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CADTH Reimbursement Recommendation

Ruxolitinib (Jakavi)

Indication: For the treatment of steroid refractory or dependent acute graft-versus-host disease in patients aged 12 years and older

Sponsor: Novartis Pharmaceutical Canada Inc.

Final recommendation: Reimburse with conditions

CADTH

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Summary

CADTH

What Is the CADTH Reimbursement Recommendation for Jakavi?

CADTH recommends that Jakavi be reimbursed by public drug plans for the treatment of steroid-refractory or steroid-dependent acute graft-versus-host disease (aGvHD) if certain conditions are met.

Which Patients Are Eligible for Coverage?

Jakavi should only be covered to treat adults and pediatric patients aged 12 years and older who have steroid-refractory or steroid-dependent aGvHD.

What Are the Conditions for Reimbursement?

Jakavi should only be reimbursed if prescribed by a specialist who has experience in the diagnosis and management of patients with aGvHD, and the cost of Jakavi is reduced.

Why Did CADTH Make This Recommendation?

- Evidence from a clinical trial demonstrated that people with steroid-refractory or steroid-dependent aGvHD treated with Jakavi experienced responses related to the resolution of signs and symptoms of graft-versus-host disease (GvHD).
- Jakavi met patients' needs of providing an oral drug option with manageable side effects that can be administered as an outpatient treatment.
- Based on CADTH's assessment of the health economic evidence, Jakavi does not represent good value to the health care system at the public list price; therefore, a price reduction is required.
- Based on public list prices, Jakavi is estimated to cost the public drug plans approximately $1.4 million over the next 3 years.

Additional Information

What Is aGvHD?

Approximately 30% to 50% of patients who receive a stem cell transplant from a donor will experience aGvHD, which occurs when the donor's cells attack the transplant recipient's cells and other body parts. aGvHD usually appears within 100 days after transplant and often affects the skin, liver, and intestines.

Unmet Needs in aGvHD

There is currently no standard of care for patients who have steroid-refractory or steroid-dependent aGvHD. Effective therapies with tolerable side effects that can improve health-related quality of life (HRQoL), reduce disease symptoms, and extend survival are needed.

How Much Does Jakavi Cost?

Treatment with Jakavi is expected to cost approximately $63,786 per patient per year.

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that ruxolitinib be reimbursed for the treatment of steroid-refractory or steroid-dependent aGvHD in adult and pediatric patients aged 12 years and older only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

Evidence from a single-arm phase II pivotal trial (REACH 1, N = 71) demonstrated that ruxolitinib achieved the predetermined threshold for a positive objective response rate (ORR) at day 28 (lower limit of the 95% confidence interval [CI] for ORR ≥ 40%). The proportion of patients who achieved ORR at day 28 was 56.3% (95% CI, 44.0 to 68.1). CDEC acknowledged the rarity of steroid-refractory and steroid-dependent aGvHD and the significant unmet need for additional treatment options in this setting given the severe nature of this disease with substantial morbidity and mortality.

Patients expressed a need for treatments that can reduce disease symptoms, improve survival and quality of life, and decrease the severity of side effects. CDEC concluded that ruxolitinib met some important patient needs by providing an oral drug option with tolerable side effects that can be administered as an outpatient treatment. CDEC acknowledged that the results for failure-free survival (FFS) and duration of response (DOR) from the REACH 1 trial were supportive of the reported improvement in ORR at day 28. No definitive conclusion could be reached regarding the effects of ruxolitinib on HRQoL as such data were not collected in the REACH 1 trial.

The cost-effectiveness of ruxolitinib is highly uncertain due to uncertainty in the sponsor's post hoc analysis of REACH 2 trial data, which was used to populate the majority of model parameters, along with concerns regarding the model structure not adequately capturing the complexity of steroid-refractory aGVHD (SR-aGvHD). As such, a base-case cost-effectiveness estimate was unable to be determined for the treatment of patients aged 12 years and older with steroid-refractory or steroid-dependent aGvHD. The committee considered exploratory analyses conducted by CADTH where the incremental cost-effectiveness ratio was $21,057 per quality-adjusted life-year, and, at a willingness-to-pay threshold of $50,000 per quality-adjusted life-year, there was a 52% probability of ruxolitinib being cost-effective. As CADTH's estimated incremental cost-effectiveness ratio is highly uncertain, price reductions are likely required to increase the probability of ruxolitinib being cost-effective.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Treatment with ruxolitinib should be initiated in patients who have clinically diagnosed grade II to IV aGvHD according to the NIH criteria (Harris et al. [2016]).[a]	Evidence from the REACH 1 trial demonstrated that ruxolitinib met the trial's prespecified efficacy outcome threshold for ORR in patients with grade II to IV aGvHD.	—

Reimbursement condition	Reason	Implementation guidance
2. Patients should have a confirmed diagnosis of corticosteroid-refractory or corticosteroid-dependent aGvHD.	Evidence from the REACH 1 trial showed that ruxolitinib met the trial's prespecified efficacy outcome threshold for ORR in patients who had corticosteroid-refractory or -dependent aGvHD. No clinical trials were identified on the safety and potential benefits of using ruxolitinib in patients with aGvHD who are not refractory to or dependent on corticosteroids.	Corticosteroid-refractory or -dependent aGvHD is defined based on criteria in the EBMT-NIH-CIBMTR Task Force[b] position statement. Corticosteroid refractory is defined by 1 or more of the following criteria: 1. progressing based on organ assessment after at least 3 days compared to organ stage at the time of initiation of a high-dose systemic corticosteroid ± a calcineurin inhibitor for the treatment of grade II to IV aGvHD 2. failure to achieve, at a minimum, partial response based on organ assessment after 7 days compared to organ stage at the time of initiation of a high-dose systemic corticosteroid ± a calcineurin inhibitor for the treatment of grade II to IV aGvHD 3. patients who fail corticosteroid taper, defined as fulfilling either 1 of the following criteria: 3.1. requirement for an increase in the corticosteroid dose to methylprednisolone ≥ 2 mg/kg per day (or equivalent prednisone dose of ≥ 2.5 mg/kg per day) 3.2. failure to taper the methylprednisolone dose to < 0.5 mg/kg per day (or equivalent prednisone dose of < 0.6 mg/kg per day) for a minimum of 7 days. Corticosteroid dependence is defined as the inability to taper prednisone under 2 mg/kg per day after an initially successful treatment of at least 7 days or as the recurrence of aGvHD activity during steroid taper.
Renewal		
3. Initial treatment with ruxolitinib should be renewed for patients who have achieved an overall response (i.e., CR, VGPR, PR, or stable disease	The CADTH review identified no evidence on the safety and potential benefits of further treatment with ruxolitinib in	—

