CADTH Reimbursement Recommendation

Ruxolitinib (Jakavi)

**Indication:** For the treatment of chronic graft-versus-host disease in adults and pediatric patients aged 12 years and older who have inadequate response to corticosteroids or other systemic therapies

**Sponsor:** Novartis Pharmaceutical Canada Inc.

**Final recommendation:** Reimburse with conditions
What Is the CADTH Reimbursement Recommendation for Jakavi?
CADTH recommends that Jakavi should be reimbursed by public drug plans for the treatment of chronic graft-versus-host disease (cGvHD) if certain conditions are met.

Which Patients Are Eligible for Coverage?
Jakavi should only be covered to treat patients aged 12 years and older who did not show an adequate response to corticosteroids or other systemic treatments.

What Are the Conditions for Reimbursement?
Jakavi should only be reimbursed if prescribed by specialists who have experience in the diagnosis and management of patients with cGvHD, and the cost of Jakavi is reduced.

Why Did CADTH Make This Recommendation?
• Evidence from a clinical trial demonstrated that Jakavi improved response outcomes related to the resolution of signs and symptoms of cGvHD.
• Jakavi met patient needs of reducing disease symptoms and providing an oral drug option with manageable side effects.
• 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. A price reduction is therefore required.
• Based on public list prices, Jakavi is estimated to cost the public drug plans approximately $24 million over the next 3 years.

Additional Information
What is Chronic Graft-Versus-Host Disease (GvHD)?
Approximately 35% to 70% of patients who receive a stem cell transplant from a donor will experience cGvHD. Chronic GvHD occurs when the donor’s cells attack the transplant recipient’s cells and body parts. Chronic GvHD usually starts 100 days or more after transplant and can last a few months or a lifetime.

Unmet Needs in Chronic GvHD
There is currently no standard of care for patients with cGvHD who have an inadequate response to corticosteroids or other systemic treatments. Effective therapies with tolerable side effects that can improve health-related quality of life, 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 chronic GvHD (cGvHD) in adults and pediatric patients aged 12 years and older who have inadequate response to corticosteroids or other systemic therapies if the conditions listed in Table 1 are met.

**Rationale for the Recommendation**

One phase III, randomized, open-label trial (REACH 3, N = 329) demonstrated that treatment with ruxolitinib resulted in added clinical benefit in patients with steroid-refractory (SR) cGvHD. The REACH 3 trial demonstrated that compared with best available therapy (BAT) ruxolitinib was associated with statistically significant improvements in overall response rate (ORR) at cycle 7, day 1 (50.5% versus 26.3% in the BAT group; stratified odds ratio = 2.98, 95% CI, 1.62 to 5.48), failure-free survival (FFS) (stratified hazard ratio = 0.315, 95% CI, 0.205 to 0.486), and the modified Lee Symptom scale with a higher rate of responders in the ruxolitinib group up to cycle 7, day 1 (odds ratio = 2.62, 95% CI, 1.42 to 4.82). CDEC acknowledged the rarity of cGvHD and the significant 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 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 reducing disease symptoms of cGvHD and providing an oral drug option with tolerable side effects that can be administered as an outpatient treatment. CDEC acknowledged that insufficient follow-up of survival outcomes led to uncertainty regarding long-term survival benefits of ruxolitinib (median FFS in the ruxolitinib group and median overall survival (OS) in both study groups was not reached). No definitive conclusion could be reached regarding the effects of ruxolitinib on health-related quality of life (HRQoL) due to a significant decline in the number of patients available to provide HRQoL assessments over time and the open-label design of the trial.

The cost-effectiveness of ruxolitinib is highly uncertain due to the sponsor’s use of a post-hoc analysis, which was used to populate the majority of model parameters, along with concerns regarding the model structure not adequately capturing the complexity of SR-cGvHD. As such, a base-case, cost-effectiveness estimate was unable to be determined for the treatment of patients aged 12 years and older with SR chronic GvHD who have inadequate response to corticosteroids or other systemic therapies. The committee considered exploratory analyses conducted by CADTH and determined that the incremental cost-effectiveness ratio (ICER) was likely closer to $1,062,977 per quality-adjusted life-year (QALY); therefore, ruxolitinib is not cost-effective at a $50,000 per QALY willingness-to-pay (WTP) threshold. A price reduction of at least 65% for ruxolitinib would be required for ruxolitinib to achieve an ICER of $50,000 per QALY compared with BAT.
### Table 1: Reimbursement Conditions and Reasons

