.

Mitigation plan for potential study challenges

The Applicant conducted a thorough and comprehensive analysis of potential data integrity and feasibility challenges associated with conducting a confirmatory clinical trial in the context of Specific Obligation following a CMA approval and developed a robust strategy to minimize the risk of its occurrence or minimize its impact on study integrity and feasibility. The PLAI tool along with a fully vetted study mitigation plan will ensure adherence to proposed study timelines.

5.3.1.4. Summary of study feasibility

In conclusion, the Applicant is of the opinion that the proposed randomized phase 3 study is feasible within the context of a CMA. This is based on the observed demand for belumosudil within the European MAP, the results of the recent feasibility survey feedback from 38 bone marrow transplant sites in 11 EU countries, the Applicant's ongoing collaborations with potential investigator sites, the Applicant's experience and internal staff to implement phase 3 studies including in cGVHD, and a detailed realistic assumption incorporated in the planning of the phase 3 study recruitment. A detailed AI-supported enrollment plan takes into account the anticipated gradual reimbursement dynamics of belumosudil across EU and the feedback of investigators and patient representatives to remove participation barriers and to enhance engagement.

To address the CHMP’s feasibility and timeliness concerns, the Applicant commits to finalize the protocol at the time of positive re-examination, initiate sites with pre-selected high-throughput centres, and provide detailed timeline for key milestones, with regular progress reports as post-authorization measures.

In a last-line, life-threatening condition with no authorised (on-label) options, CHMP has acknowledged that belumosudil produces clinically relevant, multi-organ responses with meaningful durability and steroid-sparing effects, alongside an acceptable safety profile. For a CMA, the remaining question is not whether benefits exist, but their precise magnitude, and whether the Applicant is likely to confirm it. With a randomised, BAT-controlled, ITT-only primary analysis of ORR at 6 months, and demonstrated EU-based feasibility, that standard is satisfied.

Conclusion

The Applicant is of the opinion that the comprehensive evidence demonstrates that belumosudil fulfils all criteria for CMA in patients with chronic graft-versus-host disease who have exhausted all approved treatment options.

These patients have undergone intensive chemotherapy and allogeneic stem cell transplantation for a life-threatening haematological condition, only to face debilitating cGVHD with no remaining therapeutic alternatives in European Union. Late-line cGVHD patients experience progressive multi-organ damage, irreversible fibrosis, and significant quality of life deterioration affecting their ability to work, attend school,

and participate in family life. Patient advocacy groups across Europe have highlighted this critical unmet need in publications including in *The Lancet*. This substantial unmet need is further demonstrated bymore than 600 European patients requesting access through the MAP in the last 12 months. Over more than 1300 patients across 19 EU countries have accessed belumosudil through MAPs, which would be terminated in several countries following CMA refusal.

Importantly, belumosudil demonstrates robust and reproducible efficacy results with 73% overall response rate in the pivotal study, replicated across several prospective trials in different territories (65-85% ORR) and confirmed in multiple real-world evidence datasets. Responses are durable, consistent across affected organs, independent of prior therapies and of concomitant background therapies, and allow for complete discontinuation of concomitant steroids in approximately one quarter of patients. Direct comparison with best available therapy in real-world data showed statistically significant superiority and is further supported by intra-patient comparison of outcomes vs prior therapies in the pivotal study. Twenty health authorities worldwide have recognized this compelling evidence through marketing authorizations, enabling treatment of 17479 patients globally with a well-characterized and acceptable safety profile. The 14-month average duration of belumosudil treatment in USA provides further support for the long-term benefit and disease control. Consistently, belumosudil has been incorporated in cGVHD treatment guidelines in USA (NCCN) and EU (EBMT, GITMO [IT], GETH [ES])).

The early termination of the first-line study is not informative for the established benefit in late-line patients due to fundamentally different disease biology, a pattern observed with multiple other agents used in later lines of cGVHD despite first-line failure.

The proposed confirmatory Phase 3 randomized controlled trial is demonstrably feasible, supported by surveyed EU transplant centres expressing interest within a context of CMA, by the Applicant's established operational relationships with 83% of planned study sites, and by robust enrollment projections based on successful EFC17757 experience and anticipated gradual reimbursement dynamics of belumosudil across EU. In the proposed operational plan following CMA, key study results will be available by December 2029.

Currently, European physicians must rely on off-label therapies with no established benefit-risk profile in the late-line setting. Meanwhile, belumosudil treatment with proven efficacy and safety and with convenient oral dosing and monitoring instructions, is available in 20 countries worldwide. Chronic GVHD remains a debilitating disease and with very limited approved treatment alternatives especially in Europe, the benefit of immediate access clearly outweighs the risks of awaiting additional confirmatory data.

The CHMP already accepts

- clinically relevant response proportions in late-line and
- an acceptable safety profile in the CMA context.

The Applicant addresses the residual uncertainty, *isolation* and *magnitude* of the acknowledged treatment effects magnitude in a SAT, by

- durability-focused and multi-organ sensitivity analyses responsive to the AR's critique, and
- a feasible RCT-based SOB that removes reliance on observational borrowing.

On that basis, the CMA criteria are met: the benefit/risk is positive in a last-line population with unmet need, it is likely that comprehensive data will be provided through the SOB, and the benefit to public health of immediate availability outweighs the risks inherent in the remaining uncertainties.

The Applicant therefore invites the CHMP to re-examine the provided evidence and to grant CMA for belumosudil, ensuring European patients with treatment-refractory cGVHD have timely access to this needed therapeutic option.

5.4. Report from the AHEG

Following a request from the applicant at the time of the re-examination, the CHMP convened an Ad Hoc expert Group inviting the experts to provide their views on the CHMP questions raised based on the CHMP grounds for refusal.

Report from the AHEG

The questions raised and the corresponding answers from the AHEG are listed below:

1. ***Pre-requisites for isolating the effects of a test drug in studies lacking a relevant control arm include that the event defining the primary endpoint would not occur without treatment; and moreover, that its occurrence could not be attributed to co-treatments.***

Table 62: Response determination for chronic GVHD clinical trials based on clinician assessments

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

ULN indicates upper limit of normal.

1.a) Please consider the definition of objective responses (above listed) in the KD025-213 study and comment on how such outcomes reliably isolate the effect of belumosudil in the absence of a comparator study arm, also considering the co-treatments administered.