Reimbursement condition	Reason	Implementation guidance
with significant reduction in steroid doses), according to standard NIH criteria[c] at day 28 (approximately 4 weeks).	patients who have not achieved an overall response after 4 weeks of therapy.	
4. For subsequent renewals, patients should be assessed for treatment response every 2 to 3 months, until the occurrence of any of the discontinuation criteria listed under Condition #5.	The clinical experts advised that patients should be assessed for a response to treatment every 2 to 3 months.	—
Discontinuation		
5. Ruxolitinib should be discontinued upon the occurrence of any of the following: 5.1. progression of aGvHD, defined as worsening of aGvHD symptoms or occurrence of new aGvHD symptoms 5.2. unacceptable toxicity 5.3. addition of systemic therapies (other than calcineurin inhibitors) for aGvHD after day 28 5.4. recurrence or relapse of underlying hematological malignancy.	These conditions correspond to the criteria used to determine whether treatment with ruxolitinib should be discontinued in the REACH 1 trial.	—
Prescribing		
6. Ruxolitinib should only be prescribed by clinicians who have experience in the diagnosis and management of patients with aGvHD.	This condition is required to ensure that ruxolitinib is prescribed only for appropriate patients and that patients receive optimal care for toxicity management.	—
7. Treatment with ruxolitinib must not be added to patients' concurrent treatment of systemic therapies for the treatment of aGvHD other than steroids ± calcineurin inhibitors.	As per-protocol criteria of the REACH 1 trial, the continued use of the systemic immunosuppressive regimen of corticosteroids ± calcineurin inhibitors was permitted. No evidence was identified by CADTH to support the benefit of combination therapy with ruxolitinib in patients with aGvHD, other than adding it to steroids ± calcineurin inhibitors.	—
Pricing		
8. A reduction in price	The cost-effectiveness of ruxolitinib is highly uncertain. CADTH undertook an exploratory analysis where the mean ICER was below a	—

Reimbursement condition	Reason	Implementation guidance
	WTP of $50,000 per QALY. However, the probability of cost-effectiveness remained highly uncertain, and the exploratory analysis could not address several of the model's major limitations. A 65% ruxolitinib price reduction was previously estimated by CADTH for chronic GvHD, and at that price reduction, the probability of ruxolitinib being cost-effective in the acute setting is highly likely.	
Feasibility of adoption		
9. The feasibility of adoption of ruxolitinib must be addressed.	At the submitted price, the magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption, given the difference between the sponsor's estimate and CADTH's estimate.	—

aGvHD = acute graft-versus-host disease; CR = complete response; CIBMTR = Center for International Blood and Marrow Transplant Research; EBMT = European Society for Blood and Marrow Transplantation; GvHD = graft-versus-host disease; ICER = incremental cost-effectiveness ratio; NIH = National Institute of Health; ORR = objective response rate; PR = partial response; QALY = quality-adjusted life-year; VGPR = very good partial response; WTP = willingness to pay.

[a]Harris AC, Young R, Devine S, et al. International, Multicenter Standardization of Acute Graft-Versus-Host Disease Clinical Data Collection: A Report from the Mount Sinai Acute GVHD International Consortium. *Biology of blood and marrow transplantation: Journal of the American Society for Blood and Marrow Transplantation.* 2016;22(1):4-10.

[b]Schoemans HM, Lee SJ, Ferrara JL, et al. EBMT-NIH-CIBMTR Task Force position statement on standardized terminology & guidance for graft-versus-host disease assessment. *Bone Marrow Transplant.* 2018;53(11):1401-1415.

[c]Harris AC, Young R, Devine S, et al. International, Multicenter Standardization of Acute Graft-Versus-Host Disease Clinical Data Collection: A Report from the Mount Sinai Acute GVHD International Consortium. *Biology of blood and marrow transplantation: Journal of the American Society for Blood and Marrow Transplantation.* 2016;22(1):4-10.

Discussion Points

- CDEC discussed that, although aGvHD is a rare condition, allogeneic stem cell transplant (alloSCT) and resulting GvHD contribute to a considerable utilization of health care services, and is associated with substantial morbidity and mortality due to the severe nature of the disease. The clinical experts consulted by CADTH noted that there are currently no Health Canada authorized standard care regimens specific for patients with SR-aGvHD in Canada. CDEC agreed that there was a significant unmet need for additional effective treatments for patients with corticosteroid-refractory or corticosteroid-dependent aGvHD. The committee acknowledged that there is a need for treatments that help ease patient administration, have acceptable toxicity profile, and reduce the need for hospital-based or ambulatory centre resource utilization.
- CDEC noted that while the REACH 1 trial met the predetermined threshold for ORR at day 28 (≥ 40%) in patients who received ruxolitinib, there was uncertainty regarding the magnitude of clinical benefit directly attributable to ruxolitinib due to the limitations inherent to the study design, including the single-arm, open-label trial design; a lack of formal statistical significance testing; and the relatively small sample size. CDEC discussed the results of the REACH 1 trial and agreed with the clinical experts that the reported outcomes were clinically meaningful.

- CDEC noted that Health Canada considered reviewing efficacy and safety data from the REACH 1 trial as the pivotal study and the safety data from the REACH 2 trial as supportive evidence for the aGvHD indication. This decision was the result of uncertainties around the REACH 2 trial that were identified by the FDA upon the review of raw data from the REACH 2 trial as part of a sponsor-proposed label update for the FDA approved indication for aGvHD that had been already approved based on the REACH 1 trial data. Health Canada based its efficacy assessment of the REACH 1 trial on the FDA evaluable population (N = 49), which was a subset of the REACH 1 trial's full efficacy evaluable patients (N = 71) whose data were reviewed by CADTH. CDEC agreed that the eligibility criteria in the REACH 1 trial was aligned with the Health Canada indication for steroid-refractory and steroid-dependent aGvHD. One phase III, randomized, open-label trial (REACH 2, N = 309) provided supportive evidence, and demonstrated that compared with best available therapy (BAT) ruxolitinib was associated with statistically significant improvements in ORR at day 28 (62.3% versus 39.4% in the BAT group; stratified odds ratio = 2.64; 95% CI, 1.65 to 4.22) and durable ORR at day 56 (39.6% versus 21.9%; stratified odds ratio = 2.38; 95% CI, 1.43 to 3.94). The clinical experts consulted by CADTH believed that the efficacy results from the REACH 2 trial were clinically meaningful and supportive of the reported response outcomes in the REACH 1 trial.
- Both the REACH 1 and REACH 2 trials enrolled patients 12 years of age or older. However, no patients in the REACH 1 trial and only 2.9% of patients in the REACH 2 trial were younger than 18 years. CDEC heard from the clinical experts consulted by CADTH that it would be reasonable to generalize the trial results to adolescents younger than 18 years, given that adults and adolescents are managed similarly in clinical practice. CDEC discussed the results of an observational study of ruxolitinib in children and adults with SR-aGvHD that suggested a similar treatment effect and safety profile among adults and adolescents aged 12 to 18 years.
- While ruxolitinib appeared to have more adverse events than BAT, the clinical experts consulted by CADTH noted that most treatment-emergent adverse events (TEAEs) associated with ruxolitinib could be managed with dose modifications and best supportive care. CDEC agreed with the clinical experts that no unexpected safety concerns were observed with ruxolitinib, and that patients could be adequately managed in clinical practice.

Background

GvHD is a complication associated with alloSCT. GvHD is a multisystem disorder in which the donor-derived immune cells initiate an adverse immune reaction to the transplant recipient tissues, cells, and organs, which leads to tissue damage, organ failure, or death. aGvHD typically occurs within 100 days of alloSCT and often affects the skin, liver, and intestines. aGvHD occurs in 30% to 50% of patients who undergo alloSCT. Currently, there is no consensus on standard second-line therapies for patients with SR-aGvHD. Available second-line options in Canada include extracorporeal photopheresis (ECP), mycophenolate mofetil (MMF), etanercept, infliximab, mechanistic target of rapamycin (mTOR) inhibitors, antithymocyte globulin (ATG), and interleukin-2 receptor. Currently available treatments for patients with SR-aGvHD have limited effectiveness and are associated with a number of side effects.