<table>
<thead>
<tr>
<th>Reimbursement condition</th>
<th>Reason</th>
<th>Implementation guidance</th>
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<tbody>
<tr>
<td><strong>Initiation</strong></td>
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<tr>
<td>1. Treatment with ruxolitinib should be initiated in patients who have:</td>
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<td>1.1 Clinically diagnosed cGvHD staging of moderate to severe based on NIH consensus criteria</td>
<td>Evidence from the REACH 3 trial demonstrated that ruxolitinib resulted in a statistically significant improvement in ORR in patients with the characteristic listed in this condition.</td>
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<tr>
<td>2. Patients should have a confirmed diagnosis cGvHD with inadequate response to corticosteroids or other systemic therapies</td>
<td>Evidence from the REACH 3 trial demonstrated that ruxolitinib resulted in a statistically significant improvement in ORR in patients who had corticosteroid refractory cGvHD. The CADTH review identified no clinical trial data on the safety and potential benefits of using ruxolitinib in patients with cGvHD who are not refractory to corticosteroids.</td>
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<td><strong>Renewal</strong></td>
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<td>3. Treatment with ruxolitinib 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, after 24 weeks of therapy (approximately 6 months)</td>
<td>The CADTH review identified no evidence on the safety and potential benefits of further treatment with ruxolitinib in patients who have not achieved an overall response after 24 weeks of therapy.</td>
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<td><strong>Discontinuation</strong></td>
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<td>4. Ruxolitinib should be discontinued upon the occurrence of any of the following:</td>
<td>These conditions correspond to the criteria used to determine whether treatment with ruxolitinib should be discontinued in the REACH 3 trial. CDEC did not review any evidence that indicated patients who exhibit the clinical presentations outlined in this condition would benefit from further treatment with ruxolitinib.</td>
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<td>4.1 Progression of cGvHD, defined as worsening of cGvHD symptoms or occurrence of new cGvHD symptoms</td>
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<td>4.2 recurrence or relapse of underlying hematological malignancy</td>
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<tr>
<td>Reimbursement condition</td>
<td>Reason</td>
<td>Implementation guidance</td>
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<td>5. Ruxolitinib should only be prescribed by clinicians who have experience in the diagnosis and management of patients with cGvHD.</td>
<td>These conditions are required to ensure that ruxolitinib is prescribed only for appropriate patients and that patients receive optimal care for toxicity management.</td>
<td>Ruxolitinib may be self-administered in a patient's home which 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.</td>
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<td>6. Treatment with ruxolitinib must not be added to patients’ concurrent treatment of systemic therapies other than steroids ± calcineurin inhibitors.</td>
<td>In the REACH 3 trial patients continued to receive the systemic immunosuppressive regimen of corticosteroids ± calcineurin inhibitors for SR-cGvHD, that were initiated before randomization. There is no data to support the generalization of treatment benefit to patients who receive ruxolitinib as an add on to systemic therapies other than steroids ± calcineurin inhibitors.</td>
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<td>7. A reduction in price</td>
<td>The cost-effectiveness of ruxolitinib is highly uncertain. CADTH undertook a price reduction analysis that used more appropriate assumptions. This analysis indicated that at least a 65% reduction in price is required to achieve an ICER of $50,000 per QALY. Economic model uncertainty may justify further price reductions.</td>
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<td>8. The feasibility of adoption of ruxolitinib must be addressed</td>
<td>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.</td>
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cGvHD = chronic graft-vs. host disease; CNI = calcineurin inhibitor; CR = complete response; ECOG PS = Eastern Cooperative Oncology Group Performance Status; ICER = incremental cost-effectiveness ratio; kg = kilogram; mg = milligram; NIH = National Institute of Health; ORR = overall response rate; PR = partial response; QALY = quality-adjusted life-year; SR-cGvHD = steroid-refractory chronic graft-vs. host disease.


Discussion Points

• Based on the input from clinical experts and patients, CDEC acknowledged this is a rare patient population with a significant unmet medical need for additional effective and safe treatment options in the cGvHD setting given the severe nature of this disease with substantial morbidity.
• CDEC discussed the extent to which the patient population in the REACH 3 trial reflected the reimbursement request. According to the inclusion criteria of the REACH 3 trial all patients had to have an inadequate response to steroids ± calcineurin inhibitor (CNI). In addition, patients in the REACH 3 trial were allowed to have received 1 prior systemic treatment for cGvHD in addition to corticosteroids ± CNI, which would be reflective of patients with an inadequate response to systemic treatments, other than steroids. CDEC acknowledged input from the clinical experts consulted by CADTH noting that the difference between patients who either have an inadequate response to corticosteroids alone or to multiple therapies would be unlikely to impact the treatment effect of ruxolitinib.
• The REACH 3 trial enrolled male or female patients who are at least 12 years of age. However, only 3.6% of patients in the trial were younger than 18 years. CDEC agreed with the clinical experts consulted by CADTH that it would be reasonable to generalize the REACH 3 trial results to adolescents aged less than 18 years, given that adults and adolescents are managed similarly in clinical practice and the safety profile of ruxolitinib in these patients appeared similar to the overall safety set of the REACH 3 trial. CDEC discussed the results of an observational study of ruxolitinib in children and adults with SR-cGvHD, that suggested a similar treatment effect and safety profile among adults and adolescents aged 12 to 18 years.
• While ruxolitinib appeared to have overall slightly 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 allogeneic stem cell transplantation (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 leading to tissue damage, organ failure, or death. cGvHD typically occurs 100 days or more after alloSCT and can last a few months or a lifetime. cGvHD occurs in 35% to 70% of patients who undergo alloSCT. Currently, there is no consensus on standard second-line therapies for patients with steroid-refractory cGvHD (SR-cGvHD). Available second-line options in Canada include extracorporeal photopheresis (ECP), mycophenolate mofetil (MMF), etanercept, low-dose methotrexate (MTX), infliximab, mechanistic target of rapamycin (mTOR) inhibitor (e.g., sirolimus), imatinib, rituximab, ibrutinib, low dose interleukin (IL)-2, pulsed cyclophosphamide, and rarely pentostatin. Available treatments for patients with SR-cGvHD have limited effectiveness and are associated with a number of side effects.
Ruxolitinib has been approved by Health Canada for the treatment of cGvHD in adults and pediatric patients aged 12 years and older who have inadequate response to corticosteroids or other systemic therapies. Ruxolitinib is a Janus-associated kinase inhibitor. Ruxolitinib is available as 5 mg, 10 mg, 15 mg, and 20 mg tablets. The recommended dose is 10 mg administered orally twice daily. The Product Monograph 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 GvHD reoccur during or after the taper, re-escalation of ruxolitinib should be considered.