All experts agreed that the 2014 NIH definition of objective responses in the KD025-213 study is a relevant and accepted measure of assessment of efficacy in cGVHD. Among the clinical and scientific community, there is sufficient experience in using the NIH criteria which are considered currently the best measure to assess responses in patients with cGvHD. A change of 1 or 2 points in these criteria would be considered

clinically relevant.
All experts agreed that the absence of a control arm is a limitation of the study and that a RCT would have been the best option to isolate and assess the magnitude of the effect of belumosudil. However, the experts highlighted the following aspects which they consider relevant when looking at the efficacy of belumosudil :
- The ORR is very high (73%) and it was considered unlikely that this level of efficacy would be achieved solely based on the concomitant therapies. Therefore, all experts agreed that an additional effect would be likely attributable to belumosudil. Importantly, the experts mentioned the clinical relevance of the observed reduction/discontinuation of corticosteroid and calcineurin inhibitors (CNI) observed in a fair proportion of patients in the SAT study. Corticosteroid reduction/discontinuation observed in 64.9% and 27.3 % of patients, respectively and in 46.9% and 21.9% of patients for CNIs]. This was seen as an important factor indicating of an effect.
- The sustained improvement and maintenance of effect observed (median 5.5 months) is also considered a good indicator of efficacy attributable to belumosudil.
- The presence of complete response (CR) (5%) was also considered important in these last line heavily pre-treated patients, where achievement of CR is rare.

In summary, all Experts considered that the definition and assessment of objective responses is adequate and the efficacy of belumosudil is demonstrated. The Experts also acknowledged that some level of uncertainty remains, in particular, the magnitude of the effect being impossible to assess due to the absence of a control arm.

1.b) What would be the anticipated week-to-week variability of the elements defining objective responses, in the absence of treatment changes?

The experts acknowledged that there is week-to-week variability in patients in the absence of treatment changes (e.g. based on infections and its impact on patients). This variability was, however, considered to be controlled by the fact that the changes were evaluated on a monthly basis, with appropriate assessment timepoints, leading to a clear trend showing efficacy over time. It was stated that the overall response in chronic GvHD is expected to be slow and the demonstration of the trend is most important.

In summary all Experts agreed that the week-to-week variability is unlikely to have influenced on the elements defining an objective response, considering the observed results (73% ORR), the way the assessment were made and the observed duration of response.

1.c) What would be the level of inter-observer variability ("subjectivity") in the assessment of these elements?

The Experts pointed out that a clear quantification of inter-observer variability on the NIH criteria is difficult to do but might be in the range of plus minus 1, depending on the rater's experience. They also noted that the trial was performed in specialised centres, which gives assurance of less variable outcomes. Furthermore, the study response was similar in different centres and countries (USA, Japan, China) and remarkable enough (over 70% in these heavily pre-treated patients). Similar ORR has been observed across several studies performed with belumosudil providing sufficient reassurance on the efficacy.
Furthermore, the Experts noted the correlation between the physician assessments (that could be seen as subjectivity) and the patient reported outcomes (PRO) rating, providing further reassurance.

In summary, while there may be inter-observer variability, all Experts agreed that it did not play a decisive role in the observed outcome measure.

2. **The EFC17757 study investigating belumosudil for the first-line treatment of cGvHD was stopped for futility in June 2025, while the CHMP was assessing the marketing authorisation application for Rezurock. This randomised controlled trial, in which belumosudil or placebo was added to corticosteroids in patients with newly diagnosed cGVHD, failed to demonstrate any clinical benefit or pharmacological activity of belumosudil.**
   How do the outcomes of study EFC17757 for the initial treatment of cGVHD impact your view of the anticipated efficacy of belumosudil in patients with previously treated cGVHD?

The Experts highlighted that several other therapies used as Standard of Care in the last line setting (ibrutinib, ruxolitinib, MMF) have failed to show an effect in 1st line setting. High dose corticosteroids are very efficacious in newly diagnosed cGVHD (at least 50%ORR), thus demonstration of efficacy on top of corticosteroids would be difficult to achieve for a drug tested in the first line setting.

All Experts agreed that the lack of effect observed in study EFC 17757 in newly diagnosed cGVHD patients would not impact their view on the effect observed in the SAT in third line patients. This is supported by the fact that 1st line patients and last line patients are considered as being different populations.
The experts stated that GVHD is a complex disease in which acute and chronic stages differ significantly as the disease evolves. Acute stage of cGvHD is more similar to early chronic GVHD, and transition forms between the two exist. For example, some patients may develop chronic GvHD without experiencing the acute phase of the disease. This is in contrast to late-stage chronic GvHD, which is now considered a separate form with different pathophysiology.
In early stage of the disease, T cell mediated inflammation plays the main role while in later stage, B cell involvement occurs with development of fibrotic changes overtime in resistant and refractory patients. This could also explain why several pharmacologic therapies have not shown an effect in 1L vs 3L. It is also plausible that belumosudil would have stronger effect on the fibrotic evolution than the inflammation process. (has both anti-inflammatory and anti-fibrotic effect)
In summary, all Experts agreed that the lack of efficacy in the 1L setting would not impact their view on efficacy being demonstrated in 3L patients.

The patient representative emphasized the difficulty in daily living with chronic GvHD condition and the negative impact on the quality of life.
The patient representative stated that there is a need for additional therapeutic options and that any therapeutic option to be developed would be beneficial from a patient perspective.

3. ***The applicant presently proposes as confirmatory study a randomized study to investigate the efficacy and safety of belumosudil +/- corticosteroids and/or calcineurin inhibitors versus best available therapy in participants ≥12 years of age with cGVHD after at least 2 prior lines of systemic therapy.***

   Please comment on the feasibility of this study and perceived equipoise for randomisation after an approval of belumosudil in the EU.

Most of the Experts agreed with the study design of the proposed confirmatory study, which they believe would have strong academic interest and the results would likely to be important for the scientific community. They considered the study design adequate, in particular, the possibility of a cross over, an important feature for the feasibility of the study by the clinicians.
Most of the Experts agreed that conducting a study is feasible, even considering that the drug would be granted a conditional approval. They mentioned that there are sufficient patients available to be included in the study; However, the reimbursement and availability of the drug as compassionate use would impact the recruitment and study timelines.

One expert expressed concerns about the feasibility of the study in his country as soon as approval is granted based on lacking equipoise and the study could be seen as unethical. However, he acknowledged that the crossover design might partially mitigate these concerns. This expert was of the view that a study comparing belumosudil to ruxolitinib with a NI design would be a better approach for the scientific community.

The patient representative also expressed her views that she would participate in this trial even if this meant being allocated to the best available therapy arm, at least during the initial phase of the trial.