Ruxolitinib has been approved by Health Canada for the treatment of steroid-refractory or steroid-dependent aGvHD in adult and pediatric patients aged 12 years and older. Ruxolitinib is a Janus-associated kinase inhibitor. Ruxolitinib is available as 5 mg, 10 mg, 15 mg, and 20 mg tablets. The recommended starting dose for ruxolitinib for aGvHD is 5 mg administered orally twice daily. It is recommended to increase the dose to 10 mg twice daily after at least 3 days of treatment if the absolute neutrophil and platelet counts are not decreased by 50% or more relative to the first day of dosing with ruxolitinib. The product monograph also states that tapering of ruxolitinib may be considered in patients with a response and after having discontinued corticosteroids. It is recommended to taper ruxolitinib by reducing the dose to 50% every 2 months; in the event that signs or symptoms of aGvHD reoccur during or after the taper, re-treatment with ruxolitinib should be considered.

Sources of Information Used by the Committee

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

- a review of 1 single-arm phase II trial and 1 phase III randomized controlled trial in patients aged 12 years and older with grades II to IV SR-aGvHD
- patients' perspectives gathered by 1 joint patient input cocreated by 8 patient groups: Lymphoma Canada (LC), Lymphoma and Leukemia Society of Canada (LLSC), Chronic Lymphocytic Leukemia (CLL) Canada, Myeloma Canada, the Aplastic Anemia & Myelodysplasia Association of Canada (AAMAC), the Canadian MPN Research Foundation (CMPNRF) and the Chronic Myelogenous Leukemia (CML) Network, the Myeloproliferative neoplasms (MPN) Canadian Research Foundation, and Cell Therapy Transplant Canada (CTTC)
- input from public drug plans and cancer agencies that participate in the CADTH review process
- input from 3 clinical specialists with expertise in diagnosing and treating patients with aGvHD
- input from 2 clinician groups, including CTTC (based on input from 8 clinicians) and Ontario Health (Cancer Care Ontario [CCO]) Complex Malignant Hematology (based on input from 2 clinicians)
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

Patient Input

Eight patient groups, the LC, LLSC, CLL Canada, Myeloma Canada, AAMAC, CMPNRF and the CML Network, MPN Canadian Research Foundation, and CTTC, cocreated 1 joint patient input for this review. The input was based on an online survey, and responses from a total of 68 participants were included in the patient input. Sixty patients reported having received a stem cell transplant (SCT), 6 patients reported not having received an SCT, and 2 patients did not provide an answer to this question. Out of the 60 patients that received an SCT, 49 reported

having received an alloSCT. Fifty-three patients had experienced GvHD after their SCT. Data on the type of GvHD were available for 45 of the 53 patients with GvHD: 13% experienced aGvHD, 24% experienced chronic graft-versus-host disease (cGvHD), and 62% experienced both acute and chronic GvHD. Twenty patients reported receiving ruxolitinib treatment.

Respondents indicated that they had long-lasting GvHD symptoms (3 to 5 years for 26% of respondents and more than 5 years for 28% of respondents). To manage GvHD, patient respondents reported requiring numerous medical consultations, hospital stays, and nights away from home. Respondents indicated a varying range of GvHD symptoms that significantly impacted their daily activities and caused detrimental effects on their quality of life. Respondents highlighted problems with interruption of life goals and accomplishment (career, school), difficulty sleeping, impact on mental health (stress, anxiety, worry, and problems concentration), and financial impacts. Other commonly experienced symptoms indicated by respondents included burning and redness of the skin on the palms of the hands or soles of the feet; rashes that could spread over the entire body; blisters and peeling skin; skin problems such as dryness, rash, itching, peeling, darkening, hard texture, and feeling tight; enlarged liver; liver tenderness; abnormal liver enzymes or liver failure; jaundice; dry eyes that may have a burning or gritty feeling; dry mouth with or without mouth ulcers; diarrhea; loss of appetite; stomach cramps; vomiting; weight loss; pain in muscles and joints; mobility issues and difficulties; infections; and difficulty breathing.

According to the patient input received, respondents expected new drugs or treatments to improve overall survival (OS), GvHD symptoms, quality of life, and severity of side effects. Additionally, the ability to received treatment in the outpatient setting (rather than requiring an overnight hospital stay), having access to treatment locally (rather than requiring extensive amount of travel), treatment being covered by insurance or drug plans, and the treatment being recommended by health care professionals, were perceived to be very important by respondents. Respondents who had direct experience with ruxolitinib indicated that, overall, ruxolitinib was an effective treatment that improved their quality of life, had tolerable side effects, and was a treatment that they would take again if recommended by their physician, and that they would recommend it to other patients.

Clinician Input

Input From Clinical Experts Consulted by CADTH

The clinical experts consulted by CADTH noted that there are currently no Health Canada authorized standard care regimens specific for patients with SR-aGvHD in Canada. According to the clinical experts consulted by CADTH, available second-line options in Canada include ECP, MMF, etanercept, infliximab, mTOR inhibitor (e.g., sirolimus or sirolimus), and ATG. It was noted by the clinical experts that ATG was often used as prophylaxis rather than aGvHD treatment. There was consensus among the clinical experts that there is an unmet need for effective therapies with acceptable toxicity profiles that improve HRQoL, reduce disease symptoms of aGvHD, enhance patient's performance status, and improve OS. The need for a convenient oral route of administration was highlighted to achieve high adherence and reduce the need for hospital-based or ambulatory centre resource utilization. Ruxolitinib was stated to be used as add-on therapy to a patient's immunosuppressive regimen of corticosteroids with or without calcineurin inhibitors (CNIs) in patients aged 12 years and older with grades II to IV SR-aGvHD, per the REACH 2 trial. It was agreed that ruxolitinib, as a therapy for SR-aGvHD, would likely shift the current treatment paradigm. The clinical experts consulted by CADTH agreed that patients as selected per the inclusion and exclusion criteria

of the REACH 2 trial should be eligible for ruxolitinib therapy. The clinical experts identified the following potential subgroups as being most in need of ruxolitinib therapy: patients with grade IV aGvHD who have the highest risk of death from aGvHD. Patient subgroups who would potentially benefit the least from ruxolitinib may include patients with refractory vomiting or ileus who are not able to take an oral drug such as ruxolitinib, and patients with thrombocytopenia, especially those with clinical bleeding, who may be challenging to treat with ruxolitinib and may receive an alternative second-line agent instead. Patients with active uncontrolled infections or non-aGvHD cytopenia are challenging to treat with ruxolitinib or other available second-line therapy options; ruxolitinib should be used with caution and may require dose adjustment in these patients. The clinical experts consulted by CADTH felt that it would be reasonable to generalize the REACH 2 trial results to patients who received 2 or more systemic treatments for aGvHD and to leave it up to the discretion of the treating physician to apply some flexibility in terms of using ruxolitinib in patients with overlap syndrome or grade I aGvHD.

In the opinion of the clinical experts consulted by CADTH, an accurate assessment of response in aGvHD is based on the National Institute of Health (NIH) consensus criteria, as was used in the REACH 2 trial. Response to treatment is usually assessed daily for inpatients and weekly for outpatients. The clinical experts indicated that the most clinically meaningful responses to treatment include improvements in OS (survival beyond 1 year post-alloSCT) overall response (complete response [CR] or partial response [PR]), improvements in HRQoL and performance status, and the ability to taper corticosteroids.