Sources of Information Used by the Committee

To make their recommendation, CDEC considered the following information:

- A review of 1 phase III randomized controlled trial in patients aged 12 years and older with moderate or severe SR-cGvHD.
- Patients’ perspectives gathered by 1 joint patient input co-created by 8 patient groups, the Lymphoma Canada (LC), Lymphoma and Leukemia Society of Canada (LLSC), Chronic Lymphocytic Leukemia (CLL) Canada, Myeloma Canada, Aplastic Anemia & Myelodysplasia Association of Canada (AAMAC), Canadian MPN Research Foundation (CMPNRF) and the Chronic Myelogenous Leukemia (CML) Network, 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.
- Three clinical specialists with expertise in diagnosing and treating patients with cGvHD.
- 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- co-created 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 a SCT, and 2 patients did not provide an answer to this question. Out of the 60 patients that received a SCT, 49 patients 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 acute GvHD (aGvHD), 24% experienced 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 significantly impacting patients’ daily activities and causing detrimental effects on patients’ 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 the following key outcomes: overall survival, 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, 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-cGvHD in Canada, except for ibrutinib which has been authorized since 2017 for the treatment of adult patients with SR-cGvHD but has not undergone review by CADTH and is not publicly reimbursed in Canada and available through private drug insurance only. According to the clinical experts consulted by CADTH available second-line options in Canada include ECP, MMF, etanercept, low-dose MTX, infliximab, mTOR inhibitor (e.g., sirolimus), imatinib, rituximab, ibrutinib, low dose IL-2, pulsed cyclophosphamide, and rarely pentostatin. There was consensus among the clinical experts that there is an unmet need for effective therapies with acceptable toxicity profile that improve HRQoL, reduce disease symptoms of cGvHD, enhance patient’s performance status, and improve overall survival. 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 to patients’ immunosuppressive regimen of corticosteroids ± CNI in patients aged 12 years and older with moderate or severe SR-cGvHD as per the REACH 3 trial. It was agreed that ruxolitinib, as a therapy for SR-cGvHD, would likely shift the current treatment paradigm. The clinical experts consulted by CADTH agreed that patients as selected per the inclusion/exclusion criteria
of the REACH 3 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
glucocorticoid refractory as opposed to glucocorticoid dependent cGvHD and patients with
bronchiolitis obliterans. Patient subgroups who would potentially benefit the least from
ruxolitinib may include patients with isolated lichenoid cGvHD, who may preferentially be
treated with ECP or subcutaneous low dose IL-2 rather than ruxolitinib. Patients with strictly
autoimmune cGvHD manifestations such as immune thrombocytopenia (as well as immune
hemolytic anemia, immune glomerulonephritis, and myasthenia gravis) may preferentially
be treated with rituximab. The clinical experts consulted by CADTH felt that it would be
reasonable to generalize the results from the REACH 3 trial to patients who received 2 or
more systemic treatments for cGvHD in addition to corticosteroids ± CNI as well as patients
with Eastern Cooperative Oncology Group (ECOG) of 3 or Karnofsky Performance Status or
Lansky Performance Status of less than 60% if performance status is related to cGvHD, and
its symptoms. Furthermore, it was agreed that it would be reasonable 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 and patients with mild cGvHD.

In the opinion of the clinical experts consulted by CADTH, an accurate assessment of
response in cGvHD is based on the National Institute of Health (NIH) consensus criteria, as
was used in the REACH 3 trial. Response to treatment is usually assessed every 2 to 4 weeks,
depending on the severity of cGvHD. Weekly assessment may be required initially. The clinical
experts indicated that the most clinically meaningful responses to treatment include overall
response (complete or partial response), improvements in HRQoL and performance status,
reduction in cGvHD symptoms (frequency/severity), stability of disease (no deterioration),
and improved overall survival as well as the ability to reduce the dose of immunosuppression/
corticosteroids without flare of cGvHD signs and symptoms and having to start another
agent for cGvHD.

In the opinion of the clinical experts consulted by CADTH, treatment with ruxolitinib should
be discontinued if a patient experiences cGvHD disease progression, relapse of underlying
hematologic malignancy, or experiences intolerable toxicity (e.g., anemia, thrombocytopenia
or neurologic toxicity that cannot be managed with drug interruption and or dose reduction).
Tapering ruxolitinib in responders may be considered after 24 weeks of therapy.