5.5. CHMP discussion on the grounds for refusal

5.5.1. Ground 1 (Efficacy)

Ground 1:

> *While the numerical outcomes of the pivotal SAT (KD025-213) indicated a potential to address an unmet medical need in last line cGvHD population, important uncertainties remained. Particularly, given the partially subjective nature of the endpoint, and the presence of co-treating agents, it is not evident that a single arm study in this setting isolates the effect of the experimental treatment or is capable of establishing its true magnitude.*
>
> *This concern is aggravated by the fact that the originally proposed specific obligation to the conditional marketing authorisation, a confirmatory randomised controlled trial in the first-line treatment of cGvHD (EFC17757), failed to demonstrate any clinical benefit or pharmacological activity of belumosudil. Notwithstanding the different patient population studied in a first line setting this outcome further increases the uncertainty of the demonstration of efficacy. Hence, the efficacy of belumosudil treatment has not been demonstrated.*

The applicant presented a detailed argumentation supporting the ground 1 on efficacy.

- The CHMP agreed that cGvHD is a progressive, debilitating, life-threatening disease with limited treatment options. The unmet medical need of novel therapies in patients with CGvHD was agreed.
- The safety profile of belumosudil was considered acceptable by CHMP in the context of a CMA application.
- The applicant argued that newly diagnosed cGVHD and late-line cGVHD are biologically different entities, indicating that the failed RCT in first-line treatment of cGVHD is not a reason to question the activity of belumosudil in later treatment lines. Therefore, Expert opinion was sought on this matter.

In addition, the CHMP would like to outline some key efficacy data previously acknowledged.

Responses were assessed by Investigators using criteria established by the 2014 National Institutes of Health (NIH) Consensus Development Project on Clinical Trials in cGVHD. While these criteria include a certain level of subjectivity, and the chosen definition of response as "any response at any time" introduces some arbitrariness, responses were also observed in objectively measured outcomes, such as liver function and pulmonary function, and in difficult to treat disease manifestations such as fascia/joint involvement and lung involvement. Of the 73 responders at 6 months, 66 (90.4%) demonstrated response in multiple (≥2) organs at any time point based on best response per organ. These clarifications/observations partly alleviated concerns regarding the ability of the primary endpoint to isolate effects of belumosudil; however Expert input was considered necessary for a final CHMP decision.

The time to next therapy (TTNT) was increased with belumosudil (TTNT = 13.08 months) compared with prior therapies [8.28 months (ruxolitinib) and 12.78 months (ECP)]. In addition, the data provided showed that the ORR was not associated with the type of concomitant medications (e.g. steroid only vs. steroid + CNI vs. steroid + mTOR/MMF vs. ECP vs. others).

While the true magnitude of the effect of belumosudil was considered uncertain, the observed response rate at 6 months (44.2%) is similar to what was seen for ruxolitinib in REACH-3. The Experts opinion on the interpretation of the primary endpoint supported that the efficacy observed can be considered attributable to belumosudil. The observed reduction/discontinuation of corticosteroid and calcineurin inhibitors (CNI) observed in a fair proportion of patients and the maintenance of the effect observed wit belumosudil (median 5.5 months) were also seen as important aspects indicating of an effect. The CHMP also took note that the other studies performed with belumosudil showing similar level of ORR were considered relevant by the Experts in the demonstration of efficacy.

In conclusion, taking into account the outcome of the AHEG discussion, it is agreed that belumosudil has an established potential to address an unmet medical need in the proposed target population (last line cGvHD), as required by the CMA regulation. While the exact magnitude of clinical benefit remains uncertain, due to the single arm trial (SAT) setting, nature, the definition of the primary endpoint and concomitant therapies, the observed ORR is considered at least partly attributable to belumosudil. Therefore, the CHMP considers efficacy being sufficiently demonstrated in the context of a CMA for the population in question.

Presentation of efficacy outcomes in the SmPC:

The CHMP considered that efficacy data presenting ORR results at 6-month are the most relevant and requested the applicant to include them in section 5.1.

5.5.1. Ground 2 (feasibility of SOB in the context of CMA)

Ground 2: *The Applicant's ability to provide comprehensive data post authorisation in a reasonable timeframe in the context of a conditional marketing authorisation is uncertain. The new proposed confirmatory study has not been started, and its feasibility is uncertain. The estimated data delivery is in April 2030 by then a considerable number of patients may be exposed to belumosudil in the post-marketing setting before a clinical benefit could be confirmed.*

The applicant presented the design of a new confirmatory study (SOB). While the study design (after adjusted cross-over at 6 months) was considered acceptable, feasibility of the study was uncertain. The new proposed confirmatory trial will not start before 2026, and the expected accrual rate might still be overestimated due to commercial availability of belumosudil in the context of a CMA.

In prior discussions, the applicant claimed that widespread managed access use of belumosudil was considered to block the possibility of conducting an RCT in Europe (lack of equipoise for randomisation). Therefore, it was not evident that the enrolment predictions are realistic, as the study has not yet been started, and it was not possible to predict if conducting the trial would be feasible in the evolving treatment landscape. Thus, it was also difficult to assess whether the updated timeline with an earlier deliverable of key results is realistic.

The feasibility survey provided by the applicant in its reply to the GfR is appreciated and suggests that 70% of the physicians found moderate to high, the likelihood of enrolling patients in the BAT arm of the trial.

The enrolment assumptions presented by the applicant are based on experience from successfully enrolling study EFC17757, the originally planned confirmatory trial in newly diagnosed patients. However, this trial recruited patients while belumosudil was not yet commercially available. Whether or not clinicians would still include patients in the trial after a potential CMA of belumosudil remained uncertain. Therefore, the AHEG was requested to provide its view on the feasibility of this study and perceived equipoise for randomisation after an approval of belumosudil in the EU.

The site activation acceleration, maximization of number of sites and mitigation plan for potential study challenges are acknowledged.

The proposed timelines presented by the applicant are detailed below.

Table 63: Tiimeline for conventional Randomised Controlled Trial (RCT)

Key Milestone	Estimated Timeline
CHMP CMA opinion	29 Jan 2026
Protocol final for CHMP review	30 Jan 2026
Key results shared with EMA	Dec 2029

The CHMP took into account the majority view of the Experts on the feasibility of the trial and its importance for the scientific community. The possibility of cross-over from the BAT arm to the experimental arm was highlighted as an important study feature for the physicians, when considering feasibility. The CHMP also noted that the Experts agreed that a RCT would have been preferable instead of a SAT for the demonstration of efficacy.

5.6. Expert testimonials

Five experts' testimonials have been submitted by the applicant. They have been considered by the CHMP. The CHMP acknowledged the UMN especially for later line of therapies and for patients not eligible to ruxolitinib.

5.7. Third-party scientific input

Twelve third party interventions have been received for Rezurock during the re-examination phase. They have been considered by the CHMP. The majority of interventions were received from investigators / physicians involved with the company's study drug who refer to in part own experience using belumosudil or reflection of the product in professional societies guidelines. They don't directly involve new clinical data in support of the application. The CHMP also acknowledged the UMN especially for later line of therapies and for patients not eligible to ruxolitinib. Information received were already known by CHMP, and as such had no impact on the CHMP assessment or its conclusions.