Clinician Group Input

Two clinician group inputs were provided, 1 from CTTC (based on input from 8 clinicians) and 1 from Ontario Health CCO Complex Malignant Hematology (based on input from 2 clinicians). The views of the clinician groups were overall consistent with the clinical experts consulted by CADTH, indicating that based on the evidence from the REACH 2 trial, it was anticipated that ruxolitinib would become the dominant first-line therapy for SR-aGvHD. The outcomes assessed in the REACH 2 trial were judged to be applicable to Canadian clinical practice and reflective of clinically meaningful responses. It was noted by both inputs that ruxolitinib is not considered to be as immunosuppressive as other available therapies. The clinicians from Ontario Health CCO Complex Malignant Hematology noted the drawbacks of currently available therapies, such as IV administration, which requires patients to be at the hospital; side effects and broad immune suppression; and the high price and delivery costs of treatments. It was highlighted by the input from CTTC that a Health Canada–approved and provincially funded therapy for SR-aGvHD would be an important step forward in the present target setting with existing therapies offering low response rates and high rates of toxicity. According to the input from CTTC, patient experiences with ruxolitinib (accessible via compassionate access program) and real-world effectiveness appear similar to that observed in the REACH 2 trial with low rates of toxicity.

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 ruxolitinib:

- considerations for relevant comparators
- consideration for initiation of therapy

- considerations for discontinuation of therapy
- considerations for prescribing of therapy.

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	
Would there be a patient population that would require a combination of 1 of the off-label comparator treatments and ruxolitinib for steroid-refractory aGvHD?	As per-protocol criteria of the REACH 2 trial, the continued use of the systemic immunosuppressive regimen of corticosteroids ± calcineurin inhibitors was permitted. CDEC noted that the CADTH review identified no evidence to support the benefit of combination therapy with ruxolitinib, other than adding it to steroids ± calcineurin inhibitors.
Considerations for initiation of therapy	
What would be the definition of inadequate response to corticosteroids or steroid refractoriness in aGvHD?	According to the EBMT-NIH-CIBMTR Task Force[a] position statement, patients on high-dose systemic corticosteroids (methylprednisolone 2 mg/kg per day [or equivalent prednisone dose 2.5 mg/kg per day]), given alone or combined with a calcineurin inhibitor are defined as steroid refractory in any of the following scenarios: 1. progressing based on organ assessment after at least 3 days compared to organ stage at the time of initiation of a high-dose systemic corticosteroid ± a calcineurin inhibitor for the treatment of grade II to IV aGvHD or 2. failure to achieve, at a minimum, partial response based on organ assessment after 7 days compared to organ stage at the time of initiation of a high-dose systemic corticosteroid ± a calcineurin inhibitor for the treatment of grade II to IV aGvHD or 3. patients who do not respond to corticosteroid taper defined as fulfilling either 1 of the following criteria: 3.1. requirement for an increase in the corticosteroid dose to methylprednisolone ≥ 2 mg/kg per day (or equivalent prednisone dose of ≥ 2.5 mg/kg per day) OR 3.2. failure to taper the methylprednisolone dose to < 0.5 mg/kg per day (or equivalent prednisone dose of < 0.6 mg/kg per day) for a minimum of 7 days. CDEC agreed with the clinical experts consulted by CADTH that steroid refractoriness in aGvHD is defined in the EBMT-NIH-CIBMTR Task Force position statement.
Considerations for discontinuation of therapy	
Part of the safety outcomes in the REACH 2 trial were adverse events leading to treatment discontinuation. What would be the specific adverse events that would lead to treatment discontinuation for aGvHD?	CDEC agreed that it would be reasonable to leave it to the discretion of the treating physician and the patient to determine the type of toxicity that would lead to treatment discontinuation on a case-by-case basis.

Implementation issues	Response
Considerations for prescribing of therapy	
Jakavi may be administered as an outpatient treatment that provides important patient and health care benefits compared to other therapies that require administration in a hospital or infusion clinic that have been used in the second-line setting.	CDEC acknowledged the drug plan input.
What specialist or prescriber would be required to initiate and monitor Jakavi for this indication?	CDEC agreed with the clinical experts consulted by CADTH that patients in Canadian clinical practice are assessed and managed in the bone marrow transplant follow-up clinic. All assessments and prescriptions should be undertaken by providers who are familiar with GvHD. Generally, patients with aGvHD are medically unwell to the point of requiring hospitalization. Occasionally, patients may be managed as an outpatient (e.g., with higher doses of steroids and a second-line drug, such as ruxolitinib). With response to treatment patients are generally able to transition to outpatient care.

aGvHD = acute graft-versus-host disease; CIBMTR = Center for International Blood and Marrow Transplant Research; EBMT = European Society for Blood and Marrow Transplantation; GvHD = graft-versus-host disease; NIH = National Institute of Health.

[a]Schoemans HM, Lee SJ, Ferrara JL, et al. EBMT-NIH-CIBMTR Task Force position statement on standardized terminology & guidance for graft-versus-host disease assessment. *Bone Marrow Transplant.* 2018;53(11):1401-1415.

Clinical Evidence

The REACH 1 trial is a completed, open-label, single-arm, multicentre phase II trial that evaluated the efficacy and safety of ruxolitinib in combination with corticosteroids in patients with grades II to IV SR-aGvHD. The severity grading of aGvHD was based on the NIH criteria by Harris et al. (2016). A total of 71 patients were enrolled to received ruxolitinib (5 mg orally twice daily and if hematologic parameters were stable and no treatment-related toxicity was observed after the first 3 days of treatment, the dose could be increased to 10 mg orally twice daily). The primary outcome was ORR at day 28 and the key secondary outcome was DOR at month 6. Additional secondary outcomes were OS, FFS, ORR at day 14, DOR at month 3, nonrelapse mortality (NRM), incidence of malignancy relapse or progression, relapse rate, relapse-related mortality rate, and safety.

The REACH 2 trial is a completed, international, multicentre, open-label, randomized, phase III trial of ruxolitinib (10 mg administered orally twice daily) compared with investigator's choice of BAT (i.e., ATG, ECP, MSC, MTX, MMF, mTOR inhibitors [everolimus or sirolimus], etanercept, or infliximab), in patients aged 12 years and older with grade II to IV SR-aGvHD. Patients continued to receive their systemic immunosuppressive regimen of corticosteroids with or with CNI. Staging of aGvHD was based on the NIH criteria (Harris et al. [2016]). A total of 309 patients were randomized in a 1:1 ratio to receive ruxolitinib or BAT. The primary outcome was ORR at day 28 and the key secondary outcome was the rate of durable ORR at day 56. Additional secondary outcomes were OS, FFS, ORR at day 14, DOR, best overall response (BOR), HRQoL using the Functional Assessment of Cancer Therapy – Bone Marrow Transplant (FACT-BMT), and the EQ-5D 5-Levels (EQ-5D-5L) instruments, event-free survival, NRM, incidence of malignancy relapse or progression, cumulative steroid dose until day 56, incidence of cGvHD, and safety.