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 3 trial it was
anticipated that ruxolitinib would become the dominant first-line therapy for SR-cGvHD. The
outcomes assessed in the REACH 3 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 noted the drawbacks of currently available therapies, such
as the IV administration, which requires patients to be at the hospital, side effects and broad
immune suppression, and the high price and deliver costs of treatments. It was highlighted
by the input from CTTC that a Health Canada–approved and provincially funded therapy for
SR-cGvHD 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 the experience with ruxolitinib (accessible via compassionate access program) and
real-world effectiveness appears similar to that observed in the REACH 3 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**

<table>
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<tr>
<th>Implementation issues</th>
<th>Response</th>
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<tr>
<td><strong>Relevant comparators</strong></td>
<td>As per protocol criteria of the REACH 3 trial patients continued to receive the systemic immunosuppressive regimen of corticosteroids ± calcineurin inhibitors for SR-cGvHD, that were initiated before randomization. CDEC noted that the CADTH review identified no evidence to support the benefit of combination therapy with ruxolitinib, other than adding it to steroids and ± calcineurin inhibitors.</td>
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| Would there be a patient population that would require a combination of one of the off-label comparator treatments and ruxolitinib for SR cGvHD? | CDEC agreed with the clinical experts consulted by CADTH that inadequate response to corticosteroids or steroid refractoriness in cGvHD is defined according to the 2014 NIH consensus criteria which were used in the REACH 3 trial. The definition of corticosteroid refractory cGvHD defined according to the NIH consensus criteria is, irrespective of the concomitant use of a calcineurin inhibitor:  
  - A lack of response or disease progression after administration of minimum prednisone 1 mg/kg/day for at least 1 week (or equivalent); or  
  - 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); or  
  - Increase to prednisone dose to > 0.25 mg/kg/day after 2 unsuccessful attempts to taper the dose (or equivalent). |
| What would be the definition of inadequate response to corticosteroids or steroid refractoriness in cGvHD? | |
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<tr>
<td>Ruxolitinib for the treatment of cGvHD in patients aged 12 years and older who have inadequate response to corticosteroids or other systemic therapies. What would be the other systemic therapies used that are specified in the reimbursement request for cGvHD?</td>
<td>Patients in the REACH 3 trial were allowed to have received one prior systemic treatment for cGvHD in addition to corticosteroids ± CNI, which would be reflective of patients with an inadequate response to systemic treatments, other than steroids. CDEC acknowledged input from the clinical experts consulted by CADTH noting that in Canadian clinical practice patients could have an inadequate response to a wide range of immunosuppressive agents; for example: rituximab which might be preferentially used for autoimmune cGvHD, or ECP which might be selected for isolated lichenoid mucocutaneous cGvHD. In addition, the clinical experts noted that the difference between patients who either have an inadequate response to corticosteroids alone or to multiple therapies would be unlikely to impact the treatment effect of ruxolitinib.</td>
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| Considerations for discontinuation of therapy                                                                 |                                                                                                                                                                                                       |
| Part of the safety outcomes in REACH 3 were adverse events leading to treatment discontinuation. What would be the specific adverse events that would lead to treatment discontinuation for cGvHD? | CDEC agreed that it would be reasonable to leave it up 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. |

| Considerations for prescribing of therapy                                                                 |                                                                                                                                                                                                       |
| Jakavi may be self-administered in a patient's home which 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/prescriber would be required to initiate and monitor Jakavi for this indication? | CDEC agreed with the clinical experts consulted by CADTH that ruxolitinib is an oral agent that is self-administered in a patient's home. Patients are assessed and managed in the stem cell transplantation follow-up clinic. All assessments and prescriptions should be undertaken by providers that are familiar with GvHD. Occasionally patients with severe multisystem cGvHD require admission to the hospital and treatments, including steroids and ruxolitinib, will be given on an appropriate inpatient service. |

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**Clinical Evidence**

The REACH 3 trial is an ongoing, international, multi-centre, open-label, randomized phase III trial of ruxolitinib (10 mg, oral twice daily) compared with investigator's choice of BAT in patients aged 12 years and older with moderate or severe SR-cGvHD. Patients continued to receive their systemic immunosuppressive regimen of corticosteroids ± CNI per standard of care. A total of 329 patients were randomized in a 1:1 ratio to receive ruxolitinib or BAT. Randomization was stratified by cGvHD severity per 2014 NIH consensus criteria (Jagasia et al., 2015) (moderate versus severe). The primary outcome was ORR on cycle 7, day 1 and key secondary outcomes included FFS and the modified Lee Symptom Scale. Additional

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cGvHD = chronic-graft-vs-host disease; CNI = calcineurin inhibitor; ECP = extracorporeal photopheresis; NIH = National Institute of Health; SR = steroid-refractory.

secondary outcomes were ORR at cycle 4, day 1, HRQoL, symptom severity, duration of response (DoR), best overall response (BOR), OS, non-relapse mortality, incidence of malignancy relapse or progression (MR), steroid dosing, resource utilization, and safety.

