CADTH

CADTH REIMBURSEMENT REVIEW

Stakeholder Feedback on Draft Recommendation

fostamatinib (Tavalisse)

(Medison Pharma Canada Inc.)

Indication: Chronic immune thrombocytopenia

January 27, 2022

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0701-000
Brand name (generic)	Tavalisse (fostamatinib)
Indication(s)	For the treatment of thrombocytopenia in adult patients with chronic immune thrombocytopenia (ITP) who have had an insufficient response to other treatments.
Organization	Clinician Group (Hematology) Fatimah Al-Ani, Donald Arnold, Vighnesh Bharath, Mark Blostein, Christine M. Cserti-Gazdewich, Alan Gob, Dawn Goodyear, Kuljit Grewal, Matthew Kang, Karima Khamisa, Sadiya Kukaswadia, Philip Kuruvilla, Nicole Laferriere, Loree Larratt, Alejandro Lazo-Langner, Wendy Lam, Charles Li, Zachary Liederman, Wendy Lim, Yulia Lin, Joy Mangel, Hayley Merkeley, Siraj Mithoowani, Anna Nikonova, Natalia Rydz, Mary Salib, Sudeep Shivakumar, Rosanne St. Bernard, Linda Sun, Lakshman Vasanthamohan
Contact information[a]	Name: Dr. Cyrus C. Hsia Title: Hematologist Email: [redacted] Phone: [redacted]

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

We, the clinician group, would like to thank CADTH Canadian Drug Expert Committee (CDEC) for their review and take the opportunity to respond to the Draft Recommendation on January 13, 2022 for fostamatinib. We would respectfully disagree with the draft recommendations and strongly recommend that fostamatinib be reimbursed for the treatment of thrombocytopenia in adult patients with chronic immune thrombocytopenia (ITP) who have had an insufficient response to other treatments.

- Patients in Canada have limited ITP treatment options available that are Health Canada approved (currently only romiplostim, eltrombopag, and fostamatinib). Unfortunately, none of these have CADTH recommended for reimbursement in Canada. We, as Canadians, take pride in our universal Health Care but when it comes to medication access only the privileged few who have private insurance may access these potentially life-saving therapies. This leaves most patients and physicians with little choice but to use off-label therapies with limited efficacy and potentially severe and serious side effects.
- Fostamatinib was not discussed in the American Society of Hematology (ASH) 2019 guidelines as the trials were not evaluated in those guidelines but was considered to have "robust evidence" in the 2019 International Consensus Report (ICR) along with romiplostim and eltrombopag.
- The FIT1 & FIT2 data, followed by FIT3 data are relatively large for a rare condition such as ITP. The population of ITP patients in the trials is a good representation of the ITP patient population in Canada, since many patients will have failed another second line therapy.
- Although the platelet count is strictly speaking a surrogate marker, it is well accepted as the principal indicator of disease activity and has been shown to predict clinical outcomes including

bleeding, the need for rescue therapies and quality of life once platelet count levels drop significantly. (see Arnold, Am J Hematol 2012; PMID 22847526)

- The FIT1 & FIT2 trials show that a novel therapy used in chronic ITP patients with a range of ages having numerous prior lines of therapy (median 3 with range 1-13) has potential efficacy.

In summary, ITP patients in Canada require access to medications that can reduce bleeding and improve quality of life. Fostamatinib is Health Canada approved, has a novel mechanism of action, is given orally, is generally well-tolerated, has sufficiently good evidence for its use, and offers hope to the multiply relapsed/refractory ITP patients.

