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CADTH Reimbursement Review

Belumosudil (Rezurock)

Sponsor: sanofi-aventis Canada Inc.
Therapeutic area: Graft-versus-host disease

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Abbreviations

AE	adverse event
aGVHD	acute graft-versus-host disease
allo-HSCT	allogeneic hematopoietic stem cell transplant
BAT	best available therapy
cGVHD	chronic graft-versus-host disease
CI	confidence interval
CNI	calcineurin inhibitor
CR	complete response
CS	corticosteroid
CTTC	Cell Therapy Transplant Canada
DOR	duration of response
ECP	extracorporeal photopheresis
EOT	end of treatment
FEV_1	forced expiratory volume in 1 second
FFS	failure-free survival
GC	glucocorticoid
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
GSR	global severity rating
GVHD	graft-versus-host disease
HR	hazard ratio
HRQoL	health-related quality of life
HSCT	hematopoietic stem cell transplant
IL	interleukin
IPTW	inverse probability of treatment weighting
ITC	indirect treatment comparison
KM	Kaplan-Meier
LR	lack of response
LSS	Lee Symptom Scale
MID	minimal important difference
mITT	modified intention to treat
mTOR	mammalian target of rapamycin
NIH	National Institutes of Health
OH-CCO	Ontario Health (Cancer Care Ontario)

ORR	overall response rate
OS	overall survival
PAIC	population-adjusted indirect comparison
PR	partial response
PROMIS	Patient-Reported Outcomes Measurement Information System
RCT	randomized controlled trial
ROCK	Rho-associated, coiled-coil-containing protein kinase
SAE	serious adverse event
TEAE	treatment-emergent adverse event
TTNT	time to next treatment
TTR	time to response

Executive Summary

An overview of the submission details for the drug under review is provided in Table 1.

Table 1: Background Information of Application Submitted for Review

Item	Description
Drug product	Belumosudil (Rezurock), 200 mg oral tablets once daily
Sponsor	Sanofi-Aventis Canada Inc.
Indication	For the treatment of adult and pediatric patients 12 years and older with cGVHD after failure of at least 2 prior lines of systemic therapy
Reimbursement request	As per indication
Health Canada approval status	NOC
Health Canada review pathway	Project Orbis
NOC date	March 23, 2022
Recommended dosage	200 mg once daily

cGVHD = chronic graft-vs.-host disease; NOC = Notice of Compliance.

Sources: Sponsor's submission package for review of belumosudil and belumosudil product monograph.[1,2]

Introduction

Hematopoietic stem cell transplant (HSCT) provides stem cells to patients whose bone marrow has been affected by disease, chemotherapy, or radiation.[3] The 2 main types of HSCT are autologous and allogeneic HSCT (allo-HSCT).[3] Allo-HSCT can have curative potential; however, there is a risk that the donor's stem cells will die or be destroyed by the recipient (i.e., patient) or that the donor's immune cells will attack healthy cells in the recipient; the latter is called graft-versus-host disease (GVHD).[3] Chronic GVHD (cGVHD) can involve a single organ or multiple organs throughout the body, can last for months to a lifetime, and is the leading cause of late morbidity and death after an allo-HSCT.[4,5] Patients with cGVHD face a multifaceted disease burden comprising physical, functional, and psychosocial deficits, all of which have a profound negative impact on health-related quality of life (HRQoL).[6,7] It is estimated that cGVHD occurs in 35% to 50% of patients who undergo an allo-HSCT.[8] Most patients experience cGVHD onset in the first year after an allo-HSCT, but about 5% to 10% of patients may not develop signs or symptoms until later.[9]

The treatment goals for cGVHD are to prolong survival, alleviate symptoms, control disease activity, prevent damage and disability, and maintain or improve HRQoL without causing extensive toxicity or other harms.[10] The clinical experts consulted by CADTH also noted the importance of managing the adverse effects of therapies, such as increased risk of infections. First-line treatment consists of topical or systemic corticosteroids (CSs), with or without calcineurin inhibitors (CNIs), and is generally considered standard across clinical practice guidelines for managing cGVHD.[11] In Canada, second-line options include extracorporeal photopheresis (ECP), mycophenolate mofetil, etanercept, low-dose methotrexate, infliximab, mammalian target of rapamycin (mTOR) inhibitors, imatinib, rituximab, ruxolitinib, ibrutinib, low-dose interleukin (IL) 2 (IL-2), pulsed cyclophosphamide, and pentostatin.[12] There is a lack of consensus for

standard second- and subsequent-line cGVHD therapies due to insufficient evidence to recommend any treatment over another and, according to the clinical experts, therapies after the first line depend on the site of disease presentation as well as the varying availability of treatments across jurisdictions.[12] Only ruxolitinib and ibrutinib have Health Canada indications for the treatment of cGVHD in adults and pediatric patients aged 12 years and older whose condition has an inadequate response to CSs or other systemic therapies, and the treatment of cGVHD in patients aged 1 year and older after the failure of 1 or more lines of systemic therapy, respectively.[13,14]

Belumosudil is a selective oral inhibitor of Rho-associated, coiled-coil-containing protein kinase-2 (ROCK2) and ROCK1, and is indicated for the treatment of adult and pediatric patients aged 12 years and older with cGVHD after the failure of at least 2 prior lines of systemic therapy.[1] The recommended dosage of belumosudil is 200 mg given orally once daily with food at approximately the same time each day.[1] Treatment should continue until the progression of cGVHD that requires a new systemic therapy or the occurrence of unacceptable toxicity.[1] No dose adjustments are required in adolescents aged 12 to 18 years or in patients aged 65 years or older.[1] Although no patients under the age of 18 were enrolled in the clinical development program, Health Canada indicated that the use of belumosudil in pediatric patients aged 12 years and older is supported by: evidence from studies in adults with additional population pharmacokinetic data, the expectation that drug exposure is similar between adults and pediatric patients age 12 years and older, and that the disease course is sufficiently similar in adult and pediatric patients to allow for data extrapolation.[1] The sponsor has requested reimbursement as per the approved Health Canada indication.[2]

The objective of this report is to review and critically appraise the evidence submitted by the sponsor on the beneficial and harmful effects of belumosudil 200 mg once-daily oral tablets in the treatment of adult and pediatric patients aged 12 years and older with cGVHD after the failure of at least 2 prior lines of systemic therapy.

Stakeholder Perspectives

The information in this section is a summary of input provided by the patient and clinician groups that responded to CADTH's call for input and from the clinical experts consulted by CADTH for the purpose of this review.

Patient Input

One joint input was submitted by 2 patient groups, the Leukemia and Lymphoma Society of Canada and Myeloma Canada, based on information gathered from a survey of 62 respondents conducted in July 2023 for the CADTH review of belumosudil.

The patient groups emphasized that the experience of going through cancer treatment, stem cell transplant, and receiving a GVHD diagnosis is disheartening and terrifying for both patients and caregivers. Respondents indicated that the full range of GVHD symptoms significantly affects their physical and mental health and daily activities and has detrimental effects on their HRQoL. Many patients lose their independence and require caregiver support to manage the disease.

Despite being necessary to treat cGVHD, the respondents described the negative impact of CS treatment, including the many physical, neurologic, and circulatory side effects that greatly impact HRQoL. According to the input, patients and caregivers seek a treatment that enables them to continue with their daily lives, is more accessible, improves overall survival (OS), and preserves their HRQoL, with minimal impact on work or school, finances, and social, physical, and mental health.

Of the 5 respondents who indicated having experience with belumosudil, 3 stated that the drug had a positive impact on their lives, allowed them to reduce steroid dosage, and was tolerable with minimal side effects.

Clinician Input

Input From the 2 Clinical Experts Consulted by CADTH

According to the clinical experts consulted by CADTH, there is a lack of good treatment options beyond second-line therapy for patients with cGVHD. As a result, patients with refractory or progressive disease experience an impact on their HRQoL, an impact on their ability to work and study, and have an increased risk of mortality due to cGVHD, associated organ impairment, and risk of infections.

The clinical experts indicated that belumosudil would be used as per the Health Canada indication in the third-line setting and would likely be used in combination with CSs, and that earlier use in the first- or second-line setting would require evidence from good-quality randomized controlled trials (RCTs). As per the clinical experts, patients with moderate to severe cGVHD whose condition is refractory or who are intolerant to 2 prior lines of therapy would most likely receive belumosudil.

The experts stated that partial response (PR) and complete response (CR) as well as the maintenance of stable disease with a clinically meaningful reduction in CS dose are indicators in clinical practice that a patient is responding to treatment. Improvement in functional status and symptoms and an ability to return to school or work were also noted as being important outcomes.

The reasons for discontinuing treatment identified by the clinical experts included disease progression (based on signs, symptoms, examination, laboratory tests) or having stable disease that still required significant amounts of CSs that cannot be tapered. The experts also noted meaningful adverse effects, such as derangement of liver function tests or significant gastrointestinal upset due to belumosudil, as being a reason to stop. Lastly, disease resolution in which a patient has stopped other immunosuppressants (or who may be on low-dose CSs, e.g., 10 mg) with symptom resolution is a third reason. The experts highlighted that stopping treatment in the last instance is done cautiously, as patients can experience disease flares when going off treatment.

The clinical experts noted that stem cell transplant specialists should initiate belumosudil in either a community or hospital setting, and treatment decisions may involve other specialists (e.g., respirologists).

Clinician Group Input

Two clinician groups, the Ontario Health (Cancer Care Ontario) (OH-CCO) Hematology Cancer Drug Advisory Committee and Cell Therapy Transplant Canada (CTTC) provided input for the CADTH review of belumosudil. Perspectives from OH-CCO clinicians were obtained through videoconferencing. CTTC gathered the

information through a literature review and a discussion with the CTTC board of directors and the standing committee of program directors.

Input from the clinician groups was largely aligned with that of the clinical experts consulted by CADTH. The clinician groups reiterated the variation in standard practice for treatment beyond second-line therapy based on the local funding of available options. OH-CCO indicated that responsiveness and tolerability vary among patients and that oral therapies are often preferred, while CTTC noted that current treatments are suboptimal and require high doses and prolonged use of CSs, which have many adverse effects. According to the clinician groups, the outcomes used to assess response to treatment include standard GVHD response criteria, significant functional and HRQoL improvements, and patients showing stable disease but with a significant reduction of immunosuppressive treatments. The 2 clinician groups agreed that treatment discontinuation should be considered in patients with significant intolerance or cGVHD progression. According to OH-CCO, patients receiving belumosudil should be managed by cGVHD specialists practising in inpatient or outpatient settings, while CTTC added that the drug should be prescribed only by specialists working in a clinical setting associated with allo-HSCT programs for patients whose condition is refractory to steroids or ruxolitinib.

Drug Program Input

The drug programs asked questions about: how belumosudil compares with ibrutinib, belumosudil's place in therapy, which systemic therapies are acceptable before trying belumosudil, how frequently patients should be assessed to continue treatment, how treatment discontinuation is assessed, whether cGVHD treatments can be combined, whether belumosudil can be used in patients who have experienced a failure of other treatments or who have acute GVHD (aGVHD), and how treatments should be prioritized.

The clinical experts consulted by CADTH acknowledged there was no evidence available for belumosudil versus ibrutinib, making it difficult to compare the 2 drugs. They also stated that belumosudil would be used as per its Health Canada indication and that there would need to be good RCT evidence to support using belumosudil as an earlier line of therapy. The experts noted that any 2 systemic therapies for the treatment of cGVHD (including CSs and ECP) count toward the requirement of a failure of at least 2 prior systemic treatments before accessing belumosudil. The clinical experts agreed that first authorization should be for 6 months, with renewal for patients who have experienced an overall response (i.e., CR or PR, or stable disease with significant reduction in steroid doses) every 6 months. They also indicated that drug discontinuation should occur upon cGVHD progression, but patients should continue to be treated for cGVHD if they experience a relapse of the underlying hematological malignancy (both conditions need to be treated). According to the clinical experts, treatment for cGVHD would not be indefinite for most patients but should be tapered cautiously to assess response and relapse. They noted there is no specific number of doses or years during which a patient would continue treatment, and a small number of patients who are intolerant to tapering require lifelong therapy. The experts expect that belumosudil could be used alongside other treatments for cGVHD and that it would be possible to give belumosudil to patients if they had demonstrated intolerance to other medications for cGVHD. There is currently no Health Canada indication for the use of

belumosudil in the treatment of patients with aGVHD. Given the lack of direct and indirect evidence, the experts indicated that it would be challenging to prioritize treatment options for cGVHD.

Clinical Evidence

Systematic Review

Description of Studies

Study KD025 to 213 (N =) is a phase II, open-label study with a latest data cut-off date of .[15,16] Eligible patients had to be 12 years of age or older with active cGVHD and had to have undergone an allo-HSCT and received 2 to 5 prior lines of therapy for cGVHD. Study KD025 to 208 (N = 54) is a phase IIa, dose-escalation, ongoing, open-label study with a latest data cut-off date of .[17,18] Eligible patients had to be 18 years of age or older with active cGVHD and had to have undergone an allogeneic bone marrow transplant or allo-HSCT and received 1 to 3 prior lines of therapy for cGVHD (not including ECP). In study KD025 to 213 and study KD025 to 208, patients and 17 patients, respectively, received belumosudil 200 mg once daily and there were no relevant comparator or control groups in either study (belumosudil 200 mg twice daily and belumosudil 400 mg once daily are outside of the Health Canada indication for the indication under review and are not further discussed in this CADTH report). Patients were permitted to have concomitant treatment with standard of care systemic cGVHD therapies, such as CNIs, sirolimus, mycophenolate mofetil, methotrexate, rituximab, ECP, or topical or organ-specific therapies if they had been on a stable regimen; however, initiation of a new systemic therapy was not permitted. The primary outcome of both studies was overall response rate (ORR) by investigator assessment, measured on day 1 of each 28-day cycle for cycles 2 to 5 and every other cycle thereafter until clinically meaningful disease progression or end of treatment (EOT). ORR was the only end point controlled for multiple testing. Secondary outcomes of interest to the CADTH review included duration of response (DOR), time to response (TTR), failure-free survival (FFS), OS, Lee Symptom Scale (LSS) score, and safety outcomes. Patient-Reported Outcomes Measurement Information System (PROMIS) Global Health summary scores for physical and mental functioning were exploratory outcomes in study KD025 to 213. Although the studies had 4 definitions for DOR, according to the clinical experts consulted by CADTH, the tertiary and secondary DOR definitions were considered to be the most clinically relevant. The tertiary definition of DOR was the time from first documented response to the time of initiation of a new systemic cGVHD therapy or death (reviewed by a clinical team).[15,17] The secondary definition of DOR was the time from first documented response to the time of first documented lack of response (LR).

The median age of patients was 53 years (range, 21 years to 77 years) in study KD025 to 213 and 50 years (range, 20 years to 63 years) in study KD025 to 208. There were no patients younger than 20 years old in the relevant datasets to support the pediatric portion of the indication. In both studies, more than 76% of patients had a Karnofsky Performance Score of 80 or higher, the median time from cGVHD diagnosis to study enrolment was approximately 25 months, and more than 70% of patients had severe cGVHD, according to the 2014 National Institutes of Health (NIH) consensus criteria. In total, 100% of patients in study KD025 to 213 and 88% of patients in study KD025 to 208 had 2 or more prior lines of therapy. CSs were the most

common prior cGVHD treatment (more than 99%) followed by tacrolimus in study KD025 to 213 ([redacted]%) and sirolimus in study KD025 to 208 (59%).

Efficacy Results

ORR by Investigator Assessment

In study KD025 to 213, the ORR was 72.7% (95% confidence interval [CI], 60.4% to 83.0%; P < 0.0001) as of the primary analysis cut-off date (February 19, 2020, 6 months after enrolment of 126 patients into the modified intention-to-treat [mITT] population). In study KD025 to 208, the ORR was 64.7% (95% CI, 38.3% to 85.8%) as of the primary reporting data cut-off date (February 19, 2020, corresponding to the primary analysis data cut-off date for study KD025 to 213).

At the latest cut-off date for study KD025 to 213 ([redacted]), after median [redacted] (range, [redacted]) months of follow-up, the ORR was [redacted] (95% CI, [redacted]). At the latest cut-off date for study KD025 to 208 ([redacted]), after median [redacted] (range, [redacted]) months of follow-up, the ORR was [redacted] (95% CI, [redacted]). The findings for ORR appeared to be generally similar across the subgroups.

Duration of Response

Of the patients who responded to treatment (n = [redacted]), the median Kaplan-Meier (KM) estimate for tertiary DOR (time from first response to initiation of a new cGVHD therapy or death) was [redacted] weeks (95% CI lower bound = [redacted] weeks; upper bound not reached) in study KD025 to 213; in study KD025 to 208, the median KM estimate for tertiary DOR was not reached (95% CI lower bound = [redacted] weeks; upper bound not reached). At 24 weeks, the KM estimate of the event-free probability for tertiary DOR was [redacted]% (95% CI, [redacted]) in study KD025 to 213 and [redacted] (95% CI, [redacted]) in study KD025 to 208.

The median KM estimate for secondary DOR (time from first response to time of first LR) was [redacted] weeks (95% CI, [redacted] to [redacted]) in study KD025 to 213; in study KD025 to 208, the median KM estimate for secondary DOR was [redacted] weeks (95% CI lower bound = [redacted] weeks; upper bound not reached). At 24 weeks, the KM estimate of the event-free probability for secondary DOR was [redacted] (95% CI, [redacted]) in study KD025 to 213 and [redacted] (95% CI, [redacted]) in study KD025 to 208.

Time to Response

Based on the responder population, the median TTR was [redacted] weeks (range, [redacted] to [redacted] weeks) in study KD025 to 213 and 8.1 weeks (range, 7.9 to 26.1 weeks) in study KD025 to 208. At weeks 8 and 12, the cumulative response rate was [redacted]% and [redacted]%, respectively, in study KD025 to 213, and [redacted]% and [redacted]%, respectively, in study KD025 to 208.

Failure-Free Survival

The median KM estimate for FFS was [redacted] weeks (95% CI, [redacted] to [redacted]) in study KD025 to 213 and 10.6 weeks (95% CI lower bound = 3.8 weeks; upper bound not reached) in study KD025 to 208. According to the KM estimate, the FFS probability was [redacted]% (95% CI, [redacted]) at 12 months in study KD025 to 213, and 47% (95% CI, 23% to 68%) at 12 months in study KD025 to 208.

Overall Survival

The median KM estimate for OS was not reached in either study KD025 to 213 or study KD025 to 208. According to the KM estimate, the OS probability was [redacted]% (95% CI, [redacted]% to [redacted]%) at 12 months in study KD025 to 213 and [redacted]% (95% CI, [redacted]% to [redacted]%) at 12 months in study KD025 to 208.

LSS Score

The LSS score measures changes in symptom burden using 30 items over 7 domains, where a higher score indicates more bothersome symptoms. A 7-point or greater reduction in score was considered clinically meaningful.[19] In study KD025 to 213, [redacted] patients ([redacted]%) had a 7-point or greater reduction in LSS score from baseline. In study KD025 to 208, 9 patients (52.9%) had a 7-point or greater reduction in LSS score from baseline.

PROMIS Global Health Summary Scores for Physical and Mental Functioning

The PROMIS Global Health score assesses general health, ability to carry out physical activities, emotional problems, fatigue, and pain.[15] Two summary scores are determined for physical and mental functioning, with higher scores indicating better functioning. In study KD025 to 213, [redacted] patients ([redacted]%) had a 4.7-point or greater change from baseline for physical health and [redacted] patients ([redacted]%) had a 4.7-point or greater change from baseline for mental health. This outcome was not assessed in study KD025 to 208.

Harms Results

Most patients experienced at least 1 treatment-emergent adverse event (TEAE) in study KD025 to 213 ([redacted]%) and study KD025 to 208 (100%). The most common TEAEs were diarrhea ([redacted]%) and fatigue ([redacted]%) in study KD025 to 213, and upper respiratory tract infection (52.9%), diarrhea (35.3%), fatigue (35.3%), nausea (35.3%), and increased alanine aminotransferase (35.3%) in study KD025 to 208.

In study KD025 to 213, [redacted]% of patients experienced a serious adverse event (SAE), while [redacted]% of patients in study KD025 to 208 experienced an SAE. Pneumonia ([redacted]%) was the most frequently reported SAE in study KD025 to 213. No other SAEs occurred in more than 3 patients in either study.

In study KD025 to 213, [redacted]% of patients stopped belumosudil due to an adverse event (AE), while [redacted]% of patients in study KD025 to 208 stopped the drug due to an AE.

Overall, [redacted] patients died in study KD025 to 213 (reasons included hemothorax, aspiration and respiratory failure, septic shock and multiple organ dysfunction, and recurrent acute myeloid leukemia), and 0 patients died in study KD025 to 208.

Based on the Health Canada product monograph warnings and precautions, hematologic (blood and lymphatic system disorders) and immune (infections and infestations) AEs were identified as being important to the CADTH review. Overall, [redacted]% of patients in study KD025 to 213 and [redacted]% of patients in study KD025 to 208 experienced an AE related to blood or lymphatic system disorders; anemia was the most common AE, reported by [redacted]% and [redacted]% of patients in study KD025 to 213 and study KD025 to 208, respectively. For infections and infestations, [redacted]% or patients in study KD025 to 213 and [redacted]% of patients in

study KD025 to 208 experienced an AE. Upper respiratory tract infection was the most common AE, reported by [redacted]% and [redacted]% of patients in study KD025 to 213 and study KD025 to 208, respectively.

Critical Appraisal

The main limitations with both studies are the lack of a control (or comparator) group and lack of randomization to a valid comparator, resulting in a high risk of bias due to confounding and uncertainty in causal conclusions between the study drug and possible benefits or harms. Another limitation was the knowledge of treatment assignment, resulting in an increased risk of performance bias (particularly for subjective measures) and of potentially overestimating the treatment effect of belumosudil. All patients had discontinued from the study and treatment by the latest data cut-off date and there is an increased risk of attrition bias due to missing outcomes data for longer-term results. The findings of time-to-event analyses and later time points had few patients at risk and therefore may be unstable.

Between the studies, 94 patients received the approved 200 mg once-daily dosage for a median treatment duration of around 9 months, which is a relatively small number of patients compared with the total number who could potentially receive belumosudil (i.e., those with active cGVHD who have received at least 2 prior lines of systemic therapy) for a somewhat short duration, considering that treatment can be for years. This may be especially true for OS, where few events were captured and a longer follow-up would be needed to understand the full effect of belumosudil on mortality. Also, there were no data available for patients younger than 20 years of age to support the Health Canada indication for patients aged from 12 years to younger than 20 years, though the clinical experts were of the opinion that the results for adults could be generalizable to a younger patient population, and belumosudil gained regulatory approval for a population aged 12 years and older based on pharmacokinetic analyses indicating that age and body mass did not have a clinically meaningful effect on drug pharmacokinetics.[20,21] Racial diversity was limited in the study (compared with what is expected in Canadian practice), and the prior and concomitant cGVHD therapies differed from the experts' experience in treating patients with cGVHD (which may be due to varying availability of treatments across jurisdictions and the studies taking place in the US).

GRADE Summary of Findings and Certainty of the Evidence

For pivotal studies identified in the sponsor's systematic review, Grading of Recommendations Assessment, Development, and Evaluation (GRADE) was used to assess the certainty of the evidence for outcomes considered most relevant to inform CADTH's expert committee deliberations, and a final certainty rating was determined as outlined by the GRADE Working Group.[22,23] Although GRADE guidance is not available for noncomparative studies, the CADTH review team assessed the pivotal trials for study limitations (which refer to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias to present these important considerations. Because the lack of a comparator arm does not allow for a conclusion to be drawn on the effect of the intervention versus any comparator, the certainty of evidence for trials with only a single relevant treatment group (i.e., no valid comparator) started at very low certainty with no opportunity for rating up.

The selection of outcomes for the GRADE assessment was based on the sponsor's summary of clinical evidence, consultation with the clinical experts, and the input received from the patient and clinician groups

and public drug plans. The following list of outcomes was finalized in consultation with expert committee members: response to treatment (ORR by investigator assessment, tertiary and secondary DOR, TTR, and FFS), survival (OS), disease-specific measure of symptoms (LSS scores), HRQoL (PROMIS Global Health summary scores), and harms (SAEs).

When possible, certainty was rated in the context of the presence of an important (nontrivial) treatment effect; if this was not possible, certainty was rated in the context of the presence of any treatment effect (i.e., the clinical importance is unclear). In all cases, the target of the certainty of evidence assessment was based on the point estimate and where it was located relative to the threshold for a clinically important effect (when a threshold was available) or to the null. The target of the certainty of evidence assessment was the presence or absence of a clinically important effect for ORR, tertiary and secondary DOR, TTR, FFS, and OS, based on a threshold informed by the clinical experts consulted by CADTH for this review. The target of the certainty of evidence assessment was the presence or absence of any (non-null) effect for the number of patients who had an LSS score or PROMIS Global Health summary score greater than or equal to the minimal important differences (MIDs) identified from the literature and who experienced SAEs.

For the GRADE assessments, the findings from study KD025 to 213 and study KD025 to 208 were considered together (except for PROMIS, which was assessed only in study KD025 to 213) and summarized narratively by outcome because the studies were similar in population, intervention, design, and outcome measures.

Results of GRADE Assessments

Table 2 presents the narrative GRADE summary of findings for belumosudil for patients with cGVHD.

Long-Term Extension Studies

Data from the latest cut-off dates for the ongoing studies (KD025 to 213 and KD025 to 208) were included in the main report. No additional long-term extension studies were submitted in the systematic review evidence.

Indirect Comparisons

Description of Feasibility Assessment

No direct comparative data for the use of belumosudil for the treatment of patients aged 12 years and older with cGVHD were submitted by the sponsor. As a result, a systematic literature review was conducted to identify efficacy and safety evidence of belumosudil versus other treatments for patients with cGVHD after an allo-HSCT whose condition has failed to respond to prior therapy.[25] It was known that no RCTs were available for belumosudil versus other active therapies for cGVHD; therefore, the feasibility of conducting a valid population-adjusted indirect comparison (PAIC) was assessed and was determined to be infeasible.

Table 2: GRADE Summary of Findings for Belumosudil for Patients With cGVHD (Studies KD025 to 213 and KD025 to 208)

Outcome and follow-up	Patients (studies), N	Effect	Certainty[a,b]	What happens
Response to treatment				
Proportion of patients with an ORR (CR + PR) by investigator assessment (95% CI)[c] Follow-up: 6 months	83 (2 studies)	• KD025 to 213: 727 per 1,000 (604 to 830 per 1,000) • KD025 to 208: 647 per 1,000 (383 to 858 per 1,000)	Very low[d]	The evidence is very uncertain about the effects of belumosudil on ORR by investigator assessment at 6 months vs. any comparator.
Tertiary DOR[e] event-free probability (95% CI), KM estimate Follow-up: 24 weeks	[redacted][f] (2 studies)	• KD025 to 213: [redacted] per 1,000 ([redacted] per 1,000) • KD025 to 208: [redacted] per 1,000 ([redacted] per 1,000)	Very low[d]	The evidence is very uncertain about the effects of belumosudil on tertiary DOR vs. any comparator.
Secondary DOR[g] event-free probability (95% CI), KM estimate Follow-up: 24 weeks	[redacted][f] (2 studies)	• KD025 to 213: [redacted] per 1,000 ([redacted] per 1,000) • KD025 to 208: [redacted] per 1,000 ([redacted] per 1,000)	Very low[h]	The evidence is very uncertain about the effects of belumosudil on secondary DOR vs. any comparator.
Median (range) TTR, weeks Follow-up: Median of 28.2 months in KD025 to 213 and 55.5 months in KD025 to 208	[redacted][f] (2 studies)	• KD025 to 213: [redacted] ([redacted]) • KD025 to 208: [redacted] ([redacted])	Very low[d]	The evidence is very uncertain about the effects of belumosudil on TTR vs. any comparator.
FFS probability (95% CI), KM estimate Follow-up: 12 months	[redacted] (2 studies)	• KD025 to 213: [redacted] per 1,000 ([redacted] per 1,000) • KD025 to 208: [redacted] per 1,000 ([redacted] per 1,000)	Very low[d]	The evidence is very uncertain about the effects of belumosudil on FFS vs. any comparator.
Survival				
OS probability (95% CI), KM estimate Follow-up: 12 months	[redacted] (2 studies)	• KD025 to 213: [redacted] per 1,000 ([redacted] per 1,000) • KD025 to 208: [redacted] per 1,000 ([redacted] per 1,000)	Very low[d]	The evidence is very uncertain about the effects of belumosudil on OS vs. any comparator.
Disease-specific measure of symptoms				
Proportion of patients with a ≥ 7-point reduction from baseline in LSS score Follow-up: Median of 28.2 months in KD025 to 213 and 55.5 months in KD025 to 208	[redacted] (2 studies)	• KD025 to 213: [redacted] per 1,000 • KD025 to 208: [redacted] per 1,000	Very low[d]	The evidence is very uncertain about the effects of belumosudil on LSS score vs. any comparator.
HRQoL				
Proportion of patients with a ≥ 4.7-point change from baseline in PROMIS physical functioning	[redacted] (1 study)	• KD025 to 213: [redacted] per 1,000	Very low[d]	The evidence is very uncertain about the effects of belumosudil

Outcome and follow-up	Patients (studies), N	Effect	Certainty[a,b]	What happens
summary score Follow-up: Median of 28.2 months in KD025 to 213 and 55.5 months in KD025 to 208				on the PROMIS physical functioning summary score vs. any comparator.
Proportion of patients with a ≥ 4.7-point change from baseline in PROMIS mental functioning summary score Follow-up: Median of 28.2 months in KD025 to 213 and 55.5 months in KD025 to 208	[redacted] (1 study)	• KD025 to 213: [redacted] per 1,000	Very low[d]	The evidence is very uncertain about the effects of belumosudil on the PROMIS mental functioning summary score vs. any comparator.
Harms				
Proportion of patients with ≥ 1 SAE Follow-up: Median of 28.2 months in KD025 to 213 and 55.5 months in KD025 to 208	[redacted] (2 studies)	• KD025 to 213: [redacted] per 1,000 • KD025 to 208: [redacted] per 1,000	Very low[d]	The evidence is very uncertain about the effects of belumosudil on SAEs vs. any comparator.

cGVHD = chronic graft-vs.-host disease; CI = confidence interval; CR = complete response; DOR = duration of response; FFS = failure-free survival; GRADE = Grading of Recommendations Assessment, Development, and Evaluation; HRQoL = health-related quality of life; KM = Kaplan-Meier; LSS = Lee Symptom Scale; mITT = modified intention to treat; ORR = overall response rate; OS = overall survival; PR = partial response; PROMIS = Patient-Reported Outcomes Measurement Information System; SAE = serious adverse event; TTR = time to response.

Note: All serious concerns with the study limitations (which refer to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias are documented in the table footnotes.

[a]In the absence of a relevant comparator group and knowledge of treatment assignment, conclusions about efficacy relative to any comparator cannot be drawn and the certainty of evidence is started at very low and cannot be rated up.

[b]Did not rate down for indirectness. No pediatric patients were included in the trials (i.e., the evidence is representative of adult patients); however, the clinical experts consulted by CADTH believed it would be reasonable to generalize the findings to children aged 12 years and older.

[c]ORR (CR or PR) by investigator assessment at 6 months was the only end point to be tested statistically and controlled for multiplicity in study KD025 to 213; other end points were presented only descriptively.

[d]Rated down 1 level for serious imprecision. Analysis included only [redacted] patients for mITT analyses and [redacted] patients for responder analyses, and/or is based on a small number of events; there is potential for instability in the estimate and overestimation of the true effect.[24]

[e]Tertiary DOR was defined as the time from first documented response to the time of initiation of a new systemic cGVHD therapy or death.

[f]Responder population consisted of patients in the mITT population who experienced a PR or CR at any postbaseline assessment.

[g]Secondary DOR was defined as the time from first documented response to the time of first documented lack of response, new treatment, or death.

[h]Rated down 1 level for serious imprecision. In both studies the 95% CI lower bound crossed the conservative threshold of clinically important benefit of 40% suggested by clinical experts.

Sources: Clinical Study Reports for study KD025 to 213[15] and study KD025 to 208,[17] Clinical Study Report addenda for study KD025 to 213[16] and study KD025 to 208[18] and sponsor's summary of clinical evidence.[11] The details included in the table are from the sponsor's summary of clinical evidence.

Critical Appraisal

Compared with the data available for belumosudil, potential comparator studies were heterogeneous with respect to patient characteristics, study designs (e.g., eligibility criteria, length of follow-up, timing of assessments, and outcome measures), and data availability. Specifically, the CADTH review team scrutinized the potential to perform an indirect treatment comparison (ITC) versus the 2 main comparators of relevance, ruxolitinib and ibrutinib. Compared with studies of the comparators, the KD205 to 213 study of belumosudil enrolled patients with more prior lines of therapy and more severe disease. Given the small number of patients enrolled in the studies and the fact that the eligible population in the belumosudil trial was narrower,

the CADTH review team agreed it would not have been feasible to perform a valid PAIC that fully adjusted for the differences in populations across the trials. However, as noted by Health Canada,[20] this is an important limitation of the belumosudil KD205 to 213 trial that may have been foreseen. Given that the trial was initiated in 2018 (after Health Canada's approval of ibrutinib), it may have been possible at the outset to align enrolment criteria to facilitate a valid ITC with both ibrutinib and ruxolitinib.

Studies Addressing Gaps in the Evidence From the Systematic Review

Description of Studies

Due to the lack of head-to-head data and the inability to conduct an ITC, 1 observational study using inverse probability of treatment weighting (IPTW) was summarized to provide indirect comparative evidence in the treatment of belumosudil versus best available therapy (BAT) for patients with cGVHD.[11] The observational study was conducted using real-world data from the US Optum Clinformatics Data Mart database and pooled results from the main studies (KD025 to 213 and KD025 to 208).

From the database, patients were eligible if they had at least 1 inpatient or outpatient claim with a diagnosis code for cGVHD from January 1, 2000, to the most recent available data; had at least 3 systemic lines of therapy after cGVHD diagnosis (first-line therapy must have been CSs); were 12 years of age or older; and had at least 6 months of continuous enrolment with medical and pharmacy benefits before the third line of therapy. BAT included ECP, mycophenolate mofetil, imatinib, rituximab, mTOR inhibitors, ruxolitinib, CNIs, methotrexate, ibrutinib, pentostatin, etanercept, abatacept, alemtuzumab, hydroxychloroquine, and IL-2. IPTW methods were used in an attempt to reduce the risk of bias due to confounding that would result from differences in populations across the 2 study arms. The primary outcome was FFS and secondary outcomes included rate of OS and safety events.

Efficacy Results

Median FFS was [redacted] months (95% CI, [redacted] to [redacted]) in the belumosudil group and [redacted] months (95% CI, [redacted] to [redacted]) in the BAT group (hazard ratio [HR] = [redacted]; 95% CI, [redacted]). Median OS was not estimable for the belumosudil group and was [redacted] months (95% CI, [redacted] to [redacted]) for the BAT group (HR = [redacted]; 95% CI, [redacted]).

Harms Results

The most common AEs in the belumosudil group were infections ([redacted]%), fatigue or asthenia ([redacted]%), and nausea or vomiting ([redacted]%). The most common AEs in the BAT group were infections ([redacted]%), dyspnea ([redacted]%), hypertension ([redacted]%), and anemia ([redacted]%).

Critical Appraisal

There were numerous internal validity concerns including: lack of a valid comparator, missing data for variables of interest, heterogeneity in baseline characteristics (even after IPTW procedures were applied), differences in study designs that cannot be adjusted for, and increased risk of inaccuracies in the claims database due to patients changing insurance plans and the possible miscoding of claims. Therefore, it was not possible to draw firm conclusions on how belumosudil compares with BAT from the data, as they are considered to be at high risk of bias. Moreover, data for both belumosudil 200 mg once daily and belumosudil 200 mg twice daily appeared to be pooled in the analyses, though only the former dose has

a Health Canada indication for the treatment of cGVHD. Despite the use of real-world data, which could improve generalizability, the internal validity issues minimize the utility and applicability of the findings to clinical practice in Canada.

