CADTH

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

Belumosudil (Rezurock)

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.

Sponsor: Sanofi-Aventis Canada Inc.

Recommendation: Reimburse with Conditions

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Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that belumosudil be reimbursed for the treatment of adult and pediatric patients 12 years and older with chronic graft-versus-host disease (cGVHD) after failure of at least 2 prior lines of systemic therapy only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

Two phase II, open-label trials (study KD025-213 and study KD025-208) demonstrated that treatment with belumosudil 200 mg daily produced clinically beneficial results for patients with active cGVHD. In total, [redacted] patients in study KD025-213 and 17 patients in study KD025-208 received the Health Canada–approved dose. Study KD025-213 showed that belomosudil in combination with standard systemic cGVHD therapies was associated with a statistically significant improvement in overall response rate (ORR) that was greater than 30% (which was considered clinically meaningful in the trial) at 6 months compared to baseline (ORR, [redacted]; 95% confidence interval [CI], [redacted]). Study KD025-208 was exploratory in nature and its results supported the findings from study KD025-213. CDEC acknowledged the rarity of cGVHD and the unmet need for additional treatment options in this setting given the severe nature of this disease with substantial morbidity.

Patients expressed a need for treatments that improve survival and quality of life, reduce disease symptoms, reduce corticosteroid dosages, and produce fewer adverse effects. CDEC concluded that belumosudil met some important patient needs by reducing disease symptoms of cGvHD and corticosteroid dosages, as well as providing an oral drug option that can be administered as an outpatient treatment. The clinical experts indicated that the results for duration of response (DOR), time to response (TTR), failure free survival (FFS), and overall survival (OS) in the studies were clinically important. Due to the lack of valid comparator in the pivotal studies and open-label design of the studies, no definitive conclusions could be reached regarding the effects of belumosudil on health-related quality of life (HRQoL).

Using the sponsor submitted price for belumosudil and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for belumosudil was $313,874 per quality-adjusted life-year (QALY) gained compared with best available therapy (BAT). At this ICER, belumosudil is not cost-effective at a $50,000 per QALY willingness to pay (WTP) threshold for the indicated population. A price reduction is required for belumosudil to be considered cost-effective at a $50,000 per QALY gained threshold.

Table 1. Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Treatment with belumosudil should be initiated in patients 12 years and older who have clinically diagnosed cGvHD staging of moderate to severe based on NIH consensus criteria[a]	Evidence from study KD025-213 demonstrated that belumosudil resulted in a statistically significant improvement in ORR in patients with active cGVHD. This also aligns with the Health Canada indication for belumosudil.	Moderate chronic GVHD defined according to the NIH cGVHD severity definition: at least 1 organ or site with a maximum score of 2 in any affected organ or site, or 3 or more organs or sites with a maximum score of 1 in all affected organs or sites, or a lung score of 1.[a] Severe chronic GVHD defined according to the NIH cGVHD severity definition: at least 1 organ or site with a score of 3, or a lung score of 2 or greater.[a]
2. Patients should have a confirmed diagnosis of cGvHD with inadequate response to at least 2 prior lines of systemic therapy (one line of therapy would be a CS with or without CNI)	Evidence from study KD025-213 demonstrated that belumosudil resulted in a statistically significant improvement in ORR in patients with active cGVHD who had experience with at least 2 prior lines of therapy.	Corticosteroid refractory cGvHD is defined, based on 2014 NIH consensus criteria[b], by one or more of the following criteria: • A lack of response or disease progression after administration of minimum prednisone 1 mg/kg/day for at least 1 week (or equivalent) • Disease persistence without improvement despite continued treatment with prednisone at > 0.5 mg/ kg/day or 1 mg/kg/every other day for at least 4 weeks (or equivalent) • Increased prednisone dose to > 0.25 mg/ kg/day after 2 unsuccessful attempts to taper the dose (or equivalent).
Renewal		
3. Treatment with belumosudil should be renewed for patients who have achieved an overall response (i.e., CR or PR, or stable disease with significant reduction in steroid doses), according to NIH criteria[c], after 24 weeks of therapy (approximately 6 months).	Evidence from study KD025-213 demonstrated that belumosudil resulted in a statistically significant improvement in ORR in patients with active cGVHD at 6 months.	—
Discontinuation		
4. Belumosudil should be discontinued upon the occurrence of any of the following: 4.1. Progression of cGvHD, defined as worsening of cGvHD symptoms or	In study KD025-213, 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). In addition, in study KD025-213 transient increases in CS	—