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	☒

As a clinician group, we do not feel that CADTH took into consideration our stakeholder input. There are many comments and overall essence of management that were provided by the clinician group that contradict the draft recommendations:

- "Increasing the platelet count is generally considered to be a reasonable surrogate for those two goals (to reduce bleeding and prolong life)", both of which are important to both patients and physicians. The clinician group stated: "In practice, clinicians rely on platelet response which is assumed to reduce risk of clinically relevant bleeding and, as a secondary benefit, reduce the need for rescue therapy".
- The draft recommendation is highly critical of the RCTs, even though these are considered reasonably large by the medical community for ITP trials.
- Given the heterogeneity of patients and treatment pathways, a multicentre, multinational head to head trial in ITP would be virtually impossible. Even in placebo-controlled trials, "rescue therapy" is comparable real-world management of patients who receive standard of care.
- The recommendation stated that "Published and sponsor-submitted indirect treatment comparisons with TPO-RAs and rituximab were associated with numerous limitations, precluding definitive conclusions." We agree. Yet, these data are the best available in ITP, for which any RCT data (let alone large RCTs) are rare. Besides the TPO RAs, only fostamatinib was felt to have "robust evidence" as reported in the 2019 International Consensus Report on ITP diagnosis and management. Larger studies with multiple comparator arms and multiple endpoints are infeasible and cannot be considered a realistic expectation.
- Also, in clinical practice, many ITP clinicians worldwide are leaning away from rituximab in the midst of the global pandemic. Rituximab exposure significantly attenuates antibody response to COVID-19 vaccines, and predispose patients (often high-risk patients due to post-splenectomy state, or exposure to other immunosuppressants such as azathioprine, cyclophosphamide, MMF) to increased risk of COVID-19 infection despite full vaccination.
- CADTH emphasized and discussed at length limitations of subgroup analysis and splitting the FIT1 & FIT2 data. We agree in theory; however, without these approaches, no clinical trial data would be available for this disease site. For example, secondary ITP was excluded from the trial, but this should not divert attention to its importance in primary ITP as doing so will prevent patients with primary ITP from receiving life-saving therapy.

In summary, the medical community and patients have accepted the platelet count as more than a surrogate marker: it is a reliable measure of disease activity that correlates with the clinical outcomes of bleeding and quality of life. Placebo-controlled trials provide valuable information since all patients received standard of care, thus, the use of rescue treatment is a generalizable endpoint. Finally, head to head trials in ITP, while highly desirable, are not feasible in this rare disease.

Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☒
	No	☐
Although the reasons for the recommendation are clearly stated in the "Rationale for the Recommendation" section, it does not reflect the essence or the spirit of the input from patients, clinician experts, or our clinician group. The CADTH draft recommendations are in stark contrast to the needs of patients who require access to Health Canada approved therapies and the input provided by the patient group, clinician experts, and our clinician group as outlined in part 2.		
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☐
	No	☒
NA		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☐
	No	☒
NA		

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

CADTH

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	☐
If yes, please detail the help and who provided it.		
2. Did you receive help from outside your clincian 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		
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	☐
• Clinician group that provided initial input and declarations have remained the same include: Drs. Mark Blostein, Christine Cserti-Gazdewich, Kuljit Grewal, Cyrus Hsia, Sadiya Kukaswadia, Philip Kuruvilla, Nicole Laferriere, Alejandro Lazo-Langner, Zachary Liederman, Yulia Lin, Hayley Merkeley, Siraj Mithoowani, Anna Nikonova, Sudeep Shivakumar, Lakshman Vasanthamohan • Clinicians who are providing support for this feedback include those who are new or with updated conflict of interest declarations: Drs. Fatimah Al-Ani, Donald Arnold, Vighnesh Bharath, Alan Gob, Karima Khamisa, Wendy Lam, Charles Li, Wendy Lim, Joy Mangel, Natalia Rydz, Mary Salib, Rosanne St. Bernard, Linda Sun, Indryas Woldie, Matthew Kang, Loree Larratt, Dawn Goodyear.		