Conclusions

cGVHD is a complex, multisystem disease and there is a need for safe and effective treatments that help prolong survival, alleviate symptoms, and improve HRQoL. Evidence from 2 phase II, open-label clinical studies in adult patients with cGVHD (n = [redacted]) were included in the review for belumosudil, and both studies lacked an appropriate comparator or control group. Such a study design does not allow for definitive conclusions about the efficacy and safety of belumosudil versus any comparator, as the effect estimates are likely to be confounded by concomitant treatments and the natural history of the disease. Indirect comparisons with relevant alternatives were deemed infeasible and a submitted observational IPTW study comparing belumosudil with BAT was at high risk of bias due to residual confounding. Nevertheless, study KD025 to 213 met its primary outcome of an ORR greater than 30% at 6 months of treatment; the majority of responses were partial and fewer patients experienced CR. The treatment effect point estimates for response and survival outcomes were considered potentially clinically meaningful by the clinical experts. Although there were MIDs for LSS and PROMIS from the literature, it was not clear whether the number of patients who reached the MIDs was large enough to indicate a meaningful benefit from belumosudil. Harms results were potentially confounded by the use of concomitant treatments, though the clinical experts felt that these harms would generally be manageable with adequate care. There was a relatively small number of patients who received the Health Canada–approved dosage (belumosudil 200 mg once daily) in either study and there is additional uncertainty in the long term results due to discontinuations and the immaturity of the survival data. The clinical experts indicated that the study results were generalizable, acknowledging the lack of data for patients younger than 20 years of age in the studies. It was determined that an ITC was not feasible and the sponsor-submitted observational IPTW study comparing belumosudil with BAT had important limitations (i.e., heterogeneity, missing outcomes), preventing meaningful conclusions from being made. Overall, due to the lack of informative direct and indirect evidence, it is very uncertain how belumosudil compares with other cGVHD treatments in terms of efficacy and safety.

While the results of the included studies aligned with the clinical experts' expectation that belumosudil would address the unmet needs in this patient population, there were important limitations in the included studies, leading to uncertainty in the evidence due to the trials having only a single relevant treatment group and no valid comparator.

Introduction

The objective of this report is to review and critically appraise the evidence submitted by the sponsor on the beneficial and harmful effects of belumosudil 200 mg once-daily oral tablets in the treatment of adult and pediatric patients aged 12 years and older with cGVHD after failure of at least 2 prior lines of systemic therapy.

Disease Background

Contents within this section have been informed by materials submitted by the sponsor and clinical expert input. The following has been summarized and validated by the CADTH review team.

HSCT provides stem cells to patients whose bone marrow has been affected by disease, chemotherapy, or radiation.[3] The 2 main types of stem cell transplant are autologous and allo-HSCT.[3] Allo-HSCT uses stem cells from either a matched related or unrelated donor, whereas the stem cell donor and recipient are the same individual for autologous HSCT.[3] According to the CTTC National Bone Marrow Transplant Registry, there were 13,033 transplants performed in Canada between 2008 to 2019, of which 5,672 (43.5%) were allogeneic and 7,361 (56.5%) were autologous.[26] CTTC estimates that approximately 2,200 HSCTs are performed annually in Canada, of which around 1,200 are autologous and 1,000 are allo-HSCTs.[27] While an allo-HSCT has curative potential, there is a risk that the donor's stem cells will die or be destroyed by the recipient (i.e., patient), or that the donor's immune cells will attack healthy cells in the recipient; the latter is called GVHD.[4] GVHD is a serious complication of allo-HSCT caused by a donor's T-cells (graft) viewing the recipient's healthy cells as foreign and attacking these cells.[4,28,29] Consequently, GVHD substantially compromises the clinical and HRQoL benefits and curative potential of allo-HSCT for various underlying malignancies.

GVHD is often classified into 2 main categories: aGVHD and cGVHD. Each type affects different organs and tissues and has different signs and symptoms, and patients may develop 1, both, or neither type following an allo-HSCT.[4] Acute GVHD typically affects the skin, gastrointestinal tract, or liver. Chronic GVHD normally involves a single organ or multiple organs (e.g., eyes, mouth, skin, nails, scalp, hair, gastrointestinal tract, lungs, liver, muscles, joints, and genitalia) and can last from months to a lifetime.[4] Patients with cGVHD face a multifaceted disease burden comprising physical, functional, and psychosocial deficits, all of which have a profound negative impact on HRQoL.[6,7] It is the leading cause of late morbidity and death after an allo-HSCT.[4,5] Although aGVHD and cGVHD share similarities and can overlap at times, each condition involves distinct pathologic processes and they differ in their clinical presentation.[30] Currently, there are no identified biomarkers for the diagnosis or assessment of GVHD disease activity or to differentiate between acute and chronic forms. As a result, the diagnosis is based on clinical presentation and patient interviews.[10] Ongoing inflammation and chronic fibrosis of cGVHD can lead to lasting disability and nonrelapse mortality.[4,5] The median time to onset of cGVHD is estimated to be 162 days after transplant.[31]

In 2005, the NIH Consensus Development Project on Criteria for Clinical Trials in Chronic GVHD put forth standardized criteria for the diagnosis of cGVHD that were subsequently updated in 2014.[10,32] It is recommended that a cGVHD diagnosis be distinct from an aGVHD diagnosis, with the presence of at least 1 diagnostic manifestation of cGVHD or at least 1 distinctive manifestation confirmed by a pertinent biopsy, laboratory tests (e.g., pulmonary function tests, Schirmer test), evaluation by a specialist (ophthalmologist, gynecologist) or radiographic imaging showing cGVHD in the same or another organ, unless stated otherwise.[10,32] Confirmatory biopsy, organ-specific testing, or imaging can be used to confirm the presence of cGVHD.[10] However, confirmatory testing is not always feasible and is not mandatory if a patient has at least 1 of the diagnostic findings of cGVHD.[10]

Following a diagnosis of cGVHD, the severity of the disease is usually categorized as mild, moderate, or severe.[6] The NIH Consensus Development Project has also developed a comprehensive framework for the clinical scoring of affected organ systems and for global scoring of cGVHD based on the degree of organ impact and functional impairment for the categories of mild, moderate, or severe. Mild disease involves 2 or fewer organs with a score of no more than 1 and no lung involvement. Moderate disease involves 3 or more organs with a score of 1, or at least 1 nonlung organ with a score of 2, or lung involvement with a score of 1. Severe disease involves at least 1 organ with a score of 3 or lung involvement with a score of 2 or 3.

The pathophysiology of cGVHD includes inflammation, humoral immunity, cell-mediated immunity, and fibrosis involving both T-cells and B-cells.[10] The disease process is characterized by the overproduction of proinflammatory cytokines (IL-17 and IL-21) and overactivation of proinflammatory T-cells and B-cells, which leads to an overproduction of antibodies.[33] Increasing severity of cGVHD impacts survival, as the global severity scores based on mild, moderate, or severe staging criteria for cGVHD developed by the NIH are significantly associated with both nonrelapse mortality and OS.[32,34] While mild GVHD is associated with a good prognosis, patients with severe GVHD have a poor prognosis and the 2-year OS rate is estimated to be 97%, 86%, and 62% in patients with mild, moderate, and severe GVHD, respectively.[34]

Reports from the literature estimate that cGVHD occurs in 35% to 50% of patients who undergo an allo-HSCT.[8] There is a lack of information on the prevalence of cGVHD in Canada. A US claims-based analysis from 2013 to 2018 found that the projected prevalence of cGVHD was 14,017 individual patients.[35] Within 3 years of an allo-HSCT, 42% of patients developed cGVHD.[35] While most patients experience the onset of cGVHD in the first year after an allo-HSCT, about 5% to 10% of patients may not develop signs and symptoms until later.[9]

Standards of Therapy

Contents within this section have been informed by materials submitted by the sponsor and clinical expert input. The following has been summarized and validated by the CADTH review team.

The treatment goals for cGVHD are to prolong survival and alleviate symptoms while also controlling disease activity, preventing damage and disability, and maintaining or improving HRQoL without causing extensive toxicity or other harms.[10]

In general, cGVHD is treated based on disease severity and the number and types of organs affected. First-line therapy consists of topical or systemic CSs, with or without CNIs, and is generally considered standard across clinical practice guidelines for managing cGVHD.[11] Patients with mild, localized skin disease are typically treated with topicals, while patients with moderate to severe disease are treated with systemic CSs alone or in combination with CNIs or other immunosuppressants.[11] CSs and immunosuppressants are associated with various limitations, such as increased risk in malignancy relapse, infections, myopathy, cataracts, hyperglycemia, decline in bone mass, and avascular necrosis.[11] Therefore, it is recommended that CSs be tapered in those who experience clinical improvements to decrease the risk of associated toxicities.[11] However, for approximately 50% to 60% of patients, their condition fails to respond to treatment

or the response is not durable, or they are unable to taper CSs and require second-line drugs to manage the cGVHD.[11]

Although guidelines recommend a standard first-line therapy, there is a lack of consensus for standard second- and subsequent-line therapies because there is insufficient evidence to recommend any 1 treatment over another, and because there is variation in patient management and which treatments are accessible across jurisdictions.[12] In Canada, second-line options for the treatment of cGVHD include: ECP, mycophenolate mofetil, etanercept, low-dose methotrexate, infliximab, mTOR inhibitors (e.g., sirolimus), imatinib, rituximab, ruxolitinib, ibrutinib, low-dose IL-2, pulsed cyclophosphamide, and pentostatin (rare cases).[11] Of note, only ruxolitinib and ibrutinib have Health Canada indications for the treatment of cGVHD in adult and pediatric patients aged 12 years and older who have had an inadequate response to CSs or other systemic therapies, and for the treatment of pediatric patients aged 1 year and older with cGVHD after failure of 1 or more lines of systemic therapy, respectively.[13,14] The sponsor stated that, at this time, there is no drug specifically indicated for patients with cGVHD whose condition has failed to respond to or who are intolerant to 2 or more prior lines of therapy, which is the expected place in therapy for belumosudil (i.e., third line or later).

Drug Under Review

Key characteristics of belumosudil are summarized along with other treatments available for cGVHD in Table 3 and Table 4.

Belumosudil (Rezurock) is indicated for the treatment of adult and pediatric patients aged 12 years and older with cGVHD after the failure of at least 2 prior lines of systemic therapy.[1] The recommended dosage of belumosudil is 200 mg once daily given orally with food at approximately the same time each day. Treatment should continue until the progression of cGVHD that requires a new systemic therapy, or the occurrence of unacceptable toxicity. No dose adjustments are required in adolescents aged 12 to 18 years or in patients aged 65 years or older.[1] No patients under the age of 18 were enrolled in the clinical development program. The Health Canada product monograph indicates that the use of belumosudil in pediatric patients aged 12 years and older is supported by evidence from studies in adults with additional population pharmacokinetic data, demonstrating that age and body weight had no clinically meaningful effect on the pharmacokinetics of drug substance, that the exposure of drug substance is expected to be similar between adults and pediatric patients aged 12 years and older, and that the course of disease is sufficiently similar in adult and pediatric patients to allow the extrapolation of data in adults to these pediatric patients.[1]

Belumosudil is a selective oral inhibitor of ROCK2 and ROCK1, with 50% inhibitory concentration values of approximately 100 nM and 3 µM, respectively.[1] ROCK2 plays an integral role in the cytokine cascade and the differentiation of cell types that lead to GVHD.[36] ROCK2 phosphorylates the interferon regulatory factor 4 transcription factor necessary to produce IL-17 and IL-21. The ROCK2 signalling that controls the phosphorylation of signal transducer and activator of transcription 3 is necessary for T helper 17 (Th17) cells to differentiate into follicular helper T-cells which, in turn, promote the production of self-reactive mature B-cells. Decreasing ROCK2 signalling that regulates the phosphorylation of signal transducer and activator of transcription 5 reduces the percentage of regulatory T-cells and increases the secretion of IL-10, which

decreases the preponderance of Th17 cells and follicular helper T-cells. ROCK2 also regulates the expression of genes associated with fibrosis induced by transforming growth factor beta. Due to inhibition with belumosudil, ROCK2 signalling is reduced, which may serve to restore immune homeostasis, modulate rather than suppress immune function, and avoid aberrant, fibrotic tissue repair.[36]

The sponsor has requested reimbursement as per the approved Health Canada indication.[2] Belumosudil underwent a standard review at Health Canada and was issued a Notice of Compliance on March 23, 2022.[2] Belumosudil has not been previously reviewed by CADTH.

Table 3: Key Characteristics of Belumosudil, Cyclosporine, Tacrolimus, Ruxolitinib, Ibrutinib, Rituximab, and Imatinib

Characteristic	Belumosudil	Cyclosporine	Tacrolimus	Ruxolitinib	Ibrutinib	Rituximab	Imatinib
Mechanism of action	ROCK2 and ROCK1 inhibitor	CNI	CNI	JAKi mediates cytokine and growth factor signalling (important for hematopoiesis and immune function). Ruxolitinib binds and inhibits JAK 1 and 2, which may lead to a reduction in inflammation and an inhibition of cellular proliferation	Protein kinase inhibitor	Monoclonal anti-CD20 antibody	Protein kinase inhibitor
Indication[a]	For the treatment of adult and pediatric patients ≥ 12 years with cGVHD after failure of ≥ 2 prior lines of systemic therapy	For the prevention of graft rejection following bone marrow transplant and the prevention or treatment of GVHD	None	For the treatment of cGVHD in adults and pediatric patients ≥ 12 years who have inadequate response to corticosteroids or other systemic therapies	For the treatment of adult patients with steroid-dependent or refractory cGVHD For the treatment of pediatric patients ≥ 1 year with cGVHD after failure of ≥ 1 line of systemic therapy	None	None
Route of administration	Oral	Oral	Oral	Oral	Oral	IV, SC	Oral
Recommended dose	200 mg q.d.	125 mg b.i.d.	0.2 to 0.3 mg/kg/day every 12 hours in 2 divided doses	10 mg b.i.d.	420 mg q.d.	500 mg every 7 days for 4 administrations	100 mg q.d.

Characteristic	Belumosudil	Cyclosporine	Tacrolimus	Ruxolitinib	Ibrutinib	Rituximab	Imatinib
Serious adverse effects or safety issues	Embryo-fetal toxicity	Nephrotoxicity, hypertension, malignancies and lymphoproliferative disorders, increased risk of infections, hepatotoxicity, lipoprotein abnormalities, neurotoxicity	Increased susceptibility to infection and the possible development of lymphoma	Serious bacterial, mycobacterial, fungal, and viral infections, including tuberculosis, herpes zoster, John Cunningham virus, HBV, and pneumonia	Hemorrhage; should not be used in patients with moderate or severe hepatic impairment; avoid concomitant use with a strong CYP3A inhibitor	Infusion reactions causing death, PML, tumour lysis syndrome, HBV reactivation, mucocutaneous reactions, infection, and serious and fatal cardiovascular events	Severe congestive heart failure and reduction of LVEF, rhabdomyolysis, severe hemorrhages, fluid retention, liver failure, gastrointestinal perforation

b.i.d. = twice daily; cGVHD = chronic graft-vs.-host disease; CNI = calcineurin inhibitor; CYP3A = cytochrome P450, family 3, subfamily A; GVHD = graft-vs.-host disease; HBV = hepatitis B virus; JAK = Janus kinase; JAKi = Janus kinase inhibitor; LVEF = left ventricular ejection fraction; PML = progressive multifocal leukoencephalopathy; q.d. = once daily; ROCK = Rho-associated, coiled-coil-containing protein kinase; SC = subcutaneous.

[a]Health Canada–approved indication.

Sources: Product monographs for belumosudil, cyclosporine, tacrolimus, ruxolitinib, ibrutinib, rituximab, and imatinib.[1,13,14,37-40]

Table 4: Key Characteristics of Everolimus, Sirolimus, Infliximab, Methotrexate, Mycophenolate Mofetil, Pentostatin, and ECP

Characteristic	Everolimus	Sirolimus	Infliximab	Methotrexate	Mycophenolate mofetil	Pentostatin	ECP
Mechanism of action	Protein kinase inhibitor (mTOR inhibitor)	Protein kinase inhibitor (mTOR inhibitor)	Biological response modifier	DHFR inhibitor	Inosine-50-monophosphate dehydrogenase inhibitor	ADA enzyme inhibitor	Leukapheresis-based procedure with photoactivation with 8-MOP/UVA and reinfusion
Indication[a]	None	None	None	None	None	None	None
Route of administration	Oral	Oral, IV	IV	Oral, IV, SC	Oral	IV	Extracorporeal
Recommended dose	2.5 mg q.d.	2 mg q.d.	10 mg/kg once-weekly infusion	7.5 mg/m^2 once weekly	1,000 mg q.d.	10 mg once weekly	2 to 3 sessions per week
Serious adverse effects or safety issues	Noninfectious pneumonitis (including interstitial lung disease and fatalities), infections, kidney failure	Increased susceptibility to infection, development of lymphoma, hypersensitivity reactions (anaphylactic or anaphylactoid reactions), angioedema, exfoliative dermatitis, hypersensitivity vasculitis; not recommended for use in patients with	Serious infection, tuberculosis, hepatosplenic T-cell lymphoma, and malignancy	Risk of serious toxic reactions, fetal death, and/or congenital anomalies	First-trimester pregnancy loss and birth defects, suppression of immune system, infections, cancer (e.g., lymphoma)	Myelo suppression, renal dysfunction, pulmonary toxicity	No significant adverse effects reported

Characteristic	Everolimus	Sirolimus	Infliximab	Methotrexate	Mycophenolate mofetil	Pentostatin	ECP
		liver or lung transplant					

8-MOP = 8-methoxypsoralen; ADA = adenosine deaminase; DHFR = dihydrofolate reductase; ECP = extracorporeal photopheresis; mTOR = mammalian target of rapamycin; q.d. = once daily; SC = subcutaneous; UVA = UV A.

[a]Health Canada–approved indication.

Sources: Product monographs for everolimus, sirolimus, infliximab, methotrexate, mycophenolate mofetil, and pentostatin, and literature review of ECP.[41-47]

Stakeholder Perspectives

Patient Group Input

This section was prepared by the CADTH review team based on the input provided by 2 patient groups. The full original patient input received by CADTH has been included in the stakeholder section of this report.

A joint input was submitted by 2 patient groups, the Leukemia and Lymphoma Society of Canada and Myeloma Canada, which responded to CADTH's call for patient input for the current review of belumosudil for the treatment of adult and pediatric patients aged 12 years and older with cGVHD after the failure of at least 2 prior lines of systemic therapy.

The patient group emphasized that the uncertainty of a GVHD diagnosis after the rigorous cancer and stem cell transplant experience can be nerve-wracking, disheartening, and terrifying for patients and caregivers. Respondents indicated that the full range of GVHD symptoms significantly affects their physical and mental health and daily activities, and has detrimental effects on their HRQoL. They described how the disease affects various parts of the body, including the eyes, skin, lungs, and mouth. Many patients lose their independence and require caregiver support to manage their symptoms.

The patient group stated that managing cGVHD generally requires CS treatment, which can have many physical, neurologic, and circulatory side effects and greatly impacts patient and caregiver HRQoL. It was noted that patients can experience extreme emotions while recovering from the trauma of cancer and stem cell transplant experiences.

According to the patient group input, patients and caregivers seek a treatment that enables them to continue their daily lives and routines throughout the treatment course and that is more accessible, improves OS, and preserves their HRQoL with minimal impact on work, finances, and social, physical, and mental health.

Of the 5 respondents who indicated having experience with belumosudil, 3 stated that the drug had a positive impact on their lives, allowed them to reduce steroid dosage, and was very tolerable with minimal side effects.

Clinician Input

Input From the Clinical Experts Consulted by CADTH

All CADTH review teams include at least 1 clinical specialist with expertise in the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process (e.g., providing guidance on the review protocol, assisting in the critical appraisal of clinical evidence, interpreting the clinical relevance of the results, and providing guidance on the potential place in therapy). The following input was provided by 2 clinical specialists with expertise in the diagnosis and management of cGVHD.

Unmet Needs

According to the clinical experts consulted by CADTH, there is a lack of good treatment options beyond second-line therapy for patients with cGVHD. As a result, patients with refractory or progressive disease have impaired HRQoL, an impaired ability to work and study, and an increased risk of mortality-associated organ impairment and risk of infections.

Place in Therapy

The clinical experts indicated that belumosudil would be used as per the Health Canada indication after the failure of 2 systemic treatments and would likely be used in combination with CSs. The experts also noted there would need to be good RCT evidence to support using CSs with belumosudil in a first-line setting, and ruxolitinib is currently preferred as a second-line therapy.

Patient Population

As per the clinical experts, those with moderate to severe cGVHD whose condition is refractory to or who are intolerant to 2 prior lines of therapy are most likely to receive belumosudil. The response to prior lines of therapies would be assessed based on clinical signs and symptoms, NIH clinical grading (including laboratory tests), and/or pulmonary function tests.

Assessing the Response Treatment

The experts stated that PR and CR as well as the maintenance of stable disease with a clinically meaningful reduction in CS dose are indicators in clinical practice that a patient is responding to treatment. Improvement in functional status, symptoms, and ability to return to school or work were also important outcomes.

Discontinuing Treatment

The clinical experts stated that treatment should be discontinued in patients who experience cGVHD progression (based on signs, symptoms, examination, laboratory tests) or have stable disease but still require significant amounts of CSs that cannot be tapered. The experts also noted meaningful adverse effects, such as derangement of liver function tests or significant gastrointestinal upset due to belumosudil as also being reasons to stop treatment. Lastly, disease resolution in which a patient has stopped other immunosuppressants (or who may be on low-dose CSs, e.g., 10 mg) with symptom resolution is a third reason. The experts highlighted that stopping treatment in the last instance is done cautiously, as patients can experience disease flares when going off treatment.

Prescribing Considerations

The clinical experts noted that stem cell transplant specialists should initiate belumosudil in either a community or hospital setting, and treatment decisions may involve other specialists (e.g., respirologists).

Clinician Group Input

This section was prepared by the CADTH review team based on the input provided by 2 clinician groups. The full original clinician group input received by CADTH has been included in the stakeholder section of this report.

Two clinician groups, the OH-CCO Hematology Cancer Drug Advisory Committee and CTTC responded to CADTH's call for clinician group input. Clinician perspectives from OH-CCO were obtained through videoconferencing. CTTC gathered the information through a literature review and a discussion with the CTTC board of directors and the standing committee of program directors.

According to the clinician groups, there are multiple third-line treatments available for cGVHD and variability in standard practice based on local funding of available options. OH-CCO added that responsiveness and tolerability to available therapies vary between patients, and oral therapies are often preferred. As per CTTC, current available treatments are suboptimal and require high doses and prolonged use of CSs, which are associated with an increased risk of opportunistic infections, osteoporosis, and avascular necrosis. Therefore, new therapies that reduce the mortality and symptom burden associated with steroid-refractory cGVHD are urgently needed, especially for steroid-refractory pulmonary cGVHD and cGVHD with fibrotic and sclerotic manifestations.

As per the clinician groups, standard GVHD response criteria, significant functional improvements, and better HRQoL are outcomes used to determine whether a patient is responding to treatment. CTTC indicated that a patient showing no significant change in GVHD severity but with a meaningful reduction in immunosuppressive treatments is deemed to be benefiting from the therapy.

The clinician groups agreed that the discontinuation of therapy should be considered in patients with significant intolerance or disease progression. CTTC specified that therapy with belumosudil would require prolonged treatment (greater than 1 year) until no further resolution or stable residual fibrotic changes are present.

OH-CCO stated that the treatment of patients with cGVHD with belumosudil should be managed by cGVHD specialists practising in outpatient settings; however, patients with severe disease may require treatment as an inpatient. CTTC added that this therapy should be prescribed only for patients with steroid- or ruxolitinib-refractory cGVHD by specialists working in a clinical setting associated with allo-HSCT programs.

Drug Program Input

The drug programs provide input on each drug being reviewed through CADTH's Reimbursement Review processes by identifying issues that may impact their ability to implement a recommendation. The implementation questions and corresponding responses from the clinical experts consulted by CADTH are summarized in Table 5.

Table 5: Summary of Drug Plan Input and Clinical Expert Response

Drug program implementation questions	Clinical expert response
Relevant comparators	
Ibrutinib has an indication for cGVHD; however, it was not submitted to CADTH for review for this specific indication and was not used as a comparator.	The clinical experts acknowledged that at this time, there is no direct or indirect evidence submitted for CADTH's review comparing belumosudil with ibrutinib. According to the experts, belumosudil would be used as per its Health Canada indication

Drug program implementation questions	Clinical expert response
How does ibrutinib compare with belumosudil? What is belumosudil's place in therapy?	(for the treatment of patients aged 12 years and older with cGVHD after failure of at least 2 prior systemic therapies). They added there would be a need for good RCT evidence with appropriate comparators to support using belumosudil as an earlier line of therapy.
Considerations for initiation of therapy	
Does it matter which 2 systemic therapies were tried first? Steroids are the mainstay of treatment; do they count as well? Does ECP (hospital procedure) count as a prior therapy?	The clinical experts noted that any 2 systemic therapies for the treatment of cGVHD (including CSs and ECP) count toward the requirement of a failure of at least 2 prior systemic treatments before accessing belumosudil.
Considerations for continuation or renewal of therapy	
How often should patients be evaluated to continue treatment? Is it every 6 months? Once a year?	The clinical experts suggest that the first authorization of belumosudil should be for 6 months with renewal for patients who have experienced an overall response (i.e., CR or PR, or stable disease with significant reduction in steroid doses), according to NIH criteria, after 24 weeks of therapy (approximately 6 months).
Considerations for discontinuation of therapy	
What parameters should be considered to determine whether the treatment is ineffective and needs to be discontinued?	The clinical experts agreed that belumosudil should be discontinued if there is progression of cGVHD, defined as worsening of symptoms or occurrence of new symptoms. However, the experts thought that treatment for cGVHD (e.g., with belumosudil) should continue if the patient experiences recurrence or relapse of the underlying hematological malignancy and emphasized that it would be important to treat both diseases. It is worth noting that in study KD025 to 213, patients 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, patient preference or withdrawal of consent, loss of follow-up, sponsor decision, or death (whichever occurred first).
Should therapy end after a specific number of doses or after a specific number of years, or should treatment continue indefinitely as long as the patient shows a response? What number of doses is appropriate? What number of years is appropriate?	The clinical experts stated they would not expect treatment with belumosudil to be indefinite. In their opinion, physicians would cautiously taper cGVHD treatment(s) and assess response or relapse to manage a patient's symptoms with the minimum number of drugs and dose possible. They also noted there is a small number of patients who remain on cGVHD treatments for life when tapering efforts fail. Due to treatment management being patient-specific, the experts were not able to define a number of doses or years that patients would continue on treatment.
Considerations for prescribing of therapy	
There are several treatment options in this space. Can belumosudil treatment be combined with other treatments? Studies used belumosudil on its own and with concomitant	As per study KD025 to 213 and study KD025 to 208, the clinical experts expect that belumosudil could be used alongside other treatments for cGVHD. In the studies, the permitted concomitant

Drug program implementation questions	Clinical expert response
medications. It is unclear if treatment is intended to be alone or as adjunctive therapy.	standard of care systemic cGVHD therapies included, but were not limited to, CNIs (tacrolimus, cyclosporine), sirolimus, mycophenolate mofetil, methotrexate, rituximab, and ECP.
Generalizability	
Can belumosudil be given to patients who have not experienced the failure of other therapies?	The clinical experts indicated it would be possible to give belumosudil to patients if they have demonstrated intolerance to other medications for cGVHD.
Can belumosudil be given to patients with aGVHD?	There is currently no Health Canada indication for the use of belumosudil in the treatment of patients with aGVHD.
System and economic issues	
Should treatment options be prioritized?	The clinical experts noted it would be challenging to prioritize cGVHD treatments due to the lack of direct and indirect comparative evidence available for review.

aGVHD = acute graft-vs.-host disease; cGVHD = chronic graft-vs.-host disease; CNI = calcineurin inhibitor; CR = complete response; CS = corticosteroid; ECP = extracorporeal photopheresis; NIH = National Institutes of Health; PR = partial response; RCT = randomized controlled trial.

Clinical Evidence

The objective of CADTH's Clinical Review Report is to review and critically appraise the clinical evidence submitted by the sponsor on the beneficial and harmful effects of belumosudil 200 mg once-daily oral tablets in the treatment of adult and pediatric patients aged 12 years and older with cGVHD after the failure of at least 2 prior lines of systemic therapy. The focus will be placed on comparing belumosudil with relevant comparators and identifying gaps in the current evidence.

A summary of the clinical evidence included by the sponsor in the review of belumosudil is presented in 4 sections, with CADTH's critical appraisal of the evidence included at the end of each section. The first section, the systematic review, includes pivotal studies and RCTs that were selected according to the sponsor's systematic review protocol. CADTH's assessment of the certainty of the evidence in this first section using the GRADE approach follows the critical appraisal of the evidence. The second section would include sponsor-submitted long-term extension studies; however, none were submitted. The third section would include sponsor-submitted ITCs; in this case, the sponsor submitted a feasibility assessment but no indirect comparison. The fourth section includes additional studies that were considered by the sponsor to address important gaps in the systematic review evidence.

Included Studies

The clinical evidence from the following is included in the CADTH review and appraised in this document:

- Two clinical studies or RCTs (with a single-arm relevant to this report) identified in the systematic review
- One feasibility assessment for ITCs
- One additional study addressing gaps in the evidence.

Systematic Review

Contents within this section have been informed by materials submitted by the sponsor. The following has been summarized and validated by the CADTH review team.

Description of Studies

The 2 studies included in the systematic review are summarized in Table 6. Only information for drug doses that align with the Health Canada product monograph (i.e., belumosudil 200 mg once daily) is presented in the CADTH report.

Study KD025 to 213 is a phase II, open-label study conducted at 33 sites in the US that began on October 11, 2018, and is now complete, with a primary analysis data cut-off date of February 19, 2020, and a latest data cut-off date of [redacted].[15,16] In total, [redacted] patients were randomized in a 1:1 ratio to either belumosudil 200 mg once daily (N = [redacted]) or belumosudil 200 mg twice daily (N = [redacted]), and [redacted] individuals were randomized but not treated. Randomization was stratified by prior treatment with ibrutinib (yes or no) and severe cGVHD (yes or no). Severe GVHD was defined according to the NIH cGVHD severity definitions as GVHD with at least 1 organ with a score of 3 or an NIH lung score of 2 or 3.[10] Figure 1 shows the study design for study KD025 to 213.

Study KD025 to 208 is a phase IIa, dose-escalation, open-label study conducted at 7 sites in the US that began on September 27, 2016, and is ongoing, with a primary reporting data cut-off date of February 19, 2020, and a latest data cut-off date of [redacted].[17,18] In total, 54 patients were enrolled into 3 sequential cohorts of belumosudil 200 mg once daily (N = 17), belumosudil 200 mg twice daily (N = 16), and belumosudil 400 mg once daily (N = 21). Prior to the enrolment of subsequent cohorts, the safety data in each previous cohort were evaluated after 8 patients had reached 2 months of treatment.

Both studies had a screening period (14 days and 28 days for study KD025 to 213 and study KD025 to 208, respectively) to assess eligibility. The study treatment continued in 28-day cycles until clinically significant disease progression in study KD025 to 213, or for 24 weeks of therapy in study KD025 to 208. Patients were followed up for 4 weeks in both studies and may have continued treatment for up to 3 years. The primary end point in the studies was ORR per investigator assessment (measured on day 1 of each cycle for cycles 2 to 5 and every other cycle thereafter until clinically meaningful disease progression or EOT). The secondary outcomes of interest for the CADTH review were similar between the 2 studies and included DOR, TTR, FFS, OS, LSS score, and safety outcomes. PROMIS Global Health summary scores were exploratory outcomes in study KD025 to 213.

Table 6: Details of Studies Included in the Systematic Review

Detail	KD025 to 213	KD025 to 208
Designs and populations		
Study design	Phase II, randomized, open-label, multicentre study	Phase IIa, dose-escalation, open-label, multicentre study
Locations	33 sites in the US	7 sites in the US

Detail	KD025 to 213	KD025 to 208
Patient enrolment dates	**Start date:** October 11, 2018 **Data cut-off date for primary analysis:** [redacted]	**Start date:** September 27, 2016 **Data cut-off date for primary analysis:** [redacted]
Randomized (N)	Total N = [redacted][a] • Belumosudil 200 mg q.d.: N = [redacted][b] • Belumosudil 200 mg b.i.d.: N = [redacted]	Total N = 54 • Belumosudil 200 mg q.d. (cohort 1): N = 17[b] • Belumosudil 200 mg b.i.d. (cohort 2): N = 16 • Belumosudil 400 mg q.d. (cohort 3): N = 21
Inclusion criteria	• Adults and adolescents ≥ 12 years of age • Undergone an allo-HSCT • 2 to 5 prior lines of systemic treatment for cGVHD • Received GC therapy with a stable dose for ≥ 2 weeks before screening • Persistent cGVHD manifestations • Systemic therapy for cGVHD was indicated • Karnofsky Performance Scale score ≥ 60 • Absolute neutrophil count ≥ 1.5 × 10^9/L • Platelet count ≥ 50 × 10^9/L • ALT and AST ≤ 3 × ULN • Total bilirubin ≤ 1.5 × ULN • GFR ≥ 30 mL/min/1.73 m^2	• Adults ≥ 18 years of age • Undergone an allogeneic bone marrow transplant or allo-HSCT • 1 to 3 prior lines of systemic treatment for cGVHD (not including ECP) • Received GC therapy with or without CNI therapy and/or ECP for cGVHD • Persistent active cGVHD manifestations after ≥ 2 months of steroid therapy • Karnofsky Performance Scale score > 40 • Absolute neutrophil count ≥ 1.5 × 10^9/L • Platelet count ≥ 50 × 10^9/L • ALT and AST ≤ 3 × ULN • Total bilirubin ≤ 1.5 × ULN • GFR ≥ 30 mL/min/1.73 m^2
Exclusion criteria	• Not on a stable dose or regimen of cGVHD treatment for ≥ 2 weeks before screening • Histological relapse of underlying cancer of posttransplant lymphoproliferative disease • Current treatment with ibrutinib (prior treatment permitted with a 28-day washout) • Had an FEV_1 ≤ 39% or a lung score of 3	• aGVHD • Receipt of investigational GVHD treatment within 28 days of study • Use of moderate or strong CYP3A4 inhibitors or inducers • Had relapse of the underlying cancer or posttransplant lymphoproliferative disease at screening
Drugs		
Intervention	• Belumosudil 200 mg oral tablets q.d.[b] • Belumosudil 200 mg oral tablets b.i.d.	• Belumosudil 200 mg q.d. (cohort 1)[b] • Belumosudil 200 mg b.i.d. (cohort 2) • Belumosudil 400 mg q.d. (cohort 3)
Comparator(s)	NA	NA
Study duration		
Screening phase	14 days	28 days
Treatment phase	Until clinically significant disease progression	24 weeks (6 cycles)
Follow-up phase	4 weeks Subsequent long-term follow-up every 12 weeks until study closeout (anticipated to be within 4 years of first patient enrolment)	28 (± 7) days Subsequent long-term follow-up every 8 weeks until study closeout

Detail	KD025 to 213	KD025 to 208
Outcomes		
Primary end point	ORR per investigator assessment[c] measured on day 1 of each cycle for cycles 2 to 5 and every other cycle thereafter until clinically meaningful disease progression or EOT	ORR per investigator assessment[c] measured on day 1 of each cycle for cycles 2 to 5 and every other cycle thereafter until clinically meaningful disease progression or EOT
Secondary and exploratory end points	**Secondary:** • DOR • TTR • response rate by organ system • change in GSR based on clinician-reported cGVHD activity assessment • LSS • FFS • TTNT • OS • change in CS dose • change in CNI dose • change in symptom activity based on the patient self-reported cGVHD activity assessment • PK • safety **Exploratory:** • changes in the PROMIS Global Health summary scores for physical and mental functioning • ORR per KARA • PD (biomarkers)	**Secondary:** • DOR • TTR • response rate by organ system (including GSR) • LSS • FFS • TTNT • OS • change in CS dose • change in CNI dose • change in symptom activity based on the patient self-reported cGVHD activity assessment • PFTs • change in GSR based on clinician-reported cGVHD activity assessment • PK • Safety **Exploratory:** • change in plasma cytokine expression (e.g., IL-17A, IL-21, and IL-2) after belumosudil administration and changes in immune cell subtypes in whole blood (e.g., Th17, Treg) after belumosudil administration
Publication status		
Publications	Cutler et al. (2021)[48]	Jagasia et al. (2021)[49]

aGVHD = acute graft-vs.-host disease; allo-HSCT = allogeneic hematopoietic stem cell transplant; ALT = alanine aminotransferase; AST = aspartate aminotransferase; b.i.d. = twice daily; cGVHD = chronic graft-vs.-host disease; CNI = calcineurin inhibitor; CS = corticosteroid; CYP3A4 = cytochrome P450, family 3, subfamily A, member 4; DOR = duration of response; ECP = extracorporeal photopheresis; EOT = end of treatment; FEV_1 = forced expiratory volume in 1 second; FFS = failure-free survival; GC = glucocorticoid; GFR = glomerular filtration rate; GSR = global severity rating; GVHD = graft-vs.-host disease; HSCT = hematopoietic stem cell transplant; IL = interleukin; KARA = Kadmon algorithmic response assessment; LSS = Lee Symptom Scale; NA = not applicable; NIH = National Institutes of Health; ORR = overall response rate; OS = overall survival; PD = pharmacodynamics; PFT = pulmonary function test; PK = pharmacokinetics; PROMIS = Patient-Reported Outcomes Measurement Information System; q.d. = once daily; Th17 = helper T-cell 17; Treg = regulatory T-cell; TTNT = time to next treatment; TTR = time to response; ULN = upper limit of normal.