Reimbursement condition	Reason	Implementation guidance
occurrence of new cGvHD symptoms 4.2. The dose of corticosteroids remains at or above baseline dose for more than 6 weeks 4.3. A patient experiences more than 2 cGVHD flares that require increased corticosteroid therapy in a 6 month period of belumosudil treatment	dosing (that did not exceed 1 mg/kg/day prednisone equivalent) were permitted to treat cGVHD flares, but the dose must have been reduced back to the pre-randomization 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. CDEC did not review any evidence that indicated patients who exhibit the clinical presentations outlined in this condition would benefit from further treatment with belumosudil.	
Prescribing		
5. Belumosudil should only be prescribed by clinicians who have experience in the diagnosis and management of patients with cGvHD.	These conditions are required to ensure that belumosudil is prescribed only for appropriate patients and that patients receive optimal care for toxicity management.	—
6. Treatment with belumosudil may be added to patients' concurrent treatment of steroids with or without CNIs and/or stable systemic therapies for cGVHD but should not be used with other newly initiated systemic therapies for cGVHD.	In study KD025-213, patients continued to receive the systemic immunosuppressive regimen of corticosteroids, CNIs, sirolimus, mycophenolate mofetil, methotrexate, rituximab, ECP, or topical or organ-specific therapies if they had been on a stable regimen for cGVHD that were initiated before randomization. There are no data to support the generalization of treatment benefit to patients who receive belumosudil as an add on to systemic therapies other than those listed above.	—
Pricing		
7. A reduction in price	The ICER for belumosudil is $313,874 when compared with BAT. A price reduction of 76% would be required for belumosudil to achieve an ICER of $50,000 per QALY gained compared to BAT.	—

BAT = best available therapy; CDEC = Canadian Drug Expert Committee; cGVHD = chronic graft-versus-host disease; CNI = calcineurin inhibitor; CR = complete response; ECP = extracorporeal photopheresis; NIH = National Institutes of Health; ORR = overall response rate; PR = partial response.

[a] Jagasia MH, Greinix HT, Arora M, et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-vs.-Host Disease: I. The 2014 Diagnosis and Staging Working Group report. Biol Blood Marrow Transplant. 2015;21(3):389 to 401.e381.

[b] Martin PJ, Lee SJ, Przepiorka D, et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-vs.-Host Disease: VI. The 2014 Clinical Trial Design Working Group Report. Biol Blood Marrow Transplant. 2015;21(8):1343 to 1359.

[c] Lee SJ, Wolff D, Kitko C, et al. Measuring therapeutic response in chronic graft-vs.-host disease. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-vs.-host disease: IV. The 2014 Response Criteria Working Group report. Biol Blood Marrow Transplant. 2015;21(6):984 to 999.