The REACH 3 trial enrolled patients, at least 12 years of age, who had undergone alloSCT, had evidence of myeloid and platelet engraftment (area under the curve \[ANC\] > 1,000/mm³ and platelet count > 25,000/mm³), and were diagnosed with moderate or severe cGvHD, which was determined to be corticosteroid refractory as per NIH consensus criteria (Martin et al. 2015). Patients with 2 or more systemic treatments for cGvHD in addition to corticosteroids ± CNI, impaired renal, GI function, or liver disease associated or non-associated with GvHD were excluded. The mean ages for the ruxolitinib and BAT groups, respectively, were 45.9 (standard deviation [SD]: 15.68) and 47.2 (SD: 16.17). The ruxolitinib group had a lower proportion of female patients compared to BAT (33.0% versus 43.9%), patients meeting the corticosteroid refractory 'A' criteria (37.6% versus 44.5%), and patients who only received steroid as prior systemic cGvHD/ SR/cGvHD therapy (42.4% versus 49.4%); and a higher proportion of patient with prior aGvHD of grade 2 (32.1% versus 26.2%), and patients meeting the corticosteroid refractory 'B' criteria (35.2% versus 25.6%). The majority of patients (ruxolitinib versus BAT) had severe SR-cGvHD (58% versus 54.9%), met corticosteroid refractory 'A' (37.6% versus 44.5%) or 'B' (35.2% versus 25.6%) criteria, and most patients had received either only steroid (42.4% versus 49.4%) or steroid plus CNI (41.2% versus 42.1%) as prior systemic cGvHD/ SR-cGvHD therapy. Malignant leukemia/ myelodysplastic syndrome (MDS) was the most common underlying disease (ruxolitinib versus BAT: 73.3% versus 74.4%) and the mean time of transplant to cGvHD diagnosis as well as the mean time from initial diagnosis to randomization were similar across groups (mean days: 247.0 versus 230.0 and mean years: 3.90 versus 3.52, respectively).

This CADTH review is based on the data cut-off date of May 8, 2020. Final study results are expected to occur after the completion of the study (estimated completion date is between the third and fourth quarter of 2022). A fixed sequence hierarchical testing procedure was applied for the primary and the 2 key secondary end points, which included the interim analysis (when 196 patients [60% of the targeted 324 patients] completed cycle 7, day 1 visit or discontinued earlier; July 9, 2019 data cut-off date) and the primary analysis (all 329 patients completed cycle 7, day 1 visit or discontinued earlier; May 8, 2020 data cut-off date).

**Efficacy Results**

As of the interim analysis (July 9, 2019, data cut-off date) the median FFS was not reached (95% CI, 11.9 to NE) for in the ruxolitinib group and was 5.6 (4.5 to 5.8) months in the BAT group with a stratified hazard ratio (HR) of 0.315 (95% CI, 0.205 to 0.486) in favour of the ruxolitinib group. As of the primary analysis (May 8, 2020 data cut-off date), median FFS was not reached (95% confidence interval [CI], 18.6 to NE) for the ruxolitinib group and was 5.7 (95% CI, 5.6 to 6.5) months in the BAT group with a stratified HR of 0.370 (95% CI, 0.268 to 0.510) in favour of the ruxolitinib group. FFS was not formally tested at the primary analyses, given that results reached statistical significance at the interim analysis.

As of the interim analysis (July 9, 2019 data cut-off date), the REACH 3 trial met its primary objective. The proportion of patients who achieved an overall response at Cycle 7 Day 1 was 50.5% (n = 49) (95% CI, 40.2 to 60.8) in the ruxolitinib group and 26.3% (n = 26) (95% CI, 17.9 to 36.1) in the BAT group with a stratified odds ratio of 2.98 (95% CI, 1.62 to 5.48). The proportion of patients with CR and PR was 8.2% (n = 11) and 42.3% (n = 71), respectively, in the ruxolitinib group and 3.0% (n = 5) and 23.2% (n = 37), respectively, in the BAT group. As of
the primary analysis (May 8, 2020) the ORR at Cycle 7 Day 1 was achieved by 49.7% (n = 82) (95% CI, 41.8 to 57.6) of patients in the ruxolitinib group and 25.6% (n = 42) (95% CI, 19.1 to 33.0) of patients in the BAT group with a stratified odds ratio of 2.99 (95% CI, 1.86 to 4.80). ORR at Cycle 7 Day 1 was not formally tested at the primary analyses, given that results reached statistical significance at the interim analysis. The proportion of patients with CR and PR was 6.7% (n = 11) and 43.0% (n = 71), respectively, in the ruxolitinib group and 3.0% (n = 5) and 22.6% (n = 37), respectively, in the BAT group. The ORR cycle 1, day 1 supportive analysis using the per protocol analysis set showed consistent results with the ORR results for the full analysis set.

At the primary analysis results for the modified Lee Symptom Scale suggested that the rate of responders (responders included patients achieving an improvement of at least 7 points on the total symptom score [TSS] from baseline) up to cycle 7, day 1 was higher in the ruxolitinib group (24.2% [95% CI, 17.9 to 31.5]) compared to the BAT group (11% [95% CI, 6.6 to 16.8]) with an odds ratio of 2.62 (95% CI, 1.42 to 4.82). The improvement of the TSS response was formally tested at the primary analysis as the result at the interim analysis did not reject the null hypothesis.