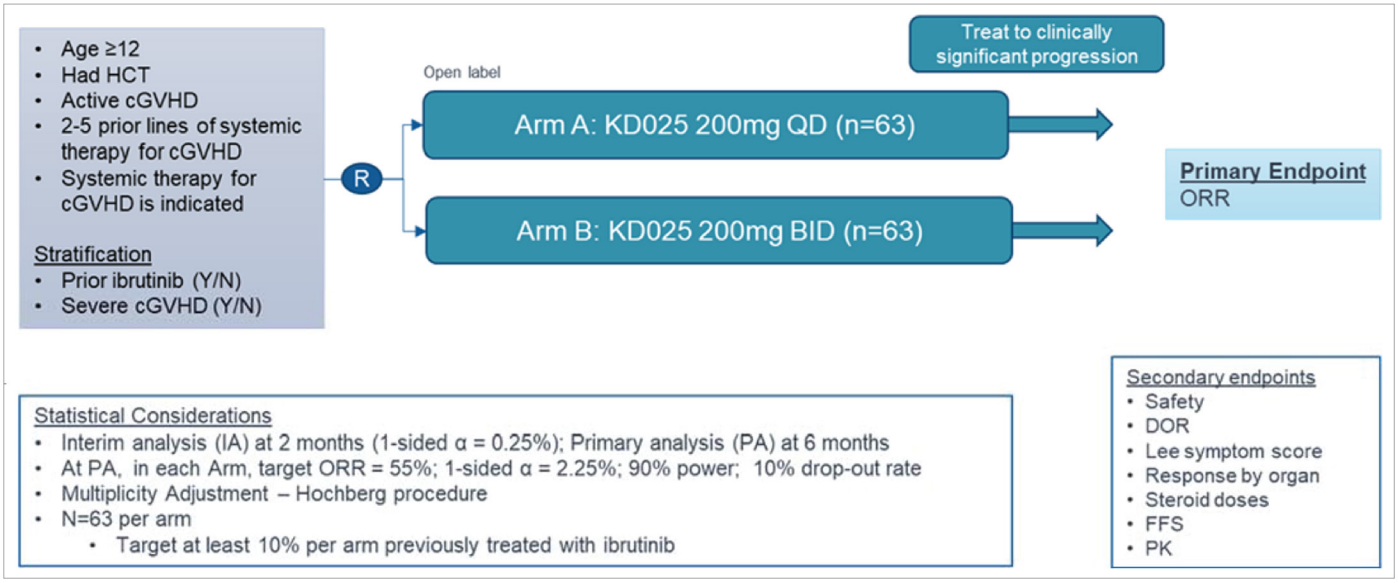
[a]The number of patients in the study as of the latest data cut-off date ([redacted]).

[b]The Health Canada–approved dosage for belumosudil is 200 mg q.d. and results are reported only for this treatment group or cohort. Patients were treated with belumosudil until clinically significant disease progression.

[c]As per the NIH consensus development project on clinical trials in cGVHD response criteria.[32]

Sources: Clinical Study Reports for study KD025 to 213[15] and study KD025 to 208[17] and sponsor's summary of clinical evidence.[11] Details included in the table are from the sponsor's summary of clinical evidence.

Figure 1: Study Design for Study KD025 to 213



BID = twice daily; cGVHD = chronic graft-versus-host disease; DOR = duration of response; FFS = failure-free survival; HCT = hematopoietic cell transplant; IA = interim analysis; KD025 = belumosudil; LSS = Lee symptom score; ORR = overall response rate; PA = primary analysis; PK = pharmacokinetics; QD = once daily; Y/N = yes or no.

Sources: Study KD025 to 213 Clinical Study Report[15] and sponsor's summary of clinical evidence.[11]

Populations

Inclusion and Exclusion Criteria

In study KD025 to 213, eligible patients had to be at least 12 years of age or older with active cGVHD and had to have undergone an allo-HSCT, received 2 to 5 prior lines of therapy for cGVHD, and received stable glucocorticoid (GC) therapy for at least 2 weeks before screening. Patients were excluded if there was evidence of histological relapse of underlying cancer of posttransplant lymphoproliferative disease, or they were receiving ibrutinib at the time of screening. In each group, the study aimed to enrol at least 10% of patients who had previously received ibrutinib.

In study KD025 to 208, eligible patients had to be 18 years of age or older with active cGVHD and had to have undergone an allogeneic bone marrow transplant or allo-HSCT, received 1 to 3 prior lines of therapy for cGVHD (excluding ECP), and received GC therapy with or without CNI therapy for cGVHD. Patients were excluded if they had aGVHD or received an investigational GVHD treatment.

Interventions

In study KD025 to 213, patients received belumosudil 200 mg once daily in 28-day cycles until clinically significant progression of disease (i.e., requiring a new systemic therapy for cGVHD), histologic recurrence of the underlying malignancy, unacceptable toxicity, death, lost to follow-up, or investigator decision. The drug was tapered after a sustained response for 6 months and cessation of all other immunosuppressants for at least 3 months as follows: belumosudil 200 mg once daily, then belumosudil 200 mg once every other day for 2 cycles, then discontinued. Patients who had not progressed or responded when belumosudil

was discontinued and who came off the study for reasons other than AEs were tapered off belumosudil by reducing the dose every 2 cycles. Patients were permitted to have concomitant treatment with standard of care systemic cGVHD therapies, such as CNIs (tacrolimus, cyclosporine), sirolimus, mycophenolate mofetil, methotrexate, rituximab, ECP, or topical or organ-specific therapies if they had been on a stable regimen; however, initiation of a new systemic therapy was not permitted. CS dose data were collected throughout the study and doses may have been tapered by the investigator after at least 2 weeks after belumosudil administration. Transient increases in CS dosing (that did not exceed 1 mg/kg/day of a prednisone equivalent) were permitted to treat cGVHD flares, but the dose had to be reduced back to the prerandomization dose within 6 weeks. Situations where the CS dose remained elevated for more than 6 weeks, or if a patient experienced more than 2 episodes of cGVHD flares that required increased CS therapy in the first 6 months of belumosudil treatment, were considered treatment failures.

In study KD025 to 208, patients received belumosudil 200 mg once daily in 28-day cycles until disease progression or unacceptable toxicity. If at least 25% of the patients in a cohort experienced grade 2 liver toxicity or a grade 3 or higher AE in the same organ or body system, or if at least 25% of patients in a cohort were discontinued for toxicity that persisted for 14 days, then dose escalation to the next cohort was halted and all patients in that dose cohort received a reduced dose. Patients could receive concomitant CS and CNI therapy and, after 4 weeks of belumosudil treatment, CS treatment could be tapered at the investigator's discretion.

Dose interruptions of up to 14 days were permitted, though patients were discontinued if interruptions were longer or if more than 1 dose reduction was required. Furthermore, treatment continued until the clinically significant progression of cGVHD (defined as disease progression that required the addition of new systemic therapy), histologic recurrence of underlying malignancy, unacceptable toxicity, investigator decision, patient preference or withdrawal of consent, lost to follow-up, sponsor decision, or death.

Outcomes

A list of efficacy end points assessed in this Clinical Review is provided in Table 7, followed by descriptions of the outcome measures in Table 8. The summarized end points are based on outcomes included in the sponsor's summary of clinical evidence as well as any outcomes identified as important to this review according to the clinical experts consulted by CADTH, stakeholder input from patient and clinician groups and public drug plans, and the sponsor's pharmacoeconomic model. Using the same considerations, the CADTH review team selected end points that were considered to be most relevant to inform CADTH's expert committee deliberations and finalized this list of end points in consultation with members of the expert committee. All summarized efficacy end points were assessed using GRADE. Select notable harms outcomes considered important for informing the deliberations of CADTH's expert committee were also assessed using GRADE.

The following considerations went into the selection of the efficacy outcomes summarized in the report and assessed using GRADE:

- Response to treatment was noted as being a current unmet need, according to the authors of clinician group input. As per the clinical experts and clinician group input, response criteria are typically used to assess patients receiving treatment for cGVHD in practice.
- Survival was identified as being a high priority according to the patient group input. It was also highlighted in the clinician group input that cGVHD greatly impacts mortality.
- HRQoL and reducing symptom burden were identified as being priorities in the patient group input and clinician group input. The LSS is a patient-reported, disease-specific measure of symptoms. PROMIS is a generic measure of health that was used in the sponsor's pharmacoeconomic model after statistical mapping to the EQ-5D.
- Harms of treatment were also noted as being important in the patient group input, clinician group input, and by the clinical experts.

Table 7: Outcomes Summarized From the Studies Included in the Systematic Review

Outcome measure	Time point	KD025 to 213	KD025 to 208
ORR (CR + PR) by investigator assessment[a]	6 months, data cut-off date	Primary[b]	Primary
DOR	6 months	Secondary	Secondary
TTR	Data cut-off date	Secondary	Secondary
Response rate by organ system (including GSR)[c]	Data cut-off date	Secondary	Secondary
FFS	12 months	Secondary	Secondary
TTNT[c]	Data cut-off date	Secondary	Secondary
OS	12 months	Secondary	Secondary
Change in LSS score	Data cut-off date	Secondary	Secondary
Change in CS dose[c]	Data cut-off date	Secondary	Secondary
Change in PROMIS Global Health summary scores for physical and mental functioning	Data cut-off date	Exploratory	Not measured
SAEs	Data cut-off date	Secondary	Secondary

cGVHD = chronic graft-vs.-host disease; CR = complete response; CS = corticosteroid; DOR = duration of response; FFS = failure-free survival; GRADE = Grading of Recommendations Assessment, Development, and Evaluation; GSR = global severity rating; LSS = Lee Symptom Scale; ORR = overall response rate; OS = overall survival; PR = partial response; PROMIS = Patient-Reported Outcomes Measurement Information System; SAE = serious adverse event; TTNT = time to next treatment; TTR = time to response.

[a]As per the National Institutes of Health consensus development project on clinical trials in cGVHD response criteria.

[b]Statistical testing for this end point was adjusted for multiple comparisons.

[c]Outcome considered to be informative for the clinical management of patients with cGVHD but not included for GRADE assessment. Outcome has been included in Appendix 1.

Sources: Clinical Study Reports for study KD025 to 213[15] and study KD025 to 208[17] and sponsor's summary of clinical evidence.[11] Details included in the table are from the sponsor's summary of clinical evidence.

Primary Outcome

ORR by Investigator Assessment

The primary outcome in both studies was ORR at the 6-month follow-up by investigator assessment.[15,17] ORR was defined as the proportion of patients who experienced a CR or PR based on the cGVHD response assessment performed on day 1 of cycle 2 through cycle 5, and then day 1 of every other cycle thereafter, as well as the EOT visit (in KD025 to 208 only). Overall response was assessed according to the 2014 NIH consensus criteria using the scores from 9 organ systems (i.e., skin, eyes, mouth, esophagus, upper gastrointestinal tract, lower gastrointestinal tract, liver, lungs, and joints and fascia) as well as the global severity rating (GSR).[50] Response was assessed relative to the baseline (cycle 1 day 1) cGVHD assessment. The overall response at each assessment time point was categorized as a CR, PR, or LR, where LR included unchanged (LR-U), mixed (LR-M), and progression (LR-P) as detailed subsequently.

- CR: Resolution of all cGVHD manifestations 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: CR or PR in at least 1 organ accompanied by progression in another organ; response was considered progression for the purposes of the analysis
  - 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

If a treated patient was lost to follow-up without a response assessment, the patient was counted as a nonresponder.

Secondary Outcomes

Duration of Response

According to the clinical experts consulted by CADTH, the tertiary and secondary DOR definitions were considered to be the most clinically relevant. The tertiary definition of DOR was the time from first documented response to the time of initiation of a new systemic cGVHD therapy or death (reviewed by a clinical team).[15,17] The secondary definition of DOR was the time from first documented response to the time of first documented LR. The sponsor also included a primary definition of DOR, which was the time from first documented response to the time of first documented deterioration from best response (e.g., CR to PR or PR to LR). For primary and secondary DOR, censoring occurred at the last documented response assessment or, if due to LR or the initiation of a new systemic therapy occurred immediately after 2 or more missed response assessments, then the event date was set as 4 weeks (1 cycle) after the last documented response assessment before this event. For tertiary DOR, censoring occurred at the last response assessment or long-term follow-up assessment, whichever was the latest and available. DOR was measured only in patients who were responders at time points similar to ORR.

Time to Response

TTR was defined as the time from first treatment to the time of first documentation of response.[15,17] TTR analyses were only conducted for patients who were responders and were also evaluated at the organ level. TTR was measured only in patients who were responders at time points similar to ORR up to week 48. Results were also provided by organ system (Appendix 1).

Failure-Free Survival

FFS was defined as the time from the first dose of belumosudil to the time of the first event that included the initiation of a new cGVHD therapy, nonrelapse mortality, or recurrent malignancy (i.e., of underlying disease).[15,17] Censoring for FFS was performed according to the last response assessment or long-term follow-up assessment, whichever was the latest and available.

Time to Next Treatment

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 the last response assessment or the long-term follow-up assessment, whichever was the latest and available.[15,17] This outcome was considered useful in informing the clinical management of individual patients with cGVHD, but not critical to decision-making, and is summarized in Appendix 1.

Overall Survival

OS was defined as the time from the first dose of belumosudil to the date of death due to any cause.[15,17]

Change in LSS Score

Changes in symptom burden were explored using the 7-day LSS score.[15,17] Symptom burden was assessed on day 1 of each cycle beginning with cycle 1 until EOT. The questionnaire consists of 30 items over 7 domains (i.e., skin, eyes and mouth, breathing, eating and digestion, muscles and joints, energy, and emotional distress). Patients indicate the degree of bother due to symptoms over the past 7 days on a scale ranging from 0 to 4, with higher values indicating worse symptoms. A domain score is calculated for each domain using the mean of all items completed if more than 50% were answered and normalizing to a 0 to 100 scale. A summary score is calculated as the average of all nonmissing domain scores if more than 50% of them are nonmissing. A higher score indicates more bothersome symptoms. A 7-point or greater reduction in the summary score is considered clinically meaningful.[19] This outcome was assessed at baseline, day 1 of cycle 2 through cycle 5, then day 1 of every other cycle thereafter, and at EOT.

Change in Corticosteroid Dose

The change in systemic CS dose as mg/kg/day prednisone equivalent over time was measured.[15,17] Dose equivalencies were as follows: 1 mg prednisone was equivalent to 4 mg hydrocortisone, 0.8 mg methylprednisolone, 0.15 mg dexamethasone, and 0.8 mg triamcinolone. Systemic CS dose over time, change and percent change from baseline to the greatest CS dose reduction during belumosudil treatment, number and percentage of patients who reduced systemic CS use, and number and percentage of patients who ever discontinued systemic CS use during belumosudil treatment were evaluated. Data were collected throughout the study until 28 days after the last dose of the study drug. Transient CS dose increases

of 1 mg/kg/day or lower were permitted to treat disease flares but had to have been reduced to the prerandomization dose within 6 weeks; otherwise, belumosudil treatment was considered to have failed in the patient. A patient who experienced 3 or more disease flares requiring an increased CS dose during the first 6 months of belumosudil treatment was also considered a belumosudil treatment failure. This outcome was considered useful in informing the clinical management of individual patients with cGVHD but not critical to decision-making, and is summarized in Appendix 1.

Safety

Safety was assessed by the proportion of patients who experienced AEs (coded using Medical Dictionary for Regulatory Activities version 20.0), SAEs, withdrawals due to AEs, and deaths.[15,17] Data were collected throughout the study until 28 days after the last dose of the study drug. Hematologic and immune AEs were notable harms included in the CADTH review.

Exploratory Outcomes

Change in PROMIS Global Health Summary Scores for Physical and Mental Functioning

The PROMIS Global Health score was developed using mixed qualitative and quantitative methods and used item response therapy-calibrated item banks for numerous patient-reported symptoms and functional domains.[15] It includes 6 questions pertaining to general health, including the patient's rating of their general health as excellent, very good, good, fair, or poor. In addition, there is a question about the patient's ability to carry out everyday physical activities (responses include completely, mostly, moderately, a little, or not at all) and a question pertaining to emotional problems such as feeling anxious, depressed, or irritable over the last 7 days (responses include never, rarely, sometimes, often, or always). Two summary scores were determined for physical and mental functioning, with higher scores indicating better functioning. There are also 2 questions regarding average fatigue (responses include none, mild, moderate, severe, and very severe) and average pain (rated on a scale from 0 = no pain to 10 = worst pain imaginable). This outcome was assessed at baseline, day 1 of cycle 2 through cycle 5, then day 1 of every other cycle thereafter, and at EOT.

Table 8: Summary of Outcome Measures and Their Measurement Properties

Outcome measure	Type	Conclusions about measurement properties	MID
LSS	The LSS is a 30-item instrument with 7 domains (skin, eyes and mouth, breathing, eating and digestion, muscles and joints, energy, and emotional distress) used to estimate symptom burden. Patients respond based on how bothered they have been by each of the domain items in the past 7 days. Options range from 0 to 4 (i.e., not at all, slightly, moderately, quite a bit, extremely). Subscale scores and summary scores range from 0 to 100, with a higher	**Validity:** 1 systematic review of 2 studies and an additional primary study demonstrated adequate construct validity (Cronbach alpha, 0.84 to 0.90).[19,51] Another study showed content validity[52] for patients with GVHD has been demonstrated. **Reliability:** Test–retest reliability was shown with a correlation of 0.79 for the summary scale and ranging from 0.70 to 0.89 for the domains in patients with cGVHD.[19] **Responsiveness:** All subscales	The MID has been estimated to range from 5 to 7 points in the summary score in patients with cGVHD.[19,53,54]

Outcome measure	Type	Conclusions about measurement properties	MID
	score indicating worse symptom burden.[19]	demonstrated responsiveness to change, except for the summary score, which had inconsistent evidence.[51]	
PROMIS Global Health summary scores for physical and mental functioning	Version 10 of the instrument comprises 10 items covering 7 domains (depression, anxiety, physical function, pain, fatigue, sleep, and social function) with 2 summary scores for physical and mental functioning.[54] Higher scores indicate better functioning on functional items and worse severity on symptom scales.[55]	A single systematic review identified no evidence for validity, reliability, or responsiveness specific to the use of the tool in patients with cGVHD.[51]	A 4.7-point change has been estimated to be a clinically meaningful difference in patients with cGVHD.[54]

cGVHD = chronic graft-vs.-host disease; GVHD = graft-vs.-host disease; LSS = Lee Symptom Scale; MID = minimal important difference; PROMIS = Patient-Reported Outcomes Measurement Information System.

Statistical Analysis

Sample Size and Power Calculation

In study KD025 to 213, the sample size was based on the primary efficacy outcome (to demonstrate an ORR greater than 30%, i.e., the lower bound of the ORR CI was greater than 30%) and the following considerations.[15] Based on the sponsor's consultation with key opinion leaders, a 30% ORR was considered clinically meaningful in the population of interest.[48] The interim analysis had a 0.0025 1-sided alpha spending function. Based on data from study KD025 to 208, a true ORR of 55% was assumed in patients with cGVHD after 1 to 3 prior lines of systemic therapy. In study KD025 to 208, the ORR was 65% in cohort 1 (200 mg once daily) as of September 13, 2018. Based on data from the same study, a 10% dropout rate was assumed. Dropouts were defined as discontinuations from belumosudil treatment before any response assessment due to reasons other than an AE related to belumosudil or cGVHD progression. Protocol Amendment 1 planned for 126 patients to be enrolled with 63 patients per treatment group based on the assumption of a 55% true ORR, 10% dropout rate, 90% power, and a 2-sided alpha of 0.045 to demonstrate an ORR larger than 30% in a single-arm study. According to Protocol Amendment 2, the planned sample size increased from 126 to 166 patients with the additional 40 patients (20 of whom would be adolescents) to be enrolled in a site-specific companion study.

In study KD025 to 208, a sample size of 16 patients per cohort was planned corresponding to more than 90% probability of at least 1 patient experiencing an AE with an underlying rate of at least 14% and more than 80% probability of at least 1 patient experiencing an AE that has an underlying rate of at least 10%.[17] Assuming a best ORR of 25%, which the sponsor determined to be clinically meaningful, the study was expected to have approximately 90% probability to show a response in at least 2 patients per cohort.[49] The study was not powered to show significant differences between cohorts with respect to efficacy or safety analyses.[49]

Statistical Testing

In study KD025 to 213, statistical analyses included the calculation of point estimates and 95% CIs by the Clopper-Pearson (exact) method for the primary outcome. The first analysis (interim) was conducted approximately 2 months after 126 patients were enrolled into the mITT population, which used a nominal 1-sided alpha of 0.0025, though there was no early study termination for efficacy and the data are not presented in this CADTH report. The second analysis (primary) was conducted approximately 6 months after 126 patients were enrolled into the mITT population, with a 1-sided alpha of 0.0225 (or 0.025 if the ORRs of both treatment groups were significant at interim). The third analysis (follow-up) was conducted approximately 12 months after 126 patients had been enrolled into the mITT population.

In study KD025 to 208, the point estimate for ORR was presented with 95% CIs calculated by the Clopper-Pearson (exact) method. No formal hypothesis testing was undertaken. The study was not powered to show significant differences between cohorts for efficacy or safety analyses and there was no early stopping for efficacy.[49] The follow-up analysis was conducted 1 year after the last patient was enrolled.

Multiple Testing Procedure

Only the primary outcome of study KD025 to 213 was adjusted for multiple comparisons using the Hochberg procedure. A 1-sided alpha of 0.0025 (for each treatment arm) was reserved for the interim analysis. The 2-sided 99.5% CIs were calculated for both treatment groups to assess efficacy. The primary analysis used a 1-sided alpha of 0.0225 (for each treatment arm) and, likewise, the 2-sided 95.5% CIs were calculated. For the remaining end points, only descriptive statistics were provided.

Data Imputation Methods

Missing data were not imputed for either study. Instead, they were reported as missing and, for categorical data, were not used to calculate percentages.

Subgroup Analyses

The following prespecified subgroup analyses were performed for ORR and DOR end points in study KD025 to 213: prior ibrutinib use (yes versus no), severe cGVHD at screening (yes versus no), number of organs involved at baseline (less than 4 versus 4 or more), number of prior lines of therapy (4 or fewer versus more than 4), duration of cGVHD before enrolment (by 50th percentile), baseline CS dose level (by 50th percentile), lung involvement at baseline (yes versus no), concomitant medication proton pump inhibitor use on cycle 1 day 1 (yes versus no), sex (female versus male), age (younger than 65 years old versus 65 years and older), and race (white versus not white).

Similarly, the following prespecified subgroup analyses were performed in study KD025 to 208: number of prior lines of therapy (1 versus 2 or more), number of organs involved at baseline (less than 4 versus 4 or more), baseline severity (severe versus not severe, where baseline activity assessment was used as a surrogate), concomitant medication proton pump inhibitor use on cycle 1 day 1 (yes versus no), refractory to most recent line of therapy before enrolment (yes versus no).

All subgroups were exploratory with no adjustment for multiplicity.

Sensitivity Analyses

No sensitivity analyses were conducted for either study.

Secondary Outcomes of the Studies

In study KD025 to 213, all secondary and exploratory outcomes were reported descriptively (KM estimates, landmark analyses, and changes from baseline) without multiplicity adjustment. In study KD025 to 208, outcomes were reported in a similar fashion, and none were adjusted for multiplicity due to the exploratory nature of the study. Landmark analyses for DOR were performed for the number and percentage of patients with a response sustained for at least 12, 20, 24, 32, 36, and 48 weeks and landmark analyses for FFS and OS were conducted at 6, 12, 18, and 24 months.

Analysis Populations

The analysis populations of the included studies are summarized in Table 9.

Table 9: Analysis Populations of Study KD025 to 213 and Study KD025 to 208

Study	Population	Definition	Application
Study KD025 to 213 and study KD025 to 208	mITT population	All randomized patients who received at least 1 dose of the study drug.	Primary population for efficacy analyses and demographic and baseline characteristics.
	Responder population	Patients in the mITT population who experienced a PR or CR at any postbaseline assessment.	Population for DOR, TTR, and some subgroup analyses.
	Nonresponder population	Any patient in the mITT population whose condition did not respond.	Some subgroup analyses.
	Safety population	All randomized patients who received at least 1 dose of the study drug (equivalent to the mITT population).	Safety analyses.

CR = complete response; DOR = duration of response; mITT = modified intention to treat; PR = partial response; TRR = time to response.

Sources: Clinical Study Report for study KD025 to 213[15] and study KD025 to 208[7] and the sponsor's summary of clinical evidence.[11] Details included in the table are from the sponsor's summary of clinical evidence.

Results

Patient Disposition

The patient disposition of the included studies is summarized in Table 10. In study KD025 to 213 (data cut-off [redacted]), of the [redacted] individuals screened, [redacted] ([redacted]%) were randomized, with ineligibility being the most common reason for screening failure. Subsequently, [redacted] patients were randomized to receive belumosudil 200 mg once daily, and all but 1 patient was treated with the study drug. In study KD025 to 208 (data cut-off [redacted]), [redacted] individuals were screened, of whom [redacted] ([redacted]%) were randomized, with ineligibility being the most common reason for screening failure. Of the randomized population, 17 patients received belumosudil 200 mg once daily. At the data cut-off dates, the median follow-ups were [redacted] months (range, [redacted] to [redacted]) for study KD025 to 213 and [redacted] months (range, [redacted] to [redacted]) for study KD025 to 208.

The proportion of responders was higher in study KD025 to 213 ([redacted]%) compared with study KD025 to 208 ([redacted]%), though the apparent difference may be due to the small number of patients in the latter study. All patients had discontinued from both the treatment and the studies as of the latest data cut-off dates. Physician or investigator decision ([redacted]%) was the most common reason for treatment discontinuation in study KD025 to 213, while disease progression ([redacted]%) was the most common reason in study KD025 to 208 (it was not clear if this was a progression of the underlying malignancy or cGVHD). Study termination by the sponsor ([redacted]%) and death ([redacted]%) were the most common reasons for study discontinuation in study KD025 to 213 and study KD025 to 208, respectively.

Table 10: Summary of Patient Disposition From Study KD025 to 213 and Study KD025 to 208 (mITT Population)

Patient disposition	KD025 to 213 Belumosudil 200 mg q.d.	KD025 to 208 Belumosudil 200 mg q.d.
Screened, N[a]	[redacted]	[redacted]
Randomized to belumosudil 200 mg q.d., n	[redacted]	[redacted]
Randomized but not treated, n	[redacted]	[redacted]
mITT, N (%)[b]	[redacted]	[redacted]
Responders	[redacted]	[redacted]
Nonresponders	[redacted]	[redacted]
Treatment ongoing, n (%)	[redacted]	[redacted]
Discontinued from treatment, n (%)	[redacted]	[redacted]
Reason for treatment discontinuation, n (%)		
Physician or investigator decision	[redacted]	[redacted]
Progression of cGVHD	[redacted]	[redacted]
Adverse events	[redacted]	[redacted]
Withdrawal by patient	[redacted]	[redacted]
Termination of study by sponsor	[redacted]	[redacted]
Progression of underlying disease	[redacted]	[redacted]
Death	[redacted]	[redacted]
Failure to meet continuation criteria	[redacted]	[redacted]
Noncompliance with study drug	[redacted]	[redacted]
Noncompliance with protocol	[redacted]	[redacted]
Disease progression[c]	[redacted]	[redacted]
Other	[redacted]	[redacted]
Study ongoing, n (%)	[redacted]	[redacted]

Patient disposition	KD025 to 213 Belumosudil 200 mg q.d.	KD025 to 208 Belumosudil 200 mg q.d.
Discontinued from study, n (%)	[redacted]	[redacted]
Reason for study discontinuation, n (%)		
Termination of study by sponsor	[redacted]	[redacted]
Death	[redacted]	[redacted]
Withdrawal by patient	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]
Termination of site by sponsor	[redacted]	[redacted]
Completion of follow-up	[redacted]	[redacted]
Other	[redacted]	[redacted]
Safety, N (%)	[redacted]	[redacted]

cGVHD = chronic graft-vs.-host disease; mITT = modified intention to treat; NR = not reported; q.d. = once daily.

[a]The number of patients screened in the overall study, which included treatment groups that received doses outside of the Health Canada indication.

[b]As per Protocol Amendment 2 ([redacted]) in KD025 to 213, the expected number of patients to be enrolled was increased from 126 to [redacted]. The additional [redacted] patients were to include [redacted] adolescents and [redacted] adults to be enrolled in a site-specific companion study and the study enrolment period was revised from 12 months to 24 months. As a result, in the updated 3-year long-term analysis, a total of [redacted] patients were randomized to the belumosudil 200 mg q.d. group, of which [redacted] patient was randomized and not treated, resulting in a total of [redacted] patients in the mITT population for the updated analysis.

[c]Study KD025 to 208 did not differentiate between progression of cGVHD and progression of underlying malignancy.

Note: Data are based on a data cut-off of [redacted], for study KD025 to 213 and [redacted], for study KD025 to 208.

Sources: Clinical Study Report addenda for study KD025 to 213[16] and study KD025 to 208[18] and sponsor's summary of clinical evidence.[11] Details included in the table are from the sponsor's summary of clinical evidence.

Baseline Characteristics

The baseline characteristics of the patients in the included studies are summarized in Table 11 and are limited to those that are most relevant to this review or were felt to affect the outcomes or interpretation of the study results.

In study KD025 to 213, the median age of patients was 53 years (range, 21 to 77 years) and there were more males ([redacted]%) than females ([redacted]%). In study KD025 to 208, the median age of patients was 50 years (range, 20 to 63 years) and there were also more males (77%) than females (23%). In both studies, most patients had a Karnofsky Performance Score of 80 or higher, the median time from cGVHD diagnosis to study enrolment was approximately 25 months, and more than 70% of patients had severe cGVHD, according to the 2014 NIH consensus criteria. Acute myelogenous leukemia, myelodysplastic syndrome, and acute lymphocytic leukemia were the most common indications for transplant in study KD025 to 213, while acute myelogenous leukemia, acute lymphocytic leukemia, and non-Hodgkin lymphoma were the most common indications in study KD025 to 208. The median number of organs involved was 4 (range, 0 to 7) with more than half of patients having at least 4 organs involved in both studies. In total, 100% of patients in study KD025 to 213 and 88% of patients in study KD025 to 208 had received 2 or more prior lines of therapy. CSs were the most common prior cGVHD treatment among all patients (more than 99%), with the next most common being tacrolimus in study KD025 to 213 ([redacted]%) and sirolimus in study KD025 to 208 ([redacted]%).

Table 11: Summary of Baseline Characteristics From Study KD025 to 213 and Study KD025 to 208 (mITT Population)

Characteristic	KD025 to 213 Belumosudil 200 mg q.d. (N = [redacted])	KD025 to 208 Belumosudil 200 mg q.d. (N = [redacted])
Age (years), median (range)	53 (21 to 77)	50 (20 to 63)
Sex, n (%)		
Female	[redacted]	4 (23)
Male	[redacted]	13 (77)
Race, n (%)		
White	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]
Asian	[redacted]	[redacted]
Unreported or unknown	[redacted]	[redacted]
Other	[redacted]	[redacted]
Karnofsky Performance Status, n (%)		
60	[redacted]	1 (6)
70	[redacted]	3 (18)
80	[redacted]	7 (41)
90	[redacted]	6 (35)
100	[redacted]	0 (0)
Time from cGVHD diagnosis to enrolment, median (range), months	[redacted]	26 (0 to 131)
NIH cGVHD severity, n (%)[a]		
Severe	[redacted]	12 (71)
Moderate	[redacted]	5 (29)
Mild	[redacted]	0 (0)
Indication for transplant, n (%)		
Acute myelogenous leukemia	[redacted]	3 (18)
Myelodysplastic syndrome	[redacted]	2 (12)
Acute lymphocytic leukemia	[redacted]	3 (18)
Chronic myelogenous leukemia	[redacted]	[redacted]
Non-Hodgkin lymphoma	[redacted]	3 (18)
Myelofibrosis	[redacted]	[redacted]

Characteristic	KD025 to 213 Belumosudil 200 mg q.d. (N =)	KD025 to 208 Belumosudil 200 mg q.d. (N =)
Chronic lymphocytic leukemia		
Multiple myeloma		
Hodgkin lymphoma		
Other		
Conditioning intensity, n (%)		
Myeloablative		9 (53)
Nonmyeloablative		7 (41)
Unknown		1 (6)
Stem cell source, n (%)		
Peripheral blood		15 (88)
Bone marrow		0 (0)
Cord blood		1 (6)
Unknown		1 (6)
HLA matching of donor and recipient, n (%)		
Matched		14 (82)
Partially matched		3 (18)
Missing		0 (0)
Relatedness of patient and donor		
Related		
Unrelated		
Organ involvement		
Median number of organs involved, n (range)		
≥ 4 organs involved, n (%)		
Skin, n (%)		13 (77)
Joints and/or fascia, n (%)		11 (65)
Eyes, n (%)		14 (82)
Mouth, n (%)		13 (77)
Lungs, n (%)		
Esophagus, n (%)		2 (12)
Upper gastrointestinal tract, n (%)		2 (12)
Liver, n (%)		0 (0)

Characteristic	KD025 to 213 Belumosudil 200 mg q.d. (N =)	KD025 to 208 Belumosudil 200 mg q.d. (N =)
Lower gastrointestinal tract, n (%)		1 (6)
Prior lines of therapy		
Median, n		3
Number of therapies, n (%)		
1		
2		
3		
4		
5		
6 or more		
Refractory to a prior line of therapy, n (%)		
Prior systemic therapy for cGVHD, n (%)		
Corticosteroids (prednisone)		
Tacrolimus		
Extracorporeal photopheresis		
Sirolimus		
Ibrutinib		
Ruxolitinib		
Mycophenolate mofetil		
Rituximab		
Cyclosporine		
Methotrexate		
Methylprednisolone		

cGVHD = chronic graft-vs.-host disease; HLA = human lymphocyte antigen; mITT = modified intention to treat; NIH = National Institutes of Health; q.d. = once daily.

Note: Data are based on a data cut-off of , for study KD025 to 213 and , for study KD025 to 208.

[a]Disease severity was determined using NIH Global Severity of cGVHD scoring.

Sources: Clinical Study Report for study KD025 to 213[15] and study KD025 to 208[17] and sponsor's summary of clinical evidence.[11] Details included in the table are from the sponsor's summary of clinical evidence.

Exposure to Study Treatments

Exposure to study treatments and concomitant medication use are summarized in Table 12. As of the latest data cut-off dates, the median treatment durations with belumosudil 200 mg once daily were months (range, to months) and months (range, to months) in study KD025 to 213 and study KD025 to 208, respectively. Mean and median adherence were greater than % and 99%, respectively, in the 2 studies.

All patients received some form of concomitant medication during the studies, with prednisone being the most common ([redacted]%) followed by systemic tacrolimus ([redacted]%).

Table 12: Summary of Patient Exposure From Study KD025 to 213 and Study KD025 to 208 (mITT Population)

Exposure	KD025 to 213 Belumosudil 200 mg q.d. (N = [redacted])	KD025 to 208 Belumosudil 200 mg q.d. (N = [redacted])
Cumulative duration (patient-years)	[redacted]	[redacted]
Treatment duration, months		
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
Treatment duration categories, n (%)		
0 to < 6 months	[redacted]	[redacted]
6 to < 12 months	[redacted]	[redacted]
12 to < 18 months	[redacted]	[redacted]
18 to < 24 months	[redacted]	[redacted]
≥ 24 months	[redacted]	[redacted]
Adherence (%)[a]		
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
Patients with any cGVHD concomitant medication, n (%)[b]	[redacted]	[redacted]
Prednisone	[redacted]	17 (100.0)
Tacrolimus (systemic)	[redacted]	[redacted]
Sirolimus (systemic)	[redacted]	[redacted]
ECP	[redacted]	[redacted]
Dexamethasone	[redacted]	[redacted]
Cyclosporine	[redacted]	[redacted]
Triamcinolone	[redacted]	[redacted]
Mycophenolate mofetil	[redacted]	[redacted]

cGVHD = chronic graft-vs.-host disease; ECP = extracorporeal photopheresis; mITT = modified intention to treat; NR = not reported; q.d. = once daily; SD = standard deviation.