5.8. Overall conclusion on grounds for re-examination

The CHMP carefully assessed

- the detailed grounds for re-examination and argumentations presented by the applicant

- the opinions put forward in the AHEG meeting.

- the third-party scientific interventions received. The majority of interventions were received from investigators / physicians involved with the company's study drug who refer to in part own experience using belumosudil or reflection of the product in professional societies guidelines. They don't directly involve new clinical data in support of the application.

Finally, the following conclusions were reached on the grounds for re-examination:

- Ground 1, Part 1 regarding the magnitude of the treatment effect of belumosudil .

The clarification put forward in the AHEG meeting have strengthened the confidence that it is reasonable to assume that belumosudil has clinical activity in the intended patient population. It should be noted that the magnitude itself remains uncertain.

- Ground 1, Part 2 regarding the impact on credibility of efficacy of belumosudil of failed first-line RCT

While post hoc reasoning is a concern, the consensus in the AHEG was that early and late cGvHD are biologically different disease entities. This supports an assumption that the failed first line trial does not negate efficacy of belumosudil in later treatment lines.

- Ground 2 regarding the feasibility of the new confirmatory trial

The AHEG provided sufficient reassurance that clinicians would be willing to put their patients forward for participation in the trial, meaning that the trial is feasible, even in the context of a CMA.

5.9. Risk Management Plan

5.9.1. Safety concerns

6. Summary of the safety concerns

Important identified risk	None

Important potential risk	None
Missing information	None

6.1.1. Pharmacovigilance plan

Not applicable.

6.1.2. Risk minimisation measures

Not applicable.

6.1.3. Conclusion

The CHMP considered that the risk management plan version 1.4 is acceptable.

6.2. Pharmacovigilance

6.2.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

6.2.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 16 July 2021. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

6.3. Product information

6.3.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

6.3.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, belumosudil is included in the additional monitoring list as

- it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU;
- it is approved under a conditional marketing authorisation [REG Art 14-a]

Therefore, the summary of product characteristics and the package leaflet include a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

6.4. Additional considerations related to the product information

Extrapolation of indication to adolescent paediatric patients from 12 years to under 18 years of age and with a body weight of ≥ 40 kg

Pharmacokinetics

PK simulations using an acceptable PopPK model indicated that with the 200 mg QD regimen exposure to belumosudil at steady state is expected to be slightly higher in adolescent patients (age ≥ 12 years and body weight ≥40 kg) compared to adult patients, but markedly less than exposure in adults treated with 200 mg BID and 400 mg QD regimens that were investigated in Phase 2 studies. Elimination of belumosudil is mainly by metabolism via several pathways, which are expected to be mature by the age of 12 years.

Extrapolation of efficacy to adolescents

The aetiology, pathogenesis and risk factors of cGVHD are similar in adolescents and in adults. As for the second-line treatment of cGVHD, only ruxolitinib is available in the EU. There is an unmet medical need in adolescent patients suffering from corticosteroid-resistant cGVHD. As the immune system of adolescents is relatively mature and comparable to adults, the treatment of cGVHD in adolescents is mostly extrapolated from the experience in adults.

Extrapolation of safety to adolescents

Safety data from adolescents treated in clinical trials data is very limited (n=8). The post-marketing data included safety data on 112 adolescent patients. The quality of the accrued data are heterogenous. From the exposure data provided, it is evident the administered dose of belumosudil for the 28 patients treated in the compassionate use setting is not known. Further, the duration of exposure over 12 months is also not known for either the post-marketing or the compassionate use setting. Nonetheless, acknowledging these limitations, it was agreed with the Applicant that the clinical trial and post-marketing data did not identify any new or unexpected safety concerns that would differ markedly from the known safety profile of belumosudil in adult GVHD patients.

Further, based on the toxicology studies in adolescent/adult animals, at clinically relevant exposures, belumosudil had no overt impact on growth and development. Belumosudil does not penetrate CNS and hence, it is not expected to have any potential impact on CNS development in the proposed adolescent population. Impact on male fertility was observed under treatment, but male rat functional fertility

impairment was reversible after a drug free period, even though histopathological testicular findings were still present. Overall, the non-clinical data appear supportive.

Efficacy outcomes in SmPC

The CHMP considered that efficacy data presenting ORR results at 6 months are the most relevant and requested the applicant to include them in section 5.1.

7. Benefit-risk balance following re-examination

7.1. Therapeutic Context

The Applicant is submitting a request for re-examination of the Marketing Authorisation Application for consideration of conditional approval of Rezurock (belumosudil).

"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".

Belumosudil is a selective Rho-associated, coiled-coil protein kinase-2 (ROCK2) inhibitor, which is thought to act on both inflammation and fibrosis.

7.1.1. Disease or condition

Chronic GVHD is a result of complex mechanisms occurring in three phases: (1) early inflammation due to tissue injury, (2) thymic injury and T- and B-cell dysregulation, and (3) tissue repair and fibrosis (Hamilton BK, Haematology 2021). Currently available data point out the similarity in the pathophysiology of cGVHD between paediatric and adult patients.

The clinical manifestations are systemic, involving multiple organs, with profound impact upon quality of life and non-relapse mortality. The most frequently involved organs include skin, mouth, eyes, liver and joints. Patients who develop cGVHD after HCT face a multifaceted burden, including physical, functional, and psychosocial deficits, which negatively influence quality of life. Presence of fibrotic skin, limited motility of joints/fascia, and/or lung involvement have the greatest effect on physical capability and quality of life. Advanced fibrotic skin involvement of cGVHD mimics the clinical picture of systemic scleroderma.

The severity of cGVHD is assessed as defined by the 2014 NIH Consensus Development Project on Clinical Trials in cGVHD (Jagasia MH *et al*. Biol Blood Marrow Transplant 2015).

7.1.2. Available therapies and unmet medical need

Allogeneic HCT is the only potentially curative therapy for many haematologic malignancies, immunodeficiencies, and bone marrow failure syndromes. Despite significant advances in transplantation protocols, cGVHD remains the leading cause of late morbidity and mortality among HCT survivors. Among transplant recipients, cGVHD occurs in approximately 30% to 70% of adults and in 6% to 33% of children.

cGVHD is a heterogeneous syndrome, and treatment typically requires prolonged use of immunosuppressive agents (median 2-3.5 years).