C. New or Updated Conflict of Interest Declarations

New or Updated Declaration for Clinician 1	
Name	*Fatimah Al-Ani*
Position	*Assistant Professor, Hematology Division, Dalhousie University*
Date	*26-01-2022*

☒	**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
Janssen	☒	☐	☐	☐
Pfizer	☒	☐	☐	☐
AstraZeneca	☒	☐	☐	☐

New or Updated Declaration for Clinician 2

Name	*Donald Arnold*
Position	*Professor, John G. Kelton Chair in Translational Research, McMaster University*
Date	*26-01-2022*
☒	**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

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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	☒	☐	☐	☐
Rigel	☒	☐	☐	☐
Amgen	☒	☐	☐	☐
Principia	☒	☐	☐	☐
Medison	☒	☐	☐	☐
Daiichi Sankyo	☒	☐	☐	☐
Sobi	☒	☐	☐	☐
Chugai and Argenx	☒	☐	☐	☐

New or Updated Declaration for Clinician 3

Name	*Vighnesh Bharath*
Position	*Hematologist, Humber River Hospital*
Date	*26-01-2022*

☒	**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

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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	☐	☐	☐	☐

New or Updated Declaration for Clinician 4	
Name	*Alan Gob*
Position	*Associate Professor, Department of Medicine, Division of Hematology,Western University*
Date	*26-01-2022*
☒	**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	☐	☐	☐	☐

New or Updated Declaration for Clinician 5	
Name	*Karima Khamisa*
Position	*Assistant Professor, University of Ottawa*
Date	*26-01-2022*
☒	**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
Pfizer	☒	☐	☐	☐
Novartis	☒	☐	☐	☐

New or Updated Declaration for Clinician 6	
Name	*Wendy Lam*
Position	*Hematologist and medical oncologist, Burnaby Hospital Regional Cancer Centre*
Date	*26-01-2022*
☒	**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

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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	☐	☐	☐	☐

New or Updated Declaration for Clinician 7	
Name	*Charles Li*
Position	*Associate Professor, University of British Columbia*
Date	*26-01-2022*
☒	**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	☐	☐	☐	☐

New or Updated Declaration for Clinician 8	
Name	*Wendy Lim*
Position	*Professor, McMaster University*
Date	*26-01-2022*
☒	**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**

Amgen	☒	☐	☐	☐
BMS-Pfizer Alliance	☒	☐	☐	☐
Pharmacosmos	☒	☐	☐	☐
Aspen	☒	☐	☐	☐
Fresenius	☒	☐	☐	☐
Alexion	☒	☐	☐	☐
Leo Pharma	☒	☐	☐	☐
Novartis	☒	☐	☐	☐
Pfizer	☐	☐	☒	☐

New or Updated Declaration for Clinician 9	
Name	*Joy Mangel*
Position	*Associate Professor, Western University*
Date	*26-01-2022*
☒	**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

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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	☐	☐	☐	☐

New or Updated Declaration for Clinician 10	
Name	*Natalia Rydz*
Position	*Assistant Professor, University of Calgary*
Date	*26-01-2022*
☒	**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

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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	☐	☐	☐	☐

New or Updated Declaration for Clinician 11	
Name	*Mary Salib*
Position	*Assistant Clinical Professor (Adjunct), Niagara Health*
Date	*26-01-2022*
☒	**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

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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	☒	☐	☐	☐

New or Updated Declaration for Clinician 12	
Name	*Rosanne St. Bernard*
Position	*Hematologist, Kitchener-Waterloo*
Date	*26-01-2022*
☒	**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

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

New or Updated Declaration for Clinician 13	
Name	*Linda Sun*
Position	*Assistant Professor, University of Alberta*
Date	*26-01-2022*
☒	**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

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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	☐	☐	☐	☐

New or Updated Declaration for Clinician 14	
Name	*Indryas Woldie*
Position	*Assistant Professor, Windsor Regional Hospital*
Date	*26-01-2022*
☒	**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

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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	☐	☐	☐	☐

New or Updated Declaration for Clinician 15	
Name	*Matthew Kang*
Position	*Assistant Professor, Joseph Brant Hospital, Burlington*
Date	*26-01-2022*
☒	**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

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

New or Updated Declaration for Clinician 16	
Name	*Loree Larratt*
Position	*Professor Emeritus, University of Alberta*
Date	*26-01-2022*

☒	**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

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

New or Updated Declaration for Clinician 17	
Name	*Dawn Goodyear*
Position	*Clinical Assistant Professor, University of Calgary*
Date	*26-01-2022*
☒	**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

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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	SR0701
Name of the drug and Indication(s)	Fostamatinib (Tavalisse) for the treatment of thrombocytopenia in adult patients with chronic immune thrombocytopenia (ITP) who have had an insufficient response to other treatments
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	☐
	No requested revisions	X

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.
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.