Note: Data are based on a data cut-off of [redacted], for study KD025 to 213 [redacted], for study KD025 to 208.

[a]Relative dose intensity (%) calculated as actual dose intensity (mg/day) divided by planned dose intensity (mg/day) multiplied by 100.

[b]More than 15% of patients in either study.

Sources: Clinical Study Report addenda for study KD025 to 213[16] and study KD025 to 208[18] and sponsor's summary of clinical evidence.[11] Details included in the table are from the sponsor's summary of clinical evidence.

Efficacy

Summarized within the main report are the outcomes considered most relevant to inform CADTH's expert committee deliberations. Appendix 1 contains additional efficacy outcomes considered to be useful in guiding the clinical management of individual patients with cGVHD but that were not critical to informing deliberations. These included response by organ system and GSR assessment, TTNT, and prednisone-equivalent dose of CSs.

ORR by Investigator Assessment

ORR results are summarized in Table 13. ORR interim analysis results for study KD025 to 213 had a P value of less than 0.001 using a 1-sided alpha of 0.0025 (data not included in this CADTH report).

In study KD025 to 213, the ORR was 72.7% (95% CI, 60.4% to 83.0%; P < 0.0001) as of the primary analysis cut-off date (February 19, 2020), 6 months after enrolment of 126 patients into the mITT population. Overall, 3 patients (4.5%) had a CR, 45 patients (68.2%) had a PR, 15 (22.7%) had an LR, and 3 (4.5%) had no response assessment. In study KD025 to 208, the ORR was 64.7% (95% CI, 38.3% to 85.8%) as of the primary reporting data cut-off date (February 19, 2020), and all responders had a PR. The 6 remaining patients (35.3%) had an LR.

As of the latest cut-off date for study KD025 to 213 ([redacted]), the ORR was [redacted] (95% CI, [redacted]). Overall, [redacted] patients ([redacted]%) had a CR, [redacted] patients ([redacted]%) had a PR, [redacted] patients ([redacted]%) had an LR, and patients [redacted] ([redacted]%) had no response assessment. As of the latest cut-off date for study KD025 to 208 ([redacted]), the ORR was [redacted]% (95% CI, [redacted]). Overall, [redacted] patients ([redacted]%) had a PR and [redacted] patients ([redacted]%) had an LR. The findings for ORR appeared to be generally similar across the subgroups.

Table 13: Summary of Overall Response Rate From Study KD025 to 213 and Study KD025 to 208 (mITT Population)

Outcome	KD025 to 213 Belumosudil 200 mg q.d.	KD025 to 208 Belumosudil 200 mg q.d.
ORR		
Primary analysis[a]	**N = 66**	**N = 17**
ORR (CR + PR), n (%)	48 (72.7)	11 (64.7)
CR	3 (4.5)	0 (0)
PR	45 (68.2)	11 (64.7)
Exact method (95% CI) of ORR[b]	60.4 to 83.0	38.3 to 85.8
One-sided exact P value (null hypothesis: ORR ≤ 30%)[c]	< 0.0001	NA
Lack of response, n (%)		
Unchanged	14 (21.2)	2 (11.8)
Mixed	0 (0)	3 (17.6)
Progression	1 (1.5)	1 (5.9)

Outcome	KD025 to 213 Belumosudil 200 mg q.d.	KD025 to 208 Belumosudil 200 mg q.d.
No response assessment, n (%)	3 (4.5)	0 (0)
Latest data cut-off date[d]	[redacted]	[redacted]
ORR (CR + PR), n (%)	[redacted]	[redacted]
CR	[redacted]	[redacted]
PR	[redacted]	[redacted]
Exact method (95% CI) of ORR[b]	[redacted]	[redacted]
Lack of response, n (%)		
Unchanged	[redacted]	[redacted]
Mixed	[redacted]	[redacted]
Progression	[redacted]	[redacted]
No response assessment, n (%)	[redacted]	[redacted]

CI = confidence interval; CR = complete response; mITT = modified intention to treat; NA = not applicable; ORR = overall response rate; PR = partial response; q.d. = once daily.

[a]Based on a data cut-off of February 19, 2020, for both studies. For study KD205 to 213, the primary analysis cut-off date corresponds with 6 months after last patient, first visit.

[b]The 2-sided exact CI was calculated using the Clopper-Pearson method.

[c]Hochberg multiplicity–adjusted P value.

[d]Results are based on a data cut-off of [redacted], for study KD025 to 213 and [redacted] for study KD025 to 208. As per Protocol Amendment 2 in KD025 to 213, the expected number of enrolled patients was increased, thus accounting for the larger number of patients at the later data cut-off.

Sources: Clinical Study Report for study KD025 to 213[15] and study KD025 to 208,[17] Clinical Study Report addenda for study KD025 to 213[16] and study KD025 to 208[18] sponsor's summary of clinical evidence.[11] Details included in the table are from the sponsor's summary of clinical evidence.

DOR

The clinical experts consulted by CADTH indicated that the tertiary and secondary DOR definitions were the most relevant to clinical practice and their results are summarized in Table 14.

Of patients who responded to treatment (n = [redacted]), the KM estimate for the median tertiary DOR was [redacted] weeks (95% CI lower bound = [redacted] weeks; upper bound not reached) in study KD025 to 213 and was not reached (95% CI lower bound = 8.1 weeks; upper bound not reached) in study KD025 to 208. At 24 weeks, the KM estimate for tertiary DOR event-free probability was [redacted]% (95% CI, [redacted]%) in study KD025 to 213 and [redacted]% (95% CI, [redacted]%) in study KD025 to 208.

The KM estimate for median secondary DOR was [redacted] weeks (95% CI, [redacted] to [redacted]) in study KD025 to 213 and [redacted] weeks (95% CI lower bound = [redacted]; upper bound not reached) in study KD025 to 208. At 24 weeks, the KM estimate for the secondary DOR event-free probability was [redacted]% (95% CI, [redacted]%) in study KD025 to 213 and [redacted]% weeks (95% CI, [redacted]%) in study KD025 to 208.

TTR

TTR results are summarized in Table 15.

Based on the responder population, the median TTR was [redacted] weeks (range, [redacted] to [redacted] weeks) in study KD025 to 213 and [redacted] weeks (range, [redacted] to [redacted] weeks) in study KD025 to 208. At weeks 8 and 12, the cumulative response rates were [redacted]% and [redacted]%, respectively, in study KD025 to 213 and [redacted]% and [redacted]%, respectively, in study KD025 to 208.

Table 14: Summary of DOR From Study KD025 to 213 and Study KD025 to 208 (Responder Population)

Outcome	KD025 to 213 Belumosudil 200 mg q.d. (N = [redacted])	KD025 to 208 Belumosudil 200 mg q.d. (N = [redacted])
Tertiary DOR		
DOR, n (%)		
Censored	[redacted]	[redacted]
Ongoing	[redacted]	[redacted]
Study discontinued	[redacted]	[redacted]
Event: New treatment	[redacted]	[redacted]
Event: Death	[redacted]	[redacted]
KM estimate of median DOR (95% CI),[a] weeks	[redacted]	[redacted]
KM estimate of DOR event-free probability (95% CI)[a]		
12 weeks	[redacted]	[redacted]
20 weeks	[redacted]	[redacted]
24 weeks	[redacted]	[redacted]
32 weeks	[redacted]	[redacted]
36 weeks	[redacted]	[redacted]
48 weeks	[redacted]	[redacted]
Secondary DOR		
DOR, n (%)		
Censored	[redacted]	[redacted]
Ongoing	[redacted]	[redacted]
Treatment discontinued	[redacted]	[redacted]
Event: Documented lack of response	[redacted]	[redacted]
Event: New treatment	[redacted]	[redacted]
Event: Death	[redacted]	[redacted]
KM estimate of median DOR (95% CI),[a] weeks	[redacted]	[redacted]
KM estimate of DOR event-free probability (95% CI)[a]		

Outcome	KD025 to 213 Belumosudil 200 mg q.d. (N =)	KD025 to 208 Belumosudil 200 mg q.d. (N =)
12 weeks		
20 weeks		
24 weeks		
32 weeks		
36 weeks		
48 weeks		

CI = confidence interval; DOR = duration of response; KM = Kaplan-Meier; q.d. = once daily.

[a]CIs were calculated using the KM method.

Note: Results are based on a data cut-off of , for study KD025 to 213 and , for study KD025 to 208.

Sources: Clinical Study Report addenda for study KD025 to 213[16] and study KD025 to 208[18] and the sponsor's summary of clinical evidence.[11] Details included in the table are from the sponsor's summary of clinical evidence.

Table 15: Summary of TTR From Study KD025 to 213 and Study KD025 to 208 (Responder Population)

Outcome	KD025 to 213 Belumosudil 200 mg q.d. (N =)	KD025 to 208 Belumosudil 200 mg q.d. (N =)
TTR		
Median (range), weeks		
Cumulative response rate, n (%)		
4 weeks		
6 weeks		
8 weeks		
10 weeks		
12 weeks		
14 weeks		
16 weeks		
24 weeks		
32 weeks		
40 weeks		
≥ 48 weeks		

q.d. = once daily; TTR = time to response.

Note: Results are based on a data cut-off of for study KD025 to 213 and for study KD025 to 208.

Sources: Clinical Study Report addenda for study KD025 to 213[16] and study KD025 to 208[18] and sponsor's summary of clinical evidence.[11] Details included in the table are from the sponsor's summary of clinical evidence.

FFS

FFS results are summarized in Table 16.

The median KM estimate for FFS was [redacted] weeks (95% CI, [redacted] to [redacted]) in study KD025 to 213 and [redacted] weeks (95% CI lower bound = [redacted] weeks; upper bound not reached) in study KD025 to 208. According to the KM estimate, [redacted]% of patients (95% CI, [redacted]%) maintained FFS at 12 months in study KD025 to 213 and [redacted]% (95% CI, [redacted]%) at 12 months in study KD025 to 208.

Table 16: Summary of Failure-Free Survival From Study KD025 to 213 and Study KD025 to 208 (mITT Population)

Outcome	KD025 to 213 Belumosudil 200 mg q.d. (N = [redacted])	KD025 to 208 Belumosudil 200 mg q.d. (N = [redacted])
FFS, n (%)		
Censored	[redacted]	[redacted]
Study ongoing	[redacted]	[redacted]
Study discontinued	[redacted]	[redacted]
Failure event: New cGVHD systemic therapy	[redacted]	[redacted]
Failure event: Nonrelapse mortality	[redacted]	[redacted]
Failure event: Recurrent malignancy	[redacted]	[redacted]
KM estimate, months		
25th percentile	[redacted]	[redacted]
Median (95% CI)	[redacted]	[redacted]
75th percentile	[redacted]	[redacted]
KM estimate of FFS probability (95% CI)		
6 months	[redacted]	[redacted]
12 months	[redacted]	[redacted]
18 months	[redacted]	[redacted]
24 months	[redacted]	[redacted]

cGVHD = chronic graft-vs.-host disease; CI = confidence interval; FFS = failure-free survival; KM = Kaplan-Meier; mITT = modified intention to treat; q.d. = once daily.

Note: Results are based on a data cut-off of [redacted], for study KD025 to 213 and [redacted], for study KD025 to 208.

Sources: Clinical Study Report addenda for study KD025 to 213[16] and study KD025 to 208[18] and sponsor's summary of clinical evidence.[11] Details included in the table are from the sponsor's summary of clinical evidence.

Overall Survival

OS results are summarized in Table 17.

The median KM estimate for OS was not reached in either study KD025 to 213 or study KD025 to 208. According to the KM estimate, the OS probability was [redacted]% (95% CI, [redacted]%) at 12 months in study KD025 to 213 and [redacted]% (95% CI, [redacted]%) at 12 months in study KD025 to 208.

Table 17: Summary of Overall Survival From Study KD025 to 213 and Study KD025 to 208 (mITT Population)

Outcome	KD025 to 213 Belumosudil 200 mg q.d. (N = [redacted])	KD025 to 208 Belumosudil 200 mg q.d. (N = [redacted])
OS, n (%)		
Censored	[redacted]	[redacted]
Alive	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]
Failure event: death	[redacted]	[redacted]
KM estimate, months		
25th percentile	Not reached	[redacted]
Median (95% CI)	Not reached	[redacted]
75th percentile	Not reached	Not reached
KM estimate of OS probability (95% CI)		
6 months	[redacted]	[redacted]
12 months	[redacted]	[redacted]
18 months	[redacted]	[redacted]
24 months	[redacted]	[redacted]

cGVHD = chronic graft-vs.-host disease; CI = confidence interval; KM = Kaplan-Meier; mITT = modified intention to treat; NA = not applicable; OS = overall survival; q.d. = once daily.

Note: Results are based on a data cut-off of [redacted], for study KD025 to 213 and [redacted], for study KD025 to 208.

Sources: Clinical Study Report addenda for study KD025 to 213[16] and study KD025 to 208[18] and sponsor's summary of clinical evidence.[11] Details included in the table are from the sponsor's summary of clinical evidence.

LSS Score

LSS scores results are summarized in Table 18.

In study KD025 to 213, [redacted] patients ([redacted]%) had a 7-point or greater reduction in LSS score from baseline. In study KD025 to 208, 9 patients (52.9%) had a 7-point or greater reduction in LSS score from baseline.

Table 18: Summary of Lee Symptom Scale Score From Study KD025 to 213 and Study KD025 to 208 (mITT Population)

Outcome	KD025 to 213 Belumosudil 200 mg q.d. (N =)	KD025 to 208 Belumosudil 200 mg q.d. (N =)
LLS score		
Patients with baseline and ≥ 1 postbaseline value		
Patients with a ≥ 7-point reduction from baseline		9 (52.9)
Patients with a ≥ 7-point reduction from baseline on 2 consecutive assessments		

LSS = Lee Symptom Scale; mITT = modified intention to treat; q.d. = once daily.

Note: Results are based on a data cut-off of , for study KD025 to 213 and , for study KD025 to 208.

Sources: Clinical Study Report addenda for study KD025 to 213[16] and study KD025 to 208[18] and sponsor's summary of clinical evidence.[11] Details included in the table are from the sponsor's summary of clinical evidence.

PROMIS Global Health Summary Scores for Physical and Mental Functioning

PROMIS results are summarized in Table 19.

In study KD025 to 213, patients (%) had a 4.7-point or greater change from baseline for physical health and patients (%) had a 4.7-point or greater change from baseline for mental health. This outcome was not assessed in study KD025 to 208.

Table 19: Summary of PROMIS Global Health Summary Scores for Physical and Mental Functioning From Study KD025 to 213 (mITT Population)

Outcome	KD025 to 213 Belumosudil 200 mg q.d. (N =)
PROMIS Global Health summary scores for physical and mental functioning, n (%)	
PROMIS physical health raw score, n (%)	
Patients with a ≥ 4.7-point change from baseline	
PROMIS mental health raw score, n (%)	
Patients with a ≥ 4.7-point change from baseline	

mITT = modified intention to treat; PROMIS = Patient-Reported Outcomes Measurement Information System; q.d. = once daily.

Note: Results are based on a data cut-off of for study KD025 to 213.

Source: Study KD025 to 213 Clinical Study Report addendum[16] and sponsor's summary of clinical evidence.[11] Details included in the table are from the sponsor's summary of clinical evidence.

Change in CS Dose

Change in CS dose results are summarized in Table 24 of Appendix 1.

In study KD025 to 213, [redacted] patients ([redacted]%) reduced their CS dose and [redacted] ([redacted]%) discontinued CS usage while receiving belumosudil. In study KD025 to 208, [redacted] patients ([redacted]%) reduced their CS dose and 4 (23.5%) discontinued CS usage while receiving belumosudil.

Harms

Harms results as of the latest data cut-off date are summarized in Table 20.

Adverse Events

Most patients experienced at least 1 TEAE in study KD025 to 213 ([redacted]%) and study KD025 to 208 (100%). The most common TEAEs were diarrhea ([redacted]%) and fatigue ([redacted]%) in study KD025 to 213 and upper respiratory tract infection ([redacted]%), diarrhea, fatigue, nausea, and increased alanine aminotransferase ([redacted]% each) in study KD025 to 208.

Serious Adverse Events

In study KD025 to 213, [redacted]% of patients experienced an SAE while 29.4% of patients in study KD025 to 208 experienced an SAE. Pneumonia ([redacted]%) was the most frequently reported SAE in study KD025 to 213. No other SAEs occurred in more than 3 patients in either study.

Withdrawals Due to Adverse Events

In study KD025 to 213, [redacted]% of patients stopped belumosudil 200 mg due to an AE, while [redacted]% of patients in study KD025 to 208 stopped belumosudil due to an AE.

Mortality

Overall, [redacted] patients died in study KD025 to 213 (due to hemothorax, aspiration and respiratory failure, septic shock and multiple organ dysfunction, and recurrent acute myeloid leukemia) and 0 patients died in study KD025 to 208.

Notable Harms

Based on the Health Canada product monograph warnings and precautions, hematologic and immune AEs were identified as being important to the CADTH review. Hematologic and immune AEs were coded as blood and lymphatic system disorders and infections and infestations, respectively.

Under the heading of blood and lymphatic system disorders, [redacted]% of patients in study KD025 to 213 and [redacted]% of patients in study KD025 to 208 experienced an AE. Anemia was the most common AE reported by [redacted]% and [redacted]% of patients in study KD025 to 213 and study KD025 to 208, respectively.

For infections and infestations, [redacted]% or patients in study KD025 to 213 and [redacted]% of patients in study KD025 to 208 experienced an AE. Upper respiratory tract infection was the most common AE reported by [redacted]% and [redacted]% of patients in study KD025 to 213 and study KD025 to 208, respectively.

Table 20: Summary of Harms Results From Study KD025 to 213 and Study KD025 to 208 (Safety Population)

AEs	KD025 to 213 Belumosudil 200 mg q.d. (N = [redacted])	KD025 to 208 Belumosudil 200 mg q.d. (N = [redacted])
Most common AEs, n (%)[a]		
Patients with ≥ 1 TEAE	[redacted]	17 (100.0)
Diarrhea	[redacted]	6 (35.3)
Fatigue	[redacted]	6 (35.3)
Dyspnea	[redacted]	[redacted]
Nausea	[redacted]	6 (35.3)
Vomiting	[redacted]	[redacted]
Headache	[redacted]	4 (23.5)
Peripheral edema	[redacted]	3 (17.6)
Cough	[redacted]	1 (5.9)
Arthralgia	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	9 (52.9)
Hypertension	[redacted]	5 (29.4)
Anemia	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]
SAEs, n (%)[b]		
Patients with ≥ 1 SAE	[redacted]	5 (29.4)
Pneumonia	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]
Patients who stopped treatment due to AEs, n (%)[b]		
Patients who stopped treatment	[redacted]	[redacted]
Deaths, n (%)		
Patients who died	[redacted]	0 (0)
Hemothorax	1 (1.5)	0 (0)
Aspiration and respiratory failure	1 (1.5)	0 (0)
Septic shock and multiple organ dysfunction	1 (1.5)	0 (0)
Acute myeloid leukemia, recurrent	1 (1.5)	0 (0)
[redacted]	[redacted]	0 (0)

AEs	KD025 to 213 Belumosudil 200 mg q.d. (N =)	KD025 to 208 Belumosudil 200 mg q.d. (N =)
AEs of special interest, n (%)[c]		
Blood and lymphatic system disorders		
Anemia		
Infections and infestations		
Upper respiratory tract infection		9 (52.9)

AE = adverse event; NR = not reported; q.d. = once daily; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

[a]Most common TEAEs by preferred term occurring in at least 25% of patients in either treatment group.

[b]Most common SAEs and withdrawals due to AEs by preferred term occurring in at least 3 patients in either treatment group.

[c]AEs of special interest to the CADTH review included hematologic and immune AEs (coded as blood and lymphatic system disorders and infections and infestations, respectively). Data reported for specific events that occurred in at least 15% of patients in either treatment group.

Note: Results are based on a data cut-off of , for study KD025 to 213 and , for study KD025 to 208.

Sources: Clinical Study Report addenda for study KD025 to 213[16] and study KD025 to 208[18] and sponsor's summary of clinical evidence.[11] Details included in the table are from the sponsor's summary of clinical evidence.

Critical Appraisal

Internal Validity

Although there were other treatment groups in study KD025 to 213 and study KD025 to 208, they were for doses that do not have a Health Canada indication for the treatment of patients with cGVHD. Therefore, the limitations that apply to single-arm studies also apply to the interpretation of the results for the belumosudil 200 mg once-daily groups.

The main limitations with both studies are the lack of valid control (or comparator) groups, resulting in a high risk of bias due to confounding and uncertainty in causal conclusions between the study drug and treatment benefits or harms. Without a valid comparison group to control for known and unknown effect modifiers, it is not possible to distinguish the observed treatment effect (benefits or harms) from a placebo effect, natural history of the disease, impact from concomitant therapies, patient characteristics, or other unaccounted for variables.[56] According to Health Canada, a study without a proper comparator may be interpreted as though there would be no response in the absence of the study drug, which may not be true, given the various other treatment options available for cGVHD, or the dose of a prior medication could be optimized to improve response.[20]

Another limitation common to both studies was the knowledge of treatment assignment by both patients and investigators. As a result, there is an increased risk of detection bias, particularly for semi-objective (e.g., ORR) and subjective measures (patient-reported outcomes and harms outcomes), and of potentially overestimating the treatment effect of belumosudil if patients and investigators believed the study drug was likely to provide a benefit. In study KD025 to 213, patients must have been receiving a stable GC dose or cGVHD regimen for at least 2 weeks before screening and could not be receiving concurrent ibrutinib during the study. However, it is possible that cGVHD regimens require more than 2 weeks to reach full effect and the 2-week minimum may not have been enough time to discern treatment benefits or harms

between belumosudil and a concomitant cGVHD treatment. Again, there is the risk of overestimating the ORR and/or harms attributed to belumosudil. Additionally, TTR results may have been confounded by the fact that patients could have started concomitant medications 2 or more weeks before study screening, and those medications may not have reached peak efficacy. The lack of standardized patient management in cGVHD has made the validity of FFS uncertain, since physicians can have differing opinions on when to administer a new treatment.[57] Also, without an appropriate comparator group, the OS results are not very informative and the data are immature in the studies.[20] In general, the LSS had adequate validity, reliability, and responsiveness based on evidence from the literature, though there was no such evidence for the PROMIS assessment for patients with cGVHD. The MIDs suggested by the sponsor for the LSS and PROMIS were supported by estimates identified from the literature; however, for both instruments, distribution-based methods (0.5 times the standard deviation) were used to estimate the MIDs internally from study data as opposed to using an anchor-based approach, the latter of which is the preferred method.[53,54] Although standardized NIH consensus criteria were used and many of the end points were objective or semi-objective in nature (i.e., ORR, DOR, TTR, FFS, and OS), responses were not evaluated by an independent review committee and there is still an increased risk of bias due to knowledge of treatment assignment.

Missing data were not imputed in the trials and no sensitivity analyses were performed to investigate the impact of the missing data. The censoring mechanisms used for the time-to-event analyses appear to be appropriate, though there may be uncertainty in the estimates at later time points as the number of patients at risk declines. As of the latest data cut-off date, 100% of patients in either study had discontinued from the treatment and the study, and only [redacted] patients in study KD025 to 208 (and no patients in study KD025 to 213) had completed the follow-up. Since patients who continue with treatment and continue to provide data tend to be healthier than those who discontinue early, there is an increased risk of attrition bias, which may be amplified by the relatively small sample sizes. Moreover, nearly [redacted]% of patients discontinued from study KD025 to 213 due to study termination by the sponsor (almost [redacted]% of patients from study KD025 to 208), though there are few details explaining why, and it is uncertain what impact this had on the results.

Due to the potential for confounding and unavoidable bias, it is difficult to make firm conclusions based on the efficacy and safety data available.

External Validity

Between the studies, [redacted] patients received the approved 200 mg once-daily dose for a median treatment duration of around 9 months, which is a relatively small number of patients compared with the total number who could potentially receive belumosudil (active cGVHD after at least 2 prior lines of systemic therapy) for a somewhat short duration, considering that treatment can be for years.

Although the indication includes pediatric patients as young as 12 years of age, there were no data available for patients younger than 20 years of age in study KD025 to 213 (pediatric patients were not eligible for study KD025 to 208). The Health Canada product monograph indicated that the use of belumosudil in pediatric patients 12 years of age and older is supported by evidence from studies in adults with additional population pharmacokinetic data demonstrating that age and body weight had no clinically meaningful effect on the pharmacokinetics of the drug substance, that the exposure of the drug substance is expected to be similar

between adults and pediatric patients age 12 years and older, and that the course of disease is sufficiently similar in adult and pediatric patients to allow the extrapolation of data in adults to these pediatric patients.[1] The clinical experts consulted by CADTH were of the opinion that the results for adults could be generalizable to a younger patient population.

To be eligible, patients must have had a Karnofsky Performance Scale score of at least 60 (at least 40 in study KD025 to 208), a glomerular filtration rate of at least 30 mL/min/1.73 m^2, a forced expiratory volume in 1 second (FEV_1) of 40% or more (study KD025 to 213), and fewer than 6 prior lines of systemic cGVHD treatment. One clinical expert consulted by CADTH suggested that although patients with low FEV_1 or an NIH lung score of 3 were excluded, these patients could potentially be treated with belumosudil in practice. Based on the study baseline characteristics, the clinical experts were of the opinion that the study patients were generally similar to those who could receive belumosudil in clinical practice in Canada, with 2 exceptions. The experts pointed out that racial diversity was limited in the study (compared with what is expected in Canadian practice), and the prior and concomitant cGVHD therapies differed from their experience in treating patients with cGVHD (which may be due to varying availability of treatments across jurisdictions and the studies taking place in the US). Nearly all patients enrolled in the studies had reported at least 2 prior lines of therapy; however, it was not clear whether other treatments had failed, which is stipulated in the Health Canada indication; therefore, it is unclear whether the study populations align perfectly with the indicated population for belumosudil. All study sites were in the US and the clinical experts noted it is possible there are differences between clinical practice and patient management between Canada and the US.

No direct evidence was submitted for the CADTH review for how belumosudil compares with other cGVHD therapies, which is an important limitation since there are many on- and off-label treatments. Without an appropriate comparator in the studies, it is challenging to contextualize and apply the results to the population of patients who may receive belumosudil in practice. Patients were ineligible if they were receiving ibrutinib, and it is unknown what effect ibrutinib would have in combination with belumosudil.

Only the primary end point of ORR at 6 months was controlled for multiplicity in the studies and all other secondary and exploratory outcomes were presented descriptively. The FDA considered the 6-month time period to be reasonable to observe a response without risking possible harms with continued treatment.[20,21] There has been debate over which definition of DOR is the most useful and the results for each definition can differ considerably.[20] The experts confirmed that the LSS and PROMIS are not typically used in clinical practice, based on their experience, though they may be used in other clinics across Canada and provide useful information that is important to patients and clinicians.

The available efficacy and safety evidence provide a relatively short-term outlook on treatment with belumosudil. Considering the external validity limitations and that the issues with internal validity remain, the clinical experts indicated that the results of the study could be generalized to patients who would be eligible for belumosudil in Canada.

GRADE Summary of Findings and Certainty of the Evidence

Methods for Assessing the Certainty of the Evidence

For the pivotal studies identified in the sponsor's systematic review, GRADE was used to assess the certainty of the evidence for outcomes considered most relevant to inform CADTH's expert committee deliberations, and a final certainty rating was determined as outlined by the GRADE Working Group:[22,23]

- **High certainty**: We are very confident that the true effect lies close to that of the estimate of the effect.
- **Moderate certainty**: We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. We use the word "likely" for evidence of moderate certainty (e.g., "X intervention likely results in Y outcome").
- **Low certainty**: Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect. We use the word "may" for evidence of low certainty (e.g., "X intervention may result in Y outcome").
- **Very low certainty**: We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect. We describe evidence of very low certainty as "very uncertain."

Although GRADE guidance is not available for noncomparative studies, the CADTH review team assessed pivotal trials that lacked a valid comparator for study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias to present these important considerations. Because the lack of a comparator arm does not allow for a conclusion to be drawn on the effect of the intervention versus any comparator, the certainty of evidence for trials that lacked a valid comparator started at very low certainty with no opportunity for rating up.

When possible, certainty was rated in the context of the presence of an important (nontrivial) treatment effect; if this was not possible, certainty was rated in the context of the presence of any treatment effect (i.e., the clinical importance is unclear). In all cases, the target of the certainty of evidence assessment was based on the point estimate and where it was located relative to the threshold for a clinically important effect (when a threshold was available) or to the null. The target of the certainty of evidence assessment was the presence or absence of a clinically important effect for ORR, tertiary and secondary DOR, TTR, FFS, and OS based on a threshold informed by the clinical experts consulted by CADTH for this review. The target of the certainty of evidence assessment was the presence or absence of any (non-null) effect for the number of patients with an LSS score or PROMIS Global Health summary score greater than or equal to the MIDs identified from the literature and who experienced an SAE.

For the GRADE assessments, the findings from study KD025 to 213 and study KD025 to 208 were considered together (except for PROMIS, which was assessed only in study KD025 to 213) and summarized narratively per outcome because the studies were similar in population, intervention, design, and outcome measures.

Results of GRADE Assessments

Table 2 presents the narrative GRADE summary of findings for belumosudil for patients with cGVHD.

Long-Term Extension Studies

Data from the latest cut-off dates for the ongoing studies (study KD025 to 213 and study KD025 to 208) were included in the main report. No additional long-term extension studies were submitted by the sponsor.

Indirect Evidence

Contents within this section have been informed by materials submitted by the sponsor. The following has been summarized and validated by the CADTH review team.

Objectives and Methods for the Summary of Indirect Evidence

No direct comparative data for the use of belumosudil for the treatment of addenda years and older with cGVHD were submitted by the sponsor. As a result, a systematic literature review was conducted to identify efficacy and safety evidence of belumosudil versus other treatments for patients with cGVHD after an allo-HSCT and whose prior therapy failed.[25] It was known that no RCTs were available for belumosudil versus other active therapies for cGVHD; therefore, the feasibility of conducting a PAIC was assessed.

The sponsor also submitted data for a naive indirect comparison of belumosudil versus BAT. A brief summary of the comparison between belumosudil, ibrutinib, and ruxolitinib for ORR, FFS, OS, LSS, and discontinuation due to AEs has been included in Table 26 of this CADTH report.

According to the submitted technical report, differences in study designs (e.g., eligibility criteria, length of follow-up, timing of assessments, and outcome measures) as well as the availability and variability of key prognostic factors would result in substantial heterogeneity precluding the feasibility of a PAIC; therefore, no indirect comparisons were conducted.

CADTH's review of the sponsor's feasibility assessment is provided subsequently.

Description of the Feasibility Assessment

The sponsor conducted a feasibility assessment to determine whether the clinical evidence identified from the literature search for the treatment of patients with cGVHD following an allo-HSCT and whose condition failed to respond to prior therapy was sufficiently similar to permit valid comparison in an ITC.[25] The authors reported that they performed the systematic literature review following National Institute for Health and Care Excellence (NICE) technology appraisal guidance[58] and the *Cochrane Handbook for Systematic Reviews of Interventions*,[59] and reported the systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.[60] The review followed an a priori protocol and the literature search was comprehensive up to April 30, 2022. The study eligibility criteria for the ITC literature search were similar to that submitted for the belumosudil systematic review (described in the main report). The exceptions were the exclusion of: adolescent patients (aged 12 years and older); etanercept, infliximab, and mTOR inhibitors (everolimus, sirolimus) as comparators; and the HRQoL outcomes in the belumosudil systematic review, which were not part of the ITC literature search eligibility criteria. Data extraction from the included studies was conducted by a single reviewer with verification by another. The risk of bias of RCTs was assessed using the Cochrane Risk of Bias Tool version 2.0,[61] with other studies evaluated using the Downs and Black checklist.[62]

A total of 610 records were identified from the database searches, of which 31 records from 22 unique studies (21 full-text publications and 1 conference abstract) were included for review; 3 were RCTs and the remaining were single-arm trials. The authors indicated that 1 of the 3 RCTs had an increased risk of bias because it lacked information on allocation concealment, and all of the trials were open-label. Among the 18 single-arm trials, 14 were considered low quality and 4 were moderate quality. The evidence included 8 studies for ECP, 4 for rituximab, 4 for imatinib, 2 for belumosudil, 2 for ibrutinib, and 2 for ruxolitinib. The patient enrolment dates ranged from 2001 to 2019, and it is likely that patient management and the treatments available have changed in that time. Most studies had a primary outcome of response rate, and the secondary outcomes often included OS, FFS, LSS, reduction in CS dose, and safety. Ten studies measured baseline cGVHD severity using NIH Global Severity scoring, which appears to be consistent with the measure used in the main clinical studies described in the CADTH report. However, there was additional variability in patient characteristics (mean age ranged from 26 years to 62 years), prior therapies (median, 1 to 4 treatments; range, 1 to 7 treatments), outcome definitions, assessment time points (range, 2 to 29 months), and the availability of results data from studies (e.g., ORR was reported in 19 studies, while disease progression, OS, and FFS were reported in 7 studies each).

Three main criteria were used to assess comparability with the belumosudil trials. Of the 20 studies (2 belumosudil studies were removed), 5 were excluded because they were conducted in countries not of interest (i.e., Asian countries). From the remaining 15 studies, 13 were excluded due to having patients who received fewer than 2 prior lines of therapy. Both of the remaining 2 studies were deemed to have differences in populations or design that made them not comparable with those in the belumosudil studies (due to patient dissimilarity, heterogeneity in outcome measures, and missing data for outcomes of interest) and thus were excluded. Of note, the phase III REACH3 trial[63] that investigated the effect of ruxolitinib 10 mg twice daily versus BAT in patients with moderate or severe GC-refractory or GC-dependent cGVHD with a history of 1 prior line of therapy was excluded due to misalignment of the inclusion criteria between the REACH3 trial and those for belumosudil (1 prior line of therapy versus 2 or more lines of therapy, respectively), and the population and outcomes data were not reported by line of therapy.

Appraisal of the Feasibility Assessment

Ibrutinib and ruxolitinib appear to be the main comparators for belumosudil, considering that both drugs have Health Canada indications for the second- or later-line treatment of patients with cGVHD.[13,14,20] The efficacy and safety of both belumosudil and ibrutinib were assessed in small single-arm trials (or only 1 arm of relevance to this review), while ruxolitinib was assessed in a somewhat larger RCT versus BAT. As a result of differences in eligibility criteria, the belumosudil KD205 to 213 trial enrolled patients with more prior lines of therapy and more severe disease, based on NIH criteria,[63] or a larger number of involved organs.[64] Given the small size of the studies (especially the single-arm trial of ibrutinib; n = 42), and the fact that the eligible population in the belumosudil trial required more prior lines of therapy, the CADTH review team agreed it would not have been feasible to conduct a valid PAIC that fully adjusted for the differences in populations between the belumosudil and ibrutinib or ruxolitinib trials. However, the CADTH review team agrees with the assessment of Health Canada[20] that this is an important limitation of the belumosudil KD205 to 213 trial. Given that the trial initiated in 2018 (after the Health Canada approval of ibrutinib), it may have been possible

at the outset to enrol populations that were similar to facilitate a valid indirect comparison to ibrutinib. Alignment of eligibility criteria would have similarly facilitated an indirect comparison with the ruxolitinib arm of the REACH3 trial. There were also differences between belumosudil and other treatments for cGVHD in the study design (e.g., study dates and possible changes in patient management over time, assessment time points, and the availability of data for outcomes of interest) and populations (e.g., patient characteristics and prior treatments) that make it challenging to compare them and make meaningful efficacy or safety conclusions.

Studies Addressing Gaps in the Systematic Review Evidence

Contents within this section have been informed by materials submitted by the sponsor. The following has been summarized and validated by the CADTH review team.

Table 21: Summary of Gaps in the Systematic Review Evidence

Evidence gap	Studies that address gaps	
	Study description	Summary of key results
Lack of a comparator arm in the clinical studies (KD025 to 213 and KD025 to 208) and conducting an ITC was deemed infeasible.	Observational study using IPTW and real-world data from the US Optum Clinformatics Data Mart database to compare the results of the 2 belumosudil studies with an active BAT arm.	• FFS: HR = [redacted] (95% CI, [redacted]) • OS: HR = [redacted] (95% CI, [redacted]) • Safety profiles differed between treatments • Various limitations prevent firm conclusions from being made

BAT = best available therapy; CI = confidence interval; FFS = failure-free survival; HR = hazard ratio; IPTW = inverse probability of treatment weighting; ITC = indirect treatment comparison; OS = overall survival.

Source: Sponsor's summary of clinical evidence.[11] Details included in the table are from the sponsor's summary of clinical evidence.