The REACH 2 trial enrolled male or female patients, ≥ 12 years of age, who had undergone alloSCT, had evidence of myeloid and platelet engraftment (absolute neutrophil count > 1,000/mm^3 and platelet count > 20,000/mm^3), and were diagnosed with grades II to IV aGvHD as defined by the NIH Consensus Criteria and which was determined to be corticosteroid-refractory as per-protocol defined criteria. The REACH 1 trial had overall similar inclusion criteria. However, there were slight variations in the definition of corticosteroid-refractoriness criterion C and engraftment. Both studies excluded patients who had received more than 1 systemic treatment for SR-aGvHD, presented with a clinical presentation resembling de novo overlap syndrome (i.e., overlap syndrome as defined by Jagasia et al. [2015]), or active uncontrolled infection. REACH 2 explicitly excluded patients with multifocal leuko-encephalopathy whereas REACH 1 did not. In the REACH 2 trial, the mean ages for the ruxolitinib and BAT groups, respectively, were 48.1 (standard deviation [SD] = 16.30) and 50.9 (SD = 14.9) years. The majority of patients (ruxolitinib versus BAT groups) were aged 18 to 65 years (83.1% versus 81.3%) with few adolescents aged 12 to 18 years or younger (3.2% versus 2.6%). Most patients were male (59.7% versus 58.7%). The aGvHD grade at baseline was mostly grade III (44.2% versus 43.9%), followed by grade II (32.5% versus 34.8%) and grade IV (19.5% versus 20.6%). The most common criterion for SR-aGvHD was "failure to achieve a response after 7 days" (46.8% versus 40.6%) followed by "failure on steroid taper" (30.5% versus 31.6%) and "progression after at least 3 days" (22.7% versus 27.7%). The ruxolitinib group had a higher proportion of patients with aGvHD organ involvement at baseline in the skin (60.4% versus 47.7%) and liver (24.0% versus 16.1%), and a lower proportion of patients with aGvHD organ involvement at baseline in the upper gastrointestinal (GI) (18.2% versus 23.9%) and lower GI (62.3% versus 74.2%). Patients' demographic characteristics and disease and alloSCTs history at baseline in the REACH 1 trial were overall similar to those in the REACH 2 trial. Comparable to the REACH 2 trial, the majority of patients in the REACH 1 trial were aged 18 to 65 years (81.7%) and the distribution of aGvHD grades was similar between the trials with grade III aGvHD in the majority of patients (46.5%), followed by grade II (31.0%) and grade IV (22.5%). Similar to the REACH 2 trial, the most common criterion for SR-aGvHD was "no aGvHD improvement after 7 days of primary treatment" (40.8%) followed by "failing corticosteroid taper" (36.2%) and "progression after 3 days or primary treatment" (23.9%). Most patients in both trials received grafts from identical human leukocyte antigen-matched donors; 60.2% in the REACH 2 trial and 63.4% in the RACH 1 trial.

The CADTH review was based on data from the following trials: REACH 1 final data cut-off date of June 5, 2019 (the study was completed on June 5, 2019); and REACH 2 data from the primary analysis (July 25, 2019), updated secondary analysis (January 6, 2020), and the final analysis (April 23, 2021), which was conducted once all patients had completed the study.

Efficacy Results

As of the primary analysis, the median duration of follow-up for OS in the REACH 2 trial was 5.04 months in the ruxolitinib group and 3.58 months in the BAT group. Median OS was 11.14 months or 339 (95% CI, 186 to not evaluable) days in the ruxolitinib group compared to 6.47 months or 197 (95% CI, 114 to 458) days in the BAT group, with a stratified hazard ratio (HR) of 0.83 (95% CI, 0.60 to 1.15). The OS results at the secondary analysis were overall consistent with those at the primary analysis in the REACH 2 trial. In the REACH 1 trial, median OS was 232.0 days (95% CI, 93.0 to 675.0) as of the final analysis.

As of the primary analysis in the REACH 2 trial, the number of patients who experienced an FFS event (i.e., hematologic disease relapse or progression, NRM, or addition of new systemic

aGvHD treatment) was 84 (54.5%) and 119 (76.8%) in the ruxolitinib and BAT groups, respectively. The median FFS was 4.99 and 1.02 months in the ruxolitinib and BAT groups, respectively, with an HR of 0.46 (95% CI, 0.35 to 0.60). The FFS results at the secondary analyses were overall consistent with those at the primary analysis in the REACH 2 trial. In the REACH 1 trial, the number of patients who experienced an event (i.e., underlying malignancy relapse or progression [n = 3], death [n = 22], addition of new systemic aGvHD treatment [n = 28], or signs or symptoms of cGvHD [n = 7]) was 60 (84.5%). The median FFS was 85.0 days (95% CI, 42.0 to 158.0).

In the REACH 2 trial, ORR at day 28 was only analyzed at the primary analysis and not reassessed at the secondary or final analyses. As of the primary analysis, the REACH 2 trial met its primary objective. The proportion of patients who achieved an overall response at day 28 was 62.3% (N = 96) (95% CI, 54.2 to 70.0) in the ruxolitinib group and 39.4% (N = 61) (95% CI, 31.6 to 47.5) in the BAT group, with a stratified odds ratio of 2.64 (95% CI, 1.65 to 4.22). The proportions of patients with CR and PR were 34.4% (N = 53) and 27.9% (N = 43), respectively, in the ruxolitinib group, and 19.4% (N = 30) and 20.0% (N = 31), respectively, in the BAT group. The REACH 1 trial met the predetermined threshold for a positive study outcome (lower limit of the 95% CI for ORR at day 28 ≥ 40%). The proportion of patients who achieved an overall response at day 28 was 56.3% (N = 40) (95% CI, 44.0 to 68.1). The proportions of patients with CR, very good partial response, and PR were 19 (26.8%), 6 (8.5%), and 15 (21.1%), respectively.

In the REACH 2 trial, durable ORR at day 56 was only analyzed at the primary analysis and not reassessed at the secondary, or final analyses. As of the primary analysis, the proportion of patients who achieved a durable ORR at day 56 was 39.6% (N = 61) in the ruxolitinib group and 21.9% (N = 34) in the BAT group, with a stratified odds ratio of 2.38 (95% CI, 1.43 to 3.94) in favour of the ruxolitinib group. Durable ORR at day 56 was not assessed in the REACH 1 trial.

As of the primary analysis in the REACH 2 trial, among the patients who achieved a CR or PR at or before day 28, median DOR was 168 days (range = 22 to 423) in the ruxolitinib group and 101 days (range = 10 to 289) in the BAT group. Results for DOR at the secondary and final analyses were consistent with the DOR results at the primary analysis. In the REACH 1 trial, the median DOR for patients who responded at any time point was 345.0 days (95% CI, 154.0 to not evaluable) with a median follow-up time of 128.5 days (range = 3 to 805 days). The 6-months event-free probabilities for DOR in patients who responded (i.e., PR, very good PR, or CR) at any time point was 62.1% (95% CI, 45.8 to 74.8).

In the REACH 2 trial, BOR was only analyzed at the primary analysis and not reassessed at the secondary or final analyses. At the primary analysis, the proportion of patients who had achieved BOR by day 28 in the ruxolitinib group was 81.8% (95% CI, 74.8 to 87.6) and 60.6% (95% CI, 52.5 to 68.4) in the BAT group, with an odds ratio of 3.07 (95% CI, 1.80 to 5.25). In the REACH 1 trial, the proportion of patients who had achieved BOR at any time point was 76.1% (95% CI, 64.5 to 85.4).

As of the primary analysis in the REACH 2 trial, a higher proportion of patients had tapered off corticosteroids in the ruxolitinib group (21.4%; 95% CI, 15.2 to 28.8) than in the BAT group (14.8%; 95% CI, 9.6 to 21.4). The proportions of patients with 50% or fewer relative dose intensity and more than 50% relative dose intensity were (ruxolitinib versus BAT group): 29.2% versus 24.5% and 68.8% versus 74.8%, respectively. The results for cumulative steroid dosing until day 56 at the secondary and final analyses were overall consistent with those at the

primary analysis in the REACH 2 trial. In the REACH 1 trial, the proportion of patients who were still receiving ruxolitinib and who had tapered off (i.e., discontinued) corticosteroids was 6.9% at day 56; the proportions of patients at day 100 and day 180 were 34.8% and 61.1%, respectively. The proportion of patients with at least a 50% decrease in corticosteroid dose relative to the day 1 (or day 2 dose) continued to increase from 23.2% on day 14 to 55.8% on day 28, and 100.0% on day 100.