At the May 8, 2020 date cut-off date, the proportion of patients that had achieved BOR (CR or PR at any time point up to and including Cycle 7 Day 1 and before the start of change/addition of systemic therapy for cGvHD) was 76.4% (95% CI, 69.1 to 82.6) in the ruxolitinib group and 60.4% (95% CI, 52.4 to 67.9) in the BAT group, with an odds ratio of 2.17 (95% CI, 1.34 to 3.52). Among the patients who achieved a BOR, median DoR was not reached (95% CI, 20.2 to NE) in the ruxolitinib group and was 6.2 (95% CI, 4.7 to 13.1) months in the BAT group.

As of the May 8, 2020 data cut-off date, 58 death events occurred across both study groups. The median duration of follow up for OS was 57.3 weeks for all patients and for each treatment group was: 56.6 weeks in the ruxolitinib group and 57.9 weeks in the BAT group. Median OS was not reached (95% CI, NE to NE) in both study groups with a stratified HR of 1.86 (95% CI, 0.648 to 1.820).

During the time interval of Day 166 to Day 168 (end of cycle 6), a similar number of patients in both study groups achieved a ≥ 50% reduction of corticosteroid dose (body weight-normalized) from baseline (ruxolitinib group: 84 patients out of 118, 71.2%; BAT group: 80 patients out of 115, 69.6%). The reduction of steroid dose in the ruxolitinib group was slightly (but consistently) higher compared to the BAT group. The number of patients with no steroids during the time interval of Day 155 to Day 168 was 37 (31.4%) in the ruxolitinib group and 32 (27.8%) in the BAT group.12

**Harms Results**

Up to cycle 7, day 1 the percentage of patients reporting at least 1 TEAE was 97.6% in the ruxolitinib group and 91.8% in the BAT group. The most commonly reported TEAEs in the ruxolitinib group (ruxolitinib versus BAT) were anemia (29.1% versus 12.7%), pyrexia (15.8% versus 9.5%), alanine aminotransferase increased (15.2% versus 4.4%), hypertension (15.8% versus 12.7%), and blood creatine increased (13.9% versus 4.4%).12 The most commonly reported TEAEs in the BAT group (ruxolitinib versus BAT) were diarrhea (10.3% versus 13.3%), anemia (29.1% versus 12.7%), hypertension (15.8% versus 12.7%), pneumonia (10.9% versus 12.7%), and nausea (9.1% versus 10.1%). The percentages of patients reporting grade 3 or higher TEAEs up to cycle 7, day 1 was similar across both study groups (57.0% of patients in the ruxolitinib group and 57.6% in the BAT group). The most commonly reported grade 3
or higher TEAE (ruxolitinib versus BAT) was anemia in the ruxolitinib group (12.7% versus 7.6%) and pneumonia in the BAT group (8.5% versus 9.5%). Other commonly reported grade 3 or greater TEAEs occurring across both treatment groups up to cycle 7, day 1 (ruxolitinib versus BAT) included neutropenia (8.5% versus 3.8%), thrombocytopenia (10.3% versus 5.7%), gamma-glutamyl transferase increased (6.7% versus 1.9%), and hypertension (4.8% versus 7.0%).

Up to cycle 7, day 1, the percentage of patients reporting serious TEAEs was 33.3% in the ruxolitinib group and 36.7% in the BAT group. The most commonly reported serious TEAE in both study groups was pneumonia, occurring in 7.9% of patients in the ruxolitinib group and 8.2% of patients in the BAT group. Other commonly reported serious TEAEs occurring across both treatment groups (ruxolitinib versus BAT) included pyrexia (4.8% versus 1.9%), febrile neutropenia (1.8% versus 1.3%), pulmonary embolism (1.2% versus 1.9%), and acute kidney injury (1.2% versus 1.9%).

Up to cycle 7, day 1, the percentage of patients discontinuing study treatment due to TEAEs was 16.4% in the ruxolitinib group and 7.0% in the BAT group. The most commonly reported TEAE leading to treatment discontinuation in both study groups was pneumonia (4.8% in the ruxolitinib group and 1.3% in the BAT group), followed by anemia (0.6% in the ruxolitinib group and 0.6% in the BAT group). Pneumothorax occurred in 1.2% of patients in the ruxolitinib group and in no patients in the BAT group.

Up to cycle 7, day 1, the numbers of patients experiencing on-treatment deaths were 13 (7.9%) and 9 (5.7%) in the ruxolitinib and BAT groups, respectively. The most common cause of on-treatment death up to Cycle 7 Day 1 was the study indication (cGvHD and/or complications attributed to treatment for cGvHD) in 12 (7.3%) and 6 (3.8%) patients in the ruxolitinib and BAT groups, respectively. One patient in the ruxolitinib group died more than 30 days after the last dose due to general physical health deterioration. One patient each died from pneumonia, sepsis, and systemic infection in the BAT group.

Up to cycle 7, day 1, the most commonly reported infections in the ruxolitinib and BAT groups were infections excluding tuberculosis (62.4% and 58.2%, respectively), other infections (48.5% and 47.5%, respectively), pneumonia (19.4% and 17.1%, respectively), and opportunistic infections (11.5% and 12.0%, respectively).

