CADTH

CADTH REIMBURSEMENT REVIEW

Stakeholder Feedback on Draft Recommendation

belumosudil (Rezurock)

(Sanofi-aventis Canada Inc.)

Indication: For the treatment of adult and pediatric patients 12 years and older with chronic graft-versus-host disease (GVHD) after failure of at least two prior lines of systemic therapy.

February 2, 2024

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CADTH does use reasonable care to prevent disclosure of personal information in posted material; however, it is ultimately the submitter's responsibility to ensure no identifying personal information or personal health information is included in the submission. The name of the submitting stakeholder group and all conflicts of interest information from individuals who contributed to the content are included in the posted submission.

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0789-000
Brand name (generic)	Rezurock (Belumosudil)
Indication(s)	For the treatment of adult and pediatric patients 12 years and older with chronic graft-versus-host disease (GvHD) after failure of at least two prior lines of systemic therapy
Organization	Cell Therapy Transplant Canada (CTTC)
Contact information[a]	Name: Kirk R. Schultz – CTTC President

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☒
	No	☒

Please explain why the stakeholder agrees or disagrees with the draft recommendation. Whenever possible, please identify the specific text from the recommendation and rationale.

Yes, we agree with the recommendation for Belumosudil as a 3rd line therapy for cGvHD although we will point out that this agent is rapidly moving to frontline therapy in the US. To date, there is no other agent that is demonstrating the efficacy that belumosudil has had and it will soon be considered the standard of care in most US and some European centers. Based on the ROCKstar trial, such patients treated with belumosudil achieve clinical benefit in response rates, overall survival and progression-free survival over outcomes currently achievable with standard therapies. In summary it is a much needed and valuable treatment for patients with chronic GvHD.

We do not agree on the following issues:

- The current recommendation "…systemic immunosuppressive regimen of corticosteroids, CNIs, sirolimus, mycophenolate mofetil, methotrexate, rituximab, ECP, or topical or organ-specific therapies if they had been on a stable regimen for cGvHD that were initiated before randomization. There are no data to support the generalization of treatment benefit to patients who receive belumosudil as an add on to systemic therapies other than those listed above." The current recommendations do not list the drugs in most common usage that would be used before starting this drug and usually would be given concomitantly, including ruxolitinib and ibrutinib. Both drugs are currently Health Canada approved and in wide usage by BMT clinicians across Canada. In addition, ruxolitinib has been publicly funded as the 2nd line therapy, approved by the CADTH. Accordingly, it needs to be included in the list of systemic regimens for cGvHD treatment, in addition to corticosteroids, CNIs, sirolimus, mycophenolate mofetil, methotrexate, rituximab, ECP, or topical or organ-specific therapies.

Pusic I, Lee C, Veeraputhiran M, Minor C, DiPersio JF. Belumosudil and ruxolitinib combination for treatment of refractory chronic graft-versus-host disease Bone Marrow Transplant. 2023 Dec 9. doi: 10.1038/s41409-023-02165-3.

-We do not agree with "4.2. The dose of corticosteroids remains at or above baseline dose for more than 6 weeks." One of the primary goals of treatment and the addition of belumosudi is to reduce the dosage of steroids as quickly as possible due to the excessive toxicity of steroids after prolonged use. This should not be a criteria for continuation of funding.

Expert committee consideration of the stakeholder input		
2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☒
	No	☐
If not, what aspects are missing from the draft recommendation?		
Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		

[a] CADTH may contact this person if comments require clarification.

Appendix 2. Conflict of Interest Declarations for Clinician Groups

- To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest.
- This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the feedback from patient groups and clinician groups.
- CADTH may contact your group with further questions, as needed.
- Please see the *Procedures for CADTH Drug Reimbursement Reviews* for further details.
- For conflict of interest declarations:
  - Please list any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.
  - Please note that declarations are required for each clinician that contributed to the input.
  - If your clinician group provided input at the outset of the review, only conflict of interest declarations that are new or require updating need to be reported in this form. For all others, please list the clinicians who provided input are unchanged
  - Please add more tables as needed (copy and paste).
  - All new and updated declarations must be included in a single document.