Discussion Points

- There was uncertainty with the clinical evidence; however, based on the input from clinical experts and patients, CDEC acknowledged this is a rare patient population with an unmet medical need for additional effective and safe treatment options in the cGVHD setting given the severe nature of this disease with substantial morbidity and mortality. cGVHD not only impacts various organ systems of the body, but greatly impacts patients' physical and mental health and HRQoL. Despite the various drug options available for treating cGVHD, few have a Health Canada–approved indication, and there remain issues with intolerance, failure of response to therapy, and associated adverse effects. CDEC acknowledged that there is a need for new treatment options that improve survival and quality of life and reduce disease symptoms.
- CDEC acknowledged that while there was no evidence for pediatric patients available for review, Health Canada indicated that the use of belumosudil in pediatric patients 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.
- CDEC discussed the lack of relevant comparator in the trials, despite there being on- and off-label options available that could be used after failure of at least 2 prior lines of systemic therapy for the treatment of cGVHD. Given the lack of a standardized treatment approach and effective treatment options, it was determined that the limitations and uncertainty were balanced with unmet needs.
- In study KD025-213, belumosudil was tapered after sustained response for 6 months and cessation of all other immunosuppressants for at least 3 months as follows: belumosudil 200 mg QD, then belumosudil 200 mg once every other day for 2 cycles, then discontinued. CDEC noted that such tapering could occur in clinical practice.
- CDEC discussed the sponsor submitted economic evaluation and noted concerns with the sponsor's modelling approach. These concerns with the modelling approach, along with the uncertainty associated with the comparative clinical efficacy and existing confidential discounts for comparators, lead to uncertainty associated with the incremental cost-effectiveness estimates of belumosudil, and may require further price reductions.

Background

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) involves transplantation of a donor's stem cells to a recipient (i.e., patient). With allo-HSCT there is a risk that the transplanted stem cells will die or be destroyed by the recipient, or that the donor's transplanted immune cells will attack the recipient's healthy cells; the latter is called graft-versus-host disease (GVHD). Chronic GVHD (cGVHD) can last for months to a lifetime and is the leading cause of late morbidity and death after allo-HSCT. Patients with cGVHD face physical, functional, and psychosocial deficits that have a profound negative impact on HRQoL. It is estimated that in 35% to 50% of patients who undergo allo-HSCT will develop cGVHD. 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 harms. First-line treatment is generally considered standard across clinical practice and consists of topical or systemic corticosteroids (CSs), with or without calcineurin inhibitors (CNIs). In Canada, second-line options include extracorporeal photopheresis (ECP), mycophenolate mofetil, etanercept, low-dose methotrexate, infliximab, mammalian target of rapamycin inhibitors, imatinib, rituximab, ruxolitinib, ibrutinib, low-dose interleukin-2, pulsed cyclophosphamide, and pentostatin. There is a lack of consensus for standard cGVHD treatment after first-line therapy due to the evidence being insufficient to recommend any treatment over another and the variability in accessing treatments across Canada. Only ruxolitinib and ibrutinib have Health Canada indications for the treatment of cGVHD in adults and pediatric patients aged 12 years and older who have inadequate response to CSs or other systemic therapies and for the treatment of cGVHD in patients 1 year and older after failure of 1 or more lines of systemic therapy, respectively.

Belumosudil is a selective oral inhibitor of Rho-associated, coiled-coil-containing protein kinase-2 (ROCK2) and ROCK1 and has been approved by Health Canada 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. The recommended dose of belumosudil is 200 mg given orally once daily (QD) and treatment should continue until progression of cGVHD that requires a new systemic therapy or occurrence of unacceptable toxicity. No dose adjustments are required in adolescents 12 to 18 years or in patients 65 years or older. 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 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.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- A review of 2 clinical studies (with a single arm relevant to the CADTH review) in patients with active cGVHD
- Patients' perspectives gathered by patient groups, including Leukemia & Lymphoma Society of Canada and Myeloma Canada
- Input from public drug plans and cancer agencies that participate in the CADTH review process
- Two clinical specialists with expertise diagnosing and treating patients with cGVHD
- Input from 2 clinician groups, including Ontario Health Cancer Care Ontario (OH-CCO) Hematology Cancer Drug Advisory Committee and Cell Therapy Transplant Canada (CTTC)
- A review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

Patient Input

One joint input was submitted by 2 patient groups, the Leukemia & 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 transplantation, 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, their 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, neurological, 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 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 have impacted HRQoL, ability to work and study, and have 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 earlier use in the first- or second-line setting would require good randomized controlled trials (RCTs) evidence. As per the clinical experts, patients with moderate-to-severe cGVHD who are refractory or 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 maintenance of stable disease with clinically meaningful reduction in CS dose are indicators that a patient is responding to treatment in clinical practice. Improvement in functional status, symptoms, ability to return to school or work were also noted as being important outcomes.