The standard initial treatment for cGVHD requiring systemic therapy is corticosteroids, with or without calcineurin inhibitors (CNIs). However, corticosteroids are associated with significant side effects and unsatisfactory outcomes. The limited activity of currently available cGVHD treatments results in patients cycling through treatments. Approximately 50% to 75% of patients with cGVHD will require at least second line treatment. Approximately half of the patients progress to third or later lines of therapy. In the long term, approximately one-third of patients with cGVHD will have relapsed or died, one-third will have discontinued therapy successfully and one third will remain on long-term treatment for cGVHD. Of patients who remain on therapy long-term, half progress to fourth- or fifth-line therapy. cGVHD not responding to therapy ultimately leads to death.

In 2022, ruxolitinib (Jakavi) was approved in the EU for the second-line therapy of cGVHD. In the EU, no new agents have been approved to address the unmet medical need for patients who have failed two or more lines of systemic treatment.

7.1.3. Main clinical studies

The main evidence of efficacy submitted in this dossier is derived from study KD025-213, which was a phase 2, non-controlled, randomized, multicentre study to evaluate the efficacy and safety of belumosudil (KD025) in subjects with cGVHD after at least 2 prior lines of systemic therapy. Eligible subjects were randomized to open-label treatment arms belumosudil 200 mg QD (arm A) or belumosudil 200 mg BID (arm B) in a 1:1 ratio. Arm A included 77 adults and 2 adolescents, Arm B 75 adults and one adolescent. Since patients in both arms received the investigational medicinal product and there is no reference study arm, the pivotal study is viewed as a "single arm" trial. The requested posology is 200 mg QD, therefore results of Arm A are of particular interest to this application.

The primary endpoint was overall response rate (ORR) at any time while on treatment.

7.2. Favourable effects

The favourable effects observed in the pivotal randomised non controlled trial are presented below for the intended posology (Arm A of the trial)

Results Arm A (n=78; ITT)

- The ORR (95% CI) with belumosudil was 73.1% (95% CI 61.8, 82.5) in Arm A. Four (5.1%) subjects achieved a complete response (CR) and 53 (67.9%) subjects achieved a partial response (PR).
- ORR at 6 months was 44.2% (95% CI 32.8, 55.9).
- K-M estimate of median primary DoR defined as time from first documentation of response to the time of first documentation of deterioration from best response was 23.9 weeks (95% CI 11.43, 50.43).
- K-M estimate of median tertiary DoR (time to new systemic immunosuppressive treatment) was 101.1 weeks (95% CI 64.29, NR)
- Time to Response (TTR) (med) was 4.43 weeks (95% CI 3.7, 80.1)

7.3. Uncertainties and limitations about favourable effects

The magnitude of the contribution of belumosudil to the outcome of treatment cannot be fully isolated in study KD025-213, as there is no control arm, the broad and partially subjective definition of a ”partial response”, and concomitant medication was commonly used. Uncertainty remains on the exact contribution of belumosudil to the measured efficacy.

Further, the true impact on time to disease progression, relapse free survival or overall survival, cannot be fully isolated without a relevant control arm.

7.4. Unfavourable effects

The safety population includes all safety data from patients from studies KD025-213, KD025-208, and KD025-217 and were analyzed according to doses administered. In the 200 mg QD group, 99% of the cGVHD patients receiving belumosudil 200 mg QD experienced at least one TEAEs (99%). The most common TEAEs per SOC were Gastrointestinal disorders (71.9%), followed by Infections and infestations (64.6%), General disorders and administration site conditions (66.7%), and Respiratory, thoracic, and mediastinal disorders (62.5%).

By PT, the most common (>25%) TEAEs were diarrhea (42.7%), fatigue (41.7%), nausea (33.3%), upper respiratory tract infection (30.2%), dyspnea (31.3%), headache (28.1%), and peripheral oedema (26.0%) and cough (25.0%).

Treatment-related TEAEs were reported in 70.8% patients and included ADRs in Gastrointestinal disorders (28.1%), Investigations (24.0%), and General disorders and administration site conditions (24.0%) SOC domains. On an individual PT level, the most common TEAEs considered related to the study drug with ≥10% incidences were fatigue (19.8%), headache (10.4%) and diarrhoea (12.5%) and nausea (11.5%), followed by AST increased (7.3%).

The most common Grade 3 or 4 adverse reactions were pneumonia (9.4%), hypertension (7.3%), musculoskeletal pain (6.3%) and hyperglycaemia (6.3%) and dyspnoea (5.2%).

SAEs were reported in 45.8% of the patients. The most commonly reported SAEs in >3 patients were pneumonia (9.4%), pyrexia (3.1%), cellulitis (2.1%). A total of 9 (9.4 %) SAEs were considered treatment-related.

Discontinuation of belumosudil due to TEAEs was reported in 21.9% of the patients in the 200 mg QD group. The most common adverse reaction leading to discontinuation of treatment was nausea (2.1%). Adverse reactions leading to dose interruption occurred in 34.4% of patients, and the most common reasons were pneumonia (6.3%) and diarrhoea (3.1%), followed by sepsis, nausea, fatigue, pyrexia, face oedema, hypotension (2.1% each).

In all, 13 (6.2%) patients with cGVHD died within 28 days of completing the study drug treatment. Most events were related to the underlying disease. In 2 cases, the cause of death was assessed as possibly related to belumosudil.

7.5. Uncertainties and limitations about unfavourable effects

The safety assessment lacks a relevant randomised comparator arm. Therefore, events caused and not caused by belumosudil cannot be formally differentiated. Moreover, belumosudil is a first-in-class compound.

The number of patients treated in the studies KD025-213 and study KD025-208 is limited. However, clinical study report of the combined long-term extension study KD025-217 of these two main studies has also been provided. These data are complemented by real world evidence, by two years of post-marketing data and by compassionate use data. The post marketing did not give rise to any new or unexpected safety signals.

7.6. Effects Table

Table 64: Effects Table for Rezurock for the treatment of patients 12 years and older with chronic graft-versus-host disease (cGVHD) after failure of at least two prior lines of systemic therapy (data cut-off 01 Sep 2022).