A. Assistance with Providing the Feedback		
1. Did you receive help from outside your clinician group to complete this submission?	No	☒
	Yes	☐
2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission?	No	☒
	Yes	☐
All HSCT program directors have had an opportunity to provide input on this response and it has been reviewed by the CTTC Board of Directors.		
B. Previously Disclosed Conflict of Interest		
3. Were conflict of interest declarations provided in clinician group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section C below.	No	☐
	Yes	☒
If yes, please list the clinicians who contributed input and whose declarations have not changed: • Kirk Schultz • Christopher Bredeson • Genevieve Gallagher • David Mitchell • Victor Lewis • Kevin Song • M. Lynn Savoie • Ravi Shah		

C. New or Updated Conflict of Interest Declarations

New or Updated Declaration for Clinician 1	
Name	Imran Ahmad
Position	Hematologist, Cellular Therapy & Transplantation Program Director, HMR, Université de Montréal
Date	25-01-2024

☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

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

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Abbvie	☒	☐	☐	☐
Genentech	☒	☐	☐	☐
InCyte	☒	☐	☐	☐
Jazz Pharmaceuticals	☒	☐	☐	☐
Medexus Pharma	☒	☐	☐	☐
Sanofi	☒	☐	☐	☐
Vertex Pharmaceuticals	☒	☐	☐	☐

New or Updated Declaration for Clinician 2

Name	Dennis Kim
Position	Professor of Medicine, University of Toronto
Date	26-01-2024
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

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

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Novartis	☐	☐	☒	☐
Sanofi	☐	☒	☐	☐

New or Updated Declaration for Clinician 3

Name	Terrance Comeau, MD
Position	Director New Brunswick Cellular Therapy Program
Date	31-01-2024
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
None	☐	☐	☐	☐

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0789-000
Brand name (generic)	belumosudil (Rezurock)
Indication(s)	For the treatment of adult and pediatric patients 12 years and older with chronic graft-versus-host disease (GVHD) after failure of at least two prior lines of systemic therapy.
Organization	OH (CCO) Hematology Cancer Drug Advisory Committee
Contact information[a]	Name: Dr. Tom Kouroukis

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☒
	No	☐
Please explain why the stakeholder agrees or disagrees with the draft recommendation. Whenever possible, please identify the specific text from the recommendation and rationale. The recommendation should include to allow flexibility in clinician management of concurrent medications.		

Expert committee consideration of the stakeholder input		
2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☒
	No	☐
If not, what aspects are missing from the draft recommendation?		

Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		

[a] CADTH may contact this person if comments require clarification.

Appendix 2. Conflict of Interest Declarations for Clinician Groups

- To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest.
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- CADTH may contact your group with further questions, as needed.
- Please see the *Procedures for CADTH Drug Reimbursement Reviews* for further details.
- For conflict of interest declarations:
  - Please list any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.
  - Please note that declarations are required for each clinician that contributed to the input.
  - If your clinician group provided input at the outset of the review, only conflict of interest declarations that are new or require updating need to be reported in this form. For all others, please list the clinicians who provided input are unchanged
  - Please add more tables as needed (copy and paste).
  - All new and updated declarations must be included in a single document.

A. Assistance with Providing the Feedback		
2. Did you receive help from outside your clinician group to complete this submission?	No	☐
	Yes	☒
If yes, please detail the help and who provided it. OH (CCO) provided a secretariat function to the group.		
3. Did you receive help from outside your clinician group to collect or analyze any information used in this submission?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
B. Previously Disclosed Conflict of Interest		
4. Were conflict of interest declarations provided in clinician group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section C below.	No	☐
	Yes	☒
If yes, please list the clinicians who contributed input and whose declarations have not changed: • Dr. Tom Kouroukis		

C. New or Updated Conflict of Interest Declarations

New or Updated Declaration for Clinician 1	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (DD-MM-YYYY)*
☐	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.
Conflict of Interest Declaration	

CADTH Reimbursement Review

Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0789
Name of the drug and Indication(s)	Belumosudil (Rezurock) for the treatment of adult and pediatric patients 12 years and older with cGVHD after failure of at least 2 prior lines of systemic therapy.
Organization Providing Feedback	FWG

1. Recommendation revisions
Please indicate if the stakeholder requires the expert review committee to reconsider or clarify its recommendation.

Request for Reconsideration	**Major revisions:** A change in recommendation **category** or patient **population** is requested	☐
	Minor revisions: A change in reimbursement **conditions** is requested	☐
No Request for Reconsideration	**Editorial revisions:** Clarifications in recommendation **text** are requested	X
	No requested revisions	☐

2. Change in recommendation category or conditions
Complete this section if major or minor revisions are requested

Please identify the specific text from the recommendation and provide a rationale for requesting a change in recommendation.