Reasons for discontinuing treatment identified by the clinical experts included disease progression (based on signs, symptoms, examination, laboratory tests) or having stable disease but still requiring 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 reason to stop. Lastly, disease resolution in which a patient has stopped other immunosuppressants (or 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, OH-CCO Hematology Cancer Drug Advisory Committee and CTTC provided input for the CADTH review of belumosudil. Clinician perspectives from OH-CCO were obtained through videoconferencing. CTTC gathered the information through literature review and discussion from 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 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, as well as 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 practicing in inpatient or outpatient settings, while CTTC added that the drug should only be prescribed by specialists working in a clinical setting associated with allo-HSCT programs for patients who are refractory to steroid or ruxolitinib.

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. The following were identified as key factors that could potentially impact the implementation of a CADTH recommendation for belumosudil:

- considerations for initiation of therapy
- considerations for continuation or renewal of therapy
- considerations for discontinuation of therapy
- considerations for prescribing of therapy
- generalizability of trial populations to the broader populations in the jurisdictions
- system and economic issues.

The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

Table 2. Responses to Questions from the Drug Programs

Implementation issues	Response
Relevant comparators	
Ibrutinib has an indication for cGVHD however it was not submitted to CADTH for review of this specific indication and was not used as a comparator. How does ibrutinib compare to belumosudil? What is belumosudil's place in therapy?	The clinical experts acknowledged that at this time, there was no direct or indirect evidence comparing belumosudil to ibrutinib submitted for the CADTH review. According to the experts, belumosudil would be used as per its Health Canada indication (for the treatment of patients 12 years and older with cGVHD after failure of at least 2 prior systemic therapies). They added that there would need to be 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?	According to the clinical experts any 2 systemic therapies for the treatment of cGVHD (including CSs with or without CNI and ECP) count towards 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?	CDEC agreed with the clinical experts that the first authorization of belumosudil should be for 6 months with renewal for patients who have achieved 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. CDEC agreed with the clinical experts that belumosudil should be discontinued if there is progression of cGVHD, defined as worsening of symptoms or occurrence of new symptoms. In addition, CDEC also recommended that belumosudil be discontinued if the dose of CS 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 a 6 month period of belumosudil treatment.
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 would not expect treatment with belumosudil to be indefinite. In their opinions, physicians would cautiously taper cGVHD treatment(s) and assess response or relapse in order to manage a patient's symptoms with the minimum number of drugs and dose possible. They also noted that 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 for. Additionally, in study KD025-213, belumosudil was tapered after sustained response for 6 months and cessation of all other immunosuppressants for at least 3 months.
Considerations for prescribing of therapy	

Implementation issues	Response
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 medications. It is unclear if treatment is intended to be alone or as adjunctive therapy.	As per study KD025-213 and study KD025-208, the clinical experts expect that belumosudil could be used alongside other treatments for cGVHD. In the studies, permitted concomitant 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 failed other therapies?	The clinical experts indicated that 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 that it would be challenging to prioritize cGVHD treatments due to the lack of direct and indirect comparative evidence available for review.

aGVHD = acute graft-versus-host disease; CDEC = Canadian Drug Expert Committee; cGVHD = chronic graft-versus-host disease; CNI = calcineurin inhibitors; CR = complete response; CS = corticosteroid; ECP = extracorporeal photopheresis; NIH = National Institutes of Health; ORR = overall response rate; PR = partial response; RCT = randomized controlled trial.