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 Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0701-000
Brand name (generic)	Tavalisse
Indication(s)	For adults with chronic ITP who have had insufficient responses to other therapies.
Organization	Platelet Disorders Support Association
Contact information[a]	Name: Jennifer DiRaimo

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

Our Ask:

The ITP patient community hopes that this draft decision could be revised to a 'reimburse with condition(s)' recommendation. Our suggested conditions could be 1) to demonstrate previous failure to at least one other second line; and 2) mandatory enrolment of all treated patients into a registry to captured efficacy and safety (see below), until there is greater comparative evidence. This would be in line with Health Canada's indication for use. The ITP community does not want to see any more lives lost to ITP in this day and age when there are so many therapies available, and many more in development too.

We would also like CADTH to consider a one- or two-year pilot where reimbursement for Tavalisse would be granted, with a commitment from us and from our physician partners to collect registry data to inform the rates of bleeding, hospital visits (including visits to hospital for critical bleeds and long-term health outcomes) and adverse events. This information will inform efficacy and safety using real world data and provide information on resource utilization. Supporting Evidence:

<u>Responsiveness</u>

ITP is an extremely heterogenous disease. Not only in terms of the clinical presentation and disease course, but also in response to different therapies. It is not possible at this time to predict which ITP patient will respond to a particular treatment, or which ITP patient will only partially respond to a particular treatment or have no clinically significant response at all. **We feel that CADTH should recommend reimbursement for Tavalisse so that treatment can be individualized and if a patient does not respond to other second line therapies, they are not 'out of luck' for something they have no control over.**

There will always be ITP patients who do not respond to Tavalisse. With regards to the FIT trial, based only on 150 participants, the number of individuals who responded to Tavalisse is favorable and supports approving Tavalisse for reimbursement. And if you couple that data with what PDSA provided CADTH from our closed Facebook support group, you will see that most of the patients actually using this drug have not responded well (or at all) to other therapies - so Tavalisse may be the only option for them.

<u>ITP Expert Opinions</u>

In Canada, we are very lucky to have several hematologists who specialize in ITP and have even been involved in the development of professional medical ITP guidelines. In regard to the comment *"There is very little evidence to guide the selection of second line or third line therapy …. ",* while we agree that the evidence is limited, there are professional guidelines that were updated in 2019 both American Society of Hematology guidelines , International Consensus guidelines from globally recognized ITP experts, as well as Choosing Wisely Canada and International guides.

Professional guidelines do not support splenectomy as a go-to second line therapy. Rituximab is not preferred over TPO-RAs in the guidelines. Rituximab is not new, but it's used off-label for ITP. While reimbursement of Rituximab would be a step forward, it still would not give Canadian hematologists the flexibility to provide a high standard of care to their patients who cannot afford to access drugs privately and would not support professional guidelines built on evidence. And patients are looking for therapies that not only work, but that do not disrupt their life. For instance, patients have expressed they would rather take an oral medication with no dietary restrictions rather have to take time off work or away from their family to receive an infusion for hours. However, if that is the only option available, many would be chose treatment over risk.

The CADTH review stated *"The clinical experts consulted stated that contemporary ITP guidelines suggest that, in general, splenectomy and Rituximab can be considered second line therapy. There are third line options available; however, the comparative efficacy of these agents are unclear"* is based on limited and outdated knowledge and appears to cherry pick therapies leaving out TPO RAs, leaving out professional medical ITP guidelines, and does not leave room for newer innovative therapies that are not considered third line, that target different mechanisms to treat ITP to increase the chance for response among those with ITP that fail to respond to first line and other second line options. Third line options are more 'supporting' options to support second line therapies. For instance, some patients have reported success adding dapsone to their TPO-RA regime when they noticed the drug started to no longer work for them. This knowledge is not widely known among all hematologists and clinical providers which is why it is crucial for CADTH to listen to respected hematologists working/researching/publishing in the area of ITP specifically.