Up to cycle 7, day 1, the number of patients reporting lipid abnormality events of any grade were 31 (18.8%) and 23 (14.6%) in the ruxolitinib and BAT groups, respectively. The most commonly reported lipid abnormalities in the ruxolitinib and BAT groups, respectively, were hypertriglyceridemia (9.7% and 8.2%), blood cholesterol increased (7.3% and 4.4%), hypercholesterolaemia (5.5% and 1.3%) and hyperlipidemia (2.4% and 2.5%).

Up to cycle 7, day 1, the number of patients reporting renal and urinary disorders of any grade were 16 (9.7%) and 17 (10.8%) in the ruxolitinib and BAT groups, respectively. The most commonly reported renal and urinary disorders in the ruxolitinib and BAT groups were acute kidney injury (2.4% and 3.8%, respectively), renal failure (1.2% and 1.3%, respectively), hematuria (1.2% and 1.9%, respectively), and proteinuria (0.6% and 1.3%, respectively).

Up to cycle 7, day 1, the most commonly reported cytopenia events of any grade in the ruxolitinib and BAT groups were erythromenia (29.7% and 12.7%, respectively), leukopenia (18.8% and 13.9%, respectively), thrombocytopenia (21.2% and 14.6%, respectively), and other cytopenias (1.2% and 1.3%, respectively).
Up to cycle 7, day 1, the most commonly reported bleeding events of any grade in the ruxolitinib and BAT groups were hemorrhage (11.5% and 14.6%, respectively), hemorrhage events (6.7% and 10.1%, respectively), bruising (4.2% and 2.5%, respectively), and GI bleeding (1.2% and 3.2%, respectively).

Critical Appraisal

The REACH 3 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 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 [e.g., modified Lee Symptom scale]) may be particular at risk of bias due to the open-label design. Furthermore, the underlying complexity of cGvHD 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 inter-physician variability in response assessments. To mitigate the impact of this bias, the investigators used standardized criteria (i.e., cGvHD disease evaluation and response assessment criteria for all organs were done according to NIH consensus criteria [Lee 2015] to evaluate responses). Patients in the BAT group who did not achieve responses were allowed to add or initiate a new systemic therapy in the BAT group up to cycle 7, day 1 without having to discontinue initial study treatment; however, patients in the ruxolitinib group were discontinued from treatment, if they changed or added a systemic therapy. This design feature may have biased the reporting of adverse events (AEs) leading to treatment discontinuation against the ruxolitinib group. The clinical experts consulted by CADTH noted that changing or initiating new systemic cGvHD therapies is reflective of clinical practice. It was felt by the clinical experts, that changes to the BAT treatment up the cycle 7, day 1 were unlikely to impact OS results, given the similar efficacy and similar responses achieved with various systemic therapies. The modified Lee Symptom scale scores were measured up to cycle 7, day 1 (cycle length = 28 days), which may not represent an accurate picture of patients’ experiences with ruxolitinib for a prolonged period of time. However, the assessment time frame coincided with the assessment of the primary outcome, ORR at cycle 7, day 1, and the clinical experts consulted by CADTH agreed that changes in symptom severity would be apparent within the first 6 Cycles after starting treatment. Given several important limitations including the non-inferential analyses, the significant decline in patients available to provide assessment over time, and the open-label design of the trial, the ability of interpret the results for the European Quality of Life 5-Five Dimensions 5-Levels (EQ-5D-5L) and The Functional Assessment of Cancer Therapy (FACT)-Bone Marrow Transplantation scores is limited.

It was noted that few patients in the trial were younger than 18 years. The clinical experts supported generalizing the study results to adolescents less than 18 years old, as these patients are managed similarly as adults in clinical practice, the safety profile of ruxolitinib in these patients was acceptable and similar to the overall safety set, and there is no biologic rational to assume that outcomes of ruxolitinib would be different between adult and adolescent patients with SR-cGvHD. It was agreed by the clinical experts that the NIH consensus criteria used in the trial for cGvHD disease and response assessment as well as the tarping schedule for treatments applied in the trial were overall reflective of Canadian clinical practice. The proportions of patients with cGvHD disease staging of mild, moderate, and severe as well as the proportions of patients meeting the SR-cGvHD criteria (‘A’ versus ‘B’ versus ‘C’) were reflective of patients seen in clinical practice.
**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:

- One additional relevant study (Moiseev et al., 2020) included in the sponsor’s submission to CADTH that reported results for ruxolitinib in adult and pediatric patients with SR-cGvHD.
- Post-hoc analyses of the REACH 3 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 AE 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 cGvHD patients (N = 43), the generalizability of these results may be limited. Moreover, as this trial was conducted in Russia, there may be limitations 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., 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 3 Trial**

Several post-hoc analyses of the REACH 3 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 ORR, duration of treatment form randomization, duration of treatment by response at and from cycle 7, day 1, resource use by study group and response at cycle 7, day 1, and weekly dosing. 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 the results from post-hoc analyses are considered exploratory and hypotheses generating only. Due to the lack of formal inferential statistical testing, the CADTH review team's ability to interpret results of such analyses is significantly limited.