Description of Studies

Due to the lack of head-to-head data and the inability to conduct an ITC, 1 observational study using IPTW has been summarized to provide indirect comparative evidence for belumosudil versus BAT for patients with cGVHD (Table 21).[11]

Populations

The observational study was conducted using real-world individual patient data from the US Optum Clinformatics Data Mart database and results from the belumosudil studies (KD025 to 213 and KD025 to 208). According to the sponsor, since all study centres in the belumosudil trials were in the US, a US database was used in an attempt to include comparable patient populations and health care practices. From the database, patients were eligible if they met the following criteria: had at least 1 inpatient or outpatient claim with a diagnosis code for cGVHD from [redacted], to the most recent available data; had at least 3 systemic lines of therapy after cGVHD diagnosis (first-line therapy must have been CSs); were 12 years of age or older; and had at least 6 months of continuous enrolment with medical and pharmacy benefits before the third line of therapy.

Interventions

Based on the information provided by the sponsor, it appears as though data for both belumosudil 200 mg once daily and belumosudil 200 mg twice daily were pooled for this analysis, although the Health Canada–recommended dose is the former for the treatment of cGVHD. BAT included the following treatments: ECP, mycophenolate mofetil, imatinib, rituximab, mTOR inhibitors (e.g., sirolimus, temsirolimus, everolimus), ruxolitinib, CNIs (e.g., tacrolimus, cyclosporine), methotrexate, ibrutinib, pentostatin, etanercept, abatacept, alemtuzumab, hydroxychloroquine, and IL-2.

Outcomes

The primary outcome in the observational study was FFS and key secondary outcomes included rate of OS, TTNT, safety events, reduction in CS use, and reduction in CNI use. FFS and OS were defined in the observational study similarly to the belumosudil studies. A list of specific safety events with International Classification of Diseases codes and their frequencies was included as well. It is likely that there are nuanced differences in the results due to the claims data being restricted by the end date for medical coverage enrolment or the end of the medical record, safety events being coded differently between clinical trials and the claims database, and that the assessment time points likely varied.

Statistical Analysis

Details of the IPTW methods and information on data extraction or how time-to-event analyses were undertaken were not available to be appraised. IPTW methods were used in an attempt to minimize the potential for confounding within included variables chosen after discussion with clinicians (i.e., age, sex, race, time from cGVHD diagnosis to the index date, number of prior lines of therapy, aGVHD history, and underlying disease history [i.e., the indication for the allograft]). It was also noted that other potential effect modifiers, such as organ involvement, were not available from the data. The index date was defined as the third to sixth line of therapy and patients could contribute multiple observations for each eligible line of therapy until the earliest medical coverage disenrollment or the end of the study. According to the sponsor's summary, an unbiased choice for time zero (from multiple eligible times) would be to use a single eligible time (e.g., the first eligible time or a random eligible time), but it was decided that this would reduce the sample size and instead, all eligible times (or a subset thereof) were included. To adjust for patients contributing multiple data points, the robust sandwich variance estimator was used.[65] The sponsor stated that a simulation study demonstrated good performance when selecting multiple lines of therapy.[66]

Results

Patient Disposition

Baseline Characteristics

Patients in the belumosudil group (N = [redacted]) and BAT group (N = [redacted]) had a mean age of approximately [redacted] years, [redacted]% to [redacted]% were male, more than [redacted]% had moderate to severe cGVHD, and both groups had a mean of [redacted] prior lines of therapy. There were notable differences in some postweighted baseline characteristics, such as that all patients in the belumosudil group received a transplant versus only two-thirds in the BAT group, and

patients in the belumosudil group tended to have a greater number of involved organs compared with the BAT group.

Efficacy

Median FFS was [redacted] months (95% CI, [redacted] to [redacted]) in the belumosudil group and [redacted] months (95% CI, [redacted] to [redacted]) in the BAT group (HR = [redacted]; 95% CI, [redacted]). The KM estimate of FFS probability at 12 months was [redacted]% (95% CI, [redacted]) in the belumosudil group and [redacted]% (95% CI, [redacted]) in the BAT group. The key drivers of failure differed between the groups; the key driver in the belumosudil group was the initiation of subsequent treatment and was relapse of malignancy in the BAT group.

Median OS was not reached for the belumosudil group and [redacted] months (95% CI, [redacted] to [redacted]) for the BAT group (HR = [redacted]; 95% CI, [redacted]). The KM estimate of OS probability at 12 months was [redacted] % (95% CI, [redacted]) in the belumosudil group and [redacted] % (95% CI, [redacted]) in the BAT group.

Harms

Harms results are summarized in Table 22. The most common AEs in the belumosudil group were infections ([redacted]%), fatigue or asthenia ([redacted]%), and nausea or vomiting ([redacted]%). The most common AEs in the BAT group were infections ([redacted]%), dyspnea ([redacted]%), hypertension ([redacted]%), and anemia ([redacted]%).

Critical Appraisal

Internal Validity

One of the major concerns with the observational study is the potential for selection bias and residual confounding as a result of the lack of randomization of patients. There was also limited information on how patients were selected from the claims data, and there may have been selection bias in the process. By relying solely on clinician opinion and not consulting the literature, it is possible that the methods used to decide which prognostic factors and effect modifiers to include were inadequate. The observational study required patients from the claims dataset to have at least 3 systemic lines of therapy, which does not align with the inclusion criteria of the belumosudil studies (between 1 and 5 prior systemic treatments). Furthermore, there were insufficient data to include all the variables of interest and several baseline characteristics remained imbalanced after IPTW procedures were applied. There was no differentiation between moderate and severe cGVHD (potentially imbalanced), and there were notable differences between treatment groups in the amount of organ involvement, number of organs involved, and use of prior lines of therapy. It would not have been possible for the analyses to adjust for the different study designs (i.e., trial versus retrospective cohort study) and there would be heterogeneity around decisions for when a new treatment is started, potential missing data, and patients lost to follow-up, which were not described within the study. There was no assessment of residual confounding and the potential for bias is high. It was unclear if there was a protocol for the observational study and there is the possibility of selective outcome reporting, especially considering that ORR, DOR, and TTR were not included in the study, despite these being key outcomes in the belumosudil studies. It is likely that there were differences in outcome definitions and assessment time points between the belumosudil studies and the claims data. The sponsor noted that the identification of relapses in the claims data may be unreliable and suggested that the same event could have

been counted more than once for patients, thus artificially inflating the numbers, though it was not possible to verify this suggestion. The sponsor also noted the risk of inaccuracies in the claims database due to patients changing insurance plans and the possible miscoding of claims. It is not possible to predict the direction bias this may have introduced. Sensitivity analyses were attempted but did not adequately correct for the incongruencies. Therefore, both the efficacy and safety results of this study should be considered in light of the limitations, and it is not possible to make firm conclusions based on the findings.

Table 22: Summary of Harms Results From the Sponsor-Submitted Observational Study

AEs	Belumosudil (N =)	BAT (N =)
Most common AEs, n (%)[a]		
Infections		
Fatigue or asthenia		
Nausea or vomiting		
Diarrhea		
Upper respiratory tract infection		
Dyspnea		
Edema		
Cough		
Headache		
Hypertension		
Anemia		
Pneumonia		
Sepsis		
Renal failure		
Thrombocytopenia		

AE = adverse event; BAT = best available therapy; TEAE = treatment-emergent adverse event.

[a]Most common TEAEs by preferred term occurring in at least 25% of patients in either treatment group.

Source: Sponsor's summary of clinical evidence.[11] Details included in the table are from the sponsor's summary of clinical evidence.

External Validity

Claims data from the US Optum Clinformatics Data Mart database could have been from as early as the year and health care practices have likely changed since then. It appears that the results from the main clinical studies for belumosudil once daily and twice daily were pooled, though only the belumosudil 200 mg once-daily dose is approved by Health Canada for the treatment of cGVHD. Moreover, it is unclear how relevant it is to pool all other available treatments as a comparator (i.e., BAT) versus comparing belumosudil with the most relevant individual treatments for cGVHD. There also remains a lack of data for pediatric patients that was not clearly supplemented by the observational data. Other limitations include the relatively small number of patients (around patients) in each treatment group and the limited long-term data available. Despite

the use of real-world data, which could improve the generalizability of the results, the internal validity issues minimize the utility and applicability of the findings to clinical practice in Canada.

Discussion

cGVHD is a complex, multisystem disease that leads to significant morbidity and mortality after an allo-HSCT.[67] It is estimated that 10% to 25% of patients who receive an allo-HSCT die from cGVHD complications.[67,68] Although there are various treatment options for cGVHD, many do not have a Health Canada indication for the disease and not all patients respond to all treatments. Treatment duration can be for many years beginning with CSs (with or without CNIs) as standard first-line therapy, though patients may require additional treatments and there is little consensus on what is the best second-line treatment for these patients.[11,12,67] Moreover, the clinical experts highlighted that there are few effective and safe options after second-line therapy, at which point patients tend to have a variable response to subsequent treatments. Belumosudil is indicated for the treatment of patients 12 years of age and older with cGVHD after the failure of at least 2 prior systemic treatments.[1]

Summary of Available Evidence

Two phase II, open-label studies were included in the sponsor's systematic review of the efficacy and safety of belumosudil 200 mg once daily in patients with cGVHD. In total, [redacted] patients and [redacted] patients in study KD025 to 213 and study KD025 to 208, respectively, received the Health Canada–approved dose, and there was no relevant comparator or control group in either study. Patients received belumosudil in 28-day cycles until clinically significant disease progression (i.e., requiring a new systemic therapy for cGVHD), histologic recurrence of the underlying malignancy, unacceptable toxicity, death, lost to follow-up, investigator decision, or EOT. The primary end point in both studies was ORR by investigator assessment. Secondary and exploratory end points of interest to the CADTH review included DOR, TTR, FFS, OS, LSS score, PROMIS Global Health summary scores, and safety outcomes. Patients in the studies had a median age of [redacted] years (range, [redacted] years to [redacted] years) in study KD025 to 213 and 50 years (range, 20 years to 63 years) in study KD025 to 208. In both studies, more than 70% of patients had severe cGVHD according to the 2014 NIH consensus criteria and 100% of patients in study KD025 to 213 and 88% of patients in study KD025 to 208 had 2 or more prior lines of therapy. There were no patients younger than 20 years old in the relevant datasets to support the pediatric portion of the indication.

No indirect evidence was included in the sponsor's submission to CADTH. The sponsor submitted a feasibility assessment for performing an ITC for belumosudil versus other cGVHD treatments and concluded it would not be reasonable to conduct an indirect comparison due to the heterogeneity in patient characteristics, study designs, and data reported across studies.

The sponsor also submitted an observational study using IPTW methods to address the gaps in the evidence, which used pooled results from the main clinical studies and real-world data from the US Optum Clinformatics Data Mart database to provide comparative evidence for the treatment of belumosudil versus BAT in patients with cGVHD. Patients were selected from the database if they had cGVHD, had had

at least 3 systemic lines of therapy after cGVHD diagnosis, and were at least 12 years old. BAT included ECP, mycophenolate mofetil, imatinib, rituximab, mTOR inhibitors, ruxolitinib, CNIs, methotrexate, ibrutinib, pentostatin, etanercept, abatacept, alemtuzumab, hydroxychloroquine, and IL-2. Outcomes of interest included FFS, OS, and safety events.

Interpretation of Results

The lack of a valid comparator in the pivotal studies means it is not possible to attribute the observed efficacy and safety findings to belumosudil with certainty, as these would be confounded by potential placebo effects, the use of concomitant treatments, and the natural history of the disease. Furthermore, 100% of patients in the studies had discontinued from both the treatment and the study and, given the minimal information provided for why patients stopped as well as the reasons and timing of censoring, it is difficult to assess what impact this had on the results. The observational IPTW study attempted to provide a comparison of belumosudil versus BAT for some outcomes, but this study had numerous methodological limitations and was at high risk of bias due to residual confounding. As a result, the available evidence was deemed insufficient to draw definitive conclusions about the efficacy of belumosudil in inducing a response versus any comparator. Herein, the findings are contextualized based on clinical expert feedback about how the results from the study might compare to the usual clinical course of cGVHD. It is also worth noting that the clinical experts indicated it might be reasonable to conduct a single-arm study in patients whose disease fails to respond to at least 2 prior lines of systemic therapy due to the limited treatment options for this patient population, and it is unethical to randomize such patients to no treatment (i.e., placebo). However, the decision to enrol patients that differed systematically from those in the relevant comparator trials limited the feasibility of performing any valid ITCs.

Efficacy

Response to treatment was noted as being an important outcome in the clinician group input and by the clinical experts. Study KD025 to 213 reached its primary end point, demonstrating an ORR of greater than 30% at 6 months of belumosudil treatment; the clinical experts consulted by CADTH noted the findings to be clinically important. The FDA considered 6 months of treatment to be a sufficient period of time that allows for a potentially clinically meaningful overall response without risking possible adverse effects from continuing treatment, so long as the response was durable.[20,21] Overall response consisted of CR or PR, though it was largely driven by patients with PR. Of the 2 response types, CR is a clear clinical benefit, but it is less obvious how much clinical benefit there is with PR.[57] The descriptive subgroup analysis results appeared generally consistent with the primary analysis, though they included a small number of patients. Although study KD025 to 208 was exploratory in nature and no statistical analyses were conducted, the results supported study KD025 to 213.

There is some debate over which of the 4 DOR definitions is most informative, and results for each outcome can vary considerably but must take into account that each definition is interpretable.[20] The tertiary DOR definition measures time from first response to initiation of a new systemic cGVHD therapy (reflecting patient management) or death, which the clinical experts suggested was the most informative measure of treatment durability, followed by secondary DOR.[21] The secondary definition measures the time to first

decline in response, but does not account for treatable flares that do not require new treatment.[69] The clinical experts suggested that the results for event-free probability for both the secondary and tertiary DOR were clinically important, as they exceeded 40%, though findings for secondary DOR were less promising and imprecise. The median TTR suggested that response may occur relatively quickly; the median TTR in study KD025 to 203 was [redacted] weeks and [redacted]% of responders experienced a response within 16 weeks. At 12 months, the probability of maintaining FFS (i.e., not having started a new cGVHD therapy, nonrelapse mortality, or recurrent malignancy) was estimated to be [redacted]% (95% CI, [redacted]%) in study KD025 to 213, which the clinical experts believed to be clinically important; the findings were supported by study KD025 to 208; however, the validity of FFS has been questioned due to the lack of standardized patient management, such as deciding when a new treatment is given (physicians must discern between disease flare and disease progression, and which next treatment is suitable and when to provide it) and the differing availability of treatments.[57] Response outcomes may have been confounded by the fact that patients could have been on other stable concomitant treatments (at least 2 weeks before screening), which may or may not have reached peak efficacy by the time patients started belumosudil.[21]

Input from the patient group, clinician group, and clinical experts indicated that survival was an important outcome. The probability of survival at 12 months was [redacted]% (95% CI, [redacted]%) in study KD025 to 213, which the clinical experts found to be clinically important. Without a proper comparator group, OS results are not very informative and no conclusions could be made about belumosudil on OS.[20] One of the main limitations with both of the survival outcomes was the immaturity of the data and the medians and/or CIs not being reached in the study; longer follow-up will be required to fully understand whether the drug addresses patients' needs for treatment that improves survival.

HRQoL was identified as an important outcome to patients and caregivers in the patient input, clinician group input, and by the clinical experts. LSS is a disease-specific measure of symptoms, while PROMIS is a generic measure that assesses a patient's overall health as well as physical, emotional, and social aspects of their life. More than half of the patients reached the 7-point MID for the LSS in study KD025 to 213 (similar proportion in study KD025 to 208). More than a third of patients reached the 4.7-point MID for the PROMIS physical health assessment and fewer than half of the patients reached the 4.7-point MID for the PROMIS mental health assessment in study KD025 to 213 (outcome not assessed in study KD025 to 208). Among patients who reach the respective MIDs, it is unclear what the minimum number of patients would need to be for belumosudil to be considered beneficial. The interpretation of the results is limited due to the lack of a control group, assessor's knowledge of treatment assignment, and missing data over time as more patients discontinued, which increased the risk of confounding, performance bias, and attrition bias.

The patient and clinician input noted the importance of reducing the dose or eliminating the use of CSs, citing the adverse effects to which the drugs are often linked. In the 2 studies, between [redacted]% and [redacted]% of patients reduced their CS dose, while approximately a quarter of patients in either study were able to discontinue CS usage while being treated with belumosudil. However, interpretation of the results may be hindered by the limited details available for this outcome. It was unclear whether any reduction in dose (even a very minor change) was counted, how long patients reduced or discontinued CSs, and how many patients increased

their dose during the studies. Additional details would help to clarify whether belumosudil helps patients avoid CS usage and the associated side effects.

Although there were no pediatric patients in the studies, belumosudil gained regulatory approval for patients aged 12 years and older based on pharmacokinetic analyses indicating that age and body mass did not have a clinically meaningful effect on drug pharmacokinetics.[20,21] Based on similar disease characteristics and management, the clinical experts indicated it would be reasonable to generalize the study results from adult patients to pediatric patients aged 12 years and older. Upon review of the baseline characteristics, the clinical experts felt the patients in the studies generally represented the patients in Canada who could receive belumosudil. Although most patients across the studies had had 2 prior treatments for cGVHD, it was not stated whether these were treatment failures (or if patients had stopped for other reasons), which is stipulated in the Health Canada indication. The clinical experts also explained that patients who need additional cGVHD treatments tend to have variable responses to later lines of therapy. The experts also indicated that it would be ideal to treat patients with belumosudil early on (i.e., after failure of 2 systemic treatments); however, this may not be the case for many patients in practice who have already received a number of therapies. Due to the limited number of effective and safe cGVHD treatments, the clinical experts stated that once a patient's disease fails to respond to belumosudil, the management strategy largely remains the same: use the next-best treatment available at that time and that is accessible. Belumosudil is an oral drug, which may offer a benefit over other treatments that require special administration or monitoring, and the clinical experts reiterated the need for effective and safe later-line therapies for patients with cGVHD.

Harms

As of the latest data cut-off, the median durations of exposure to belumosudil 200 mg once daily were [redacted] months to [redacted] months in the studies. Nearly all patients reported at least 1 AE, between [redacted]% and [redacted]% of patients reported an SAE, [redacted]% to [redacted]% stopped treatment due to an AE, and there were [redacted] deaths in study KD025 to 213. Notable harms of interest for the CADTH review included hematologic (blood and lymphatic system disorders) and immune (infections and infestations) AEs. Between [redacted]% and [redacted]% of patients reported a blood and lymphatic system disorder AE, with anemia being the most frequently reported event, while [redacted]% to [redacted]% of patients reported an infection and infestation AE, with upper respiratory tract infection as the most frequently reported event.

According to the patient group input CADTH received, it is important that new treatments produce fewer side effects compared with currently available treatments. Due to the lack of an appropriate comparator group or control group in the studies, it is difficult to confirm a causal association between belumosudil and any particular harms and, moreover, whether the drug adequately addresses patients' needs.[20,69] Based on the eligibility criteria, patients in the studies may have been healthier than the broader population who could receive belumosudil in practice and discontinuations, as well as rates and types of AEs, could reflect that. It is also more likely that a healthier patient is better able to tolerate an adverse effect and willing to remain on the study drug, thereby lowering the number of patients who withdraw from treatment compared with clinical practice. According to the FDA, elevated transaminase levels, anemia, lymphocytopenia, headache, nausea,

and diarrhea were noted as potential risks in early studies of belumosudil for other disease areas as well as in healthy volunteers, though these risks may be reduced by optimizing the drug dose.[21,69] Since patients were allowed to continue receiving stable systemic treatment and to use GCs to treat flares, it is possible that these treatments were responsible for some AEs, but it is difficult to know without an adequate control group.[21,69] The clinical experts indicated that the reported AEs were reasonable for what is known about cGVHD and the study treatments (belumosudil and concomitant drugs) and that with appropriate care, the AEs would be manageable for many patients.

Conclusion

cGVHD is a complex, multisystem disease and there is a need for safe and effective treatments that help prolong survival, alleviate symptoms, and improve HRQoL. Evidence from 2 phase II, open-label clinical studies in adult patients with cGVHD (n = [redacted]) were included in the review for belumosudil and both studies lacked an appropriate comparator or control group. Such a study design does not allow for definitive conclusions about the efficacy and safety of belumosudil versus any comparator, as the effect estimates are likely to be confounded by concomitant treatments and the natural history of the disease. Indirect comparisons with relevant alternatives were deemed infeasible and a submitted observational IPTW study comparing belumosudil with BAT was at high risk of bias due to residual confounding. Nevertheless, study KD025 to 213 met its primary outcome of an ORR greater than 30% at 6 months of treatment; the majority of responses were partial and fewer patients experienced CR. The treatment effect point estimates for response and survival outcomes were considered potentially clinically meaningful by the clinical experts. Although there were MIDs for LSS and PROMIS from the literature, it was not clear whether the number of patients who reached the MIDs was large enough to indicate a meaningful benefit from belumosudil. Harms results were potentially confounded by the use of concomitant treatments, though the clinical experts felt these harms would generally be manageable with adequate care. There was a relatively small number of patients who received the Health Canada–approved dosage (belumosudil 200 mg once daily) in either study, and there is additional uncertainty in the long term results due to discontinuations and the immaturity of the survival data. The clinical experts indicated that the study results were generalizable, acknowledging the lack of data for patients younger than 20 years of age in the studies. It was determined that an ITC was not feasible and the sponsor-submitted observational IPTW study comparing belumosudil with BAT had important limitations (i.e., heterogeneity, missing outcomes), preventing meaningful conclusions from being made. Overall, due to the lack of informative direct and indirect evidence, it is very uncertain how belumosudil compares with other cGVHD treatments in terms of efficacy and safety.

While the results of the included studies aligned with the clinical experts' expectation that belumosudil would address the unmet needs in this patient population, there were important limitations in the included studies leading to uncertainty in the evidence due to the trials having only a single relevant treatment group and no valid comparator.

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Appendix 1: Detailed Outcome Data

Note that this appendix has not been copy-edited.

Response by Organ System and GSR Assessment

Table 23 summarizes the best response (CR or PR) assessment for 9 organs: skin, eyes, mouth, esophagus, upper gastrointestinal tract, lower gastrointestinal tract, liver, lungs, and joints and fascia.[15,17] For organs other than the lungs, the system was considered to be "involved" if the baseline score was greater than 0, unless all response assessments were "not evaluable." Otherwise, the system was considered "not involved" if the baseline score was 0, unless a CR or PR assessments caused clinical review to confirm baseline involvement. Lungs were considered "involved" if FEV_1 was less than 75%, unless all responses were "not evaluable," and "not involved" if FEV_1 was at least 75%. Response assessments were categorized into 1 of the following statuses: CR, PR, progression, not evaluable, or stable. Response rate by organ system was only measured in patients who were responders at similar time points to ORR up to week 48. This outcome was considered useful in informing the clinical management of individual patients with cGVHD, but not critical to decision-making. Response by organ system and GSR assessment results are summarized in Table 23.

Table 23: Summary of Response by Organ System and GSR Assessment From Study KD025 to 213 and Study KD025 to 208 (mITT Population)

Outcome	KD025 to 213 Belumosudil 200 mg q.d. (N =)	KD025 to 208 Belumosudil 200 mg q.d. (N =)
Organ system, n (%)		
Skin, n		
CR		
PR		
Total (CR + PR)		
Eyes, n		
CR		
PR		
Total (CR + PR)		
Mouth, n		
CR		
PR		
Total (CR + PR)		
Esophagus, n		
CR		

Outcome	KD025 to 213 Belumosudil 200 mg q.d. (N =)	KD025 to 208 Belumosudil 200 mg q.d. (N =)
PR		
Total (CR + PR)		
Upper gastrointestinal tract, n		
CR		
PR		
Total (CR + PR)		
Lower gastrointestinal tract, n		
CR		
PR		
Total (CR + PR)		
Liver, n		
CR		
PR		
Total (CR + PR)		
Lungs, n		
CR		
PR		
Total (CR + PR)		
Joints and fascia, n		
CR		
PR		
Total (CR + PR)		
Best response of GSR assessment, n (%)		
Overall GSR, n		
CR		
PR		
Total (CR + PR)		

CR = complete response; GSR = global severity rating; mITT = modified intention to treat; PR = partial response; q.d. = once daily.

Note: Results are based on a data cut-off of , for study KD025 to 213 and , for study KD025 to 208.

Sources: Clinical Study Report addenda for study KD025 to 213[16] and study KD025 to 208[18] and sponsor's summary of clinical evidence.[11] Details included in the table are from the sponsor's summary of clinical evidence.

TTNT

TTNT was measured as the time from the first dose of belumosudil to the time of new systemic cGVHD treatment, censored by the last response assessment or the long-term follow-up assessment, whichever was the latest and available.[15,17] This outcome was considered useful in informing the clinical management of individual patients with cGVHD, but not critical to decision-making. TTNT results are summarized in Table 24.

Table 24: Summary of Time to Next Treatment From Studies KD025 to 213 and KD025 to 208 (mITT Population)

Outcome	KD025 to 213 Belumosudil 200 mg q.d. (N =)	KD025 to 208 Belumosudil 200 mg q.d. (N =)
TTNT, n (%)		
Censored		
Study ongoing		
Study discontinued		
Failure event: New cGVHD systemic therapy		
KM estimate, months		
25th percentile		
Median (95% CI)		
75th percentile		
KM estimate of TTNT probability (95% CI)[a]		
6 months		
12 months		
18 months		
24 months		
Cumulative failure rate, n (%)		
New cGVHD systemic therapy		
6 months		
12 months		
18 months		
24 months		

cGVHD = chronic graft-vs.-host disease; CI = confidence interval; KM = Kaplan-Meier; mITT = modified intention to treat; q.d. = once daily; TTNT = time to next treatment.

Note: Results are based on a data cut-off of , for study KD025 to 213 and , for study KD025 to 208.

[a]The probability of a patient not needing a new systemic treatment.

Sources: Clinical Study Report addenda for study KD025 to 213[16] and study KD025 to 208[18] and sponsor's summary of clinical evidence.[11] Details included in the table are from the sponsor's summary of clinical evidence.

Prednisone-Equivalent Dose of CSs

The change in systemic CS dose as mg/kg/day prednisone equivalent over time was measured.[15,17] Dose equivalencies were as follows: 1 mg prednisone was equivalent to 4 mg hydrocortisone, 0.8 mg methylprednisolone, 0.15 mg dexamethasone, and 0.8 mg triamcinolone. Systemic CS dose over time, change and percent change from baseline to the greatest CS dose reduction during belumosudil treatment, number and percentage of patients who reduced systemic CS use, and number and percentage of patients who ever discontinued systemic CS use during belumosudil treatment were evaluated. Data were collected throughout the study until 28 days after the last dose of the study drug. Transient CS dose increases of 1 mg/kg/day or lower were permitted to treat disease flares but must have been reduced to the prerandomization dose within 6 weeks; otherwise, belumosudil treatment was considered to have failed in the patient. A patient who experienced 3 or more disease flares requiring increased CS dose during the first 6 months of belumosudil treatment was also considered a belumosudil treatment failure. This outcome was considered useful in informing the clinical management of individual patients with cGVHD, but not critical to decision-making. The prednisone-equivalent dose of CS results is summarized in Table 25.

Table 25: Summary of Prednisone-Equivalent Dose of Corticosteroids From Study KD025 to 213 and Study KD025 to 208 (mITT Population)

Outcome	KD025 to 213 Belumosudil 200 mg q.d. (N =)	KD025 to 208 Belumosudil 200 mg q.d. (N =)
Prednisone-equivalent dose of CSs		
Baseline dose (mg/kg/day), median (range)		
Patients who reduced dose, n (%)		
Patients who discontinued CS usage, n (%)		
Change from baseline to greatest reduction (mg/kg/day), median (range)		
Percent change from baseline to greatest reduction (%), median (range)		

CS = corticosteroid; mITT = modified intention to treat; q.d. = once daily.

Note: Results are based on a data cut-off of , for study KD025 to 213 and , for study KD025 to 208.

Sources: Clinical Study Report addenda for study KD025 to 213[16] and study KD025 to 208[18] and sponsor's summary of clinical evidence.[11] Details included in the table are from the sponsor's summary of clinical evidence.

Table 26: Efficacy and Safety Results for Naive Indirect Comparison of Belumosudil, Ruxolitinib, and Ibrutinib

Detail	Belumosudil 200 mg q.d.		Ruxolitinib	Ibrutinib	
Study	KD025 to 213	KD025 to 208	REACH3	NCT02195869	NCT03474679
First author, year	Cutler (2021)[48]	Jagasia (2021)[49]	Zeiser (2021)[63]	Waller (2019)[70]	Doki (2021)[71]

Detail	Belumosudil 200 mg q.d.		Ruxolitinib	Ibrutinib	
Population description	Steroid-refractory cGVHD, 2 to 5 prior lines of therapy	cGVHD, 1 to 3 prior lines of therapy	Moderate or severe glucocorticoid-refractory or -dependent cGVHD	cGVHD after failure of prior therapy	Steroid-dependent or refractory cGVHD
ORR as best ORR					
Definition	Patients experiencing CR or PR according to the 2014 NIH consensus criteria	Patients experiencing CR or PR according to the 2014 NIH consensus criteria	Patients experiencing CR or PR according to the 2014 NIH consensus criteria	Patients experiencing CR or PR according to 2005 NIH consensus criteria	Patients experiencing CR or PR according to the 2014 NIH consensus criteria
Time point	Up to 12 months	Up to 39 months	Up to 24 weeks	26 months	37 weeks
N analyzed	66	17	165	42	19
CRR, n (%)	49 (74)	11 (65)	126 (76)	29 (69)	14 (74)
CR, n (%)	4 (6)	NR	20 (12)	13 (31)	2 (11)
PR, n (%)	45 (68)	NR	105 (64)	16 (38)	12 (63)
FFS					
N analyzed	66	NR[a]	165	42	19
Time point	12 months	NR[a]	6 months	18 months	15 months
FFS, n (%)	38 (57)	NR[a]	124 (75)	21 (51)	13 (67)
OS					
N analyzed	NR[b]	NR[a]	165	42	19
Time point	NR[b]	NR[a]	12 months	24 months	37 weeks
OS, n (%)	NR[b]	NR[a]	133 (81)	30 (71)	NR
LSS					
N analyzed	66	17	165	42	19
Time point	12 months	29 months	24 weeks	26 months	12 months
Improvement from baseline, n (%)	39 (59)	9 (53)	40 (24.2)	12 (29)	8 (42)
Discontinuation due to AEs					
N analyzed	65	17	165	42	19
Time point	12 months	29 months	6 months	NR	37 weeks
Discontinued	8 (19)	1 (6)	27 (16)	18 (43)	3 (16)

AE = adverse event; cGVHD = chronic graft-vs.-host disease; CR = complete response; FFS = failure-free survival; LSS = Lee Symptom Scale; NIH = National Institutes of Health; NR = not reported; ORR = overall response rate; OS = overall survival; PR = partial response; q.d. = once daily.

[a]Data were not reported for the population of interest (i.e., patients who received belumosudil 200 mg q.d.), and instead, results were pooled for the study.

[b]Data were not reported for a population consistent with the rest of the table (i.e., N = 66 patients) in study KD025 to 213.

Source: Sponsor-submitted feasibility assessment.[25]

Appendix 2: Summary and Appraisal of Pooled Data From Study KD025-213 and Study KD025-208

Note that this appendix has not been copy-edited.

Objective

The objective of this Appendix is to summarize and critically appraise the pooled data from study KD025 to 213 and study KD025 to 208 that were provided by the sponsor.[72] This summary informed the pharmacoeconomic evaluation.

Methods

The sponsor noted that study KD025 to 213 and study KD025 to 208 were similar in study design, end points (though different exploratory outcomes between the studies), frequency of efficacy and safety assessments, and eligibility criteria. The pooled analysis that was relevant to the CADTH review included only patients who had received belumosudil 200 mg once daily in the studies and had experience with at least 2 prior lines of therapy. The data cut-off dates were consistent with the individual studies in the main report: [redacted] for study KD025 to 213 and [redacted], for study KD025 to 208.

Results

Pooled efficacy results are summarized in Table 27 and pooled safety results are summarized in Table 28.

Table 27: Summary of Pooled Efficacy Analysis for Patients Who Received at Least 2 Prior Lines of Therapy

Outcome	Belumosudil 200 mg q.d. (N = [redacted])
ORR	
Best ORR, n (%)	
CR	[redacted]
PR	[redacted]
Primary DOR[a]	
Median DOR (95% CI), weeks	[redacted]
TTR[a]	
Median TTR, weeks (range)	[redacted]
Response by organ system	
Response by organ system, n / N (%)	
Skin	[redacted]

Outcome	Belumosudil 200 mg q.d. (N =)
Eyes	
Mouth	
Esophagus	
Upper gastrointestinal tract	
Lower gastrointestinal tract	
Liver	
Lungs	
Joints and fascia	
FFS	
Median FFS (95% CI), months	
Estimate of FFS probability (95% CI)	
At 6 months	
At 12 months	
At 24 months	
OS	
Median OS, months	Not reached
Estimate of OS probability (95% CI)	
At 12 months	
At 24 months	

CI = confidence interval; CR = complete response; DOR = duration of response; FFS = failure-free survival; ORR = overall response rate; OS = overall survival; PR = partial response; q.d. = once daily; TTR = time to response.

[a]Patients who responded.

Note: Results are based on a data cut-off of , for study KD025 to 213 and , for study KD025 to 208.

Source: Sponsor-provided request for additional information (requested September 8, 2023, response received September 15, 2023).[72]

Table 28: Summary of Pooled Safety Analysis for Patients Who Received at Least 2 Prior Lines of Therapy

AEs	Belumosudil 200 mg q.d. (N =)
Patients with ≥ 1 TEAE, n (%)	
Most common AEs, n (%)[a]	
Diarrhea	
Fatigue	
Nausea	

AEs	Belumosudil 200 mg q.d. (N =)
Dyspnea	
Headache	
Upper respiratory tract infection	
Peripheral edema	
Vomiting	
Cough	
SAE, n (%)	
Patients who stopped treatment due to AEs	
Deaths, n (%)	
AEs of special interest, n (%)	
Infections and infestations (any grade), n (%)	
Grade ≥ 3, n (%)	
Cytopenias	

AE = adverse event; NR = not reported; q.d. = once daily; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
Note: Results are based on a data cut-off of for study KD025 to 213 and , for study KD025 to 208.
[a]Most common TEAEs by preferred term occurring in at least 25% of patients.
Source: Sponsor-provided request for additional information (requested September 8, 2023, response received September 15, 2023).[72]

Critical Appraisal

In accordance with the Health Canada indication, the sponsor-submitted pooled analysis used to inform the pharmacoeconomic evaluation included only patients who had received belumosudil 200 mg once daily who had 2 prior systemic treatments. The analysis included patients and appeared to remove individuals from study KD025 to 208 who had only received 1 prior line of therapy ([%] patients from the total patients in the main clinical studies).

According to Health Canada, only study KD025 to 213 was appropriately designed, whereas study KD025 to 208 was an exploratory dose-finding study that lacked a specific hypothesis and was considered supportive evidence.[20] Although baseline characteristics were not provided for the individual studies in the pooled analysis, looking at the data available from the main clinical studies (refer to Table 11), most characteristics were similar between the studies. Study KD025 to 208 contributed few patients to the pooled analysis and the pooled results were generally consistent with those discussed in the main report for study KD025 to 213. The clinical experts consulted by CADTH noted a couple of eligibility criteria that may prevent the studies from being easily combined: the age groups (inclusion of adolescents in study KD025 to 213) and the different number of prior therapies (2 to 5 systemic treatments in study KD025 to 213 versus 1 to 3 systemic treatments in study KD025 to 208). Furthermore, the pooled analysis appears to be an unplanned post hoc analysis performed after data were collected, no adjustments were performed, and the data were combined

without any weighting (which is inappropriate when pooling data). When combining the data, an appropriate weight should be assigned to each study to produce a weighted average effect, as done with conventional pairwise meta-analysis. Had this been done, the small sample size of study KD025 to 208 would have provided less weight to the overall results. Based on the information provided by the sponsor, there also did not appear to be an investigation of inconsistency in the study results.

The internal and external validity of study KD025 to 213 and study KD025 to 208 described in the main report largely apply to the pooled analysis. Briefly, the key internal validity issues include the lack of control or comparator groups leading to potential confounding, knowledge of treatment assignments leading to increased risk of performance bias, and high discontinuation of patients over time resulting in a higher risk of attrition bias. Additionally, the evidence provided by the sponsor for the pooled analysis did not include HRQoL or patient-reported measures of symptoms, preventing assessment of these outcomes. The external validity issues include the lack of evidence from pediatric addenda years and older, differences in prior and concomitant cGVHD treatments compared with clinical practice according to the clinical experts, and relatively short median treatment duration and unknown long-term efficacy and harms for a disease that often requires years of clinical intervention. Although the pooled analysis included only patients who had 2 or more prior treatments, it was not clear these were all treatment failures, which is stipulated in the Health Canada indication. Also, the stable dose (minimum 2 weeks) of concomitant treatments may have been insufficient for the drugs to reach full effect before starting belumosudil making it difficult to discern potential treatment effects and harms between different drugs in the study. As a result, it is challenging to make firm conclusions from the pooled analysis due to the internal and external validity limitations and the evidence is very uncertain about the effects of belumosudil versus any comparators for cGVHD.