Clinical Evidence

Systematic Review

Description of Studies

Study KD025-213 (N = [redacted]) is a phase II, open-label study with a latest data cut-off date of [redacted]. Eligible patients must have been 12 years of age or older with active cGVHD, undergone allo-HSCT, and received 2 to 5 prior lines of therapy for cGVHD. Study KD025-208 (N = 54) is a phase IIa, dose-escalation, on-going, open-label study with a latest data cut-off date of [redacted]. Eligible patients must have been 18 years of age or older with active cGVHD, undergone allogeneic bone marrow transplant or allo-HSCT, and received 1 to 3 prior lines of therapy for cGVHD (not including ECP). In study KD025-213 and study KD025-208, [redacted] patients and 17 patients, respectively, received belumosudil 200 mg QD and there were no relevant comparator or control groups in either study (belumosudil 200 mg twice daily and belumosudil 400 mg QD 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 new systemic therapy was not permitted. The primary outcome of both studies was 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 and was the only end point controlled for multiple testing. Secondary outcomes of interest to the CADTH review included DOR, TTR, 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 KD025-213. 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). 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 KD025-213 and 50 years (range, 20 years to 63 years) in study KD025-208. 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 enrollment 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 KD025-213 and 88%

of patients in study KD025-208 had 2 or more prior lines of therapy. CSs were the most common prior cGVHD treatment (more than 99%) followed by tacrolimus in study KD025-213 (64%) and sirolimus in study KD025-208 (59%).

Efficacy Results

Overall Response Rate by Investigator Assessment

In study KD025-213, 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 KD025-208, 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 KD025-213).

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

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

Time to Response

Based on the responder population, the median TTR was [redacted] weeks (range, 3.7 weeks to [redacted] weeks) in study KD025-213 and 8.1 weeks (range, 7.9 weeks to 26.1 weeks) in study KD025-208. At weeks 8 and 12, the cumulative response rate was [redacted]% and [redacted]%, respectively, in study KD025-213 and [redacted]% and [redacted]%, respectively, in study KD025-208.

Failure-free Survival

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

Overall Survival

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

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

Patient Reported Outcomes Measurement Information System 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. Two summary scores are determined for physical and mental functioning, with higher scores indicating better functioning. In study KD025-213, [redacted] ([redacted]%) patients had a 4.7-point or greater change from baseline for physical health and [redacted] ([redacted]%) patients had a 4.7-point or greater change from baseline for mental health. This outcome was not assessed in study KD025-208.

Change in Corticosteroid Dose

In study KD025-213, [redacted] patients had their corticosteroid dose reduced and [redacted] discontinued corticosteroid usage while receiving belumosudil. In study KD025-208, [redacted] patients had their corticosteroid dose reduced and [redacted] ([redacted]%) discontinued corticosteroid usage while receiving belumosudil.

Harms Results

Most patients experienced at least 1 treatment-emergent adverse event (TEAE) in study KD025-213 ([redacted]%) and study KD025-208 (100%). The most common TEAEs were diarrhea ([redacted]%) and fatigue ([redacted]%) in study KD025-213 and upper respiratory tract infection (53%), diarrhea (35%), fatigue (35%), nausea (35%), and increased alanine aminotransferase ([redacted]%) in study KD025-208.

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

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

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

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

Critical Appraisal

The main limitations with both studies are the lack of 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 timepoints had few patients at risk and therefore may be unstable.

Between the studies, 94 patients received the approved 200 mg QD dose for a median treatment duration of around 9 months, which is a relatively small number of patients compared to 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. This may be especially true for OS where few events were captured and 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 in the 12 years to younger than 20 years of age range, 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 12 and older population based on pharmacokinetic analyses indicating that age and body mass did not have a clinically meaningful effect on drug pharmacokinetics. Racial diversity was limited in the study (compared to 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. Although GRADE guidance is not available for noncomparative studies, the CADTH review team assessed pivotal trials 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 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 GRADE assessment was based on the sponsor's Summary of Clinical Evidence, consultation with the clinical experts, and input received from 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 score), 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 achieved a LSS score or PROMIS Global Health summary scores greater than or equal to the minimal important differences identified from the literature and who experienced SAEs.