Effect	Short Description	Unit	Belumosudil + concomitant treatment (KD025-213) (ITT, n=78)	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
ORR	Overall response rate	% (95%CI)	73.1 (61.8, 82.5)	N/A	The individual contribution of belumosudil cannot be isolated	
ORR at 6 months	Overall response rate at 6 months	% (95%CI)	44.2 (32.8, 55.9)		The individual contribution of belumosudil cannot be isolated	
Unfavourable Effects (safety population for 200 mg QD; n = 96)						
TEAEs, at least one		N (%)	95 (99.0)	N/A	The absence of control arm limits a complete assessment of the safety profile	
TEAEs per SOC	Gastrointestinal disorders	n (%)	69 (71.9)	N/A		
	General disorders and administration site conditions	n (%)	64 (66.7)	N/A		
TEAEs per PT, most common	diarrhoea	n (%)	41 (42.7)	N/A		
	fatigue	n (%)	40 (41.7)	N/A		
	nausea	n (%)	32 (33.3)	N/A		
TEAEs, ≥ Grade 3	pneumonia	n (%)	9 (9.4)	N/A		

Effect	Short Description	Unit	Belumosudil + concomitant treatment (KD025-213) (ITT, n=78)	Control	Uncertainties/ Strength of evidence	References
SAE	In all	n (%)	44 (45.8)	N/A		
	pneumonia	n (%)	9 (9.4)	N/A		
Discontinuations	in all	n (%)	21 (21.9)	N/A		
Deaths	Possibly related	n (%)	2 (2,0)	N/A		

7.7. Benefit-risk assessment and discussion

7.7.1. Importance of favourable and unfavourable effects

Chronic GVHD is one of the main causes of morbidity and late non-relapsed mortality after allogeneic HSCT. Hence, there is a substantial unmet medical need for novel treatments in later lines of therapy. In the EU, ruxolitinib is presently the only authorized second-line therapy.

Belumosudil was studied in a dose-comparative trial in patients with cGVHD after at least 2 prior lines of systemic therapy, in which belumosudil was given as add-on to a variety of other drugs such as ibrutinib, ruxolitinib, MMF and following extracorporeal photopheresis. The lack of a non-belomusodil control arm, or a clear exposure response relation, resulted in issues that are characteristic of non controlled trials, such as not being able to isolate the effect of belumosudil and establish its true magnitude. This pertains also to the complex nature of the definition of "objective responses", including subjective elements. Moreover, the definition of the primary efficacy endpoint as "any response at any time" may have inflated the observed response rate, as could the effects of co-treating agents. Thus, it could be ascertained that responses as defined could not occur without belumosudil treatment.

In the pivotal study KD025-213, ORR at six months was high both in the overall population and in the indicated population (previous use of ruxolitinib), and relevant proportions of patients were responders also in landmark analyses at 6 and 12 months. In the overall population, responses were reasonably durable, as median primary DoR (time from first documentation of response to time deterioration from best response) was 23.9 weeks and tertiary DoR (time to start of new systemic immunosuppressants) was 101.1 weeks.

Also, in the majority of cases, response was reported based on improvement in two or more organs. With regards to the impact of co-treatments the following is notable: the median time to response for common cGVHD medications is around 4 weeks (except for ECP). In the pivotal trial, over 80% of participants had started their concomitant treatment 30 days or more prior to C1D1, and more than 60% of participants had started treatment more than 90 days prior to C1D1.

An AHEG meeting was conveyed to provide further input on the NIH criteria used for the primary endpoint in the SAT, the isolation of efficacy and its magnitude. The AHEG, made the following observations: The ORR is high (73%) that it was considered unlikely that this level of efficacy would be achieved solely based on the concomitant therapies. Therefore, all experts agreed that an additional effect would be likely attributable to belumosudil. The experts noted the clinical relevance of the observed reduction/discontinuation of corticosteroid and calcineurin inhibitors (CNI) observed in a fair proportion of patients in the SAT study. [corticosteroid reduction/discontinuation observed in 64.9% and 27.3 % of patients respectively and in 46.9% and 21.9% of patients for CNIs]. This was seen as an important factor indicating of an effect.

The sustained maintenance of effect observed (median 5.5 months) was also considered a good indicator of efficacy attributable to belumosudil.

In summary, it is concluded that the efficacy is sufficiently demonstrated. Available data are considered acceptable and sufficient to establish the potential for belumosudil to address an unmet medical need in the target population, in line with the requirements for a CMA. However, the exact contribution of belumosudil to the measured efficacy could not be established with certainty.

The safety profile is considered sufficiently ascertained considering the limited size of the targeted population and the proposed use under a conditional marketing authorisation. Further randomised controlled data will become available post authorisation based on the specific obligation.

In addition to the clinical trial data, data from the patient access programme and available post-marketing data are in general consistent with the known safety profile of belumosudil, with no new or unexpected safety signals identified. The safety profile is considered acceptable.

7.7.2. Balance of benefits and risks

Efficacy is considered sufficiently demonstrated. However, there remains uncertainty about the magnitude of clinical benefit, due to the nature of the primary endpoint definition as well as the presence of co-treating agents. The pivotal study establishes a potential to address an unmet medical need in last line cGvHD population.

In terms of safety, the number of patients exposed to belumosudil is limited, but considered sufficient to characterise the safety profile in last line cGvHD population. In addition to clinical trial data, available post-marketing data are in general consistent with the known safety profile of belumosudil, with no new or unexpected safety signals identified.

The above remaining uncertainties are acceptable in the context of a conditional marketing authorisation as they are offset by the unmet medical need of a last line population of patients suffering from chronic GvHD with profound impact on quality of life and related mortality. Thereby, the benefit-risk of belumosudil is considered positive in the last line setting in the context of a conditional marketing authorisation. To this end, it is imperative that treatment benefit can be sufficiently confirmed through robust and feasible confirmatory trial as a specific obligation (SOB) as outlined below.

7.7.3. Additional considerations on the benefit-risk balance

7.7.3.1. Extrapolation of indication to adolescent paediatric patients from 12 years to under 18 years of age and with a body weight of ≥ 40 kg

Pharmacokinetics

PK simulations using an acceptable PopPK model indicated that with the 200 mg QD regimen exposure to belumosudil at steady state is expected to be slightly higher in adolescent patients (age ≥ 12 years and body weight ≥40 kg) compared to adult patients, but markedly less than exposure in adults treated with 200 mg BID and 400 mg QD regimens. Elimination of belumosudil is mainly by metabolism via several pathways, which are expected to be mature by the age of 12 years.

Extrapolation of efficacy to adolescents

The aetiology, pathogenesis and risk factors of cGVHD are similar in adolescents and in adults. There is an unmet medical need in adolescent patients suffering from corticosteroid-resistant cGVHD. As the immune system of adolescents is relatively mature and comparable to adults, the treatment of cGVHD in adolescents is mostly extrapolated from the experience in adults.

Extrapolation of safety to adolescents

Safety data from adolescents treated in clinical trials data (n=8) and post-marketing data (n=112) is very limited. It was agreed with the Applicant that the clinical trial and post-marketing data did not identify any new or unexpected safety concerns that would differ markedly from the known safety profile of belumosudil in adult GVHD patients.

Further, based on the toxicology studies in adolescent/adult animals, at clinically relevant exposures, belumosudil had no negative impact on growth and development.