Pharmacoeconomic Review

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Abbreviations

AE	adverse event
BAT	best available therapy
BIA	budget impact analysis
cGVHD	chronic graft-versus-host disease
ECP	extracorporeal photopheresis
FFS	failure-free survival
GVHD	graft-versus-host disease
HR	hazard ratio
ICER	incremental cost-effectiveness ratio
IPTW	inverse probability of treatment weighting
ITC	indirect treatment comparison
OS	overall survival
PSM	partitioned survival model
QALY	quality-adjusted life-year
ToT	time on treatment
TTD	time to treatment discontinuation

Executive Summary

The executive summary comprises 2 tables (Table 1 and Table 2) and a conclusion.

Table 1: Submitted for Review

Item	Description
Drug product	Belumosudil (Rezurock), oral tablet
Submitted price	Belumosudil, 200 mg, oral tablet: $376.20
Indication	For the treatment of adult and pediatric patients 12 years and older with chronic graft-versus-host disease after failure of at least two prior lines of systemic therapy
Health Canada approval status	NOC
Health Canada review pathway	Project Orbis
NOC date	March 23, 2022
Reimbursement request	As per indication
Sponsor	sanofi-aventis Canada Inc.
Submission history	Previously reviewed: No

NOC = Notice of Compliance.

Table 2: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis PSM
Target population	Patients 12 years and older with chronic GVHD who have received at least 2 prior lines of systemic therapy
Treatment	Belumosudil
Comparator	BAT, consisting of ECP, mycophenolate mofetil, ibrutinib, methotrexate, imatinib, sirolimus, rituximab, everolimus, and a combination of cyclosporine and tacrolimus
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (40 years)
Key data sources	• KD025-213 and KD025-208 single-arm trials for belumosudil • BAT arm of the REACH3 trial for BAT (phase III trial of ruxolitinib versus BAT)
Submitted results	ICER for belumosudil versus BAT = $74,394 per QALY gained (incremental cost = $177,679; incremental QALYs = 2.39)
Key limitations	• The relative efficacy of belumosudil versus BAT was based on a naive comparison using data from the KD025-213 and KD025-208 single-arm trials (belumosudil) and the REACH3 trial (BAT). The REACH3 trial had limited generalizability to the belumosudil trials due to misalignment of the inclusion criteria between the studies (1 prior line of therapy versus 2 or more lines of therapy, respectively). It was determined that an ITC was not feasible, and the sponsor-submitted observation study had important limitations (i.e., heterogeneity, missing outcomes)

Component	Description
	preventing meaningful conclusions from being made for relative benefits or harms. • In the submitted model, the long-term extrapolation of OS and FFS beyond the available data for both belumosudil and BAT ([redacted] years for belumosudil; 2.2 years for BAT) is uncertain. • The sponsor likely overestimated the number of patients who would remain failure-free after discontinuing belumosudil. In years 2 and 10, 60% and 40% of failure-free patients receiving BAT remained on treatment respectively. For patients receiving belumosudil, during the same period, the proportion of patients remaining on treatment dropped from 52% to 9%. This would indicate many patients who discontinue belumosudil continue to receive benefits, but this same assumption is not applied to those who discontinue BAT. • The basket of drugs included in BAT and their distributions did not reflect Canadian clinical practice and are expected to vary by jurisdiction, which influences the cost-effectiveness estimates for belumosudil. • The exclusion of the costs of concomitant medications was inappropriate from the health care payer's perspective. • The impact on caregiver disutility is uncertain (informed by the published literature using multiple sclerosis as a proxy). • The impact of subsequent treatments on survival and quality of life are not captured in PSMs, as their structure does not explicitly model progression and subsequent treatments. Since more patients treated with BAT are estimated to have progressed disease, the model structure may overestimate the relative long-term treatment effect of belumosudil versus BAT.
CADTH reanalysis results	• CADTH incorporated the following changes to address the identified limitations: alternative OS and FFS extrapolations, assuming at least half of failure-free patients would remain on treatment, adjusting the components and distributions of BAT for costs, including costs associated with concomitant medications, and excluding caregiver disutility adjustments. • In CADTH's base case, the ICER for belumosudil versus BAT was $313,874 per QALY gained (incremental cost = 396,422; incremental QALYs = 1.26). A price reduction of at least 76% would be required for belumosudil to be cost-effective at a $50,000 per QALY gained threshold. • These results were driven by higher treatment costs and adjustments in FFS. The increase in treatment costs associated with belumosudil was largely influenced by adjustments to the duration of treatment, which were deemed more clinically appropriate by the experts consulted by CADTH. The reduction in incremental LYs and QALYs was due to more clinically plausible extrapolations of OS and FFS for belumosudil relative to BAT. Finally, the CADTH results do not assume that most patients receiving belumosudil will stop treatment and continue to experience large benefits.

BAT = best available therapy; GVHD = graft-versus-host disease; ECP = extracorporeal photopheresis; FFS = failure-free survival; ICER = incremental cost-effectiveness ratio; ITC = indirect treatment comparison; LY = life-year; OS = overall survival; PSM = partitioned survival model; QALY = quality-adjusted life-year.

Conclusions

CADTH's Clinical Review of the KD025-213 and KD025-208 trials of belumosudil in patients with chronic graft-versus-host disease (cGVHD) after failure of at least 2 prior lines of systemic therapy noted the lack of an appropriate comparator and a control group, and that the trials did not include patients younger than 20 years old. It was determined that an indirect treatment comparison (ITC) was not feasible and the sponsor-submitted observational study comparing belumosudil with best available therapy (BAT) had important limitations (i.e., heterogeneity, missing outcomes) preventing meaningful conclusions from being made. Overall, due to the lack of informative direct and indirect evidence, it is very uncertain how belumosudil compares with other cGVHD treatments in terms of efficacy and safety.

The sponsor submitted a pharmacoeconomic model based on a naive comparison using the KD025-213 and KD025-208 trials to inform the belumosudil arm, and the REACH3 trial to inform the BAT arm. As a result, the relative clinical efficacy of belumosudil versus relevant comparators is highly uncertain. CADTH identified several limitations with the sponsor's economic submission that could be addressed. To do this, CADTH: used observational data to inform the comparative efficacy (i.e., overall survival [OS] and failure-free survival [FFS]) of belumosudil versus BAT; revised the assumptions about time on treatment (ToT), which led to a more plausible number of patients remaining on treatment (especially in the belumosudil arm); adjusted the proportion of patients on components of BAT to align with Canadian clinical practice; aligned the analysis with the health care payer perspective by including the costs associated with concomitant medications; and included uncertain caregiver utility adjustments in a scenario analysis.

In the CADTH base case, the incremental cost-effectiveness ratio (ICER) for belumosudil versus BAT was $313,874 per quality-adjusted life-year (QALY) gained (incremental cost: 396,422; incremental QALYs: 1.26). The probability of being cost-effective at a threshold of $50,000 per QALY gained was 0%. The price of belumosudil would need to be $32,955 per year, reflecting a price reduction of 76%, to be considered cost-effective at a threshold of $50,000 per QALY gained. Cost-effectiveness was driven by the higher treatment cost of belumosudil and improvement in FFS for BAT. The CADTH results estimate higher incremental costs and lower incremental life-years and QALYs relative to the sponsor's base-case analysis. The increase in treatment costs associated with belumosudil was largely influenced by adjustments to the duration of treatment, which were deemed more clinically appropriate by the experts consulted by CADTH. The reduction in incremental life-years and QALYs was due to more clinically plausible extrapolations of OS and FFS for belumosudil relative to BAT. CADTH notes the analysis still assumes survival and quality of life gains with belumosudil of 1.84 life-years and 1.26 QALYs, respectively. Finally, the CADTH results do not assume that most patients receiving belumosudil will stop treatment and continue to experience large benefits.

Although the CADTH reanalysis attempted to address the identified limitations of the sponsor's economic submission, the cost-effectiveness of belumosudil remains highly uncertain. No robust evidence was provided in this submission to indicate a superior treatment effect of belumosudil relative to BAT. Even though CADTH used a sponsor-submitted observational study to inform the comparative efficacy rather than the sponsor's naive-comparison approach, there are important limitations to these data, preventing meaningful conclusions on the comparative benefits or harms of belumosudil. CADTH was also unable to address limitations associated with the model structure, which favoured belumosudil, as partitioned survival models (PSMs) do not capture the impact of subsequent treatments on survival and quality of life. Given the remaining uncertainty, further price reductions may be sought.

Stakeholder Input Relevant to the Economic Review

This section is a summary of the feedback received from the patient groups, registered clinicians, and drug plans that participated in the CADTH review process.

Patient input was provided by 2 groups: the Leukemia and Lymphoma Society of Canada and Myeloma Canada. Survey respondents indicated that cGVHD symptoms, such as skin problems, dry mouth with or without mouth ulcers, dry eyes, joint pain, mobility issues, and difficulty breathing negatively impact daily life. Dry eyes were found to have the most impact on the patient's quality of life, followed by skin issues, mouth issues, and shortness of breath. Respondents had experience with corticosteroids such as prednisone, which was noted to result in neurologic or circulatory side effects. Patients noted concerns regarding side effects that impact quality of life, with the most common severe side effects of current treatments being weight loss or gain, fatigue, increased hunger or thirst, and muscle pain. Respondents indicated that the most important outcomes for new treatment options include improvement in length of survival, quality of life, improved physical health, and reduced side effects. Patients with experience using belumosudil noted that side effects with treatment were minimal and tolerable, and their corticosteroid dose was able to be reduced as a result of belumosudil.

Registered clinician input was received from 2 groups: Ontario Health (Cancer Care Ontario) Hematology Cancer Drug Advisory Committee and Cell Therapy Transplant Canada. The clinician input noted that off-label treatment for cGVHD includes extracorporeal photopheresis (ECP), mycophenolate mofetil, sirolimus, everolimus, imatinib, and rituximab. There is no current standard of care as a second-line therapy. Health Canada–indicated treatments for cGVHD include ibrutinib and ruxolitinib; however, ibrutinib is not funded in Canada. If belumosudil were to be available, it is expected to be used in patients whose disease has failed to respond to these established therapies.

The drug plan input raised questions about belumosudil's place in therapy, specifically, what treatments might count as prior systemic therapies, and whether belumosudil would be used independently or in combination with other currently used cGVHD therapies. The drug plan input noted concerns with a lack of an appropriate comparator in the key clinical trials and the measurement of efficacy solely as overall response rate (complete or partial). Additionally, the drug plan input raised a question regarding the potential use of belumosudil for acute GVHD, despite the indication not including these patients.

Several of these concerns were addressed in the sponsor's model:

- clinical efficacy was based on OS and FFS
- quality of life differences by response status were captured
- costs of subsequent systemic therapies were captured in the sponsor's model.

CADTH was unable to address the following concerns raised from stakeholder input:

- the impact of treatment on corticosteroid doses, as they were not included as an outcome in the sponsor's model
- the use of belumosudil in acute GVHD would be considered a different indication for a different clinical population.

Economic Review

The current review is for belumosudil (Rezurock) for patients aged 12 years and older with cGVHD who have received at least 2 prior lines of systemic therapy.

Economic Evaluation

Summary of Sponsor's Economic Evaluation

Overview

The sponsor submitted a cost-utility analysis of belumosudil versus BAT. The model population comprised patients aged 12 years and older with cGVHD who have received at least 2 prior lines of systemic therapy. The target population is aligned with the Health Canada–indicated population and reimbursement request.

Belumosudil is available as a 200 mg oral tablet. The recommended use of belumosudil is 200 mg daily (if there is no concomitant use of proton pump inhibitors [PPIs]).[1] At the sponsor's submitted price of $376.20 per 200 mg tablet, the annual drug acquisition costs of belumosudil would be $137,313 if patients remained on therapy for a full year (and $274,626 per year if patients are on concomitant PPIs and require belumosudil twice daily).[2]

BAT consisted of a basket of the following comparator treatments: ECP, mycophenolate mofetil, ibrutinib, low-dose methotrexate, imatinib, sirolimus, rituximab, and a combination of cyclosporine and tacrolimus.[2] The distribution of BAT components was informed by the REACH3 trial and was further adjusted for the removal of treatments that were deemed not relevant for Canada by the sponsor. Dosing for each BAT comparator treatment was determined based on their respective trial and assumed to be used for a lifetime treatment duration, except for rituximab (4 weeks) and ECP (52 weeks). Acquisition costs per 4-week cycle for BAT were estimated to start at $4,587.30 in the first month and decrease to $3,546.62 for week 25 and beyond due to re-weighting based on the treatment duration of each component. Drug wastage was not considered in the base-case analysis.

The base-case analysis was conducted from the Canadian public health care payer perspective. Costs and clinical outcomes (life-years and QALYs) were modelled over a lifetime time horizon (40 years; 4-week cycle length), with costs and outcomes discounted at 1.5% annually.

Model Structure

The sponsor used a PSM with 3 mutually exclusive health states: failure-free, failure, and death. In the failure-free state, patients could discontinue treatment but remain failure-free until discontinuation, and their utilities were assigned according to 3 categories: partial response, complete response, or lack of response. In the failure state, patients were further separated according to the cause of their failure event (recurrence of their malignancy or initiation of a new cGVHD systemic therapy) and their utilities were assumed the same. The model does not incorporate the transition of patients between the health states, but rather the proportion of patients who are failure-free and the proportion who are alive at each time point are estimated independently using FFS and OS curves. A figure of the sponsor's model structure can be found in Appendix 3 (Figure 1).

Model Inputs

The baseline patient characteristics in the sponsor's model were aligned with the pooled population of the KD025-213 and KD025-208 trials, consisting of patients with cGVHD who had had 2 or more previous lines of therapy (mean age of 53.9 years; 58% male).[2]

In the complete absence of head-to-head comparisons between belumosudil and any components of BAT, the sponsor used naive-comparison methods to estimate the relative efficacy of belumosudil versus comparators.[2] Key clinical efficacy inputs (i.e., OS and FFS), time to treatment discontinuation (TTD), duration of response, and the distribution of failure events (e.g., whether due to progression or initiation of new systemic therapy) were derived from the pooled patient-level data from the KD025-213 and KD025-208 trials, which had a maximum duration of follow-up of [redacted] years ([redacted] data cut for study KD025-213, and [redacted] data cut for study KD025-208) to inform clinical efficacy for belumosudil. To inform clinical efficacy for BAT, reconstructed individual patient-level data were generated using the Guyot et al.[3] algorithms to obtain data on OS, FFS, and time to response from the REACH3 trial, which had a maximum duration of follow-up of 2.2 years.[4]

All clinical outcomes were extrapolated beyond the trial duration by fitting parametric survival curves to the belumosudil trial data and REACH3 trial data. Model selection was based on statistical fit (Akaike information criterion, Bayesian information criterion, visual inspection of goodness of fit to observed data) and clinical plausibility.[2] The sponsor selected an exponential distribution to extrapolate OS for both belumosudil and BAT and capped it using the mortality rates for the general population. For the long-term extrapolations of FFS, generalized gamma distributions were selected for both treatment arms. FFS was defined as the time between the start of treatment (belumosudil or BAT) and the addition of a new cGVHD systemic therapy, recurrent malignancy, or nonrelapse mortality. For the extrapolation of ToT, the sponsor fitted a log-normal distribution to the TTD curve of belumosudil; for BAT, the sponsor applied a hazard ratio (HR) to the belumosudil TTD curves (calibrated to the median treatment duration from the REACH3 trial) and used an exponential distribution to extrapolate beyond the trial period. In the model, the time to response and duration of response curves were used to estimate the in-response curve for each comparator and a log-normal distribution was selected for treatment arms. Patients accrued different costs and utilities within the failure-free state (based on response and duration of treatment) and the failure state (based on the reasons for failure).

The dose of belumosudil used in the model is consistent with the product monograph, where the majority of patients received 200 mg once-daily dosing, and 5% of patients were assumed to receive 200 mg twice daily.

The EQ-5D-3L scores were indirectly obtained from a mapping algorithm published by Thompson et al.[5] using the Patient-Reported Outcomes Measure Information System (PROMIS) Global Health scores assessed in the KD025-213 trial (post hoc analyses of the modified intention-to-treat population). Health state utility values were based on a regression model for the failure-free and failure health states fitted to the EQ-5D-3L utility scores (the tariff used is not stated). Within the failure-free health state, utility values were assumed to be the same for those in response (0.752 regardless of whether the patient has a complete or partial response) and slightly lower for those experiencing a lack of response (0.723). In the failure health state, the

utility value for those receiving a new cGVHD systemic therapy and experiencing recurrent malignancy was assumed to be the same (0.479) and was estimated based on utility values from other published sources[6-9] and weighted by the proportion of patients with those malignancies from the KD025-213 trial.[2] Disutility due to adverse events (AEs) was included as utility decrements based on prior National Institute for Health and Care Excellence (NICE) assessments or assumptions for the duration of the AE.[10-12]

The model included costs related to drug acquisition, administration, disease management by health state, and AEs. Drug acquisition costs and dosing were consistent with those reported in the Overview section of this report, with drug costs for belumosudil obtained from the sponsor's submission. Costs of comparator treatments were obtained from the Ontario Drug Benefit Formulary,[13] the Ontario public drug program's Exceptional Access Program,[14] and previous CADTH reviews. Administration costs for oral drugs were assumed to be zero and were included for IV treatments only.[2,15] Disease management costs varied by health state and were estimated based on feedback from the clinical experts and the previous CADTH review of ruxolitinib. Disease management costs included costs for a hematologist, gastrointestinal specialist, ophthalmologist, dermatologist, respirologist, psychiatrist, and cardiologist visits; diagnostic procedures such as a full complete blood count (CBC) panel, pulmonary function test, CT scan or ultrasound; and hospitalization or emergency department visit.[15] Costs of recurrent malignancy were included based on Canadian Institute for Health Information costs for the treatment of malignancy.[16] AE costs were estimated as a weighted average of the costs of each AE and the proportions of patients experiencing each AE based on clinical expert input.

Summary of Sponsor's Economic Evaluation Results

All analyses were run probabilistically (100 iterations for the base case and 1,000 iterations for the scenario analyses). The deterministic and probabilistic results were similar. The probabilistic findings are presented subsequently. Additional results from the sponsor's submitted economic evaluation base case are presented in Appendix 3.

Base-Case Results

Belumosudil was associated with an estimated cost of $492,661 and 4.68 QALYs over the lifetime time horizon (40 years), resulting in an ICER of $74,394 per QALY gained (incremental costs: $177,679; incremental QALYs: 2.38) versus BAT (Table 3). In the sponsor's base case, belumosudil had an approximate 28% probability of being cost-effective at a willingness-to-pay threshold of $50,000 per QALY gained. The majority (60%) of incremental QALYs associated with belumosudil were accrued beyond the trial follow-up (■ years) and were based on the sponsor's extrapolations of the trial data. Furthermore, approximately 37% of QALYs were accrued in patients in the failure-free health state with a lack of response to belumosudil, and 42% in the postprogression (failure) health state. Results were driven by the drug acquisition costs of belumosudil and gains in QALYs due to extrapolated benefits from delaying failure (despite treatment discontinuation) and additional survival. At 24 years, 12% of patients receiving treatment with belumosudil were predicted to be alive and to no longer experience any disease progression (i.e., all events from this time forward are death). The submitted model predicted that 2% of patients would be alive in the belumosudil group at the 40-year time horizon.

Table 3: Summary of the Sponsor's Economic Evaluation Results

Drug	Total costs ($)	Incremental costs ($)	Total QALYs	Incremental QALYs	ICER versus BAT ($/QALY)
BAT	314,981	Reference	2.30	Reference	Reference
Belumosudil	492,661	177,679	4.68	2.38	74,394

BAT = best available therapy; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Note: All submitted analyses were based on the publicly available prices of comparator treatments.

Source: Sponsor's pharmacoeconomic submission, based on model results from an updated economic model received on August 25, 2023, with the functionality to revise the use of seeding (100 iterations).

Additional results from the sponsor's submitted economic evaluation base case are presented in Appendix 3.

Sensitivity and Scenario Analysis Results

The sponsor performed scenario analyses considering alternative time horizons, including the use of concomitant medications, assuming a proportion of patients will require twice-daily dosing, and implementing a 5-year treatment-stopping rule. The ICER for belumosudil versus BAT varied between $59,645 and $86,459 across all scenarios. One-way sensitivity analyses demonstrated that the model was most sensitive to variations in the OS fit parameters and FFS fit parameters used to extrapolate those outcomes (ICERs ranging from $23,237 to $91,547 per QALY gained).

The sponsor conducted a scenario analysis from a societal perspective. This analysis included additional costs associated with the patient's productivity (lost time from work due to medical visits, outpatient treatment of AEs, and hospital stays) and out-of-pocket costs (travel and accommodation for treatment with ECP). In this analysis, relative to BAT, the ICER was $72,358 per QALY gained. This result was similar to the sponsor's base-case analysis using a health care payer perspective.

CADTH Appraisal of the Sponsor's Economic Evaluation

CADTH identified several key limitations to the sponsor's analysis that have notable implications for the economic analysis:

- **The comparative efficacy and safety of belumosudil is uncertain.** In the absence of direct comparative clinical evidence for belumosudil versus BAT, the sponsor considered a naive comparison, pooling the KD025-213 and KD025-208 single-arm trials for belumosudil and using reconstructed individual patient-level data from the BAT arm of the REACH3 trial for BAT. CADTH's Clinical Review team appraised the belumosudil trials and was unable to make robust conclusions about the effects of belumosudil on all efficacy measures (e.g., OS, FFS, and harms) versus any comparator. CADTH's Clinical Review team also reported that the REACH3 trial was not considered appropriate for use in an ITC due to the misalignment of the inclusion criteria between the studies (1 prior line of therapy in the REACH3 trial versus 2 or more lines of therapy in the belumosudil studies), and the population and outcome data were not reported by line of therapy. As a result, the comparative efficacy of belumosudil versus BAT is uncertain.

The sponsor also submitted an observational study from an external control arm using inverse probability of treatment weighting (IPTW) to provide indirect comparative evidence of the treatment with belumosudil versus BAT for patients with cGVHD.[17] The study was conducted using real-world data from the US Optum Clinformatics Data Mart database (for BAT) and the results from the KD025-213 and KD025-208 studies (for belumosudil). While the inferences drawn from the IPTW data on how belumosudil compares with BAT remain highly uncertain due to internal validity issues, the analysis, despite its limitations, still offers some comparative evidence as an alternative to a naive comparison.

  - CADTH was unable to draw firm conclusions from the naive comparison. The CADTH reanalysis incorporated the sponsor-submitted IPTW data to estimate the comparative efficacy of belumosudil versus BAT (for OS and FFS), acknowledging that any cost-effectiveness estimates remain highly uncertain.

- **The extrapolation of OS is uncertain.** The submitted model predicted that treatment with belumosudil would result in longer survival (by 3.39 years) versus BAT. CADTH's Clinical Review reported that the evidence on OS for belumosudil versus any comparator is uncertain. When fitting parametric distributions to support the long-term extrapolation of OS data, the sponsor selected distributions based primarily on goodness-of-fit criteria and clinical plausibility. The sponsor applied jointly fitted exponential models to predict OS beyond the trial periods ([redacted] years for belumosudil and 2.2 years for BAT). While CADTH acknowledges that the sponsor chose OS models largely based on an Akaike information criterion or Bayesian information criterion, it is important to consider that those tests assess the internal validity of the fitted models but not the extrapolated period. The clinical experts consulted by CADTH assessed the plausibility of the survival estimates at various time points generated by alternative extrapolation curves and alternatively by applying the OS HR derived from the IPTW study described earlier to the sponsor's choice of extrapolations for BAT (exponential). The clinical experts agreed that the predicted survival benefits from the sponsor's base case for belumosudil seemed very optimistic, but the survival estimates for BAT at various time points seemed more reasonable. They considered the survival estimates generated with the HR approach as more plausible to provide an approximation of the relative survival gains. However, it is important to note that this estimation may still be influenced by varying severity levels between the patients in the belumosudil trials and the observational study. Despite this uncertainty, the application of the IPTW data appeared more robust and plausible than relying on a naive comparison.
  - The CADTH reanalysis used an HR approach by applying an HR of 1.37 to the exponential distribution of BAT to derive the belumosudil OS extrapolations.
  - CADTH conducted a scenario analysis maintaining the sponsor's choice of OS extrapolations (exponential) after all other changes to the base case (as shown subsequently).
- **The extrapolation of FFS underestimated the efficacy of BAT.** The sponsor used generalized gamma curves to extrapolate FFS for belumosudil and BAT, based on the naive comparison. This resulted in the number of patients in the failure-free health state receiving BAT at years 1, 5, and 10 being 34%, 3%, and 0%, respectively. The clinical experts consulted by CADTH disagreed that at 10 years no

patients treated with BAT would remain failure-free, as some of them will respond to BAT treatment. They suggested that a more plausible estimate would be approximately 10%. They assessed the plausibility at various time points generated by alternative extrapolation curves or applying the FFS HR derived from the IPTW study to the belumosudil arm. This latter approach resulted in FFS estimates at key time points (and differences between the treatment arms) that were deemed more plausible and aligned with their clinical expectations (at 10 years, approximately 20% and 10% of patients remain failure-free in the belumosudil and BAT arms, respectively).

  - The CADTH reanalysis maintained the sponsor's use of the generalized gamma curve to extrapolate FFS for belumosudil and applied an HR of 1.33 that was derived from the IPTW study to derive the BAT FFS extrapolation.

- **The extrapolation of ToT overestimates the treatment benefits after treatment discontinuation.** The extrapolation of the TTD data beyond the trial period is uncertain. The sponsor predicts that a large proportion of patients remained failure-free without receiving treatment (and thus did not accrue treatment costs). In the sponsor's base case, the correlation between FFS and ToT was stronger for those treated with BAT than those treated with belumosudil. From years 2 to 10, while 60% to 40% of failure-free patients receiving BAT remained on treatment, the proportions dropped from 52% to 9%, respectively, for patients receiving belumosudil for the same period. The clinical experts consulted by CADTH indicated that they expect some patients to remain failure-free while tapering and to eventually discontinue treatment with systemic therapy. However, the sponsor's predicted number of patients remaining failure-free after discontinuing belumosudil was deemed unrealistic. The clinical experts consulted by CADTH indicated that due to the lack of long-term data to infer the long-lasting effects of belumosudil, it is more plausible to assume that at least half of patients who remain failure-free would continue on systemic therapy, including those patients who may have been able to reduce corticosteroid use.
  - The CADTH reanalysis maintained the sponsor's selected extrapolation of ToT, constraining it to ensure that a minimum of 50% of failure-free patients remain on treatment.
- **The distribution of patients receiving the alternative treatments included in BAT is not aligned with current Canadian clinical practice.** To estimate BAT costs, the sponsor derived the proportion of patients across possible treatments based on distributions from the REACH3 trial, adjusted based on clinical expert opinion (Table 11). When validating the sponsor's distributions with the clinical experts consulted by CADTH for this review, they noted that some therapies on the list were not available in their jurisdictions (but may be available in others) and some were rarely used in their practice, whereas some were used in much higher frequency. Specifically, the difference between the sponsor's assumption and what is expected in Canadian clinical practice is the use of ruxolitinib. The sponsor assumed that ruxolitinib would be the standard of care as a second-line treatment for cGVHD and thus excluded it from BAT in its analysis, which does not align with the feedback obtained by CADTH. Drug plans and clinical expert feedback received by CADTH for this review indicated that ruxolitinib would be routinely used as a third-line treatment option for patients with cGVHD and should be considered a relevant comparator for belumosudil. Given the variability in the treatment

used for cGVHD across Canada, the cost-effectiveness of belumosudil versus BAT will likely vary by jurisdiction.

  - To address this limitation, CADTH adjusted the proportions of patients receiving each of the treatments included in BAT to align with the expectations of Canadian clinical practice (Table 14). CADTH included ruxolitinib as a comparator treatment in BAT. CADTH notes that due to the use of a single efficacy measure for BAT (i.e., not as a weighted measure of each treatment's efficacy), changes to the BAT distribution only impact costs and not treatment efficacy.

- **The exclusion of concomitant medication costs from the analysis was inappropriate.** The sponsor excluded the costs of concomitant therapies from its base-case analysis. The clinical experts consulted by CADTH noted that many patients would receive concomitant medication while receiving treatment, which is expected to be similar for patients treated with either belumosudil or BAT for the most part. The costs of these treatments are relevant from the health care payer perspective and thus should be included in the analysis, at best, with slightly fewer patients being treated with belumosudil requiring concomitant therapies.
  - CADTH included the costs of concomitant medications in its reanalysis. The CADTH reanalysis adjusted the proportions of patients on different concomitant medications to better align with Canadian clinical practice (Table 15). CADTH notes that due to the use of a single efficacy measure for belumosudil or BAT (i.e., not as a weighted measure of each treatment's efficacy), changes to the concomitant therapy only impact costs and not treatment efficacy.
- **The model structure has important limitations for the decision problem.** The sponsor used a PSM to estimate costs and outcomes associated with the treatment of cGVHD after the failure of at least 2 prior systemic therapies. Although PSMs are routinely used in economic evaluation, this approach is not suitable when patients can experience a response on subsequent lines of therapy. In the failure health state, the model accounts for the costs of subsequent therapies over a lifetime time horizon but does not capture clinical outcomes (i.e., response). The clinical experts consulted by CADTH noted that patients can experience response in later lines of therapy and may experience survival improvements, increases in quality of life, and the discontinuation of immunosuppressant therapy; therefore, the magnitude of the benefit in the extrapolated period was estimated inaccurately.
  - CADTH was unable to address this limitation within the submitted model structure.
- **The caregiver disutility included in the base case is uncertain**. The sponsor noted that a patient's health status and well-being would have a significant impact on caregivers and therefore included caregiver disutility in its base case. It was assumed that patients in the failure-free health state (with partial response or no response) and failure health states would have a caregiver utility decrement applied each model cycle. Although caregivers are often impacted by a patient's health status, the evidence to support the degree of impact for cGVHD-specific caregivers is uncertain, as its values were informed by the published literature using multiple sclerosis as a proxy.
  - CADTH included caregiver disutilities in a scenario analysis.

Additionally, the following key assumptions were made by the sponsor and have been appraised by CADTH (refer to Table 4).

Table 4: Key Assumptions of the Submitted Economic Evaluation (Not Noted as Limitations to the Submission)

Sponsor's key assumption	CADTH comment
Treatment is assumed to impact rates of recurrent malignancy.	Uncertain. The assumption that treatment with belumosudil or BAT influences malignancy relapse rates for the underlying conditions for which patients received a stem cell transplant leading to their cGVHD is uncertain. The clinical experts consulted by CADTH indicated that the impact of systematic therapies for cGVHD is unknown at this time. While treatment itself is not expected to act on the underlying conditions, cGVHD itself may influence malignancy relapse (i.e., cGVHD may reduce the risk of malignancy in some patients or increase the risk of secondary malignancy in others).
Patients who experienced recurrent malignancy did not receive subsequent cGVHD therapy in the failed health state.	Not acceptable. The clinical experts consulted by CADTH indicated that in the event of recurrent malignancy, it would be important to treat both diseases (i.e., the malignancy and cGVHD).
Health state utility values were based on the belumosudil trials for the failure-free health state, and the literature for the failed health state. Further, it was assumed that utility values would differ based on response status (i.e., complete response, partial response, and lack of response), and by reason for failure (i.e., recurrent malignancy, new cGVHD systemic therapy).	Uncertain. Ideally, health state utility values are derived from the same population using the same instrument. The clinical experts consulted by CADTH agreed that patients' well-being may differ by response and reason for failure; however, the utilities applied in the sponsor's submission did not meet face validity.
Proportion of patients who would receive belumosudil twice daily.	Acceptable. The sponsor assumed, based on clinical expert opinion, that 5% of patients would be treated with belumosudil twice daily due to PPI or strong *CYP3A* inhibitor use. It is uncertain what proportion of patients would be on the higher-dose regimen of belumosudil, which impacts the drug cost and efficacy parameters used in the model; however, the clinical experts consulted by CADTH agreed that 5% was a reasonable assumption.
ECP costs may be outdated.	Uncertain. The source for ECP costs dated from 2006 for services provided in the US; these costs may no longer reflect the costs for providers in Canada and will likely need updates for future submissions.

BAT = best available therapy; cGVHD = chronic graft-versus-host disease; ECP = extracorporeal photopheresis; PPI = proton pump inhibitor.

CADTH Reanalyses of the Economic Evaluation

Base-Case Results

Several limitations with the sponsor's submission could not be adequately addressed (i.e., lack of head-to-head comparative clinical data, uncertainty regarding long-term clinical effectiveness, and lack of treatment effect from subsequent treatments within the model structure design).

The CADTH base case was derived by making changes in model parameter values and assumptions, in consultation with the clinical experts. These changes, summarized in Table 5, included alternative OS and FFS extrapolations, assuming at least half of patients in the failure-free health state would remain on treatment, adjusting the components of BAT, including costs associated with concomitant medications (and adjusting their distribution), and excluding caregiver disutility.

Table 5: CADTH Revisions to the Submitted Economic Evaluation

Stepped analysis	Sponsor's value or assumption	CADTH value or assumption
Corrections to sponsor's base case		
None	—	—
Changes to derive the CADTH base case		
1. OS extrapolation	Extrapolated all treatments using exponential distributions.	Extrapolated BAT using exponential distribution and applied an HR of 1.37 to derive the belumosudil curve.
2. FFS extrapolation	Extrapolated all treatments using generalized gamma distributions.	Extrapolated belumosudil using generalized gamma distribution and applied an HR of 1.33 to derive the BAT curve.
3. ToT extrapolation	• Belumosudil: Extrapolated using log-normal distribution. • BAT: Applied a hazard ratio of 1.7.	Maintained the sponsor's extrapolation methods constraining ToT such that at least 50% of patients remain on treatment, if failure-free, for both belumosudil and BAT.
4. BAT distribution	Distribution of patients on BAT components as shown in Table 11 and exclusion of ruxolitinib.	Adjusted proportions of patients on components of BAT and included ruxolitinib (Table 14).
5. Concomitant medications	Excluded.	Included concomitant medications and adjusted the proportion of patients receiving them to align with Canadian clinical practice (Table 15).
6. Caregiver disutility	Included.	Excluded.
CADTH base case	Reanalysis 1 + 2 + 3 + 4 + 5 + 6	

BAT = best available therapy; FFS = failure-free survival; HR = hazard ratio; OS = overall survival; ToT = time on treatment.

The CADTH base case resulted in an ICER of $313,874 per QALY gained for belumosudil versus BAT (incremental cost: $96,422; incremental QALYs: 1.26) with a 0% probability of being cost-effective at a willingness-to-pay threshold of $50,000 per QALY gained. Cost-effectiveness was driven by the higher treatment cost of belumosudil (approximately $353,000 per patient) and improvement in FFS for BAT. The results of the stepped analysis are presented in Table 6 (disaggregated results are presented in Appendix 4).

The CADTH results estimate higher incremental costs and lower incremental life-years and QALYs relative to the sponsor's base-case analysis. The increase in treatment costs associated with belumosudil was largely influenced by adjustments to the duration of treatment, which were deemed more clinically appropriate by the experts consulted by CADTH. The reduction in incremental life-years and QALYs was due to more clinically plausible extrapolations of OS and FFS for belumosudil relative to BAT. CADTH notes the

analysis still assumes survival and quality of life gains with belumosudil of 1.84 life-years and 1.26 QALYs, respectively.