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

Results of GRADE Assessments

Table 3 presents the narrative GRADE summary of findings for belumosudil for patients with cGVHD.

Table 3: Summary of Findings for Belumosudil for Patients with cGVHD (Study KD025-213 and Study KD025-208)

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)	• KD025-213: 727 per 1,000 (604 to 830 per 1,000) • KD025-208: 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 versus any comparator.
Tertiary DOR[e] event-free probability (95% CI), KM estimate Follow-up: 24 weeks	[redacted][f] (2 studies)	• KD025-213: [redacted] per 1,000 ([redacted] per 1,000) • KD025-208: [redacted] per 1,000 ([redacted] per 1,000)	Very low[d]	The evidence is very uncertain about the effects of belumosudil on tertiary DOR versus any comparator.
Secondary DOR[g] event-free probability (95% CI), KM estimate Follow-up: 24 weeks	[redacted][f] (2 studies)	• KD025-213: [redacted] per 1,000 ([redacted] per 1,000) • KD025-208: [redacted] per 1,000 ([redacted] per 1,000)	Very low[h]	The evidence is very uncertain about the effects of belumosudil on secondary DOR versus any comparator.
Median (range) TTR, weeks Follow-up: median 28.2 months in KD025-213 and 55.5 months in KD025-208	[redacted][f] (2 studies)	• KD025-213: [redacted] ([redacted] • KD025-208: [redacted] ([redacted])	Very low[d]	The evidence is very uncertain about the effects of belumosudil on TTR versus any comparator.
FFS probability (95% CI), KM estimate Follow-up: 12 months	[redacted] (2 studies)	• KD025-213: [redacted] per 1,000 ([redacted] per 1,000) • KD025-208: [redacted] per 1,000 ([redacted] per 1,000)	Very low[d]	The evidence is very uncertain about the effects of belumosudil on FFS versus any comparator.
Survival				
OS probability (95% CI), KM estimate Follow-up: 12 months	[redacted] (2 studies)	• KD025-213: [redacted] per 1,000 ([redacted] per 1,000) • KD025-208: [redacted] per 1,000 ([redacted] per 1,000)	Very low[d]	The evidence is very uncertain about the effects of belumosudil on OS versus any comparator.
Disease-specific measure of symptoms				
Proportion of patients with a ≥ 7-point reduction from baseline in LSS score Follow-up: median 28.2 months in KD025-213 and 55.5 months in KD025-208	[redacted] (2 studies)	• KD025-213: [redacted] per 1,000 • KD025-208: [redacted] per 1,000	Very low[d]	The evidence is very uncertain about the effects of belumosudil on LSS score versus any comparator.
HRQoL				

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

cGVHD = chronic graft-versus-host disease; CI = confidence interval; CR = complete response; DCO = data cut-off; DOR = duration of response; FFS = failure-free survival; HRQoL = health-related quality of life; KM = Kaplan-Meier; 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; TTR = time to response.

[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 that 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 KD025-213; other end points were presented only descriptively.

[d] Rated down 1 level for serious imprecision. Analysis included only 94 patients for mITT analyses and 68 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.

[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 achieved a PR or CR at any post-baseline 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.

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

Source: Study KD025-213 Clinical Study Report, Study KD025-213 Clinical Study Report Addendum, Study KD025-208 Clinical Study Report, Study KD025-208 Clinical Study Report Addendum, Sponsor's Summary of Clinical Evidence. Details included in the table are from the sponsor's Summary of Clinical Evidence.

Long-Term Extension Studies

Data from the latest cut-off dates for the on-going studies (study KD025-213 and study KD025-208) 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 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 allo-HSCT who have failed prior therapy. 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 was assessed and was determined to be infeasible.