Harms Results

In the REACH 2 trial, there were minimal differences between the harms data presented at the primary, secondary, and final analyses. The CADTH review presented harms data for the secondary data cut-off date (January 6, 2020). For the REACH 1 trial harms data for the final analysis cut-off date (June 5, 2019) were presented.

In the REACH 2 trial, as of the secondary analysis, the percentage of patients reporting at least 1 TEAE was 99.3% in the ruxolitinib group and 98.7% in the BAT group. The most commonly reported TEAEs in the ruxolitinib and BAT groups (ruxolitinib versus BAT) were anemia (40.1% versus 32%), thrombocytopenia (36.8% versus 20.7%), cytomegalovirus infection (30.9% versus 26.7%), neutropenia (24.3% versus 14.7%), and edema peripheral (24.3% versus 21.3%). In the REACH 1 trial, as of the final analysis, all patients in the REACH 1 trial experienced at least 1 TEAE (100.0%). The most commonly reported TEAEs were similar between the REACH 1 and REACH 2 trials, and included anemia (64.8%), thrombocytopenia (62.0%), hypokalemia (49.3%), neutropenia (47.9%), and edema peripheral (46.5%).

In the REACH 2 trial, the percentage of patients who experienced at least 1 grade 3 or greater TEAE in the ruxolitinib and BAT groups were 91.4% and 87.3%, respectively. The most commonly reported grade 3 or greater TEAEs in the ruxolitinib and BAT groups (ruxolitinib versus BAT) were anemia (35.5% versus 24.0%), thrombocytopenia (33.6% versus 16.7%), neutropenia (21.7% versus 12.0%), decreased platelet count (17.8% versus 15.3%), and decreased white blood cell count (13.2% versus 8.7%). In the REACH 1 trial, grade 3 or higher TEAEs occurred in 97.2% of patients. The most commonly reported grade 3 or higher TEAEs were similar between the REACH 1 and REACH 2 studies, and included thrombocytopenia (53.5%), anemia (50.7%), neutropenia (42.3%), and hyperglycemia (19.7%).

In the REACH 2 trial, the percentage of patients experiencing at least 1 serious TEAE was 66.4% in the ruxolitinib group compared to 53.3% in the BAT group. The most common serious TEAEs were sepsis, which occurred in 7.9% of patients in the ruxolitinib group and 7.3% of patients in the BAT group; pyrexia, in 6.6% of patients in the ruxolitinib group and 4.0% of patients in the BAT group; septic shock, in 6.6% of patients in the ruxolitinib group and 5.3% of patients in the BAT group; and diarrhea, in 5.3% and 2.0% of patients in the ruxolitinib and BAT groups, respectively. In the REACH 1 trial, the percentage of patients experiencing serious TEAEs was 83.1% in the REACH 1 trial. The most commonly reported serious TEAEs were similar between the REACH 1 and REACH 2 trials, and included sepsis (12.7%), pyrexia (11.3%), respiratory failure (11.3%), and lung infection (7.0%).

In the REACH 2 trial, the percentage of patients who discontinued treatment due to TEAEs in the ruxolitinib group was 27.0% compared to 9.3% of patients in the BAT group. The most commonly cited TEAEs contributing to treatment discontinuation in the ruxolitinib group were neutropenia (n = 4; 2.6%), sepsis (n = 4; 2.6%), anemia (n = 3; 2.0%), and thrombocytopenia (n = 3; 2.0%). In the BAT group, the following TEAEs were reported as reasons for treatment discontinuation: sepsis (n = 1; 0.7%), anemia (n = 1; 0.7%), thrombocytopenia (n = 1; 0.7%),

and decreased platelet count (n = 1; 0.7%). In the REACH 1 trial, TEAEs led to discontinuation of ruxolitinib treatment in 32.4% of patients. The most commonly reported TEAEs leading to discontinuation of ruxolitinib were sepsis (5.6%), acute kidney injury (2.8%), and respiratory failure (2.8%).

In the REACH 2 trial, on-treatment deaths occurred in 28.3% and 24.0% of patients in the ruxolitinib and BAT groups, respectively. The most common cause of death was the study indication of aGvHD (including aGvHD and related complications) in 21 (13.8%) and 21 (14.0%) patients in the ruxolitinib and BAT groups, respectively. In the REACH 1 trial, there were 35.2% (n = 25) of patients who had died during treatment with ruxolitinib or within 30 days of their last dose. The most common cause of death was "Other" (25.4%; n = 18) and included underlying GvHD, multiorgan failure, pulseless electrical activity arrest, and respiratory failure; many of which were counted as fatal TEAEs.

In the REACH 2 trial, serious infections were reported in 38.2% and 30.0% of patients in the ruxolitinib and BAT groups, respectively; and serious infections (grade 3 or greater) in 38.2% and 28.7% of patients, respectively. The percentage of patients experiencing at least 1 infection TEAE of any grade was 80.9% and 69.3% in the ruxolitinib and BAT groups, respectively. In the REACH 1 trial, there were a total of 58 patients (81.7%) with at least 1 TEAE infection and infestation, of which 36 patients experienced serious TEAE infections and infestations.

In the REACH 2 trial, 1 patient in each of the ruxolitinib and BAT groups reported experiencing bradycardia of any grade. No patients reported Grade 3 or higher bradycardia. In the REACH 1 trial, 2 patients were reported as experiencing bradycardia of any grade. One patient reported Grade 3 or higher bradycardia.

In the REACH 2 trial, cytopenias TEAEs of any grade (the ruxolitinib group versus the BAT group) included anemia (40.8% versus 34.0%, respectively), thrombocytopenia (56.6% versus 36.7%, respectively), leukopenia (46.7% versus 32.0%, respectively), and other cytopenias (8.6% versus 6.0%, respectively). Grade 3 or greater cytopenias TEAEs of special interest (the ruxolitinib group versus the BAT group) included anemia (36.2% versus 25.3%, respectively), thrombocytopenia (50.7% versus 32.0%, respectively), leukopenia (42.8% versus 27.3%, respectively), and other cytopenias (5.9% versus 4.7%, respectively). In the REACH 1 trial, cytopenia TEAEs of any grade included anemia (64.8%), neutropenia (47.9%), and thrombocytopenia (62.0%). Grade 3 or greater cytopenia TEAEs included anemia (50.7%), neutropenia (42.2%), and thrombocytopenia (53.5%).

In the REACH 2 trial, lipid abnormality events of any grade were reported in 9.9% and 7.3% of patients in the ruxolitinib and BAT groups. Grade 3 or greater lipid abnormality events were reported in the ruxolitinib and BAT groups by 3.9% and 2.7% of patients, respectively. Lipid abnormalities were not reported in the REACH 1 trial.

In the REACH 2 trial, the safety profile in the 9 adolescent patients was, overall, similar to that of the study safety set. REACH 1 did not include any adolescent patients.

Critical Appraisal

REACH 1

Upon a request to the sponsor for clarification on the number of patients in the REACH 1 trial who had "inadequate response to corticosteroids," "inadequate response to other systemic

therapies," or both "inadequate response to corticosteroids and other systemic therapies," the sponsor noted that 42 patients were refractory to steroids alone and 29 patients were refractory to steroids and 1 additional systemic therapy (i.e., receipt of 1 other systemic treatment in addition to corticosteroids [± CNI] for aGvHD was allowed in the REACH 1 trial). It is not known if patients who are refractory to 1 therapy, versus to multiple therapies, would respond differently to ruxolitinib. The clinical experts consulted by CADTH agreed that the difference between patients whose disease either has an inadequate response to corticosteroids alone or to multiple therapies would be unlikely to impact the treatment effect of ruxolitinib.