Table 6: Summary of the Stepped Analysis of the CADTH Reanalysis Results

Stepped analysis	Drug	Total costs ($)	Total QALYs	ICER ($/QALY)
Sponsor's base case (deterministic)	BAT	312,278	2.30	Reference
	Belumosudil	477,065	4.85	64,496
CADTH reanalysis 1: OS extrapolation	BAT	312,278	2.30	Reference
	Belumosudil	418,070	4.30	52,866
CADTH reanalysis 2: FFS extrapolation	BAT	220,430	3.07	Reference
	Belumosudil	477,065	4.85	143,781
CADTH reanalysis 3: ToT extrapolation	BAT	313,970	2.30	Reference
	Belumosudil	719,607	4.85	158,729
CADTH reanalysis 4: BAT distribution	BAT	308,001	2.30	Reference
	Belumosudil	477,065	4.85	66,321
CADTH reanalysis 5: Concomitant medications	BAT	313,027	2.30	Reference
	Belumosudil	492,159	4.85	70,110
CADTH reanalysis 6: Caregiver disutility	BAT	312,278	3.06	Reference
	Belumosudil	477,065	5.68	63,007
CADTH base case (deterministic) (1 + 2 + 3 + 4 + 5 + 6)	BAT	267,780	3.62	Reference
	Belumosudil	673,454	4.95	304,263
CADTH base case (probabilistic) (1 + 2 + 3 + 4 + 5 + 6)	BAT	273,389	3.66	Reference
	Belumosudil	669,811	4.92	313,874

BAT = best available therapy; FFS = failure-free survival; ICER = incremental cost-effectiveness ratio; OS = overall survival; QALY = quality-adjusted life-year; ToT = time on treatment.

Note: The CADTH reanalysis is based on publicly available prices of the comparator treatments. The results of all steps are presented deterministically, while the cumulative CADTH reanalysis is presented probabilistically.

Scenario Analysis Results

A price reduction analysis based on the CADTH base case indicated that, at a willingness-to-pay threshold of $50,000 per QALY gained, belumosudil would be considered cost-effective versus BAT with a 76% price reduction (Table 7).

Table 7: CADTH Price Reduction Analyses

Analysis	ICERs for belumosudil versus BAT ($/QALY)	
Price reduction	**Sponsor base case**	**CADTH reanalysis**
No price reduction	64,496	304,263
10%	55,910	270,929
20%	47,323	237,596
30%	38,737	204,262
40%	30,151	170,929
50%	21,565	137,596
60%	12,979	104,262
70%	4,392	70,929
80%	Dominant	37,595
90%	Dominant	4,262
100%	Dominant	Dominant

BAT = best available therapy; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Additionally, CADTH conducted scenario analyses using the CADTH base case to determine the impact of alternative assumptions on the cost-effectiveness of belumosudil (Table 16). The scenario that maintained the sponsor's OS extrapolation using the exponential distribution for both model arms resulted in an ICER of $234,727 per QALY gained for belumosudil versus BAT. Including the caregiver disutilities resulted in an ICER of $329,178 per QALY gained for belumosudil versus BAT, similar to the CADTH base-case results.

Issues for Consideration

- CADTH's analyses rely on publicly accessible list prices and do not reflect existing confidential prices negotiated by public plans. When existing confidential discounts for comparators are considered, greater price reductions for belumosudil may be required to achieve cost-effectiveness.
- The Scottish Medicines Consortium completed the initial assessment for belumosudil and, despite having concluded that the efficacy and safety of belumosudil relative to relevant comparators is unknown, since August 2023, belumosudil can be prescribed in Scotland within the ultra-orphan pathway while further evidence on its effectiveness is generated. After 3 years, the sponsor will provide an updated submission for reassessment to allow a decision on its routine use under NHS Scotland.

Overall Conclusions

CADTH's Clinical Review of the KD025-213 and KD025-208 trials of belumosudil in patients with cGVHD after failure of at least 2 prior lines of systemic therapy noted the lack of an appropriate comparator and a control group, and that the trials did not include patients younger than 20 years old. It was determined that an ITC was not feasible and the sponsor-submitted observational study comparing belumosudil with BAT had important limitations (i.e., heterogeneity, missing outcomes) preventing meaningful conclusions from

being made. Overall, due to the lack of informative direct and indirect evidence, it is very uncertain how belumosudil compares with other cGVHD treatments in terms of efficacy and safety.

The sponsor submitted a pharmacoeconomic model based on a naive comparison using the KD025-213 and KD025-208 trials to inform the belumosudil arm, and the REACH3 trial to inform the BAT arm. As a result, the relative clinical efficacy of belumosudil versus relevant comparators is highly uncertain. CADTH identified several limitations with the sponsor's economic submission that could be addressed. To do this, CADTH: used observational data to inform the comparative efficacy (i.e., OS and FFS) of belumosudil versus BAT; revised the assumptions about ToT, which led to a more plausible number of patients remaining on treatment (especially in the belumosudil arm); adjusted the proportion of patients on components of BAT to align with Canadian clinical practice; aligned the analysis with the health care payer perspective by including the costs associated with concomitant medications; and included uncertain caregiver utility adjustments in a scenario analysis. In the CADTH base case, the ICER for belumosudil versus BAT was $313,874 per QALY gained (incremental cost: $396,422; incremental QALYs: 1.26). The probability of being cost-effective at a threshold of $50,000 per QALY gained was 0%. The price of belumosudil would need to be $32,955 per year, reflecting a price reduction of 76%, to be considered cost-effective at a threshold of $50,000 per QALY gained. Cost-effectiveness was driven by the higher treatment cost of belumosudil and improvement in FFS for BAT. The CADTH results estimate higher incremental costs and lower incremental life-years and QALYs relative to the sponsor's base-case analysis. The increase in treatment costs associated with belumosudil was largely influenced by adjustments to the duration of treatment, which were deemed more clinically appropriate by the experts consulted by CADTH. The reduction in incremental life-years and QALYs was due to more clinically plausible extrapolations of OS and FFS for belumosudil relative to BAT. CADTH notes the analysis still assumes survival and quality of life gains with belumosudil of 1.84 life-years and 1.26 QALYs, respectively. Finally, the CADTH results do not assume that most patients receiving belumosudil will stop treatment and continue to experience large benefits.

Although the CADTH reanalysis attempted to address the identified limitations of the sponsor's economic submission, the cost-effectiveness of belumosudil remains highly uncertain. No robust evidence was provided in this submission to indicate a superior treatment effect of belumosudil relative to BAT. Even though CADTH used a sponsor-submitted observational study to inform the comparative efficacy rather than the sponsor's naive-comparison approach, there are important limitations to these data, preventing meaningful conclusions on the comparative benefits or harms of belumosudil. CADTH was also unable to address limitations associated with the model structure, which favoured belumosudil, as PSMs do not capture the impact of subsequent treatments on survival and quality of life. Given the remaining uncertainty, further price reductions may be sought.

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Appendix 1: Cost Comparison Tables

Note that this appendix has not been copy-edited.

The comparators presented in the following table have been deemed to be appropriate based on feedback from clinical experts and CADTH-participating drug plans. Comparators may be recommended (appropriate) practice or actual practice (off-label). Existing Product Listing Agreements are not reflected in the table and as such, the table may not represent the actual costs to public drug plans.

Table 8: CADTH Cost Comparison Table for Chronic Graft-Versus-Host Disease

Treatment	Strength	Form	Price ($)	Recommended dosage	Average daily cost ($)	Annual cost ($)
Recommended						
ROCK1 and ROCK2 inhibitor						
Rezurock (Belumosudil)	**200 mg**	**Oral tablet**	**376.2000[a]**	**200 mg daily**	**376.20**	**137,313**
JAK-1 and JAK-2 inhibitor						
Jakavi (Ruxolitinib)	5 mg 10 mg 15 mg 20 mg	Oral tablet	86.6275[b] 91.8338[b] 91.9914[b] 91.9930[b]	10 mg twice daily	183.67	67,039
BTK inhibitor						
Ibrutinib (Imbruvica)	140 mg	Oral capsule	99.8350[c]	420 mg daily	299.51	109,319
Actual practice (off-label use)						
Protein kinase inhibitor						
Imatinib (generics)	100 mg 400 mg	Tablet	5.2079 20.8314	100 mg daily for 1 month, after 200 mg daily for a minimum of 6 months[18]	5.21 (month 1) 10.42 (month 2+)	2,059[d]
TNF-alpha inhibitors						
Rituximab	10 mg/mL	100 mg (10 mL) 500 mg (50 mL) Vial for IV infusion	297.0000 1,485.0000	671.26 mg (or 375 mg/m^2) once weekly for 1 month followed by once monthly for 4 months[19]	107.41	16,335[e]
mTOR inhibitors						
Sirolimus (Rapamune)	1 mg 2 mg 5 mg	Tablet [f]	9.1200 Not available Not available	2 mg to 4 mg daily	18.24 to 36.48	6,658 to 13,315

Treatment	Strength	Form	Price ($)	Recommended dosage	Average daily cost ($)	Annual cost ($)
Systemic immunosuppressants						
Methotrexate (generic)	2.5 mg	Tablet	0.2513	20 mg to 30 mg once weekly[j]	0.29 to 0.43	105 to 157
Mycophenolate mofetil	250 mg 500 mg	Capsule	0.3712 0.7423	500 mg twice daily	1.48	542
Cyclosporine	10 mg 25 mg 50 mg 100 mg	Capsule	0.7115 0.7870 1.5350 3.0720	125 mg daily[j]	3.859	1,408
Tacrolimus	0.50 mg 1 mg 3 mg 5 mg 0.75 mg 1 mg 4 mg	Capsule Tablet	1.4775 1.8900 8.5188 9.4650 2.0999 2.6249 10.4994	2 mg daily[j]	3.78	1,380
Nondrug intervention						
ECP	Not applicable	Not applicable	2,060.3300[g]	2 treatments per week for the first month, then, every 2 weeks for 2 months and then, monthly for an additional 3 months[h]	84.61	30,905[i]

BTK = Bruton tyrosine kinase; ECP = extracorporeal photopheresis; JAK = Janus kinase; mTOR = mammalian target of rapamycin; ROCK = rho-associated protein kinase; TNF = tumour necrosis factor.

Note: All prices are from the lowest price option from the Ontario Drug Benefit Formulary (accessed in August 2023), unless otherwise indicated, and do not include dispensing fees. Recommended dosages are from the respective product monographs unless otherwise indicated. Daily costs are calculated based on the lowest price of the highest concentration to reach the recommended dose (fewer pills for the patient to ingest). Annual costs are based on 365 days or 52 weeks unless indicated otherwise. Everolimus, infliximab and pentostatin are not used in Canadian clinical practice according to clinical experts consulted for this review by CADTH.

[a]Sponsor's submitted price.

[b]Ontario Exceptional Access Formulary, accessed August 28, 2023.

[c]Nova Scotia Formulary, accessed August 28, 2023.

[d]Annual cost is based on a treatment duration of 7 months.

[e]Annual cost is based on a treatment duration of 5 months.

[f]Sirolimus is also available in a solution in 60 mL vials at 1 mg/mL. However, the use of tablets was assumed the preferred form when treating this patient population in jurisdictions where sirolimus is available.[20]

[g]Ontario Health Technology Assessment Series, accessed November 4, 2021.[21] Cost inflated from 2006 to 2023 Canadian dollars.[22]

[h]Dose obtained from Berger et al.[23]

[i]Annual cost is based on 15 treatments over a treatment duration of 6 months.

[j]Expert opinion.

Appendix 2: Submission Quality

Note that this appendix has not been copy-edited.

Table 9: Submission Quality

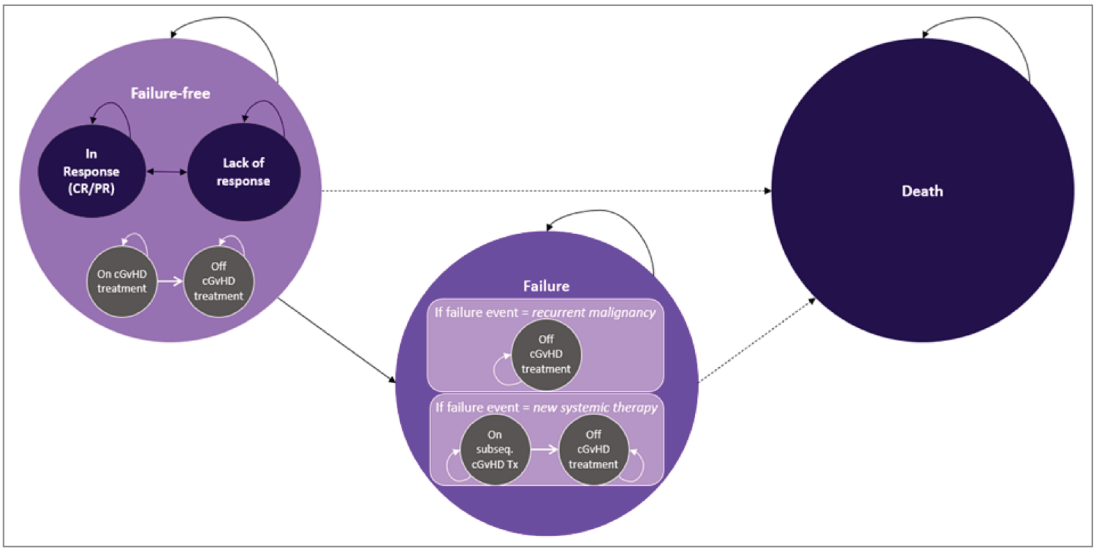
Description	Yes or no	Comments
Population is relevant, with no critical intervention missing and no relevant outcome missing.	No	Ruxolitinib was not included as a relevant comparator. Feedback from drug plans and clinical experts consulted by CADTH for this review indicated that ruxolitinib would be routinely used as a third-line treatment option for patients with cGVHD and should be considered a relevant comparator.
Model has been adequately programmed and has sufficient face validity.	No	The sponsor's submitted model included numerous IFERROR statements, which lead to situations in which the parameter value is overwritten with an alternative value without alerting the user to the automated overwriting. The systematic use of IFERROR statements makes thorough auditing of the sponsor's model impractical and it remains unclear whether the model is running inappropriately by overriding errors.
Model structure is adequate for the decision problem.	No	Refer to limitation: The model structure was inappropriate for the decision problem.
Data incorporation into the model has been done adequately (e.g., parameters for probabilistic analysis).	Yes	No comment.
Parameter and structural uncertainty were adequately assessed; analyses were adequate to inform the decision problem.	Yes	No comment.
The submission was well organized and complete; the information was easy to locate (clear and transparent reporting; technical documentation available in enough detail).	Yes	No comment.

cGVHD = chronic graft-versus-host disease.

Appendix 3: Additional Information on the Submitted Economic Evaluation

Note that this appendix has not been copy-edited.

Figure 1: Model Structure



cGVHD = chronic graft-versus-host disease; CR = complete response; PR = partial response; Tx = treatment.
Source: Sponsor's Pharmacoeconomic Submission.[2]

Detailed Results of the Sponsor's Base Case

Table 10: Disaggregated Summary of Sponsor's Economic Evaluation Results

Parameter	Belumosudil	BAT	Incremental
Discounted LYs			
Total	9.53	6.14	3.39
Failure-free	5.11	1.13	3.97
In response	2.59	0.85	1.74
Lack of response	2.52	0.28	2.24
Failure	4.43	5.01	−0.58
New cGVHD systemic therapy	3.87	4.74	−0.87
Recurrent malignancy	0.56	0.27	0.29
Discounted QALYs			
Total	4.69	2.30	2.39
Failure-free	3.61	0.84	2.77

Parameter	Belumosudil	BAT	Incremental
In response	1.88	0.64	1.24
Lack of response	1.73	0.20	1.53
Failure	1.99	2.26	−0.27
New cGVHD systemic therapy	1.74	2.14	−0.40
Recurrent malignancy	0.25	0.12	0.13
Decrement due to AEs (one-off)	0.00	0.00	0.00
Decrement associated with IV infusion	0.00	−0.01	0.01
Decrement related to caregiver time	−0.91	−0.78	−0.12
Discounted costs ($)			
Total	492,661	314,982	177,679
Drug acquisition costs	222,097	37,343	184,754
Drug administration costs	0	1,431	−1,431
Concomitant medication costs	0	0	0
Disease management costs	113,698	84,113	29,585
Failure-free	41,580	7,173	34,407
In response	11,539	3,770	7,769
Lack of response	30,041	3,403	26,638
Failure	72,118	76,940	−4,822
New cGVHD systemic therapy	56,598	69,476	−12,878
Recurrent malignancy	15,520	7,464	8,056
Cost of new cGVHD systemic therapy	150,381	184,487	−34,106
Cost of recurring malignancy	384	266	118
Adverse event management costs	371	1,212	−841
Death event costs	5,730	6,130	−400
ICER ($/QALY)	74,394		

AE = adverse event; BAT = best available therapy; cGVHD = chronic graft-versus-host disease; ICER = incremental cost-effectiveness ratio; LY = life-year; QALY = quality-adjusted life-year.

Table 11: Distribution of Patients on BAT in the Sponsor's Base-Case Analysis

Treatment	Proportion (%)
Extracorporeal photopheresis	36.3
Mycophenolate mofetil	26.8
Ibrutinib	14.3
Low-dose methotrexate	1.7
Imatinib	1.7

Treatment	Proportion (%)
Sirolimus	10.8
Rituximab	6.7
Everolimus	0.0
Infliximab	0.0
Pentostatin	0.0
Cyclosporine 125 mg b.i.d. and tacrolimus 2 mg b.i.d.	3.3
Ruxolitinib	0.0

BAT = best available therapy; b.i.d. = twice daily.

Table 12: Proportion of Patients Receiving Each Concomitant Medication in the Sponsor's Base-Case Analysis

Concomitant medication	Belumosudil q.d. (%)	Belumosudil b.i.d. (%)	BAT (%)
Prednisone	95	97	95
Tacrolimus	35	37	35
Extracorporeal photopheresis	25	35	0
Sirolimus	21	24	21
Mycophenolate mofetil	14	3	13
Budesonide	7	4	7
Montelukast	5	5	5
Azithromycin	5	5	5

BAT = best available therapy; b.i.d. = twice daily; q.d. = once daily.

Appendix 4: Additional Details on the CADTH Reanalyses and Sensitivity Analyses of the Economic Evaluation

Note that this appendix has not been copy-edited.

Detailed Results of CADTH Base Case

Table 13: Disaggregated Summary of CADTH's Economic Evaluation Results

Parameter	Belumosudil	BAT	Incremental
Discounted LYs			
Total	8.07	6.23	1.84
Failure-free	4.91	3.18	1.73
In response	2.49	1.77	0.72
Lack of response	2.42	1.41	1.01
Failure	3.17	3.05	0.12
New cGVHD systemic therapy	2.74	2.82	−0.09
Recurrent malignancy	0.43	0.23	0.20
Discounted QALYs			
Total	4.92	3.66	1.26
Failure-free	3.49	2.29	1.20
In response	1.81	1.29	0.52
Lack of response	1.68	1.00	0.68
Failure	1.43	1.39	0.05
New cGVHD systemic therapy	1.24	1.28	−0.04
Recurrent malignancy	0.20	0.10	0.09
Decrement due to AEs (one-off)	0.00	0.00	0.00
Decrement associated with IV infusion	0.00	−0.01	0.01
Decrement related to caregiver time	0.00	0.00	0.00
Discounted costs ($)			
Total	669,811	273,389	396,422
Drug acquisition costs	436,937	83,259	353,678
Drug administration costs	0	1,564	−1,564
Concomitant medication costs	29,580	1,953	27,628
Disease management costs	92,124	72,364	19,759
Failure-free	39,729	24,555	15,174
In response	10,976	7,785	3,191

Parameter	Belumosudil	BAT	Incremental
Lack of response	28,753	16,770	11,983
Failure	52,395	47,809	4,586
New cGVHD systemic therapy	40,162	41,309	−1,147
Recurrent malignancy	12,233	6,500	5,733
Cost of new cGVHD systemic therapy	104,299	107,155	−2,856
Cost of recurring malignancy	360	238	121
AE management costs	602	735	−133
Death event costs	5,909	6,121	−211
ICER ($/QALY)	**313,874**		

AE = adverse event; BAT = best available therapy; cGVHD = chronic graft-versus-host disease; ICER = incremental cost-effectiveness ratio; LY = life-year; QALY = quality-adjusted life-year.

Table 14: Distribution of Patients on BAT in CADTH's Base-Case Analysis

Treatment	Proportion (%)
Extracorporeal photopheresis	15.0
Mycophenolate mofetil	15.0
Ibrutinib	5.0
Low-dose methotrexate	1.7
Imatinib	1.7
Sirolimus	5.0
Rituximab	6.7
Everolimus	0.0
Infliximab	0.0
Pentostatin	0.0
Cyclosporine 125 mg b.i.d. and tacrolimus 2 mg b.i.d.	15.0
Ruxolitinib	35.0

BAT = best available therapy; b.i.d. = twice daily.

Table 15: Proportion of Patients Receiving Each Concomitant Medication in CADTH's Base-Case Analysis

Concomitant medication	Belumosudil q.d. (%)	Belumosudil b.i.d. (%)	BAT (%)
Prednisone	95	97	95
Tacrolimus	33	37	35
Extracorporeal photopheresis	13	13	15
Sirolimus	5	5	5
Mycophenolate mofetil	12	3	13

Concomitant medication	Belumosudil q.d. (%)	Belumosudil b.i.d. (%)	BAT (%)
Budesonide	6	4	7
Montelukast	5	5	5
Azithromycin	5	5	5

BAT = best available therapy; b.i.d. = twice daily; q.d. = once daily.

Scenario Analyses

Table 16: Summary of CADTH's Scenario Analysis Results (Deterministic)

Stepped analysis	Drug	Total costs ($)	Total QALYs	ICER ($/QALY)
CADTH base case	BAT	267,780	3.62	Reference
	Belumosudil	673,454	4.95	304,263
CADTH scenario analysis: sponsor's base case OS extrapolation (exponential)	BAT	267,780	6.12	Reference
	Belumosudil	751,096	9.53	234,727
CADTH scenario analysis: CADTH base case including caregiver disutilities	BAT	267,780	3.06	Reference
	Belumosudil	673,454	4.30	329,178

BAT = best available therapy; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Appendix 5: Submitted BIA and CADTH Appraisal

Note that this appendix has not been copy-edited.

Table 17: Summary of Key Take-Aways

Key take-aways of the BIA

• CADTH identified the following key limitations with the sponsor's analysis:
  ◦ The market uptake of belumosudil is underestimated in years 1 and 2.
  ◦ BAT components and distribution do not align with Canadian clinical practice.
  ◦ The exclusion of concomitant medication costs does not align with Canadian clinical practice.
  ◦ The assumption that no patients will receive belumosudil b.i.d. does not align with the cost-utility analysis.
• The CADTH reanalysis included adjusting belumosudil market uptake in years 1 and 2, revising BAT components, including costs of concomitant medications, and revising dosing assumptions for belumosudil.
• Based on the CADTH reanalysis, the 3-year budget impact to the public drug plans of introducing belumosudil for the treatment of patients with cGVHD whose disease has failed to respond to 2 or more prior lines of systemic therapy is expected to be $13,457,590 (year 1: $4,331,056; year 2: $4,484,061; year 3: $4,642,472). This was approximately 25% higher than the estimated impact by the sponsor and it was driven by the assumptions of a faster uptake of the new drug and the use of a b.i.d. dose in a small proportion of patients.

BAT = best available therapy; BIA = budget impact analysis; b.i.d. = twice daily; cGVHD = chronic graft-versus-host disease.

Summary of Sponsor's BIA

The sponsor submitted a budget impact analysis (BIA) estimating the incremental budget impact of reimbursing belumosudil for the treatment of patients aged 12 years and older with cGVHD after failure of at least 2 prior lines of systemic therapy. The BIA was undertaken from the perspective of a Canadian public payer over a 3-year time horizon (Q4 2024 to Q2 2027) using a top-down epidemiologic approach. The sponsor's pan-Canadian estimates reflect the aggregated results from provincial budgets (excluding Quebec), as well as the Non-Insured Health Benefits Program. Data to inform the model were obtained from various sources, including the published literature, the sponsor's internal data, and input from clinical experts consulted by the sponsor. Key inputs to the BIA are documented in Table 18.

The sponsor compared a reference scenario in which patients received a basket of BAT comparators to a new drug scenario in which belumosudil was reimbursed. The sponsor's analysis included drug acquisition costs for belumosudil based on the sponsor's submitted price. BAT was assumed by the sponsor to comprise ibrutinib, ECP, mycophenolate mofetil, methotrexate, imatinib, sirolimus, rituximab, and combination of cyclosporine and tacrolimus. The annual costs of belumosudil were based on product monograph dosing and the median duration of treatment exposure of 280 days from the KD025-213 study. Drug utilization costs for BAT were derived from each respective drug's product monograph and the CADTH report for Jakavi.[20] Costs of concomitant therapies were excluded from the base-case analysis.

Table 18: Summary of Key Model Parameters

Parameter	Sponsor's estimate (reported as year 1 / year 2 / year 3, if appropriate)
Target population	
Number of HCTs performed	809[a]
Incidence of cGVHD among HCT patients	70%[24,25]
Proportion of patients progressing to second-line therapy	50%[26-28]
Proportion of patients progressing to third-line treatment	50.3%[4]
Proportion of patients receiving pharmacotherapy	100%
Proportion of patients eligible for therapy (> 12 years)	83.01%[29]
Proportion eligible for public coverage	49.04%[b]
Number of patients eligible for belumosudil	62 / 64 / 67
Market uptake (3 years)	
Uptake (reference scenario) Belumosudil BAT	 0% / 0% / 0% 100% / 100% / 100%
Uptake (new drug scenario) Belumosudil BAT	 50% / 65% / 80% 50% / 35% / 20%
Cost of treatment (per patient)	
Cost of treatment over 1 year Belumosudil BAT	 $107,562 $22,365

BAT = best available therapy; cGVHD = chronic graft-versus-host disease; HCT = hematopoietic cell transplant.

[a]Estimated based on an incidence of approximately 0.00262%, calculated using registry data.[30]

[b]Calculated as a pan-Canadian weighted coverage from each jurisdiction's estimate derived from the Conference Board of Canada report.[31]

Summary of the Sponsor's BIA Results

The 3-year budget impact of reimbursing belumosudil for the treatment of patients aged 12 years and older with cGVHD after failure of at least 2 prior lines of systemic therapy would be $2,647,187 in year 1; $3,562,917 in year 2; and $4,540,045 in year 3; leading to a 3-year total of $10,750,149.

CADTH Appraisal of the Sponsor's BIA

CADTH identified several key limitations to the sponsor's analysis that have notable implications for the results of the BIA:

- **The market uptake of belumosudil is underestimated.** The sponsor assumed that belumosudil would have a market uptake of 50% in year 1, 65% in year 2, and 80% in year 3 based on internal market assessments. However, clinical experts consulted by CADTH for this review noted that, if

belumosudil becomes publicly funded, the uptake in the indicated population can be expected to be rapid and reach its peak almost immediately. Although they considered the market share in year 3 to be reasonable (as a proportion of patients will continue to respond well to some components of BAT), they indicated that the market uptake in years 1 and 2 was underestimated based on their clinical expectations.

    - To address this limitation, CADTH undertook a reanalysis by revising the market shares for belumosudil in the new drug scenario to 80% in years 1 and 2.

- The distribution of patients receiving the alternatives included in BAT is not aligned with current Canadian clinical practice. When validating the distribution of some BAT components (refer to Table 19), clinical experts consulted by CADTH for this review noted some misalignment. Specifically, the sponsor assumed that ruxolitinib would be the standard of care as a second-line treatment for cGVHD and thus excluded it from BAT in their analysis. This does not align with clinical feedback from drug plans and clinical experts, which suggest that ruxolitinib would be routinely used as a third-line treatment option for patients with cGVHD and should be considered a relevant comparator to belumosudil. Given the variability in the treatments used for cGVHD across Canada, the budget impact of belumosudil versus BAT will likely vary by jurisdiction.
    - The CADTH reanalysis aligned the distribution of BAT with the CADTH reanalysis of the pharmacoeconomic analysis, including the addition of ruxolitinib.
- **The exclusion of concomitant medications was inappropriate.** The sponsor's base-case analysis excluded the cost of concomitant medications. The clinical experts consulted by CADTH noted that many patients would receive concomitant medication while receiving treatment with belumosudil or components of BAT. The costs of these treatments are relevant from the public drug plans' perspective and thus should be included in the analysis.
    - The CADTH reanalysis included the costs associated with medications taken concomitantly with belumosudil. CADTH notes that the submitted model did not include an option to include concomitant medications for BAT. Given that patients are likely to receive concomitant medications when being treated with BAT as well, the price of BAT to the drug payer may be underestimated (and therefore, the budget impact may be overestimated).
    - In the application of concomitant medications, the costs of ECP were excluded in the CADTH reanalysis to align with the public drug-payer perspective of analysis.
- **The assumption that no patients will be treated with belumosudil twice daily does not align with the cost-utility analysis.** In the pharmacoeconomic submission, the sponsor assumed that 5% of patients would receive belumosudil 200 mg twice daily, and this assumption was validated by clinical experts consulted by CADTH.
    - The CADTH reanalysis assumed that 5% of patients would receive belumosudil 200 mg twice daily.
- **ToT for patients receiving belumosudil is uncertain.** Clinical experts consulted by CADTH indicated that in their opinion, approximately half of patients who remain failure-free can be expected to

continue treatment with belumosudil in the long-term. Given the clinical expectation that patients may remain on belumosudil for longer than 3 years (the time horizon of the BIA), it is important to note that there would be a significant budgetary impact in subsequent years following the time horizon of the BIA (continuing beyond year 3).
    - The CADTH reanalysis did not incorporate a longer time horizon.
- **The price of drugs paid by public drug plans is uncertain.** Both the sponsor's and CADTH's analyses are based on publicly available list prices for all comparators. Drug plan feedback indicated there are confidential negotiated prices for some of the comparators. Thus, actual costs paid by drug plans are unknown. Depending on the negotiated prices, the incremental cost of funding belumosudil to the public drug plans is uncertain.
    - CADTH was unable to incorporate the presence of confidential negotiated prices in the reanalysis.

CADTH Reanalyses of the BIA

CADTH revised the sponsor's submitted analysis by adjusting the market share for belumosudil in years 1 and 2 to reflect the expectations of clinical experts consulted by CADTH, revised the BAT components, included the costs of concomitant medications, and revised dosing assumptions for belumosudil. The changes applied to derive the CADTH base case are described in Table 19.

Table 19: CADTH Revisions to the Submitted Budget Impact Analysis

Stepped analysis	Sponsor's value or assumption	CADTH value or assumption
Corrections to sponsor's base case		
1. Perspective of analysis	Health care payer perspective (includes ECP treatment cost)	Public drug-payer perspective (excludes ECP treatment cost)
Changes to derive the CADTH base case		
1. Market uptake of belumosudil (year 1 / year 2 / year 3)	50% / 65% / 80%	80% / 80% / 80%
2. BAT components	• Ibrutinib: 14.3% • ECP: 36.3% • MMF: 26.8% • Sirolimus: 10.8% • Ruxolitinib: 0% • Cyclosporine and tacrolimus: 3.3% • (as per Table 11)	• Ibrutinib: 5% • ECP: 15% • MMF: 15% • Sirolimus: 5% • Ruxolitinib: 35% • Cyclosporine and tacrolimus: 15% • (as per Table 14)
3. Concomitant medication	Excluded	Included (for belumosudil only)[a]
4. Patients receiving belumosudil b.i.d.	0%	5%
CADTH base case	1 + 2 + 3 + 4	

BAT = best available therapy; b.i.d. = twice daily; ECP = extracorporeal photopheresis; MMF = mycophenolate mofetil.

[a]The sponsor's model did not allow the inclusion of concomitant medication for BAT.

The results of the CADTH stepwise reanalysis are presented in summary format in Table 20 and a more detailed breakdown is presented in Table 21. The CADTH reanalysis suggests that reimbursing belumosudil would be associated with an incremental cost of $4,331,056 in year 1; $4,484,061 in year 2; and $4,642,472 in year 3; for a 3-year budgetary impact of $13,457,590. CADTH notes that a 3-year BIA underestimates the total budget impact as some patients are expected to remain on therapy beyond this time horizon, and the budget impact will continue to increase.

Table 20: Summary of the CADTH Reanalyses of the BIA

Stepped analysis	Three-year total
Submitted base case	$10,750,149
Submitted base case (corrected): excluded ECP costs	$11,799,995
CADTH reanalysis 1: market uptake	$14,445,928
CADTH reanalysis 2: BAT components	$9,841,062
CADTH reanalysis 3: concomitant medications	$11,926,452
CADTH reanalysis 4: included patients in belumosudil b.i.d. dose	$12,825,158
CADTH base case (correction + reanalysis 1 + 2 + 3 + 4)	$13,457,590

BAT = best available therapy; BIA = budget impact analysis; b.i.d. = twice daily; ECP = extracorporeal photopheresis.

CADTH conducted additional scenario analysis to address remaining uncertainty, using the CADTH base case. Results are provided in Table 21.

1. Sixty-six percent public drug coverage for all provinces, to explore possibly higher coverage for oral drugs negotiated as non-oncology, as suggested by the drug plans.
2. One hundred percent public drug coverage for all provinces, to align with a scenario explored in CADTH's review of ruxolitinib.[20]
3. No treatment discontinuation over the 3-year time horizon.
4. Slower market uptake of belumosudil of 60%, 70%, and 80% in years 1, 2, and 3, respectively.

Results of CADTH's scenario analysis demonstrate that the budgetary impact is sensitive to assumptions around treatment discontinuation and public drug coverage, with an estimated 3-year total budget impact of $17,692,295 if assuming no treatment discontinuation; and $26,807,844 if 100% of patients are covered by their public drug plan, respectively.

Table 21: Detailed Breakdown of the CADTH Reanalyses of the BIA

Stepped analysis	Scenario	Year 0 (current situation) ($)	Year 1 ($)	Year 2 ($)	Year 3 ($)	Three-year total ($)
Submitted base case	Reference	1,342,600	1,390,031	1,439,137	1,489,978	4,319,146
	New drug	1,342,600	4,037,218	5,002,054	6,030,023	15,069,295
	Budget impact	0	2,647,187	3,562,917	4,540,045	10,750,149
Submitted base case (corrected)	Reference	843,201	872,989	903,829	935,759	2,712,578
	New drug	843,201	3,778,697	4,814,697	5,919,179	14,512,573
	Budget impact	0	2,905,708	3,910,867	4,983,420	11,799,995
CADTH base case	Reference	1,775,042	1,837,750	1,902,673	1,969,890	5,710,313
	New drug	1,775,042	6,168,806	6,386,735	6,612,362	19,167,903
	Budget impact	0	4,331,056	4,484,061	4,642,472	13,457,590
CADTH scenario analysis 1: 66% public drug coverage	Reference	2,385,183	1,837,750	1,902,673	1,969,890	5,710,313
	New drug	2,385,183	7,657,480	7,928,000	8,208,076	23,793,556
	Budget impact	0	5,819,730	6,025,327	6,238,186	18,083,243
CADTH scenario analysis 2: 100% public drug coverage	Reference	3,535,908	1,837,750	1,902,673	1,969,890	5,710,313
	New drug	3,535,908	10,465,319	10,835,032	11,217,807	32,518,157
	Budget impact	0	8,627,568	8,932,359	9,247,917	26,807,844
CADTH scenario analysis 3: Assume no treatment discontinuation	Reference	1,839,840	1,837,750	1,902,673	1,969,890	5,710,313
	New drug	1,839,840	7,531,661	7,797,736	8,073,211	23,402,608
	Budget impact	0	5,693,911	5,895,063	6,103,321	17,692,295
CADTH scenario analysis 4: Alternative market uptake of belumosudil	Reference	1,775,042	1,837,750	1,902,673	1,969,890	5,710,313
	New drug	1,775,042	5,086,042	5,826,227	6,612,362	17,524,631
	Budget impact	0	3,248,292	3,923,554	4,642,472	11,814,318

BIA = budget impact analysis.

Stakeholder Input

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Patient Input

The Leukemia & Lymphoma Society of Canada

About The Leukemia & Lymphoma Society of Canada

The Leukemia & Lymphoma Society of Canada — blood cancers.ca

LLSC is a national charitable status organization dedicated to finding a cure for blood cancers and its ability to improve the quality of life of people affected by blood cancers and their families by funding life-enhancing research and providing educational resources, services, and support. The Leukemia and Lymphoma Society of Canada is the largest charitable organization in Canada dedicated to blood cancer, our focus includes:

- Funding research from bench to bedside.
- Rethinking how a person navigates their blood cancer experience
- Providing targeted blood cancer information
- Offering tools for psychological and emotional support
- Empowering Canadians to take charge of their blood cancer experience through practical support and advocacy

Myeloma Canada — www.myeloma.ca

Multiple myeloma, also known as myeloma, is the 2nd most common form of blood cancer. Myeloma affects a type of immune cell called the plasma cell, found in the bone marrow. Every day, 11 Canadians are diagnosed, yet despite its growing prevalence, the disease remains relatively unknown. Myeloma is a relapsing cancer which with treatment can enter periods of remission, but myeloma will always ultimately return and require further treatment. Myeloma patients also become 'refractory' to a treatment, meaning it can no longer control their myeloma, and they require a new regimen. Myeloma Canada has existed for over 15 years to support the growing number of Canadians diagnosed with myeloma each year, and those living longer than ever with the disease through access to new and innovative therapies. Over the years, as a part of this mission Myeloma Canada has collected data on the impact of myeloma and its treatments on patients and caregivers, by conducting surveys. The compiled data are then presented to the Pan-Canadian Oncology Drug Review.