Critical Appraisal

Compared to 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. As compared to studies of the comparators, the study KD205-213 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 that it would not have been feasible to perform a valid population-adjusted indirect comparison that fully adjusted for the differences in populations across the trials. However, as noted by Health Canada, this is an important limitation of the belumosudil KD205-213 trial that may have been foreseen. Given that the trial initiated in 2018 (after Health Canada approval of ibrutinib), it may have been possible at the outset to align enrolment criteria in order 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. The observational study was conducted using real-world data from the US Optum Clinformatics Data Mart database and pooled results from the main studies (study KD025-213 and study KD025-208).

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 post-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 prior to the third-line of therapy. BAT included ECP, mycophenolate mofetil, imatinib, rituximab, mammalian target of rapamycin inhibitors, ruxolitinib, CNIs, methotrexate, ibrutinib, pentostatin, etanercept, abatacept, alemtuzumab, hydroxychloroquine, and interleukin-2. IPTW methods were used in 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] months to [redacted] months) in the belumosudil group and [redacted] months (95% CI, [redacted] months to [redacted] months) in the BAT group (hazard ratio = [redacted]; 95% CI, [redacted] to [redacted]). Median OS was not estimable for the belumosudil group and [redacted] months (95% CI, [redacted] months to [redacted] months) for the BAT group (hazard ratio = [redacted]; 95% CI, [redacted] to [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 valid comparator, missing data for variables of interest, heterogeneity in baseline characteristics (even after IPTW procedures were applied), differences in study designs which cannot be adjusted for, and increased risk of inaccuracies in the claims database due to patients changing insurance plans and possible miscoding of claims. Therefore, it was not possible to make firm conclusions on how belumosudil compares to BAT from the data, as they are considered to be at high risk of bias. Moreover, data for both belumosudil 200 mg QD 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.

Economic Evidence

Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Partitioned survival model (PSM)
Target population	Patients 12 years and older with chronic GvHD who have received at least two prior lines of systemic therapy
Treatment	Belumosudil
Dose Regimen	200 mg daily
Submitted Price	Belumosudil, 200 mg: $376.20 per tablet
Treatment Cost	$137,313 per year
Comparator	Best available therapy (BAT), consisting of extracorporeal photopheresis (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)
Key limitations	• The relative efficacy of belumosudil versus BAT was based on a naïve 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) preventing meaningful conclusions from being made for relative benefits or harms. • In the submitted model, long-term extrapolation of overall survival (OS) and failure-free survival (FFS) beyond the available data for both belumosudil and BAT (4.7 years for belumosudil; 2.2 years for BAT) is uncertain. • The sponsor likely overestimated the number of patients who will remain failure-free after discontinuing belumosudil. In years 2 and 10, 60% and 40% of failure-free patients

Component	Description
	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 cost-effectiveness estimates for belumosudil. • The exclusion of 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 partitioned survival models 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 (inc. 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; ECP = extracorporeal photopheresis; FFS = failure-free survival; ICER = incremental cost-effectiveness ratio; LY = life-year; OS = overall survival; PSM = partitioned survival model; QALY= quality-adjusted life-year.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis: the market uptake of belumosudil is underestimated in years 1 and 2; the BAT components and distribution do not align with Canadian clinical practice; the exclusion of concomitant medication costs does not align with Canadian clinical practice; and the assumption that no patients will receive belumosudil twice daily (BID) 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 three-year budget impact to the public drug plans of introducing belumosudil for the treatment of cGvHD patients who have failed 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 BID dose in a small proportion of patients.

CDEC Information

Members of the Committee:

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Dr. Edward Xie, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Peter Jamieson, Mr. Morris Joseph, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Dr. Trudy Huyghebaert, Dr. Danyaal Raza, Dr. Emily Reynen, and Dr. Peter Zed.

Meeting date: December 20, 2023

Regrets:

None

Conflicts of interest:

None