3. Clarity of the recommendation
Complete this section if editorial revisions are requested for the following elements

a) Recommendation rationale

Please provide details regarding the information that requires clarification.

b) Reimbursement conditions and related reasons

Please provide details regarding the information that requires clarification.
If applicable, clarification is required regarding reimbursement condition 6 and the related reason to outline if there are specific therapies belumosudil should not be used with. Clarification is also required regarding the intent of the following text in reimbursement condition 6: “but should not be used with other newly initiated systemic therapies for cGVHD”.

c) Implementation guidance

Please provide high-level details regarding the information that requires clarification. You can provide specific comments in the draft recommendation found in the next section. Additional implementation questions can be raised here.
Please:

- Provide examples of drugs that would constitute reasonable prior lines of therapy, beyond the CS +/- CNI outlined (for reimbursement condition 2)
- Define what constitutes a “significant reduction in steroid doses” (for reimbursement condition 3)

Outstanding Implementation Issues

In the event of a positive draft recommendation, drug programs can request further implementation support from CADTH on topics that cannot be addressed in the reimbursement review (e.g., concerning other drugs, without sufficient evidence to support a recommendation, etc.). Note that outstanding implementation questions can also be posed to the expert committee in Feedback section 4c.

Algorithm and implementation questions
1. Please specify sequencing questions or issues that should be addressed by CADTH (oncology only)
1. 2.
2. Please specify other implementation questions or issues that should be addressed by CADTH
1. 2.
Support strategy
3. Do you have any preferences or suggestions on how CADTH should address these issues?
May include implementation advice panel, evidence review, provisional algorithm (oncology), etc.

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0789-000-000
Brand name (generic)	Rezurock (belumosudil)
Indication(s)	For the treatment of adult and pediatric patients 12 years and older with chronic graft-versus-host disease (GVHD) after failure of at least two prior lines of systemic therapy.
Organization	The Leukemia & Lymphoma Society of Canada (LLSC)
Contact information[a]	Name: Colleen McMillan

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☒
	No	☐
LLSC agrees with the committee's recommendation. belumosudil meets an unmet need for additional treatment options in this setting given the severe nature of this disease and substantial morbidity. Additionally, belumosudil may provide the benefits of reducing disease symptoms, reduction in corticosteroid dosages, providing durability of response and improvement in overall survival. belumosudil can also be administered orally as an outpatient treatment.		

Expert committee consideration of the stakeholder input		
2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☒
	No	☐
This recommendation supports the need expressed by patients for treatments that improve survival and quality of life, reduce disease symptoms, reduce corticosteroid dosages, and produce fewer adverse effects. We thank the committee for this recommendation.		

Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		

[a] CADTH may contact this person if comments require clarification.

Appendix 1. Conflict of Interest Declarations for Patient Groups

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

A. Patient Group Information	
Name	*Colleen McMillan*
Position	*Advocacy Lead*
Date	*29-01-2024*
☒	I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

B. Assistance with Providing Feedback		
1. Did you receive help from outside your patient group to complete your feedback?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
2. Did you receive help from outside your patient group to collect or analyze any information used in your feedback?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		

C. Previously Disclosed Conflict of Interest		
1. Were conflict of interest declarations provided in patient group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section D below.	No	☐
	Yes	☒

D. New or Updated Conflict of Interest Declaration

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

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0789
Brand name (generic)	REZUROCK (belumosudil)
Indication(s)	For the treatment of adult and pediatric patients 12 years and older with chronic graft-versus-host disease (cGVHD) after failure of at least two prior lines of systemic therapy.
Organization	sanofi-aventis Canada Inc. (Sanofi)
Contact information[a]	[redacted]

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☒
	No	☐

Sanofi agrees with the draft recommendation as it is in alignment with the Health Canada-approved indication for REZUROCK (belumosudil) and the reimbursement request; however, we respectfully disagree with the following text in the *Rationale for the Recommendation (pg. 3, 1st paragraph):*

- *"Study KD025-208 was exploratory in nature*…." It is respectfully requested that *"was exploratory in nature"* to be removed as this is an incorrect characterization of Study KD025-208 which was a phase II, multicenter, randomized open-label, dose-finding study. Patients were enrolled into 3 sequential dosing cohorts, of which one was the Health Canada-approved dose of belumosudil 200 mg once daily. The study was adequately powered to assess efficacy assuming a best overall response rate (ORR) of 25%, which was deemed to be clinically meaningful. Given this assumption, the trial was expected to have ~ 90% probability to show a response in ≥ 2 patients per cohort.