Information Gathering

One online survey was created through SurveyMonkey. Information was gathered in July 2023. The survey was developed and distributed by LLSC and Myeloma Canada, in English only. The survey was distributed through various social media channels and directly by email.

The survey asked for input from patients and caregivers who have lived experience with Chronic Graft vs Host Disease following an allogeneic stem cell transplant.

98 respondents participated in this survey. 62 respondents answered "yes" to the question "Have you or someone you care for received an allogeneic stem cell transplant (from a donor) and subsequently developed Chronic Graft Versus Host Disease?" These 62 respondents were able to proceed with the survey.

Respondents who answered "no" to this question (36 respondents) were disqualified from the survey. The majority of respondents indicated that they were the cGVHD patient (past or present) The demographic breakdown is listed in the chart below.

Figure 1: Input From Patients and Caregivers Who Have Lived Experience with Chronic Graft vs Host Disease Following an Allogenic Stem Cell Transplant

ANSWER CHOICES		RESPONSES	
cGVHD patient (past)		25.42%	15
cGVHD patient (present)		54.24%	32
Caregiver of a cGVHD patient (past or present)		16.95%	10
Other (please specify)	Responses	3.39%	2
TOTAL			59

100 percent of respondents (59/59) answered that the allogeneic stem cell transplant recipient was 12 years of age or older at the time of transplant.

Disease Experience

A Chronic GVHD diagnosis after transplant can be a devastating blow to patients and their families who are desperate for a cure and relief from their disease. One illness is replaced with another and the mental and physical effects of cGVHD can create new and complex complications that greatly affect the quality of life of patients and their caregivers.

The uncertainty of a GVHD diagnosis after such a rigorous cancer and stem cell transplant experience can be nerve wracking, disheartening and terrifying for patients and their loved ones.

Respondents were asked to express what their thoughts and feelings were when they became aware that they had developed cGVHD after undergoing stem cell transplant.

> "Frustrated, scared, worried."
>
> "Devastated as I have been suffering for two years."
>
> "Primarily concern as to how serious the cGVHD would become and if it would be life threatening."
>
> "In my case, I developed acute GVHD soon after transplant, which gradually developed into chronic GVHD. I remember thinking that this was just the deal I had to make to survive - to trade one deadly disease (cancer) for another one where I had better chances. I also remember hoping that with good treatment the cGVHD could be kept under control and managed until it eventually dissipated on its own, which sometimes happens."
>
> "Disappointed that I developed GVHD and wondered why I went through the process just to be sick with another ailment."

> "Terrified"
>
> "I was forewarned this could happen. Not surprised but disappointed I was hit so hard with it."
>
> "Scared. Sad."
>
> "Nervousness as I wasn't sure how serious it could be or would be".

The mental effects of a cGVHD diagnosis can be just as grueling as the physical symptoms and sometimes more debilitating for patients and caregivers.

Respondents were asked, "Overall, what kind of impact would you say cGVHD had on the mental health status of the patient and/or caregivers?"

34/45 (75.56%) respondents answered that cGVHD had a "negative" to "extremely negative" impact.

Respondents were asked about the feelings they experienced related to their cGVHD experience. 23 respondents answered this question. The top answers were as follows:

- 16/23 (69.57%) Frustration/Resentment
- 16/23 (69.57%) Stress
- 15/23 (65.22%) Helplessness/Hopelessness
- 13/23 (56.52%) Sadness
- 13/23 (56.52%) Fear
- 13/23 (56.52%) Overwhelmed/Feeling out of control
- 12/23 (52.17%) Anxious/Depressed/Worried
- 9/23 (39.13%) Feeling withdrawn, lonely, isolated.

The following are direct quotes from respondents that highlight their feelings and the mental health impact of cGVHD.

> "Our mental health went on a roller coaster ride from depression to anxiety to hope and back all over again in a short period of time. Knowing the patient was dying was the worst feeling. She was very stoic, and I can't imagine what she must have been going through in her mind as she didn't talk about it much. As her caregiver, I was depressed, and many regular household routines were not as often or to our typical standards. I had a hard time sleeping, was less active, ate more and gained weight."
>
> "Terror. When it was realized it was in his eyes, mouth, liver and then spread to his lungs."
>
> "Gvhd has attacked many systems of my body Heart. Lungs. Eyes. Skin. GI. Muscles. When my CK was 3500 it was very scary. I couldn't roll over in bed. Got stuck in the bathtub. I felt totally helpless."
>
> "I have had one difficulty after another with various forms of GVHd. I have become angry and frustrated."

The impact of cGVHD on patients' and caregivers' quality of life is vast and extensive and affects various substantial areas of a patient's life beyond just disease impact. Even a slight case of GVHD can make a notable difference in the everyday life of patients and caregivers alike and both have to make many lifestyle

changes in order to adjust to their circumstances and manage the enormous burden brought on by GVHD. One respondent declared, “It impacts so much.”

Respondents were asked to select which areas of their life have been affected by their cGVHD. 43 respondents answered this question and results are shown in the chart below.

Figure 2: Areas of Life Affected by cGVHD

ANSWER CHOICES	RESPONSES	
Physical functioning	79.07%	34
Lifestyle	74.42%	32
Daily routines	65.12%	28
Self-image	65.12%	28
Mental functioning	62.79%	27
Romantic relationships	58.14%	25
Social life	55.81%	24
Family life	44.19%	19
Work life	44.19%	19
None of the above	0.00%	0
Total Respondents: 43		

Respondents elaborated with additional comments about their individual perspective on the quality-of-life impact of cGVHD:

> “My lung issues (bronchiolitis obliterans) affect high oxygen demand activities like jogging and swimming. Indeed, I was an excellent swimmer and scuba diver but can no longer do either.”
>
> “The severity of my GVHD is not high but it still impacts how I live my life. I have had to make some changes.”
>
> “While it seemed like a small price to pay for being alive, cGVHD affected my quality of life and I had to make accommodations for it.”
>
> “I am constantly suffering from pain and anxiety.”
>
> “Fatigue is a major side effect and impacts quality of life including my mental health.”

The physical pain and symptoms associated with cGVHD that patients experience vary significantly from patient to patient. However, in any case, patients and their caregivers are highly affected by their physical symptoms and discomfort. The impacts of these physical symptoms can severely limit the activities and daily lives of patients and those who care for them. In some cases, patients are unable to function. One respondent commented... “Graft vs host of the gut was very serious. I lost 40 lbs in 6 weeks. I couldn't keep meds or food down. I had to be re- hospitalized. What my family went through was traumatizing. My skin cGVHD has really impacted my day-to-day activity and severely affected and limited my movements generally

and increasing my anxiety. I'm unable to participate in most day-to-day activities due to the pain of the open wounds.

Patients can be significantly affected by not just one, but many physical effects of GVHD on various parts of their body all at once. Patients are vulnerable victims to when, how and in which parts of their body GVHD chooses to manifest. The powerless feeling that patients experience when not being able to see or having extreme eye dryness and pain because GVHD attacks their eyes, or not being able to eat because GVHD has filled their mouth with sores and ulcers is unbearable. Patients feel hopeless and caregivers are at a loss when they are limited in what they can really do to help their loved ones endure the pain they're experiencing after already having gone through so much throughout their cancer experience.

One patient described the significant physical impact of cGVHD on their eyesight and how that has greatly impacted various aspects of their life:

> "Since the graft vs host disease, I cannot read or use a screen for more than about 30 minutes. Nowadays, which job doesn't use a screen? I cannot drive for more than 40 minutes."

Respondents were asked, "How has cGVHD affected you physically? Please rate the level of impact on the following due to cGVHD, using a scale from 1 (no impact) – 5 (extremely large impact). 44 respondents answered this question, and the results are reflected in the chart below.

The following are direct quotes from respondents describing the physical symptoms of cGVHD:

> "While I feel grateful to be alive, my cGVHD is something that I have to deal with every single day! The symptoms have changed over the years with the worst of the symptoms being extremely dry eye disease. My eyes are beyond painful every day, especially when I'm not in ultra humid environments. I use special eye drops every day (both a very expensive biologic and Bion Teams which neither covered by my health plan). I even get woken up two times in the middle of each night and have to put in the drops so that I can return to sleep. These drops do not eliminate the associated pain fully."
>
> "Difficulty eating because of sores in my mouth."
>
> "Joint pain, slower to walk, muscle loss, shaking arms and legs, tired."

Respondents were asked about lifestyle impacts of cGVHD. 21 respondents answered this question. Results are reflected in Figure 3.

The symptoms associated with cGVHD, both mental and physical, are debilitating. It can make it difficult or in some cases, impossible for patients and/or caregivers to work or attend school, which can potentially add an additional financial burden to the cGVHD experience and also potentially contribute to a less fulfilling social life and a decline in mental health. 40% of survey respondents stated that they had to quit or leave work or school. This is staggering and significant to the quality of life of patients and their families. As demonstrated through respondent quotes below, some patients were never able to return to work or school.

Figure 3: Physical Symptoms of cGVHD

	1- NO IMPACT	2- SMALL IMPACT	3- MEDIUM IMPACT	4- LARGE IMPACT	5- EXTREMELY LARGE IMPACT	TOTAL	WEIGHTED AVERAGE
Eyes (dry, burning or gritty feeling)	13.95% 6	9.30% 4	18.60% 8	30.23% 13	27.91% 12	43	3.49
Skin (dryness, rash, itching, peeling, darkening, hard texture, feeling tight)	9.09% 4	13.64% 6	25.00% 11	38.64% 17	13.64% 6	44	3.34
Mouth (dry, ulcers)	11.36% 5	18.18% 8	27.27% 12	18.18% 8	25.00% 11	44	3.27
Body Hair, Nails	18.18% 8	20.45% 9	25.00% 11	18.18% 8	18.18% 8	44	2.98
Lungs (difficulty breathing, shortness of breath)	29.55% 13	18.18% 8	13.64% 6	9.09% 4	29.55% 13	44	2.91
Digestive Tract (Diarrhea, Stomach cramps, Loss of appetite, Vomiting, Weight loss)	23.81% 10	19.05% 8	26.19% 11	14.29% 6	16.67% 7	42	2.81
Muscles/Joints, Fascia (connective tissue)	20.45% 9	27.27% 12	20.45% 9	18.18% 8	13.64% 6	44	2.77
Liver	35.00% 14	17.50% 7	20.00% 8	22.50% 9	5.00% 2	40	2.45
Genitalia	30.95% 13	26.19% 11	19.05% 8	14.29% 6	9.52% 4	42	2.45
Scalp	48.84% 21	23.26% 10	9.30% 4	13.95% 6	4.65% 2	43	2.02

Figure 4: Lifestyle Impacts of cGVHD

ANSWER CHOICES	RESPONSES	
Difficulty sleeping	76.19%	16
Loss of sexual desire	71.43%	15
Problems concentrating	57.14%	12
Loss of appetite	47.62%	10
Difficulty with friend and/or family relationships	28.57%	6
Lack of support	23.81%	5
Total Respondents: 21		

One caregiver relayed her loved one's heartbreaking experience, "The patient had a successful career and had to stop working due to her health. The patient had planned on working for at least one more year before retiring to the east coast. She had to retire early and did not get to enjoy her retirement before she passed away within a few months."

Respondents were asked “What impact, if any, did cGVHD have on the patients’ or caregivers’ ability to continue with school/work (Select all that apply)” 40 respondents answered this question. Results are as follows:

- 16/40 (40%) had to leave or quit
- 10/40 (25%) had to take a temporary leave of absence
- 10/40 (25%) N/A
- 8/40 (20%) had to change schedule
- 4/40 (10%) had to take accommodations in order to continue

Respondents elaborated on the affects that cGVHD has had on their ability to work…

> “Could not work full-time ever again.”
>
> “Long leave of absence followed by very part time work, still ongoing.”
>
> “Permanently off work.”

Many patients unfortunately lose their ability to be completely independent and require caregiver support to manage their cGVHD symptoms.

- 28/45 (62.22%) respondents require(d) caregiver support
- 14/45 (31.11%) respondents did not require caregiver support
- 3/45 (6.67%) respondents stated that though caregiver support was required, they were unable to access it due to reasons such as cost or no available family member etc.

Experiences With Currently Available Treatments

cGVHD patients are generally treated with corticosteroids which come with a heavy burden of side effects that greatly impact the quality of life of patients as well as their loved ones. Corticosteroid use can cause patients to experience extreme emotions. Patients will often have trouble regulating themselves which can affect their daily functioning as well as their personal relationships. Patients on corticosteroid treatment often experience extreme behaviour changes and even “roid-rage”. This can manifest in extreme mood swings, anger, aggression, rage, depression, sadness and even suicidal thoughts, without provocation. This can be a considerable burden for patients and their families and can be extremely difficult and stressful to manage when patients and loved ones are still recovering from the trauma of the cancer and stem cell transplant experiences. Additionally, this can amplify and make more difficult the already nearly insurmountable obstacle of trying to reintegrate back into “normal” life. Patients seek additional treatment options that offer less side effects and limit the negative quality-of-life impacts of treatment for themselves and their loved ones.

Respondents were asked, “Which of the following neurological or circulatory side effects of corticosteroids have you experienced during treatment? Please select all that apply” 19 respondents answered this question and results are reflected in the chart below

Figure 5: Neurological or Circulatory Side Effects of Corticosteroids Experienced During Treatment

ANSWER CHOICES	RESPONSES	
Aggression/agitation/irritability/mood changes	73.68%	14
Swelling of the fingers, hands, feet, legs	57.89%	11
Headaches, dizziness, fainting	47.37%	9
Trouble thinking or speaking	42.11%	8
Blurred or decreased vision, eye pain or tearing	36.84%	7
Irregular heartbeat or pulse	36.84%	7
Numbness or tingling in the arms or legs	36.84%	7
Trouble walking	31.58%	6
Suicidal thoughts	10.53%	2
Total Respondents: 19		

Respondents were asked, “Which of the following other physical side effects of corticosteroids have you experienced during treatment? Please select all that apply” 20 respondents answered this question and results are reflected in the chart below.

Figure 6: Other Physical Side Effects of Corticosteroids Experienced During Treatment

ANSWER CHOICES	RESPONSES	
weight loss or gain	85.00%	17
Trouble sleeping, fatigue or weakness	70.00%	14
Increased hunger or thirst	60.00%	12
Body/muscle pain/weakness (back, sides, limbs)	55.00%	11
Skin rash, flushed or dry skin	50.00%	10
Loss of sexual desire or ability	50.00%	10
shortness of breath, cough or hoarseness	45.00%	9
Stomach cramps, nausea, vomiting or diarrhea	45.00%	9
Fever or chills	20.00%	4
Painful or difficult urination	20.00%	4
Bone fractures	0.00%	0
Total Respondents: 20		

Some respondents selected “other” and commented with additional symptoms not listed:

- Shaking hands and legs
- Tremors
- Increased blood pressure
- Muscle wasting/losing strength
- Difficulty driving (too aggressive)
- Weakened bone structure. I needed treatment for osteoporosis

Respondents elaborated on their thoughts, feelings and experiences regarding corticosteroid treatment:

> “Didn’t really understand that it could be long term and that prednisone is not a good alternative. The symptoms are terrible and need to have treatment.”
>
> “The entire time I was taking steroids I was definitely singularly focused on getting off of them. I measured the success of my doctor appointments by whether I could be tapered down a bit more off of the prednisone I was taking. If it was a good appointment, I'd get to reduce my prednisone. If it was a bit so good appointment, I'd have to wait longer to decrease the next dose or even increase it. I kept a journal about my prednisone usage. I couldn't wait to get off of it.”
>
> “The bloating of the face and stomach were difficult to tolerate and embarrassing.”
>
> “At one point on my prednisone regime I developed myopathy on my left hip. Couldn't walk for about 3 weeks and needed calcium injections.”
>
> “Taking a medication that would eliminate having to use steroid creams would be helpful.”
>
> “Prednisone is brutal. It makes you feel like you are on 20 coffees. You can't sleep, are always hungry and as a result, gain weight.”
>
> “Taking prednisone for years affected my skin, bone density loss, muscle pains, cramps and spasms plus loss of tissue.”
>
> “Prednisone was not an easy drug to tolerate, my teeth and my gums were destroyed as a result of long-term use of prednisone.”
>
> “Prednisone affected my bones and therefore resulting in taking a bone hardening pill once a week. Also, because of taking prednisone for years, my skin has become paper thin, have muscle pains and spasms and loss of padding on the ball of my feet.”
>
> “Steroid therapy has so many negative impacts on the body and results in a host of other health issues for cGVHD patients. Being on prednisone was a horrible experience. I was so bloated and cushingoid that I was unrecognizable to myself and family. Physically, it made recovery much different. Once I was saying to get off steroids, I started exercising again and my health dramatically improved. I can't emphasize the impact enough really.”

Some patients expressed concern that they would run out of treatment options to treat their cGVHD.

Respondents were asked, “Please indicate how strongly you agree/disagree with the following statement: “I am/was worried about running out of treatment options to effectively manage my cGVHD.”

- 13/44 (29.55%) Strongly agree
- 11/44 (25%) Neither agree nor disagree
- 8/44 (18.18%) Somewhat agree
- 8/44 (18.18%) Disagree
- 4/44 (9.09%) Strongly disagree

Respondents commented about their experiences with treatments for cGVHD:

> “Everyone's cGVHD is different. There is a need for targeted therapies with fewer side effects than systemic steroids.”
>
> “At first, I had very mild symptoms of cGVHD and the med team was monitoring me closely. I first had GVHD in my mouth, and then some mild skin GVHD which was reasonably under control with a prescribed mouth rinse and a cream for my skin. At first, I was not too concerned as I was told some GVHD is a good thing. Once my skin started to develop some open sores and spread, it not only has caused me the discomfort and pain but increased my anxiety level as my medical team has tried a few different treatments which have not worked. As much as I have a positive attitude in general, these ongoing attempts at treatment with no luck have significantly dampered my spirits. I’m so worried now that this can perhaps cause a relapse or even worsen GVHD symptoms into my organs. I’m really worried that no treatment to date has really helped halt my cGVHD, specifically the open wounds. It’s incredibly uncomfortable and really impairs my movements. Sometimes I feel I’m going backwards in this journey.”
>
> “Had allergic reactions to many immunosuppressants. Frustrated that referrals weren’t made quickly, or wrong diagnosis made. There have been several times where wrong diagnosis caused a significant delay in treatment.”
>
> “Lack of options and have not been explained in detail the options available.”
>
> “Required medications are paid out of pocket, and very expensive causing worry how to pay for this all.”
>
> “I felt sad initially, but I have done whatever I can on the advice of my oncologist. It was very trying and continues to be a challenge 8 years from Day 0. PHP, Rituxin, Imatinib, IgG and now Jakavi year 3.”

Improved Outcomes

Though individual patient values differ from person to person, patients and caregivers want to maintain a sense of normalcy and be able to continue with their daily lives and routines throughout the course of their treatment. Patients and caregivers deserve to have access to treatments that fight their disease and improve overall survival but also preserve their quality of life as much as possible and have a limited impact on aspects of their life such as work, finances, relationships, and physical and mental health.

27/37 (72.97%) respondents stated that having access to alternative treatment rather than corticosteroids to treat their cGVHD would have “some positive impact” to “significant positive impact” on their **physical health**. One respondent noted “Developed prednisone induced diabetes”

26/40 (65%) respondents stated that having access to alternative treatment rather than corticosteroids to treat their cGVHD would have “some positive impact” to “significant positive impact” on their **mental wellness**.

29/38 (76.32%) respondents stated that having access to alternative treatment rather than corticosteroids to treat their cGVHD would have “some positive impact” to “significant positive impact” on their **quality of life**. One respondent commented… “Would not have to deal with significant weight gain or sleep issues. Feeling jittery or have tremors.”

Respondents were asked, “Please rate on a scale of 1 (not important at all) to 5 (extremely important), which factors are/were most important to you when considering a new cGVHD treatment?” We used weighted average to summarize responses.

- 4.6/5 Improved length of survival
- 4.48/5 Improves quality of life
- 4.26/5 Degree of certainty that it will relieve cGVHD
- 4.12/5 Covered by insurance/drug plan
- 4/5 Treatment drug will not be affected by drug shortages
- 3.81/5 Outpatient treatment (no overnight hospital stay required)
- 3.74/5 Severity of side effects
- 3.45/5 Least amount of travel required for treatment
- 1.16/5 Religious considerations

Respondents were asked the open-ended question, “Ideally, what desired improvements to quality of life would you like to see from new treatments?” Respondents commented…

“Improved strength and mobility”

“I want to find back my health I had before. Easy to take No side effects.”

“Less severe side-effects with similar capabilities of treating and controlling GvHd”

“Less effects on muscle/joint pain/loss”

“I would dearly like to have more energy, stamina and muscle strength.”

“More options, more targeted, steroid-sparing therapies with fewer side effects”

“Better motor control and less emotional fluctuations”

“A treatment with reduced side effects”

Experience With Drug Under Review

Belumosudil is a very new treatment in Canada. As a result, there is very limited experience. 5 survey respondents stated that they have taken belumosudil (Rezurock®) for treatment of cGVHD and only 3 respondents provided significant responses. Respondents who answered that they have taken belumosudil (Rezurock®) to treat their cGVHD agreed that the side effects they experienced on belumosudil (Rezurock®) were minimal and very tolerable.

3/3 (100%) respondents stated that they would rate the overall side effects of belumosudil (Rezurock®) as "very tolerable."

Respondents were also asked, "How did side effects from belumosudil (Rezurock®) treatment affect you? Please rate the level of impact of each potential side effect on a scale from 1 (no impact) – 5 (extremely large impact)" 3/3 (100%) respondents rated any side effects experienced as having "no impact" or "small impact". No side effects were reported in the medium to extremely large impact range.

All respondents stated that their corticosteroid dose was able to be reduced as a result of belumosudil Rezurock® treatment. This is highly significant as:

These patients also relayed that their steroid dosage was able to be reduced as a result of treatment with belumosudil (Rezurock®). This is highly significant to patient well-being. A reduction in steroid dosage was a relief for patients and their families as the reduction was significantly beneficial to patients' health, both mental and physical, as well as improved quality of life. 3/3 (100%) respondents stated that belumosudil (Rezurock®) treatment had a "positive impact" on their home life and personal life in comparison to before treatment.

One patient commented, "Discontinuing steroids felt like an important step on the road to recovering and becoming the person I was before I got sick. Gradually losing my cushingoid appearance dramatically improved my mental health because I started to look and feel normal again."

Companion Diagnostic Test

Not appliable.

Anything Else?

cGVHD patients and their families need treatment options that will help manage cGVHD and reduce the use of corticosteroids, therefore lessening the physical and mental impacts of the side effects of these corticosteroids.

> "I am constantly shaky. Sometimes I can't even write well I'm so shaky that my writing is like scribble - it's so upsetting. My walking has been affected, I walk with a limp and often in joint pain - it's horrible and makes me feel like I'll never get better. My edema is a bit better with using Lasix daily but overall, it's been extremely uncomfortable and impedes my movements. The purple legs are also bothersome and very noticeable, which the DR said is a side effect of the steroids/prednisone".
>
> "It broke my life. Professional, social, financial, parental. As much mentally than physically, I will never

be the same anymore. I am only 54 years old, and I learned the bad news I was 47 years old...”

Figure 7: Impact on Side Effects From belumosudil (Rezurock®) Treatment

	1- NO IMPACT	2- SMALL IMPACT	3- MEDIUM IMPACT	4- LARGE IMPACT	5- EXTREMELY LARGE IMPACT	TOTAL	WEIGHTED AVERAGE
Feeling weak/Fatigue	33.33% 1	66.67% 2	0.00% 0	0.00% 0	0.00% 0	3	1.67
Infections	66.67% 2	33.33% 1	0.00% 0	0.00% 0	0.00% 0	3	1.33
Bruising/Bleeding	66.67% 2	33.33% 1	0.00% 0	0.00% 0	0.00% 0	3	1.33
High blood pressure	66.67% 2	33.33% 1	0.00% 0	0.00% 0	0.00% 0	3	1.33
Muscle or bone pain	66.67% 2	33.33% 1	0.00% 0	0.00% 0	0.00% 0	3	1.33
Swelling	66.67% 2	33.33% 1	0.00% 0	0.00% 0	0.00% 0	3	1.33
Stomach pain/Nausea/vomiting/Diarrhea	100.00% 3	0.00% 0	0.00% 0	0.00% 0	0.00% 0	3	1.00
Cough/Shortness of breath	100.00% 3	0.00% 0	0.00% 0	0.00% 0	0.00% 0	3	1.00
Headache	100.00% 3	0.00% 0	0.00% 0	0.00% 0	0.00% 0	3	1.00
Liver problems	100.00% 3	0.00% 0	0.00% 0	0.00% 0	0.00% 0	3	1.00

Comments (0)

We would strongly advise CADTH to recommend belumosudil (Rezurock®) treatment for reimbursement and increase access to this needed medication for the treatment of adult and pediatric patients 12 years and older with chronic graft-versus-host disease (GVHD) after failure of at least two prior lines of systemic therapy.

Conflict of Interest Declaration — The Leukemia & Lymphoma Society of Canada

To maintain the objectivity and credibility of the CADTH reimbursement review process, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

Did you receive help from outside your patient group to complete this submission?

No.

Did you receive help from outside your patient group to collect or analyze data used in this submission?

No.

List any companies or organizations that have provided your group with financial payment over the past 2 years AND who may have direct or indirect interest in the drug under review.

Table 1: Financial Disclosures for The Leukemia & Lymphoma Society of Canada

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Sanofi-Aventis Canada Inc. — No COI	—	—	—	—

Clinician Input

Ontario Health (Cancer Care Ontario) Hematology Cancer Drug Advisory Committee

About Ontario Health (Cancer Care Ontario) Hematology Cancer Drug Advisory Committee
OH-CCO's Cancer Drug Advisory Committees provide timely evidence-based clinical and health system guidance on drug-related issues in support of CCO's mandate, including the Provincial Drug Reimbursement Programs (PDRP) and the Systemic Treatment Program.

Information Gathering
Information was gathered by videoconferencing.

Current Treatments and Treatment Goals
There are a variety of treatments available in 3L chronic GVHD (cGVHD). The only approved treatments are ibrutinib (not funded) and ruxolitinib. Others have been used depending on availability and coverage. ECP is also a treatment that can be used.

Treatment Gaps (Unmet Needs)
Considering the treatment goals, please describe goals (needs) that are not being met by currently available treatments.

Not all patients respond or tolerate available therapies. Oral therapies are often preferred.

Place in Therapy
How would the drug under review fit into the current treatment paradigm?

This treatment would be used in 3L or higher. There should be no limit to the number of prior LOTs.

Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

This treatment would be for all patients with cGVHD for 3L and beyond.

What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

There are standard GVHD response criteria used to assess response. There could also be significant functional improvements in patients who respond to this treatment as well as better quality of life.

What factors should be considered when deciding to discontinue treatment with the drug under review?

Significant intolerance, or GVHD progression.

What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

Clinicians that are experts in the management of cGVHD. This would mostly be used in the outpatient setting. Those with severe cGVHD may require this drug as an inpatient.

Additional Information

Not applicable.

Conflict of Interest Declarations — Ontario Health (Cancer Care Ontario) Hematology Cancer Drug Advisory Committee

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please refer to the Procedures for CADTH Drug Reimbursement Reviews (section 6.3) for further details.

Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

OH-CCO provided secretariat function to the group.

Did you receive help from outside your clinician group to collect or analyze any information used in this submission?

No.

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. Please note that this is required for *each clinician* who contributed to the input.

Declaration for Clinician 1

Name: Dr. Tom Kouroukis

Position: Lead, Ontario Health (Cancer Care Ontario) Hematology Cancer Drug Advisory Committee

Date: 03-08-2023

Table 2: COI Declaration for OH-CCO Hematology Cancer Drug Advisory Committee — Clinician 1

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
No COI	–	–	–	–

Cell Therapy Transplant Canada

About Cell Therapy Transplant Canada

Cell Therapy Transplant Canada (CTTC; www.cttcanada.org) is a member-led, national, multidisciplinary organization providing leadership and promoting excellence in patient care, research, and education in the field of hematopoietic stem cell transplant and cell therapy. The CTTC advocates, nationally and internationally, for improving the outcomes and accessibility of cellular therapies and transplantation for Canadians. Representation in the CTTC includes physicians, nursing, laboratory and allied health professionals, along with an active family and caregiver group.

Information Gathering

Information was gathered through literature review, discussion and approved by two CTTC committees – the CTTC Board of Directors, and the CTTC standing committee of program directors, with representation from all 23 allogeneic stem cell transplant programs across Canada. This report was approved by both committees.

Current Treatments and Treatment Goals

The prognosis of both steroid refractory aGvHD and cGvHD is poor resulting in a significant increase in both mortality and morbidity after stem cell transplantation. There is no standard of care as a second line therapy. There are several cGvHD therapies that are currently used off label. Examples include extracorporeal photopheresis, mycophenolate mofetil, sirolimus, everolimus, imatinib, and rituximab. There is some province-to-province variation on standard practice, based on local funding of available options. Belumosudil has an excellent ability to induce response in patients that have failed these established therapies, including the newly approved ruxolitinib.

Treatment Gaps (Unmet Needs)

Considering the treatment goals, please describe goals (needs) that are not being met by currently available treatments.

Steroid refractory cGvHD is the primary non-relapse cause of post-transplant mortality. In addition, steroid refractory cGvHD has major morbidity and can include decreased mobility, liver failure, renal failure, gastrointestinal failure, cardiac failure, renal failure, keratoconjunctivitis, and stomatitis [1]. One of the most severe symptoms is the development of irreversible bronchiolitis obliterans which has a high mortality rate [2]. Based on the ROCKStar trial, belumosudil currently represents the best therapeutic option to reduce the mortality and symptom burden associated with steroid refractory cGvHD that has failed standard therapy [3]. In particular, it has the potential to significantly impact patients that have failed ruxolitinib and improve quality of life with a low risk of adverse events. It would not be appropriate to require that patients try other

therapies for steroid refractory pulmonary or sclerotic/fibrotic cGvHD prior to belumosudil, given that all these therapies were shown to be inferior to belumosudil.

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Place in Therapy

How would the drug under review fit into the current treatment paradigm?

Current available treatment options are suboptimal and new therapies are urgently needed. This is especially true for steroid refractory pulmonary cGvHD and also cGvHD that has fibrotic and sclerotic manifestations. Current therapies still require relatively high doses and the prolonged use of corticosteroids to control disease and drugs that offer the potential to decrease the long-term morbidity of steroids and minimize or reverse fibrotic changes are needed. Belumosudil represents one of the best options of currently available drugs especially for pulmonary cGvHD and fibrotic and sclerotic cGvHD. An additional benefit is the drug's potential to minimize the use of prolonged steroids will result in a reduced risk of steroid-induced opportunistic infections, osteoporosis, and avascular necrosis.

Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

All patients with steroid refractory and ruxolitinib refractory cGvHD would be expected to benefit – there are no specific subpopulations that would be appropriate for this treatment. This may be particularly helpful for those with pulmonary cGvHD based on the clinical trials' data.

What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

Given that chronic GvHD has a fibrotic component which is very difficult to resolve in a short period of time, at least 6 months (or up to 12 months) of treatment would be required before having objective assessment of clinical benefit/response. In case of complete or partial response by 6-12 months based on the NIH consensus criteria, it will determine that a patient is responding to the treatment. Also, any patient showing no significant change of their GvHD severity but with significant reduction of other immunosuppressive treatment including corticosteroids can be determined to have a clinical benefit from the treatment.

What factors should be considered when deciding to discontinue treatment with the drug under review?

Patients would be required to start therapy with corticosteroids, as this remains the initial therapy for cGvHD, but a second agent in addition to steroids is almost always required. Because the fibrotic component of cGvHD is very slow to resolve, therapy with belumosudil will require prolonged treatment until no further resolution or stable residual fibrotic changes are present. Usually this will require therapy for greater than 1 year and treatment should only be discontinued if there is no further evidence of resolution of fibrotic changes, and if the drug is discontinued, that no progression occurs. In the later situation, re-initiation of belumosudil will be required. At present there is no validated biomarkers to inform the clinician regarding discontinuation of belumosudil.

What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

This therapy would become the preferred initial therapy for patients with steroid or ruxolitinib refractory cGvHD. This therapy should only be prescribed for this indication by specialists working in a clinical setting associated with allogeneic HCT programs.

Additional Information

All patients with steroid refractory cGvHD would be well suited for this therapy, especially those with sclerotic/fibrotic manifestations. Belumosudil has not been studied in the acute GvHD setting.

Patients with aGvHD and cGvHD are managed in highly specialized stem cell transplant clinics, at a limited number of tertiary care centres across Canada. These centres have physicians and clinical teams that are experienced at managing GvHD, and we do not expect misdiagnosis to be a significant issue. Patients that are eligible for this therapy will be identified by these teams.

Conflict of Interest Declarations — Cell Therapy Transplant Canada

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please refer to the Procedures for CADTH Drug Reimbursement Reviews (section 6.3) for further details.

Did you receive help from outside your clinician group to complete this submission?

No help from outside the clinician group was obtained.

Did you receive help from outside your clinician group to collect or analyze any information used in this submission?

No help from outside the clinician group was obtained.

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. Please note that this is required for *each clinician* who contributed to the input.

Declaration for Clinician 1
Name: Kirk R Schultz

Position: Pediatric Haematologist Oncologist, BC Children's Hospital Vancouver

Date: 13-07-2023

Table 3: COI Declaration for Cell Therapy Transplant Canada — Clinician 1

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
No COI	–	–	–	–

Declaration for Clinician 2
Name: Dennis Kim

Position: Senior Hematologist, Clinician Investigator, Princess Margaret Cancer Centre, Toronto

Date: 20-07-2023

Table 4: COI Declaration for Cell Therapy Transplant Canada — Clinician 2

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Sanofi	–	X	–	–
Novartis	–	–	X	–

Declaration for Clinician 3
Name: Christopher Bredeson

Position: Head, Malignant Hematology, Transplant and Cellular Therapy, The Ottawa Hospital; Professor, University of Ottawa

Date: 24-07-2023

Table 5: COI Declaration for Cell Therapy Transplant Canada — Clinician 3

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Kite/Gilead	X	—	—	—
Novartis	X	—	—	—
Allogene	—	X	—	—

Declaration for Clinician 4
Name: Genevieve Gallagher

Position: Medical director, Programme de transplantation de cellules hématopoïétiques et de thérapie cellulaire du CHU de Québec- Université Laval

Date: 24-07-2023

Table 6: COI Declaration for Cell Therapy Transplant Canada — Clinician 4

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
No COI	—	—	—	—

Declaration for Clinician 5
Name: David Mitchell

Position: Pediatric Hematologist-Oncologist, Montreal Children's Hospital

Date: 25-07-2023

Table 7: COI Declaration for Cell Therapy Transplant Canada — Clinician 5

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
No COI	—	—	—	—

Declaration for Clinician 6
Name: Victor Lewis

Position: Director of Oncology and Blood and Marrow Transplant, Alberta Children's Hospital Calgary

Date: 24-07-2023

Table 8: COI Declaration for Cell Therapy Transplant Canada — Clinician 6

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
No COI	—	—	—	—

Declaration for Clinician 7
Name: Kevin Song

Position: Medical Director, Leukemia/BMT Program of British Columbia, University of British Columbia

Date: 25-07-2023

Table 9: COI Declaration for Cell Therapy Transplant Canada — Clinician 7

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Sanofi Canada	X	—	—	—
Janssen	—	X	—	—
Amgen	X	—	—	—
Jazz Pharmaceuticals Canada Inc.	X	—	—	—
Gilead Sciences Canada	X	—	—	—

Declaration for Clinician 8

Name: Wilson Lam

Position: Staff Physician, Hans Messner Allogeneic Blood and Marrow Transplant Program, Princess Margaret Cancer Centre; Assistant Professor, University of Toronto

Date: 25-07-2023

Table 10: COI Declaration for Cell Therapy Transplant Canada — Clinician 8

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
No COI	—	—	—	—

Declaration for Clinician 9

Name: M. Lynn Savoie

Position: Clinical Associate Professor, Division of Hematology and Hematologic Malignancies, University of Calgary

Date: 31-07-2023

Table 11: COI Declaration for Cell Therapy Transplant Canada — Clinician 9

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Sanofi	X	—	—	—

Declaration for Clinician 10

Name: Ravi M. Shah

Position: Attending Physician, Pediatric Oncology/BMT, Alberta Children's Hospital

Date: 02-08-2023

Table 12: COI Declaration for Cell Therapy Transplant Canada — Clinician 10

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
No COI	—	—	—	—

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