In a study involving many of PDSA's medical advisors who are Internationally recognized ITP specialists, Boccia et al (2020) used data from post hoc analysis of the phase 3 FIT open-label extension study vs patient subgroups by line of therapy (second line versus third-or-later-line) and stage of disease (persistent versus early or late chronic ITP) and reported: *In this post hoc analysis, fostamatinib was more effective as second-line than third-or-later-line therapy for ITP."* While Tavalisse may not be ready to be used right now as an upfront second line therapy considering the Health Canada indication which limits its use, this data suggest that this is a therapy of great value to ITP patients and at the very least should be considered if other treatments cannot work well for a particular ITP patient.

Other internationally recognized ITP specialists, Dr(s) Newland and MacDonald revealed in their 2020 study the following: *"Fostamatinib as a prodrug, and R406 as its active moiety, represent a novel treatment approach which can be orally administered and requires minimal titration; reducing both clinical time and the need for professional healthcare support. It was shown to produce a rapid, durable response among patients with long-standing ITP who were considered difficult to treat having previously received rituximab, and/or TPO-RAs or had undergone splenectomy. Subgroup analyses illustrate good overall responses independent of duration of ITP, baseline platelet count, previous TPO-RA or rituximab therapy, and prior splenectomy. These results demonstrate that fostamatinib is able to improve platelet numbers among diverse types of patients, including those with and without multiple exposures to prior ITP treatments, and those with longer and shorter durations of ITP. The findings from the FIT (1,2,3) clinical trials programme resulted in the approval of fostamatinib by the US FDA in April 2018 and the EMA in Europe in January 2020. Patients who responded to*

fostamatinib demonstrated good control of hemostasis." The findings from the above are also supported in another professional publication (Duliege AM et al, 2019) which was also authored by several of PDSA's medical advisors specializing in ITP.

CADTH's statement: *"Patients identified a need for treatments that would reduce symptoms and rates of bleeding events and improve QoL compared with currently available therapies… not demonstrated with fostamatinib (Tavalisse)"* **does not reflect the individual patient experience.** PDSA did provide CADTH with direct patient accounts demonstrating how compared to other things tried, Tavalisse was working for them. In terms of the EQ-5D for QoL, those five domains are what we use within our patient registry launched in 2017. The issue with using the EQ-5D is that these aspects of measuring QoL don't all apply to patients with ITP. There are NO mobility issues with ITP. There are NO self-care issues with ITP unless relating to excessive fatigue and depression. There generally is NO pain and discomfort with ITP. Within our ITP Natural History Study patient registry (close to 2000 participants) we have only 5 adult ITP participants (mainly from the USA) who have disclosed they have used (or are currently using) Tavalisse. We do not have the data to provide you, and likely won't in the near future, because patients in Canada cannot access this drug due to affordability issues. This is why we are suggesting our registry proposal to capture this data if it's needed for reimbursement purposes.

ITP is a rare disorder. Only a small number of all those with ITP will require treatment, an even smaller number will require access to second line therapies. Of those that require access to second line therapies only a small number of that group will not respond to traditional second line therapies (such as TPOs and Rituximab) so you are left with a pretty small number needing to use Tavalisse as a later second line therapy choice. You cannot expect the same level of evidence for a small, rare disease group.

Summary Point: ITP experts feel Tavalisse is a good therapy for some patients with ITP who may not respond well to other therapies.

Real-life cost savings

We understand there is a standard way to predict overall cost, but has CADTH considered the real-life costs? Imagine this patient scenario: No access to Tavalisse. Patient can only access steroids and IVIG. Both only work for about a week, then the platelet count decreases again, and bleeding symptoms return. Long term use of steroids has caused diabetes, mental health consequences, and fatigue and weight gain/blood pressure issues. Breakthrough bleeding can occur on steroids (but yet it's reimbursed and continues to be). A critical bleed happens at a low platelet count (can be any location) requiring hospital admission for more than one day, tests to determine the extent of the bleed, and then emergency management that likely consists of platelet transfusions, expensive and in short supply IVIG, and other therapies that increase the cost not to mention bed cost, provider cost, and cost to the patient's family (emotionally, and financially with missed work etc.) What are those relevant costs PER patient?