**Economic Evidence**

<table>
<thead>
<tr>
<th>Component</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of economic evaluation</td>
<td>Cost-utility analysis</td>
</tr>
<tr>
<td></td>
<td>Semi-Markov model</td>
</tr>
<tr>
<td>Target population</td>
<td>Patients 12 years of age or older with SR-cGvHD</td>
</tr>
<tr>
<td>Treatment</td>
<td>Ruxolitinib</td>
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<tr>
<td>Submitted price</td>
<td>Ruxolitinib:</td>
</tr>
<tr>
<td></td>
<td>• 5 mg, tablet: $86.6275</td>
</tr>
<tr>
<td></td>
<td>• 10 mg, tablet: $87.3775</td>
</tr>
<tr>
<td></td>
<td>• 15 mg, tablet: $87.5775</td>
</tr>
<tr>
<td></td>
<td>• 20 mg tablet: $87.6375</td>
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<tr>
<td>Treatment cost</td>
<td>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.</td>
</tr>
<tr>
<td>Comparators</td>
<td>Best available therapy (BAT), consisting of rituximab, extracorporeal photopheresis (ECP), imatinib, methotrexate, mycophenolate mofetil, sirolimus, and ibrutinib</td>
</tr>
<tr>
<td>Perspective</td>
<td>Canadian publicly funded health care payer</td>
</tr>
<tr>
<td>Outcomes</td>
<td>QALYs, LYs</td>
</tr>
<tr>
<td>Time horizon</td>
<td>Lifetime (40 years)</td>
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</tbody>
</table>
### Component Description

#### Key data source

| Key data source | REACH 3 trial, 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 of age or older who had SR-cGvHD after alloSCT. |

#### Key limitations

- The majority of the parameters used in the model were derived from the sponsor’s post-hoc analysis of REACH 3 data. As results from post-hoc analyses are hypothesis generating, the CADTH clinical review concluded results were likely uncertain due to various limitations.
- The sponsor considered only one direction of movement between responder health states and did not model the underlying health condition of SR-cGvHD, including outcomes identified as important by patients and clinicians. As such, the model structure does not effectively capture the health condition.
- The sponsor’s analysis assumed an indefinite OS benefit for responders, which was not reflected in their post-hoc analysis and not the expectation of clinical experts consulted for this review.
- As there is no long-term data regarding how long patients who respond on ruxolitinib will maintain their response, DoR estimates for ruxolitinib are highly uncertain. Additionally, experts noted that DoR on BAT is highly variable (dependent on the specific treatment within BAT) and that the sponsor may have underestimated long-term DoR.
- The sponsor populated BAT dosing based on their post-hoc analysis of REACH-3, which could not be validated by CADTH. Some BAT doses used in the model did not reflect published clinical studies of these treatments or their product monographs.
- 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 ruxolitinib's comparator, which influences cost-effectiveness.
- The sponsor’s incorporation of subsequent therapies for non-responders was inappropriate as it only incorporated costs of therapies which were applied perpetually until death; however, non-responders 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 data derived from the sponsor’s post-hoc analysis of REACH 3 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 clinical benefit estimated for ruxolitinib in this reanalysis may still be overestimated.
- CADTH undertook exploratory reanalyses to address limitations relating to: uncertain long-term efficacy; removing an OS benefit for responders; assuming that ruxolitinib will have a DoR that is proportionately better than BAT; changing the DoR extrapolations for BAT to better align with clinical expert expectations; aligning dosing for BAT treatments with the literature and product monographs; and, aligning the distribution of BAT treatments with clinical expert expectations.
- CADTH’s exploratory reanalysis suggests that ruxolitinib is associated with an ICER of $1,062,977 per QALY compared to BAT (including QALYs = 0.10 and costs = $106,178).
- For ruxolitinib to be considered cost-effective at a WTP threshold of $50,000 per QALY, a price reduction of at least 65% is required. However, given the uncertainty around the economic model, further price reductions may be necessary.

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**Abbreviations:**
- alloSCT = allogeneic stem cell transplantation; BAT = best available therapy; DoR = duration of response; LY = life-year; QALY = quality-adjusted life-year. SR-cGvHD = steroid-refractory chronic graft-vs. host disease; WTP = willingness to pay.
Budget Impact

CADTH identified the following key limitations with the sponsor’s analysis: First, there is uncertainty in the estimated population size because the sponsor’s approach relies heavily on clinical expert opinion. Further, the sponsor’s assumed proportion of patients eligible for public coverage underestimated the market size and budget impact. Second, there is uncertainty in the market share of ruxolitinib and its comparators. Finally, there is uncertainty in dosing, treatment duration, and the treatment cost of comparators.

CADTH reanalysis included: adopting the perspective of the public drug payer, revising market shares of comparators, assuming a higher market share and rapid uptake of ruxolitinib, and aligning dosing of rituximab, ibrutinib, imatinib and ECP with the product monographs and the published literature.

Although the sponsor suggested ruxolitinib would be associated with a budget impact of $10,440,825 over the 3-year time horizon, based on CADTH reanalysis, the budget impact to the public drug plans of introducing ruxolitinib is expected to be $10,350,040 in year 1, $7,771,389 in year 2, and $5,805,567 in year 3, for a 3-year total of $23,926,995. The estimated budget impact is sensitive to the proportion of existing patients with SR-cGvHD among alloSCT recipients.

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.

Meeting date: March 23, 2022

Regrets: Of the expert committee members, 2 did not attend.

Conflicts of interest: None