Phase II (randomized or nonrandomized) trials document safety outcomes and investigate if the estimate of effect for a new drug is large enough to use it in confirmatory phase III trials. Phase II trials may not accurately predict harm and/or effectiveness of treatments. There are numerous examples of phase III trials whose results did not support the phase II trial results. Interpretation of time-to-event end points such as OS is limited in single-arm studies. The nonrandomized design makes interpreting OS events attributable to ruxolitinib challenging, since all patients received the same treatment. The non-comparative design of the REACH 1 trial precludes the ability to assess the relative therapeutic benefit or safety of ruxolitinib against currently available therapies in Canadian clinical practice. All patients in the REACH 1 trial received at least 1 concomitant medication. For instance, CNIs and glucocorticoids were received by 88.7% and 45.1% of patients, respectively. Given the uncontrolled design of the REACH 1 trial, the effect of concomitant treatments on overall study outcomes cannot be determined. Outcomes such as observed responses, durability of responses, and survival may have been influenced by concomitant steroid or by other concomitant therapies. The REACH 1 trial had an open-label design whereby the investigator and the study participants were aware of their treatment status, which increased the risk of detection and performance bias. This had the potential to bias results in favour of ruxolitinib if the assessor (investigator or patient) believed the study drug is likely to provide a benefit. Furthermore, the underlying complexity of aGvHD and its nonspecific presentation have been acknowledged as a key challenge for the design and analysis of clinical trials in the current target setting and may contribute to subjective interphysician variability in response assessments. To mitigate the impact of this bias, the investigators used standardized criteria (i.e., aGvHD disease evaluation and response assessment criteria were done according to standard NIH criteria [Harris et al. (2016)]) to evaluate responses. No formal statical significance and hypotheses testing were performed, and thus no P values were reported. Point estimates with 95% CIs were reported to estimate the magnitude of treatment effect. The REACH 1 trial did not collect data on patient-reported outcomes. The input provided by the patient advocacy groups and the registered clinician groups, as well as the clinical experts consulted by CADTH, agreed that improvements in HRQoL and aGvHD symptom severity are important treatment goals for the present target population. aGvHD has been found to be the leading cause of morbidity in patients following alloSCT with a multitude of symptoms with varying degrees of severity.

REACH 2

The REACH 2 trial had an open-label design whereby the investigator and the study participants were aware of their treatment status, which increases the risk of detection and performance bias. This had the potential to bias results and outcomes in favour of ruxolitinib if the assessor (investigator or patient) believed the study drug is likely to provide a benefit. Subjective outcomes (i.e., adverse outcomes and patient-reported outcomes) may be at particular risk of bias due to the open-label design. Furthermore, the underlying complexity of aGvHD has been acknowledged as a key challenge for the design and analysis of clinical

trials in the current target setting and may contribute to subjective interphysician variability in response assessments.

To mitigate the impact of this bias, the investigators used standardized criteria (i.e., aGvHD disease evaluation and response assessment criteria were done according to standard NIH criteria [Harris et al., (2016)]) to evaluate responses. Overall, the magnitude and direction of this bias remain unclear. While imbalances were noted for a few baseline characteristics (e.g., prior therapy of steroid plus CNI plus an aGvHD prophylaxis; organ involvement in the skin, liver, and upper and lower GI; time from diagnosis of underlying disease to transplant; and time from diagnosis of underlying disease to screening), they were unlikely to influence clinical outcomes, according to the clinical experts consulted by CADTH. Patients in the BAT group who experienced disease progression, mixed response, or no response were allowed to add or initiate a new systemic therapy up to day 28 without being proceeded to discontinuation; however, this was considered a failure of initial BAT treatment. The clinical experts consulted by CADTH noted that changing or initiating new systemic aGvHD therapies is reflective of clinical practice. It was felt by the clinical experts that changes to the BAT treatment up to day 28 were unlikely to impact OS results, given the similar efficacy and similar responses achieved with various BAT therapies. Addition or change of systemic therapy was treated as treatment failure and therefore did not impact ORR at day 28 or the FFS outcomes. Crossover of patients from the BAT group to the ruxolitinib group after day 28 may have biased the OS and event-free survival outcomes. Patients in the BAT group could cross over to the ruxolitinib group if they failed to meet the primary end point (CR or PR at day 28), lost the response thereafter and met criteria for progression, mixed response or no response necessitating new additional systemic immunosuppressive treatment. Overall, 49 patients in the BAT group crossed over to the ruxolitinib group. Crossover of patients in the BAT group may have prolonged survival beyond what would have occurred had the patients only received their randomized study treatment. Given the limited follow-up time, the ability to interpret the OS results remains limited. During the randomized treatment phase (i.e., the period from day 1 to week 24 or end of treatment) the median duration of treatment with ruxolitinib was close to twice as long as the treatment duration with BAT: 82.5 days (range, 8 to 396) and 45.5 days (range, 2 to 218) in the ruxolitinib and BAT groups, respectively. A safety comparison between the study groups over that period may have been biased against the ruxolitinib group. Additionally, the investigator's choice of BAT treatment may have influenced the safety profile in the BAT group, as the toxicity profile of BAT treatments differs. The interpretation of results for the EQ-5D-5L and the FACT-BMT scales (i.e., the ability to assess trends over time and to make comparisons across treatment groups) is limited by the significant decline in patients available to provide assessments over time.

It was noted that few patients in the trial were aged less than 18 years. The clinical experts supported generalizing the study results to adolescents younger than 18 years old, as these patients are managed similarly to adults in clinical practice, the safety profile of ruxolitinib in these patients was similar to the overall safety set, and there is no biological rational to assume that outcomes of ruxolitinib would be different between adult and adolescent patients with SR-aGvHD.

Indirect Comparisons

No indirect treatment comparisons were included in the sponsor's submission to CADTH or identified in the literature search.

Other Relevant Evidence

The other relevant evidence section included:

- 1 additional relevant study (Moiseev et al. [2020]) in the sponsor's submission to CADTH that reported results for ruxolitinib in adult and pediatric patients with SR-aGvHD
- post hoc analyses of the REACH 2 trial that were applied in the submitted pharmacoeconomic model.

Moiseev et al. (2020) Study

Description of the Study

The article by Moiseev et al. (2020) was a prospective, single-centre, open-label study in Russia that included 75 patients with either acute (N = 32) or chronic (N = 43) SR-GvHD. The study sample included both adults and children, with half of the sample comprised of children (53% in the acute and 39% in the chronic GvHD groups). The median ages in the acute and chronic GvHD groups were 17 years (range: 1 to 67) and 21 years (range, 2 to 62), respectively. Study participants received ruxolitinib at a starting dose of 10 mg twice a day for adults, 10 mg twice a day for children weighing more than 40 kg, and 0.15 mg/kg twice a day for children weighing less than 40 kg. Previous treatments were continued if the attending physician considered it necessary. Ruxolitinib was stopped if there were signs of GvHD progression. The primary end point was ORR. ORR for acute and chronic GvHD was assessed based on the joint statement criteria by Martin et al. (2009) and the NIH criteria by Lee et al. (2015), respectively. The secondary end points included OS, toxicity, relapse, and infection complications.

Efficacy Results

The ORR was 75% (95% CI, 57 to 89) in the aGvHD and 81% (95% CI, 67 to 92) in the cGvHD group. The OS was 59% (95% CI, 49 to 74) in the aGvHD and 85% (95% CI, 70 to 93) in the cGvHD group. In patients with aGvHD and cGvHD, there were no significant differences between adults and children in any of the outcomes, including ORR (aGvHD: P = 0.31; cGvHD: P = 0.35) and survival (aGvHD: P = 0.44; cGvHD: P = 0.12).