7.7.3.2. Aspects related to the indication

Weight restriction:

The currently presented PK, efficacy and safety data are considered sufficient to support an indication in adolescents aged 12-18 years with a body weight of ≥40 kg. There is no basis for extrapolation for paediatric patients weighing less than 40 kg, which is approximately the 50th percentile for 12-year-old children. Therefore, the Applicant agreed to limit the paediatric indication to patients 12 years and older and with a body weight ≥ 40 kg.

It was agreed that weight limit is not needed for adult patients. Adult patients with body weight significantly under 40 kg are expected to be very rare, whereas the weight limit is highly relevant for adolescents (40 kg is approximately the 50th percentile for 12-year-old children).

"Last line" wording:

Current available data support an indication as last line therapy, this indication was agreed in the initial phase of the assessment by CHMP and remains unchanged:

"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"

7.7.3.3. Applicant's request for conditional marketing authorisation (CMA)

The applicant requested in the initial submission consideration of its application for a Conditional Marketing Authorisation in accordance with Article 14-a of Regulation (EC) No 726/2004, based on the following criteria:

The benefit-risk balance is positive in the following indication: "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"

It is likely that the applicant will be able to provide comprehensive data.

The Applicant proposed to conduct a confirmatory phase 3, randomized, open-label, multi-centre study design to evaluate the efficacy and safety of belumosudil versus Best Available Therapy (BAT)

This Phase 3, randomized, open-label, multi-center study will investigate the efficacy and safety of belumosudil versus BAT in participants ≥12 years of age with cGVHD after at least 2 prior lines of systemic therapy. The primary endpoint is ORR at 6 months.

More than 300 participants will be randomized 1:1 to receive either belumosudil or BAT. Belumosudil or BAT may be used as add-on therapy alongside CS and/or CNIs. The choice of BAT will be decided by the Investigator before randomization in this study. The stratification factors include use of concomitant CS and/or CNI (ie, tacrolimus and cyclosporine) at baseline (Yes versus No), severity of cGVHD at baseline according to NIH consensus diagnosis and staging criteria (2014) (moderate versus severe), and the number of prior lines of therapy (2 versus more than 2). Participants randomized to the BAT arm will have the option to cross-over to open-label belumosudil treatment upon meeting predefined criteria for initiating a new systemic therapy for cGVHD and must have completed the Week 24 disease response assessment.

The study design of the proposed phase 3 study was reviewed and agreed by CHMP in the initial assessment.

The applicant provided further information supporting feasibility; the outcome of a feasibility survey, conducted in more than 50 sites, showing about 67% interest from clinicians in RCT. Enrolment assumptions were based on the experience of the EFC17757 in the first line setting. Additionally, the applicant proposed, further measures to boost enrolment, such as site activation acceleration and maximisation of number of sites are proposed. To address the CHMP's feasibility and timeliness concerns, the Applicant commits to submit the protocol immediately after CHMP decision, initiate sites with pre-selected high-throughput centres, and provide detailed timeline for key milestones, with regular progress reports as post-authorization measures. The results are proposed to be submitted in December 2029.

Unmet medical needs will be addressed, and the applicant provided further consideration that belumosudil will provide major therapeutic advantage over the authorised methods, including ruloxitinib. This is based on ad-hoc indirect comparison analysis from the study population with different background therapies, additional analyses from the RWD study (ROCKreal). According to the applicant, these results are consistent with closely mimic the adjusted results from the primary results from ROCKreal suggesting that belumosudil effectiveness is superior to BAT in cGVHD patients with 2-5 prior LOT after receiving ruxolitinib.

Indirect comparison between the patient populations from REACH3 and KD025-213 and responses rates were provided. The baseline data indicate that participants enrolled in KD025-213 study had higher disease burden and were more heavily pre-treated.

In conclusion, the applicant claims that supportive comparative evidence, consisting of target trial emulation, intra-patient comparisons and side by side BAT benchmarks from REACH3 independently converges on a consistent treatment benefit with belumosudil in the last line population.

Additional justifications based on RWD conducted and ongoing on belumosudil as well as on the well established safety profile of belumosudil were highlighted by the applicant.

Finally the applicant's view on improved contribution to patient care is that belumosudil also offers improved contribution to patient care, particularly in its administration and monitoring requirements. Belumosudil is administered as a single 200 mg per tablet once daily (twice daily only when co-administered with proton pump inhibitors or strong CYP3A4 inducers), while ruxolitinib is available in four strengths at 5, 10, 15 and 20 mg and the recommended beginning dose in cGVHD is 10 mg twice a day. The once-daily convenient dosing of belumosudil is intended to maximize patient adherence.

Required monitoring for belumosudil is limited to monthly check of liver function tests as per the proposed EU SmPC. Dose adjustments are primarily based on liver function and drug interactions. In contrast, ruxolitinib requires more frequent dose adjustments based on platelet counts and other hematologic parameters.

In addition, belumosudil offers improved ease of use over BATs. Existing BATs require either close monitoring of plasma concentration (tacrolimus, sirolimus) or complicated administration or procedure (ECP, MMF).

In summary, the benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required.

7.7.3.4. Discussion on the absence of comprehensive data in the context of a conditional marketing authorisation

The following uncertainties render data for Rezurock not comprehensive: The exact magnitude of the contribution of belumosudil to the outcome of treatment cannot be isolated in study KD025-213, as there is no control arm, response parameters were very broad and partially subjective, and concomitant medication was commonly used. Potential impact on time to disease progression, relapse free survival or overall survival, cannot be fully isolated without a relevant control arm. The safety assessment lacks a relevant randomised comparator arm. Therefore, events caused and not caused by belumosudil cannot be formally differentiated. Moreover, belumosudil is a first-in-class compound.

While the observed response rates of the pivotal Phase 2 trial are acceptable in the last line target population, confirmation of belumosudil efficacy in an RCT is warranted. Feasibility to generate comprehensive data in a reasonable timeframe through the proposed confirmatory study is therefore essential.

7.7.3.4.1. Conclusions and recommendation on conditional marketing authorisation

As comprehensive data on the product are not available as discussed above, a conditional marketing authorisation was requested by the applicant in the initial submission.