There are 2 other items that Sanofi does not agree should be included in the draft recommendation:

- *GRADE Summary of Findings and Certainty of the Evidence (pg. 13):* It is inappropriate to apply the GRADE criteria to the included studies as it is clearly stated that GRADE guidance is not available for noncomparative studies. It is inappropriate, especially because there is no opportunity for an increased rating other than "very low certainty" strictly due to the trial design. The application of the GRADE assessment is unfair as the rating of "very low certainty" is concluded prior to the evaluation of the outcomes of the trial.
- *Critical Appraisal (pg. 16):* The sentences: *"However, as noted by Health Canada, this is an important limitation of the belumosudil KD205-213 trial that may have been foreseen. Given that the trial initiated in 2018 (after Health Canada approval of ibrutinib), it may have been possible at the outset to align enrolment criteria in order to facilitate a valid ITC with both ibrutinib and ruxolitinib."* are inappropriate and should be removed. It is not reasonable to suggest that the approval of a drug (with a different indication and target patient population) should have influenced the design of a clinical trial more than 5 to 6 years ago. Further in 2018, the methodology for indirect treatment comparisons (ITCs) was in its inception and ITCs were not a requirement of CADTH submissions, therefore it is unfair to state this as a limitation.

Expert committee consideration of the stakeholder input		
2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☐
	No	☒

The following aspects are missing from the draft recommendation:

- In the *Rationale for the Recommendation (pg. 3, 2nd paragraph)*, important benefits of an oral drug option for cGVHD are not mentioned. In the Sponsor Summary of Clinical Evidence Template (CET), reference was made to the unmet need for patients with cGVHD expressed by clinical experts in the CADTH review of ruxolitinib. When describing the unmet need, the clinical experts highlighted the need for a treatment with a convenient oral route of administration to improve adherence and reduce the need for hospital-based or ambulatory centre resource use.
- In the *Discussion Points (pg. 6, Bullet No. 2)*, it should be made clear that both Health Canada and CADTH's clinical experts concurred that the trial data can be extrapolated and is generalizable to the pediatric population (i.e., patients aged 12 years and older).
- In the *Background (pg. 6, 1st paragraph)*, the indication stated is for ruxolitinib. The indication for ibrutinib is incorrectly stated. The correct indication for ibrutinib is: "For the treatment of adult patients with steroid dependent or refractory cGVHD and for the treatment of pediatric patients age 1 year and older with cGVHD after failure of one or more lines of systemic therapy."

Clarity of the draft recommendation

3. Are the reasons for the recommendation clearly stated?	Yes	☒
	No	☐

The reasons for the recommendation are clearly stated.

4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☐
	No	☒

The following information requires clarification:

Regarding the implementation issues identified in *Table 2 (pg. 9)*:

- *Relevant comparators:* In the *Response* it should be clarified that ibrutinib is indicated for the treatment of adult patients with steroid dependent or refractory cGVHD and for the treatment of pediatric patients age 1 year and older with cGVHD after failure of 1 or more lines of systemic therapy. The ibrutinib indication clearly differentiates it as a 2nd line option, given that corticosteroids (CS) are standard 1st line treatment. Ibrutinib is not a relevant comparator for belumosudil which is indicated for use after failure of at least 2 prior lines of systemic therapy. The optimal place in therapy for belumosudil is after failure of at least 2 prior lines of systemic therapy. The positioning of belumosudil as an alternative 3rd-line agent to additional best available therapy (BAT) reflects the need for choice of a 2nd-line therapy by the prescriber from the wide range of potential 2nd-line therapies that are currently being used in Canada.

5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☐
	No	☒

The following information requires clarification.