The cap for what is considered appropriate to fund based on QALY's may not be appropriate because the QALY calculation cannot be accurately assessed when you simply compare the benefits of treatment approach A to treatment approach B. For reason's already explained, it's not possible to compare treatment approaches in that way because not all ITP patients respond to the same therapy, not all therapies are used long-term, and many ITP patients are using more than one therapy at a time, and thus this entire calculation maybe based on questionable data. Not to mention, QALY calculations have their limitations, and often require further mathematical solutions to address such limitations. Can CADTH provide the breakdown of how the prices per QALY was made? Does

CADTH's economic analysis of projected costs capture that not everyone who is eligible to use the drug (if reimbursement was approved) would actually respond to the drug?

When considering costs, CADTH has an obligation to the Canadian people to also make ethical decisions. One could argue that it is unethical to reimburse steroids for long-term use but not better second line therapies that may increase the chance for long term remission when you know you are doing more harm than good? In Ontario and many other provinces, a splenectomy is needed before access to more robust therapies can even be applied for. Splenectomy success is only 60% at best and the overall cost and burden and risk are significant. IVIG is very expensive. Immunoglobulins are in limited supply. PDSA is part of the Canadian Blood Services Working group designed to explore strategies to ensure Canadian patients sustain an adequate supply. Much of Canada's supply is from other countries, such as the US, where the shortage is already a reality.

We understand some literature has been published that supports earlier upfront use of Tavalisse, but at this time, PDSA would support reimbursement with conditions if that means access to this drug can occur for individuals who do not respond (or do not respond well) to other second line options. It is unknown how many ITP patients will (and will not) respond to Tavalisse, the later may be significant.

Summary Point: While CADTH has looked at the economic reality in a standard way, we are concerned about the costs associated with not reimbursing Tavalisse on our overall health care system.

Summary of PDSA's Response to CADTH:

We respectfully request that CADTH consider changing the recommendation for Tavalisse to 'reimbursement with condition(s)'. These conditions might include mandatory enrolment in a patient registry to capture real world data on efficacy and safety.

Sincerely,

Jennifer DiRaimo, MS, CCGC
Genetic Counsellor/Research Program Manager
Platelet Disorder Support Association

Caroline Kruse
President and CEO
Platelet Disorder Support Association

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	☐

We want to thank you CADTH for taking the time to review whether fostamatinib (Tavalisse) should be recommended for reimbursement for adults with ITP. Although the outcome is not what we were expecting or hoping for, it's clear a lot of aspects were considered in this analysis, and we appreciate the time you spent on this.

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

We understand the information within the draft decision, we just want the committee to review our response and take that into consideration before finalizing their recommendation.		
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☐
	No	☒
No implementation issues were suggested since the decision by CADTH was to not recommend reimbursement. We hope our response will influence the committee members to recommend reimbursement with conditions, as discussed above.		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☐
	No	☒
The decision was made to not recommend reimbursement for Tavalisse and this wasn't based on conditions. We feel this could be a good next step: to reimburse with conditions. We hope our response will influence the committee members to recommend reimbursement with conditions, as discussed above.		

[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	*Jennifer DiRaimo*
Position	*Research Program Manager*
Date	*18 February 2022 – We had initially sent in a letter vs completing this form. Our letter (containing the same information) was sent in by the deadline.*
☒	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	☐
However, I did connect with Dr. Donald Arnold (at McMaster) to discuss the option of a pilot study to collect data with our physician partners to provide CADTH with the information it needs to further inform about Tavalisse's efficacy and safety. Dr. Arnold is one of PDSA's Canadian Medical Advisors.		
2. Did you receive help from outside your patient group to collect or analyze any information used in your feedback?	No	☒
	Yes	☐
n/a		

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**
Amgen	☐	☐	☐	☒
Novartis	☐	☐	☐	☒
Rigel	☐	☐	☐	☒