The product falls within the scope of Article 14-a of Regulation (EC) No 726/2004 concerning conditional marketing authorisations, as it aims at the treatment of a life-threatening disease. In addition, the product is designated as an orphan medicinal product. The product is considered to fulfil the criteria of a conditional marketing authorisation

The following conditions are applicable to a CMA:

- It is agreed that belumosudil contributed to the response rate that was observed in the pivotal trial, thus efficacy is sufficiently demonstrated. Even though the exact magnitude of this effect is uncertain, this can be acceptable in the context of a CMA for a population with a substantial unmet medical need. There are no major safety concerns observed. Therefore, it is agreed that the benefit-risk balance of the medicine is positive; this condition is met.
- it is considered likely that the applicant will be able to provide comprehensive data post-authorisation within a reasonable timeframe as confirmed by the Experts. While the new proposed confirmatory trial has not yet started, the AHEG provided sufficient reassurance that clinicians would be willing to put their patients forward for participation in the trial, on the feasibility of the trial. The expected accrual rate might be overestimated due to commercial availability of belumosudil in the context of a CMA, however the Applicant will provide regular updates on the enrolment and mitigation process are proposed to address potential under recruitment. Therefore, this condition is met.

Unmet medical need

An unmet medical need will be addressed, as an additional and novel therapeutic option is given for patients with cGvHD in the last line setting after having received at least two prior lines of systemic therapy including ruxolitinib. Adult and paediatric cGvHD patients (12 years and older with a body weight of at least 40 kgs) when other treatment options provide limited clinical benefit, are not suitable, or have been exhausted have an overall poor prognosis as few authorised treatment options with established efficacy and safety are available.

Rezurock provides a treatment option for which a clinically meaningful benefit was demonstrated with respect to complete response, overall response rate and duration of response. Thus, the availability of Rezurock as third line therapy fulfils an unmet medical need taking into account that there are no satisfactory methods available for patients prior administration of belumosudil.

More specifically, since the indication is clearly limited to a last line patient population, when other treatment options provide limited clinical benefit, are not suitable, or have been exhausted, this would mean that there are no satisfactory methods available for patients prior administration of belumosudil.

In conclusion the UMN is substantial in this last line cGvHD population.

The benefit of the medicine's immediate availability to patients is greater than the risk inherent to the fact that additional data are still required. This condition is met, considering the observed efficacy and safety, the limited treatment options for last line cGvHD, and the fatality of the disease, offset by uncertainties surrounding the magnitude of the effect size of belumodusil and timelines of the proposed SOB to provide comprehensive data.

The Applicant proposal to conduct a Phase III randomized controlled study in the third line setting as a specific obligation is endorsed. This is a randomized, open-label, multi-centre study to investigate the efficacy and safety of belumosudil versus BAT in participants ≥12 years of age with cGVHD after at least 2 prior lines of systemic therapy, including ruxolitinib. A total of approximately more than 300 participants will be

randomized 1:1 to receive either belumosudil or the BAT. The stratification factors include severity of cGVHD at baseline according to the NIH consensus diagnosis and staging criteria (2014) (moderate vs severe) and the number of prior lines of therapy (2 vs > 2). The results of the proposed SOB will be submitted in Q4 2029. The study design of the proposed study was reviewed and agreed by CHMP at time of the Oral explanation, with the exception of using an external control arm. This external control arm has now been removed from the newly proposed study design submitted in the re-examination procedure, which is agreed. Furthermore, a cross-over is now delayed to after 6 months, thereby avoiding the bias for the primary endpoint introduced by an early crossover. This cross-over option at 6 months was highlighted also by the Experts as an important feature when discussing feasibility.

In conclusion, the conditions for a conditional marketing authorisation are met.

The CHMP considers the following measures listed in section 9 necessary to address the missing data in the context of conditional marketing authorisation.

8. Recommendations following re-examination

Based on the arguments of the applicant and all the supporting data on quality, safety and efficacy, the CHMP re-examined its initial opinion and in its final opinion concluded by majority decision that the benefit risk of the above-mentioned medicinal product is positive and therefore recommends the approval of the granting of the conditional marketing authorisation for the above-mentioned medicinal product.

Divergent positions

Divergent positions to the majority recommendation are appended to this report.

9. Specific obligations following the marketing authorisation

9.1. Proposed list of specific obligations following the marketing authorisation

Specific Obligations:

Area[1]	Description[2]	Due date
Clinical	In order 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, the MAH shall submit the final results of Study EFC22965, a Phase III, randomised, open-label, multi-center study of belumosudil versus BAT according to an agreed protocol.	
	Final report due date	Q4 2029
	Yearly recruitment report updates	

Area[1]	Description[2]	Due date
		February 2027, February 2028, February 2029.

9.2. List of recommendations

Recommendations pertain to quality, non-clinical (e.g. ERA, PK/PD, PAES if not key to the B/R). **Description of post-authorisation measure(s)**
1. The results of the tablet crushing study with subsequent oral administration is recommended to be submitted post-authorisation, once available. If the study confirms that tablet crushing is feasible, the product information should be updated accordingly to reflect these findings.
2. Belumosudil was *in vitro* a competitive and/or time-dependent inhibitor of CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP3A4/5. The clinical relevance of these *in vitro* signals is not known at present. The Applicant should conduct a clinical study to evaluate if belumosudil as a clinically relevant inhibitor of these CYP enzymes.

APPENDIX

DIVERGENT POSITION DATED 29 January 2026

DIVERGENT POSITION DATED 29 January 2026

Rezurock EMEA/H/C/006421/0000

The undersigned members of the CHMP did not agree with the CHMP's majority opinion recommending the granting of a Conditional Marketing Authorisation (CMA) for belumosudil in 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.

The unmet need for a treatment of cGVHD in later disease stages is fully acknowledged. However, the reasons for the divergent negative opinion were as follows:

- While the numerical outcomes of the pivotal randomised non-controlled trial KD025-213 suggest a potential to address an unmet medical need in a last line cGvHD population, important uncertainties remained. Particularly, given the partially subjective nature of the endpoint, and the presence of confounding treatments, a non-controlled trial in this setting is not appropriate to isolate an effect of the experimental treatment respectively its true magnitude. In addition, the applied endpoint definition leads to exaggerated Overall Response Rate (ORR).

  This concern is aggravated by the fact that the originally proposed specific obligation to the CMA, a confirmatory randomised controlled trial in the first-line treatment of cGvHD (EFC17757), failed to demonstrate any clinical benefit or pharmacological activity of belumosudil. This trial was terminated early due to a pre-planned futility analysis. Notwithstanding the different patient population studied in a first line setting, this outcome further increases the uncertainty regarding the demonstration of efficacy. Hence, the efficacy of belumosudil treatment has not been demonstrated.

- The Applicant's ability to provide comprehensive data post authorisation in a reasonable timeframe in the context of a conditional marketing authorisation remains unclear. The newly proposed confirmatory trial has not yet started enrolment, and its feasibility is considered questionable. This is due to the fact that once the product is approved by CMA, a randomised controlled comparison of belumosudil vs. 'best available therapy' in the approved patient population, as proposed, is difficult to be performed. The open-label design of the trial further compromises the ability of the trial to provide robust and unbiased confirmatory evidence.

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