Harms Results

The most common adverse event was hematological toxicity, with 79% and 44% of grade III to IV neutropenia occurring in the acute and chronic GvHD groups, respectively. There were no significant differences in toxicity between adults and children.

Critical Appraisal

Given the single-arm observational design, interpretation of the study results is limited. Due to the lack of a comparator group and blinding, it is difficult to determine the effectiveness of the treatment on the study outcomes. Given the relatively small sample size of patients with aGvHD (n = 32), the generalizability of these results may be limited. Moreover, as this trial was conducted in Russia, there may be limitations in generalizing these findings to the Canadian context.

Relevance for CADTH Review

In the REACH III trial, the number of patients aged 12 to 18 years represented a small proportion of the study sample (3.6%). In the study by Moiseev et al. (2020), approximately 50% of the study sample included children younger than 18 years of age. Hence, this

additional study supplements the evidence for ruxolitinib in patients younger than 18 years of age.

Post Hoc Analyses of the REACH 2 trial

Several post hoc analyses of the REACH 2 trial were conducted, and the results were applied to the submitted pharmacoeconomic model. High-level summaries of the methods and results of the post hoc analyses were provided by the sponsor. The post hoc analyses included OS by response, DOR by response at day 28, duration of treatment by response at day 28, duration of treatment by individual initial BAT, duration of treatment from randomization, and resource use by study group for initial hospitalization and response at day 28 for readmissions. The CADTH review team was unable to conduct a rigorous evaluation of the conduct and reporting of the post hoc analyses as only a high-level summary of methods was provided by the sponsor. Overall, the CADTH methods team concluded that results from post hoc analyses are considered exploratory and hypotheses-generating only. Due to the lack of formal inferential statistical testing, the ability to interpret results of such analyses is significantly limited.

Economic Evidence

Table 3: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Semi-Markov model
Target population	Patients 12 years of age or older with steroid-refractory acute graft-versus-host disease
Treatment	Ruxolitinib
Submitted price	Ruxolitinib: 5 mg tablet: $86.6275 10 mg tablet: $87.3775 15 mg tablet: $87.5775 20 mg tablet: $87.6375
Treatment cost	At the sponsor's submitted price of $87.3775 per 10 mg tablet, the annual cost of ruxolitinib therapy would be $63,786 if patients remained on therapy for a full year.
Comparator	BAT, consisting of ATG, ECP, MTX, MMF, SIR, ETA, INF
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (15 years)
Key data source	The REACH 2 trial was a multi-centre, randomized, phase III, open-label trial comparing the efficacy and safety of oral ruxolitinib with the investigator's choice of BAT in patients 12 years or older who had SR-aGvHD after alloSCT.

Component	Description
Key limitations	• The majority of the parameters used in the model were derived from the sponsor's post hoc analysis (which allowed for stratified results by response status at day 28) of the REACH 2 study's data. As results from post hoc analyses are hypothesis generating, the CADTH clinical review concluded that the results were uncertain due to various limitations. • The sponsor considered only 1 direction of movement between responder health states and did not model the underlying condition of SR-aGvHD (including outcomes identified as important by patients and clinicians) or the natural history of the disease. As such, the model structure does not effectively capture the health condition. • The modelled population does not fully align with the proposed Health Canada indication and the sponsor's reimbursement request does not align with the available evidence. The model is specific to aGvHD; therefore, based on the submitted evidence in a steroid-refractory population, the cost-effectiveness of chronic GvHD, subgroups of aGvHD, and those with an inadequate response to systemic therapies is unknown. • The sponsor's approach to modelling OS did not align with the REACH 2 trial as it was based on response at day 28, not treatment arm, and was informed by the sponsor's uncertain post hoc analysis. • The sponsor populated BAT and ruxolitinib dosing based on their post hoc analysis of the REACH 2 trial, which could not be validated by CADTH. Some BAT doses used in the model did not reflect published clinical studies of these treatments. • There is significant variation among clinicians and between jurisdictions regarding the distribution of BAT treatments being used. This adds uncertainty, as different distributions of treatments change the cost of BAT, which influences cost-effectiveness. • The sponsor's incorporation of subsequent therapies for nonresponders was inappropriate as it only incorporated costs of therapies, which were applied perpetually until death, and did not consider any potential clinical benefits (i.e., nonresponders could never transition to having a response on a subsequent therapy, which experts deemed to be inappropriate).
CADTH reanalysis results	• Due to the highly uncertain nature of the clinical data derived from the sponsor's post hoc analysis of the REACH 2 trial and due to the inappropriateness of the model structure, CADTH was unable to derive a base-case analysis. Instead, an exploratory reanalysis was conducted that used more appropriate assumptions, though CADTH notes the magnitude of the clinical benefit estimated for ruxolitinib in this reanalysis may still be overestimated. • CADTH undertook exploratory reanalyses to address limitations related to the model not capturing long-term outcomes of SR-aGvHD and uncertain long-term efficacy; adopting an approach to OS that aligned with the REACH 2 trial rather than the post hoc analysis; aligning dosing for ruxolitinib and BAT treatments with the literature; modelling duration of treatment by individual BAT KMs; and aligning the distribution of BAT treatments with clinical expert expectations. • CADTH's exploratory reanalysis suggests that ruxolitinib is associated with an ICER of $21,057 per QALY compared to BAT (incremental QALYs = 0.06; incremental costs = $1,279) over a 1-year time horizon. However, at a willingness-to-pay threshold of $50,000 per QALY, there was a significant degree of uncertainty, with a 52% probability of ruxolitinib being cost-effective. In analyses that reduced the price of ruxolitinib by 10% and 25%, the probability of ruxolitinib being cost-effective increased to 57% and 62%, respectively. Given the uncertainty in the results and the presence of other limitations that could not be addressed (e.g., the sponsor's uncertain model structure and inputs derived from the post hoc analysis), price reductions are likely required.

aGVHD = acute graft-versus-host disease; alloSCT = allogeneic stem cell transplantation; ATG = anti-thymocyte globulin; BAT = best available therapy; ECP = extracorporeal photopheresis; ETA = etanercept; GvHD = graft-versus-host disease; ICER = incremental cost-efficiency ratio; INF = infliximab; KM = Kaplan-Meier; MMF = mycophenolate mofetil; MTX = methotrexate; LY = life-year; OS = overall survival; QALY = quality-adjusted life-year; SIR = sirolimus; SR-aGvHD = steroid-refractory acute graft-versus-host disease.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis:

- There is uncertainty in the estimated population size because the sponsor's approach relies heavily on clinical expert opinion. Furthermore, the sponsor's assumed proportion of patients eligible for public coverage underestimated the market size and budget impact.
- There is uncertainty in the market share of ruxolitinib and its comparators.
- There is uncertainty in dosing, treatment duration, and the treatment cost of comparators.

CADTH reanalysis included adopting a public drug plan perspective (excluding ECP treatment cost); revising the market share of ruxolitinib and comparators based on expert opinion; and aligning dosing of etanercept, infliximab, MMF, and sirolimus with published literature.

Based on CADTH reanalysis, the budget impact to the public drug plans of introducing ruxolitinib is expected to be $419,840 in year 1, $483,866 in year 2, and $508,562 in year 3, for a 3-year total of $1,412,268. The estimated budget impact is sensitive to the proportion of patients with acute GvHD who are steroid refractory.

CDEC Information

Members of the Committee

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, and Dr. Peter Zed.

Initial meeting date: April 27, 2022

Regrets: None

Conflicts of interest: None

Reconsideration meeting date: July 27, 2022

Regrets: 1 CDEC member did not attend.

Conflicts of interest: None