Regarding the reimbursement conditions and reasons in *Table 1 (pg. 4):*

- ***Initiation****:* The definition of moderate and severe cGHVD according to the 2014 NIH global severity of cGVHD criteria requires correction. The correct definitions are: Moderate cGVHD is defined as 3 or more organs involved with no more than score 1 OR at least 1 organ (not lung) with a score of 2 OR a lung score of 1. Severe cGVHD is defined as at least one organ with a score of 3 OR a lung score of 2 or 3. Additionally, the 3rd bullet of *"Increased prednisone dose to > 0.25 mg/kg/day after 2 unsuccessful attempts to taper the dose"* is the definition of steroid-dependent cGVHD. Please ensure these definitions are correctly transcribed from the 2014 NIH Consensus publications.
- ***Renewal****:* There lacks implementation guidance regarding what constitutes a *"… significant reduction in steroid doses according to NIH criteria…"* The reference cited (Lee et al., 2015) does not provide guidance regarding reduction in steroid doses. Rather the document specifically

states that it addresses only the measurement of clinical responses and does not address reduction in steroid dosing that does not rely on direct assessment of organ responses.

- ***Discontinuation****:*
    - *Criterion 4.1,* Please clarify that progression of cGVHD should be assessed using the organ-specific cGVHD response assessment, as defined by the 2014 NIH Consensus Development Project on Criteria for Clinical Trials for cGVHD (i.e., previously referred to in the table as the 2014 NIH Consensus Criteria).
    - *Criterion 4.2*, Please remove *"at or"* from the criterion as the definition of treatment failure pertaining to CS dosing in Study KD025-213 was that transient increases in CS dosing (that did not exceed 1 mg/kg/day prednisone equivalent) were permitted for the treatment of a cGVHD flare, but the dose must have reduced back to the pre-randomization dose (i.e., baseline or CS dose at Cycle 1, Day 1) within 6 weeks. <u>If the dose remained elevated</u> from baseline for more than 6 weeks, this was considered a belumosudil treatment failure. As the criterion currently reads, discontinuation would occur if the CS dose returned to the baseline dose. In Study KD025-213, CS dose reduction was a pre-specified secondary outcome. During treatment with belumosudil, 50 (64.9%) patients had their CS dose reduced from the baseline dose and 21 (27.3%) discontinued CS use. In the primary analyses for KD025-213, the ORR was 72.7% which suggests patients are responding to belumosudil even if the CS dose has not been reduced from baseline. Please also refer to the *Considerations for discontinuation of therapy* in Table 2 (pg. 9) where it states *"… CDEC also recommended that belumosudil be discontinued if the dose of CS <u>remained elevated</u> for more than 6 weeks…"* (i.e., not that it was '<u>at</u>' baseline).
- ***Prescribing****:* There lacks implementation guidance on what specialties could potentially be considered to have 'experience' in the diagnosis and management of patients with cGVHD (e.g., stem cell transplant specialists, respirologists, specialists working in a clinical setting associated with allo-HSCT as per the clinician input received).
- ***Pricing***: Sanofi acknowledges the re-analyses of the economic model conducted by CADTH that translates to the recommended price reduction recommendation. However, we respectfully disagree regarding the appropriateness of the extrapolations of failure-free survival (FFS) and time on treatment (ToT) implemented in the CADTH re-analyses.
    - The CADTH reanalyses assumed at least half of the patients would remain on therapy in the failure-free state. The submitted analyses provided ToT curves that realistically maintained the relative difference versus belumosudil over time. Based on the advice received from multiple Canadian clinical experts that reviewed the extrapolations and landmark analyses from all time to event analysis, it was deemed appropriate that patients can be failure-free and not on treatment, e.g., from both the belumosudil and REACH-3 trials (for ruxolitinib), median time on treatment was shorter than the FFS. Physicians were aligned with the base case assumptions in the model, noting that this is the standard approach to therapy, and is currently being utilized for patients treated with ruxolitinib.
    - In the case of the BAT FFS curves, CADTH assumed increased efficacy of the BAT arm in its extrapolation than the sponsor submitted base case. Considering the analyses was a naïve comparison using data from the KD025-213 and KD025-208 single-arm trials (belumosudil) and the REACH3 trial (BAT), the efficacy of BAT is not likely to be understated in the naïve analyses due to a more heavily pre-treated population associated with the belumosudil efficacy inputs. The belumosudil patient population was a more heavily pre-treated patient population (median three (3) prior lines of systemic therapies) while the REACH3 trial was in a patient population where the median prior lines of systemic therapy was one (1).

[a] CADTH may contact this person if comments require clarification.